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Pregnancies Complicated by Gestational Diabetes and Fetal Growth Restriction: Fetal and Maternal Body Composition

A thesis submitted in partial satisfaction of the requirements for the degree Master of Science in Clinical Research

by

Katie Marie Strobel

2022

ABSTRACT OF THE THESIS

Pregnancies Complicated by Gestational Diabetes and Fetal Growth Restriction: Fetal and Maternal Body Composition

by

Katie Marie Strobel

Master of Science in Clinical Research

University of California, Los Angeles, 2022

Professor Janet S. Sinsheimer, Chair

INTRODUCTION: Maternal body composition may influence fetal/neonatal body composition.

OBJECTIVE: To investigate the relationship between maternal and fetal body composition.

METHODS: Three cohorts of women were studied: healthy mothers, mothers with gestational diabetes (GDM), and otherwise healthy mothers with a growth-restricted fetus (FGR). MRI measured quantitative traits of maternal body composition (visceral adipose tissue volume (VAT), subcutaneous adipose tissue volume (SAT), pancreatic and hepatic proton-density fat fraction (PDFF)) and fetal body composition (abdominal SAT and hepatic PDFF).

RESULTS: GDM fetuses had greater SAT volume than FGR fetuses and greater hepatic PDFF than FGR (280 [261, 295] vs. 220 [205, 235] mm^3) and healthy fetuses (GDM 5.2 [4.2, 5.5]%, FGR 1.9 [1.4, 3.7]%, healthy 3.2 [3, 3.3]%). Fetal hepatic PDFF was associated with maternal SAT (r=0.47, p=0.02), VAT (r=0.62, p=0.002), and pancreatic PDFF (r=0.54, p=0.008). Fetal SAT was associated with infant birth weight z-scores (r=0.48, p=0.02).

CONCLUSION: In this study, maternal adiposity and GDM status were associated with fetal hepatic fat.

The thesis of Katie Marie Strobel is approved.

David Elashoff

Kara Lynne Calkins

Holden H. Wu

Janet S. Sinsheimer, Committee Chair

University of California, Los Angeles

2022

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Author Contributions: KMS, KLC, and HHW conceptualized and designed the study. KMS recruited and consented all subjects. KMS, SS, SGC, AA, and RM assisted with the data collection and interpretation. KMS performed all the data analysis under the guidance of DE. KMS wrote the thesis, and all authors edited and approved the final draft of the manuscript.

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INTRODUCTION:

Infants born to mothers with gestational diabetes mellitus (GDM) or who have a history of fetal growth restriction (FGR) are at increased risk for future childhood obesity, insulin resistance, dyslipidemia, cardiovascular disease, and non-alcoholic fatty liver disease (NAFLD).[1] Women with GDM have increased circulating inflammatory cytokines and expression of placental proteins that mediate inflammation compared to healthy pregnant women.[2] This inflammatory in utero milieu may alter the fetal genome leading to an increase in insulin resistance during the childhood and adulthood years.[2] FGR infants are also at risk for later obesity and insulin resistance due to global DNA hypomethylation in the liver and reduced pancreatic beta cell mass.[3] FGR infants exhibit satiety dysregulation secondary to impaired leptin and ghrelin, further exacerbating their risk for obesity.[4]

Body composition plays an important role in obesity and metabolic syndrome.[5] In infants, increased fat mass and rapid weight gain from birth to two years of age have been associated with later onset obesity, insulin resistance, hypertension, and NAFLD.[6,7] Visceral adipose tissue (VAT) releases free fatty acids into the circulation, which can lead to insulin resistance, dyslipidemia, hypertension, and NAFLD.[8,9] Pancreatic steatosis is also associated with an increased risk for type 2 diabetes.[10] Mothers with increased fat mass had an increased risk of gestational diabetes,[11] and their children have higher waist-to-hip ratios.[12] Infants with a history of FGR have decreased fat mass and fat-free mass.[13] Lack of fat free mass has been associated with poor neurodevelopment[14] and a higher tertile body mass index.[15]

In this pilot prospective cohort study, we aimed to use a motion-compensated FB MRI technique to assess body composition in maternal-fetal dyads in the third trimester. We

hypothesized that 1) increased maternal VAT volume and GDM status would be positively associated with fetal hepatic PDFF and SAT volume, 2) FGR infants will have lower fetal SAT volume, and 3) fetal hepatic PDFF and SAT volume would be positively associated with infant birth growth parameter z-scores.

MATERIALS/SUBJECTS AND METHODS:

Study Population:

Singleton pregnant women who were less than 36 weeks gestation were eligible for this study. All women provided informed consent prior to participating in the study. There were three groups: women with healthy pregnancies, women with pregnancies complicated by GDM, and women with pregnancies complicated by FGR. A healthy pregnancy was defined as pregnancy without fetal anatomic abnormalities, chromosomal abnormalities, FGR, or GDM. GDM was defined as a positive glucola screen at 26 to 32 weeks gestation.[23] FGR was defined as fetal weight and abdominal circumference $<10^{th}$ percentile on ultrasound for a given gestational age or per obstetrician documentation on at least two medical notes.[24] Exclusion criteria included multiple gestations, fetuses with congenital or chromosomal abnormalities, mothers with prediabetes (hemoglobin A1C ≥5.5 %) or type II diabetes, and common contraindications to MRI (*e.g.*, claustrophobia, metal implants in the body).

Study Procedure:

Research MRI exams were performed between 30 to 36 weeks gestation in a non-fasting state. In order to prevent inferior vena cava compression, women were scanned in the lateral decubitus position. Subjects were given hearing protection. The scan was performed using body and spine array coils on a 3T MRI scanner (MAGNETOM Skyra or Prima, Siemens Healthineers). T_2-weighted (T2W) half-Fourier acquisition single-shot turbo spin-echo (HASTE)

scans in coronal, axial, and sagittal orientations were obtained of the fetus for anatomic reference. Free breathing MRI scans were performed using a prototype 3-D stack-of-radial multi-echo gradient echo Dixon sequence to image the fetal abdomen, fetal neck to the thorax, fetal thorax to the pelvis, and maternal abdomen in axial orientation.[25,26] If time and the subject permitted, a repeat fetal abdominal scan was performed and the scan with better image quality was selected for analysis. The multi-echo images from the Dixon sequence were used to calculate 3D quantitative PDFF maps (0-100%) based on a seven-peak fat model and a single effective R_2* per voxel. For body composition analysis, abdominal MR images and PDFF maps from the 3D axial acquisitions (contiguous slices) were analyzed to measure hepatic PDFF, pancreatic PDFF, SAT volume, and VAT volume. Parameters for MRI sequences are similar to the methods by Armstrong *et al*.[21] These MRI sequences were in accordance with the Food and Drug Administration guidelines. The overall MRI exam time was approximately 45 to 60 minutes.

Fetal Liver Image Reconstruction:

MR images and PDFF maps were reconstructed and calculated by vendor provided software on the scanner. In three subjects, the free breathing 3-D stack-of-radial MR images and PDFF maps had higher levels of radial streaking artifacts. To improve image quality, we applied an offline reconstruction method that used a phased-array beamforming technique to suppress the artifacts.[27,28]

Measurement Procedure:

Body composition was measured on MRI by a trained researcher (KS) using medical image analysis software (Horos, thehorosproject.org). All annotated regions of interest were reviewed and verified by an abdominal radiologist with over nine years of experience (RM).

Fetal Body Composition:

We measured fetal SAT volume and hepatic PDFF. We were unable to visualize and measure VAT volume. **Figure 1** shows examples of fetal measurements. Fetal SAT volume was measured on free breathing 3-D stack-of-radial MRI scans from the level at the mid-liver and the top of the bladder, while referring to corresponding sagittal and axial T2W HASTE images for anatomic reference. Volume was calculated by multiplying the area of SAT on a slice by the thickness of the slice. A surrogate of fetal SAT volume was then obtained by calculating the average of the volume from the measurements on the two slices (mid-liver and top of bladder). Fetal liver PDFF was measured on the free breathing 3-D stack-of-radial scans. Slices of the liver dome, mid-liver, and inferior liver were compared with the corresponding T2W HASTE axial and sagittal slices to confirm region of interest (ROI) placement. One 3-cm^2 ROI was placed on each slice while avoiding blood vessels, bile ducts, and regions with increased noise. The liver PDFF was calculated as the mean of these three measurements.

Maternal Body Composition

We measured hepatic PDFF, pancreatic PDFF, SAT volume, and VAT volume on free breathing 3-D stack-of-radial MRI. **Figure 2** shows examples of maternal measurements. Maternal liver PDFF was measured by placing one 5-cm^2 ROI on each of three slices (liver dome, mid-liver, and inferior liver) while avoiding blood vessels, bile ducts, and regions of increased noise. The mean PDFF of these three ROI measurements was calculated. Pancreatic PDFF was measured by outlining the entirety of the pancreas on each slice where it was visible while excluding surrounding vessels, bowel, and fat.[29] The mean PDFF across all slices was calculated. SAT was defined as the adipose tissue above the muscle fascia and below the skin in the abdomen, from the level below breast tissue to below the uterus (approximately 30 slices).

VAT was defined as fat around the abdominal organs, from the level of the liver dome to just below the uterus (approximately 30 slices). SAT (or VAT) volume was calculated by multiplying the area of SAT (or VAT) on each slice by the slice thickness and summing across all slices.

Clinical Information Collection:

Maternal information was collected with a focus with specific risk factors for maternal and childhood obesity and metabolic syndrome (*e.g.* pre-pregnancy body mass index (BMI), weight gain during pregnancy, family history of metabolic disease, the type of GDM treatment, and the etiology of FGR). Infant birth information and growth parameters were collected. The means and standard deviations to calculate z-scores were obtained from Fenton *et al*. for preterm infants (<37 weeks gestational age) and the World Health Organization for term infants.[30,31] Small for gestational age was defined as <10th percentile for birth weight using the appropriate growth chart. A research electronic data capture (REDCap) database was used for data management.[32]

Data Analysis:

All statistical analysis was conducted using JMP Pro version 15.0 (SAS, Carey, NC).

Power Calculation:

Five subjects in the GDM cohort and 10 in the healthy cohort provides 80% power to detect an effect size of least a Cohen's d of 1.7 for differences in hepatic fat between the FGR group and the healthy and GDM group. This calculation assumes a 10% dropout in each group using a two-sample t-test and a two-sided significance level of 0.05. The t-test is a simplification of the linear regression model analysis plan and provides a conservative estimate of the minimally detectable effects size. The study is not powered for a stepwise regression, as one would generally need at least 20 subjects per candidate variable.

Cohort Characteristics:

Frequency (%) was used for descriptive variables. Variables were compared between cohorts using Fischer's exact tests. Continuous variables were described with medians and interquartile ranges. Continuous variables were compared between cohorts using Kruskal-Wallis tests with Dunn's tests for pairwise comparisons.

Body Composition Comparisons:

All body comparisons utilized all the women involved in the study. Fetal body composition measurements were correlated to maternal pre-pregnancy BMI, maternal weight gain during pregnancy, gestational age at the time of MRI, infant birth z-scores, maternal SAT volume, maternal VAT volume, maternal pancreatic PDFF, and maternal liver PDFF using linear regression models and Spearmen correlation coefficients. Maternal body composition measurements were compared to maternal pre-pregnancy BMI, maternal weight gain during pregnancy, gestational age at time of MRI, and fetal body composition measurements using linear regression models and Spearmen correlation coefficients. To further investigate associations with fetal hepatic PDFF, a multivariable linear regression model was conducted using stepwise backward variable selection to minimize BIC. Candidate variables were selected based on biological relevance and significant correlations. The following candidate variables were selected: pre-pregnancy BMI, maternal SAT volume, VAT volume, pancreatic PDFF, and GDM status (yes/no).

RESULTS:

Cohort Characteristics:

From September 2020 to July 2021, pregnant women were recruited to participate in the study (**Figure 2).** Maternal, fetal, and infant characteristics are described in **Table 1**. Four GDM

women required insulin; one mother's GDM was diet controlled. The etiology in four FGR cases was uteroplacental insufficiency; the etiology in one FGR case was poor maternal nutrition. Fetuses with FGR were more likely to be admitted to the neonatal intensive care unit compared to healthy and GDM cohorts (p=0.04).

Mothers with GDM had greater VAT volume than mothers with healthy pregnancies (p=0.04) and a higher pancreatic PDFF compared to the mothers in the FGR cohort (p=0.03). Fetuses of GDM mothers had significantly greater SAT volume (p=0.002) and hepatic PDFF (p=0.008) than growth restricted fetuses. Fetuses of GDM mothers had significantly greater hepatic PDFF than fetuses of healthy mothers (p=0.002) and greater SAT volume then healthy mothers but this was not significantly different (p=0.10).

Fetal Body Composition Associations with Maternal Characteristics:

Fetal SAT volume positively correlated with gestational age at time of the MRI (r 0.45, p=0.03) with an increase of 8.6 mm^3 per week during gestation. All other maternal and fetal body composition parameters did not correlate with gestational age (all p-values >0.05).

Maternal pre-pregnancy BMI was positively associated with maternal SAT volume (12161 $mm^3/kg/m^2$; r=0.64, p=0.001), maternal pancreatic PDFF (0.27%/kg/m^2; r=0.57, p=0.005), maternal VAT volume (8466 $mm^3/kg/m^2$; r=0.85, p<0.001), and fetal hepatic PDFF (0.11%/kg/m^2; r^2=0.53, p=0.01). Maternal weight gain in pregnancy was negatively associated with maternal VAT volume (-318mm^3/kg; r=0.54, p=0.03) and maternal pancreatic PDFF (-0.41%/kg; r=0.69, p=0.001). Maternal weight gain in pregnancy was not associated with other maternal body composition parameters or fetal body composition parameters (p>0.05 for all). Maternal serum glucose levels one hour after a glucola challenge were positively associated with

maternal pancreatic PDFF (0.025%/mg/dL; r^2=0.21, p=0.03), fetal SAT volume (0.42 mm^3/mg/dL; r^2=0.35, p=0.01), and fetal liver PDFF (0.013%/mg/dL; r^2=0.18, p=0.04).

Fetal SAT volume was positively associated with maternal pancreatic PDFF (5.1 mm^3/%; r=0.42, p=0.04). Fetal SAT volume was not associated with maternal hepatic PDFF, maternal SAT volume, or maternal VAT volume (p>0.05 for all). Fetal hepatic PDFF was positively associated with maternal pancreatic PDFF (0.27%/%; r=0.54 p=0.008), SAT volume ($5.9*10^{-6}$%/mm^3; r=0.47 p=0.02), and VAT volume ($1.39*10^{-5}$%/mm^3; r=0.62, p=0.002) (**Figure 4**).

When conducting a multivariable linear regression model, maternal SAT volume and GDM status were selected with an r=0.81, Bayesian information criterion 50. When controlling for maternal SAT volume, GDM status increased fetal liver PDFF by 0.9 ([0.51, 1.3], p=0.001). When controlling for GDM status, maternal SAT volume positively increased fetal hepatic PDFF by 0.0393%/10,000 mm^3 ([0.0049%/10,000 mm^3, 0.073%/10,000 mm^3], p=0.03).

Subject Characteristic Associations with Infant Growth Parameters:

Fetal SAT volume was positively associated with infant birth weight z-score, increasing by 0.02 z-score units per 1 mm^3 of subcutaneous fat volume (r=0.48, p=0.02). Maternal body composition was not associated with any infant growth parameters. Maternal weight gain in pregnancy was positively associated with infant birth length z-score, increasing 0.18 z-score units per 1 kg weight gain (r=0.46, p=0.03).

DISCUSSION:

In this pilot study, we examined the relationship between maternal adiposity and fetal body composition in uncomplicated pregnancies, pregnancies with GDM, and pregnancies complicated by FGR using free breathing MRI. Consistent with other studies, fetal SAT volume increased with gestational age[21,33] and was associated with birth weight z-score.[34,35] Maternal

pre-pregnancy BMI was positively correlated with fetal hepatic PDFF, maternal pancreatic PDFF, maternal SAT volume, and maternal VAT volume. Consistent with obstetrician recommendations of limited weight gain in the setting of obesity, maternal weight gain in pregnancy was negatively associated with maternal VAT volume and pancreatic PDFF.[36] Maternal pancreatic PDFF, SAT volume, and VAT volume positively correlated with fetal hepatic PDFF. Our multivariable regression model suggested that GDM and SAT volume were significant contributors of fetal hepatic PDFF compared to VAT volume and pre-pregnancy BMI.

In our study, the GDM cohort had a greater amount of fetal SAT volume and fetal hepatic PDFF compared to the healthy and FGR cohort. Previous literature has shown greater SAT volume in fetuses whose mother have GDM in comparison to fetuses of healthy women with a normal BMI .[34] In our study, there was no statistically significant difference in fetal SAT volume between the GDM group and healthy group, but there was a trend in greater fetal SAT in GDM compared to healthy fetuses. This negative finding may be because of our small sample size. For example, to detect the difference found in study there would need to be 85 healthy subjects and 42 gestational diabetes subjects (assuming 80% power, one sided, alpha 0.05). Moreover, two of the healthy subjects had a pre-pregnancy BMI > 25 kg/m^2; one subject was overweight and the other subject was obese. As a result, we are unable to accurately disentangle the effects of maternal obesity and GDM on fetal body composition.

There are several mechanisms that may explain why GDM fetuses have increased SAT volume and altered body composition as a fetus and infant. First, pregnancies complicated by GDM are hallmarked by an increase in placental glucose, amino acid, and fatty acid transport, which increases the fetus's endogenous production of insulin and insulin-like growth factor 1.[37]

Insulin-like growth factor-1 has been associated with an increase in SAT in mice.[38] Second, the metabolite profile in amniotic fluid is altered fetuses exposed to GDM. One study found N1-methyl-4-pyridone-3-carboxamide, 5'-methylthioadenosine, and kynurenic acid were significantly associated with both degree of GDM and fetal growth.[39] Last, leptin and adiponectin, two hormones involved in energy metabolism and insulin regulation, are increased in infants born to mothers with GDM. One study found infants of GDM mothers at delivery had increased umbilical cord blood leptin and adiponectin.[40] Umbilical cord blood leptin was positively associated with SAT.

In this study, FGR fetuses had decreased hepatic PDFF and SAT volume. In ultrasound studies of FGR fetuses and infants, decreased abdominal SAT in infants was associated with a lower infant triceps and subscapular skinfold thickness and infant abdominal circumference.[41] The FGR cohort likely had less SAT due to a nutrient deprived state the in utero state. In this study, four women had placental insufficiency and one woman had insufficient caloric intake. A lower fat mass in the fetus may predispose one to metabolic diseases. In animal models, a lower fat mass was associated with insulin resistance.[13] Studies have found that increased weight gain and BMI in small for gestational age infants led to higher fat mass as a toddler[14] and insulin resistance at six years old.[42] These findings are consistent with the theory that an early adiposity rebound is associated with a later childhood obesity.[43]

Although most previous research regarding fetal body composition has focused on SAT, our study also assessed fetal hepatic and pancreatic PDFF. Fetal hepatic PDFF was positively correlated with maternal adiposity and GDM status. To date, there is no literature examining human fetal hepatic fat. In a study of pregnant guinea pigs, maternal and fetal hepatic fat content measured by MRI was greater in the animals exposed to a Western diet than the animals exposed

to a standard diet.[44] In a murine study, fetal livers of pregnant mice fed a high-fat diet and who developed NAFLD were compared fetal livers of pregnant mice who were fed a standard diet. Fetal liver inflammation, apoptosis[45], steatosis, and oxidative stress were notably increased in the mice whose mother's had NAFLD compared to the control group.[46] These fetal liver changes have been associated with impaired glucose tolerance and decreased insulin sensitivity at postnatal day 15.[47,48] Fetal hepatic fat appears may play an important role in future metabolic health.[49] Future longitudinal studies are needed on animals and humans to understand the relationship between GDM and maternal obesity and NAFLD.

Maternal adiposity influences fetal adiposity. In our study, women with increased pancreatic PDFF, SAT volume, and VAT volume had increased fetal liver PDFF. In previous ultrasound studies, maternal VAT depth in the second trimester was positively associated with an increase in birth weight.[50,51] There have been no studies to date that have examined the relationship between maternal pancreatic fat and the offspring's adiposity. One animal study found increased visceral adiposity in mice on a high fat diet was associated with impaired pancreatic function in pregnant mice.[52] We suspect that maternal adiposity alters fetal body composition and infant growth through epigenetic changes involving adiponectin. Compared to the SAT of lean women, the SAT of obese women is characterized by an increase in methylation of the adiponectin gene and subsequent decreased adiponectin mRNA.[53] Women with increased adiposity have less adiponectin, which has an inverse relationship with FGR.[54] Low circulating adiponectin in obese mothers does not limit insulin's effect, leading to aberrant placental nutrient transfer and excessive fetal growth.[54]

In this study, a pregnancy complicated by GDM was associated with an increase in fetal SAT volume and hepatic PDFF. Glucose tolerance test results at 1 hour had a positive linear

relationship with fetal SAT volume and hepatic PDFF. GDM was the primary driver of fetal hepatic PDFF in the multi-variable linear regression model despite a small sample size. Infants born to mothers with GDM had increased fat-mass and skinfold thickness, and maternal serum glucose level had the strongest relationship with infant adiposity.[55] One study examining infants born to obese mothers using 1.5T MR spectroscopy found that infants of obese mothers with GDM had increased hepatic fat compared to infants of healthy mothers without GDM.[56] Another study examining fetal SAT volume utilizing MRI found that fetuses at 24 weeks had little fat and no meaningful differences. However, at 34 weeks gestation, the overweight/GDM cohort had increased fetal SAT volume compared to controls.[34]

In our study, all women in the GDM cohort were overweight or obese and almost all women required medications to manage their GDM. In fetuses of pregnant mice exposed to a Western diet, hepatic steatosis was noted. However, when these mice were given metformin early in pregnancy, the amount of fetal hepatic fat between the two groups was comparable.[45] In an MRI study examining fetal SAT volume in women without GDM and women with GDM with a BMI <30 kg/m^2 and >30 kg/m^2, those with a BMI <30 kg/m^2 did not differ in fetal SAT volume than those without GDM.[33] These findings emphasize the need for future research to examine the complex relationship between adiposity and GDM.

We recognize our study's limitations. MRI machines are costly, loud, not easily accessible, and require subjects to be in an enclosed space. Second, while hepatic PDFF has been validated with biopsy in adults, it has not been validated in the fetus.[57] Third, fetal motion can impact image quality. To mitigate this, we avoided placing ROIs in motion affected areas. Fourth, due to our small pilot sample size, we could not disentangle the relationship between insulin resistance and maternal adiposity. Moreover, we could not explore how diet controlled,

successfully treated, and uncontrolled GDM alters specific outcomes. Lastly, we did not longitudinally measure body composition during pregnancy and infancy. Future follow-up would be required to better if maternal and fetal body composition are truly associated with future childhood and adulthood obesity and various metabolic complications.

In conclusion, to our knowledge, this is the first study to quantify maternal body composition and fetal hepatic PDFF at the same time using free-breathing MRI technology. Fetal SAT volume was positively associated with infant birth weight z-score. Fetuses exposed to GDM had a greater amount of fetal SAT volume compared to growth restricted fetuses and hepatic PDFF compared to fetuses with growth restriction and fetuses of healthy mothers. We also noted that maternal pre-pregnancy BMI, pancreatic PDFF, VAT volume, and SAT volume was positively correlated with fetal hepatic PDFF. We speculate that maternal adiposity and insulin resistance increase fetal hepatic fat content and risk for future obesity and NAFLD in the offspring.

TABLE AND FIGURES

Table 1. Characteristics of the Maternal-Infant Dyads. Categorical values are represented as percent (n). *p<0.05 compared to pregnancies with gestational diabetes mellitus. BMI: body mass index. NICU: neonatal intensive care unit. PDFF: proton density fat fraction.

	Healthy Pregnancies (N=10)	**Gestational Diabetes Pregnancies (N=5)**	**Fetal Growth Restriction Pregnancies (N=5)**	**p-value**
Maternal age (years)	34.5 (29.8, 38)	33 (30.5, 36.5)	35 (27.5, 36)	0.80
Pre-pregnancy BMI (kg/m^2)	23.9 (21.9, 26.2)	31 (27.6, 32.5)	22.7 (20.6, 33.3)	0.10
Weight gain in pregnancy (kg)	14.1 (14.1, 16.9)*	10.9 (5.1, 12.1)	13.4 (8.5, 15.9)	0.03
Race	30 (3) Asian 70 (7) White	100 (10) White =	40 (4) Asian 60 (6) White	0.30
Hispanic Ethnicity	20 (2)	80 (8)	20 (2)	0.08
Glucose tolerance test at 1 hour (mg/dL)	87 (67, 112)*	182 (157, 191)	131 (102, 146)	0.005

Gestational age at time of MRI (weeks)	32.7 (32.3, 34.5)	35.3 (32.9, 35.7)	33.4 (31.7, 34)	0.27
Gestational age at delivery (weeks)	39.4 (37.8, 41.1)	38.1 (37.5, 39.8)	38.4 (35.3, 39.7)	0.31
Vaginal delivery	90 (9)	100 (10)	60 (6)	0.57
APGAR 5 minutes	9 (9, 9)	9 (9,9)	9 (8, 9.8)	1.0
Birth weight z-score	0.13 (-0.8, 0.5)	-0.3 (-0.8, 0.8)	-2.1 (-2.4, -0.2)	0.09
Birth length z-score	0.59 (0.2, 2.2)	0.5 (-0.8, 0.8)	-1.3 (-2.6, 0.6)	0.11
Birth head circumference z-score	-0.32 (0.4, -1.6)	1.4 (-2, 1.6)	-1.1 (-2.6, -0.5)	0.25
Fetal subcutaneous adipose tissue volume (mm^3)	241 (232, 255)	280 (261, 295)	220 (205, 235)*	0.003
Fetal liver PDFF (%)	3.2 (3.0, 3.3)*	5.2 (4.2, 5.5)	1.9 (1.4, 3.7)*	0.004

Maternal subcutaneous adipose tissue volume (mm^3)	157,319 (126,300, 200,028)	216,264 (161,461, 325,975)	159,197 (84,024, 339,707)	0.40
Maternal visceral adipose tissue volume (mm^3)	97,593 (78,014, 121,081)*	169,626 (137,736, 227,035)	96,787 (82,327, 184,784)	0.03
Maternal liver PDFF (%)	2.1 (1.8, 2.8)	3.2 (2.1, 3.8)	2.2 (1.1, 5.0)	0.43
Maternal pancreatic PDFF (%)	6.6 (5.8, 7.4)	10.0 (7.6, 13.0)	5.5 (4.1, 7.2)*	0.03

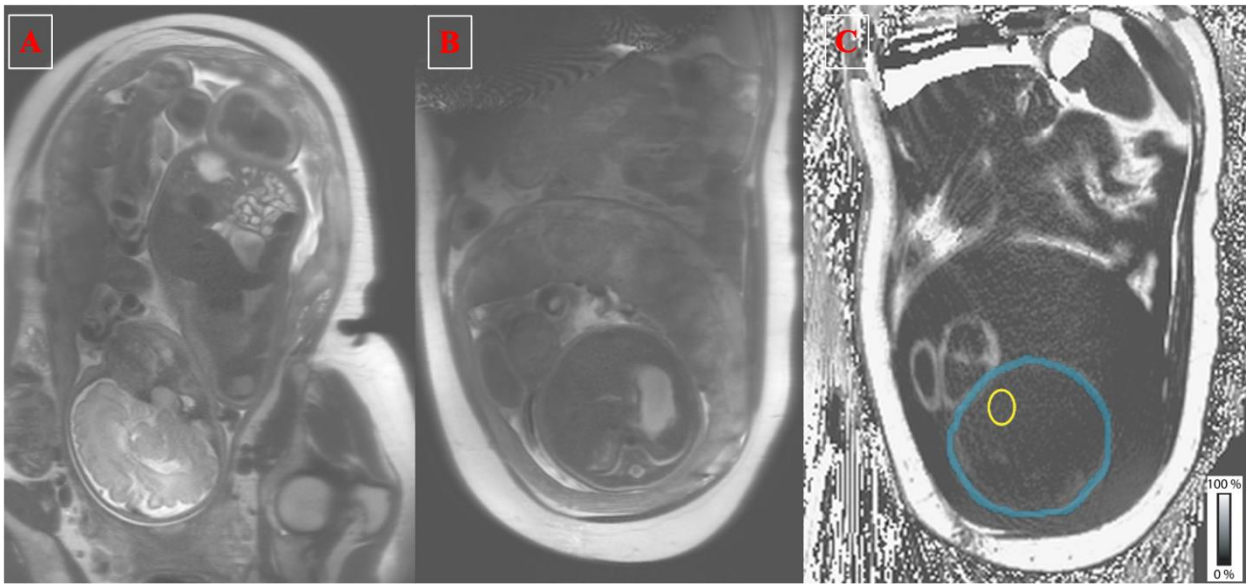


Figure 1. Fetal body composition measurements on MRI. This figure shows a fetus whose mother has gestational diabetes. **A.** Image from a sagittal T_2-weighted (T2W) half-Fourier acquisition single-shot turbo spin-echo (HASTE) sequence. **B.** Image from an axial T2W HASTE sequence. **C.** Proton-density fat fraction (PDFF) map from a free-breathing 3-D stack-of-radial gradient echo sequence. As shown by the grayscale bar for PDFF values (0-100%), white pixels have high fat content and dark pixels have low fat content. The images in B and C are matched at the level of the lower liver. The blue annotation represents fetal subcutaneous fat. The yellow oval is a 3-cm^2 region of interest used to measure fetal hepatic PDFF.

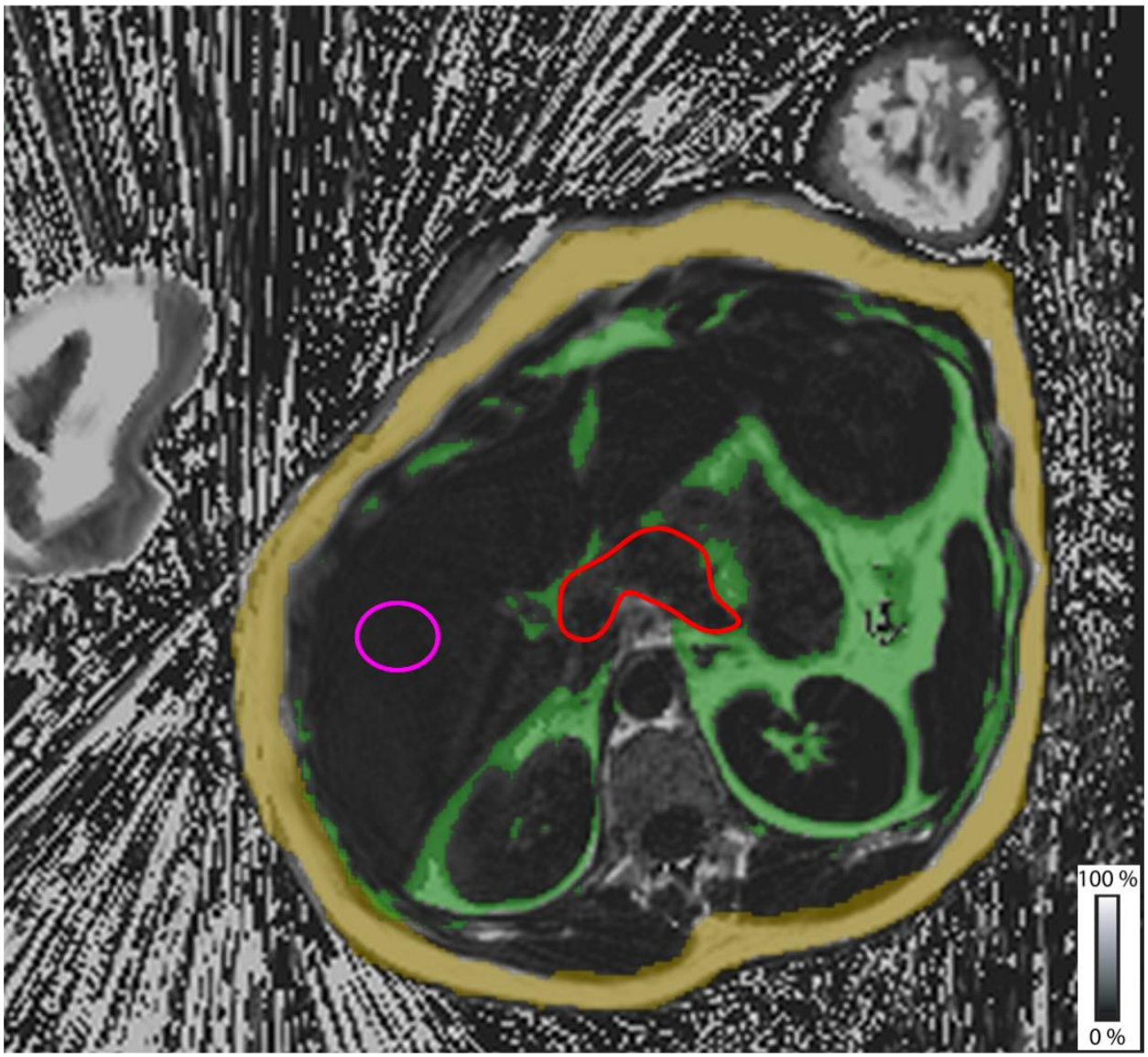


Figure 2. Maternal body composition measurements on a proton-density fat fraction (PDFF) map from free-breathing MRI. As shown by the grayscale bar for PDFF values (0-100%), white pixels have high fat content and dark pixels have low fat content. The yellow annotation represents subcutaneous adipose tissue. The green region represents visceral adipose tissue. The magenta 5-cm^2 region of interest was used to measure maternal liver PDFF. The red contour outlines the maternal pancreas.

Figure 3. Diagram showing the subject recruitment in the three cohorts. Seven women were recruited in the fetal growth restriction cohort. Two women did not complete the study due to maternal anxiety during the MRI scan.

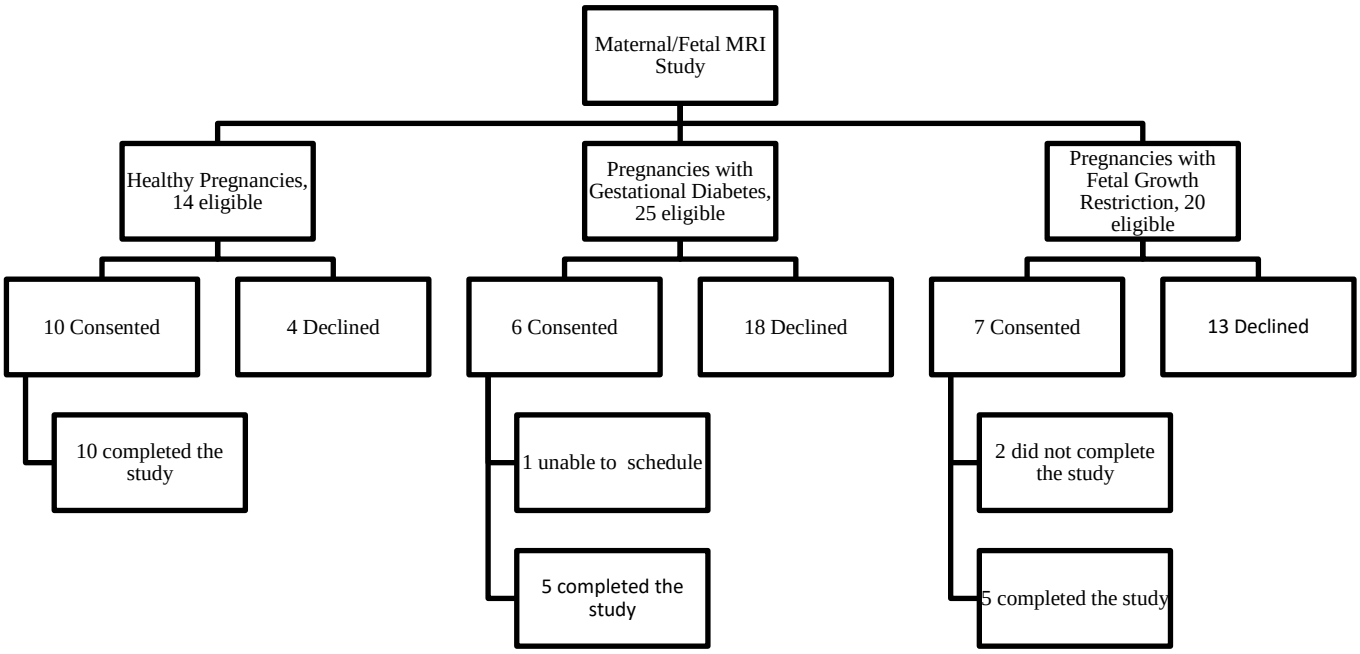
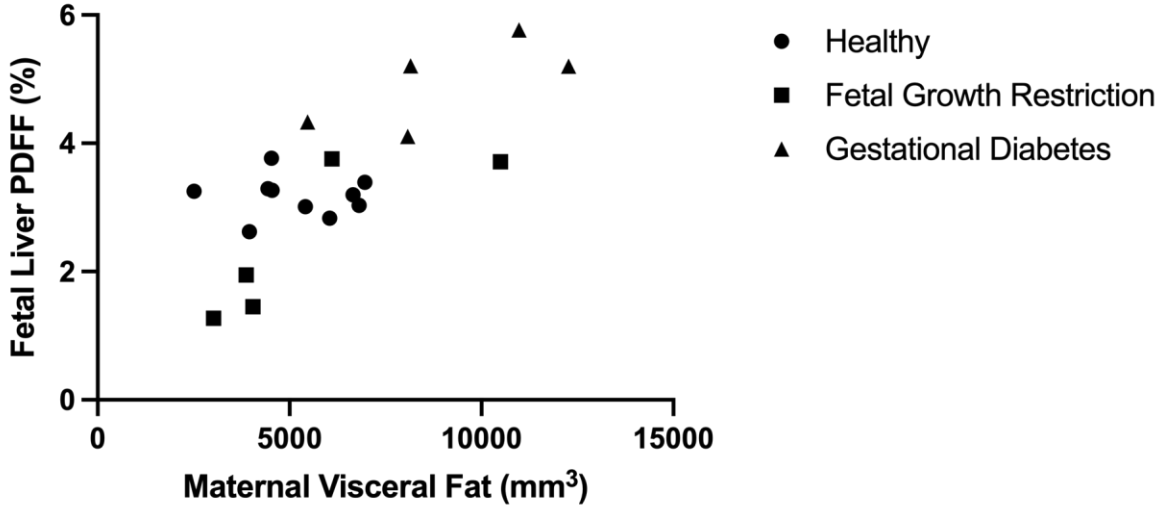


Figure 4. Relationship between fetal hepatic proton-density fat fraction (PDFF) (%) and maternal visceral fat volume (mm^3). Circles represent the healthy pregnancies. Squares represent pregnancies with fetal growth restriction. Triangles represent pregnancies with gestational diabetes.



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