

Original article

A Retrospective segmentation analysis of placental volume by magnetic resonance imaging from first trimester to term gestation

Rachel L. León, Kevin T. Li, Brandon P. Brown

Abstract

Background: Abnormalities of the placenta affects 5-7% of pregnancies. Since disturbances in fetal growth are often preceded by dysfunction of the placenta and/ or attenuation of its normal expansion, placental health warrants careful surveillance. Currently, there is limited normative data available for placental volume by magnetic resonance imaging (MRI).

Objective: To determine normative ranges of placental volume by MRI throughout gestation.

Materials and Methods: In this cross-sectional retrospective analysis, MRI examinations of pregnant females obtained between 2002 and 2017 at a single institution were reviewed. Semi-automated segmentation of the placenta was performed in images obtained on patients with no radiologic evidence of maternal or fetal pathology, using Philips Intellispace Tumor Tracking Tool.

Results: Placental segmentation was performed in 112 women and had a high degree of interrater reliability (single measure intraclass correlation coefficient = 0.978 with 95% CI 0.956, 0.989; $p < 0.001$). Normative data on placental volume by MRI increased nonlinearly from 6 and 39 weeks gestation, with wider variability of placental volume at higher gestational age (GA). Placental volumetric data was fit to a polynomial curve of third order described as placental volume = $-0.02 \cdot GA^3 + 1.6 \cdot GA^2 - 13.3 \cdot GA + 8.3$. Placental volume showed positive correlation with estimated fetal weight ($p = 0.03$) and birth weight ($p = 0.05$).

Conclusion: This study provides normative placental volume by MRI from early first trimester to term gestation. Deviations in placental volume from normal may prove to be an imaging biomarker of adverse fetal health and neonatal outcome and further studies are needed to more fully understand this metric.

Assessment of placental volume should be considered in all routine fetal MRI examinations.

This is the author's manuscript of the article published in final edited form as:

León, R. L., Li, K. T., & Brown, B. P. (2018). A retrospective segmentation analysis of placental volume by magnetic resonance imaging from first trimester to term gestation. *Pediatric Radiology*, 48(13), 1936–1944. <https://doi.org/10.1007/s00247-018-4213-x>

Introduction

Abnormalities of the placenta affects 5-7% of pregnancies [1, 2]. Evidence is accumulating that the placenta is directly responsible for both the immediate and long-term health of the fetus [3, 4]. Fetal growth is the primary indicator of overall fetal health, and birth weight is strongly linked to infant survival [5]. Since disturbances in fetal growth are often preceded by dysfunction of the placenta and/or attenuation of its normal expansion [6], placental growth and development warrant careful surveillance. Normal placental imaging demonstrates increasing size and heterogeneity as gestation progresses (Fig. 1), but this progression does not always occur. Imaging studies that can identify predictors of impending fetal growth disruption should be a major focus of efforts to improve fetal and neonatal health outcomes. Abnormal placental volume may prove to be an imaging biomarker of an adverse fetal environment and provide an opportunity for intervention before fetal health is compromised.

Evaluation of the placenta is part of routine antenatal ultrasound (US), but the lack of soft tissue contrast and narrow field of view can limit this technique. Furthermore, depending on placental location within the uterus, US may be limited by its ability to penetrate tissues. When fetal growth becomes compromised, umbilical artery Doppler US studies are frequently used to assess fetal blood supply and provide an indirect assessment of the placenta. Noncontrast MR imaging has become more accessible and useful for more detailed evaluation in the setting of fetal anomalies, but currently, little to no quantitative information about the placenta is obtained from these studies. One contributor to our limited understanding of abnormal placental growth is the lack of established normative data, particularly normal ranges for placental volume by MRI. In 2001, Duncan, *et al.* published the first large scale study of fetal organ volume and placental volume throughout gestation using echo-planar MRI at 0.5 Tesla [7]. In 2016, those ranges were updated in a study of placental growth by MRI at 1.5 Tesla in the second and third trimesters in a longitudinal cohort of 20 healthy pregnant women [8]. However, little is known about placental volume in the first trimester or if this small sample size accurately represents population norms, as no larger studies have replicated these findings to date.

The objective of our study was to determine placental volume by MRI from early first trimester to term gestation. We used semi-automated segmentation of the placenta to create normative ranges of placental volume by MRI throughout gestation in a radiologically normal cohort of pregnant women.

Material and Methods

Study Participants

The Institutional Review Board of our academic health care system approved this retrospective cross-sectional imaging study with waiver of participant consent. The institutional radiology database was queried for MR imaging of pregnant females between 2002 and 2017 and images were categorized by diagnosis. Imaging was performed for a variety of clinical indications including concern for fetal pathology, suspected invasive placenta, or concern for maternal intra-abdominal inflammatory process. Imaging studies with any radiologic evidence of maternal or fetal pathology, as determined by the clinical radiology report and chart review, were excluded from analysis. Any immediate maternal or fetal postnatal abnormality documented in the chart was assessed for its impact on the placental size; studies with intrapartum documentation of placenta accreta were excluded from analysis. Imaging studies with multiple gestation were excluded from analysis, as well as imaging studies on fetuses who were later found to have pathology later in pregnancy or at birth. Studies from pregnancies resulting in a neonate with birthweight below the 3rd percentile or above the 97th percentile for GA were also excluded.

Maternal clinical and demographic information was obtained by retrospective chart review, including age, height, weight, BMI, gestational age (GA), parity, race, health conditions (specifically tobacco use, hypertension, and diabetes) and medications used during pregnancy. Gestational age was determined by either first trimester US or last menstrual period. In patients for whom GA information was not available in the maternal medical record, MRI measures of the fetal biparietal diameter, anteroposterior cerebral dimension, anteroposterior pons, transverse cerebellar dimension, overall brain maturation, and femur length were compared to published normative data to determine GA at time of MRI [9]. Clinical information about the fetus was obtained by chart review and included fetal sex,

estimated fetal weight percentile by US obtain within 30 days of MRI; and for those infants that were later born within our medical system, GA at delivery, and growth parameters at birth including weight, length and occipito-frontal circumference.

MRI Studies

Imaging studies were obtained on a Siemens 1.5 tesla scanner between years 2002 and 2013 (MAGNETOM Avanto-Fit; Siemens, Erlangen, Germany) and on a Siemens 3.0 tesla scanner between 2014 and 2017 (MAGNETOM Skyra; Siemens, Erlangen, Germany). Exact pulse sequences differed depending on the indication for MRI but placental segmentation was performed using either the half-Fourier acquisition single-shot fast spin-echo (SSFSE) sequence or the balanced steady-state free precession (SSFP) gradient echo sequence. All scans utilized for placental segmentation included three planes of imaging.

Image Analysis

Magnetic resonance studies, prior to segmentation, were reviewed to ensure adequate quality of placental imaging and those with inadequate visualization of the placenta (partially outside field of view, low resolution, or motion artifact) were excluded from analysis (n=43). Semi-automated placental segmentation was performed on images in the maternal axial plane, which frequently (but not uniformly) corresponded to the placental axial plane. We found that this plane allowed for clearest demarcation of placental margins (Fig. 2). Segmentation was performed by a single observer (R.L.L., physician in fellowship) using Philips Intellispace® software Tumor Tracking Tool (Koninklijke Philips N.V., Amsterdam, Netherlands). Although propagation of the region of interest (ROI) with edge detection occurred automatically through the image series, manual adjustment of the ROI was performed in each slice of the selected sequence to ensure accuracy. Volume of the ROI was calculated based on slice thickness by the software and recorded for analysis. A subset of images of the study population were measured by a second observer (B.P.B., pediatric radiologist, 5 years post-fellowship experience) to assess interrater reliability.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics 24 (IBM, Armonk, New York, USA). Placental volume data was fit to a polynomial curve of third order and differences from expected placental volume based on the equation of the best-fit curve were calculated for each patient measurement. Correlation of the nonparametric placental volume data with continuous, nominal or ordinal dependent variables was determined by the Spearman's *rho*, Mann-Whitney U, or Kruskal-Wallis tests, respectively. Intraclass correlation coefficient (ICC) using a two-way random model to measure absolute agreement was calculated to determine interrater reliability on a subset of the total population analyzed [10]. For all analyses, the level of significance was set at $p < 0.05$.

Results

Study Population

A total of 1,010 abdominal or fetal MR imaging studies of pregnant women were performed at our institution between 2002 and 2017 for concern for maternal or fetal pathology. There was a total of 848 studies excluded from analysis due to positive finding of radiologic abnormality in mother or fetus, leaving 155 studies (16%) with no maternal or fetal radiologic abnormality. A total of 43 studies were excluded due to inadequate placental imaging, an additional 4 studies were excluded due to multiple gestation, and 3 studies were excluded due to neonatal birthweight $<3^{\text{rd}}$ percentile or greater than 97^{th} percentile (Fig. 3). Placental segmentation was performed on a total of 112 MRI. Gestational age at time of MRI ranged from 6 to 39 weeks. There were seven MRI studies for which GA was not available and was determined by fetal biometry. Maternal age ranged from 16 to 45 years with an average age of 26 years. Of the included women, 25% were primiparous, 42% were multiparous, 18% were grand-multiparous (gravida 5 or more) and 15% had no available information on parity. The clinical indication for MRI was divided nearly equally between maternal (48%) and fetal concerns (46%). An additional 6% of MR imaging examinations came from healthy volunteers recruited in a prior investigation (Table 1). The majority of maternal indication for MRI were right lower quadrant pain with no abnormality on imaging and the majority of the fetal indications were concern for absent cavum septum pellucidum

ultimately found to have normal anatomy on MRI. Neonatal characteristics were available for 60% of the study population. Neonates delivered on average at 38 2/7 weeks gestation and weighed an average of 3,181 grams at birth.

Placental Volume

Between six and nine weeks gestation the mean placental volume was 10.1 mL, which increased to a mean of 1,039 mL by term (Table 2). The equation that best described the placental volume increase throughout gestation in this population ($R^2 = 0.75$) is reported below, where GA is expressed in weeks (Fig. 4):

$$\text{Placental volume} = -0.02*GA^3 + 1.6*GA^2 - 13.3*GA + 8.3$$

A high degree of interrater reliability was found between the subset of placental volume measurements representing 30% of the total population studied, with an average measure ICC of 0.978 (95% CI = 0.956, 0.989; $p < 0.001$). No subjective difference in placental volume or ability to discern placental margins was noted between imaging studies at 1.5 versus 3.0 Tesla or based on sequence used to perform segmentation (SSFP versus SSFSE). Placental location within the uterus was recorded, with most placentae located anteriorly (47%), followed by 38% in posterior position, and 5% located laterally. Inferiorly located placentas in this cohort were exclusively observed in women in the first trimester of pregnancy and any imaging with the finding of placenta previa beyond the first trimester was deemed abnormal and excluded from analysis.

Spearman's *rho* test for this nonparametric data set demonstrated no correlation between placental volume and maternal pre-pregnancy weight, height, BMI, or age (Table 3). There was a positive correlation between estimated fetal weight and placental volume ($\rho = 0.378$, $n = 32$, $p = 0.03$). Birth weight percentile had a similar positive association with placental volume ($\rho = 0.249$, $n = 61$, $p = 0.05$). In the few cases of maternal hypertension ($n = 12$) in our data set, no statistically significant differences in placental volume were measured ($p = 0.90$). Similarly, for those with maternal diabetes mellitus ($n = 8$), no correlation with placental volume was found ($p = 0.90$). Information on maternal medications and level of

control of these conditions were not available. Tobacco use was documented in the medical chart of 27 women in the study, but no information on amount or duration was recorded, and there was no significant association with placental volume ($p=0.11$).

Discussion

The present study provides normative placental volume by MRI measured as early as 6 weeks gestation and as late as 39 weeks gestation in 112 women whose imaging studies showed no fetal or maternal radiologic abnormalities. We found a nonlinear relationship between placental volume and GA with increasing variability in placental volume at higher gestational ages. A large portion of our sample data represent the time when most women would be referred for fetal MRI in response to concerns on US in the mid-second trimester. Our results add to the placental volume data reported in recent MRI placental segmentation studies with smaller cohorts [8, 11, 12].

In the prospective study by Langhoff, *et al.*, the authors provide longitudinal placental volume in seven repeated MRI scans from second trimester to term gestation in a cohort of 20 healthy, primiparous women using no medications and with body mass index of 18 to 30 [8]. This data set has the advantage of excluding women with complicating conditions that likely affect placental volume. Langhoff *et al.* also performed placental segmentation seven times on each participant, providing information on interval placental growth. Our placental volume data are significantly higher, particularly at higher GA compared to Langhoff *et al.*, slightly lower than those reported by Duncan *et al.*[7], and very close to those described by Andescavage *et al.* [11]. For example, placental volume at term gestation is approximately 1,250 mL in the report by Duncan *et al.*, compared to our volume of 1,039 mL between 37 and 40 weeks, approximately 1,000 mL at term by Andescavage *et al.*, and 787 mL between 37 and 39 weeks in the report by Langhoff *et al.* These variations can likely be attributed to differences in populations studied, imaging equipment, segmentation tools, and technical experience. Both our patient population and the one described by Duncan *et al.* include a large number of multiparous women, which has been shown in

previous studies to be associated with larger volume of the delivered placenta [13]. In addition, Duncan *et al.* obtained images with 0.5 Tesla MRI, which likely affected resolution and complicated determination of the placental plane at the basal plate [7]. At both 1.5 and 3.0 Tesla magnetic strengths, we found that placental contrast with amniotic fluid at the chorionic plate was easily visualized in all sequences, but the demarcation of the basal plate was slightly more difficult to discern in our earlier studies at lower magnetic field. We observed that these tissue planes are equally discernible on both SSFSE and SSFP sequences.

There were also differences in segmentation software used in each of these studies. Andescavage *et al.* utilized ITK-SNAP, while Langhoff *et al.* measured placental volume with a segmentation tool by Circle Cardiovascular Imaging, Inc. Our use of the Philips Intellispace Tumor Tracking Tool for segmentation analysis allows our results to be comparable to those obtainable by most radiologists who evaluate fetal MR imaging. This tool allows users to reproducibly measure the placenta in multiple places of MR imaging sequences. Although the Tumor Tracking Tool was created for the purposes of repeated measures of tumors to determine response to chemotherapy, this segmentation tool demonstrated excellent precision with only 0.1 – 0.6 cm³ discrepancy in tumor volume by imaging compared with excised hepatic tumor size in rabbits [14]. In addition, our interrater reliability statistics demonstrate a high degree of reproducibility of placental volume measurements by this method.

Alternative methods of placental volumetric analysis have been reported previously with US imaging comprising the majority of these studies. New US technologies have been developed to render three-dimensional organ reconstructions and have proven useful in assessing placental shape, but have limitations in volumetric analysis. Namely, the low soft tissue contrast limits the ability to clearly discern the tissue plane that creates the interface between uterus and basal plate of the placenta. Likewise, the narrow field of view of US limits full visualization of the placenta, forcing software and technician to piecemeal together imaging of the complete organ. Placental volumetric analysis by US, therefore, has had varying degrees of success [15-24] with some reports showing low levels of intra- and interrater reliability [17, 24, 25]. Volumetric analysis of the placenta by US is most concordant with MRI

measurements in the first trimester [16, 18, 23] as later US measurements significantly underestimate placental volume. Placental volumes from term pregnancies reported in some studies are significantly less than the delivered, partially exsanguinated placenta [15, 19], underscoring the fact that US is not the ideal imaging technique for placental volume beyond the first trimester. Compared to one of the largest US placental volumetric analyses reports [15], our data correlate well in the first half of pregnancy, but show increasingly larger discrepancies beyond the second trimester. Although this US study has the benefit of including 423 patient measurements, it is limited by the fact that most placental volume measures were obtained at 12 and 20 weeks gestation, thus relying heavily on extrapolation to determine the remainder of the placental growth curve.

With US readily available in most obstetric practices and significantly more cost-effective than MRI, it is well-suited as a screening examination for abnormalities of the placenta. In our retrospective cohort, only 16% of patients referred for fetal MRI due to concerns for maternal or fetal abnormalities over the 15-years of this study, were found to be radiologically normal, demonstrating the high specificity of prenatal US in identifying fetal anomalies. Increasing evidence suggests that MRI provides reliable additional data useful for prognostication, treatment planning, and even guidance for intrauterine intervention, for those select cases where it is indicated. Its utility has been particularly well-established for evaluation of fetal intracranial anomalies. Accordingly, the number of referrals for fetal MRI are steadily increasing at our institution.

Despite the advantages of MRI to study the intrauterine environment, there are limitations to studies, such as the one presented here. Our data is limited by its observational nature. Each patient in our study was referred for MRI for a specific maternal or fetal concern, demonstrating a potential selection bias in our population, although only imaging without radiologic abnormalities was included in our analysis. In addition, our study population reflects the demographics of our location with few non-Caucasian women and a high number of overweight and obese women in this cohort, although no correlation was found between placental volume and weight or BMI. As with all retrospective studies, we cannot draw conclusions on the causative relationships between placental volume and clinical factors

analyzed here. Information on maternal hypertension, diabetes, and tobacco use was collected by medical chart review, but was only available for 82% of subjects, and there were no data collected on whether medical management of these conditions was successful. Likewise, fetal outcome and growth parameters at birth were unknown for a large portion of our study participants, as many women who underwent MRI received the remainder of their obstetric care outside our hospital system. These limitations highlight the need for future investigations of placental volume in larger, prospective cohorts in a more diverse study population. Future studies, should not, however, be limited to primiparous women or only those with normal BMI, as this does not accurately reflect population norms. Future investigations may also examine changes in placental signal intensity compared to an internal control, such as muscle, to determine whether this may be predictive of placental abnormalities. In addition, studies of placental volume in patients with maternal and fetal pathology will also be necessary to clarify how this metric can best be used to identify fetuses at risk of impaired placental growth.

A key question raised by this study is the physiologic relevance of placental volume; specifically, how placental volume relates to placental function *in vivo*. We do not yet know whether a larger placenta uniformly enhances blood flow to the fetus, or whether in some cases, placental growth may be deleterious to fetal health. The case of the morbidly adherent placenta poses a particularly uncertain clinical scenario. With Cesarean section rates (the greatest risk factor for morbidly adherent placenta) climbing [26], studies suggest that we should expect increasing incidence of morbidly adherent placenta. Understanding the hemodynamic effects of the invasive placenta will be paramount to the obstetric management of these patients. Advanced MRI analysis techniques evaluating placental function, such as intravoxel incoherent motion (IVIM) of diffusion-weighted imaging have promising application to placental imaging research, specifically in elucidating the hemodynamic consequences of abnormal placental volume [27-30].

Alterations of placental structure and function in cases of fetal pathology are also poorly understood. In fetuses with congenital heart disease, placental growth as compared to birthweight percentile is larger than in healthy fetuses [11]. This may be interpreted as placental compensation for the

structurally abnormal heart and subsequent disruption of normal blood flow patterns resulting in decreased oxygen delivery to target organs. In fetal gastroschisis, we know that placental microstructure is altered, with evidence of vascular hyperplasia or chorangiogenesis reported within the terminal chorionic villi of delivered placentas from these patients [31]. Chorangiogenesis is thought to arise in states of chronic low-level hypoxemia, as encountered with gestation at high altitude [32]. Coupled with the high rate of intrauterine growth restriction in cases of gastroschisis, the conclusion arises that this placental remodeling is likely associated with an attempted compensation of the organ. How this structural change at the microscopic level translates into a functional compensation of the placenta *in vivo* remains unknown. Abnormalities of the placenta in other forms of fetal pathology are less well defined. Since the placenta is almost entirely of fetal origin, there is good reason to postulate that aberrations in placental structure and/or function may exist concomitant with other forms of fetal pathology.

In addition, many studies exist establishing the effects of maternal exposures on placental growth and subsequent effects on the fetus. Perhaps the best studied of these is maternal smoking, which has well known deleterious effects on placental and fetal growth [33] and imparts significantly elevated risk of both fetal and early neonatal mortality [34]. Pathologic characteristics of the placenta exposed to maternal smoking include decreased placental vascularization, thickening of the villous and trophoblast membranes, and higher rates of syncytiotrophoblastic necrosis [35]. Using MR imaging, Anblagan, *et al.* demonstrated that maternal smoking is associated with smaller fetal organ size including reduced brain and placenta volume [33]. Contrast-enhanced MR imaging studies in non-human primates have shown that nicotine exposure alone also adversely affects placental hemodynamics [36]. Similar studies demonstrating *in vivo* functional effects of maternal smoking on the placenta in humans have not yet been reported. Maternal diabetes is also a well-defined fetal exposure with adverse effects. It leads most often to increased placental volume and surface area at birth but with villous immaturity [37]. As in maternal smoking, the *in vivo* characterization of dysglycemia on the placenta is uncertain. The use of advanced MR imaging techniques may be the key to understanding the pathophysiology of these and other specific exposures on

placental structure and function.

Conclusion

This study provides normative placental volume ranges by MRI from early first trimester to term gestation. Future studies are indicated to determine normative placental volume in larger and more diverse populations in order to further refine this metric, which may prove to be an imaging biomarker of fetal and neonatal health outcomes. Assessment of placental volume should be considered in all routine fetal MRI examinations.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of retrospective study, formal consent is not required.

Table 1. Patient Characteristics.

Total MRI Analyzed	112
GA in weeks at MRI, mean (range)	25 6/7 (6 0/7 - 39 3/7)
Maternal age in years, mean (range)	26.7 (16 - 45)
Parity, n (%)	
Primiparous	28 (25)
Multiparous	47 (42)
Grand Multiparous (G5+)	20 (18)
Unknown	17 (15)
Race or Ethnicity, n (%)	
Caucasian	71 (63)
African-American	24 (21)
Asian	4 (3)
Hispanic	1 (<1)
American-Indian	1 (<1)
Unknown	11 (10)
Maternal BMI, n (%)	
Underweight (BMI <18.5)	2 (2)
Normal weight (BMI 18.5-25)	28 (25)
Overweight (BMI 25-30)	17 (15)
Obese (BMI >30)	23 (20)
Unknown	42 (38)
Indication for MRI, n (%)	
Maternal	50 (48)
Fetal	55 (47)
Clinical Study	7 (6)

GA: gestational age; **BMI:** body mass index

Table 2. Placental volume characterized by gestational age.

Weeks Gestation (n)	Range Placental Volume (mL)	Mean Placental Volume (mL)	SD	SEM
6 0/7 to 9 6/7 (3)	8.4 - 11.8	10.1	1.7	1.0
10 0/7 to 12 6/7 (5)	19 - 44	36.0	9.9	4.4
13 0/7 to 15 6/7 (5)	21 - 121	69.4	41.7	18.6
16 0/7 to 18 6/7 (7)	75 - 257	146.2	79.9	39.9
19 0/7 to 21 6/7 (9)	182 - 355	251.2	66.9	22.3
22 0/7 to 24 6/7 (18)	199 - 689	367.8	129.5	30.5
25 0/7 to 27 6/7 (20)	259 - 637	460.8	89.3	20.5
28 0/7 to 30 6/7 (15)	334 - 1024	561.7	193.6	50.0
31 0/7 to 33 6/7 (10)	373 - 1145	693.0	193.3	61.1
34 0/7 to 36 6/7 (17)	432 - 1090	717.9	194.8	47.2
37 0/7 to 40 6/7 (3)	883 - 1262	1039.3	198.0	114.3

SD: standard deviation; SEM: standard error of the mean

Table 3. Spearman's ρ correlation with placental volume.

	n	Mean (SD)	ρ	p-value
Maternal Age (years)	112	26.7 (6.2)	0.106	0.27
Maternal Weight (kg, pre-pregnancy)	70	74.6 (19.4)	0.118	0.33
Maternal Height (cm)	73	164 (7.1)	0.054	0.65
Maternal BMI (pre-pregnancy)	70	27.9 (7.6)	0.103	0.40
Estimated Fetal Weight Percentile	32	28.9 (25.5)	0.378*	0.03*
Birth Weight Percentile	61	47.7 (27.6)	0.249*	0.05*
Birth Length Percentile	48	59.8 (27.2)	0.125	0.40

BMI: body mass index; SD: standard deviation; statistical significance indicated by * for $p < 0.05$.

Figure Legends

Fig. 1: Increasing heterogeneity and complexity of the placenta (*) across gestation in T2 single-shot fast spin-echo images in the coronal plane in 35 year old female at 10 weeks and 3 days gestation (A), in the axial plane in a 33 year old female at 23 weeks 5 days gestation (B), and in the axial plane in a 25 year old female at 37 weeks 6 days gestation (C).

Fig. 2: Placental segmentation using Philips Intellispace Tumor Tracking Tool performed on imaging study from 23 year old female at 33 weeks and 5 days gestation.

Fig. 3: Flow chart of study population with description and number of imaging studies excluded from analysis.

Fig. 4: Placental volume by gestational age in radiologically normal cohort of 112 pregnant women demonstrating nonlinear distribution of placental volume across gestation and increasing variability in placental volume at higher gestational ages, with best-fit curve described by the third order polynomial equation.

References

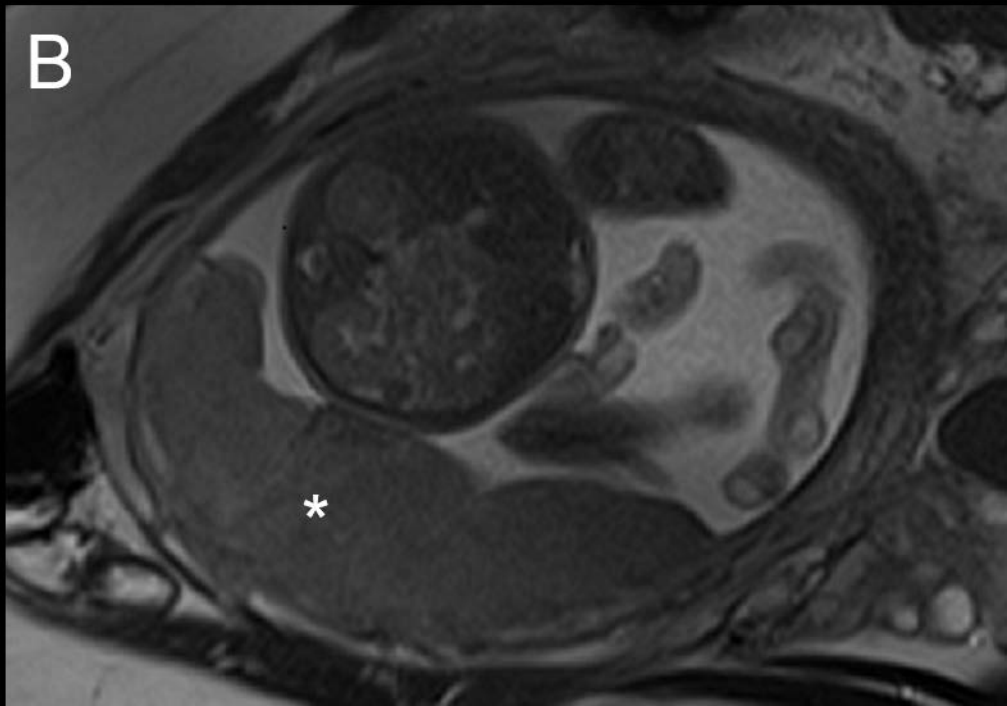
1. Silver RM (2015) Abnormal Placentation: Placenta Previa, Vasa Previa, and Placenta Accreta. *Obstetrics and gynecology* 126:654-668.
2. Hladunewich M, Karumanchi SA, Lafayette R (2007) Pathophysiology of the clinical manifestations of preeclampsia. *Clinical journal of the American Society of Nephrology : CJASN* 2:543-549.
3. Gluckman PD, Hanson MA, Cooper C, et al (2008) Effect of in utero and early-life conditions on adult health and disease. *The New England journal of medicine* 359:61-73.
4. Godfrey KM (2002) The role of the placenta in fetal programming-a review. *Placenta* 23 Suppl A:S20-27.
5. McIntire DD, Bloom SL, Casey BM, et al (1999) Birth weight in relation to morbidity and mortality among newborn infants. *The New England journal of medicine* 340:1234-1238.
6. Maulik D, Frances Evans J, Ragolia L (2006) Fetal growth restriction: pathogenic mechanisms. *Clinical obstetrics and gynecology* 49:219-227.
7. Duncan KR, Sahota DS, Gowland PA, et al (2001) Multilevel modeling of fetal and placental growth using echo-planar magnetic resonance imaging. *Journal of the Society for Gynecologic Investigation* 8:285-290.
8. Langhoff L, Gronbeck L, von Huth S, et al (2016) Placental Growth during Normal Pregnancy - A Magnetic Resonance Imaging Study. *Gynecologic and obstetric investigation*.
9. Kline-Fath B, Bahado-Singh R, Bulas D (2014) Fundamental and advanced fetal imaging: ultrasound and MRI. Lippincott Williams & Wilkins.
10. Koo TK, Li MY (2016) A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *Journal of chiropractic medicine* 15:155-163.
11. Andescavage N, Yarish A, Donofrio M, et al (2015) 3-D volumetric MRI evaluation of the placenta in fetuses with complex congenital heart disease. *Placenta* 36:1024-1030.
12. Derwig IE, Akolekar R, Zelaya FO, et al (2011) Association of placental volume measured by MRI and birth weight percentile. *Journal of magnetic resonance imaging : JMRI* 34:1125-1130.
13. Wallace JM, Bhattacharya S, Horgan GW (2013) Gestational age, gender and parity specific centile charts for placental weight for singleton deliveries in Aberdeen, UK. *Placenta* 34:269-274.
14. Pellerin O, Lin M, Bhagat N, et al (2013) Comparison of semi-automatic volumetric VX2 hepatic tumor segmentation from cone beam CT and multi-detector CT with histology in rabbit models. *Academic radiology* 20:115-121.
15. Arleo EK, Troiano RN, da Silva R, et al (2014) Utilizing two-dimensional ultrasound to develop normative curves for estimated placental volume. *American journal of perinatology* 31:683-688.
16. Aye CY, Stevenson GN, Impey L, et al (2015) Comparison of 2-D and 3-D estimates of placental volume in early pregnancy. *Ultrasound in medicine & biology* 41:734-740.
17. Cheong KB, Leung KY, Li TK, et al (2010) Comparison of inter- and intraobserver agreement and reliability between three different types of placental volume measurement technique (XI VOCAL, VOCAL and multiplanar) and validity in the in-vitro setting. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology* 36:210-217.
18. Collins SL, Stevenson GN, Noble JA, et al (2013) Rapid Calculation of Standardized Placental Volume at 11 to 13 Weeks and the Prediction of Small for Gestational Age Babies. *Ultrasound in Medicine and Biology* 39:253-260.
19. de Paula CF, Ruano R, Campos JA, et al (2008) Placental volumes measured by 3-dimensional ultrasonography in normal pregnancies from 12 to 40 weeks' gestation. *Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine* 27:1583-1590.

20. Pala HG, Artunc-Ulkumen B, Koyuncu FM, et al (2016) Three-dimensional ultrasonographic placental volume in gestational diabetes mellitus. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet* 29:610-614.
21. Simcox LE, Higgins LE, Myers JE, et al (2017) Intraexaminer and Interexaminer Variability in 3D Fetal Volume Measurements During the Second and Third Trimesters of Pregnancy. *Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine.*
22. Titapant V, Cherdchoogiat P (2014) Nomogram of placental thickness, placental volume and placental vascular indices in healthy pregnant women between 12 and 20 weeks of gestation. *Journal of the Medical Association of Thailand = Chotmai het thangphaet* 97:267-273.
23. Meengeonthong D, Luewan S, Sirichotiyakul S, et al (2017) Reference ranges of placental volume measured by virtual organ computer-aided analysis between 10 and 14 weeks of gestation. *Journal of clinical ultrasound : JCU.*
24. Jones NW, Raine-Fenning NJ, Mousa HA, et al (2011) Evaluating the intra- and interobserver reliability of three-dimensional ultrasound and power Doppler angiography (3D-PDA) for assessment of placental volume and vascularity in the second trimester of pregnancy. *Ultrasound in medicine & biology* 37:376-385.
25. Florido J, Ocon O, Luna del Castillo Jde D, et al (2014) Analysis of measurement process of placental volume in early pregnancy: an interobserver reliability study. *Journal of perinatal medicine* 42:559-564.
26. Zhang J, Troendle J, Reddy UM, et al (2010) Contemporary cesarean delivery practice in the United States. *American journal of obstetrics and gynecology* 203.
27. Alison M, Chalouhi GE, Autret G, et al (2013) Use of intravoxel incoherent motion MR imaging to assess placental perfusion in a murine model of placental insufficiency. *Investigative radiology* 48:17-23.
28. Moore RJ, Strachan BK, Tyler DJ, et al (2000) In utero perfusing fraction maps in normal and growth restricted pregnancy measured using IVIM echo-planar MRI. *Placenta* 21:726-732.
29. Sohlberg S, Mulic-Lutvica A, Lindgren P, et al (2014) Placental perfusion in normal pregnancy and early and late preeclampsia: a magnetic resonance imaging study. *Placenta* 35:202-206.
30. Siauve N, Chalouhi GE, Deloison B, et al (2015) Functional imaging of the human placenta with magnetic resonance. *American journal of obstetrics and gynecology* 213:S103-114.
31. Payne NR, Simonton SC, Olsen S, et al (2011) Growth restriction in gastroschisis: quantification of its severity and exploration of a placental cause. *BMC pediatrics* 11.
32. Tissot van Patot M, Grilli A, Chapman P, et al (2003) Remodelling of uteroplacental arteries is decreased in high altitude placentae. *Placenta* 24:326-335.
33. Anblagan D, Jones NW, Costigan C, et al (2013) Maternal smoking during pregnancy and fetal organ growth: a magnetic resonance imaging study. *PLoS one* 8:e67223.
34. Cnattingius S, Haglund B, Meirik O (1988) Cigarette smoking as risk factor for late fetal and early neonatal death. *Bmj* 297:258-261.
35. Jauniaux E, Burton GJ (2007) Morphological and biological effects of maternal exposure to tobacco smoke on the feto-placental unit. *Early human development* 83:699-706.
36. Lo JO, Schabel MC, Roberts VH, et al (2015) Vitamin C supplementation ameliorates the adverse effects of nicotine on placental hemodynamics and histology in nonhuman primates. *American journal of obstetrics and gynecology* 212:370.e371-378.
37. Huynh J, Dawson D, Roberts D, et al (2015) A systematic review of placental pathology in maternal diabetes mellitus. *Placenta* 36:101-114.

A

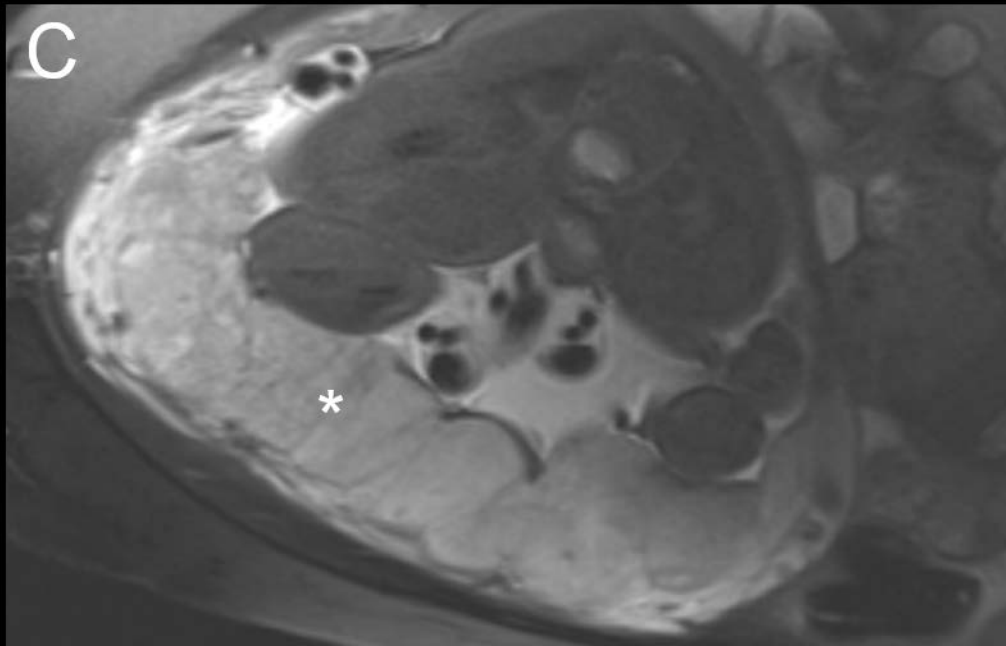


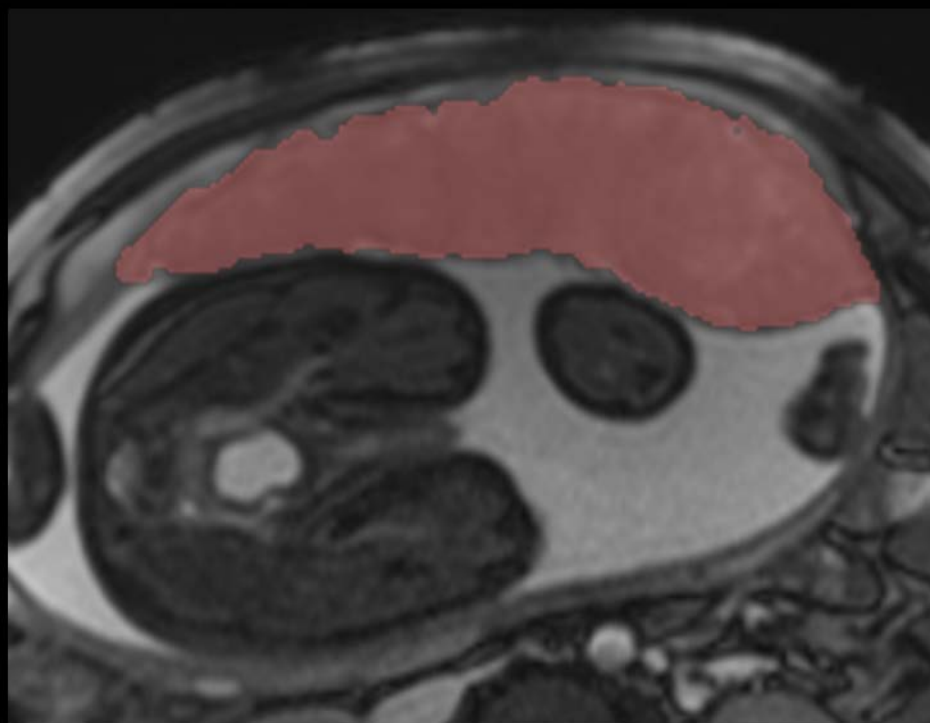
B



C

*





1,010 MRI studies in pregnant women
2002-2015

848 excluded due to maternal or
fetal radiologic abnormality

43 excluded due to inadequate
placental imaging

4 excluded due to multiple
gestation

3 excluded due to fetal birth
weight >97th percentile or <3rd
percentile

112 MRI studies in pregnant women
with singleton gestation and no
maternal or fetal radiologic abnormality

