

Prediction of Birth Weight and Neonatal Adiposity Using Ultrasound Assessment of Soft Tissue Parameters in Addition to Two-Dimensional Conventional Biometry

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Keywords

Estimated fetal weight · Fractional limb volume · Neonatal adiposity · Prenatal · Ultrasound

Abstract

Introduction: We aim to evaluate the supplementary predictive value of soft tissue markers, including fetal limb volumes, for fetal birth weight and fat tissue weight. **Methods:** This is a prospective study of 60 patients undergoing term induction of labor. Ultrasound was performed 48 h before birth, and 2D sonographic measurements, subcutaneous tissue thickness, and 3D fetal limb volumes were taken. Birth weight and neonatal fat weight were assessed by plethysmography. Clinical data were collected. The relation between ultrasound and neonatal outcomes was assessed by univariate and multivariate predictive models. The estimated and actual birth weights were compared applying different published formulas, and systematic and random error were collected and compared. **Results:** 3D fetal limb volumes showed a strong relation to birth weight, absolute weight, and relative fat weight. The Lee 6 formula performed better than either Hadlock 3 or Lee 3 with the lowest random error. Fractional limb volumes involve a highly reproducible technique, with excellent correlation (intra-class coefficient

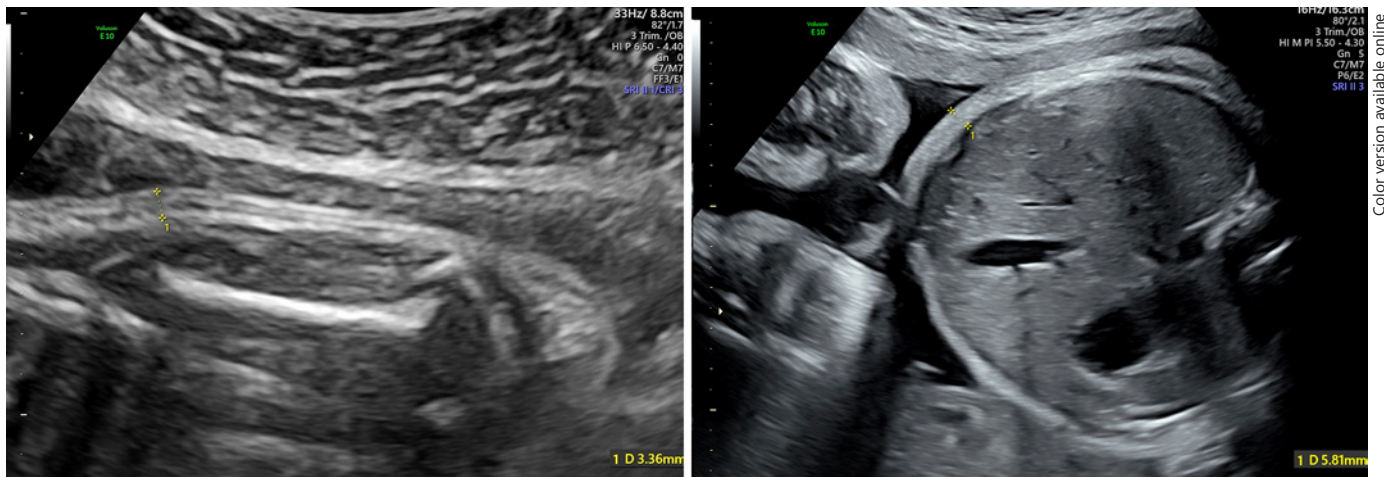
>0.90) for both inter- and intra-observer reliability. The prevalence of estimated EFW measures within 10% error from the actual birth weight was 71.7% with the Hadlock 3 model and 95.0% with the Lee 6 model ($p = 0.09$). **Conclusion:** Late assessment of 3D fetal limb volume in upper and lower extremities is not only useful for accurately predicting birth weight but is a useful marker for prediction of birth fat tissue weight.

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Introduction

Accurate determination of abnormal fetal growth remains an important objective of prenatal care. Both fetal growth restriction and macrosomia are associated with an increased risk of intrauterine death [1–4]. Both cohorts of infants are prone to obesity, type II diabetes, and cardiovascular disease in later life [5, 6].

Traditional techniques to assess fetal size include clinical measurement of symphysis fundal height or ultrasound measurement of fetal biometry, but neither of these methods is particularly accurate [7, 8]. 2D ultrasound assessment of fetal biometry has reported a sensitivity of 30–40% and specificity of 80–90%, respectively,



Color version available online

Fig. 1. Ultrasound measurement of subcutaneous tissue thickness (left: subscapular, right: abdominal).

for estimation of birth weight. Individual estimates of fetal weight may be inaccurate by $\pm 10\text{--}15\%$ [9]. Many existing formulas for estimating fetal weight become inaccurate at extremes [10]. As a consequence, routine third trimester ultrasound in low-risk populations has not been shown to reduce perinatal mortality but is associated with an increase in interventions [11].

Estimates of fetal weight may also fail to identify nutritionally deplete fetuses. Neonatal fat constitutes 14% of total birth weight and accounts for 46% of the variance in birth weight [12]. Low body fat percentage is associated with increased risks of neonatal hypoglycemia, difficulties in feeding, and longer lengths of postnatal stay [13]. Babies that have low or high body fat percentage are also more likely to become obese and develop type II diabetes during childhood and early adulthood [14].

In fetal life, estimated fetal weight correlates poorly with newborn fat weight [15]. Several groups have reported assessment of upper and lower limb fat weight and of abdominal, subscapular, or cheek fat thickness as a means of detecting fetal growth restriction or macrosomia prenatally [16–18]. Ultrasound quantification of soft tissues may improve our ability to evaluate fetal intrauterine nutritional status and growth and distinguish small or large from normally grown fetuses [19, 20]. We aim to examine whether the accuracy and precision of fetal weight estimation can be improved by combining conventional 2D sonographic measurements with subcutaneous tissue thickness and fetal limb volumes. We also aim to establish the utility of a composite estimate of fetal fat weight made prior to delivery for predicting newborn adiposity after birth.

Methods

This was a prospective cohort study performed at Royal Prince Alfred Hospital between December 2016 and December 2017. Pregnant women with singleton pregnancies who had been admitted to the antenatal ward prior to term induction of labor were approached and asked to take part in the study. This study investigates the hypotheses that 3D measures of fetal limb volumes can be reliably assessed in clinical practice and that a combination of 2D and 3D biometric measures performs better than 2D measures alone in estimating fetal weight. We also hypothesize that subcutaneous tissue thickness and 3D limb volumes are of value in estimating neonatal adiposity. Women were scanned immediately prior to their induction, and the findings of the ultrasound examination were compared to findings after birth. Women with multiple gestations, known fetal chromosomal abnormalities, and/or congenital structural abnormalities were excluded from the study. This study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study was approved by the hospital ethics committee (RPAH X15-0322), and all women gave written informed consent.

Pregnancies had previously been dated either by last menstrual period, in women with regular cycles without antecedent oral contraceptive use, or by measurement of crown rump length in the first trimester of pregnancy. Ultrasound measures were used for those women dated by LMP if there was a discrepancy of >4 days from the first trimester scan.

The ultrasound examination was performed by 1 of 2 sonologists (J.G.F. or R.M.) using a GE Voluson E8 or E10 system (General Electric Medical Systems, Milwaukee, WI, USA) with a 4- to 8-MHz curved transducer and a 3D probe (RAB6-D). Standard fetal biometric measures were obtained (biparietal diameter [BPD], HC, abdominal circumference [AC], and femoral length) [21]. Fetal abdominal subcutaneous tissue was measured in the axial plane used to measure the AC, on the anterior abdominal wall anterior to the margin of the ribs (Fig. 1a). The image was magnified so that the abdomen took up $>75\%$ of the screen. Subscapular fat was imaged with the fetus in a prone or lateral posture, so the

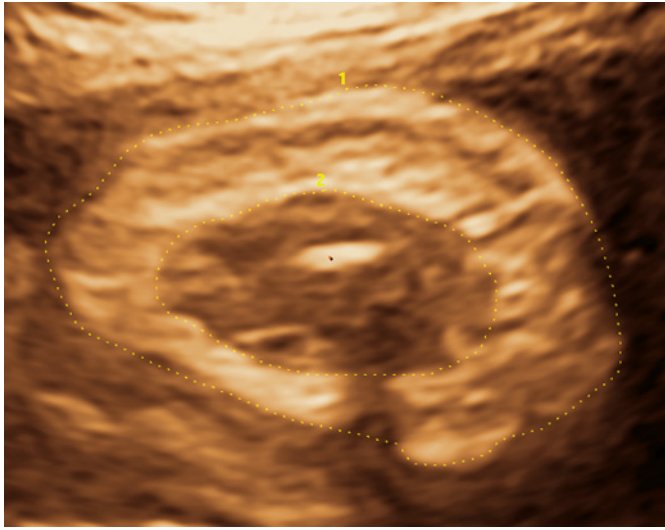


Fig. 2. Fractional area of fetal limb delineating lean (inner) area and total limb area. The fat area is defined as the difference between them (outer).

entire scapula was seen. The calipers were positioned to measure the subcutaneous tissue using the internal skin surface and the bony margin of the lower end of the scapula as boundaries (Fig. 1b) [17]. Two measurements were taken, and the average value was used for analysis.

3D volumes were obtained from the upper (arm) and lower (thigh) fetal extremities using the methodology described by Lee et al. [21]. The plane of acquisition and size of the acquisition box were adjusted for an optimum view of the bone diaphysis and total inclusion of the soft tissues to be analyzed. Two different volume files were acquired for each limb for further off-line analysis using commercially available software (4D-View vr14.0; GE Healthcare). Fractional limb volumes for the arm (AVol) and thigh (TVol) were calculated using automated software “5 transverse planes” method [20]. A total fractional limb volume and a central lean fractional volume (representing muscle and bone) were obtained by hand tracing the area of interest (Fig. 2). The fat fractional volume was obtained by subtracting the lean fractional volume from the total limb fractional volume. Two sets of calculations were collected from each volume for the same extremity, and the average value was included for further analysis. Estimations of birth weight were calculated using the Hadlock (model 3) equation; incorporating HC, AC, and femoral length [22]; Lee model 3 (AC, BPD, and AVol); and Lee model 6 (AC, BPD, and TVol) formulas [20].

Pregnancy outcome data were collated from the patient’s medical record including information for the clinical indication for induction of labor, mode of delivery, gestational age at birth, and newborn gender. Neonatal body composition, providing measures of birth weight, birth fat weight, and birth lean weight, was assessed within 2 h of birth by air displacement plethysmography using a PeaPod (Cosmed Inc., Concord, CA, USA) [23].

An inter- and intra-observer study was performed in 20 randomly selected patients where both sonologists independently

made fractional limb volume measurements and collected volume datasets in a blinded manner. In these patients, 3 different measures were performed for each patient from the same blinded author (J.G.F.) for the intra-observer study.

Qualitative variables were expressed as frequency (percentage), and quantitative variables were expressed as mean (standard deviation [SD] as dispersion measure). Intra-class correlation class analysis was used for assessing the inter- and intra-observer correlation using a one-way random effects model. Kolmogorov-Smirnov’s test was performed to assess the normality of data. Prediction of birth weight and neonatal adiposity was estimated by univariate linear regression analysis for each maker, being further integrated into a multivariate model if the marker was assessed as being statistically significant ($p < 0.05$).

The performances of predictive formulas were assessed by calculating the error (difference between estimated weight and birth weight). Systematic error was expressed as $(\text{estimated weight} - \text{birth weight}) \times 100 / (\text{birth weight})$, whereas random error was defined as the SD of the systematic error. The significance of the mean error being different from zero was assessed by Student’s t test. As previously described, a correction factor was calculated for both Lee formulas by subtracting the decimal form of the mean systematic error from 1 [24]. The prevalence of measures estimated within 10% of birth weight error was estimated for each formula and compared using McNemar’s test for paired nominal variables. Statistical analyses were performed using SPSS 18.0 software (IBM Analytics, Chicago, IL, USA).

Results

The baseline characteristics of the 60 patients recruited to the study are shown in Table 1. The clinical indications for induction of labor were postdates pregnancy (31.6%), maternal diabetes (15.0%), suspected intrauterine growth restriction (11.6%), maternal hypertensive disease (8.3%), suspected large for gestational age fetus (5.0%), and other indications (28.3%). The male/female ratio of newborns was 0.94. The birth weight distribution in the study population is depicted in the histogram shown in Figure 3. Kolmogorov-Smirnov’s test confirmed a normal distribution of these data ($p = 0.85$).

All measurements were made in each case. The time taken to calculate each limb volume was 2.4 (SD 1.2) min. The data examining inter- and intra-observer variability showed high levels of correlation (Table 2). All of the measures, with the exception of subscapular fat thickness, correlated with the infant’s birth weight in univariate analysis (Table 3). Multivariate analysis showed that a combination of AC and all the measures related to limb volumes were significantly correlated with infant birth weight (Table 3).

The diagnostic accuracy and precision for predicting birth weight using formulas that have previously been

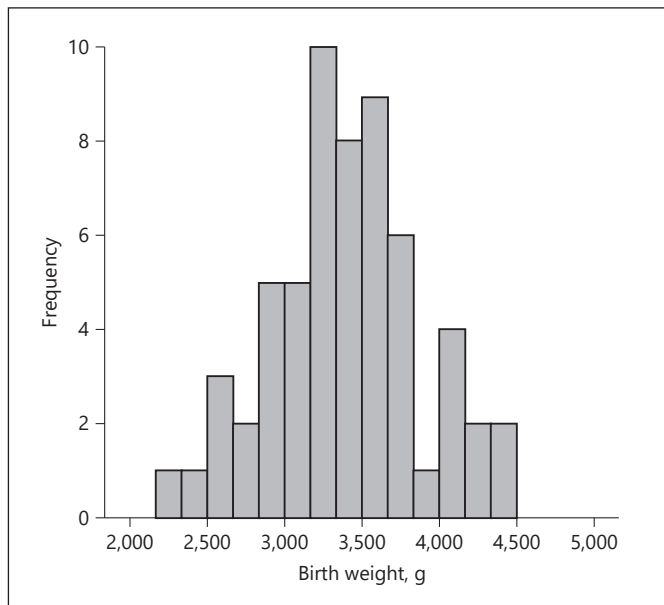


Fig. 3. Histogram depicting birth weight distribution in the study population.

presented are reported in Table 4. Systematic correction factors were calculated for Lee's formulas (using the methodology that had been prescribed) and were 1.040 for Lee's model 3 and 1.018 for Lee's model 6. The prevalence of estimated EFW measures within 10% error from the actual birth weight was 71.7% with Hadlock 3 model compared to 93.3% with Lee 3 model (p 0.09) and 95.0% with Lee 6 model (p 0.09).

The value of the various ultrasound markers for predicting birth and lean fat weight (expressed in grams) is displayed in Table 5. AC and all limb volume measurements were significantly associated with birth fat weight and birth lean weight. When integrated into a multivariate predictive model, only AC reached statistical significance for birth lean weight (Table 5).

Discussion

In addition, we present a predictive study for targeted prediction of fat and lean birth weight. This study presents a late-term prediction model of the birth weight incorporating a detailed analysis of the fetal body composition and relating it to a postnatal analysis. It also emphasizes the different values of predictive formulas when adding the 3D estimation of fetal limb volumes.

Table 1. Descriptive measures of the study population ($n = 60$)

Variable	Mean (SD)
Gestation at delivery, weeks	39.1 (1.5)
<i>Mode of delivery</i>	
Vaginal	43 (71.7%)
Caesarean section	17 (28.3%)
<i>Ultrasound measures</i>	
AC, mm	342.6 (26.7)
Estimated fetal weight – Hadlock 3, g	3,417 (569)
AFT, mm	5.7 (1.5)
SSFT, mm	5.1 (1.3)
Total AVol, mm ³	37.3 (11.9)
Total TVol, mm ³	87.8 (20.7)
Fat AVol, mm ³	19.6 (5.9)
Fat TVol, mm ³	37.5 (11.9)
Lean AVol, mm ³	17.8 (4.3)
Lean TVol, mm ³	50.3 (10.2)
<i>Postnatal measures</i>	
Birth weight, g	3,380 (483)
Birth lean weight, g	3,017 (371)
Birth fat weight, g	352 (139)

SD, standard deviation; TVol, thigh volume; AVol, arm volume; AC, abdominal circumference; SSFT, subscapular fat thickness; AFT, abdominal fat thickness.

This prospective study offers valuable information in regard to accuracy of different formulas for prediction of birth weight incorporating fetal limb volume. Estimates of fetal weight appear to be improved by including assessment of either the 3D AVol (Lee's model 3) or TVol (Lee's model 6), and the Lee 6 model performed slightly better in this late-term population. Using this formula, 95% of estimated weights lay within 10% of actual birth weight. We also found that capturing and calculating fractional limb volumes involve a highly reproducible technique, suitable for clinical application, with excellent correlation (intra-class coefficient >0.90) for both inter- and intra-observer reliability. There is growing evidence that neonatal assessment of fat mass is of value in identifying infants that have perinatal complications. In this study, we have been able to show that fetal fat mass can be accurately estimated using 3D volumes.

There are more than 70 publications that describe models for estimating fetal weight that are recognized as having variable performance with respect to accuracy and precision [10]. The Hadlock 3 formula, incorporating 2D measures of the head and AC and femur length, is generally accepted as having minimal systematic error but rel-

Table 2. Intraclass correlation study (intra- and interobserver)

	Intra-observer 1		Intra-observer 2		Interobserver	
	ICC	95% CI	ICC	95% CI	ICC	95% CI
TVOL	0.93	0.91–0.95	0.97	0.95–0.99	0.80	0.51–0.92
AVOL	0.92	0.88–0.96	0.96	0.91–0.98	0.89	0.65–0.93

ICC, intra-class coefficient; 95% CI, 95% confidence interval (upper and lower limits); AVol, arm volume; TVol, thigh volume.

Table 3. Univariate and multivariate analyses of the value of each ultrasound marker for predicting birth weight

Ultrasound measure	Univariate analysis		Multivariate analysis	
	<i>p</i> value	<i>R</i> ²	<i>p</i> value	95% CI
AC	<0.001	0.62	<0.001	3.22; 8.80
Total TVol	<0.001	0.77	0.02	2.63; 24.23
Total AVol	<0.001	0.59	0.003	32.49; 143.63
Lean TVol	<0.001	0.74	0.003	5.71; 26.15
Lean AVol	<0.001	0.54	0.01	135.83; 19.76
Fat TVol	<0.001	0.62	0.01	2.46; 16.72
Fat AVol	<0.001	0.41	0.004	129.40; 26.19
AFT	0.02	0.10	0.66	–29.51; 45.89
SSFT	0.91	–0.02	–	–

Variables with *p* < 0.05 in the univariate analysis were further incorporated into the multivariate model. 95% CI, 95% confidence interval (upper and lower limits for the unstandardized coefficient); AC, abdominal circumference; TVol, thigh volume; AVol, arm volume; AFT, abdominal fat thickness; SSFT, subscapular fat thickness.

Table 4. Accuracy and precision of previously reported formulas that estimate fetal weight using 2D (Hadlock 3) or a combination of 2D and 3D (Lee 3 and Lee 6) ultrasound

	Mean (SD)	Systematic error	Random error	<i>p</i> value*
Hadlock 3 (BPD/HC/AC/FL)	3,417 (569)	1.06%	9.78%	0.47
Lee 3 (AC/AVol/BPD)	3,237 (515)	–3.99%	7.19%	0.001
Lee 6 (AC/BPD/TVol)	3,322 (575)	–1.83%	6.55%	0.08
Lee 3 corrected ^a	–	–0.16%	7.47%	0.87
Lee 6 corrected ^a	–	–0.03%	6.67%	0.97

SD, standard deviation; AC, abdominal circumference; BPD, biparietal diameter; FL, femoral length; AVol, arm volume; TVol, thigh volume. * *p* values calculated as difference from zero (i.e., demonstrate systematic deviation). ^a Correction factors were 1.040 for Lee 3 and 1.018 for Lee 6.

atively large random error; the impact of this level of random error is that clinicians have to anticipate that estimated fetal weights will vary from absolute birth weight by 10–15%, and this is most pronounced at the extremes of birth weight. A number of factors such as the experi-

ence of an operator, measurement protocol, and standard of equipment have a significant influence on systematic error, whereas random error cannot be corrected because it is inherent in the technique used to acquire this information [9].

Table 5. Effectiveness of ultrasound soft tissue markers for prediction of birth adiposity

	Univariate analysis		Multivariate analysis	
	<i>p</i> value	<i>R</i> ²	<i>p</i> value	95% CI
<i>Birth fat weight, g</i>				
AC	<0.01	0.21	0.63	−0.002; 0.002
Total TVol	<0.001	0.44	0.29	−0.003; 0.011
Total AVol	<0.001	0.28	0.86	−0.066; 0.077
Lean TVol	<0.001	0.44	0.07	−0.002; 0.031
Lean AVol	<0.001	0.33	0.13	−0.068; 0.009
Fat TVol	<0.001	0.30	0.53	−0.024; 0.012
Fat AVol	0.02	0.14	0.74	−0.093; 0.128
AFT	0.58	0.01	–	–
SSFT	0.64	0.01	–	–
<i>Birth lean weight, g</i>				
AC	<0.001	0.69	<0.001	3.310; 10.009
Total TVol	<0.001	0.72	0.28	−0.037; 0.126
Total AVol	<0.001	0.62	0.48	−81.498; 165.302
Lean TVol	<0.001	0.64	0.41	−18.501; 43.300
Lean AVol	<0.001	0.48	0.33	−92.502; 33.070
Fat TVol	<0.001	0.60	0.28	−34.422; 32.970
Fat AVol	<0.001	0.47	0.70	−227.248; 156.408
AFT	0.05	0.10	0.65	−32.782; 50.824
SSFT	0.37	0.02	–	–

Variables with *p* < 0.05 in the univariate analysis were further incorporated into the multivariate model. 95% CI, 95% confidence interval (upper and lower limits for the unstandardized coefficient); AC, abdominal circumference; TVol, thigh volume; AVol, arm volume; AFT, abdominal fat thickness; SSFT, subscapular fat thickness.

Our findings support the reports of other investigators who have found that precision of estimating fetal weight is improved by incorporating fractional limb volume. Lee et al. [19] used fractional AVol and limb volume in addition to 2D biometric measurements to develop a series of models for birth weight estimation. Lee’s models 3 (BPD, AC, and AVol) and 6 (BPD, AC, and TVol) had the lower systematic errors (0.12–0.18%) and more precise random error (6.6–6.6%) than Hadlock’s model 3 formula [20]. Our data also match the conclusion of groups who have validated these formulas by adding a correction factor, identifying small systematic errors caused by using automated fractional limb volume calculations, rather than manually traced borders in analysis [24]. Nevertheless, our measurements were performed with manual tracing; therefore, this systematic error cannot be attributed to this variable. Having ruled out an

asymmetrical distribution of our sample with the use of a histogram (Fig. 2) and a normality distribution test, we can hypothesize that this deviation can be caused by the unique characteristics of this late-term population where the “far right” extreme of the Lee model curve is applied. This trend to a statistically significant underestimation in larger babies has been reproduced in other studies [21], and it is particularly remarkable in Lee’s model 3. In contrast, Lee’s model 6 reproduces a lower systematic error in this population which is not significantly different from 0 and might be more accurate for late-term weight prediction.

Fractional limb volumes add a soft tissue component to weight estimation and a more robust assessment of fetal nutritional status. These data have also been used to predict neonatal adiposity. In a study of 44 fetuses assessed at 28- and 36-week gestation, Moore et al. [25] showed that fetal fractional limb volume is associated with neonatal adiposity measured using anthropometric measurements at birth and air displacement plethysmography 2 weeks after birth. Air displacement plethysmography is recognized to be a very accurate way of measuring body fat composition in neonates and can be used to identify infants at risk of hypoglycemia. In our study, while we found that a number of 3D ultrasound measures were associated with neonatal fat and lean weight, we were not able to demonstrate value in combining a number of measures to estimate neonatal body composition. Delineating fat and lean tissue areas is time-consuming, and it is interesting that our data suggest that there is little added value in manipulating volumes beyond measurement of total limb volume. Our results agree with previous studies which found the total fractional limb volume to be a better predictor of total birth weight and birth fat weight [26]. In contrast, other studies found that the fractional thigh or arm fat volume approximated neonatal fat weight more closely [27]. The selective prediction of the fetal fat compartment is interesting as a targeted detection of babies with increased or depleted adipose tissue might be useful for a clinical selection of newborns at increased risk of clinical complications, as infants of diabetic mothers or IUGR [5, 6, 28, 29].

The measure of subcutaneous fetal thickness at different levels has been correlated with neonatal weight and adiposity measured with skinfold technique in full-term pregnancies [30]. Nevertheless, their predictive value in our sample for birth weight and neonatal body composition estimated by the PeaPod was inferior to the fetal limb volume method. Further studies are necessary to evaluate their reproducibility in this population.

Strengths of our study included prospective recruitment and the use of the Peapod (air plethysmography) for defining neonatal fat weight. Limitations include small sample size, making assessment of multivariate algorithms difficult and limiting the numbers of “large” and “small” infants recruited and measured. A large multicenter population would be useful for assessing clinical outcomes derived from increased or decreased adiposity (hypoglycemia, shoulder dystocia, etc.) and evaluate if 3D ultrasound assessment of limb volume is useful for predicting these complications.

This study provides further support for inclusion of 3D limb volume measures in estimation of fetal weight. While these measures correlate well with neonatal fat weight, we were unable to develop a multivariate model for estimation of body composition. Larger studies will be of value in determining whether inclusion of 3D volumes in estimation of fetal weight improve perinatal outcomes.

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Statement of Ethics

This study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study was approved by the hospital ethics committee (RPAH X15-0322), and all women gave written informed consent.

Conflict of Interest Statement

The authors have no conflict of interests to declare.

Funding Sources

No funding source declared for this study.

Author Contributions

All authors (J.G.F., R.M., M.S., and J.H.) made significant contributions in design of the work, acquisition of data for the work, drafting of the work, critical revision of its content, and final approval of the version to be published.

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