1H MRS as a Biomarker for Placental Insufficiency in the Growth Restricted Fetus

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Purpose: Placental insufficiency commonly leads to fetal growth restriction (FGR) and stillbirth[1]. When diagnosed antenatally the only effective treatment is delivery which, if preterm, is itself associated with increased morbidity and mortality. Although FGR indicates that the fetus has been exposed to placental insufficiency for a long period of time, there is a need for an acute biomarker to inform timing of delivery. Placental glutamine and glutamate (Glx) could provide this acute biomarker. In vivo ^{1}H spectroscopy has the potential to directly detect placental Glx. We hypothesise that the ratio of Glx and choline (Cho) could be a useful marker of placental function. Glutamine plays a vital role in the production of the nucleotides and amino sugars required for cell proliferation[3]. There is evidence that glutamate is produced in the fetal liver and is used in the synthesis of glutamine in the placenta[3, 4]. In ^{1}H spectra the presence of choline is a marker of cell proliferation. Here the in vivo placenta ^{1}H spectra acquired from 4 restricted growth pregnancies and 4 gestation matched healthy pregnancies have been characterised. To our knowledge this has never previously been reported in-utero in the human placenta.

Method: 4 women with growth restricted and 4 gestation matched controls with a singleton pregnancy were recruited. Fetal growth restriction was defined as a fetal abdominal circumference <10th centile for gestation. All spectra were acquired at 3T (Siemens Verio, Siemens Healthcare, Germany). A single voxel PRESS technique was employed with TR/TE/NSA=1500ms/30ms/96, bandwidth=2000Hz and water suppression bandwidth of 50Hz. A 20×20×40mm voxel was positioned within the placenta. An optimised adjustment protocol was applied to shim currents resulting in typical water peak line widths of between 15-35Hz. Significant movement of the placenta was not expected during spectral acquisition and data was acquired with the mother free breathing throughout. Women were placed in a left lateral position on the scanner bed to avoid vena cava compression. Signal was received from selected elements of the spine matrix coil and a body matrix surface coil positioned over abdomen. Care was taken to acquire spectra with the placenta positioned at isocentre. Placenta spectral peak amplitudes were estimated using the Quest algorithm available in JMRUI (http://www.mrui.uab.es/mrui). This required a metabolite basis set (including contributions for Glx, Cho and fatty acid) to be generated using NMR-Scope also available in JMRUI. Our analysis technique was validated using adult brain spectra with a brain-specific basis set.

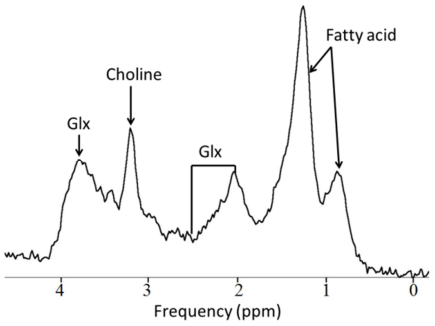

Figure 1: An example of a ^{1}H spectrum of the placenta from a healthy pregnancy indicating glutamine and glutamate (Glx), choline (Cho) and fatty acid.

	Glx/Cho ratio
FGR 1	1.96±0.11
Control 1	3.93±0.41
FGR 2	2.54±0.08
Control 2	4.52±0.36
FGR 3	2.83±0.19
Control 3	3.96 ±0.15
FGR 4	2.87±0.10
Control 4	3.50±0.18

Table 1: Ratios of glutamine and glutamate (Glx) to choline (Cho) in fetal growth restricted pregnancies and gestation-matched controls.

Results/Discussion: An example spectrum from one of the control subjects is shown in Figure 1. In all spectra the Quest algorithm detected the presence of Cho at 3.2ppm and Glx between 2.06-2.44ppm and at ~3.78ppm. These frequencies are in accordance with the observation of these metabolites in adult brain spectra. Quantification of Glx in the brain is challenging as it overlaps with the dominant NAA peak at ~2.02ppm. In the placenta there is no NAA peak making this less difficult. Other metabolites such as alanine and leucine may also contribute to the peak observed at ~3.78 but the literature suggests that Glx is present in the placenta in much higher concentrations than other amino acids[3]. The Glx/Cho ratios for 4 FGR placentas and 4 gestation-matched healthy placentas are shown in Table 1. In each case the Glx/Cho ratio for the FGR placentas are lower than in that of their matched control.

Conclusion: This preliminary study has shown that the Glx/Cho ratio may be a potential biomarker of placental insufficiency. The acquisition of adequate placenta spectra is technically demanding and can be adversely affected by several factors e.g. large scale motion of mother or fetus and position of placenta relative to the surface coil. Therefore further work is required to develop robust acquisition and analysis protocols for this purpose.

References: (1) Kramer M, Olivier M, McLean F et al. Impact of intrauterine growth retardation and body proportionality on fetal and neonatal outcome. Pediatrics.1990;86:707-13, (2) Denison F, Semple S, Stock S et al. Novel use of proton magnetic resonance spectroscopy (1HMRS) to non-invasively assess placental metabolism. PLOS ONE. 2012; 7 (8): 1-8. (3) Self J, Spence T, Johnson G et al. Glutamine synthesis in the developing placenta. Biol Reprod. 2004; 70: 1444-1451. (4) Novak D, Beveridge M. Glutamine transport in human and rat placenta. Placenta. 1997 (18):379-386.

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