



Published in final edited form as:

J Perinatol. 2022 July ; 42(7): 860–865. doi:10.1038/s41372-022-01340-6.

Measuring intrauterine growth in healthy pregnancies using quantitative magnetic resonance imaging

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Abstract

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Author Contribution Statement

AA was responsible for the manual data collection and providing original draft and final review of the manuscript

KK and NA were responsible for MRI data collection, critical review and editing of the manuscript along with final review

DK was responsible for the semi-automated process in MR image analysis, critical review and editing of the manuscript along with final review

RI was responsible for statistical analysis and creating figures, critical review and editing of the manuscript along with final review

AB and CL were responsible for study design and objectives, interpreting results, critical review and editing of the manuscript along with final review

JQ was responsible for screening, approaching and enrolling eligible subjects, critical review and editing of the manuscript along with final review

ACG and HKA were responsible for identifying and arbitrating potentially eligible subjects, interpreting results, critical review and editing of the manuscript along with final review

NA was responsible for study design and objectives, oversight of data collection and analysis, interpreting results, critical review and editing of the manuscript along with final review

Conflict of Interest

The authors report no conflicts of interests

Objective—The aim of this study was to determine in utero fetal-placental growth patterns using *in vivo* three-dimensional (3D) quantitative magnetic resonance imaging (qMRI).

Study Design—Healthy women with singleton pregnancies underwent fetal MRI to measure fetal body, placenta, and amniotic space volumes. The fetal-placental ratio (FPR) was derived using 3D fetal body and placental volumes (PV). Descriptive statistics were used to describe the association of each measurement with increasing gestational age (GA) at MRI.

Results—Fifty-eight (58) women underwent fetal MRI between 16–38 completed weeks gestation (mean=28.12±6.33). PV and FPR varied linearly with GA at MRI (rPV,GA=0.83,rFPR,GA=0.89, p value<0.001). Fetal volume varied non-linearly with GA (p-value < 0.01).

Conclusions—We describe in-utero growth trajectories of fetal-placental volumes in healthy pregnancies using qMRI. Understanding healthy in utero development can establish normative benchmarks where departures from normal may identify early in utero placental failure prior to the onset of fetal harm.

Keywords

quantitative MRI; placenta; fetal growth; volume; normative growth

Introduction

Healthy placental development is critical for normal growth and development of the fetus which can influence offspring health well into adulthood^{1, 2, 3, 4, 5}. Placental dysfunction continues to be a leading cause of perinatal morbidity and mortality, including fetal growth restriction (FGR), pre-eclampsia, and stillbirth^{1, 2, 3, 4, 5, 6, 7}. Even in infants who survive the perinatal period, impaired placental function is strongly associated with the development of future chronic diseases^{1, 2, 8, 9}.

The birthweight-placental weight ratio (BWPW) has been proposed as a metric of placental efficiency, namely, placental ability to adequately support optimal fetal growth^{10, 11}. Increased BWPW implies increased nutrient transfer per gram of placenta, while decreased BWPW suggests decreased nutrient transfer per gram of placenta, otherwise termed placental insufficiency^{10, 11}. Maternal, fetal and environmental health can influence placental and subsequent fetal weight, with evidence of both morphologic and functional adaptations of the placenta, and thus placental efficiency¹². Despite a wide range of BWPW ratios associated with normal growth, both low and high ranges of BWPW are associated with adverse maternal and fetal outcomes. A higher BWPW ratio has been described in pregnancies with elevated uterine artery and umbilical artery Doppler pulsatility indices¹¹, whereas a lower BWPW ratio has been associated with maternal obesity, diabetes, pre-eclampsia, as well as impaired neonatal transition and neonatal-intensive care admission^{10, 11}. While the BWPW ratio can provide information regarding *in utero* conditions, including potential insults and adaptation, its utility is limited until the post-partum period^{10, 11, 13}. Evidence points to improved clinical outcomes when high-risk conditions are detected *in-utero*^{14, 15, 16}, yet despite this link, there remains a lack of reliable *in-vivo* tools to assess placental function.^{17, 18, 19, 20, 21, 22, 23, 24, 25, 26} To address the current research

gaps, the objective of the current study was to determine *in-vivo* fetal-placental growth patterns in healthy pregnancies using three-dimensional (3D) quantitative MRI (qMRI). The hypothesis of this study was that fetal body and placental volumes would increase with advancing gestational age (GA), with variable fetal body-placental ratios during the same gestational window.

Methods

Study design & patient population

We recruited healthy pregnant women with singleton pregnancies of 16–38 weeks' gestation to enroll in a prospective observational study at Children's National Hospital (CNH).

We included a total of 58 healthy pregnant women with no significant past medical history, including any chronic or pregnancy-related comorbidities, and normal prenatal screening serum (first trimester screen and alpha fetoprotein), genetic, and anatomical imaging studies. Women with multiple gestations, contraindications to MRI, or gestational comorbidities such as diabetes or hypertension were excluded. The study was approved by the Institutional Review Board of CNH, and written informed consent was obtained from all study participants as part of an ongoing prospective observational study.

MRI acquisition

The recruited study participants underwent fetal MRI in the supine or lateral position, based on maternal comfort (GE Discovery MR450 1.5T MRI Scanner using 8-channel cardiac array coil (receive only)) without the use of contrast or sedation. Dedicated T2 weighted-images of the placenta and fetal body-amniotic space were acquired in the single MRI session with the following parameters:

- Placenta: axial single shot fast spin echo (SSFSE) images of the placenta were acquired with the following parameters: TR=1100ms, TE=160ms, slice thickness=4 mm and matrix 256×192, no gap, no overlay. For placenta, the acquisition time was 45 seconds.
- Fetal body-amniotic space: 3D steady-state free precession (SSFP) images of the intrauterine cavity were acquired with the following parameters: TR =2.8ms, TE =1.1ms, slice thickness=3mm, flip angle=35, matrix size=256×192, FOV =36cm. The total sequence acquisition time was between 12–14 seconds, based on the size of the fetal body in sagittal plane.

Post-processing: image segmentation & volume calculations

Placenta segmentations were manually performed by one of two trained scientists using ITK-SNAP software.³¹ The placenta-uterine interface was identified by change in signal quality (decreased intensity compared to surrounding tissue) and using the adjacent uterine wall as a guide (see supplementary figure). To segment the fetal body and amniotic fluid, we developed a fully automatic deep learning-based method. A 3D U-Net deep learning model was trained on 62 fetal MRI scans and validated on 20 scans ranging from 18 to 38 weeks gestation. A U-Net CNN architecture with 7 encoding blocks and 7 decoding blocks was chosen. Each block constitutes a Convolutional layer, Batch Normalization layer and

Parametric ReLU activation layer. Focal tversky loss and dice similarity coefficient were elected as the evaluation criteria to train and validate the model²⁷. Each 3D MR scan and its respective normalized mask were broken into patches of size 64×64×64 with stride 2×2×2. Each patch and its mask were randomly augmented between –180° to 180° along 3 axes (i.e., x, y, and z) during training. The model was trained for 1000 epochs, 10 steps per epoch with a batch size of 4. Dice similarity coefficient was used to measure the segmentation accuracy.³² Segmentations of the fetal body and amniotic space were obtained from the described in-house pipeline and then manually corrected (Figure 1)²⁷.

Volumetric analysis

Once the fetal body, placenta, and amniotic space were either semi-automatically or manually segmented as described above, the volumes for each segmentation were extracted from ITK-SNAP software in mm³ and converted to cm³ (Figure 1)²⁷. The fetal body-placental ratio (FPR) was derived for each subject using individual volumes.

Clinical data

Clinical and demographic data were extracted from the medical records. Maternal data included race, ethnicity, body mass index (BMI), fetal sex, and gestational age (GA) at MRI. Neonatal outcomes including GA at birth, birthweight (BW) at delivery, and corrected birthweight (BW z-score) were derived from BW and GA at delivery using the Fenton growth chart²⁸.

Statistical analysis

Descriptive statistics characterized each volume measurement in the cohort. We performed intra-rater reliability analysis for the manual fetal body and amniotic fluid segmentations. We investigated pairwise association of each volume measurement (fetal body, placenta, and amniotic space volumes, as well as the FPR) with GA graphically with scatterplots. For linear associations, we reported Pearson's correlation to measure the strength of association and used chi-square test to determine whether the correlation was significantly different from zero. For non-linear association, we fit a 3parameter logistic function

$$\text{logit (GA)} = \text{Asym}/(1 + \exp((x_{\text{mid}} - \text{GA})/\text{scal})),$$

where Asym is the asymptotic maximum value of the volume, x_{mid} is the gestational age when volume is half of the maximum, and scal is the scaling parameter of the growth rate. We tested the statistical significance of each parameters with a t-test using function nlm in the R statistical package²⁹. The pairwise scatterplots show the fit (linear, or non-linear) as a solid line, the R² measure of goodness-of-fit for linear fits, the model-based 95% confidence band (shaded), and the 95% prediction band (between dashed lines). We also explored the association of measured volumes with GA across maternal and fetal characteristics, including race/ethnicity and fetal sex with multivariate modeling, and whether departure from (linear or non-linear) pattern of association with GA were associated with maternal and neonatal outcomes by investigating association of these outcome measures with residuals from the nonlinear fits.

Results

Characteristics of our cohort

We studied a total of 58 healthy pregnant women who underwent fetal MRI between 16 and 38 completed weeks gestation (mean=28.12±6.33). One subject was excluded after delivery due to a postnatal genetic diagnosis in the neonate. The remaining pregnancies were carried to term, resulting in the delivery of phenotypically normal neonates with birth weights appropriate for GA. Clinical and demographic data are presented in Table 1.

MRI quality evaluation and segmentation validation

Two out of the remaining 57 images were discarded due to poor image quality or artifact, leaving 55 images available for analysis. The two discarded images were from fetuses at 25.7- and 26.6-weeks' gestation. Automated segmentation time ranged from 1.5 – 2 minutes, depending on size. Dice indices for segmentations obtained from our in-house pipeline were 0.89 for fetal body and 0.95 for amniotic fluid. Intra-reliability ratios for volumes acquired from manual segmentation were 0.933 for fetal body and 0.79 for amniotic fluid.

Fetal and placental growth as a function of gestational age

There was a positive linear association between GA at MRI and both placental volumes (Pearson's correlation $r_{GA,PV}=0.83$, $p < 0.001$) and the FPR (Pearson's correlation $r_{FPR,GA}=0.89$, $p < 0.0001$) (Figures 2–3). There was no significant association between GA at MRI and amniotic fluid volume (Pearson's correlation $r_{FV,GA}=0.19$) (Figure 4), with a mean volume of 609 cm³ (± 244 cm³). There was also a positive association between GA at MRI and fetal body volumes, with a derived 3-parameter logistic shape non-linear function of:

$$FBV = 3508.55 / (1 + e^{(32.11 - GA/4.65)})$$

where FBV = fetal body volume, GA = gestational age at evaluation (Figure 5).

Multivariate modeling of measured volumes revealed that apart from GA, covariate analyses of race/ethnicity or fetal sex were not significant ($p = 0.27 - 0.78$). Correlation of residuals from non-linear fit of fetal volume revealed an association of residuals with gestational age at birth ($r=0.83$) and birth weight z-score ($r=0.70$).

Discussion

In this study, we report in-vivo growth trajectories for the fetal body and placenta and derived FPR during the second and third trimesters of healthy pregnancies using 3D qMRI. We found a strong linear relationship between GA and both placental volumes as well as FPR and describe a 3-parameter logistic fit for fetal body volumes across GA. There was no significant association between GA and amniotic fluid volumes. Collectively, these measures can inform fetal-placental growth and wellness.

Placental Volume

Abnormalities in placental weight have been associated with adverse fetal outcomes. In healthy pregnancies, placental growth precedes the growth of the fetus and the fetus responds accordingly to changes in the placenta³⁰. The positive association between placental volume and advancing GA has been shown in both healthy^{31, 32, 33, 34}, and high-risk conditions^{19, 20}. Similar to the study by León et al. and Langhoff et al., we only recruited healthy pregnant women with no abnormalities to investigate placental development and efficiency in low-risk populations^{33, 34}. However, unlike previous studies, we report placental volume independently, but also relative to fetal growth, to better understand intrauterine influences on fetal wellness.

Fetal Body Volume

Accurate measures of fetal growth are critical to identifying at-risk fetuses for FGR or fetal macrosomia, and subsequent peripartum and long-term morbidity^{35, 36, 37}. Fetal growth estimates rely on both clinical measures of the gravid uterus and on sonography, with only a few studies of MRI based metrics^{31, 32, 34}. Despite the relatively small numbers compared to sonographic studies of fetal growth, data show that fetal MRI performed immediately prior to delivery may predict birthweight with greater accuracy than ultrasound (US), particularly for fetuses with suspected intrauterine growth restriction or macrosomia^{38, 39, 40, 41, 42, 43, 44, 45, 46}. A recent meta-analysis compared the accuracy of US and MRI in predicting fetal macrosomia and found that MRI was more specific than US³⁷. The PREMACRO study is a large prospective clinical study currently underway that directly compares US-EFW and MRI-EFW at 36 weeks gestation to determine whether MRI can improve the detection of neonates < 95th centile⁴⁴. Consistent with the literature, our results showed that fetal body volumes had a significant positive association with GA. Based on a 3-parameter logistic function, we developed a formula to quickly estimate fetal body volume based on the log of GA. We also note a correlation of fetal body volume with GA at birth and birth weight z-score. Should these observations be validated in future prospective studies, fetal body volume measures may be able to more accurately identify compromised pregnancies. This would be particularly relevant for infants born SGA or LGA where current biometric methods perform with decreased accuracy, and given that these growth disturbances are associated with increased risk of perinatal mortality and morbidity, particularly for those with comorbid prematurity^{47, 48, 49, 50}.

Placental Efficiency

Previous studies found a significant association between placental volume as measured by MRI and birth weight percentile ($P<0.0001$),³¹ estimated fetal weight ($P=0.03$) and birth weight ($P=0.05$)³⁴. While the BWPW ratio is a common metric to assess placental efficiency, a major criticism is that it fails to differentiate between growth-restricted and appropriate growing fetuses,⁵¹ and relies on ex-vivo placental weight. In this work, we report in-vivo measurements and show that under healthy conditions, the FPR increases with gestation. This increase in the FPR, representing greater efficiency in nutrient transfer from the placenta coincides with exponential fetal growth that occurs in late gestation. The ability to interrogate and reference independent volumes along with the FPR provides a

more robust assessment of in-vivo fetal-placental wellness. It is important to emphasize that the BWPW used in clinical practice compares weights while the FPR in our study incorporates volumes. Differences in body composition (such as changes in bone density or increases in fat deposition) may explain why the linear relationship that we found between GA and FPR does not match the exponential weight relationship described in literature from US biometry. The provision of normative trajectories can provide the foundation from which high-risk conditions, including late-onset growth failure, can be better explored and understood. Deviations in individual volumes along with FPRs, even in the absence of overt small for gestation fetuses, may better identify growth-restricted fetuses, a major challenge with current diagnostic assessments.

Amniotic Fluid Volumes

We report a range of normative amniotic fluid volumes in the second and third trimesters of pregnancy, adding to the limited studies on this topic in fetal MRI^{52,53}. In clinical practice, US is still the main modality used to assess amniotic fluid volume, but its accuracy is controversial^{53,54,55}. A previous study had shown that MRI is a more accurate predictor of amniotic fluid volume compared to US⁵³. We did not observe a strong temporal evolution of amniotic fluid over GA, likely due to the highly dynamic nature of the production and resorption of amniotic fluid. The lack of a strong relationship may partly be explained by motion artifacts. Although not statistically significant, our graph provides normative ranges across the second half of gestation and showed an inverted U-shaped curve, a pattern similar to that seen in prior studies based on sonographic measurements of amniotic fluid volume⁵⁶. Quantifying amniotic fluid volume with MRI may become a useful antenatal tool, especially in pregnancies where poly- or oligohydramnios risk is suspected, once normative ranges of typical amniotic fluid volumes are validated.

Limitations

Despite the strengths of this work, there are limitations that deserve mention. Motion artifacts are a limitation that can degrade image quality but there are ongoing technological advancements to address this. Pre-pregnancy factors that are known to influence fetal growth, such as maternal body mass index, were not available for this study. Related, the mean maternal age of our study participants was 36 (advanced maternal age category) which may limit the generalizability of these results. While our results revealed an association between fetal body volume, birth weight and term gestation, the relationship between volume and weight varies across gestation with changing tissue composition and density. Despite these limitations, previous studies report improved accuracy with 3D over traditional 2D measures and suggest that this method may better capture growth anomalies than standard biometry alone^{57,58,59,60}. Future studies will need to examine fetal-placental growth patterns in high-risk pregnancies to determine the accuracy of 3D volumetry in detecting small for gestational age (SGA) and large for gestational age (LGA) fetuses and infants, and to relate these with long-term outcomes. These are currently underway. Similarly, developing population based normative values warrants larger validation studies, ideally with a prospective multi-centered approach; these studies should include comprehensive assessments of pre-pregnancy maternal health and nutrition status and include the entire spectrum of child-bearing maternal ages. While the focus of our study

is on qMRI, we acknowledge that there are barriers to MRI that may limit its widespread clinical utility including but not limited to the high cost of MRI, limited access to the imaging device, relatively long processing time compared to other imaging modalities, and user training/expertise required for its use and application. Despite these limitations, if qMRI can more accurately identify growth complications and better inform delivery timing to minimize neonatal complications, it may serve as an important adjuvant to current screening tools for high-risk pregnancies.

Conclusions and future directions

In conclusion, this study uses qMRI to develop normative trajectories of fetal body volumes, placental volumes and FPRs, along with normative ranges of amniotic fluid volumes. Since the FPR is available prenatally, it may allow for a more robust prenatal diagnostic and screening platform for abnormal placental function and impaired fetal growth. Future work should include serial, longitudinal studies to determine if placental dysfunction can be identified prior to the onset of compromised fetal growth and prevent neonatal complications. Larger studies are needed to develop large regional and ethnicity specific fetal-placental growth charts. Additional studies should consider the concurrent acquisition of fetal US and MRI to allow for direct comparisons of fetal growth by each modality and to better elucidate the clinical advantages, if any, of one over the other. Future studies should also focus on investigating fetal-placental trajectories in growth restricted fetuses to determine the added value of MRI as a diagnostic tool.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We would like to acknowledge our funding sources: Supported by National Institutes of Health (1U54HD090257, R01-HL116585, K23HD092585-01A1).

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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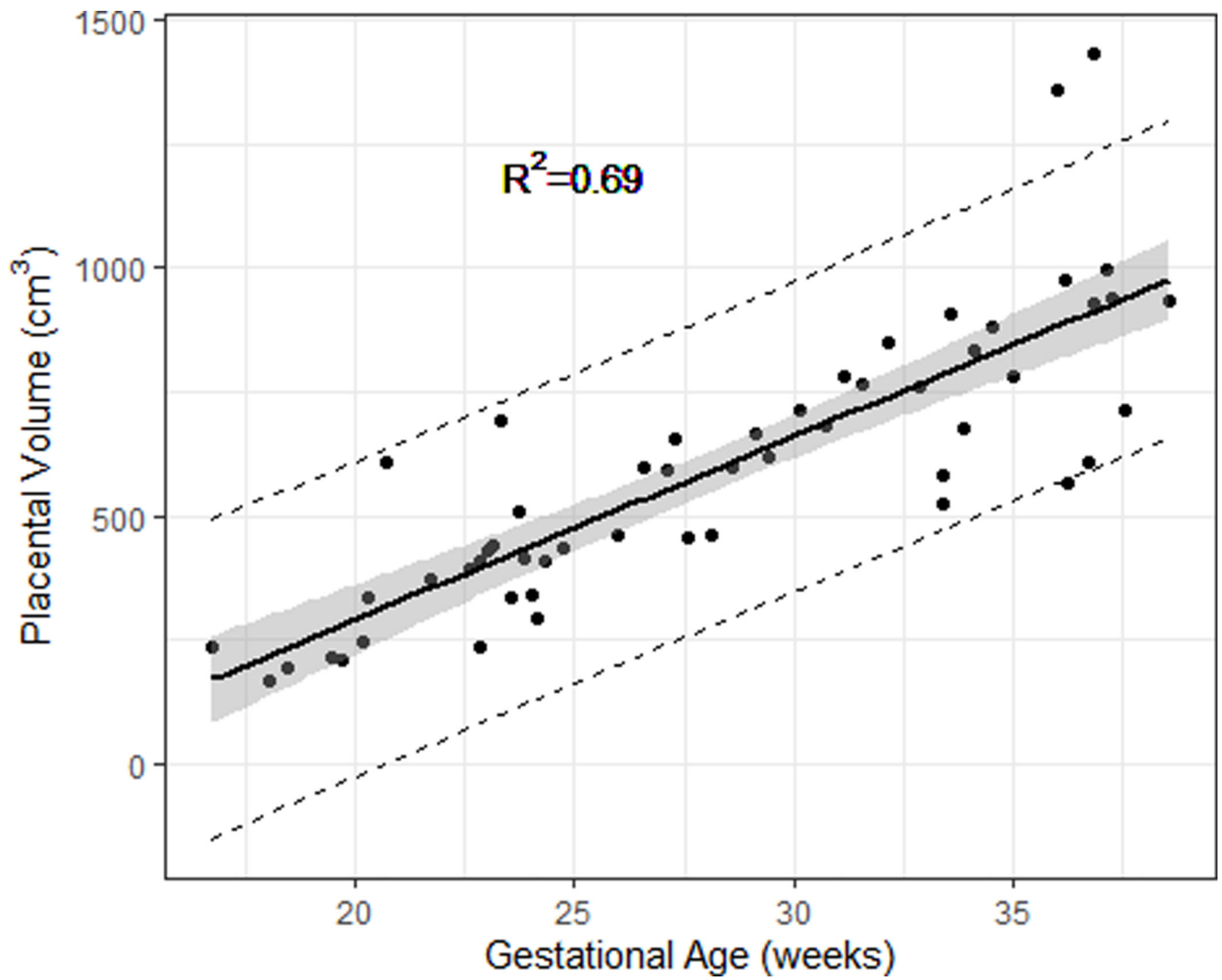


Figure 1:

In vivo placental volumes across gestation in a cohort of healthy, singleton pregnancies. Linear fit (solid line), model-based 95% confidence band (shaded area), and 95% prediction band (area between dashed line), and the R^2 measuring the goodness of linear fit.

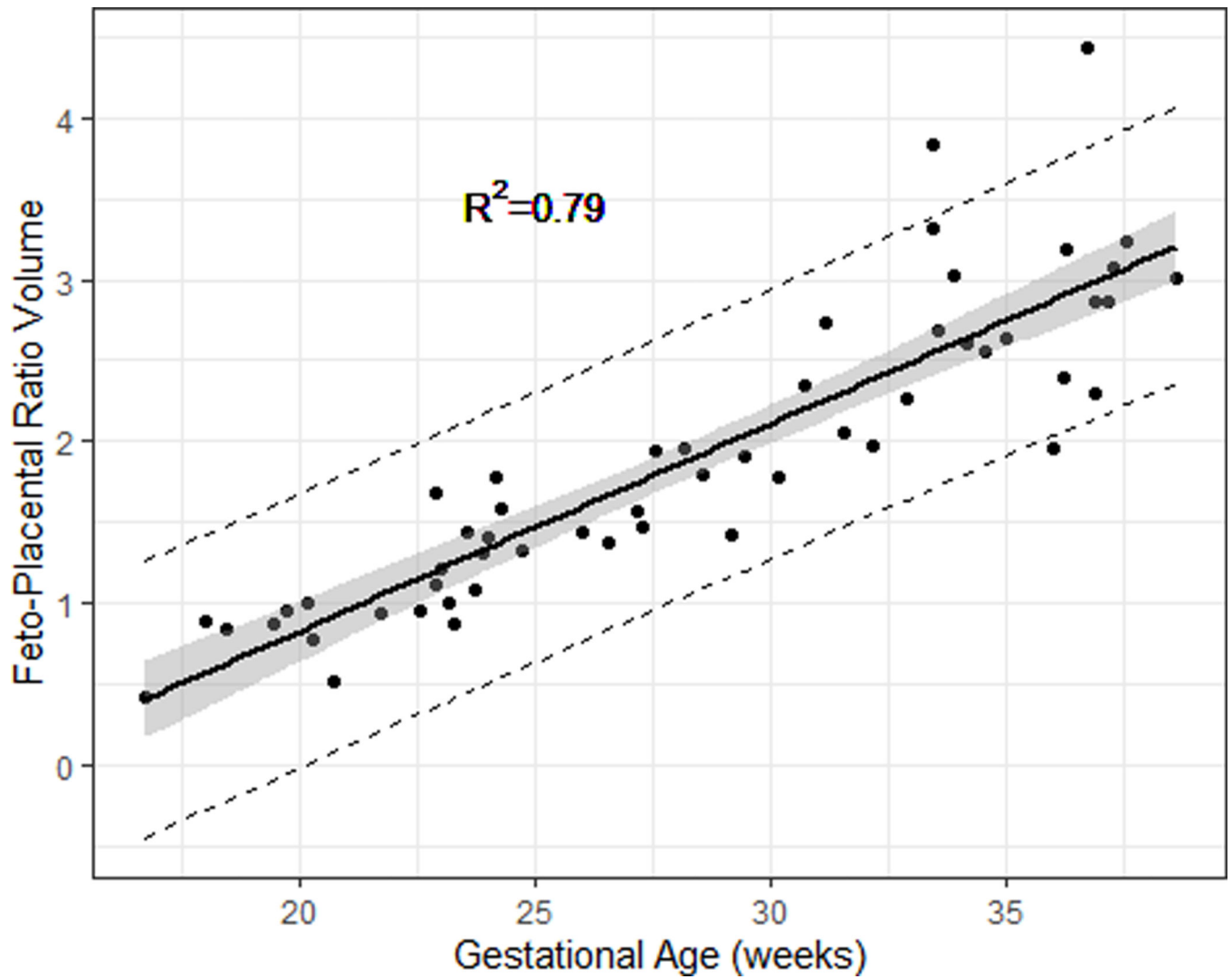


Figure 2:

In vivo measures of the fetal-placental ratio (ratio of fetal volume to placental volume) across gestation in a cohort of healthy, singleton pregnancies. Linear fit (solid line), model-based 95% confidence band (shaded area), 95% prediction band (area between dashed line), and the R^2 measuring the goodness of linear fit.

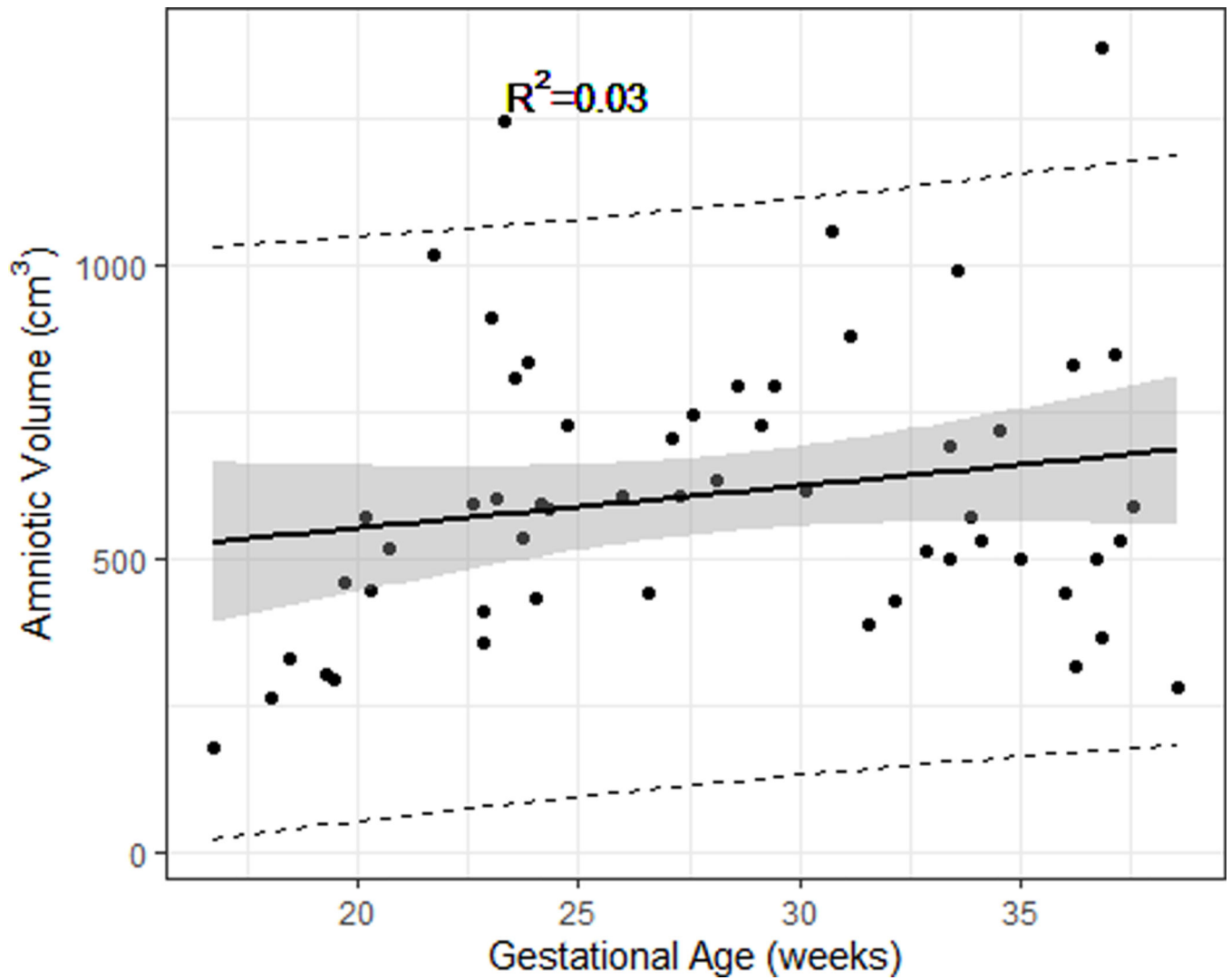


Figure 3: In vivo amniotic fluid volumes across gestation in a cohort of healthy, singleton pregnancies. Linear fit (solid line), model-based 95% confidence band (shaded area), 95% prediction band (area between dashed line), and the R^2 measuring the goodness of linear fit.

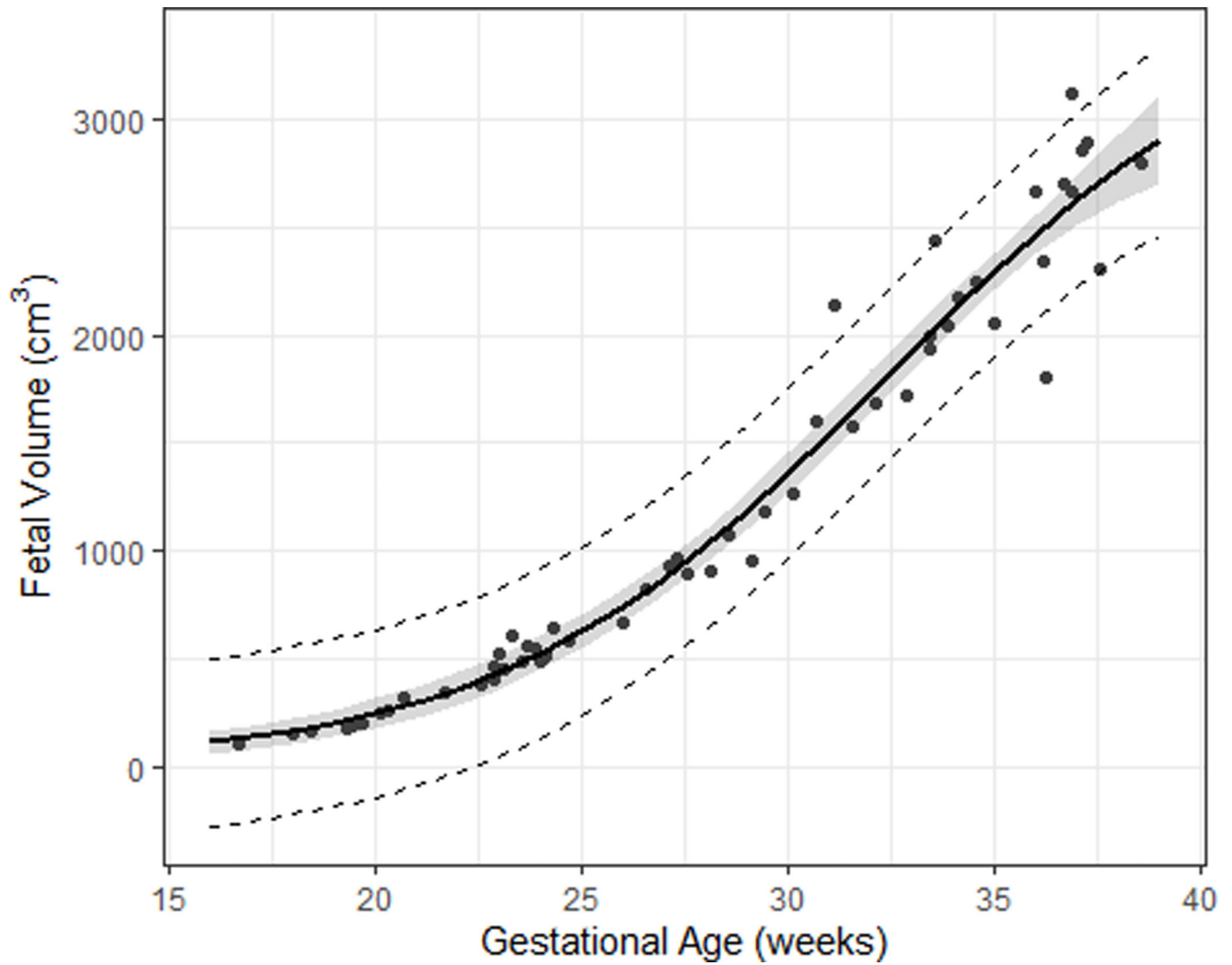


Figure 4: In vivo fetal body volumes across gestation in a cohort of healthy, singleton pregnancies. Non-linear, logistic function, fit (solid line), model-based 95% confidence band (shaded area), and 95% prediction band (area between dashed line).

Table 1.

Demographic and clinical characteristics of our cohort

	Healthy fetuses (n=55)
Maternal age at delivery in years [†]	36.70 ± 4.99
Maternal race or ethnicity [‡]	
Black	12 (21.8%)
White	31 (56.4%)
Other or unknown	8 (14.5%)
Hispanic	2 (3.6%)
Maternal gravida [‡]	
Primigravida	20 (36.4%)
Multigravida	35 (64.6%)
Fetal GA at MRI scan [†]	28.11 ± 6.33
GA at birth [†]	39.86 ± 1.40
Male fetus [‡]	28 (50.9%)
Birth weight [†]	3480 ± 840
Birth weight z-score [†]	-0.21 ± 0.95
Birth length in cm [†]	50.89 ± 2.14
Head circumference in cm [†]	34.88 ± 1.54
Ponderal index [†]	2.56 ± 0.25

Abbreviations: GA=gestational age

[†]Values are reported in mean, standard deviation.[‡]Values are reported in n (%).