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

C. Wright[1], D. M. Morris[2,3], P. N. Baker[1,4], I. P. Crocker[1], P. A. Gowland[5], G. Parker[2,3], and C. P. Sibley[1]

[1]Maternal & Fetal Health Research Centre, University of Manchester, Manchester, United Kingdom, [2]Imaging Science and Biomedical Engineering, University of Manchester, Manchester, United Kingdom, [3]Biomedical Imaging Institute, University of Manchester, Manchester, United Kingdom, [4]Faculty of Medicine & Dentistry, Univerity of Alberta, Alberta, Canada, [5]Sir Peter Mansfield Magnetic Resonance Imaging Centre, University of Nottingham, Nottingham, United Kingdom

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. An ongoing problem 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, T_1 and T_2. 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 carried out 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 T_1 and T_2 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. Corresponding T_1 and T_2 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).

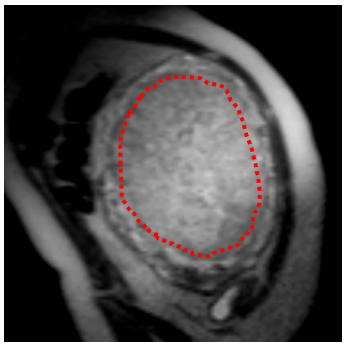
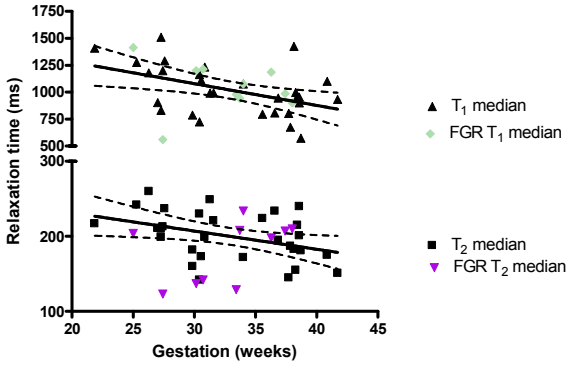


Figure 1



Graph 1

Figure 2. Structural scan through the placenta at 36 weeks showing typical placental region of interest outline in red. Graph 1. Showing correlation and linear relationship between relaxation times and gestational age for normal pregnancy, 95% confidence bans shown. T_1 and T_2 values for FGR placentas also plotted.

Results - The MRI measurements were obtained in a group of 30 women gestational age 21.9-41.7 weeks (mean 32.9). A significant negative correlation was seen between relaxation times and gestational age at time of scan (T_1 p=0.01, T_2 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; **T_1= 1684 + (-20.2*w*), p=0.01, r^2 = 0.22**, **T_2= 280 + (-2.4w), p=0.03, r^2 =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 T_2 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 T_1 or T_2 values between normal and FGR groups (p=0.65, p=0.11 respectively, Mann-Whitney) .However, 4 of the 10 T_2 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 placenta. 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 T_2, 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.

References - [1] Sibley et al *Paed. Res.* 58: 827 2005 [2] Mayhew et al *Placenta* 24 : 219 2003 [3] Gowland et al *MRI* 16: 241 1998 [3] Myers et al *BJR* 71:549 1998 [4] Whitby et al *Clin. Rad.* 59: 1114 2004 [5] Fram et al MRI 53: 201 1987. **Acknowledgements** –This work is supported by the UK MRC and Wellcome Trust