Examining intrauterine growth restriction due to placental insufficiency in fetal guinea pigs in utero using MRI

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Target Audience: Researchers interested in the use of MRI to detect metabolic disease, particularly with respect to its fetal origins.

Purpose: An intrauterine growth restricted (IUGR) fetus is one that is not growing to the extent of its genetic potential, as defined by its personalized growth curve.[1] IUGR is seen in approximately 5% of all births and is the second leading cause of perinatal morbidity and mortality.[2] IUGR fetuses have also been shown to be at an increased risk for later life metabolic and cardiovascular disease.[3] IUGR caused by placental insufficiency reduces nutrient and oxygen transport to the developing fetus. Along with reduced total size, these fetuses are often asymmetrically growth restricted due to a brain sparing mechanism in which brain growth is prioritized at the expense of abdominal organs and muscle tissue.[1] Adaptations to this suboptimal *in utero* environment such as altered fat storage, muscle development, and altered response to insulin can progress into postnatal life, setting up the offspring for later life disease.[1] Thus in the current study we sought to utilize MRI to observe developmental abnormalities such as asymmetrical growth and altered fat deposition *in utero*.

Methods: For the current study, pregnant guinea pigs were used due to their similarity to humans regarding adipose tissue development during fetal growth.[4] Pregnant guinea pigs were anaesthetized and scanned ~60 days into an ~68 day gestation. Two maternal groups were scanned: a Placental Insufficiency group (N = 7, 24 pups) where ablation was performed on branches of the uterine artery in order to restrict blood flow to the placentae, and a Sham Control group (N = 3, 13 pups). Imaging was performed at 3T (MR750, GE, Waukesha, WI) using a 32 coil receive array under a protocol approved by the institution's Animal Use Subcommittee. T_1- and T_2-weighted images were acquired with TR/TE/flip angle = 5.1ms/2.4ms/15° and 2000ms/120ms/90°, respectively, with voxel dimensions = 0.875x0.875x0.9mm^3 for both acquisitions. IDEAL water-fat images were also collected for each guinea pig with TR/ΔTE/flip angle = 9.4ms/0.974ms/4° and voxel dimensions = 0.933x0.933x0.9 mm^3. The T_1- and T_2-weighted images (Figure 1a,b) were used to segment fetal liver, brain, and total fetal volumes. IDEAL fat-only images (Figure 1c) were used to segment total and visceral fetal adipose volumes. Liver fat fractions were determined using proton density fat fraction (PDFF) maps.

Results: IUGR is often defined as the top 10% of brain to liver volume ratio. Since our study included an intervention to increase rates of IUGR, a cut-off was chosen to include 25% of the population**.** Thus, for this study, an IUGR pup was defined as one in which the brain to liver volume ratio (BLVR) was above 0.80 (Figure 2). As a result, the study population consisted of 8 IUGR and 28 normal pups. Normalized by fetal volume, IUGR fetuses had significantly smaller livers (0.053±0.008 vs 0.063±0.011, p=0.03) but larger brains (0.047±0.008 vs 0.036±0.005, p<0.001) than the normal group. IUGR pups had less total adipose tissue normalized to fetal volume than normals (0.090±0.039 vs 0.136±0.040, p=0.04), but no difference was seen in the proportion of adipose tissue deposited in visceral depots (p=0.99). Furthermore, liver PDFF was not significantly different between groups (22±9% vs 23±5%, p=0.66).

Discussion: The relative reduction in liver volume coupled with an increase in brain volume is characteristic of the brain sparing often seen in IUGR cases caused by a placental dysfunction. A consequence of reduced liver growth is a reduction in the fetus's ability to produce fatty acids, leading to the reduction in adipose tissue deposition in the IUGR pups in the current study. The absence of a difference in liver fat fractions between groups could be caused by a reduction in fatty acid transport out of the liver, as is often seen in response to a period of starvation.[5]

Conclusions: We have demonstrated the use of MRI for detecting developmental differences in IUGR fetuses in guinea pigs *in utero*. Future studies relating the differences seen *in utero* to those seen after birth, as well as translation to human imaging, are possible.

References: 1) Lausman A, *et al. J Obstet Gynaecol Can* 2012; 34(1): 17–28. 2) Peleg D, *et al. Am Fam Physician* 1998; 58(2): 453-460. 3) Briana DD and Malamitsi-Puchner A. *Eur J Endocrinol* 2009; 160: 337-347. 4) Castañeda-Gutiérrez E, *et al. Am J Clin Nutr* 2011; 94(6 Suppl): 1838S-1845S. 5) Kneeman JM, *et al. Therap Adv Gastroenterol* 2012; 5(3): 199–207.

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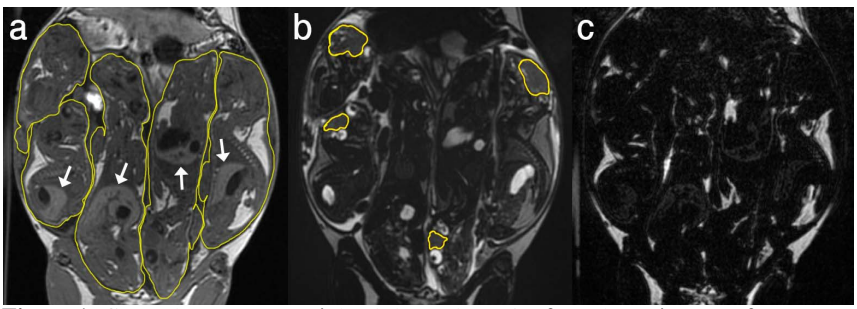

Figure 1: Coronal T_1- (a), T_2-weighted (b), and IDEAL fat-only (c) images of a pregnant guinea pig that had undergone ablation of the uterine arteries to promote IUGR. Fetuses are contoured in yellow in (a) and fetal livers are denoted by white arrows. Fetal brains are contoured in yellow in (b). Images have been cropped to highlight fetuses only.

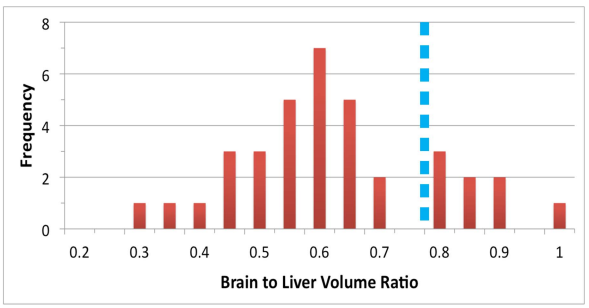

Figure 2: Histogram of brain to liver volume ratio used to define IUGR. The dashed blue line at a brain to liver volume ratio of 0.8 represents the cut-off value separating IUGR from normal pups.