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The use of antenatal fetal Magnetic Resonance Imaging in the assessment of patients at high risk of preterm birth

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Abstract

Preterm birth, defined as birth occurring prior to 37 weeks gestation is a common obstetric complication affecting 8% of pregnancies and is associated with significant morbidity and mortality. Infection/inflammation has been implicated in both the aetiology of preterm birth itself and associated neonatal pulmonary and neurological morbidity. Treatment options are currently limited to prolongation of the pregnancy using cervical cerclage, pessaries or progesterone or administration of drugs including steroids to promote lung maturity and neuroprotective agents such as magnesium sulphate, the timing of which are highly critical. Although delivery is expedited in cases of overt infection, decisions regarding timing and mode of delivery in subclinical infection are not clear-cut. This review aims to explore the use of Magnetic Resonance Imaging (MRI) in the antenatal assessment of pregnancies at high risk of preterm birth and its potential to guide management decisions in the future.

Background

Preterm birth (PTB), defined as birth less than 37^{+0} weeks gestation, is a significant health issue, projected to cost health services in England and Wales £939 million per year[1]. Morbidity is inversely correlated to gestational age, with the most severe adverse outcomes associated with very PTB, defined as occurring less than 32^{+0} weeks gestation. These births account for 1.4% of all deliveries in the United Kingdom[2], affecting 13500 individuals every year. Of children that are born very preterm, neurodevelopmental sequelae are responsible for a significant proportion of the associated morbidity. Up to 10% of surviving infants will develop motor impairments in the form of cerebral palsy (CP)[3] and 25-50% will suffer cognitive, behavioural, attention and socialisation deficits. In addition PTB is associated with significant pulmonary morbidity including respiratory distress syndrome and bronchopulmonary dysplasia.

Treatments are currently limited to mechanisms aimed at prolongation of the pregnancy, encompassing cervical cerclage, pessaries and supplemental progesterone, promoting lung maturity by the appropriate timing of administration of antenatal steroids and administration of the neuroprotective agent magnesium sulphate in labour. However, despite these treatments and although survival rates have improved over the last decade for extremely preterm infants born between 22 and 26 weeks, rates of disability are unchanged[4].

The intrauterine environment may contribute to and compound the associated neonatal morbidity. Infection has been implicated in both the aetiology of spontaneous PTB and subsequent cerebral and pulmonary pathology. When overt chorioamnionitis is present, prolongation of the pregnancy is detrimental and associated with an increased risk of cerebral palsy[5] and iatrogenic delivery is in the best interest of both the mother and the child. However, subclinical infection is known to be common, particularly at lower gestations but methods of assessing this are limited. Decisions regarding the timing of delivery are therefore not clear cut, the risks of prematurity being weighed against the likelihood and significance of infection in the fetal compartment.

The ability to accurately assess fetal development and pathology and the consequences of in utero infection as well as to accurately time when spontaneous PTB is likely to occur may significantly improve subsequent neonatal morbidity. This review will explore how antenatal Magnetic Resonance Imaging (MRI) may add to the clinical picture in pregnancies at high risk of PTB and help guide management decisions.

MRI

MRI is a non-invasive imaging technique which has been increasingly utilised for assessing the fetus over the last 20 years, partly due to its excellent safety profile[6-8], good soft tissue contrast and anatomical delineation, and its ability to provide additional information to obstetric ultrasound[9]. MRI is particularly useful in assessing the fetal brain, providing more accurate cerebral biometry, superior visualisation of the posterior fossa and assessment of sulcal formation[10, 11]. More recently it has also been used in the assessment of non-cerebral fetal structures including the thorax[12] and renal tract[13]. In addition, the development of advanced MRI techniques in the fetus including diffusion[14] imaging and spectroscopy[15] have facilitated the analysis of tissue microstructure and function of not just fetal tissues but also the maternal reproductive tract.

MRI uses a static magnetic field, which aligns the nuclear magnetisation of ions within tissue. Radiofrequency pulses are applied which alter their alignment. As they return to their original state a radiofrequency signal is produced which is detected by a receiver coil placed over the maternal abdomen. Fourier transformation results in the generation of an image. Image contrast can be weighted in order to optimally assess specific structures. Tissues return to their resting states via a combination of T1 and T2 relaxation: T1 is the time required to regain longitudinal magnetization and T2 the transverse relaxation time. Tissue with a high water content such as unmyelinated white matter is seen as low signal intensity (SI) on T1 weighted images and high SI on T2 weighted images (see Figure 1).

Magnetic resonance spectroscopy (MRS) works on the same principles as MRI but instead of an image, Fourier transformation results in the generation of a chemical spectrum. Metabolites that can be assessed using this technique include, N-acetyl aspartate (NAA), Choline (Cho), Creatine (Cr), Myo-inositol (Myo-ins) and Lactate[15]. Diffusion weighted imaging is a functional MR technique which provides quantitative information about water motion and tissue microstructure[16, 17] apparent diffusion coefficients (ADC) can be created to give a quantitative assessment of this process and maps generated. In addition advanced diffusion imaging, suitable for tractography and microstructural modelling, can now be obtained from the fetus. Although more challenging in the mobile fetus, detailed assessment of the tissue microstructure in vivo by measuring diffusion anisotropy (directional dependence) such as occurs within white matter tracts in the brain is now possible [18] see Figure 3.

MRI in the second and third trimesters of pregnancy is considered to be a safe imaging modality using both 1.5T and 3T scanners[19]. Theoretical risks are threefold: from the static magnetic field, the radiofrequency field (which causes heating) and from the time-varying magnetic field (resulting in noise). To minimise these risks, patients and staff must undergo a comprehensive metal check to ensure they are metal free before entering the scanner room, the scanner manufacturer establishes Specific Absorption Rates (SAR) for each pulse sequence used[8], the maternal temperature is kept less than 37.5^{o}C, the mother is given ear protection, louder sequences are kept to a minimum acquisition time, interspersed with quieter sequences and software such as Softtone can also be used to reduce noise.

A full assessment of the fetus, uteroplacental unit and cervix can be obtained in approximately one hour. Although performing MRI examinations on women at high risk of PTB can be challenging due to cost implications and access to imaging prior to delivery, our research group has demonstrated its feasibility.

Assessment of Fetal Anatomy

Although 2D and 3D ultrasound can give extremely detailed pictures of fetal anatomy, views can be restricted by fetal position and maternal habitus and the use of a vaginal probe may be undesirable, for example in cases of ruptured membranes. MRI can provide additional information to ultrasound including assessment of appropriate cortical folding[20], identification of haemorrhage[21], white matter injury and elucidation of causes of ventriculomegaly e.g. confirmation of corpus callosal agenesis[21]. The development of advanced MR techniques such as diffusion imaging have also enabled the assessment of tissue microstructure and identification of lesions not visible on conventional imaging. An ADC map can be seen in Figure 4.

Detailed information, which may facilitate appropriate counselling and help guide neonatal management plans can be obtained from assessment of a number of organs within the fetus.

Brain

Infection has been implicated in the aetiology of spontaneous PTB and subsequent cerebral pathology. Chorioamnionitis is associated with intra-ventricular haemorrhage[22, 23] and pro-inflammatory cytokines, including IL-6, TNF alpha and IL-10, within maternal and fetal circulations have been linked to both overt and subtle white matter damage[24]. Animal models have indicated infection as the major aetiology for neuronal aberrations associated with spontaneous PTB[25]. It is therefore plausible that the process of injury to the developing brain actually commences in the antenatal period.

Studies in preterm infants have utilised the early application of MRI as an outcome prediction tool for subsequent motor impairment: parenchymal lesions including haemorrhage, periventricular leukomalacia, infarction and reduction of white matter are associated with the development of CP[26]. Abnormalities in diffusion imaging [27-29] and MRS[30], also predict poor neurodevelopmental outcome. Abnormal cortical folding in infants born extremely preterm has also been shown to be associated with poor neurodevelopmental outcome at two years, particularly receptive language[31]. However, no studies to date have assessed the

brain antenatally in a group of fetuses that deliver very preterm to assess whether these processes begin during late pregnancy and whether there is correlation with neonatal MRI findings.

The development of advanced MRI techniques has now enabled assessment of cortical folding[20], subtle white matter injury and haemorrhage in the fetus: information not previously obtainable using conventional ultrasound imaging techniques. Volumetry of cerebral structures MRS[32], and diffusion imaging can now also be obtained from a fetal MRI. Such information about brain development may be useful with respect to counselling of parents with regards to longer-term outcomes as well as helping clinical decision making with regards to the timing of delivery or therapeutic interventions.

The timing of delivery may be altered if brain injury is known to have begun antenatally, particularly if this is related to an infected intrauterine environment. Although adverse neurodevelopmental outcomes are inversely correlated to gestation[33] the presence of intra-uterine infection is a known antecedent of cerebral palsy[34] and in the presence of overt brain injury obstetricians may elect to deliver the fetus earlier in order to prevent further injury to the developing brain.

In addition, administration of magnesium sulphate to the mother has been demonstrated to reduce the incidence of cerebral palsy[35]. However, questions remain unanswered as to the appropriate dose and timing of administration[36]. It is currently given in early labour however, no studies have been performed to assess if the process of brain injury has actually begun by this stage. If this is the case, benefit may be conferred by its administration prior to the onset of labour.

Further research is therefore needed in order to fully understand the relationship between infection and fetal brain development in the antenatal period in women at high risk of PTB. Correlation of fetal and early neonatal MR imaging may also enable prediction of antenatal antecedents of postnatal pathology. In such cases

administration of magnesium sulphate or timely delivery during the antenatal period may prevent the development of overt lesions postnatally.

Lungs

Lung hypoplasia is a significant cause of morbidity and mortality associated with extreme prematurity, particularly where preterm premature rupture (PPROM) of membranes occurs, antenatal prediction is therefore highly desirable for both antenatal counselling and planning subsequent neonatal care. In addition when there is a period of prolonged oligohydramnios occurs, although overall survival has improved [37, 38] morbidity is still significant with 40% or survivors developing bronchopulmonary dysplasia[39].

Ultrasound has been used to assess antenatal lung biometry as a proxy for pulmonary hypoplasia. Methods included thoracic circumference[40, 41] and lung length, the latter of which proved superior and a good predictor of pulmonary hypoplasia predicting >90% of cases, confirmed by lung weight at postmortem[42]. Ratios of thoracic measurements have also been generated which additionally allow for the effects of gestation including thoracic circumference to abdominal circumference, biparietal diameter, head circumference or femur length, heart area to thoracic area ratio[43-45].

Ultrasound assessment of three dimensional lung volumes has been attempted, assessing right and left lungs separately to avoid inclusion of mediastinal structures[46]. Vergani et al demonstrated that these normograms were reliable for prediction of pathological pulmonary volumes[47]. Volumetric measurements have been found to be more reproducible when MRI is used to evaluate the tissue than 3D ultrasound[48]. MRI also offers better tissue contrast, a larger field of view and images are independent of fetal position. MRI assessment of fetal lungs is becoming more commonplace for conditions such as congenital diaphragmatic hernia (CDH) and congenital cystic adenomatoid malformation (CCAM). In these conditions MRI can provide volumetric assessment of normal lung tissue, important determinants of prognosis in CCAM, CDH

and can be used to predict pulmonary hypertension. The use of fetal lung to body volume has been shown to useful in the predicton of chronic lung disease in fetuses with CDH[49]. One study (n=22) reports the use of MRI volumetry of fetal lung assessment in cases of PPROM, finding a significant reduction in lung volume, particularly in cases of subsequent neonatal death[50].

Infection may also be implicated in this process; some studies have shown that chorioamnionitis is associated with a decrease in respiratory distress syndrome but a subsequent increase in bronchopulmonary dysplasia[51, 52], however, the data is heterogeneous and there may be confounding factors. Further research is needed to investigate lung development during this critical period and MRI is well placed to do this. Automated multi-atlas lung segmentation has been developed, generating accurate reproducible lung volumes. Overlapping T2 weighted stacks of the fetal thorax are obtained in the transverse plane. Segmentations are estimated using a multi-atlas approach relying on 17 manually delineated lung images. Images pre and post automated segmentation can be seen in Figure 5.

Amniotic fluid Index

Ultrasound assessment of amniotic fluid volume is a semi-qualitiative assessment by measuring a single deepest vertical umbilical cord free pool or the amniotic fluid index. Although useful surrogate assessments they do not measure the true amniotic volume and over/under estimates can easily ensue. Zaretsky et al compared MRI assessment of amniotic fluid volume with the volume collected at Caesarean section, finding better correlation between the MRI estimation and the actual volume at delivery than with the deepest pool measured on ultrasound[53]. Roberts and Mitchell found the largest amniotic pocket in serial ultrasound examinations on 20 patients with PPROM correlated with pulmonary hypoplasia when the maximum vertical pocket was less than 1.5cm[42]. A higher rate of fetal infection/inflammation associated with oligohydramnios has been proposed to be attributable to the antimicrobial properties of amniotic fluid[54] or a reduction in renal blood flow as a consequence of microbial products[55]. The AFI can be segmented from coronal, axial and sagittal planes using software such as ITK-SNAP to generate a 3D volume (see figure 6).

Fetal Thymus

Evidence suggests that neonatal morbidity is a continuation of activation of the fetal inflammatory response syndrome (FIRS), a condition characterised by systemic inflammation. Diagnosis of the fetal inflammatory response antenatally is challenging. Although amniocentesis can identify intra-amniotic infection/inflammation this is an invasive procedure.

The thymus has an integral role in the development of the fetal immune system. And is the main site of T-cell development. Located in the anterior mediastinum over the pericardial surface and extending into the base of the neck its development begins early in gestation and is completed by 20 weeks, continuing to grow in size until one year of age[56]. Studies in neonates have indicated a reduction in thymic size at birth (evaluated by measuring the cardiothymic silhouette to thoracic ratio on a chest X-ray) in very low birthweight preterm infants in the presence of histological chorioamniotis in the placenta[57]. A sheep model has also indicated that after lipopolysaccharide induced chorioamnionitis, the thymus to body weight ratios were reduced by 40% five days later parallel to an equivalent reduction in circulating lymphocytes[58].

The fetal thymus has been assessed using ultrasound, either measuring its perimeter[59], a thymic to thoracic ratio[60] or using 3D ultrasound[61]. It has also been shown that measurements of thymic volume using MRI is feasible [62]. An MRI illustrating the fetal thymus can be seen in Figure 7. Di Naro et al assessed 31 women with preterm labour between 24 and 32 weeks gestation and intact membranes. The perimeter of the fetal thymus was measured sonographically and an amniocentesis was performed for the assessment of infection of the amniotic cavity. Placentas and umbilical cords were also examined for the presence of chorioamnionitis/funisitis post delivery. 16 women delivered preterm and 10 women had evidence of intra-amniotic infection. In all cases of intrauterine infection and in 24% of cases without intrauterine infection the fetal thymus perimeter was below the 5^{th} centile for gestational age. The fetal thymus was less than the 5^{th} centile in 100%, 71.4% and 12.5% of patients with histologic signs of funisitis and isolated chorioamnionitis

and without histologic signs of infection respectively. Although this study utilised ultrasound, when membranes are ruptured poorer views of fetal anatomical structures are obtained, consequently MRI assessment of thymic volume could be of significant value in establishing the FIRS and whether intra-amniotic infection is likely to have occurred and may help the decision making process regarding timing of delivery. Further studies are required to investigate this further.

Prediction of the timing of delivery

Accurately predicting when a woman is likely to deliver is important, facilitating timely hospital admission to ensure access to appropriate neonatal facilities whilst avoiding unnecessary and prolonged hospital stays and ensuring appropriate timing of antenatal therapies such as corticosteroids. It is known that the maximum benefit of steroids is conferred when delivery occurs between 24 hours and seven days subsequent to administration[63], reducing the incidence of neonatal mortality, respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, systemic infection, the need for respiratory support and neonatal intensive care admission[64]. The critical timing of steroids has be highlighted by a recent mini-commentary by Cythia Gyamfi-Bannerman[65]: although the optimum timing of steroids is known to be within this critical timeframe, studies have indicated that only 20% of women in threatened preterm labour delivered within a 24 hour to seven day period.

However, antenatal steroids administration is not without risks, a recent Cochrane review indicated that administration of a single course of steroids resulted in a reduction of birthweight of infants born between one and seven days after administration compared with placebo and in those delivered more than seven days after the first dose. Where repeated courses were given although a reduction in respiratory morbidity was noted, this was at the expense of a slight reduction in the mean birthweight[64]. Consequently it is important to ensure that steroids are given appropriately and enhanced prediction of which women are likely to delivery within a week time frame can facilitate targeted corticosteroid administration.

Current techniques for the prediction of PTB include biophysical and biochemical screening and a thorough clinical history. Transvaginal ultrasound has been utilised in numerous research studies to assess cervical length and is a common clinical test used in the evaluation of women at high risk of PTB. Although it is not routinely used in a low risk population, its use in such women is debated[66]. The prediction of PTB can be further enhanced by utilising algorithms encompassing cervical length, clinical history and quantitative fetal fibronectin obtained from a vaginal swab taken from the posterior fornix[67]. Although these techniques are extremely useful in guiding management decisions transvaginal ultrasound is often not used in cases where the membranes have ruptured due to the risk of introducing infection.

The cervical length can be measured easily on MRI (see figure 8) but in addition, Masselli et al used diffusion imaging during an antenatal MRI to assess if ADC values in the maternal cervix correlated with delivery within a seven day period. MRIs were performed on asymptomatic women where a sonographic measurement of the cervix less was than 15mm between 23 and 28 weeks gestation (n=30). Eight women delivered within six days of the MRI scan and they were found to have subglandular cervical ADC values that were significantly higher than the women who delivered after seven days from imaging[68].

Although standard clinical practice would be to administer steroids at the time of PPROM, as the highest risk of delivery is within the first 24 hours, where delivery does not occur and a second course of steroids is considered, assessing the maternal cervix with diffusion weighted imaging at the time of a fetal MRI may guide decisions regarding the timing of subsequent doses of steroids in these women.

Monitoring/ investigating the mechanism of action of treatment

MRI has also been used to assess the mechanism of action of pessaries inserted around the cervix, when the cervical length is reduced, in an attempt to prevent further shortening and dilatation. A randomised controlled trial of asymptomatic singleton pregnancies with a cervical length <25mm between 18-22 weeks found that a

pessary reduced delivery prior to 34 weeks by four-fold[69]. Cannie et al performed an MRI in 54 high risk pregnancies with a sonographic short cervix before and serially after pessary insertion and a control group of low risk pregnancies with no risk factors for PTB. They reported that in singleton pregnancies at high risk of PTB the uterocervical angle was less acute and the cervical length shorter than in the control population. They reported that failure of pessary placement occurred in 15% of patients, which was detected by MRI and enabled its replacement. After successful insertion the uterocervical angle becomes more acute reducing the incidence of delivery prior to 34 weeks[70].

Although cervical length can be monitored using ultrasound, views are often limited by pessary-induced shadowing. MRI additionally facilitates the objective measurement and monitoring of the uterocervical angle. Although it would clearly be unfeasible to assess all pregnancies with Arabin pessaries with MRI, certain cases may benefit, for example where views of the cervix are poor on ultrasound or if there are concerns regarding correct placement.

Conclusion

We believe that assessment of pregnancies at high risk of PTB using MRI is a feasible technique and in may provide insight into fetal pulmonary and cerebral development, assessment of intrauterine infection, prediction and guidance of timing delivery and provide a means of targeting the timing of antenatal corticosteroids for optimal benefit. Understanding the disease processes in this cohort may also facilitate the accurate targeting and appropriate timing of therapeutic agents in the future given to attenuate injury to the brain and lungs and consequently reduce long term morbidity.

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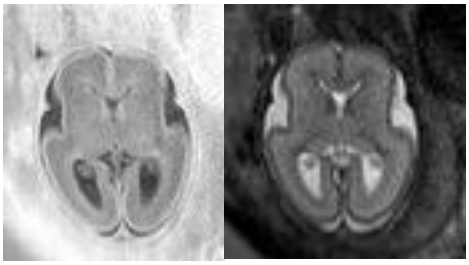


(a) (b)

Figure 1: Snapshot inversion recover T-1 weighted (a) and T2 (b) weighted MRI images of the fetal brain in the transverse plane in a patient at high risk of preterm birth with premature rupture of the membranes at 24^{+4} weeks gestation on a 1.5Tesla MRI scanner.

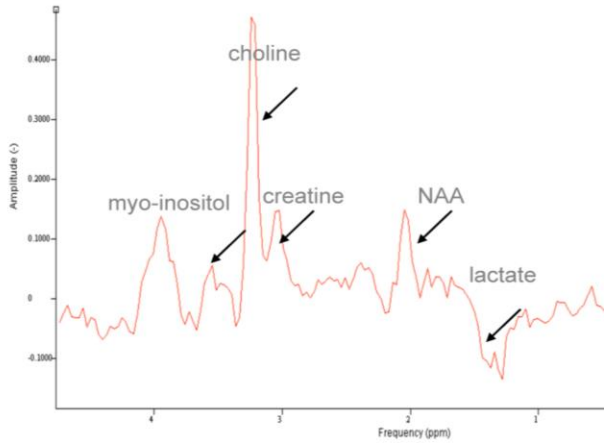


Figure 2: Example of a fetal spectrum, at an echo time of 136ms, illustrating the presence of Myo-inositol (3.5ppm), Choline (3.2ppm), Creatine (3.0ppm), N-acetylaspartate (NAA 2.0ppm) and Lactate (inverted bifid peak at 1.3ppm) acquired at 1.5 Tesla

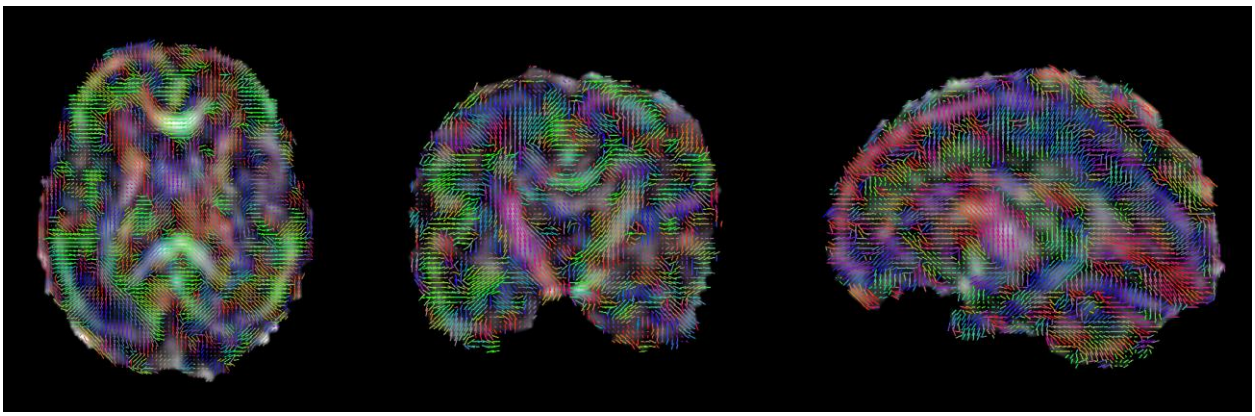


Figure 3: Axial, coronal and sagittal slices of the fractional anisoptropy map of a fetal brain after dynamic distortion and motion correction of a x week fetus acquired on a 3T MRI scanner. These results show high anisotropy in the cortex and maturing white matter structures such as the splenium, as expected in early brain development.

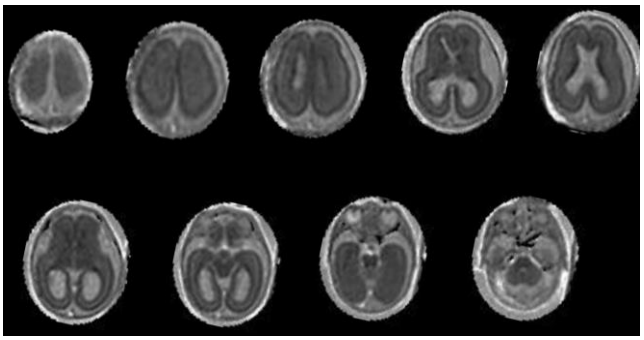
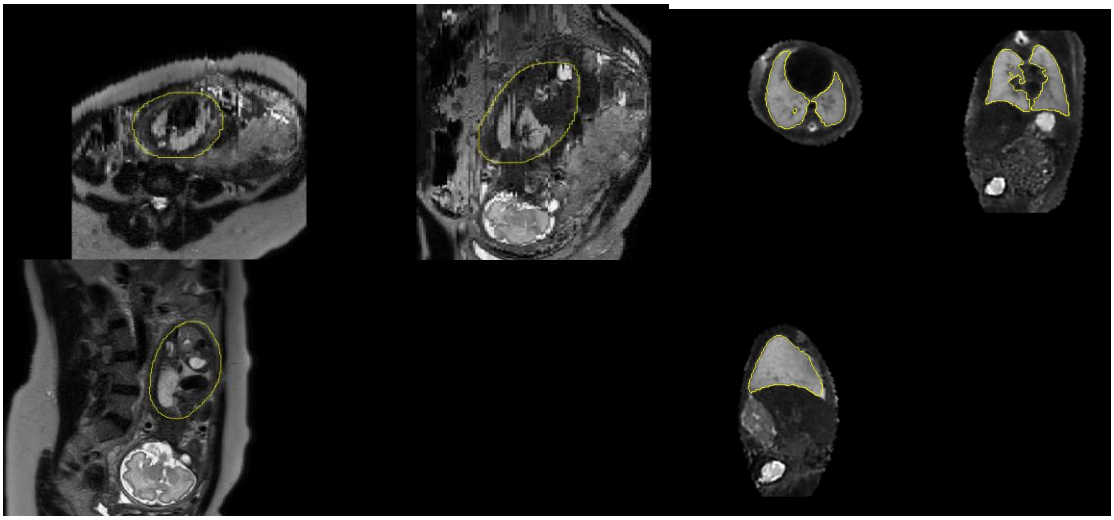


Figure 4: An apparent diffusion co-efficient map of a 24^{+0} fetal brain. An ADC value in a specific region of interest can be generated by placing a voxel in the area to be analysed.



(a) (b)

Figure 5: (a) Raw T2 MRI data of fetal thorax acquired from a fetus at 31+1 weeks gestation. (b) Images following automated segmentation of the fetal lungs.

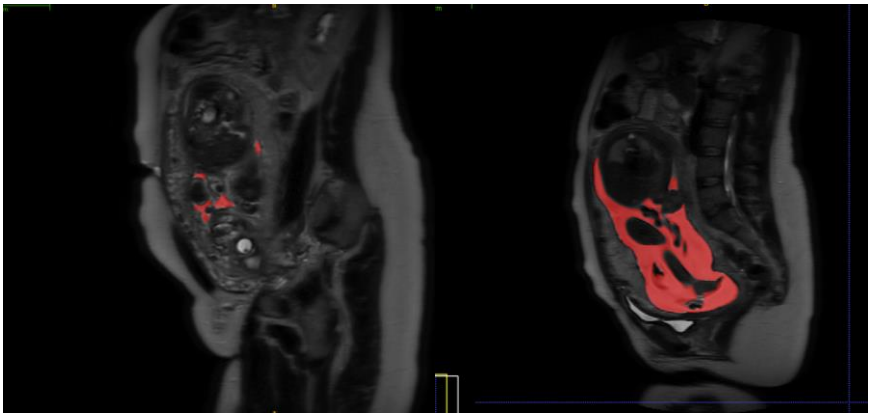
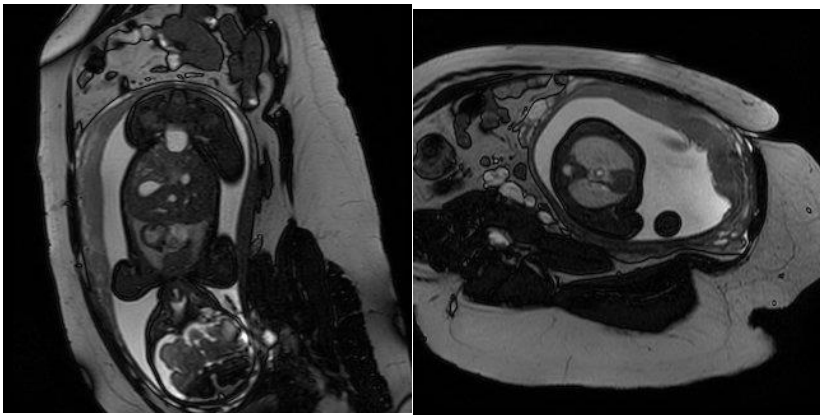


Figure 6: T2 weighted images obtained on a 1.5T MRI scanner showing (a) oligohydramnios in a 31^{+1} week fetus with prelabour preterm rupture of membranes (b) normal amniotic fluid volume in a 28^{+1} week fetus.



(a) (b)

Figure 7: T2 weighted image illustrating the Fetal thymus at 31+6 weeks gestation in the coronal (a) and axial (b) planes

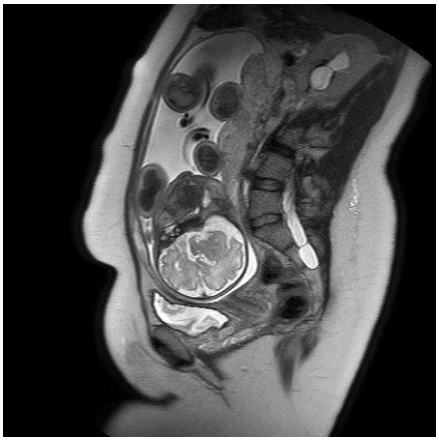


Figure 8: T2 weighted image in the sagital plane of a 32 week fetus illustrating the maternal cervix

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