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Measuring Venous Blood Oxygenation in Fetal Brain using Susceptibility Weighted Imaging

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Abstract

Purpose—To evaluate fetal cerebral venous blood oxygenation, Y_v , using principles of MR susceptometry.

Materials & Methods—A cohort of 19 pregnant subjects, with a gestational age of 31.6 $\pm$ 4.7 weeks were imaged using a modified susceptibility weighted imaging (SWI) sequence. Data quality was first assessed for feasibility of oxygen saturation measurement and data from 5 subjects (mean $\pm$ std gestational age of 33.7 $\pm$ 3.6 weeks) was finally chosen for further quantitative analysis. SWI phase in the superior sagittal sinus was used to evaluate oxygen saturation using the principles of MR susceptometry. Systematic error in the measured Y_v values was studied through simulations.

Results—Simulations showed that the systematic error in Y_v depended upon the assumed angle of the vessel, θ , relative to the main magnetic field and the error in that vessel angle $\delta\theta$. For the typical vessel angle of $\theta=30^\circ$ encountered in the fetal data analyzed, a $\delta\theta$ as large as $\pm 20^\circ$ led to an absolute error, δY_v , of less than 11%. The measured mean oxygen saturation across the 5 fetuses was $66\% \pm 9.4\%$ (range 55.7% to 74.4%). This average cerebral venous blood oxygenation value is in close agreement with the value in the published literature.

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Conclusion—We have reported the first *in-vivo* measurement of human fetal cerebral venous oxygen saturation using MRI.

Keywords

Susceptibility weighted imaging; SWI; fetal; brain; oxygen saturation; susceptometry

Introduction

Utilization of oxygen for aerobic metabolism during development is an integral part of the growth process of the human fetus, particularly from the second trimester onwards(1). The oxygen demand for metabolic purposes of the feto-placental unit increases with increasing gestational age(1,2). Disruption of this oxygen supply could lead to fetal cerebral hypoxia-ischemia, eventually leading to hypoxic ischemic injury (HII) to the developing brain. HII is a debilitating condition, often associated with postnatal developmental delay/deficits(3–5). The severity of brain injury depends on the nature and severity of the hypoxic-ischemic insult and gestational age of the fetus at the time of insult(3). A large number of clinical risk factors are associated with HII or stroke in the fetal brain including but not limited to: pre-eclampsia, placental abruption, maternal or fetal infection, congenital heart disease, maternal drug abuse etc(3,6–9). Recent studies show that the incidence of perinatal stroke is 1 in 1600 to 5000 births(8,10). While it is known that fetuses who suffer strokes *in-utero* are at increased risk of neurodevelopmental disorders(3,11), particularly hemiplegic cerebral palsy(12,13), the epidemiology of these strokes and pathways for prevention remain unclear(14,15). A major issue in studying brain damage *in-utero* in humans is that it remains undiagnosed until late(9). Methods for *in-utero* identification of ischemic injury to the fetal brain are limited and in some cases the diagnosis has to wait until the post neonatal period when injury becomes evident in neuroimaging or when affected children fail to reach developmental milestones(9,16–18). Hence, non-invasive imaging methods for identifying HII *in-utero* are of clinical interest and may help in the better prediction of long-term outcome(19).

Fetal magnetic resonance imaging (MRI) is increasingly gaining prominence as a clinical tool for radiologic evaluation of congenital anomalies in the developing fetus; especially neuro-developmental abnormalities(20). MR imaging has been shown to be more sensitive and provides greater specificity compared to ultrasound in the evaluation of central nervous system (CNS) abnormalities in the fetus(20–23). HII, cerebrovascular disorders (occlusive type like focal stroke or non occlusive type like aneurysms, arterio-venous malformations etc.) and intracranial hemorrhages are some of the few CNS anomalies that are often evaluated using MR(6). Cerebral hypoxic-ischemia often involves decreased arterial oxygen supply to the brain and a concomitant change in cerebral venous oxygen saturation. The ability to measure fetal cerebral blood oxygenation would make it possible to evaluate the oxygen extraction fraction; and along with blood flow rate measurements also evaluate the cerebral metabolic rate of oxygen consumption (CMRO₂)(24), an important parameter in the evaluation of cerebral oxygen metabolism(25). While fetal cerebral blood flow rates may be measured using Doppler ultrasound, other methods are required for measuring fetal blood oxygenation. The current methods for measuring human fetal blood oxygenation are often

invasive and/or can only be applied to fetuses intrapartum(26–28). Recently, a non-invasive method for blood oxygenation measurement in-utero was developed based on trans-abdominal near infra red spectroscopy (NIRS)(29). However, this method can only be applied to near term fetuses (>36weeks gestation) due to methodological limitations of NIRS.

Blood oxygen level dependent (BOLD) MR imaging is highly sensitive to changes in blood oxygenation levels(30–32) and has been used in quantitative assessment of cerebral metabolic rate in stroke and multiple sclerosis patients(33–35). Susceptibility weighted imaging (SWI) is an MR imaging methodology which takes advantage of the BOLD mechanism to generate not only venograms of the brain, but also to quantify venous oxygenation levels(36–40). In this work, we applied SWI and the principles of MR susceptometry to evaluate fetal cerebral blood oxygenation in humans. Specifically, we used the SWI phase images to evaluate putative venous oxygen saturation from the superior sagittal sinus of the fetal brain in-utero. The superior sagittal sinus, which carries most of the cerebral venous return, was chosen for measurement due to its relatively large size compared to other venous structures in the developing brain. Possible systematic error in this SWI-phase based venous oxygenation measurement was also assessed through simulations.

Materials & Methods

Theory

Phase from a gradient echo MRI experiment provides a direct measure of the field perturbation within a tissue relative to its immediate background via Eq. [1]. Here, γ is the proton gyromagnetic ratio, B is the field perturbation, TE is the echo time of the experiment and ϕ is the phase difference between the tissue and its immediate background. For an infinitely long cylinder with a magnetic susceptibility difference of χ , inside a uniform external magnetic field, the field perturbation is given by Eq. [2] where θ is the angle made by the long axis of the cylinder with the main magnetic field B_o (see Figure 1a):

$$\Delta\phi = -\gamma \cdot \Delta B \cdot TE \quad [1]$$

$$\Delta B = \frac{\Delta\chi}{6} \cdot (3\cos^2\theta - 1) \cdot |B_o| \quad [2]$$

Due to the paramagnetic nature of deoxyhemoglobin, veins carrying deoxygenated blood have a magnetic susceptibility, χ_{vein} , different from the surrounding parenchyma. This susceptibility is dependent on the deoxyhemoglobin content in the vein(41). The relation between the venous oxygen saturation, Y_v , and their magnetic susceptibility is given by Eq. [3] where χ_{do} is the magnetic susceptibility difference between fully deoxygenated and fully oxygenated blood and Hct is the blood hematocrit.

$$\Delta\chi_{vein} = \Delta\chi_{do} \cdot (1 - Y_v) \cdot Hct \quad [3]$$

$$Y_v = 1 - \frac{6 \cdot |\Delta\phi_{sss}|}{\Delta\chi_{do} \cdot Hct \cdot (3\cos^2\theta - 1) \cdot (|\gamma B_o| \cdot TE)} \quad [4]$$

Making the assumption that superior sagittal sinus (SSS) vessel could be modeled as an infinitely long cylinder, SSS oxygen saturation can be evaluated using Eq. [4] which is in turn obtained(42,43) from Eqs. [1] to [3]. Here ϕ_{sss} is the difference between the phase inside the SSS vein and the background parenchyma. The value of χ_{do} for fetal blood is assumed to be the same as that for the adult blood, which is 0.27 parts per million (ppm) in cgs units(44,45) or $4 \cdot \pi \cdot 0.27 = 3.39$ ppm in SI units. Fetal blood hematocrit values appropriate for gestational age (GA) were obtained from the literature(46). They were estimated using the linear regression equation $Hct = 22.9\% + GA \cdot 0.5\%$ which provides the normal range of fetal blood hematocrit across different gestational ages(46). Here GA is gestational age in weeks. Using Eqs. [1] through [4], the error in measured Y_v is obtained by propagating error in phase to error in χ_{vein} and consequently error in Y_v :

$$\delta\chi_{vein} = \frac{6 \cdot \delta(\Delta\phi_{sss})}{(3\cos^2\theta - 1) \cdot |\gamma B_o| \cdot TE} \quad [5]$$

$$\delta Y_v = \frac{-\delta(\Delta\chi_{vein})}{\Delta\chi_{do} \cdot Hct} \quad [6]$$

where δ (parameter) denotes the error within that parameter.

Subject Recruitment

Nineteen pregnant women who were receiving routine obstetric care at XXXX, were non-consecutively recruited in this study. Pregnant women, between the age of 18 to 38 years and who were between 19 and 40 weeks gestation were approached for recruitment. Singleton, uncomplicated pregnancies with normal ultrasound examination, reporting no contraindications for MRI were eligible to participate. The imaging study was approved by the local institutional review board and was compliant with HIPAA regulations and written informed consent was obtained prior to the research MRI scan. The mean gestational age of the fetuses included in this study was 31.59 $\pm$ 4.65 weeks (range 19 6/7 to 38 5/7 weeks). Study participants were followed longitudinally to assure that they developed no complications during pregnancy.

MR Imaging

Fetal MR imaging was carried out on a 3T Siemens Verio system (Erlangen, Germany) using a 4 channel body flex array coil, along with the spine coil. In some cases of subjects with large girth, an additional 2 channel flex extremity coil was used. Image data from the fetal brain was acquired using routine anatomical scans followed by SWI sequences. Anatomical data was acquired using T2-HASTE sequence with the following parameters: TR=3000msec, TE=140msec, slice thickness = 3mm, in-plane resolution = $0.87 \times 0.87\text{mm}^2$, acquisition matrix size = 320 $\times$ 320, BW = 372 Hz/pixel and flip angle = 75°.

Fetal Susceptibility Weighted Imaging (fetal-SWI)—The conventional SWI sequence(37) was adapted in the following manner for both two dimensional (2D-SWI) and three dimensional (3D-SWI) data acquisition versions for fetal imaging. The modification was to allow for fast data acquisition within a single maternal breath-hold. For the 2D version, a single echo 2D SWI sequence was implemented at 3.0T with the following imaging parameters: TR= 280msec, TE between 15 to 18.7msec, bandwidth = 199Hz/pixel, flip angle = 32°, acquisition matrix size between 448 × 168 and 448 × 175, in plane resolution between 0.78mm x 1.56mm and 0.85mm x 1.7mm and slice thickness = 3.5mm. Images were interpolated to a square pixel size in-plane to either 0.78×0.78mm² or 0.85×0.85mm². A total of 10 to 11 slices were collected within a total acquisition time of 22 to 24seconds.

For the 3D fetal SWI sequence, the following imaging parameters were used: TR 23msec, TE between 13.5 to 17.3msec, flip angle-10°, bandwidth of 219Hz/pixel, voxel size of 0.78mm x 1.56mm in-plane with a slice thickness of 3 or 3.5 mm and an acquisition matrix size of 448 × 175. Images were interpolated to a square pixel size in-plane, i.e., to 0.78×0.78mm². A total of 16 slices were acquired. In addition to a parallel imaging factor of 2, partial-Fourier reconstruction in both phase and slice direction was used to reduce the total data acquisition time to between 22 and 24 seconds. Both 2D-SWI and 3D-SWI sequences were acquired under maternal breath-hold condition.

In all subject scans, both T2-HASTE and SWI data (either 2D-SWI or 3D-SWI or both) were acquired multiple times to achieve appropriate fetal brain coverage or when fetal motion was encountered. SWI data was always acquired axial to the fetal brain. In some subjects, both 2D and 3D SWI data were acquired when scan time restrictions permitted.

Data Analysis

Fetal-SWI image data were first reviewed for general quality and artifacts. SWI data from two subjects could not be analyzed due to unavoidable fetal motion or severe magnitude aliasing artifacts. In the remaining 17 subjects, fetal-SWI data were reviewed for proper visualization of superior sagittal sinus (SSS) in both magnitude and phase images. Due to severe partial voluming and/or very small vessel size, in twelve of the subjects, phase from SSS could not be properly measured. Only in the remaining 5 subject datasets was the phase data in the SSS amenable for further quantitative oxygen saturation analysis. Hence, the following description of data analysis procedure pertains only to the 2D or 3D data from these 5 subjects. Since SWI scans were often repeated in each subject to ensure complete fetal brain coverage, the SSS was often visualized in more than one acquisition for a given subject. Table 1 provides a summary of the subject information and the number of fetal-SWI scan sets analyzed. The average gestational age of these 5 subjects was 33.7+/-3.6 weeks (range 28 2/7 – 36 3/7 weeks).

Oxygen Saturation Measurement from Phase—Raw phase images from the fetal-SWI data were first filtered using a mild homodyne high pass filter(47) of size 32×32 to remove background field inhomogeneities due to air-tissue interface. In each of the fetal brain SWI data sets from a given subject, 3 consecutive slices were chosen such that there is

no considerable displacement of the SSS vessel lumen between these three consecutive slices. This was to ensure that the segment of SSS with the least curvature was chosen which was relatively perpendicular to the imaging slice. Mean and standard deviation of the phase values from the SSS, seen in the posterior aspect of the fetal brain in the three consecutive slices, were then measured. Phase images were zoomed by a factor of 4 and a region of interest (ROI) was manually drawn within the vessel to avoid the boundary voxels to minimize partial volume effects. A nearest neighborhood algorithm was used for image zooming. The average number of voxels within these ROIs across all subjects was 41.5 ± 15.14 voxels after mapping the boundary back into the original images. In each slice, mean and standard deviation of phase from a reference region, was also measured from the white matter of the fetal brain. The phase difference ϕ_{SSS} was then obtained by subtracting the phase measured in the reference region from the phase measured in the SSS vessel ROI. The fetal head is usually in an arbitrary orientation within the mother's womb, as illustrated in Figure 1b. Since SWI data were acquired axial to the fetal brain, the slice normal vector from the image header information (Digital Imaging and Communications in Medicine - DICOM standard) was utilized to evaluate the angle, θ , that the SSS vessel segment made with the main magnetic field B_0 . Substituting the values of ϕ_{SSS} , θ , TE, Hct, χ_{do} , γ and B_0 into Eq. [4], the value of Y_v was obtained. The error associated with each measurement from a given slice was evaluated using Eqs. [5] and [6], taking into account the standard deviations of both background and SSS ROI phase measurements. Finally, the oxygen saturation values obtained from each slice and each fetal-SWI dataset for a given subject were averaged to obtain the mean Y_v value for that subject. Associated standard error was also evaluated.

Simulations

To evaluate the systematic errors expected from measurement methods employed in this study, a digital phantom of an adult brain was used (40,48). Specifically, errors expected due to deviation from the assumption of the SSS being an infinitely long cylinder (which includes the influence of vessel shape and vessel curvature) and due to the influence of high pass filtering of phase data were evaluated. A 3D digital brain phantom (40,48) with isotropic voxel size of 0.5 mm was constructed by segmenting structures from adult brain MRI data, containing the cerebrum, the cerebellum, gray matter (GM), white matter (WM), red nucleus (RN), substantia nigra (SN), crus cerebri (CC), thalamus (TH), caudate nucleus (CN), putamen (PUT), globus pallidus (GP), cerebrospinal fluid (CSF), and the major venous vessels including the superior sagittal sinus. Tissue magnetic susceptibility values in parts per million (ppm) for the structures SN, RN, PUT, and GP, were adapted from Haacke et. al (39) and others were from Wharton et. al. (49). The following are the susceptibility values in ppm used in the model: RN = 0.13, SN = 0.16, CC = 0.03, TH = 0.01, CN = 0.06, PUT = 0.09, GP = 0.18, venous vessels = 0.45, GM = 0.02, CSF = 0.014, and WM = 0. A susceptibility of 0.45 ppm used in the venous vessels corresponded to a venous oxygen saturation (Y_v) of 70% for a hematocrit (Hct) value of 0.44. All structures were set inside a $512 \times 512 \times 512$ zero filled matrix and phase was simulated from this susceptibility matrix using the forward field perturbation method (50,51). To study the situation of arbitrary fetal brain orientation, the field for the digital brain phantom was simulated for three different slice-normal angles relative to B_0 : $+30^\circ$, 0° , -30° , as illustrated in Figure 2. Imaging

parameters used for simulation were $B_0=3T$ and a TE of 18msec which is similar to the TE used for fetal imaging. Random noise and background field inhomogeneities from sinusoids(52) were not included as they did not have a direct influence on the primary goals of these simulations which were to: a) evaluate the influence of an infinitely long cylinder approximation for the superior sagittal sinus and b) evaluate the influence of the amount of phase information lost from the SSS due to high pass filtering on the final oxygen saturation measurements.

Simulated phase data was homodyne high pass filtered(47) using a 32×32 filter size. Following the same procedure used on fetal SWI data described above, measurements of oxygen saturation were obtained from both the original simulated phase ($Y_{v,sim}$) and high pass filtered phase data ($Y_{v,sim-HPfilt}$) in 3 consecutive slices and averaged. Vessel angle was taken to be 0° for calculation of Y_v because the SSS vessel segment in the posterior aspect of the brain is almost parallel to B_0 when a person is laying in supine position within the MRI system. The measured Y_v values were then compared with the initially assumed value of 70% and absolute error in, δY_v , was calculated relative to this value. This procedure was carried out at 3 different locations along the length of the SSS as shown in Figure 2, to evaluate the influence of SSS curvature. The locations were chosen such that the SSS vessel segment at location-I deviated slightly from being parallel to B_0 by $20^\circ \pm 1^\circ$. At location-II, the vessel segment angle was $12^\circ \pm 1^\circ$ and at location-III, the vessel segment was almost parallel ($0^\circ \pm 1^\circ$) to B_0 . These angles were measured manually by determining the angle made by a vector tangential to the vessel centerline with a vector parallel to B_0 . The value of Y_v is dependent on $\cos \theta$ and hence is independent of the sign of θ . Thus, the simulation of the brain volume at +30 and -30 relative to B_0 is equivalent to a θ value of 30° and $\delta\theta$ values of $\pm 20^\circ$ (location-I), $\pm 12^\circ$ (location-II) and $\pm 1^\circ$ (location-III) for the SSS.

Finally, from filtered and unfiltered simulation data, deviation of the measured oxygen saturation, $\delta Y_{v,sim} = (70 - Y_{v,sim})\%$ and $\delta Y_{v,sim-HPfilt} = (70 - Y_{v,sim-HPfilt})\%$ respectively was evaluated and compared for these three different locations. For an infinitely long cylinder, the theoretically expected absolute error δY_v due to an error in vessel angle θ can be given by:

$$Y_v - Y_{v,m} = \delta Y_v = \frac{18 \cdot \Delta\phi_m}{\Delta\chi_{do} \cdot Hct \cdot |\gamma B_0| \cdot TE} \left[\frac{\cos^2(\theta_m + \delta\theta) - \cos^2(\theta_m)}{(3 \cdot \cos^2(\theta_m + \delta\theta) - 1) \cdot (3 \cdot \cos^2(\theta_m) - 1)} \right] \quad [7]$$

Here $\delta\theta$ is the error in vessel angle, i.e., the actual vessel angle is $\theta_m + \delta\theta$, whereas the assumed vessel angle is θ_m , ϕ_m is the measured phase inside the cylinder, $Y_{v,m}$ is the measured oxygen saturation in the cylinder and Y_v is the actual oxygen saturation (or ground truth). Results from the simulations were compared with the theoretically predicted error. A brain model phantom, rather than a vessel-only model(53) was used in simulations to enable us to use the white matter as the reference region and follow the same measurement procedure for measuring ϕ_{SSS} as used in the fetal data.

Results

Simulations

For an infinitely long cylinder, figure 3 plots the theoretically expected δY_v as a function of assumed vessel angle θ for different values of $\delta\theta$ ($\pm 1^\circ$, $\pm 12^\circ$, $\pm 20^\circ$) using Eq. [7]. Following parameter values were used in generating the plot in Figure 3: $B_0 = 3$ Tesla, TE 18ms, Hct=0.44, $Y_v=70\%$ and $\chi_{do} = 4 \cdot \pi \cdot 0.27$ ppm. It is evident from Figure 3 that δY_v is dependent not only on the magnitude and sign of $\delta\theta$, but also on the assumed vessel angle θ .

Table 2 summarizes the results from simulations. There is systematic under- or over-estimation of Y_v , which is dependent on the initial angle of the vessel segment. Deviation from the assumed value of θ for a given vessel segment due to curvature also influences the error which is evident in the varying absolute error in Y_v from location-I to location-III for a fixed vessel angle.

Theoretical predictions from Eq. [7] of absolute error in Y_v for an infinitely long cylindrical vessel which is parallel to the field, are in good agreement with corresponding errors from simulations at $\theta=0^\circ$ (see Figure 3 and Table 2). For example, for a $\delta\theta$ of $\pm 20^\circ$ a δY_v of -5.27% is found in Figure 3 which is in very good agreement with $\delta Y_{v,sim} = -5.5\%$ measured from location-I in the simulations where the SSS vessel segment is making an angle of $+20^\circ$ with B_0 (see Figure 2). Furthermore, Figure 3 also shows that while for $\theta=0$, a positive or negative $\delta\theta$ always leads to a δY_v with the same sign and amplitude, the same is not true for non-zero vessel angles. For example, for $\theta = +30^\circ$ the value and sign of δY_v is different for $\delta\theta=+20^\circ$ and $\delta\theta=-20^\circ$. This is also seen in the results from simulations (Table 2).

Quantitatively, for a $\theta=30^\circ$ and $\delta\theta$ of -20° , -12° and -1° , Figure 3 predicts an error value $+15.7\%$, $+11.1\%$, $\mp 1.1\%$ respectively for δY_v . These values are larger than those obtained from simulations for $\delta Y_{v,sim}$: $+9.2\%$, $+10.2\%$ and 6.9% respectively, for corresponding values of θ and $\delta\theta$. The same is true for $\delta\theta$ values of $+20^\circ$, $+12^\circ$ and $+1^\circ$ (location-III) where the error values $\delta Y_{v,sim}$ obtained from the SSS in simulations is less than the theoretically predicted δY_v for an infinitely long cylinder (Figure 3). This could be due to the influence of the shape of the vessel cross-section which is not cylindrical and is changing along the length of the vessel as can be seen from Figure 2. Nonetheless, simulations show that even for large values of $\delta\theta=+20^\circ$ and $\theta = -30^\circ$, the systematic absolute error in Y_v is less than 11% (Table 2). High-pass filtering of phase did lead to a loss of phase information from the vessel which led to $Y_{v,sim}$ being different from $Y_{v,sim-HPfilt}$. The absolute difference between $Y_{v,sim}$ and $Y_{v,sim-HPfilt}$ was, however, less than 3% in all the cases.

Fetal SWI data

In the analyzed data from the 5 fetuses, the values of θ that the SSS vessel segments made with B_0 ranged from 26.9° to 36.8° degrees. A representative set of fetal SWI magnitude and phase images are shown in Figure 4. The SSS is clearly visualized in the posterior aspect of the brain on the axial images. The measured oxygen saturation values from the SSS from the 5 fetuses are plotted in Figure 5 across their respective gestational ages. Oxygen saturation values in the SSS along with the corresponding standard errors were $70 \pm 4.4\%$ in subject-1, $73.8 \pm 7.7\%$ in subject-2, $56.1 \pm 7.5\%$ in subject-3, $74.4 \pm 11.4\%$ in subject-4, and $55.7 \pm 6.4\%$ in

subject-5. Averaged over the 5 fetuses, the oxygen saturation within the SSS is $66 \pm 9.4\%$. The standard deviation of 9.4 quoted here represents the variation of the mean values across subjects and not the standard error.

Discussion

In this study, phase from susceptibility weighted images was used to evaluate oxygen saturation of the SSS in the fetal brain. To the best of our knowledge, this is the first study applying MRI for measuring cerebral venous oxygenation in the human fetus. The method employed in this paper for measuring Y_v is quite similar to the one used in the adult brain previously(42,43,54). Recently, various Fourier Transform based methods for quantitative susceptibility mapping from MR phase data have been developed(39,40,49,55,56). These methods make it possible to create a map of venous oxygenation throughout the brain (39,40). Unfortunately these methods could not be applied in this study due to poor image resolution.

Results from simulations provided an indication of the systematic errors that could be expected due to deviations from model assumptions, i.e., when the assumption that the SSS vessel segment could be modeled as an infinitely long cylinder, is violated. Influence of violation of these assumptions had been investigated previously by Li et. al.(53) for the SSS vessel segment in adults. For the case of $\theta=0^\circ$, our simulation results for absolute error $\delta Y_{v,sim}$ in the SSS (Table 2) are in good agreement with those obtained by Li et. al., and are also in good agreement with the theoretically predicted errors from Eq. [7] for an infinitely long cylinder (see Figure 3). While for $\theta=0^\circ$ the systematic absolute errors in Y_v are on the order of 5%, when the assumed vessel angle deviates from zero, these errors increase. Nonetheless, $\delta Y_{v,sim}$ is still within 11% for $\delta\theta$ as large as $\pm 20^\circ$ and assumed vessel angle of $\pm 30^\circ$ (see Table 2). The deviation of the errors obtained in simulations for non-zero vessel angles of $\pm 30^\circ$, from those predicted by Eq. [7] for an infinitely long cylinder could be due to the non-cylindrical shape of the SSS. In the analyzed fetal data, the vessel angle was generally close to 30° which is why the situation of $\theta=\pm 30^\circ$ was simulated to evaluate the magnitude of expected systematic error in Y_v .

The standard errors for the measured Y_v varied from one subject to another due to a) different number of SWI datasets analyzed and b) due to different magnitude signal to noise ratios partially owing to different echo times used. The average magnitude SNR was 9.4 ± 3.4 across all the fetal-SWI datasets analyzed. Despite these errors, the average value of the oxygen saturation measured is in good agreement with fetal cerebral venous oxygen saturation values in the literature. Vintzileos et al(29) measured cerebral venous oxygen saturation using trans-abdominal near infra-red spectroscopy in 6 fetuses who were of 36 weeks or older gestational age. They measured this to be $61\% \pm 14.8\%$, which is in close agreement with the average oxygenation in the SSS across the 5 subjects in this study which is $66\% \pm 9.4\%$.

Hematocrit values within the fetus vary with gestational age(46). Furthermore, the relative ratios of fetal hemoglobin and adult hemoglobin within the red blood cells also changes as a function of gestational age(57). In this study, Hct values for fetuses at different gestational

ages were obtained from the reference curves calculated by Boulot et al(46). These reference curves were obtained through measurements from 541 normal fetal blood samples obtained through cordocentesis. It is important to note that for absolute oxygen saturation measurement using MRI, we require the knowledge of fetal blood hematocrit. Nonetheless, the methods presented here could be employed to evaluate relative oxygen saturations within a fetus.

Due to lack of appropriate studies on magnetic properties of fetal blood, in this work it is assumed that the χ_{do} value of fetal blood is same as that of the adult blood. It is known that fetal blood contains predominantly fetal hemoglobin (HbF) which has a different chemical conformation and slightly different optical absorption properties(58) in the near infrared range compared to that of adult hemoglobin (HbA). It also has considerably higher oxygen affinity compared to HbA. Furthermore, relative ratios of HbF and HbA within the red blood cell changes with gestational age of the fetus(57). All of these factors could lead to fetal blood having $\chi_{do-fetal}$ different from χ_{do} of the adult blood. However, this remains to be investigated.

Long echo times are typically required for SWI and this makes it challenging in its application to fetal imaging due to fetal motion and maternal breathing. Larger fields of view in fetal imaging necessitate larger matrix size in data sampling which further increases scan time. Keeping in view the above aspects, in this work, appropriate parameter changes were applied to the conventional SWI sequence for fetal-SWI imaging. However, due to severe partial voluming, magnitude aliasing and fetal motion, data from only 5 of the 19 fetuses scanned were usable in this work. This low data usability issue could largely be improved with higher resolution imaging. Higher resolution data helps to ensure that the venous vessel of interest occupies a sufficient number of voxels and that there is sufficient phase information within and outside the vessel allowing for more accurate susceptibility mapping(59). Moreover, since susceptibility maps can be reconstructed from shorter echo time data as well(40), higher resolution may in turn help to reduce the scan time further by relaxing the long echo time requirement for SWI. Higher through plane resolution data also allows for proper ascertainment vessel angle. The challenge in acquiring high resolution fetal imaging data is fetal motion which necessitates high speed data acquisition. High resolution and fast data acquisition are usually mutually competing goals and often require employing novel and tailored methods(60–64). Development of appropriate fast imaging methods with high resolution reconstruction of both magnitude and phase MRI data would greatly benefit MR based quantitative oxygenation assessment methods in the fetus.

In conclusion, in this work, MR susceptibility weighted imaging is applied for quantitative assessment of fetal cerebral venous blood oxygenation. Measured oxygen saturation values are in agreement with those published in the literature. In contrast to the few non-invasive methods currently available for quantitative assessment of fetal blood oxygenation(26,28,29), using MRI allows us to make these measurements in the fetus at gestational ages earlier than 36 weeks. The ability to measure fetal cerebral oxygenation is very important as it opens the doors to the possibility of quantitatively studying hypoxic ischemic injury in-utero in at risk pregnancies. With blood flow measurements from

ultrasound or from MR imaging itself, it may be possible to obtain global cerebral metabolic rate of oxygen(24) in the fetal brain.

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Figure 1.

A) Illustration of vessel angle made with respect to the main magnetic field B_0 . B) Determination of the vessel angle in fetal imaging; illustration of the vessel angle made by the superior sagittal sinus in the fetal brain when the fetus is arbitrarily oriented within the maternal womb. With the acquisition of SWI data axial to fetal brain, determination of the angle made by the SSS in the posterior aspect of the brain is carried out using the vector normal to the slice. An implicit assumption in this angle determination is that the SSS vessel segment is perpendicular to the SWI imaging slice.

Figure 2.

Phase images from simulations with corresponding θ values as illustrated. Simulations were carried out for 3 different relative orientations of the axial slice-normal relative to B_0 , i.e., three different θ values. A) Sagittal phase image illustrating the three locations where phase measurements for determination of Y_V were carried out. B) Axial images corresponding to the central slice at the locations shown in (A). Images were zoomed by a factor of 4 and cropped to show phase in the SSS for the three different θ values of 0° , $+30^\circ$ and -30° .

Figure 3.

Absolute error in Y_v for an infinitely long cylinder, plotted as a function of the vessel angle, θ , for different values of $\delta\theta$. The various curves are calculated using Eq. (7) for which the following parameters were used: $Hct=0.44$, $\chi_{do} = 4 \cdot \pi \cdot 0.27$ ppm, $TE = 18ms$, $B_o = 3$ Tesla and $Y_v=70\%$. The curves are plotted for 6 different values of $\delta\theta$, $\pm 1^\circ$, $\pm 12^\circ$ and $\pm 20^\circ$ closely matching the parameters in the simulations.

Figure 4.

Representative examples of magnitude and phase images from several fetal SWI data sets. A) Magnitude image of the fetal brain from a fetus at 36 3/7 weeks gestation. B) The corresponding phase image. The arrow head points to the superior sagittal sinus. C) Magnitude image of the fetal brain from a fetus at 28 2/7 weeks gestation. D) The corresponding phase image. In this second example, the extra-vascular dipolar phase associated with the magnetic susceptibility of the superior sagittal sinus vein (arrow) is evident in (D).

Figure 5.

Oxygen saturation values measured from 5 fetal brain SWI data plotted across their gestational age. The mean oxygen saturation across 5 fetuses was $66\% \pm 9.4\%$. The standard deviation here represents across-subject variation.

Table 1

Summary of fetal SWI data-sets analyzed

	GA (Weeks)	Hematocrit (Hct)	# of Fetal-SWI data sets analyzed
Subject-1	35	0.508	3
Subject-2	36 3/7	0.517	4
Subject-3	37 1/7	0.522	2
Subject-4	28 2/7	0.465	2
Subject-5	32	0.489	1

Table 1: The table provides the number of fetal SWI datasets analyzed in each subject for measurement of cerebral venous blood oxygenation. Hematocrit values appropriate for the gestational age of the fetus were obtained from the reference values in Boulot et al⁴⁶.

Table 2

Results from the simulations.

Location	$\delta Y_{v,sim} = 70 - Y_{sim} \%$	$\delta Y_{v,sim-HPfilt} = 70 - \delta Y_{v,sim-HPfilt} \%$
theta=0°		
I	-5.5	-7.3
II	-2.1	-4
III	-1.6	-3
theta = -30°		
I	-7.6	-9.3
II	-4	-6.6
III	5.7	3.5
theta = +30°		
I	9.2	6.4
II	10.4	8
III	6.9	5.4
(-ve deviation implies an overestimation of Y_v)		
Hct = 0.44, $B_0=3T$, TE=18msec and input Y_v value of 70% were used in simulations.		

Table 2: The table summarizes results from the simulations. Systematic absolute error, $\delta Y_{v,sim}$, in the quantified Y_v relative to the input value of 70% is tabulated. Absolute error in Y_v due to high pass filtering of phase, $\delta Y_{v,sim-HPfilt}$, is also shown. $Y_{v,sim}$ - Measured oxygen saturation in SSS from simulated phase. $Y_{v,sim-HPfilt}$ - Measured oxygen saturation in SSS from phase images obtained after high pass filtering the simulated phase using a 32×32 filter size.