Assessment of Placental Morphology and Magnetic Resonance Imaging Biomarkers at 1.5 Tesla

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Background – Fetal Growth Restriction (FGR) is a serious complication which occurs in pregnancy and is responsible for increased mortality perinatally and is a risk factor for chronic conditions during development. There are many causes for FGR, e.g. maternal diet or substance abuse; these will affect the placenta which is responsible for providing oxygen, nutrients and removing waste products. The "placental phenotype"[1] has been identified in FGR, where common structural and functional changes are observed in the placenta. FGR is normally determined by ultrasound (US), which has limited ability to determine structural changes in the placenta. Previous Magnetic Resonance Imaging (MRI)[2] investigations of the placenta looked at the potential of imaging biomarkers and showed qualitative differences between normal and FGR pregnancies. These studies were conducted at 0.5 T and the use of higher field strength may be of benefit. The diagnosis of FGR even after birth is difficult, conventionally using standardised birth weight charts. This technique fails to capture small babies growing normally or large babies who have failed to fulfil their growth potential due to FGR and this misidentification makes the biomarkers unreliable as indicators of FGR because the standard identification is poor. This is addressed by collecting the placenta after in-vivo imaging and delivery to allow for histology relevant to FGR to be evaluated.

Methods – Following informed consent approved by the local ethics committee, scanning was carried out using a 1.5 T Intera Scanner (Philips Healthcare, Best, Netherlands) 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 outside the bore to reduce potential for claustrophobia. Relaxation times T_1 and T_2 were determined in the placenta as biomarkers for comparison with histology. Whilst no reports of harm as a result of MRI scanning have been observed in follow ups [3], all scans were restricted to a specific absorption rate (SAR) of 2 W/Kg to minimise heating and gradient slew rates were restricted to 50% of maximum to reduce noise exposure. These represent hard limits on optimisation of the scanning parameters in order to: (i) Minimise scanner time for the pregnant women, (ii) Acquire each image within the minimum time to reduce the chances of fetal motion rendering the image unusable, (iii) Cover the placenta at a resolution to allow for identification of structural differences across the placenta. This resulted in an MR protocol based around the single shot fast spin echo sequence used routinely in fetal scanning [4] to obtain the 30 slice structural image, resolution 3x3x3 mm in 36 seconds, Figure 1 showing different slices (A & B) with the placenta outlined in red. T_1 and T_2 were assessed in the same geometry using a 3D multiple flip angle fast field echo (FFE; spoiled gradient echo) technique with angles 2,10 & 20 degrees and a 2D multi slice spin echo (FSE, double echo) sequence using echo times of 6.3 ms and 200 ms respectively. Histology was carried out on the collected placentas which were fixed, wax embedded and sectioned to allow for staining with hematoxylin/eosin to determine the portion of villi (involved in the oxygen exchange) and fibrin (an indicator of damage) within the placenta [3].

Results – The MRI measurements were obtained in a group of 10 women in regions free from motion artefact and not suffering from partial volume effects, gestational age 22-41 weeks (mean 33), for whom corresponding placental morphological measurements were available. To increase the sensitivity of the biometric parameters and remove the effects of placental size, not related to FGR, the ratio of the average fibrin area per sample to the average villous area per sample was calculated. The histological samples were taken from 8 representative samples from the placenta and this was repeated for the MRI analysis. The MRI results for the region average T_1 and T_2 correlate significantly with gestational age at time of scanning, P = 0.030 and P = 0.031 respectively (SPSS 16, Spearman's signed rank test, 2 -tailed), as shown in Figure 2 with the R-squared values. The fibrin area: villous area ratio correlates significantly with T_1, P = 0.005 and with T_2, P = 0.041, shown in Figure 3 with R-squared values. This was a one tailed test in support of the hypothesis that villous area decreases as fibrin increases.

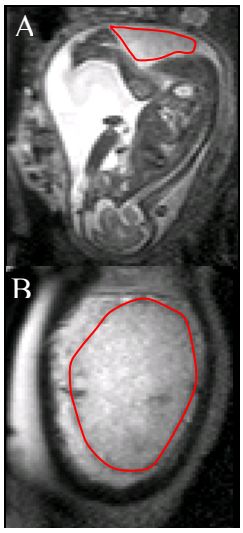

Figure 1 Placenta outlined in red on structural images

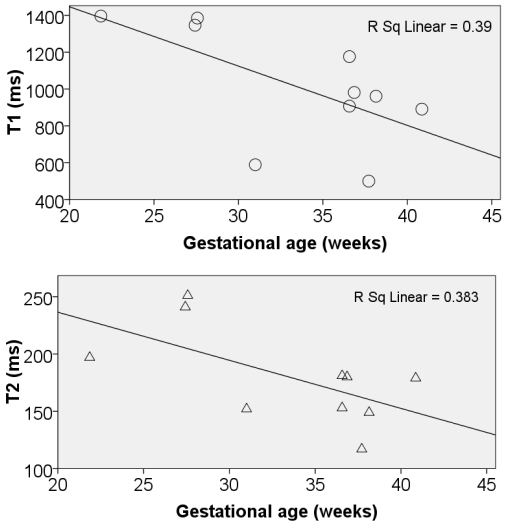

Figure 2 Relaxation times in ms (T_1, O & T_2, Δ) plotted against gestational age at time of scanning

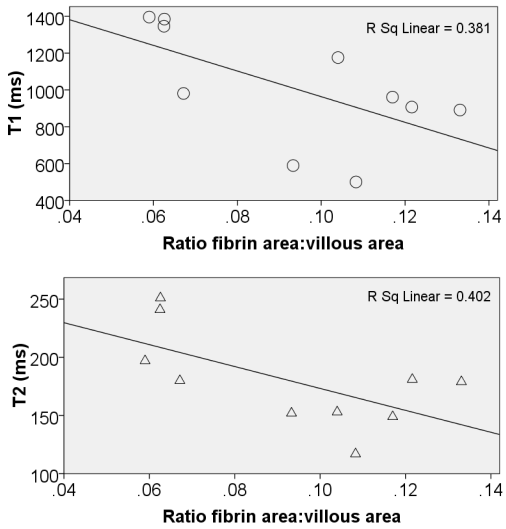

Figure 3 Relaxation times in ms (T_1, O & T_2, Δ) plotted against ratio of fibrin to villous area

Discussion – These results represent the first correlation of relaxation times obtained *in-utero* with histological morphology results in the placenta. Other more complex MRI techniques [5] have shown limited applicability at lower field strength. The correlation of the placental MRI biomarkers with placental morphometry indicates that the MRI is picking up structural changes related to FGR and indicates that this form of investigation has a role to play in FGR pregnancies where these parameters will be affected by providing histology information non invasively before delivery. The values obtained for the biomarkers are in reasonable agreement with the previous work [2], given the differences in field strength and protocols used. The significant changes observed are also in agreement where biomarkers reduced with FGR in line with an increase in the amount of damage and as the amount of contributing tissue reduce relative to the damage.

References – [1] Sibley et al *Paed. Res.* 58: 827 2005 [2] Gowland et al *MRI* 16: 241-247 1998 [3] Myers et al. *BJR* 71:549-51 1998 [4] Whitby et al *Clin. Rad.* 59: 1114-1120 2004 [5] Ong et al *BJOG* 110: 909-915 2003

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