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Prospective association of fetal liver blood flow at 30 weeks gestation with newborn adiposity

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Abstract

Background—The production of variation in adipose tissue accretion represents a key fetal adaptation to energy substrate availability during gestation. Because umbilical venous blood transports nutrient substrate from the maternal to the fetal compartment, and the fetal liver is the primary organ where nutrient inter-conversion occurs, it has been proposed that variations in the relative distribution of umbilical venous blood flow shunting either through ductus venosus or perfusing the fetal liver represents a mechanism underlying this adaptation.

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The findings of this study were presented at the 37th annual meeting of the Society for Maternal-Fetal Medicine, Las Vegas, NV, January 23-28, 2017.

Objective—The objective of the present study was to determine whether fetal liver blood flow assessed *before* the period of maximal fetal fat deposition (i.e., the third trimester of gestation) is prospectively associated with newborn adiposity.

Study design—A prospective study was conducted in a cohort of 62 uncomplicated singleton pregnancies. Fetal ultrasonography was performed at 30 weeks gestation for conventional fetal biometry and characterization of fetal liver blood flow (*f*LBF; quantified by subtracting ductus venosus flow from umbilical vein flow). Newborn body fat percentage was quantified by Dual Energy X-Ray Absorptiometry (DXA) imaging at 25.8 ± 3.3 (mean ± SEM) postnatal days. Multiple regression analysis was used to determine the proportion of variation in newborn body fat percentage explained by *f*LBF. Potential confounding factors included maternal age, parity, pre-pregnancy body mass index (ppBMI), gestational weight gain, gestational age at birth, infant sex, postnatal age at DXA scan, and mode of infant feeding.

Results—Newborn body fat percentage was 13.5 ± 2.4% (mean ± SEM). *f*LBF at 30 weeks gestation was significantly and positively associated with newborn total fat mass ($r = 0.397$, $p < 0.001$) and body fat percentage ($r = 0.369$, $p = 0.004$), but not with lean mass ($r = 0.100$, $p = 0.441$). After accounting for the effects of covariates, *f*LBF explained 13.5% of the variance in newborn fat mass. The magnitude of this association was particularly pronounced in non-overweight/non-obese mothers (ppBMI <25, n = 36), in whom *f*LBF explained 24.4% of the variation in newborn body fat percentage.

Conclusions—*f*LBF at the beginning of the third trimester of gestation is positively associated with newborn adiposity, particularly among non-overweight/non-obese mothers. This finding supports the role of *f*LBF as a putative fetal adaptation underlying variation in adipose tissue accretion.

Keywords

fetal ultrasonography; liver blood flow; body composition; body fat percentage; pre-pregnancy body mass index

Introduction

The deleterious consequences of childhood obesity are well established.[1,2] Newborns exhibit substantial variation in fat mass accretion over gestation.[3] This inter-individual difference has been shown to track across infancy into childhood, and to relate to future risk of obesity and metabolic dysfunction.[4–6] Moreover, once established, obesity is extremely difficult to reverse, highlighting the critical importance of primary prevention.[7] Based on the convergence of a large body of epidemiological, clinical and experimental evidence in humans and animals, it is increasingly apparent that the origins of obesity (adiposity) can, in part, be traced back to developmental processes during intrauterine life[8–10] (*i.e.*, the concept of the fetal origins of health and disease).[11,12] The elucidation of the determinants, underlying mechanisms, and biomarkers of fetal programming of obesity and metabolic dysfunction represents an area of active investigation.[13–15]

Broadly, it appears that there are two pathways that link intrauterine conditions to increased newborn (and subsequent infant and child) adiposity. The first, a *passive* process, is a direct

consequence of over-nutrition and the availability of excess energy substrate, a scenario most commonly associated with maternal obesity.[16,17] The second, an *active* process, represents a fetal adaptation to energy substrate insufficiency. The fetus exhibits a wide array of structural and functional adaptations in response to intrauterine conditions (*i.e.*, the concept of developmental plasticity).[18] Among these, variation in energy substrate availability (oxygen and other essential nutrients) represents a condition of particular salience, and variation in fat mass accretion represents an adaptation of considerable importance. When oxygen is limited, fetal adaptations prioritize brain growth, irrespective of whether other essential nutrients are limited or not.[19,20] However, when oxygen is adequate but other essential nutrients are limited, fetal adaptations prioritize adipose tissue accretion,[21,22] presumably because adipose tissue constitutes a key buffer against limited nutrient supply, particularly to meet the brain's energy requirements during early postnatal life.[23] Indeed, the infant brain requires and utilizes approximately 40–60% of the infant's total energy needs,[24] and adipose tissue-derived ketone bodies can provide as much as 25% of this requirement.[25] The evolutionary significance of this adaptation likely represents the reason why human infants have substantially higher body fat and also larger brains than other mammals.[23]

The fetus is capable of *de novo* synthesis of various nutrients (fatty acids, triglycerides, amino acids, glycogen)[26–28] using substrates transported across the placenta and carried in umbilical venous blood to the fetal compartment. The fetal liver is the primary site where this inter-conversion and *de novo* synthesis occurs. Under conditions of relative essential nutrient deficiency, one way to ensure the provision of a greater supply of maternally-derived nutrient substrate to the fetal liver (relative to other organs) is accomplished by altering the relative proportion of umbilical venous blood flow shunting through the ductus venosus (DV) *vis a vis* the amount perfused into the fetal liver. Increased fetal liver blood flow (↑LBF) is associated with increased hepatic nutrient synthesis, including precursors of adipose tissue such as fatty acids and triglycerides,[21,22] whereas increased DV shunting (i.e., flow away from the liver) is associated with increased blood supply to the brain (the 'brain-sparing' effect). Under conditions of relative nutrient excess, such as in the context of maternal overweight/obesity, the accretion of fetal fat would be expected to be less dependent on hepatic nutrient synthesis (given the higher concentrations among overweight/obese mothers of maternal and fetal lipids and glucose[16] and increased expression of placental fatty acid transporters[29]). Therefore, in this scenario, variation in ↑LBF would be expected to feature less prominently in the process of fetal fat accretion.

Based on this line of reasoning, Godfrey and colleagues have previously proposed that measures of variation in ↑LBF may constitute a non-invasive biomarker for the amount of fetal adipose tissue accretion, particularly among pregnancies characterized by the *absence* of fetal hypoxia and *absence* of over-nutrition.[21] Currently there are only a few studies that have addressed this hypothesis, and one of their limitations is that they have assessed ↑LBF after the majority of fetal fat deposition has already occurred (*i.e.*, in late gestation).[30,31]

For these reasons, the primary aim of our study was to determine whether ↑LBF measured before the period of maximal fat deposition (*i.e.*, in the early third trimester) is prospectively associated with newborn body composition, specifically newborn body fat percentage. We

hypothesized that among pregnancies where there is no evidence of fetal hypoxia, *a*) variation in ƒLBF would be prospectively associated with newborn adiposity, and *b*) the magnitude of this association would be particularly pronounced in non-overweight/ non-obese mothers.

Materials and Methods

Study population

Our study population was comprised of 62 mother-newborn dyads from a prospective cohort study of the association of biological and behavioral processes in human pregnancy with newborn, infant and child health outcomes at the University of California, Irvine, Development, Health and Disease Research Program. These subjects represented the subset from the larger cohort in whom *all* measures of ƒLBF and newborn DXA imaging were available. There were no significant differences between the socio-demographic, obstetric and birth outcome characteristics of the study population and the larger cohort. Women with a singleton, uncomplicated pregnancy were recruited in the late first or early second trimester. Maternal exclusionary criteria were uterine anomalies, pre-existing major medical co-morbidities, conditions associated with neuroendocrine and immune dysfunction (endocrine, hepatic or renal disorders), use of systemic corticosteroids, smoking, and illicit drug use. Newborn exclusionary criteria included congenital malformations, chromosomal abnormalities, major perinatal complications associated with neurological consequences, and preterm birth <34 completed weeks. The study protocol was approved by the Institutional Review Board, and written informed consent was obtained from all mothers.

Prenatal ultrasonography

Fetal ultrasonography was performed at approximately 30 weeks gestation for fetal biometry and Doppler velocimetry. Each of the conventional fetal biometry measures were obtained in duplicate and averaged. Per standard clinical criteria, gestational age was confirmed before 16 weeks using an algorithm combining last menstrual period and fetal biometry.[32] All fetal measurements were performed by the same obstetrician (SI) using a Voluson i (GE Healthcare, Milwaukee, WI), with a trans-abdominal 4MHz curved array transducer that included color Doppler and pulsed Doppler (3 MHz) facilities (RAB4–8-RS).

The umbilical vein (UV) and ductus venosus (DV) were identified either in a sagittal plane or in an oblique plane transecting the fetal upper abdomen. Blood flow (Q) was calculated as $Q\ (ml/min) = h \times (D/2)^2 \times TAMX$, where D= vessel inner diameter (mean of 5–10 measurements),[33] TAMX= time-averaged maximum velocity (mean of 2 measurements) and h= spatial blood velocity profile coefficient (UV=0.5; DV=0.7).[34] $TAMX_{UV}$ was obtained during a 3–5 sec period. $TAMX_{DV}$ was calculated as the mean during three cardiac cycles. D_{UV} was measured in the straight portion of the intra-abdominal UV before hepatic parenchymal branching, and D_{DV} was measured at the inlet of DV as previously described.[21,35] Intra-observer coefficients of variation for $TAMX_{UV}$, $TAMX_{DV}$, D_{UV}, and D_{DV} were 6.8%, 6.6%, 6.4%, and 9.3%, respectively (6.7%, 6.4%, 6.3%, 9.1% with ppBMI<25, and 7.1%, 6.9%, 6.6%, 9.7% with ppBMI≥25). ƒLBF was calculated as UV flow (Q_{UV}) – DV flow (Q_{DV}). Because fetal liver size could potentially influence ƒLBF[36] and

fetal abdominal circumference (AC) is a proxy of fetal liver size[37] (*f*LBF was, in fact, significantly correlated with AC [r=0.295, p=0.020] in the present cohort), a measure of *f*LBF corrected for AC (*f*LBF/AC) was also calculated.

Umbilical artery (UA) waveform was also obtained using Doppler ultrasound at the free-loop portion of the umbilical cord floating in the amniotic fluid. Middle cerebral artery (MCA) waveform was obtained in the proximal segment of MCA (in three consecutive cardiac cycles) during fetal quiescence. UV, DV, UA, and MCA Doppler flow velocities were obtained keeping the insonation angle <30°. Absent or reversed end-diastolic velocity waveform of UA,[38,39] pulsatility index of MCA (MCA-PI) below 5th centile, and cerebro-placental ratio (MCA-PI divided by UA-PI) less than 5th centile [40–42] were used for screening chronic fetal hypoxic state.

Birth outcomes

Gestational age at birth, birth weight, and infant sex were abstracted from the medical record. Birth weight percentile was determined using national norms.[43]

Infant body composition

Newborn body fat percentage was assessed by whole body Dual Energy X-Ray Absorptiometry (DXA) imaging using a Hologic Discovery scanner (QDR 4500A, Hologic Inc, Bedford, MA, USA) in the pediatric scan mode.[44] Potential measurement issues at birth relate to rapid shifts in fluid volume and body composition that can occur in the weeks after birth.[45] Therefore, newborn DXA scans were performed at approximately one month postnatal age. Calibration using Hologic's anthropomorphic Spine QC Phantom was performed before each scan. Infants lay supine while sleeping, wearing only a disposable diaper and swaddled in a light cotton blanket. Movement artifact could affect DXA image, however, we performed a rescan if the image quality was unsatisfactory due to infant movement. Newborn body fat percentage was calculated from newborn fat mass and lean mass measures using the Hologic Analysis Version 12.1 software.

Pre-pregnancy body mass index (ppBMI) and gestational weight gain (GWG)

ppBMI was calculated using pre-pregnancy weight (by maternal self-report) and height measured at first prenatal visit. Self-reported pre-pregnancy weight was highly correlated with the maternal weight measured at the 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 GWG per week (GWG/week) was categorized as inadequate, adequate, or excessive, based on the Institute of Medicine (IOM) recommendations.[46]

Statistical analysis

Pearson product moment correlations were used to assess bivariate first-order associations among continuous variables, and the Student's t test or one-way analysis of variance was used to test group differences. We considered *a priori* the following potential confounding variables in the relationship between *f*LBF and newborn body fat percentage: maternal age, parity, ppBMI, GWG/week, gestational age at birth, infant sex, postnatal age at DXA, and mode of infant feeding. The subset of these variables that were significantly associated in

bivariate analysis with newborn body fat percentage were included in subsequent multivariate analyses.

First, the association of *f*LBF at 30 weeks with newborn body composition measured by DXA (fat mass, lean mass, and body fat percentage) was determined using bivariate analysis. This association was also examined in subgroup analysis stratified by maternal ppBMI as non-overweight/non-obese (ppBMI<25) or overweight/obese (ppBMI≥25). Next, multiple linear regression was used to quantify the association between *f*LBF and newborn body fat percentage, with adjustment for potential confounding factors. Using the same set of covariates, the relative contribution of *f*LBF in explaining variation in newborn body fat percentage was derived from the partial correlation coefficient in the multiple linear regression model. We repeated all analysis replacing *f*LBF by *f*LBF/AC to correct for liver size. All statistical analyses were performed using SPSS version 22.0 (SPSS Inc, Chicago, IL), with statistical significance determined at $p<0.05$.

Results

The maternal socio-demographic and obstetric characteristics are summarized in Table 1. Descriptive statistics of the fetal blood flow parameters are shown in Table 2. $TAMX_{UV}$, $TAMX_{DV}$, D_{UV}, D_{DV}, Q_{UV}, and Q_{DV} were consistent with previous reports.[35,47] Mean UA-PI, MCA-PI, and cerebro-placental ratio were 1.00 ± 0.02 (mean ± SEM), 1.89 ± 0.05, and 1.98 ± 0.07, respectively. There was no fetus with absent or reversed end-diastolic UA flow or MCA-PI <5th centile. One fetus was excluded because of low cerebro-placental ratio (<5th centile).[40]

Mean gestational age at birth was 39.5 ± 1.1 weeks (mean ± SEM), and 53% of newborns were male. Mean birth weight was 3458 ± 21 g, and mean birth weight percentile was 51.2 ± 3.5%. Mean postnatal age at DXA scan was 25.8 ± 3.3 days. The mean total mass, fat free mass, and fat mass was 4366 ± 26 g, 3750 ± 22 g, and 616 ± 18 g, respectively. Mean newborn body fat percentage was 13.5 ± 2.4%, which is consistent with previous reports.[48] At the time of DXA scan, 28 infants were breast-fed, 11 were formula-fed, and 23 were mixed-fed.

In bivariate analysis, *f*LBF at 30 weeks was significantly and positively associated with newborn total fat mass ($r=0.397$, $p=0.001$) and body fat percentage ($r=0.369$, $p=0.004$) (Figure 1a), but not with lean mass ($r=0.100$, $p=0.441$) or birth weight percentile ($r=0.132$, $p=0.306$). The correlation between *f*LBF and newborn body fat percentage was particularly pronounced among newborns of mothers with ppBMI <25 ($r=0.456$, $p=0.005$), compared to newborns of mothers with ppBMI≥25 ($r=0.299$, $p=0.261$). (Figure 1b)

Estimates from the multiple regression model associating *f*LBF with newborn body fat percentage after covariate adjustment are presented in Table 3. *f*LBF independently explained 13.5% of the variance in newborn body fat percentage (partial correlation coefficient=0.368, $p=0.004$). Each 50 mL/min increase of *f*LBF (range from 14.1 to 168.0 ml/min) was linearly associated with a 2.6% higher newborn body fat percentage. Among newborns of mothers with ppBMI<25, *f*LBF explained 24.4% of the variance in newborn

body fat percentage (partial correlation coefficient=0.494, p=0.003). This relationship remained statistically significant after fLBF was corrected for AC, suggesting that the observed effect is not a function of fetal liver size (Table 4). The association between fLBF and newborn body fat percentage was not significant among overweight/obese mothers (ppBMI≥25).

Finally, because gestational diabetes may influence fetal size and body composition over and beyond maternal ppBMI,[49] we repeated all analyses after excluding the 3 subjects with gestational diabetes. There was, however, no appreciable change in the significance and magnitude of the above-described effects of fLBF on newborn adiposity.

Comment

To the best of our knowledge, this is the first study to demonstrate a prospective association of fLBF assessed *before* the period of maximal fetal fat deposition (*i.e.*, the third trimester of pregnancy)[30,31] with newborn adiposity. Our principal findings are that fLBF in the early third trimester explains a substantial proportion of the variance in newborn adiposity, and that this relationship is more pronounced among non-overweight/non-obese mothers (ppBMI<25).

After accounting for the effects of parity, infant sex, and postnatal age at DXA, fLBF at 30 weeks gestation accounted for 13.5% of the variation in newborn body fat percentage. This effect was independent of fetal abdominal size (AC), suggesting that the effect of fLBF was not simply a consequence of greater fetal liver size. Thus, our finding replicates and extends the earlier observation that fLBF at 36 weeks gestation is positively associated with newborn fat mass.[21] The fetal liver is one of the primary sites of *de novo* synthesis of essential nutrients required for adipose tissue accretion. The importance of fetal hepatic *de novo* lipogenesis in creating the subcutaneous energy reservoir is well established.[50–52] Fatty acid synthesis is mediated by lipogenic enzymes including acetyl-CoA carboxylase, fatty acid synthase and glucose-6-phosphate dehydrogenase, whose activity is high in fetal life.[53] The production of growth factors and hormones implicated in the regulation of fetal growth (*e.g.*, hepatocyte growth factors, insulin-like growth factors, leptin) is mediated by processes occurring within the liver.[54–56] For example, in fetal sheep, experimental manipulations that increase fLBF induce hepatic growth factor synthesis and soft tissue accretion.[57]

The association between fLBF and newborn body fat percentage was particularly pronounced in newborns of non-overweight/non-obese mothers, in whom fLBF explained 24.4% of the variation in newborn body fat percentage. This finding is consistent with that from an earlier study that reported a stronger association between fLBF and newborn adiposity in the offspring of thinner mothers.[21] In overweight/obese mothers, obesity-related elevations of maternal triglycerides, fatty acids, and placental fatty acid transporters result in higher fetal triglycerides that, in turn, are a major source of fetal fat deposition.[29,58]

Some strengths of our study include the prospective ascertainment of fetal liver blood flow *before* the period of maximal fetal adipose tissue accretion[30,31] and the direct ascertainment of newborn body composition. Unlike many of the previous studies of newborn adiposity

that have relied on proxy indicators such as ponderal index (that provide indirect estimates of fat mass and correlate only moderately with measures of adiposity[59]), we used newborn DXA imaging to directly obtain reliable measures of newborn body composition.[44,60]

In terms of potential limitations, greater measurement error in fetal ultrasonography may occur in overweight/obese women because of the thicker maternal subcutaneous fat layer and lower resolution of the ultrasound images. However, in our study, the reliability estimates of Doppler flow velocimetry and vessel diameter were comparable across the non-overweight/non-obese and overweight/obese groups. We also note that the fetal liver receives venous blood flow not only from the umbilical vein but also from the portal vein, whose flow was not evaluated in the present study. Portal vein flow, however, accounts for only a small proportion of fLBF and is not believed to be a source of nutrient substrate from the placenta.[61] We used fetal abdominal circumference as a proxy measure of fetal liver volume. Direct measurement of fetal liver volume measurement with 3D ultrasonography[62] might add precision, and this represents a future research direction. As noted earlier, we performed the neonatal DXA scan at approximately one month postnatal age, to avoid potential artifacts related to the rapid fluid shifts that are known to occur in the first weeks following birth. Because neonatal fat mass was not estimated *immediately* following birth, it is possible that postnatal factors such as postnatal age at scan and type of feeding may have exerted an additional influence on the fat mass measure. However, our analysis did adjust for the effects of these variables (i.e., postnatal age at DXA scan and mode of infant feeding).

A question of interest and future direction of this research is the elucidation of the determinants of variation in fLBF, including but not limited to measures of maternal nutritional and metabolic state (*e.g.* essential fatty acids, essential amino acids) that have been shown to affect infant body composition.[27,63,64] It is also possible that measures of fLBF using quantitative 3D power Dopper ultrasound may improve precision, and this too warrants future investigation.[65]

In conclusion, fLBF at 30 weeks gestation was positively associated with newborn adiposity. Our findings support and extend Godfrey et al's formulation regarding fLBF as a putative mechanism underlying fetal adaptations to energy substrate availability.[21] The present finding provides further evidence that variation in newborn adiposity may be conditioned, in part, by developmental processes during intrauterine life. These findings may also potentially provide a basis for the development of biomarkers and intervention strategies during pregnancy that may modify newborn adiposity and subsequent obesity and metabolic dysfunction risk.

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Abbreviations

AC	Abdominal circumference
DV	Ductus venosus

D_{DV}	Vessel diameter of ductus venosus
D_{UV}	Vessel diameter of umbilical vein
DXA	Dual Energy X-Ray Absorptiometry
***f*LBF**	Fetal liver blood flow
GA	Gestational age
GWG	Gestational weight gain
PI	Pulsatility index pp
BM	pre-pregnancy BMI
Q_{UV}	Blood flow volume of umbilical vein
Q_{DV}	Blood flow volume of ductus venosus
$TAMX_{UV}$	Time-averaged maximum velocity of umbilical vein
$TAMX_{DV}$	Time-averaged maximum velocity of ductus venosus
UA	Umbilical artery
UV	Umbilical vein

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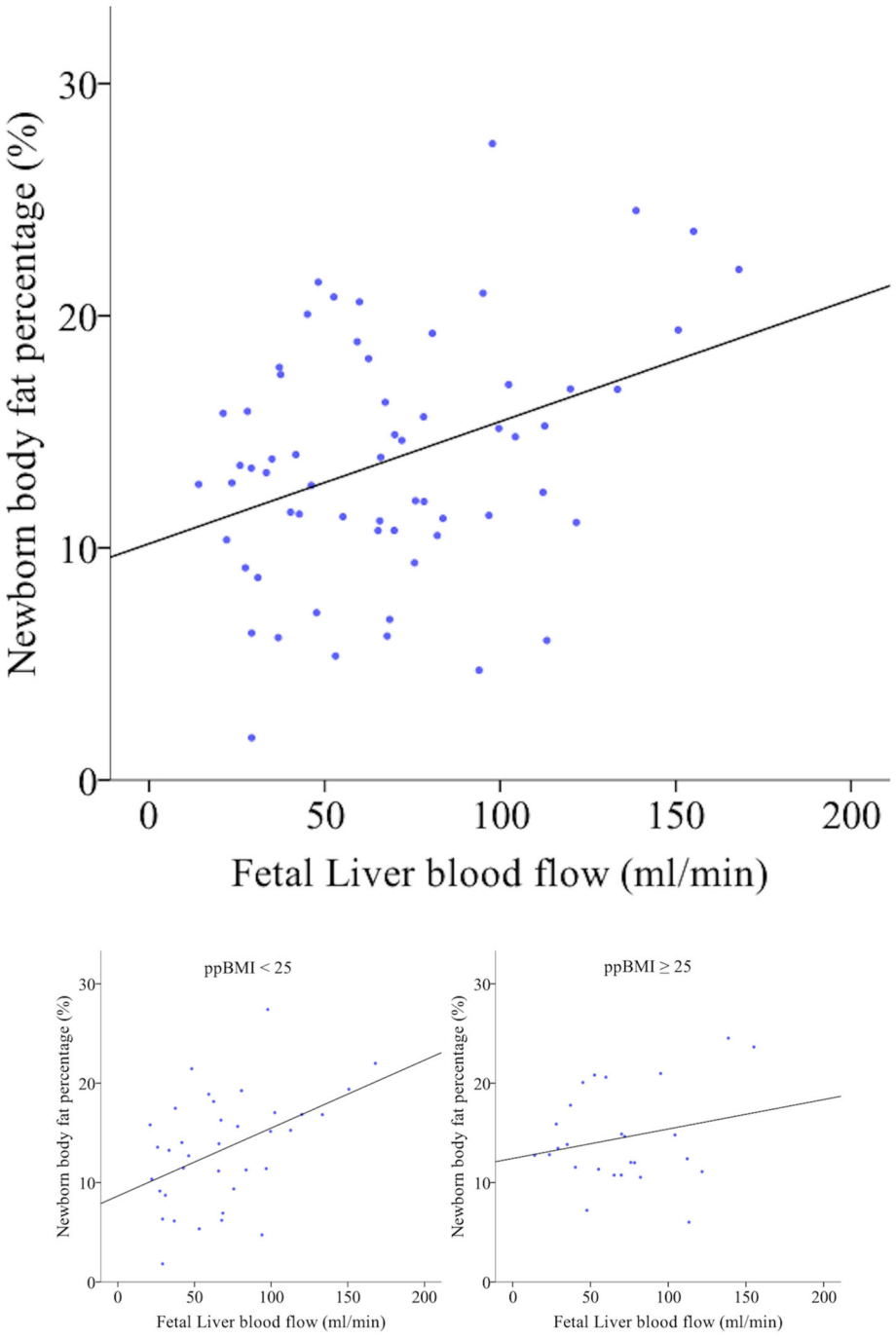

Figure 1.

Figure 1a. Scatterplot depicting the association between ƒLBF at 30 weeks gestation and newborn body fat percentage. ƒLBF at 30 weeks gestation significantly correlated with newborn body fat percentage ($r = 0.369$, $p = 0.003$).

ƒLBF, fetal liver blood flow.

Figure 1b. Scatterplot of ƒLBF and newborn body fat percentage stratified by maternal ppBMI. Correlation between ƒLBF and newborn body fat percentage was particularly

pronounced with mothers whose ppBMI <25 (N = 36, $r = 0.456$, $p = 0.005$), and not with ppBMI ≥25 (N = 26, $r = 0.229$, $p = 0.261$).

*f*LBF, fetal liver blood flow; ppBMI, pre-pregnancy BMI.

Table 1

Maternal socio-demographic and clinical characteristics

Characteristics	N = 62	(%)
Age, years *	28.6 ± 2.2	
Race/Ethnicity		
Non-Hispanic White	26	(42%)
Hispanic White	25	(40%)
Others	11	(18%)
Pre-pregnancy BMI, kg/m^2 *	25.7 ± 2.2	
BMI <25	36	(58%)
BMI ≥25	26	(42%)
Gestational weight gain, kg *	14.6 ± 2.3	
<IOM	10	(16%)
= IOM	18	(29%)
> IOM	34	(55%)
Gestational weight gain per week, kg/week *	0.37 ± 0.13	
Parity (primiparous)	22	(36%)

* Data are presented as mean ± SEM.

< IOM, = IOM, > IOM; less than, equal to, greater than Institute of Medicine recommendations.

Table 2

Fetal biometry and blood flow parameters measured by ultrasonography (N = 62)

Parameters	Measure
Gestational age at ultrasound scan	30.5 ± 1.2
Abdominal circumference, mm	269.0 ± 4.5
Estimated fetal weight, g	1641 ± 201
Estimated fetal weight (percentile), %	53.0 ± 2.0
Umbilical vein	
Diameter, mm	5.40 ± 0.11
Time averaged maximum velocity, cm/s	14.77 ± 0.40
Volume flow, mL/min	103.7 ± 4.90
Ductus venosus	
Diameter, mm	1.71 ± 0.05
Time averaged maximum velocity, cm/s	34.7 ± 1.22
Volume flow, mL/min	34.4 ± 2.17
Liver blood flow, ml/min	69.3 ± 4.68

Data are presented as mean ± SEM.

Table 3

Multiple regression model associating ΔLBF with newborn body fat percentage

	Unstandardized B		Standardized β	*P* value
	Coefficients	**95% CI**	**Coefficients**	
Parity	2.346	−0.216 – 4.908	0.202	0.072
Infant sex	0.154	−2.331 – 2.640	0.014	0.901
Postnatal age at DXA	0.191	0.082 – 0.300	0.377	0.001
ΔLBF	0.050	0.017 – 0.084	0.331	0.004

ΔLBF, fetal liver blood flow; CI, confidence interval; DXA, Dual Energy X-Ray Absorptiometry.

Table 4

Multiple regression models predicting newborn body fat percentage from ΔLBF and ΔLBF/AC, stratified by maternal ppBMI

	Total (N = 62)		ppBMI <25 (N = 36)		ppBMI ≥25 (N = 26)	
	β*	*P* value	β*	*P* value	β*	*P* value
ΔLBF	0.331	0.004	0.463	0.003	0.107	0.558
ΔLBF/AC	0.275	0.017	0.457	0.010	0.068	0.685

ΔLBF, fetal liver blood flow; AC, abdominal circumference; ppBMI, pre-pregnancy BMI.

*Standardized β controlled for parity, infant sex and postnatal age at DXA scan.