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● *Original Contribution*

SHEAR WAVE ELASTOGRAPHY IN THE LIVING, PERFUSED, POST-DELIVERY PLACENTA

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Abstract—The placenta is the critical interface between the mother and the developing fetus and is essential for survival and growth. Despite the widespread use of ultrasound imaging and Doppler in obstetrics and gynecology and the recent growth of elastographic technologies, little is known about the biomechanical (elastic shear wave) properties of the placenta and the range of normal and pathologic parameters that are present. This study uses a well-developed protocol for perfusing whole placentas, post-delivery, to maintain tissue integrity and function for hours. In this model, the placenta is living, whole and maintained within normal physiologic parameters such as flow, arterial pressure and oxygen, throughout examination by ultrasound, Doppler and shear wave elastography. The preliminary results indicate that normal placental tissue on the fetal side has shear wave speeds on the order of 2 m/s, in a range similar to those of animal livers. Some abnormalities are found outside this range, and thus, elastographic measures of the placenta may provide useful assessments related to the state of the tissue. (E-mail: kevin.parker@rochester.edu) **© 2016 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Elastography, Obstetrics, Placenta, Tissue characterization, Shear waves.**

INTRODUCTION

The placenta is a complex entity fulfilling the functions of many major fetal organs, allowing communication between two separate organisms (mother and embryo/fetus) and ensuring the growth and survival of the fetus. The human placenta is of the discoidal villous, hemomonochorial type (Corner 1944; Mossman 1987). In addition to the placenta's critical role *in utero*, the fetal circulation in the human placenta under *in vitro* perfusion can be considered a prototype for other human capillary beds.

Using *in vitro* human dual perfusions, we previously found that both ultrasound and magnetic resonance (MR) techniques of years past could be used to investigate placental fetal and maternal blood flow and its vascular regulation. Panigel et al. (1996) brought to attention these biophysical techniques for assessing the placenta. Abramowicz et al. (1999) visualized the fetal vasculature using ultrasound B-scan and Doppler imaging enhanced with Albunex microbubbles (Molecular Biosystems, San Diego, CA, USA) and evaluated the regulation of blood flow in the lobule. In addition, one of the first reviews on MR and the placenta was published by Mattison et al. (1988), projecting the potentials we now can pursue more than 20 y later. Further, the placenta *in vitro* was studied to examine contrast with manganese using MR (Miller et al. 1987), as well as to define the glycolytic process in the human placenta by detecting phosphorus using MR for ATP, ADP, AMP and inorganic phosphorus (Malek et al. 1995, 1996). In the review by Avni et al. (2015), there was no evaluation of MR elastography for the placenta.

Improved diagnostic assessment of the placenta could enable earlier recognition of adverse conditions such as intra-uterine growth restriction, a major clinical public health problem, which is defined as the failure of the fetus to achieve its optimal growth (Conde-Agudelo et al. 2013). Intra-uterine growth restriction affects up to 11% of all pregnancies in the developing world (de Onis et al. 1998) and is associated with hypertensive

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disorders of pregnancy, autoimmune disease, diabetes, smoking, infection, malnutrition, hypertension and unexplained factors (Kady and Gardosi 2004).

Elastography is well established in a number of organs. The shear wave speed within tissues can be linked to the elastic or viscoelastic properties, which can be useful in detecting some pathologies (Parker et al. 2011). However, the biomechanical properties of the normal placenta have not been studied extensively. A recent publication (Cimsit et al. 2015) reported the potential use of placental elastography to predict preeclampsia. Two other studies reported shear wave speeds on post-delivery specimens (Calle et al. 2015; Sugitani et al. 2013). Currently, many unresolved issues remain with respect to elastography of the placenta, including the range of normal values, possible dependence on physiologic variables such as fetal blood pressure and flow and effects of specific pathologies. The aim of this study was to provide initial estimates of placenta stiffness under a range of conditions.

METHODS

Eleven human placentas from healthy, uncomplicated term pregnancies were obtained immediately after cesarean section delivery, placed in a plastic container and transported to the perfusion laboratory within 20 min. Because the placenta is considered a surgical tissue specimen for disposal and no clinical (Health Insurance Portability and Accountability Act) identifiers were associated with this research tissue, patient consent was not required for the study of these placentas, in accord with the World Medical Association's Declaration of Helsinki. The study protocol was reviewed and approved by the Research Patients Review Committee at the University of Rochester. The post-delivery placenta was examined grossly, and catheters were introduced and sutured in place in fetal veins and arteries. The arterial catheters were connected to a pump per previously described methods (Miller et al. 1985, 1993), and the placenta was placed fetal side (chorionic plate) up in a water bath heated to 37°C. An open perfusion system (*i.e.*, without recirculation) was used. Fetal flow was approximately 3–6 mL/min and was controlled by maintaining fetal arterial pressure $<$40 mm Hg except when studying vasoconstrictors. Placental functions that can be studied through this perfusion model include hemodynamics, trans-placental transport, cellular uptake, endocrine function and metabolism. Criteria for effective dual perfusion have been published previously (di Sant'Agnese et al. 1987; Miller et al. 1993); those most commonly employed are oxygen consumption, glucose consumption, lactate production, human chorionic gonadotropin production, net fetal oxygen transfer and fetal pressure and flow rates. Hemodynamic control consisted of instantaneous pressure readings using a BPS-STA pressure sensor (Vernier Software and Technology, Beaverton, OR, USA) connected to the fetal arterial circuit, with recording every 5 s and maintenance of fetal arterial flow at approximately 3–6 mL/min. The fetal pressures that were obtained were not as strongly pulsatile as physiologic systolic and diastolic pressures in humans, but maintained a normal range of flow and pressure in the system.

Placental elastography images were generated using a Siemens Antares scanner (Siemens Medical Solutions, Malvern, PA, USA) and VF10-5 probe (Siemens Medical Solutions) at 5 MHz with our custom single-track-location shear wave elasticity imaging (STL-SWEI) pulse sequences and accelerated processing (McAleavey et al. 2009b). This approach has a spatial resolution on the order of the push pulse separation, approximately 2 mm in this study. The error has been found to be $\pm 3\%$ in significant (5-dB signal-to-noise ratio) noise (Langdon et al. 2015). Placentas were placed on an acoustically absorbing pad, immersed in a buffered saline bath at 37°C and scanned during perfusion.

The transducer was introduced in a plastic bag containing ultrasound gel at room temperature, and the bag was applied directly to the bath surface over the fetal side and was supported by a movable mechanical arm so as not to exert pressure on the placental surface. In color Doppler mode, the transducer was positioned where an area containing vascular flow could be found and was then fixed in place. Color and Doppler spectral signals were obtained but were marginally above the noise floor unless contrast was injected. Because the perfusate did not contain red blood cells, the ultrasound contrast agent Optison (GE Healthcare, Wauwatosa, WI, USA; supplied in 3-mL vials with 5–8 $\times 10^8$ microspheres 3–4.5 μm in diameter) was injected into the arterial side of the fetal circuit to provide adequate scattering from the perfusate. Boluses of 0.1–0.5 cc were injected into the perfusate reservoir supplying the fetal circuit. Two vasoactive substances were also employed in experiments 5–11. First, U46619 (Caymen Chemical, Ann Arbor, MI, USA), a thromboxane agonist and a potent vasoconstrictor, was injected into the fetal artery. The dosage employed (1 mL, 10^{-6} mol/L) was pharmacologic and corresponded to concentrations previously used by other authors in perfusion experiments (Abramowicz et al. 1999; Maguire et al. 1998; Myatt et al. 1998). After 10 more min, 1 mL of nitroglycerin (American Regent, Shirley, NY, USA), a potent vasodilator, was injected, and again Optison was added after 1 min.

RESULTS

Generally, the shear wave speed (SWS) color images of the placentas in our study were not homogeneous and uniform (Fig. 1). Local variations were seen and, in some cases, were related to the location of a major artery, or proximity to the chorionic plate or an abnormality such as an infarct. The raw velocity waveforms for the single-tracking-location shear wave elastography imaging (STL-SWEI) method were used to calculate the shear wave within local regions, as noted in Figure 2 (Elegbe and McAleavey 2013; Langdon and McAleavey 2014; McAleavey et al. 2009a, 2009b). The shear wave speed measurements from the fetal side of the perfused placenta are illustrated in Figure 3. Within a typical 1 × 1-cm region of interest (ROI) within the placenta, shear wave pairs were measured at 520 locations. The data revealed a mean SWS of 1.92 m/s with a standard error of ±0.05 m/s, and generally, the values were in the range 1.5–2.5 m/s, similar to values obtained in animal livers (Barry et al. 2014, 2015; Parker et al. 2015). The comparison is germane, as livers represent another highly vascularized soft tissue.

The investigations in experiments 5–11 were also aimed at assessing the sensitivity of the SWS in the placenta to a number of parameters including the applied pressure/flow, the effects of vasoconstrictors and vasodilators and any gross pathologies. Figure 4(b, c) illustrates

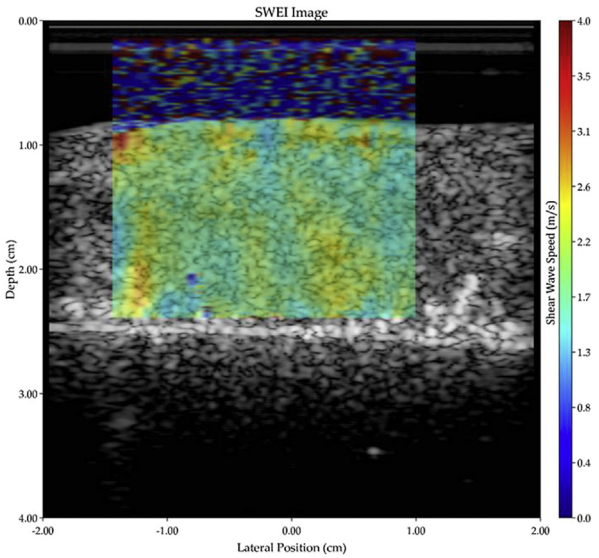

Fig. 1. B-Scan of perfused, whole placenta with color overlay representing shear wave speed on a scale from 0 to 4 m/s. Higher shear wave speeds are propagated in more stiff elastic materials. The placenta is oriented with the chorionic plate up. The typical shear wave speed color image exhibits some variation, with most values near 2 m/s, a value consistent with elastic responses of some other soft tissues. SWEI = shear wave elastography imaging.

the same cross section as Figure 4(a), but after injections of U46619 (vasoconstrictor) and eventually nitroglycerin (vasodilator), respectively. The response is generally heterogeneous and localized, with some regions demonstrating increased SWS after U46619 (see the *boxed region* in Fig. 4a). There are many possible reasons for the localized effect (Whittle et al. 1985), but these require further investigation. However, the regions that do respond can have increased SWS that rises above the baseline range; one representative example is shown in Figure 5. Figures 4(c) and 5 also illustrate the relaxation that follows a few minutes after the injection of vasodilator. An analysis of the data illustrated in Figures 4 and 5 using the Tukey–Kramer test indicated that the baseline measurements (B1, B2) significantly differed ($p < 0.05$) from the measurements after injection of vasoconstrictor (VC1–VC6 and VD) in this placenta. In these experiments, the pressure at the fetal artery was initially set to a low physiologic value of 30–40 mm Hg, and after vasoconstrictor injection, the pressure increased (under constant pump fluid output) to approximately 100 mm Hg within a few minutes, with a slow relaxation after the later vasodilator injection. These pressure changes would be consistent with changes in resistance and diameter of the branches of the vascular tree (Guyton 1971). However, in comparison, in the absence of vasodilation or vasoconstriction agents, we found that the baseline value of the fetal SWS, held at constant position of the ROI, was relatively insensitive to changes (within ±5% variability) in applied flow/pressure within physiologic levels of 30–60 mm Hg.

Some spontaneous infarct regions are occasionally seen in otherwise normal placentas. An example is given in Figure 6. The infarcted region is located in the smaller ROI, approximately 3 × 3 mm, whereas the larger ROI, approximately 8 × 5 mm, is located within the fetal side of the placenta. The infarct region has a significantly higher SWS (median: 2.9 m/s) compared with that of the normal placenta ROI (median: 1.5 m/s).

DISCUSSION

The main finding of this study is that the range of SWS of the normal, perfused, post-delivery placenta on the fetal side is between 1.5 and 2.5 m/s. These are higher SWSs than the median value (≈0.9 m/s) reported in normal pregnancies by Cimsit et al. at (2015) at 20–23 wk. Post-delivery measurements of shear wave speed from other recent studies were in the ranges of approximately 0.9–2.7 m/s (Sugitani et al. 2013) and 1.4–2.8 m/s (Calle et al. 2015).

The appearance of the placenta on our SWS color maps exhibited some local variation with elevated

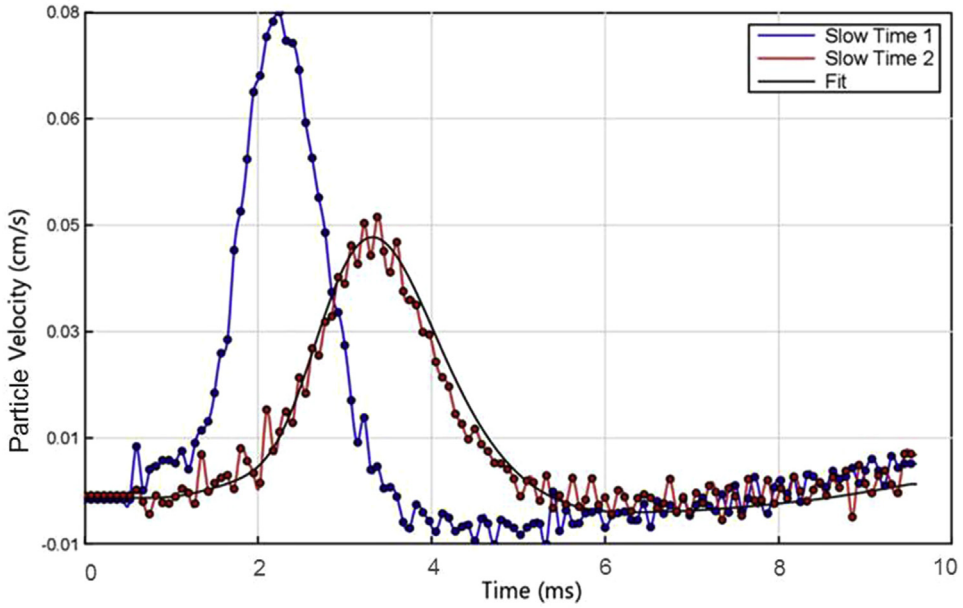

Fig. 2. Shear wave motion in tissue resulting from radiation force push pulses at two locations, approximately 2 and 4 mm lateral to the center of the push pulses. Vertical scale: Local tissue velocity (in cm/s); horizontal scale: time (ms) after the acoustic radiation force push pulse. These data form the basis of elastography measurements.

SWS, or stiff regions, explained in some cases by close proximity to a major artery, the chorionic plate or an abnormality such as an infarct. When the perfusion pump is adjusted within the physiologic range of 30–60 mm Hg, there is little change in the SWS measurement on the fetal side of the placenta. However, when flow volume is held constant while a vasoconstrictor is introduced, the arterial pressure markedly increases, and in some regions increased SWSs were observed, whereas in other regions there was little change. The increase in arterial pressure is consistent with the constriction of vessels creating a more resistant vascular bed in aggregate. But local variations in response are evident, and these were noted in the response of Doppler signals in our previous study (Abramowicz et al. 1999) and in physiologic studies on the effects of vasoconstrictors in other animal models (Whittle et al. 1985). In terms of tissue biomechanics, under the microchannel flow model (Parker 2014, 2015), a decrease in vessel diameter across the vascular bed of some region in tissue would increase the stiffness or hardness of that region, which would increase the SWS. The effect of vasodilators, at some interval after injection of the vasoconstrictor, was a slow reversal of the elevated pressure and elevated SWS; however the physiology of these manipulations and the interaction of the two agents are not simple.

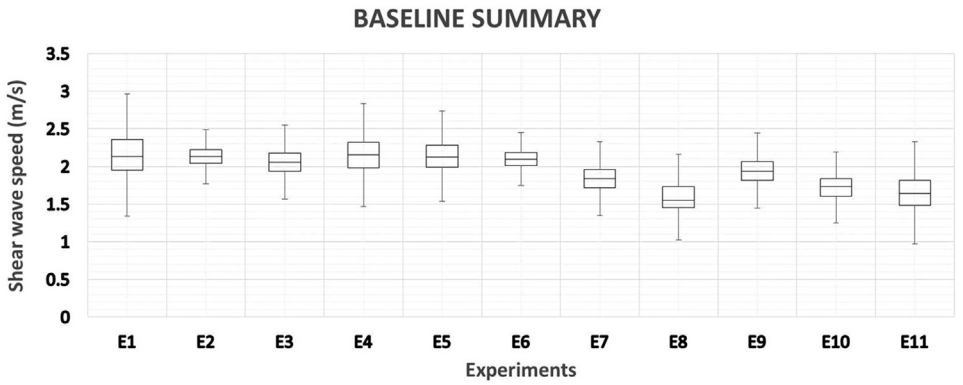

Fig. 3. Summary of baseline shear wave speed (m/s) measurements from the fetal side of the perfused placentas, by sample number. Generally the shear wave speeds are in the range 1.5 to 2.5 m/s. Data are illustrated as conventional box plots, with median, first and third quartiles and then ±1.5 times the interquartile range.

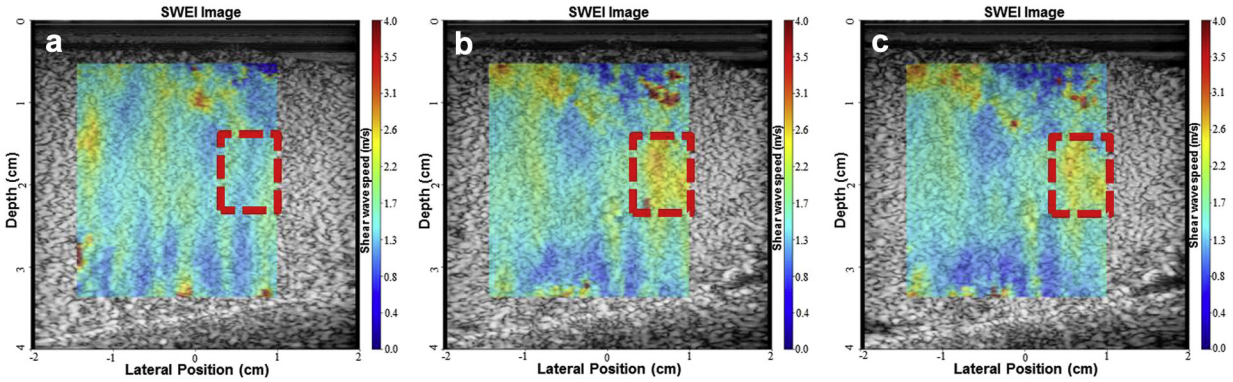

Fig. 4. B-Scans and shear wave color maps of a placenta: (a) normal perfusion; (b) after injection of a vasoconstrictor; (c) later, after injection of a vasodilator. The vasoconstrictor and vasodilator caused an elevation of arterial pressure and then a slow relaxation, respectively. SWEI = shear wave elastography imaging.

We note that the STL-SWEI method employed in these studies has been compared with other methods in phantom and tissue studies (Elegbe and McAleavey 2013; Langdon and McAleavey 2014; McAleavey et al. 2009a, 2009b). The single-track approach has advantages in estimating displacements in the presence of speckle statistics of tissue, and this results in low bias and high reproducibility. We recently reported that Scholte waves can be present at the interface of tissue and fluid, and these may play a role in any measurements near the boundary (Mercado et al. 2015). In theory, Scholte waves would produce slightly reduced shear wave speed measurements near the boundary; however, in the placenta, the presence of the chorionic plate and the major fetal arteries at the surface would complicate the analysis. The study of surface waves along the chorionic plate is left for future research.

Some limitations of this study include the lack of maternal side perfusion, which would more closely replicate the *in vivo* conditions. Gross examinations of the placentas revealed that the fetal side of the placenta was not degraded during the 3-h perfusion study. For this and a number of physiologic reasons, we expect that measurements taken on the highly vascularized and perfused fetal side would be reasonably consistent given single or double (fetal side plus maternal side) perfusions of post-delivery placentas. *In vivo* conditions have a range of additional factors including the two different arterial pulses from the maternal and fetal sides at different heart rates, and the requirement to produce shear wave displacements across the overlying tissues; it is thus likely that *in vivo* studies will be subject to reduced accuracy and precision, but these factors remain for further research.

Another limitation of this study is the imperfect perfusion of the entire placenta caused by the unresolved clots and emboli that can form in the 20-min interval between delivery and catheterization/perfusion. If these are

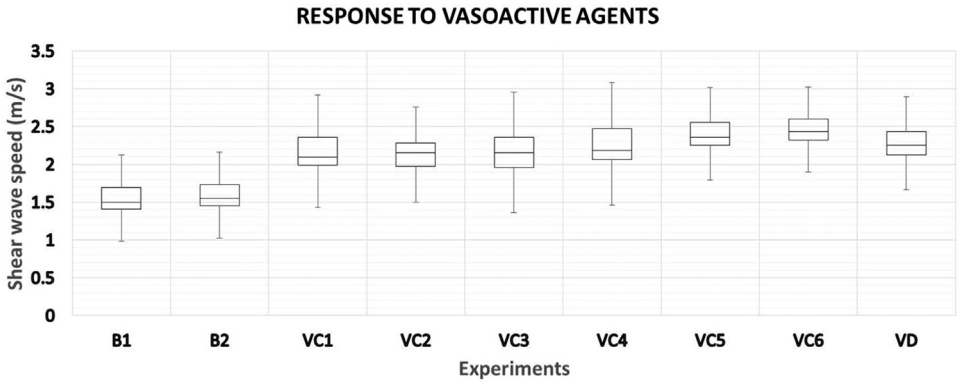

Fig. 5. Summary of shear wave speed results for a placenta before and after injection of a vasoconstrictor followed by a vasodilator. Data were taken from a region of interest corresponding to the *dashed regions* in Figure 4. B1 and B2 represent baseline values. VC1–VC6 were taken after injection of a vasoconstrictor. VD was taken after injection of a vasodilator. B1 and B2 were found to be significantly ($p < 0.05$) different from the subsequent measurements. Data are illustrated as conventional box plots, with the median, first and third quartiles and then ±1.5 times the interquartile range.

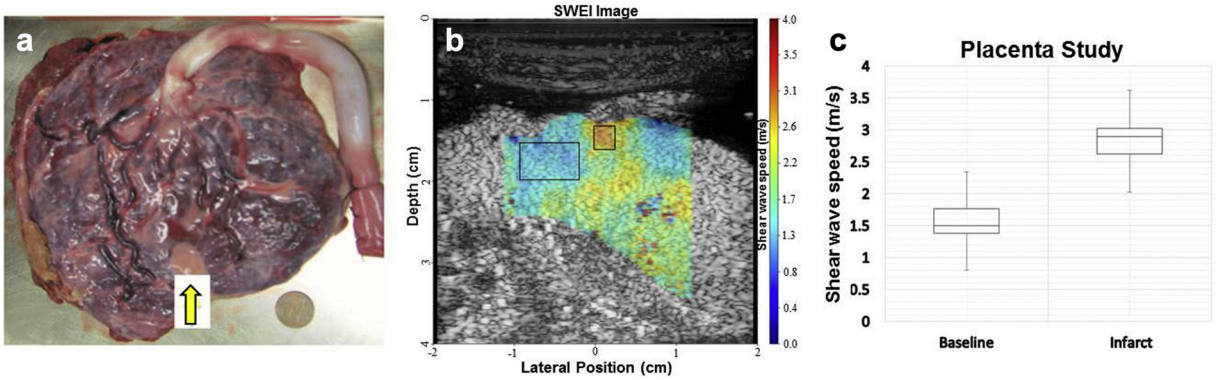

Fig. 6. (a) Placenta with infarct (*yellow arrow*). (b) Image of same placenta revealing softer normal (larger region of interest box) and harder infarct (smaller region of interest box) regions. (c) Comparison of measurements of shear wave speed from normal and infarct regions, illustrating the inherent elastic contrast between normal and infarcted tissues. SWEI = shear wave elastography imaging.

present and are not cleared by the perfusate, some localized reductions in perfusion are possible. Gross blockages will be visualized as the absence of Doppler signals; however, more subtle reductions or small regional reductions are less visible. This points to the usefulness of combining Doppler and SWS data sets over a 3-D volume in follow-up studies.

Additional research is required to fully characterize normal and pathologic states of the placenta associated with hypertension, diabetes, smoking, malnutrition and other adverse conditions. *In vivo* studies are also required to assess the dependency of elastographic measures on gestational age.

CONCLUSIONS

Our preliminary results indicate that normal placental tissue on the fetal side has shear wave speeds in a defined range around 2 m/s, comparable to the tissue elasticity of animal livers. Some abnormalities are observed outside this range; thus, elastographic measures of the placenta can provide useful assessments related to the state of the tissue.

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