Blood Oxygenation of Human Fetal Brain in the Second and Third Trimester

Pavan Kumar Jella[1], Uday Krishnamurthy[1,2], Jaladhar Neelavalli[1,2], Swati Mody[1], Lami Yeo[3,4], E. Hernandez-Andrade[3,4], E. Ehterami[1], M.D. Cabrera[1], S.J. Korzeniewski[3], E.M. Haacke[1,2], Sonia Hassan[3], and Roberto Romero[3]

[1]Department of Radiology, Wayne State University, Detroit, MI, United States, [2]Biomedical Engineering, Wayne State University, Detroit, MI, United States, [3]NICHD, NIH, DHHS, Perinatology Research Branch, Detroit, MI, United States, [4]Obstetrics and Gynecology, Wayne State University, Detroit, MI, United States

Introduction: A major issue in studying fetal hypoxic ischemic injury in-utero in humans is that tools for identification of fetal brain injury in-utero are limited and in some cases the diagnosis does not occur until the post neonatal period when the injury becomes evident in neuroimaging. Hence, non-invasive imaging methods for assessing hypoxic-ischemic brain injury in-utero are of high clinical interest which may help in better prediction of long-term outcomes [1]. The ability to measure fetal blood oxygenation helps in assessing fetal oxygen utilization [2]. Along with blood flow parameters, it is possible to assess the metabolic rate of fetal oxygen utilization which can in turn help identify chronic or acute hypoxia in the fetus. As a first step towards this, we had established recently the feasibility of quantifying fetal blood oxygenation using susceptibility weighted magnetic resonance imaging (SWI) and principles of susceptometry [3]. In this study we have extended this work to quantify differences in blood oxygenation in the human fetal brain in second and third trimesters.

$$Y_v = 1 - \frac{6 \cdot |\Delta\varphi|}{\Delta\chi_{do} \cdot Hct \cdot (3\cos^2\theta - 1) \cdot (|\gamma B_o| \cdot TE)} \quad -Eqn.(1)$$

Material and Methods: **Theory:** SWI phase data ($\Delta\varphi$) provides a direct measure of the field perturbation (ΔB) within a tissue relative to its immediate background. Due to the paramagnetic nature of deoxyhemoglobin in the venous blood, it has different magnetic susceptibility ($\Delta\chi_{vein}$) compared to the surrounding parenchyma which is dependent on its oxygen saturation [4-6]. This difference in the magnetic susceptibility of the venous blood has a direct relation to the oxygen saturation (Y_v), which is given by the Eqn. (1) where, $\Delta\chi_{do}$ is the magnetic susceptibility difference between fully deoxygenated and fully oxygenated blood, Hct is the blood hematocrit (which varies as a function of gestational age (GA) as *Hct = 0.29 + GA*0.0064* [7]), TE is the echo time of the experiment, θ is the angle made by the long axis of the cylinder with the main magnetic field B_o, and γ is the proton gyromagnetic ratio. Measuring $\Delta\varphi$ from a relatively straight section of a vein, Yv was obtained using Eq. 1.

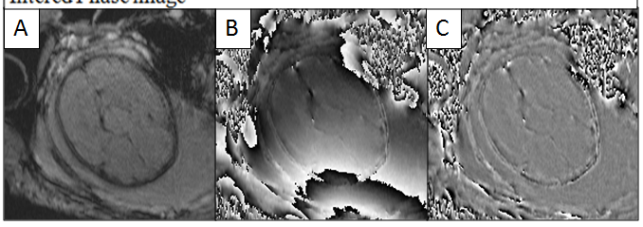
MR Imaging: 2D and 3D fetal-SWI data (see Table 1 for sequence parameters) from 27 pregnant subjects, 13 in second trimester (mean GA = 23 weeks) and 14 in third trimester (mean GA = 33 weeks) with normal singleton pregnancies were analyzed. Subjects were recruited and scanned on a 3T Siemens Verio system in accordance with local IRB guidelines after written informed consent was obtained. No sedation was used for this fetal MRI scan study. Study participants were followed longitudinally to assure that they developed no complications during pregnancy. SWI data was acquired axial to the fetal brain, often under maternal breath-hold condition (2D and 3D SWI acquisition time: 22-24 sec); using modified conventional SWI sequence [8].

Table 1: MR Imaging Parameters

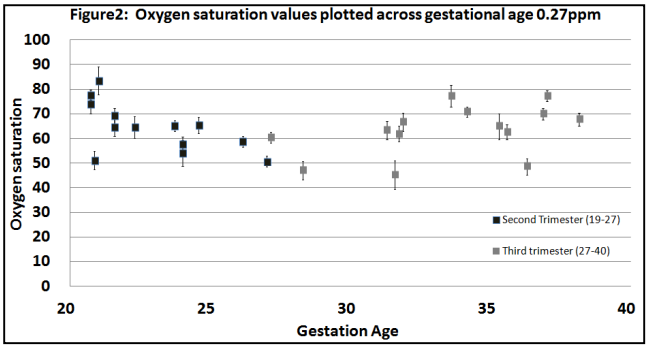
Sequence Mode	TR (ms)	TE (ms)	Flip Angle in degrees	In plane reconstructed voxel size (mm)	Slice Thickness (mm)	BW (Hz/pixel)	# of Slices
2D	250 to 280	15 to 18.7	32°	0.78 x 0.78 mm^2 or 0.85 x 1.70 mm^2	3.5mm	199	10 or 11
3D	20 to 23	13.5 to 17.3	10°	0.78 x 0.78	3 to 3.5mm	219	16

Data Analysis: Raw phase images from the fetal-SWI data were filtered using a mild homodyne high pass filter [9] of size 48x48 to remove background field inhomogeneities. Mean and standard deviation of,$\Delta\varphi$, vessel phase measurements within relatively straight sections of the superior sagittal sinus (SSS) in 38 subjects. Phase in white matter of the fetal brain was used as reference tissue relative to which $\Delta\varphi$ was measured. The angle θ, that the vessel segment's long axis makes with B_o, was ascertained using image orientation information from the DICOM header. Substituting the values of $\Delta\varphi_{sss}$, θ, TE, Hct, $\Delta\chi_{do}$, γ and B_o in Eq. (1), the value of Y_v was obtained. A $\Delta\chi_{do}$ value of 0.27 ppm cgs units was assumed for fetal blood [11]. A paired t-test with was performed to evaluate differences in the measured blood oxygenation between the second trimester group and third trimester.

Figure 1: A. Magnitude Image; B. Original phase image; C. High pass filtered Phase image



Results: Figure 1 shows representative SWI magnitude and phase images of the fetal brain. Figure 2 shows the putative oxygen saturation measured from 27 fetal brain SWI data plotted across their GA. The mean cerebral venous oxygen saturation across the 13 fetuses in the second trimester was 64.3+/-10%, and across 14 fetuses in their third trimester was 63+/-10%. There was no statistical difference between these groups in the measured cerebral blood oxygenation. The standard deviation here represents across subject variability. The average value of fetuses in third trimester is in close agreement with the fetal cerebral venous oxygen saturation, (61±14%), measured using trans-abdominal near infrared spectroscopy (NIRS) by Vintzileos et al [10].



Discussions: In this cross-sectional study, we evaluated cerebral blood oxygenation differences between second and third trimester fetuses using MR susceptometry. We see no statistical difference between these groups and find that the human fetal cerebral blood oxygen saturation across second and third trimester is 63.7+/-10%. This is in good agreement with recent reports on oxygen extraction fraction studies in neonates which remained almost constant during the neonatal growth period [12]. Susceptibility mapping methods were not viable in this study due to the low image resolution. We expect that with future developments in speed and hence resolution, that the use of quantitative susceptometry or mapping will play an important role in the future studies of oxygen saturation in the fetus. This MR based technique has the advantage of measuring cerebral venous oxygenation as early as 19 weeks of gestation until term, compared to the other noninvasive techniques existing today, which can only be employed at late gestational ages of 36 weeks and older [10]. Along with fetal blood flow measurements, MR based assessment of fetal blood oxygenation could open the doors for studying fetal brain hypoxic ischemic injury in-utero.

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