Relaxation Times as Biomarkers of Placental Tissue Morphology in Fetal Growth Restriction (FGR).

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Introduction - Fetal growth restriction (FGR) is a serious complication of pregnancy, in which the fetus fails to reach its own genetically determined growth potential. Compared with appropriately grown infants, it is associated with significantly higher rates of perinatal morbidity and mortality as well as poor neurological outcomes and chronic diseases in adult life. In difficult problems in obstetrics is the difficulty in diagnosing and predicting FGR. Placental insufficiency is a major cause of this condition and accumulating evidence indicates that several aspects of placental structure and function are altered, forming the basis for the concept of an abnormal placental phenotype of FGR [1]. Various morphological changes are associated with this phenotype; such as impoverished development of the placental villi, increased fibrin deposition and changes in exchange barrier surface area and thickness [2]. MRI provides a range of quantitative indices that may useful in non-invasive placental morphological assessment including relaxation times, T₁ and T₂. Previous studies at 0.5 T, have suggested differences in these indices in complicated pregnancies[3].

Hypothesis - The observed differences in placental relaxation times in FGR are related to the altered placental morphology seen in this condition. To begin testing this hypothesis, we investigated placental relaxation times in utero at 1.5 T (allowing inherent improvements in signal-to-noise ratio and spatial resolution) and assessed morphology of these placentas stereologically in normal pregnancies. Furthermore, we assessed placental relaxation times in a number of women with FGR pregnancies.

Methods - Scanning was conducted using a 1.5 T Phillips Intera Scanner using a 5 channel phased array cardiac coil positioned to maximise placental signal. The pregnant women were positioned supine, using a foam wedge to support a left-lateral tilt, preventing inferior vena caval compression and introduced feet first into the magnet with their heads at the edge bore to reduce potential for claustrophobia. Relaxation times T₁ and T₂ were determined in the placenta with protocols co-localised to a structural scan. This imaging was based upon the single shot fast spin echo sequence used routinely in fetal scanning[4] to obtain a 30 slice structural image, resolution 3x3x3 mm in 36 seconds; Figure 1. Figure 1. Corresponding T₁ and T₂ scans were performed using a 3D multiple flip angle fast field echo (FFE; spoiled gradient echo) technique with angles 2,10 & 20 degrees[5] and a 2D multi slice spin echo (FSE, double echo) sequence using echo times of 6.3 ms and 200 ms respectively. Relaxation time values reported are median values obtained by fitting each voxel was within a selected region of interest. Placental morphology was assessed stereologically following delivery; using a systematic approach adapted from Mayhew[2]; fixed, wax embedded sections were analysed to allow quantification of placental compartment volumes (villous tissue, the volume of the intervillous space (maternal blood filled), fetal capillary volume and fibrin volume) and placental surface area densities (villous surface area and fetal capillary surface area).

Results - The MRI measurements were obtained in a group of 30 women gestational age 21.9±1.7 weeks (mean 32.9). A significant negative correlation was seen between relaxation times and gestational age at time of scan (T₁ p=0.01, T₂ p=0.03 Pearson’s). Linear regression analysis gave a model for relaxation times, where w is weeks gestation, as follows, also shown in Graph 1; T₁ = 1684 + (-20.2w), p=0.01, r² = 0.22, T₂ = 280 + (-2.4w), p=0.03, r² = 0.16.

No significant correlations were observed between relaxation times and stereological variables when the group was considered as a whole (n=17). Significant correlations were observed between T₂ and the fibrin volume and secondary variable fibrin: villous volume ratio (p=0.02, 0.03 respectively, Spearman’s) when only women scanned within a week of delivery were considered (n=7). This analysis was performed in an attempt to remove the significant influence of gestational age on relaxation times, as scans were performed a various times from 21-41 weeks, but stereological analysis always performed following placental delivery. There were no significant differences in T₁ or T₂ values between normal and FGR groups (p=0.65, p=0.11 respectively, Mann-Whitney). However, 4 of the 10 T₂ values for FGR pregnancies lay below the 95th confidence band; interestingly these pregnancies had the most severe FGR, in terms of need for early delivery.

Discussion - These results represent the first correlations of placental relaxation times obtained in utero with stereologically assessed morphology of the placentas. The most important finding is the clear relationship between relaxation times and gestation, supporting that the placental structural changes occurring as pregnancy advances are likely to influence relaxation times and suggesting that these indices may be a useful biomarker in FGR, where the morphological differences are more marked. Placental fibrin content is correlated with T₂, although the overall findings support that several variables are likely to play a role in determining relaxation times. The significant correlations are seen when the interval between scan and stereology is minimized and we will aim to scan women close to delivery in ongoing studies where possible. Although preliminary, the data from women with FGR pregnancies are interesting and we will continue to investigate these trends.