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Research paper

Wave reflections in the umbilical artery measured by Doppler ultrasound as a novel predictor of placental pathology

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Background: The umbilical artery (UA) Doppler pulsatility index is used clinically to detect elevated feto-placental vascular resistance. However, this metric is confounded by variation in fetal cardiac function and is only moderately predictive of placental pathology. Our group developed a novel ultrasound methodology that measures wave reflections in the UA, thereby isolating a component of the Doppler signal that is specific to the placenta. The present study examined whether wave reflections in the UA are predictive of placental vascular pathology.

Methods: Standard clinical Doppler ultrasound of the UAs was performed in 241 pregnant women. Of these, 40 women met narrowly defined preset criteria for the control group, 36 had maternal vascular malperfusion (MVM) and 16 had fetal vascular malperfusion (FVM). Using a computational procedure, the Doppler waveforms were decomposed into a pair of forward and backward propagating waves.

Findings: Compared to controls, wave reflections were significantly elevated in women with either MVM ($p<0.0001$) or FVM pathology ($p = 0.02$). In contrast, the umbilical and uterine artery pulsatility indices were only elevated in the MVM group ($p<0.0001$) and there were no differences between women with FVM and the controls.

Interpretation: The measurement of wave reflections in the UA, combined with standard clinical ultrasound parameters, has the potential to improve the diagnostic performance of UA Doppler to detect placental vascular pathology. Identifying women with FVM pathology is particularly challenging prenatally and future investigations will determine if women at risk of this specific placental disease could benefit from this novel diagnostic technique.

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Research in Context

Evidence before this study

Placental vascular pathology is a causal factor in a large proportion of pregnancy complications. A key component of fetal health assessment is measurement of the pulsatility of the umbilical artery blood velocity waveforms using Doppler ultrasound, an indirect measurement of feto-placental vascular resistance. However, the umbilical artery pulsatility index is confounded by physiological variables such as the fetal heart rate and is only moderately predictive of placental pathology. We have developed a novel ultrasound methodology called wave reflection analysis that isolates the portion of the pulsation that is specific to the placenta. In healthy pregnancies, we have shown the pulsation of the umbilical artery waveform is explained by the presence of wave reflections.

Added value of this study

In this study, we recruited 241 pregnant women for wave reflection analysis using standard obstetric ultrasound equipment and placental pathology assessment. We demonstrated that wave reflections in the umbilical artery are significantly elevated in women with maternal and fetal vascular placental pathology compared to healthy controls.

Implications of all the available evidence

These findings have the potential to extend the utility of umbilical artery Doppler to improve diagnosis of placental pathologies. This is particularly promising for fetal vascular malperfusion where there is currently no reliable method of detection prenatally. Wave reflections arise from transitions in biomechanical properties of blood vessels, and finding strong reflections in pathologic pregnancies provides a mechanistic link between abnormal Doppler waveforms and vascular pathology.

Introduction

Placental pathology is present in over half of cases of fetal growth restriction (FGR) [1] and stillbirth [2]. Maternal vascular malperfusion (MVM) is the most common placental disease associated with FGR [3] and is often the cause of preventable stillbirth [4]. Although the pathologic features of MVM are well-defined by pathologists [5,6], current standard-of-care diagnostic methods including placental imaging, uterine artery Doppler ultrasonography and maternal serum biomarkers are only moderately predictive. This gap in clinical care was illustrated in a recent prospective study of 856 low-risk women, where the optimal combination of ultrasound examination and angiogenic biomarkers achieved only moderate precision in predicting MVM placental pathology [7]. Fetal vascular malperfusion (FVM) is a less common pathologic finding but one that is also associated with FGR and other adverse outcomes such as stillbirth, perinatal stroke and peripheral vascular injury [8]. FVM is much more difficult to diagnose prenatally and is almost always only recognized by pathological examination. This may be because the underlying intermittent umbilical cord obstruction is only loosely associated with cord hyper-coiling, and routine ultrasounds in appropriately grown fetuses do not search for evidence of umbilical cord disease [9].

There is therefore a need for better diagnostic methods, particularly in late gestation, when varying degrees of cardiovascular maturation contribute to a greater uncertainty in the interpretation of Doppler waveforms presently used to detect clinically significant placental vascular diseases. Our group has previously shown that wave reflections are present in human umbilical arteries (UAs) [10] using a novel ultrasound methodology [11] that isolates the component of the Doppler signal that is specific to the placenta, thereby controlling for confounding variables especially fetal cardiac function. The wave reflection model decomposes the UA Doppler waveform into a forward propagating velocity wave travelling from the fetal heart and a backward propagating wave that arises when the forward wave encounters changes in vascular resistance. The phenomenon of wave reflections explains the variation in UA Doppler waveforms along the umbilical cord, with increasing diastolic velocities towards the placental end [10]. We have previously demonstrated the utility of wave reflection metrics in differentiating between healthy control and growth-restricted murine fetuses [12,13] and that wave reflections are associated with the vascular morphology of the feto-placental arterial tree [12]. In the present study, we determined whether wave reflections in the UA could discriminate between healthy controls and women that would subsequently be found to have placental pathology (MVM or FVM). We also compared the reflected wave metrics with the conventional UA and uterine artery pulsatility indices (PI).

Methods

Ethics: Ethics approval was obtained from the ethics boards of The Hospital for Sick Children (Toronto, ON, Canada) (REB Number 1000051548), Mount Sinai Hospital (REB Number: 15-0279-A) and Johns Hopkins Medicine (IRB Number: 00082717). All experiments were performed in accordance with the guidelines of each institution.

427 women between the ages of 18−45 years with a singleton pregnancy and a body mass index of less than 45 kg/m^2 were recruited for fetal ultrasound examination from Mount Sinai Hospital (Toronto, ON, Canada) and Johns Hopkins Medicine (Baltimore, MD, USA). Written informed consent was obtained from each participant. Ultrasound examinations were conducted between 26 and 32 weeks of gestation by certified sonographers using either a Philips iU22 (Philips Healthcare Andover, MA, USA) or GE Voluson e10 (GE Healthcare, Chicago, IL, USA) ultrasound system. Data were collected and analyzed as described in detail previously [11]. Briefly, blood velocity measurements were collected using pulsed Doppler ultrasound at both the fetal and placental end of each UA (Fig. 1). The measurements are acquired asynchronously with the scanner operating in standard clinical mode with up to 12 consecutive waveforms collected for each position on each artery. All of the waveforms collected were used for analysis. Datasets were excluded for poor signal-to-noise ratio, high levels of fetal breathing or motion artifact and heart rate variability greater than 10 beats/min between measurements. Analysis was performed on the Doppler waveforms as presented by the scanner user interface and did not require reference to raw radio-frequency data. The envelope of the maximum instantaneous velocity was defined automatically for each Doppler waveform as described in Stortz et al. [11], split into individual cardiac cycles and aligned to produce a cardiac cycle average velocity waveform for the fetal end and for the placental end of the UA(s). Modeling the reflection as a linear system with a parameterized impulse response, the observed velocity waveforms were decomposed into forward and reflected components. This approach assumes the reflections are generated within the placenta and that the geometric properties and vascular tone of the vascular tree do not change over the course of the examination. The frequency dependent reflection coefficient was calculated as $\Gamma_h = B_h/F_h$, where B_h and F_h are respectively the hth harmonic Fourier coefficients for the representations of the reflected and forward wave. Reflection waveforms were summarized in terms of the magnitude of the first harmonic wave reflection coefficient ($|\Gamma_1|$). For the reflection coefficient, when the root mean square error (RMSE)

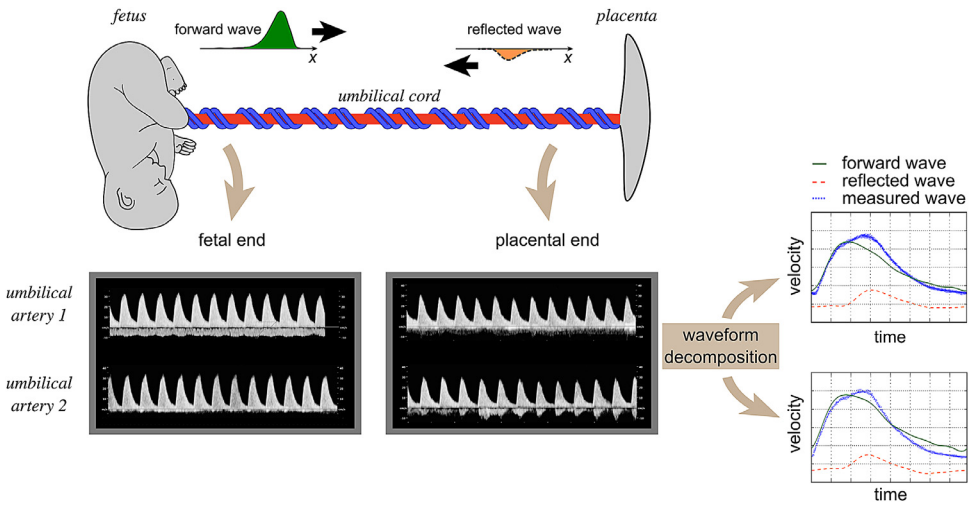

Fig. 1. Illustration of wave reflection methodology. Umbilical artery Doppler waveforms (positive flow in representative images) are collected from both arteries at both the fetal and placental end. Using a parameterized impulse response function, the measured waveforms are decomposed into forward and reflected waveforms.

between the modeled and measured velocities was <1.5% of the mean velocity, the solution was considered valid.

In addition, pulsed Doppler spectra of the fetal middle cerebral artery (MCA) and the uterine arteries were collected. For the latter, the measurements were taken at the crossover point of the right and left proximal uterine arteries [14]. The pulsatility index for each artery was computed from the traced average Doppler waveforms as the difference between the peak systolic and end-diastolic velocities, divided by the mean velocity over the fetal cardiac cycle. The cerebro-placental ratio (CPR) was calculated as the MCA PI/UA PI. The uterine artery pulsatility index and the CPR are routinely used as markers of placental dysfunction [7] and adverse pregnancy outcomes [15].

Obstetrical data were obtained from the participants' medical records. Birth weights were categorized into percentile groups according to neonatal sex and gestational age (in completed weeks) and small for gestational age (SGA) was classified as less than the 10th centile according to standard growth charts [16]. After delivery, placentas were fixed in 10% formaldehyde for 48 h and then evaluated by experienced pediatric perinatal pathologists using the Amsterdam working group definitions for placental lesions [6]. Gross findings included placental weight and dimensions, number of cord vessels, cord insertion and cord coiling. The umbilical cord, fetal membrane roll and placental disc were cut into a series of 2 cm thick slices to inspect for gross lesions. The sections were then paraffin-embedded, cut into 4 μm thick sections and stained with hematoxylin and eosin to assess microscopic abnormalities.

For the purpose of analysis, we categorized the cases based on placental pathology findings at delivery: (1) control (no or minor pathology, without vascular malperfusion), (2) maternal vascular malperfusion and (3) fetal vascular malperfusion. For the control group we excluded women with chronic hypertension, pre-gestational diabetes mellitus, major fetal abnormalities, birth at less than 37 weeks' gestation, and fetal birth weight $\leq$ 25th centile [17]. The diagnostic criteria for MVM included at least one macroscopic finding (i.e. placental weight < 10th centile, multi-focal infarction, retro-placental hemorrhage) and at least one histologic lesion (i.e. distal villous hypoplasia, accelerated villous maturation, syncytial knots, decidual vasculopathy) [18]. FVM was diagnosed based on finding more than one focus of avascular villi (≥45 avascular villi over three sections) and/or two or more occlusive or non-occlusive thrombi in the chorionic plate or major stem villi.

Statistics: All statistical tests were performed using the R statistical software package (www.r.project.org). Data are reported as mean ± standard deviation. The PI values and wave reflection parameters were averaged to provide the overall mean PI and $|\Gamma_1|$. To analyze the clinical characteristics, clinical ultrasound parameters and wave reflection parameters, a Fisher's exact test was used for categorical variables and a one-way ANOVA was used for continuous variables to evaluate the effect of group (control, MVM, FVM). If the ANOVA was significant, Tukey post hoc tests were performed. When calculating p-values for each coefficient in our model, we estimated the degrees of freedom using the Satterthwaite approximation for unequal variances [19]. A value of $p < 0.05$ was taken to be significant. Receiver operating characteristic (ROC) curves [20] were computed to compare the extent that the $|\Gamma_1|$ could aid in differentiating between control and placental pathology (MVM or FVM). The area under the ROC curves (AUC) was calculated using the pROC package in R [21]. The optimal cut-off for discrimination based on $|\Gamma_1|$ was determined using the Youden index [22]. Estimating that 25% of the cohort will have placental pathology and anticipating a ROC with an AUC of 0.8 or greater for predicting pathology based on the wave reflection coefficient, a sample size of 100 is sufficient to estimate the AUC with a precision of ± 0.057 [20]. Moreover, the study is powered at 0.9 for detecting an AUC as low as 0.71 with a 0.05 chance of type I error [21].

Role of Funders: The funders played no role in the study design, data collection, analysis or interpretation of the data, or drafting of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 427 women who consented to participate in the study, 241 women underwent ultrasound examination during the appropriate gestational window and had their placenta assessed for pathology (25 withdrew and 161 had placentas that were not sent for pathological examination). Forty-two of the women were recruited at Johns Hopkins Medicine and 199 women at Mount Sinai Hospital. There were no differences in maternal demographics (maternal age, body mass index) between study sites. Forty of the 241 (17%) women met the criteria for the control group. Placental histopathologic examinations were performed blinded to the Doppler findings. Thirty-six (15%) women met the criteria for MVM and 16 (7%) for FVM. There were no cases that met the diagnostic criteria for both MVM and FVM pathology. All of the women with MVM and FVM pathology were recruited at Mount Sinai Hospital. The remaining 149 women had non-diagnostic findings or rarer placental diagnoses (e.g. massive

subchorionic thrombohematoma, chronic histiocytic intervillositis, chronic deciduitis) and were excluded from further statistical analysis. Among the 92 study datasets retained, the umbilical artery measurements met preset data quality criteria for at least one UA in 86 datasets. The six datasets that were excluded from analysis were from women with MVM pathology. The clinical characteristics of the 86 participants are summarized in Table 1. In the group of women who developed MVM or FVM placental pathology, 68.9% had adverse pregnancy outcomes (preelampsia or SGA birth). Women with MVM had significantly higher rates of preeclampsia compared with those without placental pathology (26.7% vs. 0%). While the birth weights in the FVM group were significantly higher than the MVM group, both women with FVM and MVM pathology had higher rates of SGA birth compared to controls (46.7% and 70.0% vs. 0%). Seven (43.8%) of the 16 FVM cases showed evidence of pathological umbilical cord abnormalities including cord entanglement at delivery, cord diameter less than 8 mm or hypercoiling [23]. There was one stillbirth in the FVM group.

The 86 participants provided a total of 172 pairs of UA waveforms for analysis, corresponding to 172 decomposed waveforms and 172 reflection coefficients (one per artery). 15 of the UA decomposed waveforms were excluded because of low Doppler signal quality and 20 because the decomposed waveforms were not adequately fit by the wave reflection model (root mean square error $> 1.5\%$). The first harmonic reflection coefficient was elevated by 55% in the MVM group (MVM: 0.34 ± 0.11 vs. control: 0.22 ± 0.11, $p < 0.0001$, by Tukey post hoc test following one-way ANOVA) and 41% in the FVM group (FVM: 0.31 ± 0.10 vs. control: 0.22 ± 0.11, $p = 0.02$, by Tukey post hoc test following one-way ANOVA), respectively compared to controls (Fig. 2a). The first harmonic reflection coefficient was not significantly different between the FVM and MVM groups ($p = 0.5$, by Tukey post hoc test following one-way ANOVA). While the primary hypothesis was that the magnitude of wave reflections would differ between healthy feto-placental circulations and the two most common placental vascular pathologies (MVM, FVM), we have included the data for the participants with non-diagnostic findings or rarer placental pathologies to provide context with the range of variation in a heterogeneous sample.

The clinical ultrasound-derived parameters were significantly different between women with MVM pathology and controls. The UA mean PI was significantly increased by 48% (MVM: 1.26 ± 0.44 vs. control: 0.85 ± 0.14, $p < 0.0001$, by Tukey post hoc test following one-way ANOVA) and the uterine artery mean PI was increased by 77% (MVM: 1.29 ± 0.45 vs. control: 0.73 ± 0.19, $p < 0.0001$, by Tukey post hoc test following one-way ANOVA) in women with MVM pathology (Fig. 2b and c). The cerebroplacental ratio was significantly decreased by 35% in the MVM group compared to controls (MVM: 1.54 ± 0.63 vs. control: 2.37 ± 0.47, $p < 0.0001$, by Tukey post hoc test following one-way ANOVA) (Fig. 2d). For the group of women with FVM pathology, there were no significant differences in the UA mean PI (FVM: 0.97 ± 0.23, $p = 0.4$, by Tukey post hoc test following one-way ANOVA), uterine artery mean PI (FVM: 0.89 ± 0.31, $p = 0.2$ by Tukey post hoc test following one-way ANOVA) or cerebroplacental ratio (FVM: 1.99 ± 0.55, by Tukey post hoc test following one-way ANOVA) compared to controls. ROC analysis for the ability of the wave reflection coefficient to discriminate between pathology (MVM or FVM) and control gave an AUC value of 0.78. The point on the ROC curve that optimizes sensitivity and specificity is a $|\Gamma_1|$ value of 0.23. At this threshold, the sensitivity and specificity are 0.86 and 0.73 respectively.

Discussion

In this study, we found that wave reflections were larger in women with placental vascular pathology compared to healthy pregnancies. This was true for both MVM and FVM placental disease and contrasted with standard clinical ultrasound parameters (UA and uterine artery PIs) that were only elevated in MVM pathology. The first harmonic reflection coefficient acts as a measure of hemodynamic impedance that is specific to the placenta because the formulation explicitly controls for upstream factors such as cardiac output that may bias other metrics [10,11]. The placentas in the control group had low reflection coefficients, suggesting that the impedance of the placental vascular system is well matched to the umbilical cord and has a branching vessel pattern that is structured to transmit rather than reflect hemodynamic pulses. This is consistent with placental vascular development where blood flow to the placenta increases with gestational age via a decrease in vascular resistance. The placentas with MVM and FVM pathologies had elevated reflection coefficients that suggest one or more distal sites of high hemodynamic impedance and/or a large impedance mismatch. While it is not known where the identified reflection arises within the placenta, the capillaries within the terminal villi are a likely source. In both MVM and FVM pathology, the structure of the villi is abnormal (hypermature villi with an increase in syncytial knots or distal villous hypoplasia in MVM and avascular or karyorrhectic villi in FVM). Our group recently used computational modeling to explain the forward and reflected waves using micro-computed tomography images of the feto-placental vasculature in the mouse (Saghian, unpublished data, 2021). We found that the terminal load impedance (capillary and/or vein) had a significant role in creating the observed reflected waveform.

The predictive performance of the first harmonic reflection coefficient was moderate. Combining the wave reflection coefficient with other metrics used clinically for surveillance (i.e. UA and uterine artery PI, fetal biometry, and maternal blood testing) has the

Table 1
Comparison of maternal demographics and pregnancy and neonatal outcomes.

Characteristic	Control ($n = 40$)	MVM ($n = 30$)	FVM ($n = 16$)*	Other ($n = 149$)
Maternal age at delivery (years)	33 ± 4	33 ± 4	34 ± 3	33 ± 4
BMI (kg/m^2)	24 ± 3	27 ± 6[a] ($p = 0.01$)	24 ± 3[b] ($p = 0.04$)	25 ± 5
Gestational hypertension	0 (0/40)	26.7 (8/30)[a] ($p < 0.0001$)	6.7 (1/15)	10.1 (15/149)
Preeclampsia	0 (0/40)	26.7 (8/30)[a] ($p = 0.0006$)	6.7 (1/15)	2.0 (3/149)
Cesarean delivery	40.0 (16/40)	76.7 (23/30)[a] ($p = 0.005$)	46.7 (7/15)[b] ($p = 0.03$)	42.3 (63/149)
Gestational age at delivery (wks)	39 ± 1	34 ± 3[a] ($p < 0.0001$)	38 ± 2[b] ($p < 0.0001$)	38 ± 2
Birth weight (g)	3700 ± 400	1700 ± 700[a] ($p < 0.0001$)	2900 ± 900[a,b] ($p < 0.0001$)	3000 ± 600
Female	37.5 (15/40)	40.0 (12/30)	53.3 (8/15)	53.0 (79/149)
SGA	0 (0/40)	70.0 (21/30)[a] ($p < 0.0001$)	46.7 (7/15)[a] ($p < 0.0001$)	11.4 (17/149)

Data are mean ± standard deviation or % (n/N) unless otherwise specified. BMI, body mass index; FVM, fetal vascular malperfusion; MVM, maternal vascular malperfusion; SGA, small for gestational age. *Other* includes the participants with non-diagnostic findings or rarer placental pathologies (shown for comparison and not included in the statistical analysis).

* Clinical outcome data were missing from one participant (stillbirth).

[a] differences when compared with Control.

[b] differences when compared with MVM.

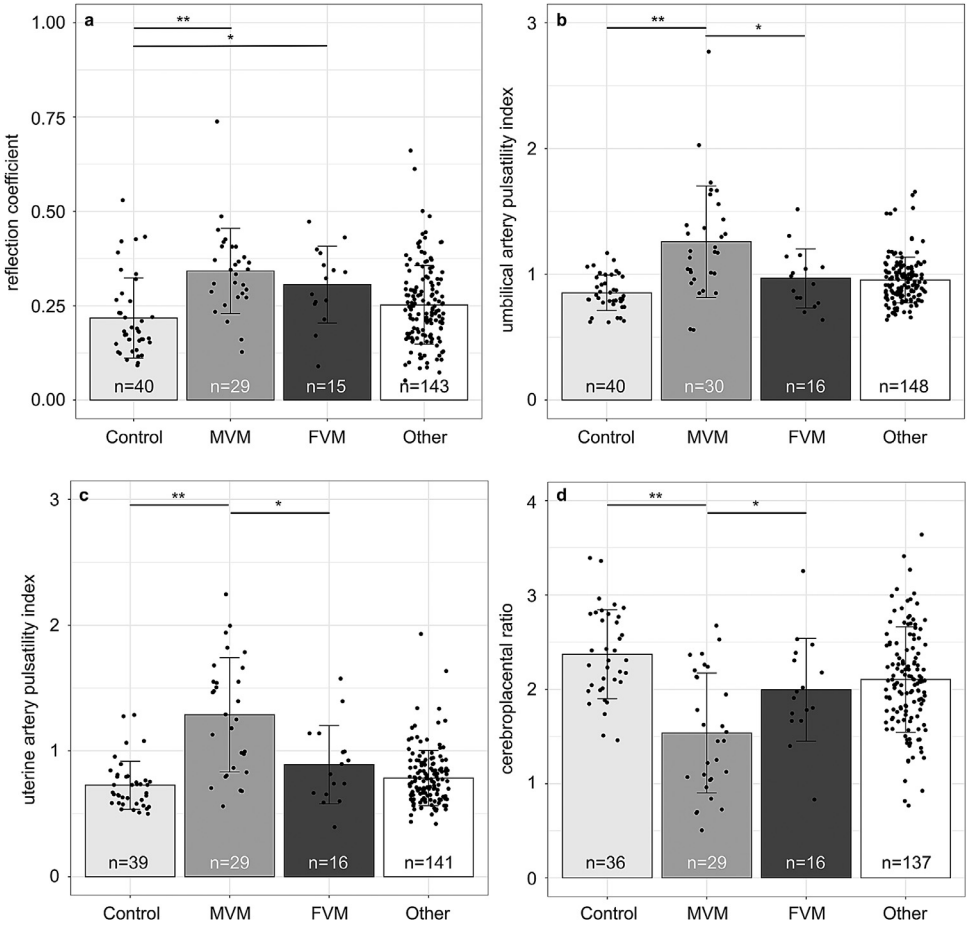

Fig. 2. Comparison of ultrasound-derived parameters stratified based on placental pathology. (a) The first harmonic reflection coefficient, (b) umbilical artery mean pulsatility index, (c) uterine artery mean pulsatility index, and (d) cerebroplacental ratio. Data are mean ± standard deviation. FVM, fetal vascular malperfusion; MVM, maternal vascular malperfusion, Other includes the participants with non-diagnostic findings or rarer placental pathologies (shown for comparison and not included in the statistical analysis). *n* refers to the number of participants. $^{**}p < 0.0001$ and $^{*}p < 0.05$.

potential to improve diagnosis of placental pathologies. While the first harmonic reflection coefficient was elevated for both MVM and FVM cases, UA and uterine artery mean PI values were only elevated for MVM pathology. Once an increased first harmonic wave reflection coefficient was identified, a differential diagnosis would determine whether the pathology was MVM or FVM based on whether the UA and uterine mean PI were elevated or not. Depending on the gestational age at time of diagnosis, the management approach may be quite different (e.g. more intensive fetal monitoring vs. Cesarean section delivery). In cases of FVM, elevated UA PI is thought to be transient and would likely be missed by ultrasound screening [8]. The explanation for why the wave reflection coefficient is more sensitive to pathology in cases of FVM will be the subject of future investigations using computational modeling.

One limitation of this study is that the methodology is more technically demanding than current clinical Doppler assessments due to the requirement of stringent data quality and measurements at both the placental and fetal end of the UA. Moreover, the Doppler measurements are not acquired at the same time and variations between measurements could result in inconsistent data. Acquiring the multiple ultrasound waveforms is more time consuming than a routine exam and a small number of exams may need to be repeated – 7% of datasets (6 of 92) were not usable in the present study. However, beyond the initial data quality control of the images, the waveform analysis is fully automated and non-biased making it straight-forward for use in the clinical setting. Emerging technologies such as three-dimensional vector-flow ultrasonography [24] have the potential to improve the wave reflection measurements. In addition to advancements in ultrasound technology, several groups are using novel in-vivo MRI approaches for placental pathology detection including blood oxygen level-dependent (BOLD) MRI [25], diffusion weighted imaging [26] and intravoxel incoherent motion MRI [27]. The criteria for participants to be included in the control group were chosen conservatively and many of the participants that were excluded had normal pregnancy outcomes. A larger study population would allow us to detect important but uncommon types of placental pathology and perinatal outcomes such as chronic villitis of unknown etiology and stillbirth.

The principal finding of this work is that wave reflections are elevated in pregnancies with MVM and FVM pathology and, in combination with standard ultrasound parameters, have the potential to improve diagnosis of these pathologies. This is particularly promising for FVM where there is currently no reliable method of detection. The data used in this study were collected using standard clinical ultrasound equipment and automated computational analysis and is therefore easily translated to use at other centers.

Declaration of Competing Interest

The authors have nothing to disclose.

Contributors

Lindsay S Cahill: Conceptualization, Formal analysis, Data curation, Funding acquisition, Writing – original draft preparation. Greg Stortz: Methodology, Software, Data curation, Writing – reviewing

and editing. Anjana Ravi Chandran: Data curation, Project administration, Writing – reviewing and editing. Natasha Milligan: Data curation, Project administration, Writing – reviewing and editing. Shiri Shinar: Investigation, Data curation, Writing – reviewing and editing. Clare L Whitehead: Investigation, Data curation, Writing – reviewing and editing. Sebastian R Hobson: Investigation, Writing – reviewing and editing. Viji Ayyathurai: Investigation, Data curation. Anum Rahman: Methodology, Software, Writing – reviewing and editing. Rojan Saghian: Methodology, Software, Writing – reviewing and editing. Karl J Jobst: Conceptualization, Funding acquisition, Writing – reviewing and editing. Cyrethia McShane: Data curation, Project administration. Dana Block-Abraham: Investigation, Data curation, Writing – reviewing and editing. Viola Seravalli: Investigation, Data curation, Writing – reviewing and editing. Melissa Laurie: Investigation, Data curation, Writing – reviewing and editing. Sarah Millard: Investigation, Data curation, Writing – reviewing and editing. Cassandra Delp: Data curation, Project administration, Writing – reviewing and editing. Denise Wolfson: Data curation, Project administration, Writing – reviewing and editing. Ahmet Baschat: Conceptualization, Supervision, Funding acquisition, Writing – reviewing and editing. Kellie Murphy: Conceptualization, Funding acquisition, Writing – reviewing and editing. Lena Serghides: Conceptualization, Funding acquisition, Writing – reviewing and editing. Eric Morgen: Conceptualization, Funding acquisition, Investigation, Data curation, Writing – reviewing and editing. Christopher Macgowan: Conceptualization, Supervision, Funding acquisition, Writing – reviewing and editing. W Tony Parks: Conceptualization, Funding acquisition, Investigation, Data curation, Writing – reviewing and editing. John C Kingdom: Conceptualization, Supervision, Funding acquisition, Writing – reviewing and editing. John G Sled: Conceptualization, Supervision, Funding acquisition, Writing – reviewing and editing. Lindsay S. Cahill, John C Kingdom and John G Sled verified the underlying data. All authors have read and approved the final version of the manuscript.

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Data sharing statement

Data available on request from the authors.

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