

Fetal brain during a binge drinking episode. A dynamic susceptibility contrast fetal brain perfusion study.

P. Kochunov¹, C. Castro², G. Schatten³, D. Purdy⁴, H-Y. Wey¹, and D. Davis¹

¹Research Imaging Institute, UTHSCSA, san antonio, TX, United States, ²Ob / Gyn and Reproductive Sciences, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States, ³Pittsburgh Development Center, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States, ⁴Siemens Healthcare USA, Malvern, PA, United States

Introduction: Detrimental effects of chronic maternal alcohol consumption on fetal brain are well documented. Alcohol freely crosses the placental barrier and causes extensive CNS damage, stunted brain growth, and is the leading cause of mental retardation in the USA. While the teratogenic properties of alcohol are well known, the mechanisms by which alcohol-induced damage is produced in the CNS are still largely unknown. We present findings of changes in dynamic susceptibility contrast (DSC) in fetal brain of a non-human primate (baboon) during a protocol designed to approximate a binge drinking episode.

Methods: Animal subjects. Three pregnant dam (*Papio hamadryas Anubis*) were imaged at the 24th week of pregnancy. Baseline DSC fetal brain perfusion studies were followed by administration of ethyl alcohol. Imaging was performed using a 3 T Siemens Tim Trio scanner equipped with multi-channel body array coils. Animal handling and anesthesia were described elsewhere. All experiments were performed under IACUC-approved protocols.

Sequence details. Perfusion imaging with a gradient echo EPI sequence was used to evaluate DSC in the fetal brain tissue and the nearby uterus and placenta. Parameters were adjusted to obtain a high temporal (TR=3sec) and spatial (1.2 x 1.2 x 1.9mm) resolution, acquiring 15 slices for full fetal brain coverage with no slice gaps. Respiratory gating was used to reduce motion artifacts.

Protocol. The protocol started with a 30 minute control DSC study, injecting a bolus of gadodiamide (OMNISCAN) (dose was calculated based on human adult dose equivalency) after five minutes. Next, alcohol was administered to the dam via a gastro-nasal catheter to achieve a blood-alcohol level content (BAC) of ~0.16. This is equivalent to the consumption by an adult human of 4-6 alcoholic drinks, approximating a binge-drinking episode. The dam's BAC was monitored using a blood gas technique. Once the desired BAC level was achieved, about 90 min after alcohol administration, a second DSC imaging session was commenced under the same conditions, e.g., a 5 min baseline was followed by contrast administration and imaging for 25 minutes.

Image analysis. EPI images were motion corrected and the intensity variations were measured by placing one ROI over the fetal brain and a second ROI covering the maternal uterus and placenta. ROI intensity values were normalized to the average values of the scans during the 5 min baseline acquisition.

Results: Figure 1 (top) showed that the average signal intensity in the uterus and placenta showed a rapid decline immediately following contrast administration. The trends were qualitatively similar before and after alcohol administration, with a minimum seen at about 1 min following the contrast injection. However, following alcohol administration, the signal showed a more pronounced peak (81% vs 84%) and showed a higher rate of recovery (0.5%/min versus 0.2%/min, respectively) possibly due to alcohol-induced vasodilatation. The trends in the fetal brain, Figure 2 (bottom), were qualitatively different before and after alcohol administration. Prior to alcohol administration, only minute amounts of contrast agent were observed in the fetal brain. The minimal signal intensity (99.2% of the baseline value) was observed at about 7.5 min after contrast administration, indicating that placental permeability all but prevented the high molecular weight (592) gadodiamide from entering the fetal blood pool. However, following the administration of alcohol, gadodiamide was observed entering fetal cerebral circulation, reducing the signal by ~4% within 7 minutes. In addition we observed rapid elimination of the contrast agent by 15 min following contrast injection, possibly due to increases in cerebral blood flow.

Discussion. We observed significant differences in DSC in fetal brain before and after administration of alcohol, which might explain some of the teratogenic effects associated with maternal alcohol consumption. We hypothesize two mechanisms to

Figure 1. Changes in average intensity for uterus and placenta (top) and fetal brain (bottom) before (blue) and after (red) alcohol administration

explain our findings. First, alcohol-induced vasodilatation changes the permeability of placental villi to the high molecular weight compound; second, alcohol changes fetal cerebral blood flow, possibly due to vasodilatation, producing hyperperfusion. We are conducting further studies of these hypotheses by performing quantitative calculation of the contrast trends using T2* relaxation data that were acquired as the part of the study.

Conclusion: Imaging studies in primate could elucidate the teratogenic mechanisms associated with maternal alcohol consumption.

Acknowledgment: This work was supported, in part, by the K01 #EB006395, NIH #P51-RR013986, 1R01AG029412-01, P01 HD047675 and R24 RR013632.