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Association of ultrasound-based measures of fetal body composition with newborn adiposity

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Summary

Background: Newborns exhibit substantial variation in gestational age-adjusted and sex-adjusted fat mass proportion. The antecedent characteristics of fetal body composition that are associated with newborn fat mass proportion are poorly understood.

Objective: The aim of this study was to determine whether a composite measure of fetal fat mass is prospectively associated with newborn adiposity.

Methods: In a longitudinal study of 109 low-risk pregnancies, fetal ultrasonography was performed at approximately 12, 20 and 30 weeks gestation. Estimated fetal adiposity (EFA) was derived by integrating cross-sectional arm and thigh per cent fat area and anterior abdominal wall thickness. Newborn per cent body fat was quantified by Dual Energy X-Ray Absorptiometry. The association between EFA and newborn per cent body fat was determined by multiple linear regression.

Results: After controlling for confounding factors, EFA at 30 weeks was significantly associated with newborn per cent body fat (standardized β = 0.41, p < 0.001) and explained 24.0% of its variance, which was substantially higher than that explained by estimated fetal weight (8.1%). The observed effect was driven primarily by arm per cent fat area.

Conclusions: A composite measure of fetal adiposity at 30 weeks gestation may constitute a better predictor of newborn per cent body fat than estimated fetal weight by conventional fetal biometry. Fetal arm fat deposition may represent an early indicator of newborn adiposity. After replication, these findings may provide a basis for an improved understanding of the ontogeny of fetal fat deposition, thereby contributing to a better understanding of its intrauterine determinants and the development of potential interventions.

Keywords: fetal body composition, fetal fat mass, newborn adiposity, per cent body fat.

Abbreviations: DXA, dual energy X-Ray absorptiometry; GDM, gestational diabetes; GWG, gestational weight gain; EFA, estimated fetal adiposity; ROC, receiver operating characteristic; AUC, area under the curve

Introduction

The public health significance of childhood obesity is well established (1,2). Obesity, or more precisely increased adiposity, in infancy is associated with a higher prevalence and earlier onset of adverse health outcomes including insulin resistance, dyslipidemia, hypertension and the metabolic syndrome (3,4). Newborns exhibit substantial variation in fat mass proportion, and this inter-individual difference tracks across infancy into childhood (5). Moreover, obesity is extremely difficult to reverse, highlighting the importance of primary prevention (2).

Based on the convergence of epidemiological and experimental evidence, the origins of obesity can, in part, be traced back to developmental processes during intrauterine life (6). Consequently, the elucidation of antecedent conditions that modulate fetal growth and body composition is an area of active investigation (7,8). The success of this effort requires
the development of reliable measures for the identification of physiological and pathophysiological variations of fetal growth and fat deposition.

Fetal ultrasonography is currently the most practical method to assess fetal size and body composition, and most studies have used conventional biometry to calculate estimated fetal weight (9). However, estimated fetal weight is an indirect measure of fat mass and only modestly correlates with newborn fat mass (10). Recent improvements in ultrasound imaging have enabled better tissue characterization and more reliable quantification of fetal fat deposition at specific anatomical sites (11). To date, only a relatively small number of studies of fetal body composition have been conducted, and they have primarily used single-site measurements of fetal subcutaneous fat in the extremities and abdomen (12,13). An important limitation of these studies is that they have assessed fetal fat deposition at or close to term gestation (14), thereby restricting their utility for the quantification of fetal body composition before the period of maximal fat accretion in the third trimester (15).

In terms of the infant obesity, most previous studies have relied on ponderal index or body mass index. These are indirect estimates of fat mass and correlate only moderately with measures of adiposity (16). We, therefore, used a direct measure of newborn per cent total body fat assessed by dual energy X-Ray absorptiometry (DXA) (17).

Our aims were to (i) determine whether a composite, multi-site measure of fetal fat mass (arm, thigh and abdomen) assessed before the period of maximal fetal fat deposition (i.e. the third trimester) is prospectively associated with newborn adiposity; (ii) identify the relative contributions of the specific fetal sites in accounting for variation in newborn adiposity; and (iii) assess the utility of the composite measure of fetal fat mass in the third trimester for predicting newborn adiposity.

Materials and methods

Study population

The study population was composed of 109 mother-newborn dyads recruited from an on-going, prospective cohort study conducted at the University of California, Irvine, Development, Health and Disease Research Program. Women with a singleton pregnancy were recruited in the late first or early second trimester. Maternal exclusionary criteria were uterine anomalies, pre-existing major medical comorbidities (hypertension or diabetes), use of antenatal systemic corticosteroids and illicit drug use. Newborn exclusionary criteria were congenital malformations, chromosomal abnormalities, major perinatal complications and preterm birth less than 34 completed weeks. The study was approved by the Institutional Review Board, and written informed consent was obtained from all mothers.

Prenatal ultrasonography

Fetal two-dimensional ultrasound was performed at all three antenatal visits (approximately 12, 20 and 30 weeks) to assess biparietal diameter, head circumference, abdominal circumference and femur length. Estimated fetal weight was calculated using the four-parameter model (9).

Measures of fetal adiposity were obtained at the second and third study visits, but not at the first visit, because fetal fat deposition is histologically evident only after 14–16 weeks (18). We selected the mid-upper arm, mid-thigh and abdomen to measure fat mass because it can be reliably quantified by ultrasound at these anatomical sites (12,13). Three-dimensional ultrasound was used to acquire total contours of arm and thigh, then analysed offline using appropriate software (4D View 9.0, GE Healthcare, Milwaukee, WI, USA) to determine subcutaneous fat area with standardized cross-sectional images (13).

Briefly, we identified the midpoint of the humerus and femur, and measured the total cross-sectional area and the lean mass area. The fat area was calculated as difference between these two measures. Per cent fat area was defined as the ratio of fat area to the total area. Subcutaneous fat thickness in the abdomen was measured as the high-echoic region anterior to the margins of the ribs, proximal to the cord insertion (12).

Each of the measurements was obtained in duplicate and averaged. All ultrasound scans were performed using a Voluson i (GE Healthcare) with trans-abdominal 4-MHz curved array transducer (RAB4-8-RS) by one of the three obstetricians with training in fetal ultrasonography (SI, KS and MO). Inter-observer coefficient of variation for arm per cent fat area, thigh per cent fat area and anterior abdominal wall thickness were 8.2%, 9.7% and 9.9%, respectively, and intra-observer coefficient of variation were 7.2%, 7.4% and 7.5%, respectively.

Birth outcomes

Birth weight, gestational age at birth and infant sex were abstracted from the medical record.

Infant body composition

Newborn adiposity was quantified by DXA using a Hologic Discovery scanner (QDR 4500A, Hologic...
Inc, Bedford, MA, USA) in the paediatric scan mode (17). Potential measurement issues at birth can relate to ensuring similar timing of measurement relative to delivery, rapid changes in body composition that occur soon after delivery, water loss in first few days of life and potential individual variation in these factors (19). Therefore, newborn DXA scans were performed at approximately 1 month postnatal age. Calibration using the anthropomorphic phantom was performed before each scan. Infants lay supine while sleeping, wearing only a disposable diaper and swaddled in a light cotton blanket. Per cent body fat was determined using the Hologic Analysis Version 12.1 software (Hologic Inc, Bedford, MA, USA). The DXA scan of one newborn was excluded from the analysis due to unsatisfactory image quality.

Obstetric risk conditions
Obstetric risk factors were defined as the conditions considered pertinent to affect fetal body composition, including gestational diabetes (GDM), gestational hypertension, pre eclampsia, genital tract infection, recurrent vaginal bleeding or severe anaemia (12,20). Nine mothers had GDM, and 11 mothers had other obstetric risk conditions (Table 1).

Pre-pregnancy body mass index and gestational weight gain
Pre-pregnancy body mass index (BMI) was calculated using pre-pregnancy weight (by maternal self-report) and height measured at first prenatal visit. Pre-pregnancy weight was highly correlated with the maternal weight measured at her first prenatal visit \( r = 0.99, p < 0.001 \), justifying its use in this context. Maternal total weight gain during pregnancy was abstracted from the medical record, and gestational weight gain per week (GWG/week) was calculated. Because pre-pregnancy BMI and GWG both may exert effects on newborn adiposity (21,22), and because the effect of GWG is conditional upon pre-pregnancy BMI (inter-correlation coefficient = −0.50, \( p < 0.001 \), the interaction term between the two parameters \( \text{pre-pregnancy BMI} \times \text{GWG/week} \) was used in the analysis.

Data analysis
Adjustment of fetal measures for gestational age at ultrasonography
Gestational age was confirmed using an algorithm combining last menstrual period and fetal biometry as per standard clinical criteria (23). Gestational ages of study subjects varied because of the timing of ultrasonography (three antenatal visits ranged between 10–16, 18–23 and 28–32 weeks, respectively). We therefore corrected for the effects of variation in gestational age at assessment by centering at a mean gestational age for each visit (12.9, 20.5 and 30.4 weeks, respectively) and residualizing the ultrasound measurements for these mean gestational ages. Briefly, after confirmation of the linear relationship between fetal ultrasound measure and gestational age at scan, the product of the regression coefficient and centred gestational age was calculated. This product was added to or subtracted from the measured value to calculate the adjusted value of fetal parameters. This procedure standardizes the fetal measures across all subjects at the centred gestational ages, enabling comparisons across subjects.

Estimated fetal adiposity
We derived a composite measure of fetal adiposity using arm per cent fat area, thigh per cent fat area and anterior abdominal wall thickness. Because these

| Table 1 Maternal sociodemographic and clinical characteristics |
|---------------------------------|-----------------|
| Characteristics                  | \( N = 109 \)  |
| Age, years*                      | 28.4 ± 4.9     |
| Race/ethnicity                   |                 |
| Non-Hispanic White               | 46 (42)        |
| Hispanic White                   | 43 (40)        |
| Others                           | 20 (18)        |
| Annual income, $                 |                 |
| Below 30 000                     | 33 (30)        |
| 30 000–50 000                    | 26 (24)        |
| 50 000–100 000                   | 39 (36)        |
| Over 100 000                     | 11 (10)        |
| Pre-pregnancy BMI, kg m\(^{-2}\)* | 27.6 ± 6.6                |
| Gestational weight gain, kg*     | 13.2 ± 6.5     |
| Gestational weight gain per week, kg week\(^{-1}\)* | 0.37 ± 0.17              |
| Parity (primiparous)             | 40 (37)        |
| Smoking                          | 4 (3.7)        |
| Gestational diabetes             | 9 (8.3)        |
| Pregnancy induced hypertension/preeclampsia | 4 (3.7)  |
| Recurrent infection              | 2 (1.8)        |
| Recurrent vaginal bleeding        | 4 (3.7)        |
| Severe anaemia**                 | 1 (0.9)        |
| Caesarean delivery               | 37 (34)        |

*Data are presented as mean ± SD. **Defined as haematocrit <30%. BMI, body mass index.
parameters have different units of measurement, we first converted each of the measurement units to standardized (\(z\) scores based on our study population. We then computed the mean (unweighted) of the three \(z\) scores as a composite estimate of fetal adiposity (EFA). Inter-observer reliability of EFA was evaluated using intra-class correlation coefficients, and was estimated to be 0.90.

**Statistical analysis**

Pearson product moment correlations were used to assess bivariate associations among continuous variables, and the Student’s \(t\)-test was used to test group differences. We considered the following potential confounding factors in the relationship between EFA and newborn adiposity: maternal age, parity, race/ethnicity, socioeconomic status (annual family income), pre-pregnancy BMI, GWG/week, obstetric risk factors, gestational age at birth, infant sex, postnatal age at DXA and mode of infant feeding. The subset of these variables that were significantly associated with newborn per cent body fat was then selected for subsequent multivariate analyses.

First, associations of EFA with newborn per cent body fat were examined using bivariate analysis. Next, multiple linear regression was used to quantify the association between EFA and estimated fetal weight with newborn per cent body fat, with adjustment for potential confounding factors (aim 1). Using the same set of covariates, we then decomposed the composite summary EFA measure to identify the relative contributions of the specific fetal fat mass sites (arm, thigh and abdomen) in explaining variation in newborn per cent body fat, as quantified by the partial correlation coefficient associated with these components in multiple linear regression model (aim 2). Lastly, to assess the utility of fetal fat mass measures at the third trimester for predicting ‘high’ newborn per cent body fat (defined as \(\geq\)75th sample percentile, found to be 17.3\%), we employed logistic regression and receiver operating characteristic (ROC) curve analyses (aim 3). ROC curves were generated by considering all possible cut points from the estimated linear predictor resulting from a logistic regression model. Predictive model selection was performed by using cross-validation to estimate the out-of-sample classification error of proposed models. Potential covariates assessed in predictive models included only those covariates that could be measured at the third trimester. The top-performing model that included site-specific EFA measurements at 30 weeks was selected based upon a fivefold cross-validated area under the ROC curve (AUC) estimate. The predictive performance of this model was then compared with that of the top-performing model omitting the site-specific EFA measurements.

All statistical analyses were performed using SPSS ver.22.0 and R ver.3.2.1 with statistical significance determined at \(p < 0.05\).

**Results**

Descriptive statistics of the maternal characteristics and of the fetal parameters are summarized in Tables 1 and 2, respectively. Gestational age at birth was 39.2 ± 1.4 weeks (mean ± SD), and 54% of newborns were male. Mean birth weight was 3371 ± 476 g. Postnatal age at DXA was 26.6 ± 10.2 d, and total mass and fat mass were 4290 ± 725 g and 624 ± 339 g, respectively. Newborn per cent body fat was 13.9 ± 5.7%, which is consistent with previous reports (16,24). Fifty-two infants were breastfed, 14 were formula-fed and 43 were mixed-fed.

Bivariate analysis indicated significant associations of maternal age, parity, the interaction term of pre-pregnancy BMI and GWG/week, GDM, gestational age at birth and postnatal age at DXA with newborn per cent body fat. Per cent body fat was higher in females (14.9 ± 5.5%) compared with males (13.1 ± 5.9%), but this difference was not statistically significant (\(p = 0.107\)). In our study population, there was no statistically significant effect of race/ethnicity on newborn adiposity measures.

Estimated fetal weight at 30 weeks, but not at 13 and 20 weeks, was significantly associated with newborn per cent body fat \((r = 0.230, p = 0.016)\). EFA at 30 weeks, but not at 20 weeks, was significantly associated with newborn total fat mass \((r = 0.423, p < 0.001)\) and per cent body fat \((r = 0.457, p < 0.001)\) (Fig. 1). After controlling for the potential confounding factors, EFA at 30 weeks was significantly associated with newborn per cent body fat (partial correlation coefficient = 0.490, \(p < 0.001\) and explained 24.0\% of its variance (Table 3), while estimated fetal weight explained 8.1\% of its variance (partial correlation coefficient = 0.284, \(p = 0.032\)).

The results of post hoc analyses to identify the relative contributions of the specific fetal fat mass sites in accounting for variation in newborn per cent body fat are presented in Fig 2. Specifically, a 1\% increase in arm per cent fat area was associated with a 0.36\% increase in newborn per cent body fat [95% confidence interval (CI): 0.23–0.51\%; \(p < 0.001\)].

Figure 3 presents the ROC curve for the top-performing predictive model that included site-specific EFA measurements at 30 weeks. This model included arm per cent fat area and anterior abdominal
wall thickness at 30 weeks, maternal age and pre-pregnancy BMI. The fivefold cross-validated estimate of the AUC for this model was 0.74 (95% CI: 0.64–0.85). In contrast, the top-performing predictive model excluding site-specific EFA measurements resulted in an AUC of 0.64 (95% CI: 0.53–0.75). The inclusion of site-specific EFA measurements results in approximate 15.6% relative increase in the AUC for predicting high newborn per cent body fat.

Finally, because fetuses of GDM mothers may have different growth trajectories and exhibit differences in body fat at birth compared with infants without GDM (25), we repeated all analyses after excluding the nine subjects with GDM. There was no appreciable change in the significance and magnitude of the previously described effects of EFA on newborn adiposity.

Discussion
To the best of our knowledge, this is the first study to demonstrate a prospective association of fetal fat mass (assessed before the period of maximal fetal fat deposition (15)) with newborn adiposity. The principal findings are as follows: firstly, our composite measure of fetal fat mass (EFA) at the beginning of the third trimester independently accounted for a significant proportion of the variation in newborn adiposity after controlling for potential confounding factors. Secondly, EFA was a better predictor of newborn adiposity than conventional fetal biometry. Thirdly, fetal arm fat mass at the beginning of the third trimester appears to be a novel marker that leads to better prediction of newborn adiposity.

After accounting for the effects of pre-pregnancy BMI, GWG, GDM, gestational age at birth and postnatal age at DXA, EFA at 30 weeks explained 24.0% of the variance in newborn per cent body fat, whereas estimated fetal weight explained only 8.1% of its
variance. The observation that this association is evident as early as the beginning of the third trimester suggests that quantification of fetal fat mass before the fetus accrues the majority of fat tissue could reliably account for a substantial proportion of the variation in newborn adiposity. The clinical significance of this finding is that it may be possible to implement interventions for primary prevention of newborn adiposity prior to the acceleration of fetal fat deposition. Although our study quantitatively documents evidence of fetal fat deposition at 20 weeks, the absence of an association of these measures with newborn adiposity suggests insufficient variation of fat deposition between fetuses at this gestational age.

Our study indicated that fetal arm fat and abdominal fat at 30 weeks independently and additively explained variations in newborn adiposity. This effect was driven primarily by arm per cent fat area, which alone explained 20.4% of the variation of newborn per cent body fat. Another recent study also has reported that variations in the fetal arm fat area in the late third trimester differentiated newborns with low compared with high fat mass (26). It appears that the pivotal time of growth acceleration of arm volume is around 28 weeks (27), which precedes thigh volume by approximately 2 weeks (28). These findings suggest measures of fetal arm fat mass may

| Table 3 Multiple regression model associating EFA at 30 weeks gestation with newborn per cent body fat |
|-----------------|-----------------|-----------------|-----------------|
|                  | Unstandardized β [95% CI] | Standardized β Partial correlation | P value         |
| Maternal age    | 0.131 [-0.040–0.301] | 0.112            | 0.151            | 0.131            |
| Parity          | 1.034 [-0.906–2.974] | 0.087            | 0.106            | 0.293            |
| Gestational diabetes | 1.716 [-1.361–4.792] | 0.083            | 0.111            | 0.271            |
| Pre-pregnancy BMI | -0.048 [-0.194–0.099] | -0.054          | -0.065          | 0.519            |
| GWG/week        | -3.352 [-9.282–2.577] | -0.098          | -0.112          | 0.265            |
| Interaction of pre-pregnancy BMI and GWG/week | 0.917 [0.234–1.600] | 0.220          | 0.259          | 0.009            |
| Gestational age at birth | 0.771 [0.160–1.381] | 0.192          | 0.244          | 0.014            |
| Postnatal age at DXA scan | 0.219 [0.148–0.289] | 0.439          | 0.524          | <0.001          |
| EFA at 30 weeks gestation | 3.705 [2.391–5.018] | 0.410          | 0.490          | <0.001          |

BMI, body mass index; CI, confidence interval; DXA, Dual Energy X-Ray Absorptiometry; EFA, estimated fetal adiposity; GWG/week, gestational weight gain per week.

Figure 2 Post-hoc analysis of the relative contributions of fetal arm and thigh per cent fat area and anterior abdominal wall thickness at 30 weeks gestation explaining variation in newborn per cent body fat (adjusted for maternal age, parity, interaction term of pre-pregnancy BMI and maternal gestational weight gain per week, gestational diabetes, gestational age at birth and postnatal age at DXA scan). *p < 0.05, **p < 0.001. BMI, body mass index; DXA, Dual Energy X-Ray Absorptiometry.

Figure 3 Estimated ROC curves for best fitting predictive models of high newborn per cent body fat, defined as ≥75th sample percentile. The best fitting model included arm per cent fat area and anterior abdominal wall thickness at 30 weeks gestation, maternal age and pre-pregnancy BMI (red line). The comparison model excluded arm per cent fat area and anterior abdominal wall thickness at 30 weeks gestation (blue line). Models were chosen using fivefold cross-validation and reported AUC estimates and 95% confidence intervals are based upon the cross-validated samples. AUC, area under the curve; BMI, body mass index; CI, confidence interval; EFA, estimated fetal adiposity; ROC, receiver operating characteristic; wk, week.
represent an important early marker of newborn adiposity. This is also consistent with observations from studies of fat deposition in offspring of GDM mothers, wherein GDM was associated specifically with greater fetal arm fat mass in the early third trimester (20).

In addition to the three anatomical sites we used to estimate fetal fat mass, there are other areas of fat deposition such as cheek, ribs and buttocks (11), whose quantification was not available in the current study. However, these latter measures are yet to be endorsed as reliable measurements. Fetal limb volume in the late third trimester has recently been proposed as a useful measure for predicting newborn adiposity (29). It accounts for a significant improvement in explaining the variation in newborn adiposity as compared with estimated fetal weight, which is consistent with the present study. Measures of fetal limb fat volume may also improve accuracy of fat estimation, and this warrants future investigation.

The association between fetal fat mass and newborn adiposity remained robust after adjustment for the most likely confounding factors. Inclusion of site-specific EFA measurements at 30 weeks contributed to 15.6% relative increase in the AUC for the prediction of high newborn per cent body fat. A question of interest and future direction of this research is the elucidation of the determinants of variation in fetal fat mass, including maternal nutritional (e.g. fatty acid status (30) and metabolic state (e.g. insulin resistance (12,20)) that, in turn, could facilitate the development of potential clinical interventions in the future.

The major strength of this study is the prospective, longitudinal design that enabled serial tracking of fat deposition across gestation. Furthermore, we measured newborn adiposity using DXA, one of the standard techniques for the direct measurement of fat mass. A possible limitation of performing the DXA at 1 month postnatal age is that it follows a period of rapid early postnatal growth. We note, however, that in the analysis we adjusted for postnatal age at DXA as a potential confounding factor.

In conclusion, our findings provide greater insight into changes in fetal body composition and its relationship to newborn adiposity. We have introduced the concept of EFA as a new method to evaluate fetal body composition, and demonstrated its feasibility in a study population of uncomplicated pregnancies. If these findings are replicated, it is possible that EFA may lead to a better understanding of the dynamics of fetal growth and body composition and help differentiate fetuses with a higher body weight (estimated fetal weight) from those with a greater fat mass (EFA). It is also possible that the ability to detect extreme variations in fetal fat deposition may provide greater insight in understanding the origins of alterations of fetal body composition as in pathophysiological conditions such as fetal growth restriction and fetal macrosomia. This then may potentially provide a basis for the development of the interventional strategies during pregnancy that may modify newborn adiposity and subsequent obesity.

Conflict of interest
No conflict of interest was declared.

Author contributions
S.I., F.W., K.S., M.O., C.B., S.E. and P.D.W. designed the research; S.I., K.S., M.O. and C.I. collected the data; S.I., F.W., K.S., M.O., C.B., S.E., D.L.G. and P.D.W. analysed and interpreted the data. All authors were involved in writing the paper and had final approval of the submitted and published versions.

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