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Abstract

Purpose: Analysis of fetal adipose tissue volumes may provide useful insight towards assessment of overall fetal health, especially in cases with abnormal fetal growth. Here we assess whether fetal adipose tissue volume can be reliably measured using 3D water-fat MRI, using a quantitative assessment of the lipid content of tissues.

Materials and Methods: 17 women with singleton pregnancies underwent a fetal MRI and water-only and fat-only images acquired (modified 2-point Dixon technique). Water and fat images were used to generate a fat signal fraction (fat/(water+fat)) from which subcutaneous adipose tissue was segmented along the fetal trunk. Inter-rater (3 readers) and intra-rater reliability was assessed using intraclass-correlation coefficients (ICC) for 10 image sets. Relationships between adipose tissue measurements and gestational age and estimated fetal weight percentiles were examined.

Results: The ICC of the inter-rater reliability was 0.936 ($P < 0.001$), and the ICC of the intra-rater reliability was 0.992 ($P < 0.001$). Strong positive correlations were found between adipose tissue measurements (lipid volume, lipid volume/total fetal volume, mean fat signal fraction) and gestational age.

Conclusions: 3D water-fat MRI can reliably measure volume and quantify lipid content of fetal subcutaneous adipose tissues.

Brief Rationale

Fetal adipose tissue increases in volume throughout pregnancy and abnormal subcutaneous tissue volumes have been measured with variable success with ultrasound and MRI. In our study, we are the first to use 3D-water fat MRI, a technique sensitive to the amount of free lipid within a tissue, to assess the amount of lipid in fetal subcutaneous adipose tissue as measured by the fat signal fraction (FSF). Here we show that the FSF increases with gestational age, indicating that water-fat MRI is sensitive to the increasing lipid content of fetal adipose tissue through mid-late gestation.

Introduction

It has been suggested that the trigger for abnormal fat deposition and metabolism is set *in utero* [1] as both limited and excessive fetal growth are associated with increased risks for obesity and metabolic syndrome later in life [2, 3, 4]. Differences in adipose tissue in neonates, normally 14% of weight at birth, explain 46% of the variation seen in birth weight [5]. As well, neonates of obese mothers with gestational diabetes have been found to have abnormal fat distribution when measured 1-3 weeks after birth [6]. Ultrasound and magnetic resonance imaging (MRI) have found that fetal adipose tissue thickness and/or volume is altered with diabetic pregnancies, growth restriction and macrosomia [7, 8, 9, 10, 11, 12, 13, 14, 15]. This suggests that assessment of fetal fat development *in utero* has the potential to provide additional insights into fetal health and nutritional status, especially in circumstances where altered metabolism may put the fetus at risk for adverse pregnancy outcomes [16, 17].

As fetal adipocytes develop, the amount of lipid they contain increases, a process for which 3D water-fat MRI is sensitive. Previous MRI studies have differentiated adipose tissue (fat) from lean tissue (water) based on different T1 values, an intrinsic MRI tissue property [10, 12, 18]. These methods, however, have been restricted to assessing the volume of subcutaneous tissue as they are not able to measure the relative amounts of lipid and water within tissues. Water-fat MRI is capable of separating the water signal from the lipid signal, allowing water-fat MRI to provide a quantitative ratio of signal from lipid and signal from water in a tissue. Measuring the lipid content of the fetal adipose tissue may give more insight into the expansion of adipose tissue in fetal development, while adding to the tools used to assess fetal health in late pregnancy.

The objective of this study is to assess whether fetal adipose tissue volume can be measured reliably using 3D water-fat MRI. We hypothesize that water-fat MRI will be sensitive to increases in both the adipose tissue lipid volume and lipid content as function of gestational age (GA), mirroring the increased lipid deposition as the fetus grows. This study aims to provide an initial demonstration of the ability of MRI to measure fetal adipose tissue development during the third trimester of pregnancy., If successful, these measurements would be useful for assessment of abnormal fetal growth and metabolic health.

Materials and Methods

This study was approved by the Western University Research Ethics Board (HSREB# 103845). Between January 2014 and October 2015, pregnant women over the age of 18 with singleton pregnancies between 29 and 35w GA were recruited from Obstetrics clinics at London Health Sciences Centre for the sole indication of participation in the MRI-study. Patients with medical contraindications or body habitus preventing them to safely undergo a non-contrast MRI were excluded. Consenting participants underwent a fetal MRI in a wide-bore (70 cm diameter) 1.5T MRI (General Electric Optima 450w, Milwaukee, WI, USA) with a 32-coil abdominal phased array. Women were positioned supine or rolled towards a left lateral decubitus position with a cushion under either their back or their right side for comfort. Scout images (T2 weighted Single Shot Fast Spin Echo (SSFSE)) were acquired to locate the fetus and determine its orientation. Water-only and fat-only images were produced during a maternal breath hold with a modified 3D two-point Dixon (LAVA Flex) acquisition in a plane axial to the fetal abdomen (TR 6.0-6.4 ms, flip angle 5°, Field of View 48 cm, 160×160 pixels, slice thickness 4 mm, 38-82 slices, 2× parallel MRI acceleration with ARC, acquisition time 10-24 s).

Total fetal volume was manually segmented from 2D SSFSE images using OsiriX (v5.6)[19] by tracing the boundary of the lower signal intensity of the fetus relative to the high signal intensity of the amniotic fluid. MRI estimated fetal weights (MRI EFW) were calculated from total fetal volume using a fetal density formula (MRI EFW = 0.12 + 1.031 × fetal volume) [20]. [21]

Clinical data on both maternal and fetal characteristics were collected prospectively from mothers and from infants after delivery. Sonographic estimates of fetal weight were taken from closest ultrasound studies prior to the date of the MRI (range 0-35 days) using the Hadlock 2 formula [22]. MRI EFW percentiles have previously been shown to be more accurate than ultrasound EFW percentiles when measured within 3 hours of caesarean delivery [23]. The EFW calculated from both MRI and ultrasound were then used with custom weight standards from Gardosi and Francis (2015) to calculate the fetal weight percentiles [21]. Birthweights were recorded from infant charts and birthweight percentiles were calculated using the standards from Kramer *et al.* [24].

Fat signal fraction image volumes were calculated voxel-by-voxel from the fat and water signal intensities (Fat Signal Fraction = Fat/(Water+Fat)) for the entire MRI volume collected, which always included fetal abdomen. Using OsiriX v5.6 (Pixmeo, Bernex, Switzerland); 3D fat signal fraction volumes were reformatted to axial to the fetal abdomen when the original images were not oriented optimally, usually due to fetal movement after scout images. The fetal trunk subcutaneous adipose tissue (fTSAT) was manually segmented from the fat signal fraction images by manually tracing the boundary of high fat signal fraction of the adipose tissue relative to the approximately zero fat signal fraction of the surrounding tissues (amniotic fluid and internal fetal tissues). This segmentation was performed in all slices (25 -51 slices) between the axillary and hip skin folds.

The lipid volume within the fTSAT region was calculated by correcting the manually segmented fTSAT volume by the mean fat signal fraction of that volume in each slice. Through this method, we were able to correct for partial volumes and determine the quantitative amount of lipid in the fTSAT. Measured variables included the amount of lipid in the fTSAT (lipid volume), lipid volume normalized to fetal volume (lipid volume/fetal volume) and the mean fat signal fraction in the fTSAT (fat signal fraction; FSF).

To assess inter-rater reliability, three independent readers (SG, CO and DM) each manually segmented 10 fat signal fraction sets and the segmented volumes were compared using intraclass correlation coefficient (ICC). Intra-rater reliability was assessed by one reader (SG) with 10 fat signal fraction sets manually segmented twice two months apart with the segmented volumes compared using ICC.

To examine bivariate relations between fetal fat measurements (lipid volume, lipid volume/fetal volume, and FSF) and GA at MRI and MRI EFW percentile: Pearson correlations and linear regression analyses were used. All statistical analyses were conducted in SPSS v.24 (IBM Corporation, Armonk, NY, USA), and p-values <0.05 were considered statistically significant.

Results

Eighteen women were recruited for the study. One participant with a high BMI (61 kg/m^2) was successfully positioned in the MRI bore but was unable to commence imaging due to claustrophobia. The remaining 17 participants provided images of adequate quality for segmentation of the fetal trunk subcutaneous adipose tissue; intra-abdominal fat content was insufficient for segmentation.

The mean number of previous pregnancies was 1 (range 0-2), and the mean maternal age at delivery was 32 years (range 23-41 years). Mean pre-pregnancy BMI of participants was 34.6 kg/m^2 (range 19.2-52.5 kg/m^2). Most participants were recruited from our specialized clinic for elevated BMI and pregnancy, resulting in a high percentage of participants with a pre-pregnancy BMI in the obese categories (76%). Seventeen percent of the participants had a BMI in the normal range, while 6% were overweight. Seventy percent of the participants were non-diabetic, 6% had pre-existing type 1 diabetes, 12% had pre-existing type 2 diabetes, and 12% had gestational diabetes. The mean gestational age at MRI was 32 weeks (range 29-34), and 53% of the fetuses examined were female. The mean birthweight percentile was 58.1 (range 0.5-96.6), with 12% of the fetuses below the 10^{th} and 23% above the 90^{th} percentile.

Total fetal volume and fTSAT volume were segmented for all 17 participants. Figure 1 shows a visualization of the fetal fat with the fTSAT segmentation highlighted in green, created using 3D Slicer (v4.5.0)[25, 26, 27]. The ICC for the inter-rater reliability was 0.936 ($p < 0.001$), and the ICC for the intra-rater reliability was 0.992 ($p < 0.001$).

Figure 1 also shows the fTSAT segmentation for two different participants. The fetuses have different gestational ages at MRI (C; 30 weeks and D; 34+1 weeks) and very different FSF (C = 12% and D = 30%) with different lipid volumes (C = 10 mL and D = 80 mL), illustrated with different greyscale values within the segmented regions. It is important to note that both fetuses have similar ultrasound EFW percentiles (C = 98% and D = 96%), suggesting that FSF and lipid volume are affected by gestational age.

Over the GA period studied, fetal lipid volume showed a rapid increase from 4 mL at 30 weeks to 48 mL at 34 weeks gestation (Figure 2A), or 0.3% to 1.8% lipid volume/fetal volume. This is paralleled by an increase in FSF from 10% to 24% from 30 to 34 weeks (Figure 2B). These

increases demonstrate the positive correlations between GA at MRI and lipid volume ($r = 0.63$, $p = 0.007$), GA at MRI and lipid volume/fetal volume ($r = 0.65$, $p = 0.005$), and GA at MRI and FSF ($r = 0.65$, $p = 0.005$) (Figure 2A & B).

The relationships between fat measures and fetal weight indices were also examined. Custom EFW percentiles calculated from MRI volumes were positively correlated with lipid volume ($r = 0.62$, $p = 0.009$), lipid volume/fetal volume ($r = 0.55$, $p = 0.022$) and FSF ($r = 0.60$, $p = 0.012$) (Figure 2C & D). Due to the small sample size and heterogenous population, we did not analyze for differences in the FSF or lipid volume of the fTSAT with BMI less than or greater than 30 kg/m^2 (n = 4; BMI < 30 kg/m^2, and n = 13; BMI ≥30kg/m^2), maternal diabetes (n = 12; non-diabetic, and n = 5; diabetes), IUGR or macrosomia (n = 11; 10^{th} percentile<BW<90^{th} percentile, n = 2; BW <10^{th} percentile, and n = 4; BW >90^{th} percentile).

Discussion

We describe a method for measuring fetal abdominal subcutaneous adipose tissue with 3D water-fat MRI, for the first time allowing monitoring of fetal fat development by assessing the lipid content of adipose tissue rather than tissue volume alone. Measurements were made by defining a region of interest in the fetal trunk based on soft tissue landmarks that were easily and consistently recognizable regardless of fetal position, size or GA. This methodology resulted in a segmentation technique with excellent inter- and intra-rater reliabilities.

We observed a rapid fat accumulation between 29 and 34w GA, with an increase from 10 to 24% in FSF and from 4 to 48 mL in trunk subcutaneous tissue volume. Previous studies describe a rapid increase in fetal subcutaneous tissue thickness in fetal leg and abdomen between 29 and 40

weeks with MRI [11], or 19 and 40 weeks with ultrasound [28, 29]. These findings highlight the importance of this GA window for fetal subcutaneous fat development.

The increase in FSF during this time is of interest since the measurement of FSF is a much more direct indicator of adipocyte lipid content than adipose tissue volume. Indeed, the FSF measured in the fetuses at all GA studied was below that of mature adult adipose tissue. Even at birth, neonatal adipose tissue is not fully developed as neonatal fat fractions have been reported to be 67.7% [30] and 77.9% [31], compared to a fat fraction of approximately 90% in adults [31]. The linear regression indicates a fetal fat fraction of 24% at 34w, suggesting that a further rapid increase in fat fraction and lipid volume can be expected between 34 and 40w GA.

In our study, we elected to measure fetal abdominal fat development because abdominal subcutaneous tissue thickness measured by ultrasound is correlated to neonatal body composition while allowing for assessment of intraabdominal fat. However, none of the fetuses had any measurable amounts of intraabdominal fat, possibly because very little intraabdominal adipose tissue develops at this gestational age [12] or there is not enough lipid accumulation to be visualized with MRI. The lowest measurable FSF in our study was 4%, based on the noise signal in amniotic fluid (data not shown), and therefore intra-abdominal or intrahepatic fat fractions below this percentage should not be reported.

Water-fat MRI is a MRI technique that provides separate water and fat images. In this study, these images were acquired using a modified 2-point Dixon technique; this technique has a faster image acquisition, making it less likely to be affected by fetal motion. Additionally, it has better signal-to-noise efficiency than other water-fat MRI, which will allow it to measure relatively lower fat fractions [32, 33]. While this sequence has recognized limitations of sensitivity to T2* effects (caused by e.g. iron) and incomplete fat spectrum modelling (MRI fat signal at multiple

frequencies due to the complex chemical structure of triglyceride)[34], recent work has demonstrated that these effects do not cause bias in estimates of fat fraction with modified 2-point Dixon in fTSAT [35]. However it should be noted that Giza *et al*. did demonstrate biases in estimates of fat fraction with modified 2-point Dixon in other tissues including the liver [35].[36]

Our study was limited by the small sample size, its cross-sectional nature and high percentage of patients with elevated BMI. In our institution, 44% of women are overweight or obese, with 20% of the total maternal population having a BMI greater than 30 kg/m^2 (unpublished data). This pilot study demonstrated the feasibility of MRI in the early third trimester in a large-bore MRI, even in patients with significant obesity (BMI>40; n=5). Due to the small sample size and heterogenous population, we were unable to comment on normal values for GA or 'normal' and 'abnormal' fat development. While FSF is strongly affected by gestational age, other factors including maternal BMI, maternal diabetes, fetal sex and natural variation in fetal growth and development could also be contributing to the FSF differences seen in our study data.

Future studies with comparisons between normal pregnancies and those affected by high maternal BMI, maternal diabetes, and fetal growth extremes (fetal growth restriction and macrosomia) are needed to establish the utility of fetal fat measurements in clinical practice or research.

We also acknowledge some limitations of our manual segmentation method. First, a fetal position with a curved rather than straight spine resulted in an inability to extend the segment to the axillary or hip skinfold on both right and left sides of the fetus, in which case the measurement leading to the smallest trunk volume was chosen. This resulted in an underestimation of fetal fat volume, which can be overcome by performing segmentations in a

program that allows editing in 3D, so that the start/end points can be drawn between the left and right sides. Second, partial volume effects would lower the mean FSF and lead to a universal and likely consistent underestimation of fetal fat accumulation. More accurate estimates of FSF may be obtained using a segmentation program that allows for the segmentation to be eroded to exclude such partial volume pixels.

Future research should include measuring fat fractions in pregnancies in women of normal BMI with gestational weight gain within the recommended IOM limits (11.5-16 kg [37]), and at both earlier and later GA, to determine the MRI growth and development trajectories of fetal adipose tissue. Limitations in lowest threshold for fetal fat measurement (4%) will limit the earliest gestation that changes in subcutaneous fat content can be adequately measured.

In conclusion, we have shown that fetal fat volumes can be reliably measured while correcting for the lipid content of the adipose tissue using 3D water-fat MRI. We have also confirmed our hypothesis that fetal adipose tissue lipid volume and lipid content increase with GA. Further investigation with a larger sample size and MRI quantitative proton-density fat fraction measurement should be pursued to further investigate the potential utility of these fat measurements.

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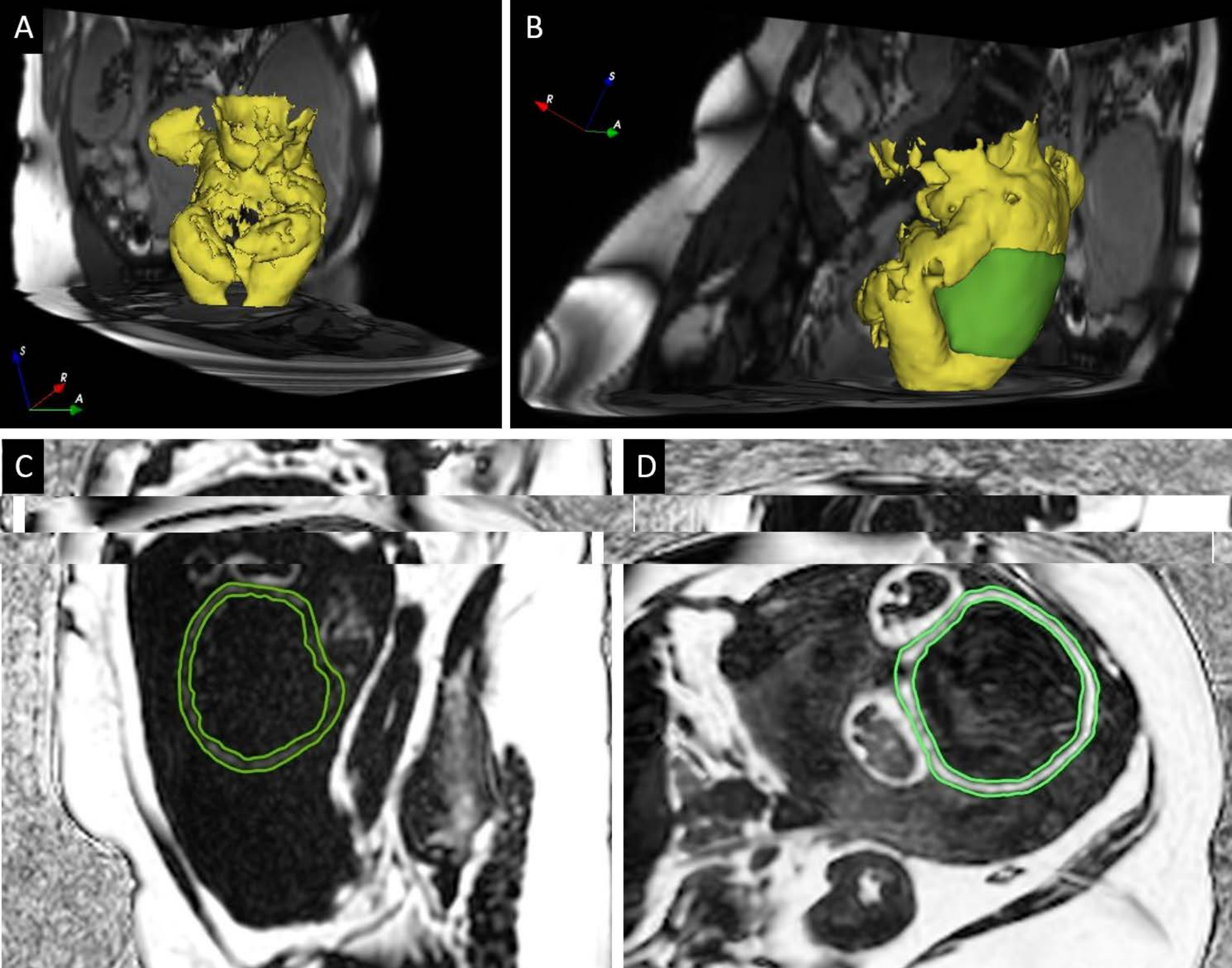
Figure Legends

Figure 1: A) 3D rendering of total fetal fat, B) 3D rendering of fTSAT segmentation on total fetal fat, C) 2D fTSAT segmentation on fetus with 10 mL lipid volume and D) 2D fTSAT segmentation on fetus with 80 mL lipid volume. 3D renderings in panel A shows the distribution of fat above a 10% fat signal fraction threshold. The rendering in B is shown in a different orientation so that the limbs do not obscure the upper and lower boundaries of the fTSAT segmentation demonstrated in green. Three orthogonal planes of FIESTA images are shown to reference maternal anatomy and axes marker included to indicate maternal orientation. The 2D images in panels C and D show fetuses that had similar US EFW percentiles (C=98%, D=96%) but different lipid volumes, in part due to differences in the mean fat signal fractions (C=12%, D=30%). This can be seen as a brighter segmented region in panel D than panel C. It is also important to note that these fetuses have different gestational ages at MRI (C=30 weeks and D=34+1 weeks). 2D images are displayed axial to the fetal abdomen to show comparison of slices through the umbilicus.

Figure 2: A) Gestational age versus lipid volume, B) gestational age versus mean fat signal fraction, C) custom MRI EFW percentile versus lipid volume and d) custom MRI EFW percentile versus mean fat signal fraction. A positive correlation was found between gestational age and lipid volume ($p = 0.007$), between gestational age and mean fat signal fraction ($p=0.005$), between custom MRI EFW percentile and lipid volume ($p = 0.009$), and between custom MRI EFW percentile and mean fat signal fraction ($p = 0.012$). Lipid volume error bars represent a 5% estimated error in lipid volume measurement; some error bars are too small to be visualized. Fat signal fraction measurement error bars represent the standard deviation of values across slices measured.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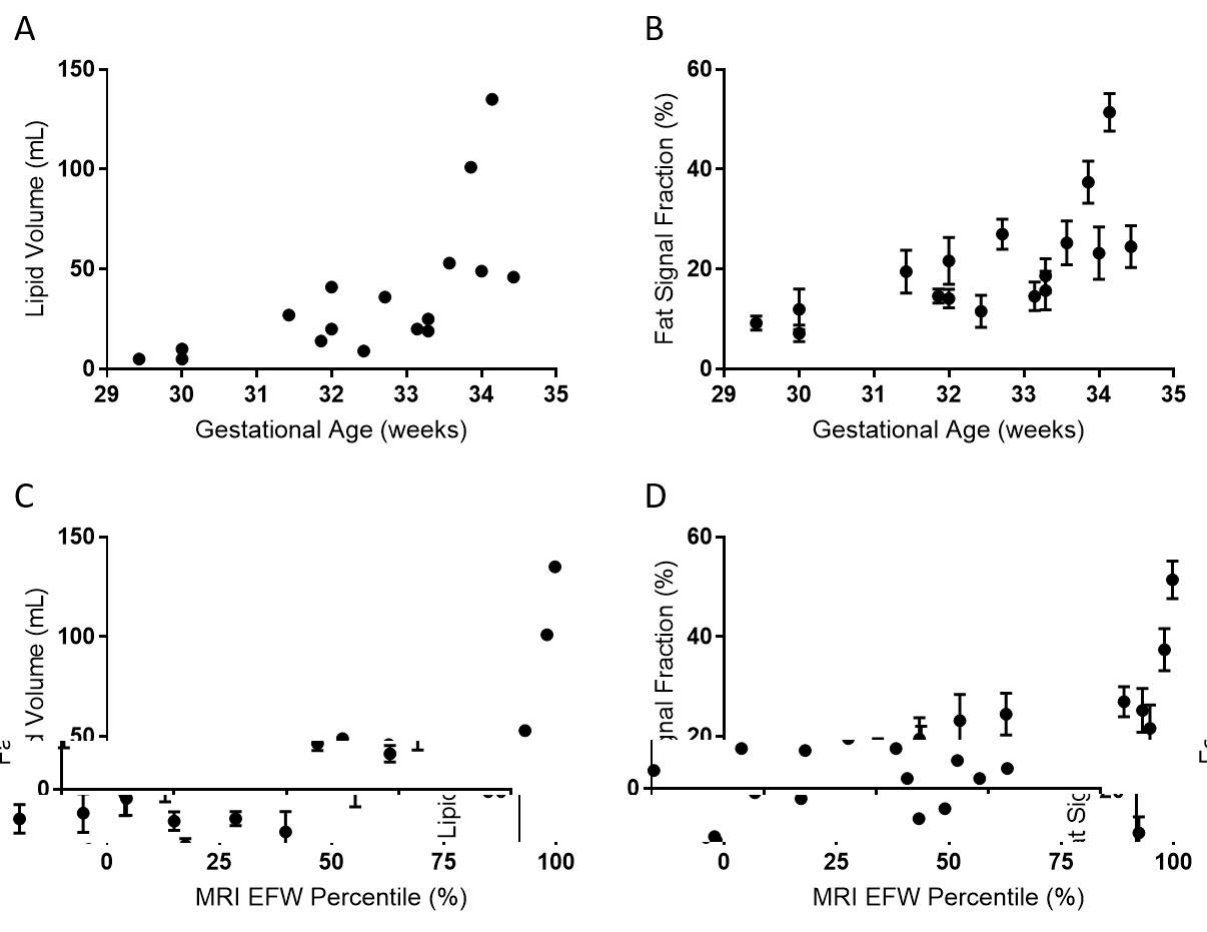
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