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Abstract title: Altered biochemical profiles in fetuses with congenital heart disease

Background: Congenital heart disease (CHD) is one of the most common congenital birth defects, affecting ~1% of all live births. The origins of neurodevelopmental dysfunction in infants with congenital heart disease (CHD) are increasingly finding their footprints in fetal life. Previous studies have reported disturbances in fetal brain metabolism in CHD; however, these studies have been cross-sectional in nature with modest sample sizes.

Objective: The objective of this study was to prospectively compare fetal biochemical profiles in a large cohort of health and CHD fetuses using proton magnetic resonance spectroscopy (1H-MRS).

Study Design/Methods: We prospectively enrolled 328 pregnant women of which, 219 had healthy fetuses and 109 had fetuses diagnosed with CHD. Pregnant women were scanned during the second and third trimester of pregnancy ranging from 18 to 39 weeks gestational age (GA). Mean GAs for healthy fetuses was 31.2 ± 4.2 weeks and 31.7 ± 5.1 weeks for CHD fetuses. SSFSE images acquired in all three planes were used as a guide to place the voxels in the central brain of the fetal brain for spectroscopic measurements. Spectra were acquired using PRESS localization sequence (TE/TR: 144/1500 ms). 192 averages of water suppressed spectra were acquired along with 16 averages of water unsuppressed spectra from a 30x30x30 mm3 voxel placed in the central brain. Phase and frequency correction were performed using programs written in Matlab and spectra were quantified in the 'LCModel' program using water as an internal reference. Data with CRLB >20% for total Choline (tCh) were excluded from further analysis. For all other metabolites, exclusion criteria included CRLB>100%. NAA and Cre concentrations are lower in early GA, hence, exclusion criteria of CRLB>100% is used in this study which is higher than 20% that has traditionally been used to avoid biasing the metabolite concentrations to higher values. Statistical analysis included linear regression to assess metabolic trajectory as a function of GA and diagnostic status.

Results: Results from generalized estimating equations with diagnostic status and GA as variables showed significant increase in tNAA, tCh, tCr across advancing GA ($p<0.0001$). Fetuses with CHD had significantly lower tNAA/tCh ratios compared to control fetuses ($p=0.02$). Our results also showed higher levels of Lac ($p=0.01$) and tCh ($p=0.02$) in CHD fetuses compared to healthy fetuses across all GAs. All conventional MRI studies for control and CHD fetuses showed no structural injury. Higher levels of brain lactate in CHD fetuses suggests the presence of anaerobic metabolism, while lower NAA/Ch ratios suggest neuronal injury in the absence of demonstrable injury on conventional MRI.

Conclusions: In a large prospective observational study, we report slower increase in tNAA/tCh ratio and higher Lac in fetuses diagnosed with CHD compared to control fetuses, suggesting neuronal injury and anaerobic metabolism. These data demonstrate that metabolic alterations in CHD fetuses are prevalent and may be an important early biomarker for subsequent risk of brain injury in this high-risk population.