

# Maternal Stress Alters Hippocampal Development in Fetuses with Congenital Heart Disease

Yao Wu<sup>1</sup>, Mary T. Donofrio<sup>2</sup>, Kushal Kapse<sup>1</sup>, Gilbert Vezina<sup>3</sup>, Catherine Limperopoulos<sup>1</sup>

1. Department of Developing Brain Research Laboratory, Children's National Health System, Washington, DC 20010, USA
2. Division of Cardiology, Children's National Health System, Washington, DC 20010, USA
3. Department of Diagnostic Imaging and Radiology, Children's National Health System, Washington, DC 20010, USA

**BACKGROUND:** Maternal stress and anxiety during pregnancy are associated with impaired hippocampal growth in human fetuses and young infants. However, the prevalence of maternal stress in pregnant women diagnosed with a fetal congenital heart defect (CHD) is poorly understood. Moreover the extent to which in utero hippocampal development in CHD fetuses is impaired in the setting of maternal stress is unknown.

**OBJECTIVE:** 1) To determine the prevalence of prenatal maternal stress in women carrying fetuses diagnosed with CHD, and 2) to examine the impact of maternal stress on hippocampal volumetric growth and shape in CHD fetuses using quantitative in vivo MRI.

**DESIGN/METHODS:** We prospectively recruited pregnant women with a fetal diagnosis of CHD requiring neonatal cardiac surgery. All pregnant women underwent fetal MRI on a 1.5T GE scanner (single shot fast spin echo; TR/TE: 1100/160 ms; flip angle: 90°). We performed 75 MRIs in 45 CHD fetuses (29 males, 16 females) between 22-39 weeks of gestation; 30 pregnant women underwent two fetal MRIs. Left/right hippocampi and total brain volume (TBV) were manually delineated on 3D reconstructed T2W MRI scans using ITK-Snap software. The Perceived Stress Scale (PSS) was completed by all pregnant mothers on the same day of the fetal MRI. A PSS cut-off score above 15 was used to define higher than average stress. Spherical harmonic description (SPHARM) was used to measure the surface difference of the hippocampi between groups with low vs high stress, controlling for TBV.

**RESULTS:** Over half (51.9%) of pregnant women with fetal CHD tested positive for high maternal stress. Left and right hippocampal volumes in CHD fetuses were significantly smaller in the high-stress group compared to the low-stress group (left:  $p < 0.001$ ; right:  $p = 0.03$ ), controlling for TBV (Table 1). Regional impairments in hippocampal development in CHD fetuses whose mothers had elevated prenatal stress were noted in the medial aspect of the left hippocampal head (blue), the inferior aspect of right hippocampal head (blue) and medial view of right hippocampal body (red) (Figure 1).

**CONCLUSIONS:** Our data show that maternal stress is common in pregnancies complicated by fetal CHD and adversely affects global and regional hippocampal development. The long-term impact of altered in utero hippocampal development on later neurocognitive outcomes in infants with CHD is unknown and currently under study.

Acknowledgment: This study was funded by NIH-R01 HL116585-01.

Table 1. Hippocampal volumes of CHD fetuses with low vs high maternal stress (cut-off score=15).

Groups	Left hippocampus (cm <sup>3</sup> )	Right hippocampus (cm <sup>3</sup> )
Low stress (PSS<15)	0.510 ± 0.156	0.522 ± 0.161
High stress (PSS≥15)	0.449 ± 0.128	0.477 ± 0.138
P value	<0.001	0.03

Figure 1. The surface difference of the hippocampus in CHD fetuses with low vs high maternal stress.

