Investigating Fetal Body Composition with Free-Breathing Magnetic Resonance Imaging

Lead Study Investigators: Katie Strobel, MD, UCLA, Department of Pediatrics, Division of Neonatology
Kara Calkins, MD, MS, UCLA, Department of Pediatrics, Division of Neonatology
Holden Wu, PhD, UCLA, Department of Radiology

Collaborators: Carla Janzen, MD, PhD, Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine
Rinat Masamed, MD, Department of Radiology
Tahmineh Romero, MS, Division of General Internal Medicine and Health Services Research
Michelle Tsai, MD, Department of Obstetrics and Gynecology
Thalia Wong, MD, Departments of Obstetrics and Gynecology, Division of Maternal Fetal Medicine

Version Date: 4/2020

CONTENTS

SECTION 1. STATEMENT OF THE PROBLEM

1.1 OBJECTIVE

This study's goals are to: 1) use free-breathing magnetic resonance imaging (FB-MRI) to measure fetal body composition in the third trimester and 2) determine how the FB-MRI quantitative measurements compare to growth parameters at birth.

1.2 HYPOTHESES AND SPECIFIC AIMS

To accomplish our objectives, our aims and hypotheses are as follows:

Specific Aim 1:
In a prospective study in women with healthy pregnancies and women with fetuses that have intrauterine growth restriction (IUGR) and gestational diabetes, we will quantify fetal subcutaneous, visceral, and brown adipose tissue volumes and proton-density fat fraction (PDFF) using FB-MRI in the third trimester.
Hypothesis 1: Using a FB-MRI technique we will find the following,

1) The growth restricted fetus will have less visceral, subcutaneous, and brown adipose tissue volume and PDFF when compared to healthy fetuses and fetuses whose mothers have gestational diabetes.
2) Fetuses whose mothers have gestational diabetes will have a greater subcutaneous and visceral adipose tissue volume and PDFF compared to healthy fetuses.

Specific Aim 2:
In a prospective study in pregnant women and their fetuses, we will compare volume and PDFF measurements of fetal visceral, subcutaneous, and brown adipose tissue obtained with FB-MRI to birth growth parameters of these infants.
Hypothesis 2: The volume and PDFF of fetal visceral and subcutaneous adipose tissue will correlate positively with birth weight and length z-score.

1.3a. BACKGROUND:

Pediatric obesity is a public health crisis with increasing prevalence worldwide. 19% of children and adolescents in the United States are obese[1]. Pediatric obesity is associated with an increased risk for adult onset metabolic syndrome, which refers to the co-occurrence of obesity, insulin resistance, dyslipidemia, hypertension, and non-alcoholic fatty liver disease[2]. There is also a tremendous amount of evidence suggesting that obesity and the metabolic syndrome have fetal origins due to abnormal fetal growth and maternal conditions[3-6].

Impaired fetal growth is a major cause of perinatal morbidity and mortality. Infants with intrauterine growth restriction (IUGR) and infants who are born small for gestational age (SGA) and large for gestational age (LGA) have an increased risk for future obesity, insulin resistance, cardiovascular disease, and associated metabolic complications. IUGR infants have been found to have insulin resistance due to epigenetic changes in the liver and reduced pancreatic beta cell mass[3]. IUGR infants also exhibit satiety dysregulation secondary to impaired leptin and ghrelin[4].

Maternal conditions such as obesity and hyperglycemia in pregnancy may also play a role in the infant's risk factors for obesity. Meta-analyses demonstrated that a maternal body mass index (BMI) in the obese range, glycemia, and birthweight are related to childhood obesity and insulin resistance[5,6]. In short, a person's fetal experience and birth weight appear to be surrogates for future metabolic health.

Body composition parameters can also be important biomarkers for future metabolic health. Body composition is the measurement of the different tissues of the body including adipose tissue muscle, and bone. Fat can be categorized by location (visceral vs. subcutaneous) and type (white vs. beige vs. brown). Visceral fat is located beneath the abdominal muscles while subcutaneous fat sits directly beneath the skin. Visceral fat is composed of mainly white fat and is metabolically active. Visceral fat releases free fatty acids into the circulation which can lead to insulin resistance[7], dyslipidemia[7], hypertension[8,9], and fatty liver[8,9]. Studies demonstrated a significant correlation between the proportion of visceral adiposity in children and adults with obesity and the metabolic syndrome[7]. In infants, increased fat mass gains and rapid weight gain (weight z-score >0.67 in the first two years of life) have been associated with later onset obesity, insulin resistance, hypertension, and non-alcoholic fatty liver disease[8,9].

In contrast to white adipose tissue, brown adipose tissue is responsible for thermogenesis and energy expenditure, and is generally located near the spine, and supraclavicular, axillary, and supraclavicular regions. Traditionally, brown adipose tissue was thought to be only present in the newborn. However, research now demonstrates that brown adipose tissue is present in children and adults[10].When compared to white adipose tissue, brown adipose tissue has a higher water:adipose tissue ratio, is mitochondria-rich, and has a dense supply of capillaries for oxygen consumption. Research demonstrates that brown adipocytes may protect against insulin resistance and obesity. There is now research being conducted on how to convert visceral white adipose tissue to brown adipose tissue[11].

It is important to be mindful that body composition can be measured using different technologies: dual-energy X-ray absorptiometry (DXA), computed tomography (CT), ultrasound, air displacement plethysmography (ADP, commercially known as the PeaPod), and magnetic resonance imaging (MRI). DXA and ADP cannot be used in a fetal model due to poor image quality. DXA is able to estimate the amount of subcutaneous and visceral adipose tissue within the android region, and correlates well with

CT[12]. However, DXA and CT both require radiation, which is undesirable for the fetus and child. While ultrasound does not involve radiation, is an inexpensive imaging tool, and can be used in the utero and extra-utero environment, ultrasound is dependent on the skill of the sonographer and results can be variable. In contrast, MRI is a noninvasive imaging tool that does not involve ionizing radiation and can be used to accurately and longitudinally quantify the volume of adipose tissue. MRI can also measure the proton-density fat fraction (PDFF) in percent, which is used as a biomarker for tissue fat content.

Fetal MRI is becoming increasingly utilized as an adjunct to ultrasound for maternal or fetal conditions related to pregnancy. The American College of Obstetricians and Gynecologists released a statement in 2017 stating that MRI is not dangerous and should be used prudently to answer a clinical question. Today, MRI is commonly utilized in cases of placenta accreta[13] and fetal anomalies such as congenital diaphragmatic hernia, congenital heart disease, and neurological anomalies. There are difficulties with fetal MRI due to lack of control of fetal movement. Our group has developed a free-breathing (FB) MRI technique and has utilized this technology in adults, pregnant women, adolescents, and infants[14-18].

To date, there has been little research pertaining to fetal body composition using MRI. Previously, using T1-weighted MR images, it has been difficult to detect adipose tissue in the second trimester[19,20]. Blondiaux et al (2018) looked at subcutaneous adipose tissue in T1-weighted images starting in the second trimester and found the signal was isointense at 26 weeks and all areas were hyperintense by 33 weeks in a progressive fashion from the nuchal region, buttocks, thigh and back[21]. However, now using 3T MRI for fetal imaging, subcutaneous adipose tissue is more easily identified in the mid and late second trimester[22].

1.3b. PRELIMINARY DATA:

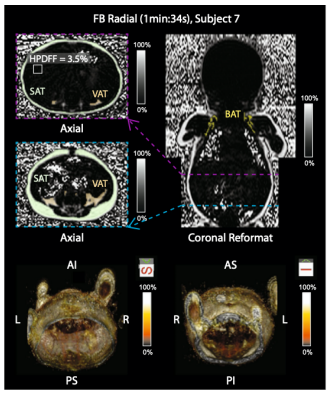

Figure 1. Radial free-breathing MRI was performed on infants. Visceral (VAT), subcutaneous (SAT) and brown adipose tissue (BAT) was measured on the PDFF maps.

Our research group's goal is to use FB-MRI to better understand the early origins of obesity so that we can develop strategies to prevent and treat this disease. In adolescents, we have performed FB-MRI scans to quantify hepatic fat and compared these results to reference breath-held (BH) MRI scans[16]. BH-MRI exhibited artifacts and on average covered only 74% of the liver[16]. In contrast, FB-MRI demonstrated significantly higher image quality and covered 100% of the liver[16]. Moreover, when image artifacts in BH-MRI were avoided, hepatic PDFF from FB-MRI significantly correlated with BH-MRI with a concordance correlation coefficient of >0.99[16]. In infants, we have used FB-MRI to quantify subcutaneous adipose tissue, visceral adipose tissue, brown adipose tissue, and hepatic fat (Figure 1)[18]. Of note, elevated hepatic PDFF was measured in an infant born large for gestational age to a mother with insulin resistance and was noted to be greater compared to control infants[18]. In summary, these data show that FB-MRI can measure body composition and suggest that the capabilities of FB-MRI can be extended to the fetus.

1.4 JUSTIFICATION FOR THE STUDY:

Significance and Innovation

Pediatric obesity is a significant public health problem in the United States. Pediatric obesity is easy to diagnose, but difficult to treat. If there were early predictors in utero of risk for developing obesity, then early intervention programs could be applied and close nutritional monitoring by the general

pediatrician could be performed. To solve this problem, we propose a novel imaging technology, FB-MRI, to quantify body composition. Based on our preliminary evidence, we believe FB-MRI will allow:

- Early prediction of preliminary growth
- Close nutritional monitoring given known amount of adipose tissue

While we know this is an expensive tool that cannot be practically used in the clinical setting, this can be a tool to help further research on pediatric obesity. This may also lead to development of further cost effective tools for the clinical setting.

Investigators

Katie Strobel is well positioned to lead this study under the close guidance of her mentors Dr. Calkins and Dr. Wu. This study team is multi-disciplinary in nature and emphasizes team science. Dr. Strobel is a fellow physician who has worked with Dr. Calkins for the last three years on research on neonatal growth in the congenital gastrointestinal anomaly population. Her work in the gastroschisis population is funded by NIH T32 Gastroenterology grant. She will also be obtaining a Masters in Clinical Research during her fellowship.

Dr. Calkins has a Masters in Clinical Research and has been conducting clinical/translational research with a focus on biomarker science, predictive modeling, and pediatric liver diseases for over seven years. The Neonatology division has provided Dr. Calkins with start-up funds to conduct her clinical/translational research, and she has secured a career development award along with private foundation funding. Moreover, the Neonatology division provides full support for Dr. Calkins' research assistants.

Dr. Wu has worked on the development of new MRI technologies and their translation to clinical applications for over ten years. Dr. Wu's research focuses on new quantitative MRI methods and biomarkers, robust free-breathing 3D MRI, and MRI-guided interventions for body cancers and diseases. He is especially committed to the research of new MRI techniques to improve the characterization of NAFLD. The research in Dr. Wu's lab is supported by intramural Radiology and University grants, industry projects, and federal agencies.

Dr. Calkins and Dr. Wu have applied for an NIH/NIDDK R01 grant for their free-breathing MRI research in children and infants, and have received a very promising score (11th percentile), and anticipate funding in the near future.

SECTION 2.

2.1 STUDY DESIGN
This is a prospective pilot study that will be used to generate data to provide a power analysis for a larger, longitudinal study that will follow fetuses at risk for obesity.

2.2 PRIMARY OUTCOMES:
The primary outcome will be visceral adipose tissue volume and PDFF for the three patient populations: mothers with growth restricted fetuses, mothers with gestational diabetes, and mothers with healthy pregnancies.

2.3 SECONDARY OUTCOMES:
The secondary outcomes will be subcutaneous and brown adipose tissue volume and PDFF, as well as hepatic PDFF, for the three patient populations listed above. Another secondary outcome will be growth parameters of the neonates.

2.4 POTENTIAL RISKS AND BENEFITS:
Subjects may receive no benefit from participating in this study. However, information from this study may improve the understanding of childhood obesity, inform management strategies, and may help prognosticate which infants are at higher risk for obesity.

The research MRI scans required for this study do not require sedation, involve ionizing radiation, or require any contrast administration. MRI scans are a painless test. In other words, the FB-MRI performed for research purposes will NOT require contrast or sedation. However, patients/subjects can experience claustrophobia inside the MRI scanner. Patients with a history of claustrophobia will be excluded from this study. Noise from the scanner during an MRI scan will be mitigated by providing earplugs and headsets to the patients/subjects. Lastly, because MRI scans use magnetic fields, subjects with any metal (e.g., internal metal clips or implants) will be excluded from the study. All subjects will be asked to remove any metal (i.e. earrings, metal belts, etc).

Because information will be collected from each subjects' medical record, there is the possibility of a breach of confidentiality. However, all precautionary measures will be taken to ensure that confidentiality and privacy is maintained, and that data is stored securely. All conversations with subjects and their families will occur in a private setting.

All data will be coded. A code will be kept, but it will be kept on a password protected computer and in a password protected file separate from the data. All clinical data will be entered in RedCap, a secure web-based data management system provided by the Clinical Translational Science Institute at UCLA that only the research team will have access to. Continuous data generated from the radiological studies will be entered into a password protected Excel Sheet, on a password protected computer, that only the study team has access to. Research MRI data and analyzed information will be stored on a password protected computer with encrypted storage media.

All informed consents/assents will be stored in Dr. Calkins' office, which is only accessible with a key by the study team, in a locked cabinet in accordance to local IRB guidelines.

SECTION 3. METHODS

3.1 STUDY POPULATION

In this study, anticipating a 10-15% dropout rate, we plan to recruit 18 mothers: 6 healthy pregnant women, 6 women with IUGR fetuses, and 5 mothers with gestational diabetes.

3.1.1 INCLUSION AND EXCLUSION CRITERIA

INCLUSION CRITERIA:

- Pregnant women with singleton pregnancies (healthy cohort)
- Pregnant women with fetuses with weights < 10th percentile weight for gestational age (IUGR cohort)
- Pregnant women with gestational diabetes (diabetes cohort)

EXCLUSION CRITERIA:

- Pregnant minors
- Major congenital anomalies or disease processes in the fetus
- Fetus with known chromosomal anomalies
- Mothers who do not plan to deliver at UCLA
- Multiple pregnancy (i.e. twins, triplets, etc)
- History of claustrophobia
- Contraindications to MRI such as metallic devices in the body that are not MRI compatible

3.2.1. SCREENING

Screening will occur by a variety of methods by all primary investigators, collaborators and their colleagues. Medical charts for the potentially eligible subjects at UCLA Obstetrics and Gynecology clinics will be screened to determine eligibility by PI Strobel and collaborators. A HIPAA waiver will be obtained and the information will only be collected if consent is provided. The number of subjects screened, eligible, and consented will be recorded to track recruitment.

3.2.2. CONSENT/ASSENT PROCEDURES

Consent/assent will be obtained before enrollment for all subjects and per local institutional review board guidelines. Consent will be diligently sought in an ethical manner and obtained using a multidisciplinary approach (research coordinator, principal investigators and co-investigators). Consents/assents will be provided to both English and Spanish; the process of consenting/assenting will occur in the subject's primary language. Subjects will be provided with written material, including a study flier/brochure, and will be given ample time to review the material and to ask questions. Consent will also be obtained again prior to MRI procedure.

The research team will work with the primary medical team to coordinate the introduction of the study either before or after their medical visit in order minimize disturbing the family and work-flow of the clinic.

3.2.3. MRI IMAGING AND CLINICAL INFORMATION OBTAINED

A. MRI Exams

All MRI scans will be performed on 3 T scanners (e.g., Skyra or Prisma, Siemens) in the outpatient Magnetic Resonance Research Center (MRRC) at 300 UCLA Medical Plaza without sedation. Our newly developed FB-MRI quantification technique leverages a multi-echo 3D stack-of-radial sampling trajectory with golden-angle acquisition ordering to suppress motion artifacts and enable free-breathing imaging of the abdomen in around 5 minutes. In addition, our FB-MRI technique is compatible with data under sampling to accelerate the free-breathing scan to 1-2 min. In this study, we will optimize the parameters of our FB-MRI technique (spatial resolution, spatial coverage, acceleration factor) to balance trade-offs between scan time, image quality, fat quantification accuracy, and patient comfort/compliance. Subjects will be provided ear plugs to limit amount of noise from MRI machines. Time to complete scan and study will be recorded.

B. Clinical Information Obtained:

Data will be collected and include: maternal age, gravida and para status, gestational age at time of image, gestational age at birth, maternal demographic data, maternal anthropometrics, and pregnancy information. Neonatal data will also be collected such as delivery, demographics and anthropometrics. This information will be collected and entered into a web-based database (RedCap) using coded name.

C. MRI Data Analysis:

MRI scans will be reviewed by co-investigator Dr. Masamed and any clinically concerning incidental findings will be reported to the primary care clinician. No formal interpretation is rendered, and copies of images cannot be provided. MRI data will be reconstructed by Siemens scanner software to produce 3D fat-water separated images and PDFF maps. The FB-MRI radial data will be transferred to a separate workstation for custom reconstruction of 3D fat-water-separated images and PDFF maps and analysis. PDFF values will be directly measured from regions of interest in the 3D PDFF maps to characterize fat content. The distribution/extent of subcutaneous fat, visceral fat, and brown fat will be manually delineated/drawn on the 3D MRI images and PDFF maps and used to calculate volume of different types of adipose tissue. This work will be performed by PI Strobel with validation from PI Wu.

D. Satisfaction Survey:

A satisfaction survey will be obtained from participant regarding consent process, coordination of scan, MRI scan time and how we can improve our study.

SECTION 4. ANALYTICAL PLAN

4.1 SAMPLE SIZES AND POWER ESTIMATES

This study will not be powered considered that this is a pilot study. Previous studies by our group in infants/children have used a sample size of 10 to 20 subjects, and these sample sizes were feasible and adequate to develop a new protocol

4.2 AVAILABLE POPULATION

Recruitment will occur in the UCLA Santa Obstetrics and Gynecology clinic (2001 Santa Monica Blvd. Santa Monica, CA), UCLA Westwood Obstetrics and Gynecology clinic (200 Medical Plaza St. Los Angeles, CA), and UCLA Maternal Fetal Medicine clinic (200 Medical Plaza. Los Angeles, CA). We anticipate based on available data, that there are approximately 10 mothers with growth restricted fetuses per month seen in the UCLA maternal fetal medicine clinic. There are approximately 12 mothers with gestational diabetes seen per month per Obstetrics and Gynecology clinic (Westwood and Santa Monica). There are approximately 40 healthy mothers seen per month per clinic.

4.3 PROJECTED RECRUITMENT TIME

Based on the available population and expected consent rate, we anticipate it will take approximately six months to recruit mothers for each cohort. Patients will have MRIs performed in the third trimester (28 weeks to 40 months), and infant data will be collected after completion of pregnancy.

Table. Study timeline, * means completed

Career Development Plans	Y1	Y2	Y3
-IRB approval for prospective study	X		
-Complete retrospective data analysis	X		
-Meet with OB groups for patient recruitment	*		
-Prospective study fetal MRI data collection		X	X
-Complete data collection, prepare manuscript, and submit abstracts		X	X

4.4 STATISTICAL ANALYSIS PLAN

Comparisons will be considered statistically significant at the $p<0.05$ level. No adjustments for multiple comparisons will be made considering the exploratory nature of this study. The effect sizes measured in this exploratory grant will be used as the basis for power calculations for future grant applications.

Data will be reported in terms of medians and interquartile ranges and frequencies. Ultrasound growth parameters and birth growth parameter z-scores will be calculated per fetal growth, WHO, and Fenton growth charts, respectively. Generalized linear models for repeated measures will be used to compare weight and length z-scores to each type of adipose volume and PDFF measurement. Generalized linear models for repeated measures will be used to compare maternal BMI prior to pregnancy to adipose tissue volumes and PDFFs. Generalized linear models for repeated measures will be used to compare ultrasound growth parameters to adipose tissue volumes and PDFFs. ANOVA analyses will compare visceral, subcutaneous, and brown adipose tissue volumes, and hepatic PDFF across different groups (gestational diabetes, IUGR and healthy infants).

4.5 DATA MONITORING PLAN

A Data Safety Monitoring Plan is not required considering the nature of this study.

SECTION 5. ADVERSE EVENTS

5.1 Report adverse events

Any adverse events will be reported to the OHRPP.

5.2 Potential Adverse Events

There is some risk with MRI that are similar to risks associated with a clinical MRI.. While the time required is limited, there is risk for claustrophobia.. in order to minimize this risk, mothers with a history or suspicion of claustrophobia will be excluded from participation. Morever, should the subject experience any sensation of claustrophobia, the research related procedure will be terminated. Should claustrophobia occur, terminating the FB-MRI will result in the alleviation of symptoms. Noise from the scanner during MRI exam will be mitigated by providing earplugs and headsets to the patients/subjects. Lastly, because of MRIs using a magnetic fields, subjects with any metal will be excluded from the study. All subjects will be asked to remove any metal objects prior to study (e.g. earrings, belts).

Because there is a component of chart review required, there is a possibility of breech of confidentiality. However, all precautionary measurements will be taken to ensure that confidentiality and privacy are maintained, and data will be stored securely. All conversations with subjects will occur in a private setting. All personal information, research data and records will be de-identified, coded and securely stored to prevent access by unauthorized personnel.

5.3 Interim Monitoring Plan and Stopping Rules

We will not conduct a preliminary analysis.

REFERENCES

1. Hales CM et al. Prevalence of obesity among adults and youth: United States, 2015–2016 (2017). NCHS data brief, no 288. Hyattsville, MD: National Center for Health Statistics.
2. Mauno Vanhala. Childhood weight and metabolic syndrome in adults (1999). Annals of Medicine, 31:4, 236-239. DOI: 10.3109/07853899908995885
3. Thorn Stephanie Ret al. The Intrauterine Growth Restriction Phenotype: Fetal Adaptations and Potential Implications for Later Life Insulin Resistance and Diabetes (2011). Semin Reprod, 29 (3): 225-236
4. Ross MG and Desai M. Developmental programming of offspring obesity, adipogenesis, and appetite (2013). Clin Obstet Gynecol, 56(3):529–536. doi:10.1097/GRF.0b013e318299c39d
5. Vohr & Boney. Gestational diabetes: The forerunner for the development of maternal and childhood obesity and metabolic syndrome? (2008). The Journal of Maternal-Fetal & Neonatal Medicine, 21:3, 149-157,DOI: 10.1080/14767050801929430
6. Hillier TA et al. Childhood Obesity and Metabolic Imprinting (2007). Diabetes Care, 30 (9) 2287-2292; DOI: 10.2337/dc06-2361
7. Wang, Y et al. Predictive value of visceral adiposity index for type 2 diabetes mellitus (2015). *Herz* 40, 277–281 doi:10.1007/s00059-014-4175-1
8. Pfister KM et al. Early body composition changes are associated with neurodevelopmental and metabolic outcomes at 4 years of age in very preterm infants (2018). *Pediatr Res* 84(5):713–718. doi:10.1038/s41390-018-0158-x
9. Hui LL, Schooling CM, Leung SS, et al. Birth weight, infant growth, and childhood body mass index: Hong Kong's children of 1997 birth cohort (2007). *Arch Pediatr Adolesc Med*. 162(3):212–218. doi:10.1001/archpediatrics.
10. Virtanen KA et al. Functional brown adipose tissue in healthy adults (2009). *N Engl J Med* 360(15):1518–1525. doi:10.1056/NEJMoa0808949
11. Li Q et al. Resveratrol derivative BTM-0512 mitigates obesity by promoting beige remodeling of subcutaneous preadipocytes (2017). *Acta Biochim Biophys Sin (Shanghai)*. 49(4):318–327. doi:10.1093/abbs/gmx009
12. Bosch TA et al. Visceral adipose tissue measured by DXA correlates with measurement by CT and is associated with cardiometabolic risk factors in children (2015). *Pediatr Obes*. 10(3):172–179. doi:10.1111/ijpo.249
13. Chu C, Zhao S, Ding M, et al. Combining Clinical Characteristics and Specific Magnetic Resonance Imaging Features to Predict Placenta Accreta. *J Comput Assist Tomogr*. 2019;43(5):775–779. doi:10.1097/RCT.0000000000000894
14. Armstrong T et al. Free-Breathing Liver Fat Quantification using a Multiecho 3D Stack-of-Radial Technique (2018). Magnetic Resonance in Medicine; 79(1):370-382.
15. Armstrong, T et al. 3D mapping of the placenta during early gestation using free-breathing multiecho stack-of-radial MRI at 3T (2019). J. Magn. Reson. Imaging, 49: 291-303. doi:10.1002/jmri.26203
16. Armstrong T et al. Free-Breathing Quantification of Hepatic Fat in Healthy and NAFLD Children Using a Multiecho 3D Stack-of-Radial MRI Technique (2018). Pediatric Radiology, 48:941-953.
17. Ly K et al. Free breathing MRI Assessment of Body Composition in Healthy and Overweight Children—An Observational Study (2019). Journal of Pediatric Gastroenterology and Nutrition: 68 (6), 782-787. doi: 10.1097/MPG.0000000000002309

18. Armstrong, T. et al. Free Breathing 3D Quantification of infant body composition and hepatic fat using a stack-of-radial magnetic resonance imaging technique. Pediatr Radiol (2019) 49: 876. https://doi.org/10.1007/s00247-019-04384-7
19. Berger-Kulemann et al. (2011). Quantification of the subcutaneous fat layer with MRI in fetuses of healthy mothers with no underlying metabolic disease vs. fetuses of diabetic and obese mothers. *Journal of Perinatal Medicine*, 40(2), pp. 179-184. Retrieved 12 Jan. 2020, from doi:10.1515/jpm.2011.122
20. Anblagan et al. Measurement of fetal fat in utero in normal and diabetic pregnancies using magnetic resonance imaging (2013). Ultrasound in obstetrics and gynecology 42:3.
21. Blondiaux et al. Developmental patterns of fetal fat and corresponding signal on T1-weighted magnetic resonance imaging (2018). Pediatric Radiology 48:317–324
22. Victoria, T., Jaramillo, D., Roberts, T.P.L. et al. Fetal magnetic resonance imaging: jumping from 1.5 tesla to 3 tesla (2014). Pediatr Radiol 44: 376. https://doi.org/10.1007/s00247-013-2857-0