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Assessing the Clinical Value of Foetal MRI for Non-CNS Abnormalities

Rodwan Tumi

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…..To the living memory of my father…..

**ABSTRACT**

**Objectives**: The purpose of this study was to assess the value of *f*MRI in addition to prenatal USS in evaluating foetal non-CNS abnormalities and whether information available from the *f*MRI would change diagnoses or alter patient management and/or counselling thus impacting on clinical care. In addition, the diagnostic accuracy and postnatal impact of both imaging methods was also assessed.

**Methods**: Both prospective and retrospective assessment of all foetuses in second and third trimesters with suspected non-CNS abnormalities referred to Sheffield Teaching Hospitals for *f*MRI between November 2011 and February 2020. Two expert panel assessments were performed. The first expert panel analysed scans in an antenatal perspective in order to determine the value of *f*MRI in shaping patients’ care pathways. The second expert panel analysed scans results in comparison to final postnatal outcome diagnoses for diagnostic accuracy and impact on postnatal care.

**Results:** Four-hundreds eighty-one foetuses with suspected non-CNS abnormalities were included. Study cohort was divided according to foetal body region involved into six groups. Chest (n=132), GUS (n=142), abdomen (n=128), skeletal (n=43), neck (n=13) and miscellaneous (n=23). Final comparison with postnatal outcome was achieved in 204 foetuses (69 chest, 58 GUS, 52 abdomen, 13 skeletal, 6 neck and 6 miscellaneous cases. Overall (second panel assessment) *f*MRI had a diagnostic accuracy of 87.7% compared to 69.6% of prenatal USS and it added information in 21.5% that was deemed to have changed diagnoses, management and/or counselling in 7.8% of the foetuses. Both scans diagnostic accuracies varied according to foetal body region with 100% accuracy for both in the neck cohort, chest (*f*MRI=95.6%, USS=81%), skeletal (*f*MRI=92%, USS=69%), abdomen (*f*MRI=88%, USS=69%), miscellaneous (*f*MRI=83%, USS=66.6%) and GUS (*f*MRI=75.8%, USS=53%). First expert panel assessment found that *f*MRI provided additional information in over 60% of the cases and that could have changed the diagnoses, management and/or counselling in 40% of cases.

**Conclusion**: *f*MRI provides high diagnostic accuracy in detecting foetal non-CNS pathologies especially foetal chest, abdomen and skeletal abnormalities. It also provides additional useful information to prenatal USS that is useful for clinical management both before and after delivery in all foetal body abnormalities.

**Abbreviations**

**AGTR** Angiotensin II Receptor

**ASD** Atrial Septal Defect

**BMI** Body Mass Index

**BMP** Bone Morphogenetic Protein

**BPS** Bronchopulmonary Sequestration

**CAKUT** Congenital Anomalies of the Kidneys and Urinary Tract

**CCAM** Congenital Cystic Adenomatoid Malformation

**CDH** Congenital Diaphragmatic Hernia

**CHAOS** Congenital High Airway Obstruction Syndrome

**CHARGE** Coloboma, Heart defects, atresia Choanae, Retardation of growth, Ear abnormalities

**CMV** Cytomegalovirus

**CNS** Central Nervous System

**CPAM** Congenital Pulmonary Airway Malformation

**CRIS** Radiology Information System software

**CT** Computerised Tomography

**CTPA** Computerised Tomography of Pulmonary Arteries

**DA** Duodenal Atresia

**DMSA** Dimercaptosuccinic Acid scan

**DNA** Deoxyribonucleic Acid

**DWI** Diffusion Weighted Imaging

**ECG** Electrocardiogram

**ECMO** Extra Corporeal Membrane Oxygenation

**ELS** Extralobar Sequestration

**EPI** Echo Planar Imaging

**EUROCAT** European Registration of Congenital Anomalies and Twins

**EXIT** EX-utero Intrapartum Treatment

**FFE** Fast Field Echo

**FGFR** Fibroblast Growth Factor Receptor

**FID** Free Induction Decay

**FLASH** Fast Low Angle Shot

***f*MRI** Foetal Magnetic Resonance Imaging

**FOV** Field Of View

**GA** Gestational Age

**GE** Gradient Echo

**GI** Gastrointestinal

**GIT** Gastrointestinal Tract

**GUS** Genitourinary System

**GW** Gestational Week

**ScHARR** School of Health and Related Research

**HASTE** Half Fourier Single-shot Turbo spin Echo

**HPA** Health Protection Agency

**ICNIRP** International Commission on Non-Ionising Radiation Protection

**ILS** Intralobar Sequestration

**IMPAX** Radiology Information System/Picture Archiving and Communications System

**IUFD** Intrauterine Foetal Death

**IUGR** Intrauterine Growth Restriction

**IV** Intravenous

**JMIS** Jessop’s Maternity Information System

**KUB** Kidneys Ureter Bladder

**LHR** Lung to Head Ratio

**MAG** Mercaptuacetyltriglycine scan

**MCDK** Multicystic Dysplastic Kidneys

**MCUG** Micturating Cystourethrogram

**MDT** Multidisciplinary Team

**MHRA** Medicines and Healthcare products Regulatory Agency

**MR** Magnetic Resonance

**MRI** Magnetic Resonance Imaging

**NHS** National Health Service

**NICE** National Institute for Health and Care Excellence

**OA** Oesophageal Atresia

**PACS** Clinical Picture Archiving and Communication System

**PAX** Human Paired box Genes

**PEL** Pelvis

**PNS** Peripheral Nerve Stimulation

**PUJ** Pelvi-Ureteric Junction

**PUV** Posterior Urethral Valves

**REC** Research Ethics Committee

**RF** Radiofrequency

**SALL** Spalt Like transcription factor

**SAR** Specific Absorption Rate

**SCT** Sacrococcygeal Teratoma

**SE** Spin Echo

**SIX** SIX Gene

**SSFP** Steady State Free Precession

**SSFPS** Steady State Free Precession Sequence

**SSFSE** Single-Shot Fast Spin Echo

**STH** Sheffield Teaching Hospitals

**STIR** Short Tau Inversion Recovery

**SWI** Susceptibility Weighted Imaging

**TE** Echo Time

**TFE** Turbo Field Echo

**TFR** Tumour Foetal Ratio

**TGF** Tumour Growth Factor

**TI** Inversion Time

**TIS** Intestine

**TOF** Tracheooesophageal Fistula

**TOP** Termination of Pregnancy

**TORCH** Toxoplasmosis Rubella Cytomegalovirus Herpes simplex

**TR** Repetition Time

**US** Ultrasound Scan

**USS** Ultrasound Scan

**VACTERL** Vertebral defects Anal atresia Cardiac defects Tracheooesophageal fistula Renal anomalies Limb abnormalities

**VSD** Ventricular Septal Defect

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# Chapter 1

# INTRODUCTION

Foetal Magnetic resonance imaging (*f*MRI) has become more widely used in clinical practice and for research purposes since its first report in the early 1980’s. In its early introduction, foetal motion was a major obstacle against imaging the foetus and therefore its use was very limited. It was used occasionally for evaluation of the placenta or maternal organs. Foetal motion has previously been reduced by the use of muscle relaxants to help obtain better visualisation of the foetus and *f*MRI scanners were of low field strengths (0.08-0.35 T) with limited range of sequences; namely T1-weighted, inversion recovery and proton density which all took long time to perform (Smith 1985; Baert & Prayer 2011; McRobbie 2003). However, development of ultrafast sequences made foetal movements less of a problem and the use of muscle relaxants for foetal sedation is finally no longer required (Lan *et al.*, 2000; Chen and Levine, 2001). Some of the challenges that faces *f*MRI around the world today include its high cost and lack of experienced radiologists. The main technical challenge for *f*MRI today remains the constant rapid change in growth and function of the foetus throughout the pregnancy (Baert and Prayer, 2011).

Prenatal Ultrasound Scan (USS) remains the first choice imaging modality for evaluating foetal abnormalities due to its low cost and wide availability (Estroff, 2009; Wataganara *et al.*, 2016). However, *f*MRI too is used nowadays either to confirm those abnormalities or to find more details where prenatal USS is uncertain or to assess some aspects of foetal organ functions. *f*MRI role in the imaging of suspected foetal Central Nervous System (CNS) abnormalities has been well established and is being used regularly to further investigate these abnormalities in various centres around the world where *f*MRI is available. In 2017, the MERIDIAN study, in which 570 foetuses were included to measure the diagnostic accuracy of both prenatal USS and *f*MRI in the imaging of CNS abnormalities, concluded that *f*MRI provided superior diagnostic accuracy and advised for its routine use as an adjunct to prenatal USS whenever such abnormalities are suspected (Griffiths *et al.*, 2017). However, it has been also used almost routinely in the actual clinical practice nowadays to investigate for other non-CNS abnormalities, although there are no current set of guidelines regarding its use in the imaging of those abnormalities. It is likely that *f*MRI would be of a similar benefit for non-CNS abnormalities but a formal investigation is required prior to the use of limited NHS resources. Without established evidence that support the use of *f*MRI in imaging of non-CNS abnormalities, we might be putting patients in unnecessary risks, wasting NHS resources and wasting patients’ and involved experts and personnel’s time. Currently, referrals for *f*MRI are made entirely by referrer’s own choices and decisions. Some foetal medicine experts prefer to rely entirely on prenatal USS information while others seek *f*MRI further clarifications. Lack of guidelines might be responsible for this split between the experts. This can be avoided by conducting more research that reflects the actual clinical practice in this field to determine the clinical value of *f*MRI in the imaging of those body regions. This will also help to establish a reference database for *f*MRI that radiologists can refer to if needed.

This chapter also aims to give an overview of the *f*MRI, brief summary of its physics, sequences and advantages.

## Aims of the Study

The primary aim of this study is to provide practical evidence on what clinical data can be added by *f*MRI over the data available from prenatal USS and whether this data can change diagnoses or alter patient management and/or counselling.

The secondary aim is to evaluate the impact of *f*MRI on patients.

The third aim is to measure for health economics.

**Research question**

Does *fMRI* for non-CNS abnormalities add clinical value to prenatal USS in a way that alters patients’ diagnoses, management and/or counselling?

**Hypothesis**

*f*MRI provides valuable information to prenatal USS that alters patients’ diagnoses, management and/or counselling.

## MRI system

The MRI system is usually located in a separate unit that is equipped to withstand scanner’ heavy weight and is also equipped with shielded walls, doors, windows (against RF signals) and its own secure door system to prevent entry of unauthorised personnel with ferromagnetic items. The MRI system consists of different components that are distributed in different rooms in the MRI unit. Hospitals differ in the organisation of MRI units but they usually have a magnet room in which they keep the magnet, coils, physiological monitoring accessories and piped medical gases, a technical room with all supporting electronics and a control room that houses the MR console. Inputting patient details, selection and modification of scan acquisition parameters and viewing of the images are all done in the console room. The MR system is composed of the following:

Magnet (heart of MR system): it is used for generation of a strong constant magnetic field. It is the most important part of the system. There are three types of magnets used in MRI. Superconducting magnets producing medium to high field strengths (≥ 0.5 T), their magnetic field is always present and they require a cryogenic cooling liquid (liquid helium) to maintain a low temperature. Permanent magnets producing field strengths up to 0.3 T, here also magnetic field is always present. Resistive and electromagnets producing strengths up to 0.6 T, but their magnetic field can be switched off as they are electrically powered magnets.

RF transmitter and receiver coils: it is used for excitation and detection of MR signal. A transmit coil is usually built within the MR scanner bore and it surrounds the whole or part of the body and is responsible for generation of electromagnetic radiofrequency pulses. Resultant MR signals from the body are detected by receiver coils.

Magnetic field gradients: localisation of MR signals by production of short-term spatial variations in magnetic field strength across the patient. Stronger gradient fields and quicker switching rates increases the potential for faster scanning. There are usually three sets of gradient coils built within the magnet bore, one for each direction. These coils are responsible for the loud tapping noise that can be heard during an MRI scan.

Computer system: used to operate and control the scanner, view and archive the images.

Couch (patient table) and aids for patient position and comfort. Communication between the operator’ console and the patient in the magnet bore is usually achieved by an intercom device.

Physiological monitors such as electrocardiography (ECG) and pulse monitor. Live visual patient monitoring is also possible in some MRI systems via closed circuit TV (CCTV). Patients usually have access to hand-held alarms or panic buttons to use in case of emergencies (McRobbie, 2003).

## Generation of MRI signal

MRI consists of three key component fields: a static magnetic field, a time-varying (gradient) magnetic field and an electromagnetic radiofrequency pulse field. The static field is measured in Tesla units (1T=10,000 gauss) and is always on. It is produced by a superconducting magnet that weighs approximately 7000 N and able to produce field strengths up to 10T and more. It requires a very expensive coolant (liquid helium) to maintain magnet temperature (McRobbie, 2003) and superconductivity. Gradient fields are produced by passing current through cylindrical coils that fit inside the MR scanner bore. This field will alter the main static field in a certain pattern, changing the precessional frequency (resonance frequency) of the protons. Gradient fields are responsible for spatial encoding of MR signal. They are usually three in number and their profiles can be controlled in magnitude, time and direction. The pulsed electromagnetic radiofrequency field is produced by specialised transmit coils that are placed inside the scanner or next to the patient. RF pulses are released at a frequency that is near or equal to the Larmor frequency that is responsible for proton resonance (McRobbie, 2003; Bahado-Singh and Goncalves, 2013). Protons with hydrogen atoms are either in constant motion or precession, and with hydrogen nuclei being charged particles themselves, this precession creates a small magnetic moment.

The static magnetic field forces hydrogen atoms of the mother and the foetus to align themselves longitudinally with the direction of the applied magnetic field (Larmor precession) resulting in a net magnetic moment (*M)* that is parallel to the strength of the applied magnetic field (*B*ₒ). Applying RF pulses perpendicular to *B*ₒ and equal to the Larmor frequency will tilt the net magnetic moment away from *B*ₒ. Cessation of RF pulses will result in the nuclei returning to equilibrium and realign themselves again parallel to *B*ₒ, this is known as relaxation. When the nuclei relax, they release energy and emit electromagnetic RF signal (Free-Induction Decay (FID) response signal) which in turn is measured by specific coils to reconstruct an image. Adding gradient magnetic fields at specific time points of the sequence to *B*ₒ will encode the spatial information in the MR signal. Gradient pulses are used for slice selection, phase encoding and frequency encoding. The RF pulse is repeated in a specific rate and the period of its application is known as the repetition time (TR), and the period between the application of RF pulse and the FID response signal is known as echo time (TE). These time periods can be controlled to produce contrast for different body tissues. Tissues with higher proton densities will have higher FID response signals and these determine tissues contrast. Other factors that determine tissue contrasts in MR images are the relaxation times T1 and T2. T1 indicates the time taken by the excited nuclei to return to equilibrium state after ceasing the RF pulse. It occurs when 63% of longitudinal magnetisation returns to equilibrium. T2 represents the time taken for the FID response signal to decay. It occurs when 63% of proton transverse magnetisation is lost. T2 is always shorter or equal to T1 (McRobbie, 2003; Bahado-Singh and Goncalves, 2013). Echoes generated after applying RF pulses are either spin echo (SE) or gradient echo (GE). SE is the most commonly used sequence in MRI and is produced by applying an electromagnetic RF pulse at 90° angle followed by a second refocusing pulse at 180°. GE is produced by applying single a RF pulse at less than 90° (without using the 180° refocusing pulse) thus producing T2\* dephasing. Because it uses only one RF pulse, GE sequences have a shorter TE and is therefore usually much faster than spin echo sequences (Chen and Levine, 2001; McRobbie, 2003).

## *f*MRI Sequences

Sequences are basically computer software programmes designed to control MR imaging system hardware. They work by applying different RF pulse angles, TR and TE. Sequences are designed to highlight specific features for specific tissues. MRI sequences used in foetal imaging differ from those used in paediatric and adult imaging. They are designed to overcome foetal motion and maternal breathing movements by providing very short acquisition time and high spatial resolution. Phased-array coils are used to target specific areas to be investigated, the closer the coil to the body area the stronger the signal and hence improved image quality as a result. Common sequences used in *f*MRI include:

### T2-weighted sequences

Standard T2-weighted sequences used in *f*MRI include single-shot fast spin-echo (SSFSE) and half-Fourier single-shot turbo spin-echo (HASTE). All information needed for an image can be acquired in a single TR and a complete image acquisition is achieved in less than 1 second (Glastonbury and Kennedy, 2002). These sequences have the characteristics to allow for small FOV (min 170 mm) and provide high tissue contrast, which explain why they are sometimes considered to be the best sequences to depict foetal brain anatomy (Brugger *et al.*, 2006). Setting of *f*MRI parameters to achieve the best tissue contrast, depends on some factors such as the gestational age and the target region. To image the foetal body with SSFSE, it is advised to use shorter echo times especially when assessing signal intensity of the foetal lungs. Longer echo times (>250 ms) are used when evaluating foetal cystic lesions because they allow sequences to depict internal contents of the lesions such as the congenital cystic adenomatoid malformation (Breysem *et al.*, 2003).

### Steady-state free-precession sequence (SSFP)

This is a fast T2-weighted imaging technique that produces images with good tissue contrast. However, SSFP sequences have large FOV which might prevent detection of delicate information especially in foetuses of earlier gestations (Brugger, Stuhr, et al. 2006; Chen & Levine 2001; Ertl-Wagner et al. 2002; Chung et al. 2000).

### Thick-slab T2-weighted sequences

These sequences are designed to provide a new look at the intrauterine contents. They provide a 3D impression of the foetus and can be acquired in less than one second. Slice thickness should be at least 15 mm to create a 3D impression. Foetal size, position and amniotic cavity dimensions dictate the maximum slice thickness. Thick-slab imaging provides a global view of foetal anatomy or pathology and the whole foetus can be visualised in one image (Brugger *et al.*, 2006).

### Echo-planar imaging (EPI)

Echo-planar imaging sequence provided short imaging times when first introduced into practice but provided insufficient tissue contrast and image resolution for foetal brain assessment (Brugger and Prayer, 2004). Nowadays, it is used in conjunction with diffusion-weighted imaging or as a localising sequence (Caire *et al.*, 2003). Total acquisition of an EPI image is achieved in milliseconds, largely eliminating motion artefacts. It has been used to measure foetal organ volumes, assess perfusion state of the placenta and the foetal brain and to produce ungated foetal cardiac movies (Baker *et al.*, 1994; Duncan *et al.*, 1999).

### Diffusion-weighted imaging (DWI)

DWI sequence is generally highly sensitive to motion and was exclusively used to image the foetal brain before the introduction of the ultrafast sequences (Schaefer *et al.*, 2000; Thoeny *et al.*, 2005; Brugger and Prayer, 2006). With the introduction of the ultrafast sequences, DWI has undergone an extensive development and its applications became significantly expanded (Colagrande *et al.*, 2006; Manenti *et al.*, 2006). With the help of echo-planar imaging, DWI acquisition time is reduced to be acquired in less than 20 seconds and is increasingly used in foetal MRI today. DWI is also highly sensitive in detecting hypoxic-ischemic lesions of the foetal brain (Borowska-Matwiejczuk *et al.*, 2003; Girard *et al.*, 2003). It is particularly beneficial in imaging structures such as the kidneys and teeth due to their anisotropic properties.

### T1-weighted sequences

These are fast multi-planar spoiled gradient acquisitions in the steady state sequences. An example of T1 weighting is the Fast-Low Angle Shot (FLASH) sequence which is considered the most robust. Structures vary in their appearances from dark for fluids to bright for tissues. Tissues with fat content have bright appearances while tissues with water content have mid-grey appearances.

### Short Tau (TI) Inversion Recovery (STIR)

This is a spin echo sequence with an extra 180˚ preparation pulse used to flip the longitudinal magnetisation into the opposite direction resulting in a zero-net magnetic moment for different tissues at different times (inversion times) based on their longitudinal relaxation time. To generate a measurable MR signal, a 90° pulse is applied to convert longitudinal magnetisation into a transverse magnetisation. Inversion Time (TI) is the time interval between the application of the initial 180° pulse and the 90° pulse. STIR is a fat suppression sequence in which fat appears very dark and fluids appear bright. It is unaffected by field inhomogeneity and low field strengths.

### Advantages and Disadvantages of *f*MRI and USS

Tables 1 and 2 summarises advantages and disadvantages of *f*MRI and prenatal USS. USS is more readily available in most centres, less expensive and more straightforward to perform. It provides real-time nature of imaging which is especially useful when looking at neuromuscular disorders and entrapment syndromes. When combined with its doppler characteristic of flow assessment in organs and vessels, USS adds a dimension of physiologic data on top of anatomical evaluation. Furthermore, USS provides higher spatial (ability to differentiate two adjacent structures from each other) and temporal resolutions (duration of time required for acquisition of a single shot) than MRI, thus in the context of foetal cardiac imaging, USS is the primary modality for evaluating the foetal heart. There are also 3D- and 4D USS techniques capable of depicting real-time volume data sets of the heart that can be displayed in any plane.

*f*MRI faces practical challenges when it comes to imaging the foetal heart such as its small size, fast rate and lack of cardiac gating signal which synchronizes image data acquisition to the cardiac cycle. Nevertheless, there is a growing interest and development of promising MRI sequences and techniques to overcome those challenges. Overlapping slice scanning, radial k-space sampling, retrospective same direction and multi-planar reformatting reconstruction techniques are all examples of different techniques used on SSFP sequences to study foetal cardiac structures with promising results. Cine-MR sequences provide dynamic and functional images of the foetal heart. When combined with SSFP sequences, it provides real-time measurements with quick and successive acquisition (Dong *et al.*, 2020). Furthermore, the application of a newly developed doppler USS device for gated cardiac MRI produced successful results (Kording *et al.*, 2018). In this technique, an external doppler US device was used to provide a cardiac gating signal for MRI to synchronise data acquisition with foetal cardiac cycle.

In optimal circumstances (such as adequate amniotic fluid and good foetal position), three/four-dimension USS provide better observation of real-time foetal behaviour and rendering of foetal surface anatomy than *f*MRI.

Transvaginal USS produces greatly improved resolution and image quality especially early on in pregnancy as compared to transabdominal USS due to higher frequencies applied by the transvaginal probe and the absence of interference implied by the anterior abdominal wall.

However, transvaginal USS provides smaller field of view, less comfortable for the patient and also affected by foetal position, amount of liquor and maternal habitus.

Both scans are operator dependant. Interpretation of images require appropriate knowledge of foetal anatomy, pathology, development, maturation and experience in differentiating between true lesions and artefacts. it is important to point out that USS is more operator dependant and thus subjective to the operator at that time, whereas MRI is more consistent.

*f*MRI is able to provide large field of view (FOV) in any imaging plane, making it ideal for foetuses with complex anomalies where visualisation of these anomalies within the context of the whole foetal body aids proper interpretation of these images. *f*MRI also has advantages in cases of maternal obesity, oligohydramnios and being less affected by foetal position which all limit the value of prenatal USS. Furthermore, Ossification of the foetal skull reduces the information obtained by prenatal USS but it does not affect *f*MRI. Individual foetal organs can be more visualised by *f*MRI and are more easily distinguished from each other (Simon *et al.*, 2000).

Both modalities are under continues development. MRI technical developments include e.g. parallel imaging using Simultaneous Acquisition of Spatial Harmonics (SMASH) which reduced MRI scan time significantly (Sodickson and Manning, 1997), the use of multiplexed sensitivity encoding (MUSE) method to correct the motion induced phase errors in segmental EPI without acquiring 2D navigators, readout-segmented EPI method to reduce geometric distortion and T\*2 blurring by taking a series of EPI acquisitions to cover k-space in a mosaic pattern, PROPELLER (Periodically Rotated Overlapping Parallel Lines with Enhanced Reconstruction) method to reduce image distortion and T\*2 blurring spiral imaging using spiral trajectories to trace k-space in a radiating pattern rather than a line by line scan offering intrinsic motion compensation through gradient moment nulling and efficient use of gradient power, reduced field FOV methods to reduce image distortion and T\*2 blurring by skipping phase-encoding lines, compressed sensing methods to improve the reconstruction for acquisition by exploring data sparsity in diffusion volumes (referred to as q-space samples) and scan time for each volume (k-space) (reconstruction of MRI image from highly under-sampled data), enhanced scan efficiency with Simultaneous multi-slice techniques (SMS) by acquiring multiple diffusion-encoded slices simultaneously, 3D multi-slab acquisitions using gradient echo in diffusion MRI to obtain high SNR efficiency to achieve higher spatial resolution (Wu and Miller, 2017). More recently, machine deep-learning methods have been proposed to improve the reconstruction quality in parallel imaging MRI by better image regularisation and k-space completion (Knoll *et al.*, 2019).

MRI magnets had significant technological developments since its first use. Forty years ago, resistive magnets were first used in clinical MRI with low strength ranges (0.1-0.7T). It was until the mid 80s when high quality clinical MRI with superconducting electromagnets became commercially available and for the first time higher strengths (up to 1.5T) could be used clinically (3T for research only), which later became the standard clinical field strength. Due to the increased sensitivity produced by the higher strengths, RF-coil design, fast imaging, protocols, speed and contrast have also undergone significant improvements. Today, clinical MRI is widely and routinely used providing high soft tissue contrast at field strengths up to 3T (7-11.7T for research only) (Moser *et al.*, 2017). MRI techniques further improved with the introduction of miniaturized fibre-optic transmission systems which reduced the total size of interconnections in phased array coils and offered a solution for RF heating problems (Memis *et al.*, 2008).

USS technology and its application in healthcare have continued to mature. Since its first use as a clinical investigation tool in the early 40s, manufacturers moved beyond basic 2D imaging to offer new ways to reconstruct images to enhance evaluations and their interpretation. New technological developments such as echocardiogram, doppler, coloured doppler, 3D ultrasound technology, 4D real-time capabilities and ultrasound guided biopsies came into existence. Today, integration of Artificial Intelligence (AI) into USS systems simplified image acquisitions across all its applications in healthcare. AI offers automation of time-consuming tasks, quantification, selection of ideal images, visual mapping and anatomical intelligence with minimal operator interaction. Vendors also continue to improve ultrasound workflow by producing newer generation ultrasound systems with faster processing times and more ergonomic features.

As computing power continues to advance, frame rates continue to increase as well. Together with better resolution and improved colour doppler scans, the future will be brighter for 3D USS in various applications in healthcare.

Table 1 Advantages and Disadvantages of prenatal USS.

|  |  |
| --- | --- |
| Advantages | Disadvantages |
| Availability | Operator dependant |
| Convenient | Obstructed view |
| Comparatively inexpensive | Limited by foetal position |
| Real time interpretation | Limited by ossifications and oligohydramnios |
| Superior for imaging calcified lesions | Limited by maternal obesity and pelvic bones |
| Guidance for diagnostic and therapeutic procedures | Limited field view |

Table 2 Advantages and Disadvantages of fMRI.

|  |  |
| --- | --- |
| Advantages | Disadvantages |
| Superior tissue contrast | Expensive |
| Large field of view allows visualisation of the whole foetus and association with maternal structures | Not widely available |
| Not limited by foetal position | High false positives and non-specific findings |
| Not limited by ossifications or oligohydramnios | Avoided in first trimester |
| Not limited by maternal obesity or pelvic bones | Contrast is avoided |
| Offline interpretation | Operator dependant |

## *f*MRI safety

There is no known risk of non-ionising radiation exposure to the foetus by *f*MRI and no harmful effects have been identified in more than three decades of clinical use of *f*MRI in pregnancy (Shellock and Crues, 2004). However the strong static and gradient magnetic fields and electromagnetic RF pulses are thought to be possible hazards to the foetus (Plunk and Chapman, 2014) and although there is no reported adverse effects on the foetus, it is still advisable to take caution for imaging in pregnancy, and theoretical risks for *f*MRI still exist (De Wilde *et al*., 2005).

In *f*MRI, the foetus is exposed to magnetic fields that are thousands of times stronger than that of the earth (Plunk and Chapman, 2014). Several experiments that evaluate human tissue exposure to strong static magnetic fields have failed to demonstrate any changes to cell growth, DNA damage, temperature regulation or other biological effects (Schenck, 2000). Each of the three components of MRI (static magnetic field, radiofrequency (RF) electromagnetic fields and time-varying magnetic gradient fields) is related to possible hazards. Biological effects, projectiles, malfunctioning and/or moving medical device implants are related to the static magnetic field. For RF electromagnetic fields the main concerns are tissue heating, implant heating and implant interference. Time-varying gradients are mainly related to peripheral nerve stimulation (PNS) and acoustic noise. However, for *f*MRI, the hazards concerned are the biological effects of the static and time-varying magnetic fields, the heating effects of the pulsed RF and the acoustic noise produced by the spatial encoding gradients (De Wilde *et al*., 2005).

Assessing the exposure risk from *f*MRI to the foetus is difficult as multiple static field strengths, gradient strengths, and RF pulses are used. Several studies involving both animal and human participants have evaluated the risks of *f*MRI to the developing foetus. One study looked at the mid-gestation exposure of pregnant mice to 0.35T *f*MRI (Heinrichs *et al.*, 1988). It showed a reduction in the crown-rump length of the embryos. Another study by Carnes & Magin (1996) found some effects on foetal growth and testicular development from exposure of mice embryos to 4.7T field strength. Their results showed; decreased foetal weight, reduction in crown-rump length, increased postpartum death rate and decreased spermatogenesis. However, Magin *et al*. (2000) found that long term exposure of mice to 4T *f*MRI has no effects on foetal growth and postnatal development. A study by Chew *et al.* (2001) reported no statistical differences in the rate of blastocyst formation in mice exposed to 1.5T *f*MRI.

Human research studying the effect of the three *f*MRI components on the foetus showed no evidence of existing hazards. Baker *et al*. (1994) investigated the long-term effects of 0.5T *f*MRI in a three year follow up study of 20 children imaged during pregnancy by EPI. There was no evidence of any morbidity or disability associated with the modality. Another study investigated the foetal growth in 74 foetuses imaged at 0.5T using EPI and 148 foetuses as a control group with no statistically significant differences observed (Myers *et al.*, 1998). Some studies assessed the changes in foetal heart rates during *f*MRI setting. Monitoring the heart rate in 16 foetuses in their third trimester on 1.5T using a HASTE sequence demonstrated no changes in heart rate (Poutamo *et al.*, 1998). Michel *et al*. (2003) found no changes in the heart rate of 8 term foetuses during 1.5T scans with T1-Weighted scans. For EPI, a study by Vadeyar *et al*. (2000) in which the heart rate of 10 term foetuses scanned at 0.5T was monitored and revealed no changes in foetal heart rate.

For evaluating the risk to the foetus from static magnetic fields exposure, Schenck (2000) found no harmful effects. However, some sensory effects e.g. metallic taste, vertigo and magneto-phosphenes were related to high static magnetic fields. Growth of cultured human cells was not significantly influenced by the exposure of non-homogenous static magnetic fields (Sato *et al.*, 1992). A survey of reproductive health among 1421 pregnant female MR workers who were exposed to fringe fields, showed no statistically significant results in terms of birth weight, gestational age and pregnancy outcome (Kanal *et al.*, 1993).

Several animal studies were carried out to evaluate the risk of exposure to static magnetic fields. Ueno *et al*. (1994) studied the development of frog embryos exposed to strong magnetic fields up to 8T and concluded that there was no effect on rapid cleavage, multiplication or differentiation of cells in frog embryos. Another study by Nakahara *et al.* (2002) on the effects of long-term exposure of Chinese hamster ovary cells for up to 4 days to a 10T static magnetic field found no effects on cell growth rate, cell cycle distribution or micronucleus frequency. In addition, Santini *et al*. (1994) concluded no effect on myoblast membrane dielectric properties of chick embryos exposed to 1, 3 and 5mT static magnetic fields. When studying the effects of 7T magnetic field exposure on egg hatching of *Heliothis* *virescens* (tobacco bugworm), Pan (1996) found a reduction and delay in the hatching rate. Static magnetic fields can adversely and irreversibly affect the migration and differentiation of cerebellar cortex cells of chick embryos (Espinar *et al.*, 1997). The International Commission on Non-Ionising Radiation Protection (ICNIRP 2009) stated that *f*MRI must be performed with caution if using systems more than 4T, as there is a lack of data regarding safety of static magnetic fields.

Hazards related to the pulsed RF fields in the form of thermal heating and contact burns constitute the main safety issues in *f*MRI (MHRA, 2015). In the UK, burn incidents resulting from RF fields are the most frequently reported MRI incidents to the Medicines and Healthcare products Regulatory Agency (MHRA), with 63 burn incidents reported in over 7 million scans performed between 1990 and 2006 (De Wilde *et al.*, 2007). Most of the radiofrequency fields applied are transformed into heat energy in body tissues (Shellock, 2000), the effect of such energy depends on radiofrequency power deposition in tissues known as Specific Absorption Rate (SAR) (De Wilde *et al.*, 2007). To ensure that thermal heating does not exceed safety limits, all MRI machine manufacturers have safety limits on SAR levels programmed into the pulse sequences (Plunk and Chapman, 2014). Tissues adapt thermo-regulatory mechanisms (peripheral vasodilatation) to dissipate heat to overcome the elevation in temperature. Certain body areas dissipate heat less efficiently such as the eyes (De Wilde *et al.*, 2007; MHRA, 2015). Advice from the Health Protection Agency (HPA) regarding protection of patients undergoing *f*MRI stated that there is lack of clarity regarding the effects of increased heat loads on the foetus and pregnant women and they should be imaged with caution (HPA: Health Protection Agency, 2008). It is advised that *f*MRI of pregnant women is only done after thorough risk/benefit analysis, particularly in the first trimester (ICNIRP, 2004). The ICNIRP (2004) report recommendation regarding foetal exposure to RF fields stated that heating hazard can have potential teratogenic effects, thus *f*MRI is recommended to be performed in the normal mode and that exposure duration should always be reduced to a minimum. Elevated temperature can produce harmful effects on the developing foetus particularly at the stage of organogenesis (Edwards *et al*., 2003). Little information is available about temperature elevation as a result of RF fields in *f*MRI and there is a severe shortage of studies assessing the heating hazard. Levine *et al*. (2001) investigated the potential heating effect in two pregnant pigs imaged at 1.5T using a HASTE sequence. They measured the temperature rise by inserting fibre optic probes into the amniotic fluid and foetal brain. No significant results were observed, however the results cannot be generalised as the study was limited by involving only two pigs imaged by only one sequence.

Time-varying electromagnetic field gradients can induce electric fields and circulating currents in conductive tissues. The strength of these induced fields will depend on the rate of change of the magnetic field and body tissue impedance (which is primarily resistive at frequencies below 1 MHZ).

If of appropriate frequency and of sufficient intensity, these currents can potentially interfere with the normal function of nerve cells and muscle fibres, leading to their stimulation. The extent of this stimulation depends on pulse shape and its repetition time. Tissue response can vary from discomfort and tingling feelings to twitching and limb movements (Peripheral Nerve Stimulation). In extreme cases, the stimulation can be sufficient to cause ventricular fibrillation, a more serious response to electrical currents. Frequencies of up to about 5 kHz are needed to produce peripheral nerve stimulation and between 10 Hz and 100 Hz to produce fibrillation. Nerve and muscle cells become progressively less excitable and responsive to electrical stimulation of higher frequencies >5 kHz (Ham *et al.*, 1997; De Wilde *et al.*, 2007; MHRA, 2021). As far as *f*MRI is concerned, biological effects and acoustic noise resulting from gradient magnetic fields are the main safety issues for the foetus. A nested case control study by Lee *et al*. (2002) raised some concerns over the rate of clinical miscarriages among participants exposed to *f*MRI. Rodegerdts *et al*. (1999) conducted a study to evaluate the teratogenic effects of time-varying magnetic gradients on foetal human fibroblasts and showed no statistically significant differences in cell proliferation between exposed and control groups and provided no support to any teratogenic effects of gradient fields.

One of the most important concerns regarding the safety of *f*MRI is the acoustic noise. This is the loud “knocking” sound that is generated by the rapid changes in current in the gradient coils. The noise varies in loudness in different commercial MRI systems depending on their design but generally it rises with greater magnetic field strengths, approaching 120dB in 3T MRI systems (Price *et al.*, 2001). By 28 GW (Gestational Weeks), all foetuses are capable of reacting to sound stimuli more than 28dB and it has been suggested that the foetus can be affected by loud noises (Brezinka *et al.*, 1997). Mothers can be protected from *f*MRI noise using earplugs supplied to them before the scan, however the foetus is not. In an attempt to measure the sound intensity that reaches the foetus inside the uterus, Glover *et al*. (1995) observed acoustic noise volume attenuation up to 30dB using a hydrophone inserted into a male volunteer’s stomach (resembling the gravid uterus). Despite this finding, there are still some grounds for concern because there is marked individual variation in attenuation according to body habitus particularly in cases with oligohydramnios, response of maternal tissue to different frequency levels and the fact that the magnet used in the study was only 0.5 T in strength. One could also argue that using a stomach to resemble a gravid uterus in only one male participant is not ideal because of the very small sample size in addition to the large anatomical and physiological variations. Location, size of uterus and foetus and amount of amniotic fluid are only some of the factors that could potentially affect their results.

Risk of exposure of foetuses to noise greater than 80dB in volume has been investigated both in animals and humans in some studies and harmful effects were encountered including low birth weights and raised foetal corticosteroid levels. Corticosteroid levels were three times higher the resting levels in offsprings of rats subjected to unpredictable noise stress for 60 days during pregnancy (Weinstock *et al.*, 1992). The level of Human Placental Lactogen in the serum of pregnant mothers subjected to aircraft noise was lower than those who were not exposed to noise and the difference became significant after 36 GW. Low levels of Human Placental Lactogen of subjects in the noise area were associated with lower birth weights (Ando and Hattori, 1977). Baker *et al*. (1994) investigated the development of 18 children imaged prenatally using EPI in a 3 year follow up study. It was found that 16 out of the 18 passed their hearing distraction test at 8 months’ age, however hearing of the two cases that failed the test were found to be within normal limits following further assessments. When performing otoacoustic emission tests as part of the newborn hearing screening programme in England in 103 neonates after exposure to acoustic noise by 1.5T *f*MRI during pregnancy, Reeves *et al*. (2010) found no association between *f*MRI exposure during second and third trimesters of pregnancy and neonatal hearing impairment.

Furthermore, Strizek *et al.* (2015) examined the effects of exposure to routine MRI at 1.5T during pregnancy on foetal growth and neonatal hearing function in a retrospective case-control study of 751 neonates exposed to *f*MRI and 10042 nonexposed neonates. They found no adverse effects of exposure to 1.5T *f*MRI on neonatal hearing or birth weight percentiles. However, only healthy newborns were included in their study and *f*MRI could have affected infants susceptible to hearing impairment secondary to confounding risk factors. Also, their study design did not allow for follow up examinations to evaluate long-term adverse effects of MR imaging exposure during pregnancy.

Therefore, evidence remains inconclusive regarding possible consequences of acoustic noise on foetal health (Hepper and Shahidullah, 1994; American Academy of Pediatrics, 1997; Butler *et al.*, 1999) and *f*MRI is used with caution, careful choice of magnet strength and care taken to keep the scan time as short as possible whilst obtaining diagnostic information.

# Chapter 2

# Indications of *f*MRI

*f*MRI is useful in cases with compound foetal anomalies or where prenatal USS is inconclusive (Baert and Prayer, 2011; Saleem, 2014). It should be undertaken as part of a specialist foetal medicine referral to aid diagnosis, management and counselling of foetuses with suspected diagnoses and to provide extra information in foetuses with uncertain outcome where termination is possible. *f*MRI started in the 1980’s with focus on the imaging of foetal CNS and since then, its clinical value has been well documented to be superior to prenatal USS in imaging the foetal CNS (Whitby *et al.*, 2001; Levine, 2002). Therefore, it remains the most common reason for *f*MRI referrals today. Oligohydramnios or anhydramnios are also other major indications for *f*MRI. Pregnancies with these complications are usually difficult to assess by USS whereas *f*MRI provides clearer views of the foetal anatomy allowing to help define any existing abnormalities (Simon *et al.*, 2000). *f*MRI is used in the clinical practice nowadays to investigate for abnormalities other than that of the CNS or where oligohydramnios is a problem. It is used for abnormalities of the foetal chest, abdomen, GUS, neck and less frequently musculoskeletal system for both diagnosis and management (Levine, 2001; Frates *et al.*, 2004).

To Understand the important role of prenatal USS and *f*MRI as prenatal diagnostic scans, we must understand common foetal pathologies (in which both scans are used) and how they could affect the foetus and the family. In this section of the introduction, we will illustrate the various indications of *f*MRI in the clinical practice today and try to discuss in detail those included in this study. The indications will be categorised according to foetal body region involved into chest, abdomen, GUS, neck, musculoskeletal and miscellaneous. A brief description of the appearances of the contents of these regions on *f*MRI will be also included.

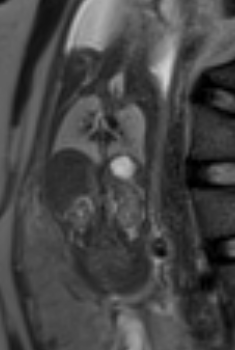
## CHEST

Imaging of the foetal chest is one of the most common indications for *f*MRI. Congenital foetal chest abnormalities can manifest in the chest wall or contents of the thoracic cavity includes the lungs, thymus, heart and major vessels, airways, mediastinum and diaphragm**.** Congenital Pulmonary Airway Malformation (CPAM) and Congenital Diaphragmatic Hernias (CDH) are the most common indications among them. Less common indications of *f*MRI in the chest include: bronchial atresia spectrum lesions, sequestrations, bronchogenic cysts and tumours (Mehollin-Ray *et al.*, 2012).

### Appearance on *f*MRI:

Assessing the foetal lungs is usually the primary and most important reason for imaging the foetal chest with *f*MRI*.* *f*MRI can assess lung volumes with a high degree of accuracy using MR volumetry and it also evaluates their maturity according to T2-weighted signal intensities. Foetal lungs appear as hyperintense solid structures on *f*MRI because of their alveolar fluid content (Figure-1). Trachea and bronchi appear as hyperintense tubular structures. The thymus gland displays a homogenous signal intensity on SSFSE sequences and it is easily visualised in the anterior mediastinum especially in the third trimester. It has a lower signal intensity than that of the lungs but higher than that of the heart. *f*MRI is not usually used to visualise the foetal heart and USS (foetal Echo) is often used instead as it is considered to be superior to *f*MRI in evaluating heat defects with added benefits of blood flow measurements. However, *f*MRI can be useful in the imaging of certain heart anomalies such as cardiomegaly, pericardial effusion, heart tumours and position anomalies(Martin *et al.*, 2012; Prayer and Brugger, 2007)**.**

## 



Lungs

Bronchi

Figure 1 Coronal T2-Weighted Image showing Foetal Lungs and Bronchi as hyperintense structures (arrowed).

## Classification of congenital lung malformations:

Congenital cystic Lesions of the lung are a rare spectrum of anomalies that affect the foetal lungs, most commonly CPAMs (Congenital Pulmonary Airway Malformations), pulmonary sequestrations, congenital lobar emphysema and bronchogenic cysts (Durell and Lakhoo, 2014). These cystic lung lesions are detected more often nowadays owing to the increased use of obstetric ultrasound allowing for improved perinatal planning and neonatal management.

Langston classification of congenital lung lesions remains the most widely used (Langston, 2003). Langstone highlighted major pathological findings for the malformations noted and provided the following classification:

**Bronchopulmonary malformations:**

CPAM

Bronchogenic cyst

Bronchopulmonary sequestration (BPS)

Bronchial atresia

**Pulmonary hyperplasia and associated anomalies:**

CPAM type 3

Laryngeal atresia

**Congenital lobar over-inflation (emphysema)**

**Other cystic lesions:**

Simple cysts

Lymphatic cysts

Mesothelial cysts

Enteric cysts

Pleuro-pulmonary blastomas

Many of these lesions are very rare and none of our participants were diagnosed with them. However, it is important to discuss pathology, clinical features and management of the lesions found in our participants.

### CPAM:

Formerly known as CCAM is a rare congenital anomaly of the lower respiratory tract. Although rare, it is the most common congenital lung disease. It affects the development of the terminal respiratory tracts in which hamartomatous proliferation of these tracts into a gland-like (adenomatoid) tissue results in a non-functioning multi-cystic malformation without proper alveolar formation. Most CPAMs are detected prenatally with USS or *f*MRI and usually involves one lung segment but may involve more than one and may occur as bilateral. Rarely, CPAMs might only be detected later in life or during adulthood as incidental findings or due to manifestations of its own complications (Feng *et al.*, 2012).

#### Incidence:

The true prevalence of this condition among the population is unknown due to the lack of published population incidence. Most of the available data is unlikely to reflect the true population prevalence as it is largely derived from single specialised centres rather than incidence in whole population. However the estimated incidence is 1:11,000 to 1:35,000 with no known preference for lung side, sex or race (Gornall *et al.*, 2003; Durell and Lakhoo, 2014), although some studies report that it is more common in males (Langston, 2003) and the majority are left sided (Sapin *et al.*, 1997).

#### Aetiology:

The pathogenesis and causes of CPAM are poorly understood. There are no known genetic or chromosomal abnormalities or inheritance patterns that could be linked to the pathogenesis of this condition. However, in reviewing the literature, some studies have linked the pathogenesis of CPAM to a number of theories including maturation arrest in lung embryogenesis (MacSweeney *et al.*, 2003; Kuru *et al.*, 2004), abnormal tissue proliferation, airway obstruction and dysplastic or metaplastic changes to lung tissues (Sfakianaki, AK. Copel, 2012).

#### Classification:

CPAM was classified by Stocker *et al*. (1977) into five types according to the bronchopulmonary tree embryologic level involved in the malformation and histologic features. It is important to distinguish between these five types as they differ in histopathological features, clinical manifestation, malignant potential and prognosis. The five types are as follows:

*Type 0 CPAM* in which the malformation originates from the trachea or the bronchus. This is characterised by solid appearance and is very rare and lethal.

*Type 1 CPAM* in which the malformation originates from the distal bronchus or proximal bronchiole is the most common type of CPAM, 50-70% of cases, and usually presents with large dominant cysts (usually multilocular) surrounded by smaller cysts. This type carries good prognosis following successful management, although, rarely, malignant transformation into broncho-alveolar carcinoma has been reported (MacSweeney *et al.*, 2003)

*Type 2 CPAM* in which the malformation originates from terminal bronchioles and it accounts for 15-20% of cases. This type is characterised by small cysts, usually smaller <2cm in diameter, and frequently associated with other anomalies such as renal agenesis, cardiac anomalies and pulmonary sequestration.

Type 3 CPAM, accounts for 10% of cases, in which the malformation originates from acinar-like tissue. It is characterised by small cysts <5cm in diameter, solid appearance and entire lobe involvement. Prognosis of this type varies depending on the size of the masses, but it is generally thought to be poor.

Type 4 CPAM accounts for 5-15% of cases and it originates from alveoli. It is characterised by larger cysts and single lobe involvement. This type has malignant potential and has been associated with pleuropulmonary blastoma (MacSweeney *et al*., 2003).

CPAMs are also classified according to cyst size into microcystic <5cm or macrocystic >5cm in diameter. This classification is used frequently by radiologists and foetal medicine experts to describe CPAMs prenatally. Microcystic CPAMs usually form larger masses and thus associated with poorer prognosis (Scott Adzick *et al*., 1985). Stocker *et al*. (1977) adapted this form of classification in his five types of CPAMs, making type 3 only microcystic while type 1,2 and 4 can be macrocystic or mixed.

#### Management:

*f*MRI is becoming increasingly used to confirm prenatal USS suspicion of CPAMs. Appearances of these malformations on *f*MRI are used by radiologists to distinguish between subtypes of CPAMs; cystic or solid hyperintense lesions. *f*MRI is also thought to provide valuable information about the condition of any existent normal lung tissue alongside these malformations (Martin *et al*., 2012).

The course of this condition shows large variations in different cases. In majority of cases, CPAMs do not enlarge during pregnancy and may in fact regress in size and completely disappear spontaneously before delivery. National Institute for Health and Care Excellence (NICE) guidelines and patient.information websites advise to use the watch and wait management approach with asymptomatic and mildly symptomatic patients (NICE, 2005; Tidy, 2015a). In some foetuses however, CPAMs grow rapidly in size and cause major problems during pregnancy and may result in foetal death. In a retrospective study to determine antenatal and short-term neonatal outcome of CPAMs, Tran *et al.* (2008) found that 38% of cases with antenatally diagnosed CPAMs appeared to resolve, 29% appeared to regress, 10% remained unchanged and 21% appeared to enlarge. Therefore, it is extremely important to follow up such cases with regular antenatal scanning.

Depending on the clinical condition of the foetus, size of the lesion and the presence of any associated anomalies, antenatal care including counselling should be tailored to each patient. Timing, place and mode of delivery should be discussed with the patient and early involvement of neonatal medicine experts and paediatric surgeons should be considered.

Management of CPAM largely depends on severity and on the clinical condition of the foetus. Surgical resection of CPAMs is the treatment of choice in symptomatic patients either early in life or later if patients develop complications. Surgical intervention during pregnancy in the form of thoracocentesis (drainage of large cysts), thoraco-amniotic shunts (to maintain drainage of fluid into the amniotic space), intra-lesion injection of sclerosing agents, laser ablation or in utero CPAM resection (lobectomy) is rarely required but can be of benefit in selected cases with large pleural effusions or hydrops (Adzick *et al*., 1998; Witlox *et al*., 2011).

Some studies have promoted the use of steroid therapy during pregnancy to resolve hydrops, reduce foetal demise and improve perinatal and neonatal mortality (Tsao *et al*., 2003; Witlox *et al*., 2011). However, variable response to steroids was reported in a study that involved fifteen foetuses with CPAMs treated with steroids prenatally (thirteen of which were hydropic) giving a survival rate of 53% (Morris *et al*., 2009). The use of prenatal steroid therapy remains highly controversial and further investigation is needed in order to determine the association between prenatal steroid therapy and the resolution of CPAMs associated hydrops and perinatal survival rate.

#### Complications:

The pathophysiology of this condition can produce a wide variety of complications owing to the pathology itself or to the mass effect produced by the lesion or both. Complications may include: perinatal death, hydrops, pulmonary hypoplasia, polyhydramnios, respiratory distress, prematurity, pulmonary hypertension, pneumothorax, surgery, recurrent lung infections and small risk of malignant transformation (Tran *et al*., 2008; MacSweeney *et al*., 2003).

#### Follow up:

Antenatal care including follow up with serial scanning with prenatal USS and/or *f*MRI is very important to monitor the condition.

After delivery, babies will usually be regularly followed up with serial scanning in the form of X-rays, US scans and CT scans until early years of life.

### Bronchopulmonary Sequestration (BPS):

BPS also known as accessory lung, is a congenital non-functioning accessory lung tissue, a malformation formed from the bronchopulmonary foregut. It has no communication to the tracheobronchial tree, favourably affects the lower lobe and characterised by an anomalous systemic blood supply, usually from the aorta. It is a rare condition with an estimated incidence of 1 in 15,000 births and 6% of all congenital lung malformations (Peters *et al.*, 2013). It can be associated with other congenital anomalies e.g. congenital heart defects, CDH and CPAM. Hybrid lesions are the co-presentation of BPS and CPAM. The cause of BPS remains unknown, no chromosomal, genetic or hereditary links were ever established to BPS. It is classified anatomically into two types:

Intralobar sequestration (ILS): or Intrapulmonary sequestration where the malformation arises within and surrounded by normal functioning lung tissue. This is the most common type of BPS accounting for two thirds of all cases. ILS may present later in life with recurrent chest infections if not surgically removed earlier. ILS is less commonly associated with other congenital anomalies.

Extralobar sequestration (ELS): or extrapulmonary sequestration which arises outside of the lung tissue covered with its own separate pleura. It has a male prediction and accounts for one third of BPS. It can be in close proximity to the lung tissue (above the diaphragm) or in the abdomen (below the diaphragm). ELS may present early after birth with respiratory distress or remain asymptomatic. It is more commonly associated with other congenital anomalies.

#### Management:

These lesions are usually picked up prenatally by prenatal USS. In the clinical practice in many centres in the UK today, these lesions are confirmed by the use *f*MRI. These lesions appear on *f*MRI as well defined hyperintense masses with or without hypointense septa *(Huang et al*., 2004). Surgical removal of the accessory tissue is the treatment of choice for BPS. Surgery is usually done in the first year of life. All intra-lobar sequestrations should be surgically removed during early life, usually by resection of the segment involved or the entire lobe (lobectomy). Large or symptomatic ELS are surgically removed sparing the lungs. Some are in favour of resection of all BPS to prevent recurrent chest infections and avoid high cardiac output failure in neonates particularly with large lesions. However, resection of asymptomatic ELS is controversial with no established evidence of its benefits (Laberge *et al*., 2004). Partial or total spontaneous resolution of BPS have been reported in some cases (García-Peña *et al*., 1998). A trail of coil embolization of the feeding vessel in BPS that enhances necrosis and eventually fibrosis of the lesion has been successful in selected cases (Yeh *et al*., 2006). BPS carries a good prognosis and those successfully treated tend to lead normal lives.

### Bronchogenic cysts:

Bronchogenic cysts (or bronchial cysts) are rare congenital malformations of the bronchopulmonary foregut. They are usually singular fluid-filled cysts that arise from abnormal buddings of the tracheobronchial tree. The majority of these cysts are found within the mediastinum (more common in the middle mediastinum) and less often within the lung parenchyma (Yoon *et al*., 2002). They are usually asymptomatic and found incidentally on regular prenatal check-ups or later in life when the chest is imaged. These cysts do not usually communicate with airways and remain typically fluid-filled. However, they do on some occasions and become air-filled instead. Large cysts may produce compression effects on the surrounding parenchyma and result in respiratory distress. Therefore, the place of delivery should be carefully planned ahead as newborn might need high level of care (Ramenofsky *et al.*, 1979).

Bronchogenic cysts are typically benign by nature but have a rare tendency to malignant transformation (Baert and K, 2007).

#### Management

Treatment of bronchogenic cysts is highly controversial. Some authors strongly advise on surgical resection of all cysts whether symptomatic or not. They fear later complications of these lesions such as enlargement, infection, haemorrhage and malignant transformation (Ramenofsky *et al.*, 1979; Baert and K, 2007). In clinical practice, small asymptomatic cysts can be followed with radiological imaging.

### Congenital Diaphragmatic Hernia (CDH):

This is the most common indication of *f*MRI in the chest. CDH is a developmental defect in the diaphragm, a thin muscle layer that separates thoracic from abdominal contents, allowing the latter to migrate up into the chest cavity. CDH occurs very early in pregnancy around 10 GW (it is not known when exactly CDH occurs, some studies report as early occurrence as 4 GW). The diaphragm starts to develop approximately 4 GW from infoldings of several structures. Final closure of these structures to form the diaphragm normally occurs around 8 GW. The right side of the diaphragm closes slightly earlier than the left side.

A defect in the diaphragm will allow some or all the abdominal contents; may include the stomach, small and large intestine, liver, spleen or kidney, to be displaced into the chest cavity. This will take up space that was normally reserved for the lungs to develop properly and result in their failure to grow (pulmonary hypoplasia) and high blood pressure in the lungs (pulmonary hypertension).

It can be an isolated defect or can be associated with other chromosomal syndromes. It is usually unilateral and occurs more commonly on the left side.

#### Incidence:

CDH is a rare condition with an estimated incidence of about 4 neonates out of every 10,000 births in the UK (0.04%).

#### Aetiology:

The pathogenesis and causes of CDH are poorly understood. Genetic or chromosomal abnormalities could be responsible for CDH but pathogenesis remains unclear with a number of hypotheses available. One of the earliest studies conducted to investigate the toxicological effects of various herbicides found a potential link between nitrofen (2,4-dichloro-phenyl-p-nitrophenyl ether) and diaphragm malformations in animals. Administration of a specific amount of this toxin to animal models at a specific time resulted in diaphragmatic abnormalities remarkably similar to CDH in human infants in about 50% of the foetuses (Ambrose *et al*., 1971). Studies on this herbicide toxin became to be commonly recognised as the nitrofen-animal-model.

Subsequent studies on this model suggested that early exposure of animal models to nitrofen resulted in pulmonary hypoplasia even before the development of the diaphragmatic defect. This opened a whole new area of controversy as to whether lung hypoplasia is a result or a cause of the diaphragmatic defect. As a result of these studies, the dual-hit hypothesis came into light postulating the pathogenesis of pulmonary hypoplasia in CDH as a result of two developmental insults. The first insult could be due to genetic, chromosomal or environmental factors that occur to the lungs during early embryogenesis causing the lungs to be hypoplastic even before the development of the diaphragm. The second insult occurs as a result of the diaphragmatic defect causing the abdominal viscera to migrate up into the chest cavity producing a compression effect on the lungs (Keijzer *et al*., 2000).

One major flaw of the nitrofen-animal-model is that the use of the herbicide nitrofen is not linked yet to human CDH. Another hypothesis to the pathogenesis of CDH is linked to vitamin A/retinoic acid signalling pathway. The link between this pathway and early foetal development is already established in animal models. Rats on a vitamin A deficient diet throughout gestation developed diaphragmatic defects. Moreover, supplementation of vitamin A to nitrofen exposed rats, reduces CDH incidence in the offspring. This shed the light on a possible link between the nitrofen-animal-model and vitamin A/retinoic acid signalling pathway. It could be that nitrofen is associated with CDH because it perturbs the retinoid signalling pathway. Many studies found that nitrofen might serve as a down regulator of the retinoic signalling pathway by inhibiting the synthesis of retinol dehydrogenase-2, a key enzyme of the pathway (Lohnes *et al*., 1994; Mey *et al*., 2003; Babiuk *et al.*, 2004; Sugimoto *et al*., 2008). However, all these data are produced from studying animal models with limited results in humans.

The sole source of vitamin A to humans is found only in diet. Worldwide, vitamin A deficiency is endemic to developing countries. However, there is no corresponding increase in CDH incidence in those countries. The reason behind this demographic difference is unknown but the lack of accurate birth defects registries in the developing world might be one of the reasons.

There have been few human studies looking at the pathogenesis of CDH and its association with vitamin A. Some of these studies demonstrated lower levels of retinol and retinol-binding protein from cord blood in neonates with CDH (Major *et al*., 1998; Beurskens *et al*., 2010). In a case control study of 50 CDH pregnancies demonstrated that vitamin A intake below the daily recommended requirement is associated with an increased risk of CDH (Beurskens *et al*., 2013). Another more recent study in Japan involved 40 cases of CDH singleton pregnancies found that low maternal dietary intake of vitamin A in early pregnancy was inversely associated with CDH (Michikawa *et al*., 2019).

#### Classification:

CDH is classified according to the anatomical location of the diaphragmatic defect into 3 main types:

Bochdalek hernia: is the most common type of CDH with a posterolateral hernial defect. This type is usually large and more commonly affects the left side of the chest 75-90% of cases. It is also associated with a poorer outcome.

Morgagni hernia: is a rare type of CDH characterised by an anterior hernial defect through the foramen of Morgagni. This type is usually small and more often affects the right side of the chest. Two thirds of cases are asymptomatic but can present with similar features to the bochdalek type.

Congenital Hiatal hernia: is a very rare type of CDH in which the stomach herniates through the oesophageal hiatus.

#### Management:

Although prenatal USS is the gold standard modality for the initial diagnosis of CDH, *f*MRI is used to assess lung volumes, liver position, associated malformations identifying hernial sacs and differentiating hernia subtypes (which are associated with specific compilations) (Lyons *et al*., 2015; Mehollin-Ray *et al*., 2012). *f*MRI is superior to prenatal USS in providing excellent tissue contrast resolution that permits clear differentiation between structures with similar appearances such as lungs and small intestine (Martin *et al*., 2012). It is also used to evaluate foetal lung maturation by assessing their volume and signal intensity (Balassy *et al*., 2010). Once CDH diagnosis is confirmed prenatally, multidisciplinary approach takes place. Paediatric surgeons, neonatologists, obstetricians and radiologists should be involved and introduced to families prior to delivery to discuss different options available to them. One of the options available is termination of pregnancy especially if CDH is associated with multiple anomalies or lethal chromosomal syndromes e.g. Edward’s or Patau’s syndromes. Postnatal management of CDH requires advanced neonatal care in tertiary centres and place of delivery should be discussed and determined with families prenatally. Babies with CDH might need very intensive support immediately after birth. The clinical condition of the baby immediately after birth will dictate the support needed to stabilise their condition. Forms of support can range from little oxygenation to mechanical ventilation to extracorporeal membrane oxygenation (ECMO). After a period of foetal stabilisation and if they survive the first critical few days then surgery will take place.

Surgical repair of the diaphragmatic defect is the gold standard approach. In the UK, the surgical procedure mostly used in the NHS is the thoracoscopic repair in which herniated abdominal contents are reduced and the diaphragmatic defect is sutured or patched. In some complex cases open surgeries are needed. Length of hospitalisation needed for babies recovering from surgery depends on their condition and presence of any complications but usually takes few weeks. The majority of cases after having CDH surgical repair have good exercise tolerance and lead normal lives (NICE, 2011; Health, 2020).

#### Complications:

CDH is a life-threatening condition and its complications depend largely on its severity with a 50% survival rate. Severity of CDH is determined by four factors. First, defect size, larger defects will allow more abdominal contents to be herniated into the chest cavity, hence more pressure on the heart and lungs. Second, timing of abdominal contents herniation into the chest. If the lungs had a better chance to sufficiently mature and expand before the pressure opposed by the herniation occurs, then they will have a better chance to re-expand by removing the pressure with surgical repair. Third, lung size or lung-to-head ratio (LHR) which is a numeric estimation of the lung size based on measurements of foetal lungs visible on US or more accurately *f*MRI. LHR < 1.0 is associated with poorer prognosis. *f*MRI measures the lung volume, rather than rely on a ratio, and compared this to the expected volume of the same gestational age to give a percentage of expected. Lung volumes of less than 34% of the expected have very poor prognosis. Fourth, the amount and type of herniated contents, diaphragmatic hernias containing large parts of abdominal viscera are associated with poorer prognosis. CDH with liver up (liver herniation into the chest cavity) is associated with worse prognosis. A systematic review and meta-analysis of the literature included 407 livers up CDHs and 303 livers down CDHs showed significantly lower survival rate (45%) for the liver up group compared with liver down group (73%).

For mild, small defect CDHs, good outcome is often achievable with sufficient cardiopulmonary support pre- and post-surgery. Severe cases on the other hand have a lower survival rate with higher risk of long-term complications.

Short term complications of CDH include death, Respiratory failure, Pulmonary hypertension, pulmonary hypoplasia and surgery.

Long term complications may include CDH recurrence after surgical repair, respiratory issues including recurrent infections, pulmonary hypertension, developmental delay, gastrointestinal complications including e.g. intestinal obstruction, nutritional problems, gastroesophageal reflux disease.

In most cases CDH occurs as an isolated problem with no other associated anomalies. However, it can sometimes manifest as part of much more complex pathologies or chromosomal syndromes such as trisomy 21 (Down’s syndrome), Trisomy 18 (Edward’s syndrome), Trisomy 13 (Patau’s syndrome) and Monosomy X (Turner’s syndrome). The most common associated anomaly with CDH is congenital heart defects. All these associated anomalies and chromosomal syndromes have complications of their own which affect prognosis and overall survival rate.

#### Follow up:

Neonates who have had CDH repair require structured and streamlined follow up to optimise their management and improve outcome. Our institution guidelines for discharge planning for all infants post repair of CDH include respiratory team review, chest x-ray one week prior to discharge, Echo to rule out pulmonary hypertension, nutritional assessment, newborn screening as per Public Health England, routine immunisation and referrals to appropriate specialities if indicated. Guidelines for follow up management for all infants post CDH repair at our institution include a minimum of 2 reviews with neonatal surgical nurse specialist within 6 weeks post discharge, paediatric respiratory and surgery reviews 6 weeks and then every 12 weeks (or as needed) post discharge until 1 year of age then to be a minimum of yearly reviews. Chest x-rays are required as indicated and at 6 weeks post discharge, 1 year of age and then yearly. Children will have neurodevelopment assessment by neonatologists at age 2 and pulmonary function tests yearly starting at age 5.

### Pleural effusion:

Also known as hydrothorax refers to accumulation of fluid in the chest cavity. It is a rare condition with an unknown incidence but has been estimated of approximately 1:15,000 births and twice as common in males (Longaker *et al*., 1989). It is thought that true incidence might be much higher as many of foetal pleural effusion cases are asymptomatic and often too small to be detected by antenatal imaging. Pleural effusions can be primary or secondary. Primary pleural effusions are generally chylous; secondary to lymphatic leakage, occur in isolation, unknown cause and can be unilateral or bilateral. Secondary pleural effusions are usually secondary to more generalised foetal anomalies or as a result of hydrops fetalis. It can be associated with congenital heart defects viral infections, CPAM, CDH and chromosomal abnormalities such as Down’s syndrome (about 20%), Turner’ syndrome and trisomy 18 (Cao *et al*., 2017). Mortality rate reported ranges from 30-68% for antenatally detected, untreated, unilateral and/or bilateral pleural effusions (Longaker *et al*., 1989; Estroff *et al*., 1992; Ruano *et al*., 2011; Smith *et al*., 2005). Factors associated with poor prognosis include young gestational age (<33wk), preterm delivery (<30wk), presence of hydrops, bilateral effusion, mediastinal shift and presence of other associated anomalies (NICE, 2006; Longaker *et al*., 1989). The major complication of pleural effusion is the compression effect to the surrounding lungs heart and vena cava. Compression prevents normal lung growth and development resulting in pulmonary hypoplasia. Mediastinal shift, cardiac and vena caval compression reduces the venous return to the heart, resulting in a low cardiac output which consequently results in hydrops. Management depends on level of severity and presence of complications and associated anomalies. Most of isolated small unilateral pleural effusions undergo spontaneous resolution in-utero or soon after delivery. A review of 11 foetuses with antenatally detected unilateral and/or bilateral pleural effusions showed spontaneous resolution in 6 foetuses (54%), only 1 foetus of these 6 had a bilateral effusion. Those do not resolve spontaneously or large more severe effusions that produces respiratory compromise are treated with immediate drainage and intensive respiratory support. Prenatal thoracocentesis is sometimes required to allow normal lung growth and prevention of hydrops with pleural amniotic shunting reserved for recurrent effusions. Survival rate post pleural amniotic shunting is about 48% (Smith *et al*., 2005; NICE, 2006).

### Emphysema:

Congenital lobar emphysema or lobar overinflation refers to a rare congenital lung abnormality characterised by progressive hyperinflation of one or more pulmonary lobes. The incidence of prenatally detected lobar emphysema is not reported in the literature but it is known to be twice as common in males (Lincoln *et al*., 1970). Overinflation of pulmonary lobes occurs due to partial or complete occlusion of their bronchi resulting in air entrapment in the lobes. This will consequently cause compression effects to the surrounding lung parenchyma and eventually lead to mediastinal shift with further compression on surrounding structures. Lobar emphysema usually involves one lobe, left upper lobe being the most commonly affected lobe (60%) (Thakral *et al*. 2001). However, it may affect any lobe and may involve more than one lobe. Occlusion of the bronchus can be due to extrinsic or intrinsic causes. Extrinsic causes include any pathology that causes compression on the bronchus leading to its partial or complete obstruction e.g. bronchogenic cysts, tumours vascular anomalies and enlarged lymph nodes. Intrinsic causes include those which cause occlusion within the bronchus such as congenital cartilage defect, aspirated meconium, mucous plaques and granulation tissue. Histopathological resection of emphysematous lobes demonstrated cartilaginous abnormalities in about third of cases in one study (Mei-Zahav *et al*., 2006). In another study, cartilaginous abnormalities were responsible for 20% of cases while no specific cause was found in the remaining 80% (Karnak *et al*., 1999). Overall, no clear cause can be identified in about half of the patients and is therefore considered to be idiopathic type of congenital lobar emphysema (Demir *et al*. 2019; Olutoye *et al*., 2000).

Management should be carefully planned ahead of delivery. Depending on clinical severity of the condition, babies with congenital lobar emphysema may be asymptomatic or present with respiratory distress with rapid deterioration of symptoms. Lobectomy is the treatment of choice for the severely symptomatic patients. However, conservative management with regular follow up should be trialled with milder presentations (Karnak *et al*., 1999; Thakral *et* *al*., 2001).

## ABDOMEN

*f*MRI has been used in conjunction with prenatal USS to diagnose foetal Gastrointestinal Tract (GIT) anomalies such as duodenal obstruction, oesophageal atresia, liver and spleen masses, jejunal, ileal and colonic atresias and cloacal malformations. It is also used in foetuses with suspected abdominal wall defects such as gastroschisis and omphalocele (Shinmoto *et al*., 2000; Shinmoto and Kuribayashi, 2003). GIT abnormalities are often first detected or suspected by prenatal USS. They are usually suspected in the presence of certain scan findings such as polyhydramnios, dilatation of the small bowel, hyperechoic intestine (Saguintaah *et al*., 2002). These findings are not necessarily specific to certain anomalies and sometimes can be normal variants or due to temporary causes e.g. obstruction (Irish *et al*., 1997; Weeks *et al.*, 1997).

### Appearance on *f*MRI:

The foetal abdomen contains many organs and each has its own imaging characteristics on prenatal scanning. Therefore, this section will aim to discuss different normal and common abnormal findings on prenatal imaging.

Contrast media is usually used in adults to obtain better visualisation of the GIT. This is avoided in the foetal setting and the natural contents of the foetal GI tract itself such as meconium and amniotic fluid are used instead. The amount of these substances is directly related to gestational age, and obtaining good quality scan images relates to the gestational age and the developmental stage of the foetus (Brugger and Prayer, 2006).

With progression in foetal development, the T2-hyperintense and T1-hypointense amniotic fluid gradually fills the GI tract. The amount of amniotic fluid that can be swallowed by the foetus increases gradually in volume until it reaches a maximum of 750ml/day in a full term foetus (Richard, 1976; Brugger and Prayer, 2006). Foetal swallowing starts before the end of the first trimester (around 10th GW) and only small amounts of amniotic fluid reach the bowel. However, by 25 GW, larger amounts of amniotic fluid enter the bowel and this is thought to enhance scan quality by providing a more abundant contrast media (Richard, 1976). The characteristic T2-hyperintensity of amniotic fluid allows the depiction of oral, pharyngeal and laryngeal anatomy. T2-hyperintense amniotic fluid fills the oesophagus, stomach and duodenum in normal foetuses. However, due to oesophageal and duodenal contraction waves, these parts of the GI tract can sometimes appear temporarily empty (Huisman and Kellenberger, 2008). In conditions associated with oligohydramnios e.g. bilateral renal agenesis, the whole bowel appears empty because the foetus has no fluid to swallow. T2-hypointense and T1-hyperintense meconium can fill the rest of the GI tract from the distal ileum downwards depending on the GA of the foetus. The combination of distal meconium to proximal amniotic fluid allows comparison between upper and lower GI tracts with T2-signal intensity gradually decreasing and T1-signal intensity gradually increasing (Huisman and Kellenberger, 2008). The small bowel and the rectum are the first to fill with meconium at around 17 GW, then as the foetus develops meconium is seen more proximally within the large bowel and the small bowel becomes fluid filled again (Hyde *et al.*, 2020).

#### Oesophagus:

Oesophagus is not normally seen on *f*MRI unless pathological. Occasionally normal oesophagus appears on T2-weighting as hyperintense tubular structure behind the trachea. Certain scan findings such as presence of polyhydramnios and a small or underfilled stomach in a foetus usually raises the suspicion of oesophageal anomalies.

#### Stomach:

By 18 GW, the foetal stomach is usually visible by *f*MRI as a fluid filled structure in the left upper abdomen. It mimics the appearance of an adult stomach and its size directly correlates to gestational age. Its wall and folding of mucosa are visible by 20 and 29 GW, respectively. The pyloric area and the first part of duodenum can also be demonstrated by *f*MRI (Brugger and Prayer, 2006). The gastric contents should always appear as T2-hyperintense and T1-hypointense (Figure-2) unless there is blood in the amniotic fluid (intra-amniotic bleeding) that leads to T1-hyperintensity. Scarce amount of intra-gastric amniotic fluid results in poorly visualised stomach. This should always alert the examiner to look for oesophageal anomalies e.g. Oesophageal Atresia (OA) (Barnewolt, 2004).

In certain foetal anomalies such as left sided CDH and gastric herniation, the position of the stomach might be affected and it can be visualised inside the thoracic cavity (intrathoracic stomach) (Shinmoto et al., 2000; Al-Assiri *et al*., 2005). Abnormalities affecting the size of the stomach such as microgastria (small stomach; which can be found in right-sided isomerism), or enlarged stomach (which can be found in gastric outlet obstruction or duodenal atresia) can be clearly identified by *f*MRI (Brugger and Prayer, 2006)

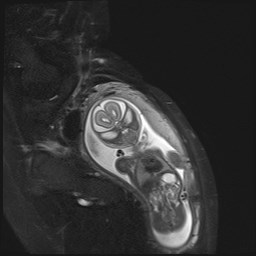
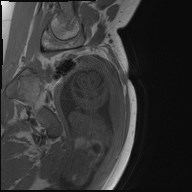


Figure fMRI showing the Stomach (arrowed). a) Coronal T1-Weighted Image showing the stomach and its amniotic fluid content as a dark hypointense structure. b) Coronal T2-Weighted Image showing the stomach and its amniotic fluid content as a bright hyperintense structure.

a

bb

Figure 2 fMRI showing the Stomach (arrowed). a) Coronal T1-Weighted Image showing the stomach and its amniotic fluid content as a dark hypointense structure. b) Coronal T2-Weighted Image showing the stomach and its amniotic fluid content as a bright hyperintense structure.

#### Small and Large intestines:

Foetal small intestine develops from the proximal to distal direction (cranio-caudal) and from 20 GW onwards their anatomy and function strongly resembles that of a new-born (Vachon *et al.*, 2000). Before 24 GW, the foetal intestine has a characteristic patchy appearance due to the fluctuation in T2-weighted signal intensity between hypointensity and isointensity to muscle. In this developmental stage, the small intestines are only 2-3 mm in diameter and filled with small amounts of fluid and thus their T2-weighted signal intensity is either low or neutral to muscle. Distinction between different parts of the bowel is difficult in such an early stage because they have similar signal intensities (Brugger and Prayer, 2006).

The developed swallowing mechanism and the development of gastric emptying becomes evident after 24 GW. These will ultimately increase the amount of fluid inside the intestine and loops of small intestine become visible with a high T2-weighted signal. T1-weighted characteristic hypointensity signal of the small bowel (particularly proximal duodenum) may not be evident at this stage partly due to the numerous secretions from the intestine itself, the liver and the pancreas that are mixed with the amniotic fluid (Brugger and Prayer, 2006). Identification of different parts of the bowel depends on the signal gradient carried by each part. Small intestine loops are usually visible in the left upper abdomen as T2-hyperintense areas (figure-3-a) while distal loops which are T2-hypointense are usually seen in the right lower abdomen. By comparing T1-weighted hyperintensity of the meconium to the moderate intensity of the abdominal organs, reconstruction of maximum intensity projection and rotational views of the colon can be created (Huisman and Kellenberger, 2008).

The colon appears as a tube-like structure with a circuitous course within the abdomen. It is filled with meconium whose signal characteristics play the key role in *f*MRI. In normal foetuses, meconium is found in the distal parts of small intestine and the entire colon at later gestational ages but the extent of meconium in the large bowel is gestational age dependent (Hyde *et al.*, 2020). It is formed of various intestinal secretions mixed with desquamated intestinal epithelium and amniotic fluid. It has a low signal on T2-weighting, a high signal on T1-weighting (Figure-3-b) and an intermediate signalon steady-state free-precession sequences (Table-3).

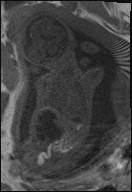
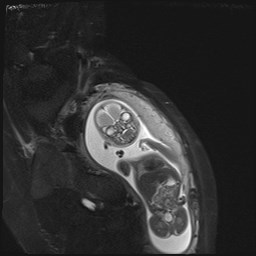


Figure fMRI showing Small and Large Intestines. a) Coronal T2-Weighted Image showing proximal Small Intestine loops seen as bright tortuous structures in the left upper abdomen (arrows). b) Sagittal T1-Weighted Image showing foetal Colon as a bright slightly tortuous tube-like structure filled with hyperintense Meconium (arrows).

Figure 3 fMRI showing Small and Large Intestines. a) Coronal T2-Weighted Image showing proximal Small Intestine loops seen as bright tortuous structures in the left upper abdomen (arrows). b) Sagittal T1-Weighted Image showing foetal Colon as a bright slightly tortuous tube-like structure filled with hyperintense Meconium (arrows).

a

b

Table 3 *f*MRI signal of body fluids: Urine, Amniotic fluid and Meconium.

|  |  |  |
| --- | --- | --- |
| **Foetal fluid** | **T2-weighting** | **T1-weighting** |
| **Urine** | Hyper-intense | Hypo-intense |
| **Amniotic fluid** | Hyper-intense | Hypo-intense |
| **Meconium** | Hypo-intense | Hyper-intense |

These variations in signal intensities help to distinguish different parts of the colon (Brugger and Prayer, 2006). The characteristic signal intensity of meconium on T1-weighting allows excellent visualisation of the colon with clear distinction from the adjacent organs (Rubesova *et al.*, 2009). Meconium is thought to have its high signal intensity feature due to its abundance of fatty acids, amino acids, organic acids and ketone bodies (Righetti *et al.*, 2003). T1-weighting can visualise the foetal colon as early as 20 GW when the meconium is formed. At 19 GW, meconium starts to accumulate distally with the rectum being filled first with a typical topographical association with the bladder (Saguintaah *et al.*, 2002; Veyrac *et al.*, 2005). The foetal rectum is usually the first part of large bowel to be visualised on *f*MRI. It appears as a hyperintense tubular structure in the foetal pelvis. Detection of T1-hypointense signal from the rectum should raise the suspicion of the presence of a fistula between the rectum and the urinary bladder. Furthermore, an intermediate T2 signal intensity in a dilated rectum might be associated with congenital megacolon (Hirschsprung’s disease)(Ohgiya *et al.*, 2001).

However, with progressing gestational age, both small bowel and the colon become filled with large amounts of meconium and this makes it difficult sometimes to differentiate between small and large intestine (Saguintaah *et al.*, 2002; Veyrac *et al.*, 2005; Brugger and Prayer, 2006).The proximal large bowel (right ascending and transverse colon) contain smaller amounts of meconium than the distal parts of bowel (descending and sigmoid) (Saguintaah *et al.*, 2002). However, *f*MRI has been reported in the literature to provide high quality visualisation of the entire large bowel in advanced gestational age (Rubesova *et al.*, 2009) except for the vermiform appendix which is not usually detected by *f*MRI and this may be due to its small size (Malas *et al.*, 2004).The normal meconium pattern has been described at each gestational age (Hyde *et al.*, 2020).

Being able to detect the condition and location of bowel by prenatal imaging is of extreme importance not only in finding intestinal abnormalities but also in confirming and better understanding the nature of other existing anomalies e.g. in left CDH (the ascending colon and segments of the transverse colon can be found inside the chest) and in omphalocele (the whole colon is sometimes outside the abdominal wall) (Brugger and Prayer, 2006). A study on 15 foetuses with suspected bowel dilatation, Manganaro *et al.* (2015) concluded that prenatal USS is only able to detect loop dilatation proximal to the site of obstruction without giving much information about the distal part (could not visualise amniotic fluid and meconium beyond site of obstruction) whereas *f*MRI detected the level of obstruction, presence and amount of amniotic fluid and meconium proximal and distal to the obstruction site. This information is very important to understand the nature of the pathology and could give a hint about the extent of the obstruction and whether it is partial or complete. Bowel obstruction might occur in proximal (duodenal/jejunal) or distal parts. *f*MRI appearances will depend on the site of obstruction: with T2-hyperintensity/T1-hypointensity in proximal obstructions and T2 hypointensity/T1-hyperintensity proximal to the obstruction in distal obstructions. However, with Ileal obstructions (e.g. Ileal atresia) *f*MRI may provide intermediate signal intensity on T1 and T2 due to the presence of mixture of amniotic fluid and meconium (Saguintaah *et al.*, 2002; Manganaro *et al.*, 2015). In a study that aimed to investigate the ability of T2-Weighted *f*MRI to detect foetal bowel malposition, Kheiri *et al.* (2016) demonstrated that prenatal USS was not able to detect bowel malposition in most of the 64 cases included in the study, whereas *f*MRI detected the anomaly in most of the cases (52/64 cases) which then was confirmed either by postnatal examinations or autopsies.

#### Liver:

The foetal liver appears on *f*MRI as T2-hypointense and T1-hyperintense organ in the right upper quadrant extending across the whole of the upper abdomen (Figure-4). The two lobes of the liver are not distinguishable by T1 and T2 sequences, while EPI is able to demonstrate between them, although the strength of signal intensity depicted is not always constant and may vary with GA as demonstrated in a study that involved 25 healthy foetuses in which changes in foetal hepatic signal intensity on EPI was seen between 20 and 26 GW. These changes are thought to be due to the activity of foetal liver in the process of erythropoiesis (Duerr *et al.*, 2001). Foetal hepatic tissue signal intensity might also be affected by oxygen saturation level (Semple *et al.*, 2001). Furthermore, signal intensity might be affected by the nature of the pathology affecting the liver e.g. in congenital hemochromatosis (abnormal deposition of iron in the liver) *f*MRI has a characteristic appearance of the liver with extremely low signal on T2\* sequences because excess iron causes magnetization of the affected tissue resulting in signal loss (Gradient- echo T2\* sequence is more sensitive than spin-echo T2 sequences in detecting iron deposition) (Martí-Bonmati *et al.*, 1994; Coakley *et al.*, 1999; Goitein *et al.*, 2013).

Hepatic vasculature is best depicted using SSFPS with ductus venosus detected as early as 21 GW (Brugger and Prayer, 2006). The umbilical vein appears as a tubular structure with a high T2 signal intensity entering the antero-medial surface of the liver (Huisman and Kellenberger, 2008). Foetal hepatic haemangioma usually appear as isointense solitary hepatic parenchymal lesions on T1-weighting and hyperintense on T2-weighting (Lyons *et al.*, 2015)

Being able to detect the position of the liver prenatally is very important in determining the liver condition itself and nature and extent of the other conditions such as CDH in which foetal liver lobes can be found inside the chest cavity (T1-weighted sequences are usually used to confirm the position of the liver) and omphalocele where part or whole of the hepatic tissue can herniate outside the abdominal wall (Shinmoto and Kuribayashi, 2003; Daltro *et al.*, 2005). *f*MRI can also detect foetal hepatic tumours such as hepatoblastoma, haemangio-endotheliomas (Shinmoto *et al.*, 2000) and liver haemangiomas (Hill *et al.*, 2005).

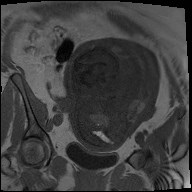
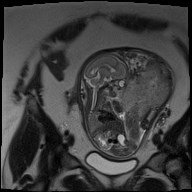


Figure fMRI showing foetal Liver (arrowed). a) Sagittal T2-Weighted Image showing the liver as a dark hypointense structure. b) Sagittal T1-Weighted Image showing the Liver with intermediate hyperintensity.

Figure 4 fMRI showing foetal Liver (arrowed). a) Sagittal T2-Weighted Image showing the liver as a dark hypointense structure. b) Sagittal T1-Weighted Image showing the Liver with intermediate hyperintensity.

#### Gallbladder:

The gallbladder is a pear-shaped small, cystic, fluid filled, organ located in the right upper quadrant rooted within the lower surface of the liver. Foetal bile has a high T2 signal and a low T1 signal intensity and it can be detected on *f*MRI from 18 GW. In normal foetuses, biliary ducts are not detected (Brugger *et al*., 2010). An absent gallbladder on *f*MRI could be due to a congenital anomaly (agenesis) or it could be due to gallbladder contraction (Brugger and Prayer, 2006).

#### Spleen:

Development of the spleen begins during the 5th week. The foetal spleen can be seen by 20 GW on *f*MRI. It is visualized as a T2-hyperintense and T1-hypointense organ dorsal and lateral to the stomach within the left upper abdominal quadrant. However, it can also appear with a homogenous signal intensity that mimics the liver (Huisman & Kellenberger 2008; Brugger & Prayer 2006; Levine *et al*. 1998; Shinmoto & Kuribayashi 2003; Ertl-Wagner *et al*. 2002). Finding the precise location of the spleen can be sometimes challenging on prenatal scans. Despite its connection to the stomach via the gastro-splenic ligaments, the position of the spleen is highly variable (Brugger and Prayer, 2006). The presence of multiple spleens (polysplenia) is also difficult to distinguish on prenatal scanning from a large lobulated spleen, whereas detecting its complete absence (asplenia) can be much easier (Huisman and Kellenberger, 2008).

#### Pancreas:

The pancreas is hard to recognize on *f*MRI. Its appearance on *f*MRI is highly controversial, with some authors believing it has an inhomogeneous isointense T2-weighted signal and a hyperintense T1-weighted signal in relation to the liver (Brugger & Prayer 2006) while others believe the opposite in which the pancreas appear as T2-hyperintense and T1-isoointense structure compared to the liver (Huisman & Kellenberger 2008).

## Congenital Gastrointestinal (GI) Malformations

The complex embryonic development of the GI tract merits a wide variety of its structural defects. In the past, GI malformations were commonly diagnosed in neonatal or childhood periods. It is possible nowadays to diagnose many of these structural defects with advanced radiological imaging and antenatal screening. GI tract anomalies are often associated with other birth defects or anomalies, in particular congenital heart defects (Tulloh *et al.*, 1994).

Types of congenital gastrointestinal malformations include:

Clift lip and palate

Oesophageal atresia (OA)

Tracheoesophageal fistula (TOF)

Oesophageal duplication

Absent stomach

Duodenal atresia

Small bowel obstruction

Hepatic calcifications

Liver tumours

Enlarged gallbladder

Anorectal atresia

Abdominal wall defects:

Exomphalos

Gastroschisis

Abdominal cysts:

Choledochal cysts

Mesenteric cysts

Hepatic cysts

Enteric duplication cysts

While many of these GI tract anomalies are extremely rare, it is important to discuss the anomalies found in our participants.

### Oesophageal Atresia (OA) and Tracheoesophageal Fistula (TOF)

OA is a developmental defect caused by incomplete division of the primitive foregut into the trachea (anteriorly) and oesophagus (posteriorly). Although it is rare with a prevalence of 1 in 3000-4500 live births, it remains one of the most common congenital anomalies of the oesophagus. It is often associated with fistula formation between the trachea and the oesophagus (TOF) (van Lennep *et al.*, 2019). Aetiology of this defect remains unidentified. There has been some attribution to the teratogenic effects of antithyroid drugs but that is only to foetuses of hyperthyroid mothers on those medications (Andersen *et al.*, 2013). OA and TOF are strongly associated with other defects whether of the bowel such as duodenal and anal atresias or outside the GI tract such as the cardiovascular and genitourinary systems. Two of the commonly known associations are VACTERL and CHARGE associations.

VACTERL is a collective term describing a frequent non-random pattern occurrence of multiple congenital anomalies; Vertebral defects (V) such as hemivertebrae and scoliosis, Anorectal defects (A) such as anal atresia, Cardiovascular defects (C) such as ventricular septal defects, TOF (T), OA (E), Renal anomalies (R) such as agenesis and Limb deformities (L). The presence of at least three of these components is needed for a VACTERL diagnosis (Solomon, 2011).

CHARGE association describes the non-random appearance of the following:

Coloboma, Heart defects, Atresia choanae, Retarded development, Genital hypoplasia and Ear abnormalities (Pagon *et al.*, 1981).

Moreover, OA and TOF have been associated with other chromosomal abnormalities such as Down’s, Edward’s and Patau’s syndromes.

Pregnancies with OA and TOF foetuses are often small for gestational age, usually present with polyhydramnios as they are unable to swallow amniotic fluid and absent or small stomach on prenatal USS scan. Afterbirth, newly born babies typically present with chocking, respiratory distress, swallowing and feeding problems if undiagnosed in the antenatal period.

**Subtypes of OA and TOF**

There are five subtypes of OA and TOF based on the anatomy of the defect. Type C is the most common form.

Type A: only OA present without fistula formation. Lack of continuity between the proximal and distal segments of the oesophagus.

Type B: atresia of the distal segment of the oesophagus and connection of the proximal segment to the trachea with TOF.

Type C: atresia of the proximal segment of the oesophagus and connection of the distal segment to the trachea with TOF.

Type D: connection of both oesophageal segments to the trachea with two separate fistulas.

Type E: also known as H type fistula in which there is no atresia and the oesophagus connects to the stomach but there is a TOF connecting the trachea to the oesophagus.

#### Management:

OA and TOF carry a high incidence of associated anomalies that could reach 70%, therefore *f*MRI is thought to be most useful in detecting those anomalies. OA has a typical appearance on T2-weighted sagittal *f*MRI of a transiently distended midline hyperintense pouch (Lyons *et al.*, 2015).Babies with suspected OA or TOF should be delivered in tertiary hospitals with high level of neonatal intensive care and paediatric surgery. The key treatment is surgical correction of the anomaly with the aim of restoring normal anatomy. Usually, these babies need extensive workup and some supportive management for stabilisation before surgery. In some cases, depending on the nature of the defect, presence of any accompanying anomalies and condition of the baby, more than one surgery is required (Tidy, 2015b).

Prognosis and survival rates largely depend on the condition of baby at delivery and the presence of birth defects.

#### Complications:

Immediate complications of OA and TOF include respiratory distress, choking, feeding problems, aspiration pneumonitis, surgery and those related to the corrective surgery such as failure of anastomosis, leakage of anastomosis, recurrence of the fistula and stricture formation.

Later complications include tracheomalacia, bronchomalacia, recurrent chest infections, oesophageal dysmotility and gastroesophageal reflux disease.

### Duodenal atresia

Is a congenital malformation of the duodenum caused by failure in recanalization of the solid duodenal lumen in the early embryonic stage (6-8 GW) resulting in complete blockage or lack of continuity between the small bowel and the stomach (Santulli and Blanc, 1961). It is a rare condition with a prevalence of about 1 in 10,000 live births in UK and Europe (Bethell *et al.*, 2020; Best *et al.*, 2012). Duodenal atresia is the most common cause of foetal bowel obstruction. It is distinguished from duodenal stenosis by the presence of complete luminal obstruction of the duodenum, whereas the obstruction is incomplete with stenosis.

In general, obstruction of foetal duodenum may result from atresia, stenosis or malrotation. In duodenal obstruction related to malrotation such as in midgut volvulus, then the appearance of hyperintense meconium on T1-weighted imaging may suggest abnormal bowel position.

Duodenal atresia may present as an isolated condition or be part of other defects or chromosomal abnormalities. Up to 50% of duodenal obstruction cases are associated with other abnormalities (Lyons *et al.*, 2015). The exact aetiology is unknown but genetic and chromosomal abnormalities may play a role in some cases. It is commonly associated with Down’s syndrome (trisomy 21), about one third of babies born with duodenal atresia have Down’s syndrome (Choudhry *et al.*, 2009).

Duodenal atresia might be complicated with polyhydramnios which is caused by inability of the foetus to pass the amniotic fluid down the GI tract. The typical radiological appearance of a double bubble sign (dilatation of proximal duodenum and stomach) and polyhydramnios should raise the suspicion of duodenal atresia. Afterbirth, babies usually present with bile-stained vomiting (worsens with feeding), distended abdomen and absent bowel sounds.

#### Management:

The treatment of choice for duodenal atresia is surgery. Initial management to stabilise the baby is usually required during the first few days of life. Surgical correction of the defect with re-anastomosis of the bowel parts in the form of duodeno-duodenostomy or duodeno-jejunostomy. If not associated with other abnormalities, babies, once they have recovered from surgery, usually have an excellent prognosis (Bethell *et al.*, 2020).

### Hepatic calcifications

Are areas of hyperechogenic signal intensities depicted by prenatal USS within the foetal liver. These are uncommon findings with an estimated incidence of 1 in 1750 (Bronshtein and Blazer, 1995). They can be singular or multiple areas with higher incidence on the right lobe of the liver. Most of hepatic calcifications are found incidentally during routine antenatal scans. Less frequently they are associated with other abnormalities or chromosomal syndromes (Simchen *et al.*, 2002). In most cases of isolated hepatic calcifications, no underlying cause can be found. In some cases, in utero infections or hepatic vascular pathology may play a role. Management depends on the presence of other associated abnormalities but generally no treatment is required for isolated calcifications (Pata *et al.*, 2012).

### Abdominal Cysts

Abdominal cysts are common findings during prenatal USS scan or *f*MRI. In most cases the exact nature of these cystic masses is uncertain, and confirmation of diagnosis is challenging. However, the most likely diagnosis is suggested based on the appearance, anatomy, relation of these cysts to the surrounding structures and exclusion of other diagnoses. The following are common differentials for abdominal cysts:

**Choledochal cysts:** are congenital cystic dilatations of the biliary ducts. This might affect any part of the biliary tree whether intrahepatic or extrahepatic. It is an extremely rare condition within the western population with a prevalence of about 1 in 100,000 live births but it is more common among the Asian population (1 in 1,000) and four times more prevalent in females (Singham *et al*., 2009). Aetiology of choledochal cysts remains unclear. The majority of Choledochal cysts are found antenatally during antenatal scans but they can sometimes be missed and present later in childhood or adulthood. Choledochal cysts are visualised on *f*MRI as T2-weighted hyperintense cystic masses under the inferior surface of the liver (MacKenzie *et al*. 2001 and Chih-Ping Chen *et al*. 2004). Typical presentations of choledochal cysts include jaundice, right upper quadrant abdominal mass and abdominal pain. Complications of choledochal cysts include liver cirrhosis, liver abscess, portal hypertension, pancreatitis, stone formation and cholangiocarcinoma (Franko *et al*., 2006). Surgical excision of these cysts with corrective anastomosis to restore the biliary tree anatomy is the treatment of choice (Henderson, 2015).

**Mesenteric cysts:** are rare congenital cystic anomalies that occur in the GI mesentery. The aetiology of these cysts is uncertain but a number of theories regarding their development are reported in the literature. One popular theory postulates that these cysts result from proliferation of ectopic lymphatics in the mesentery without proper communication with the lymphatic system which results in obstructed lymphatic drainage (Coran *et al*., 2006). These lesions are variable in size and contents; they may contain serous fluid or chylous or haemorrhage, and can be simple or multiple, unilocular or multilocular. They are typically asymptomatic and found incidentally during routine antenatal scans. Management is conservative for asymptomatic cases (Pithawa *et al*., 2014).

**Enteric duplication cysts:** (commonlyknown as duplication cysts) are rare developmental malformations of the GI tract with prevalence of about 1 in 4,500 births (Schalamon *et al.*, 2000). They can originate anywhere in the gut with the jejuno-illeal part of small intestine being most commonly affected. These cysts may or may not communicate with the intestinal lumen and can be cystic or tubular structures of variable size. No certain aetiology has been established but there are several theories in the literature. The most commonly accepted theories are the abnormal recanalization of the embryonic GI tract or the persistence of embryonic diverticulae (Rajah *et al.*, 1998; Li *et al.,* 1998; Sharma *et al.*, 2015). Duplications cysts may present as an isolated finding or in associations with other abnormalities such as vertebral anomalies (Bentley and Smith, 1960). Large cysts can cause foetal intestinal obstruction and result in polyhydramnios. Management is by surgical excision of these cysts.

### Ascites

Refers to accumulation of free fluid in the foetal peritoneal cavity. It often presents in the hydrops fetalis spectrum but can rarely present as an isolated abnormality. Ascites can be classified into mild, moderate and severe. Causes of isolated foetal ascites include bowel perforation, bowel atresia, cyst rupture, intrauterine infections, genitourinary anomalies and idiopathic causes. It can also be associated with chromosomal abnormalities, CPAM, CDH exomphalos, dilated bowels, cardiac defects, ventriculomegaly, placental mass and hydronephrosis (El Bishry, 2008). In many cases isolated foetal ascites presents as a transient finding which resolves spontaneously with advancing pregnancy. However, intervention is required to treat the underlying cause and ascitic drainage is sometimes necessary in some cases. Isolated ascites can sometimes develop to hydrops fetalis which is a more serious condition associated with higher mortality and it will be discussed further later in this chapter under the miscellaneous section (Page 97) (Veluchamy *et al*., 2020).

### Abdominal tumours

The most common foetal abdominal tumours are neuroblastoma and teratoma. Neuroblastomas usually originate from foetal adrenal glands and about 50% of them are cystic or heterogeneous. They are often detected in the third trimester and very rarely grow in size or metastasize (typically to the liver). Teratomas present as mixture of cystic and solid lesions that can affect any site (commonly targeting foetal coccyx forming sacrococcygeal teratomas) (Lyons *et al.*, 2015). *f*MRI provides a useful technique to measure tumour volume in relation to foetal weight (Tumour Foetal Ratio; TFR), the composition of the tumour (solid and cystic elements) and the internal and external components which can be used to predict perinatal outcome (Rodriguez *et al.*, 2011).

## Abdominal wall defects

*f*MRI is used to diagnose, assess and classify abdominal wall defects with axial T2 weighting being the most useful in visualising the anomaly and in determining the position of the umbilical cord. T1-weighted sequences are most helpful in defining the course of the intestine in foetal abdominal wall defects (Shinmoto *et al.*, 2000; Shinmoto and Kuribayashi, 2003). Both scans can also detect occurring complications with this anomaly e.g. appearance of intestinal dilatation in coexistence with abdominal wall defects are usually suggestive of an obstruction (Huh *et al.,* 2010). *f*MRI is also thought to be extremely helpful in detecting any associated abnormalities which are used to predict peri- and postnatal outcomes. *f*MRI also plays an important role by estimating lung volumes which are predictors of poorer pulmonary outcomes in foetuses with giant abdominal defects (Akinkuotu *et al.*, 2015).

### Omphalocele

Omphalocele or exomphalos is the herniation of abdominal contents out of the abdominal cavity into the umbilical cord through a midline defect in the anterior abdominal wall at the centre of umbilical cord insertion. The most common contents of the hernia sac are small and or large bowel. It is characterised by the presence of a three layer membrane (outer amniotic layer, middle Wharton’s jelly layer and inner peritoneal layer) covering the hernia contents that similarly covers the umbilical cord (Sadler, 2010). The presence of this membrane covering is very important as it distinguishes omphalocele from gastroschises. Omphalocele is an uncommon condition with a total prevalence of about 3 in 10,000 births (Prefumo and Izzi, 2014). The aetiology remains unclear with many theories reported in the literature. Physiologically the foetal gut herniates into the umbilical cord and returns to the abdominal cavity before 11-12 GW. One widely accepted theory believes that omphalocele occurs when the gut remains in the umbilical cord and fails to return to the abdomen. However, physiological herniation never involves the liver which is found in many omphaloceles (Khalil *et al.*, 2012). Other theories based on the previous one explain that failure of progression of normal embryonic development arrests the return of abdominal contents into the abdominal cavity and that liver herniation occurs in a later stage (Khan *et al.* 2019). Other theories involve maternal risk factors playing a role in omphalocele formation. These include maternal age with both very young or advanced maternal age considered high risk, maternal obesity, prenatal use of known teratogenic medications and gestational diabetes (Frolov *et al.* 2010). Omphaloceles are associated with other genetic and chromosomal abnormalities especially trisomies, almost half of omphalocele foetuses have trisomies particularly trisomy 18 and also have a high association with other non-syndromic malformations of the musculoskeletal, urogenital and cardiovascular systems (Stoll *et al.*, 2008). The smaller the omphalocele the higher the risk of a chromosomal abnormality (Emanuel *et al.*, 1995).

Omphaloceles can be classified according to their predominant anatomical location into epigastric, umbilical and hypogastric omphaloceles. They can also be classified according to their size into small, giant and ruptured omphalocele (Rijhwani *et al.*, 2005; Verla *et al.* 2019).

#### Management

Once an omphalocele is detected antenatally, prenatal counselling comes into effect to help the family decide on the best course of action. If they opted to continue with the pregnancy, then a multidisciplinary team including obstetrics, paediatric surgeons and neonatologists should determine the timing, place and mode of delivery. Reduction with surgical repair of the defect is the gold standard treatment. Prognosis depends largely on the co-existence of other syndromes or malformations. Mortality rate is about 10% for foetuses with isolated omphalocele. However, it increases to 80-90% when associated with other abnormalities. Smaller omphaloceles tend to be more frequently associated with other abnormalities and therefore carry worse prognosis (Emanuel *et al.* 1995).

Occasionally omphaloceles might develop a complication *in utero* in which the membrane covering rupture and the gut becomes free floating. This mimics the appearance of gastroschisis and therefore differentiation becomes more challenging.

### Gastroschisis

Is a defect in the anterior abdominal wall through which foetal gut herniates into the amniotic cavity. Commonly foetal intestine herniates in gastroschisis but other parts of the GI tract like stomach and liver may herniate as well. Unlike omphalocele, the umbilical cord is intact in gastroschisis. This defect in the abdominal wall is usually found on the right side with the umbilical cord attached to its left side. Characteristically, the protruded gut has no membranous sac covering it and it is usually swollen, inflamed, short and covered with a fibrous layer as a result of exposure to the surrounding amniotic fluid. Furthermore, being outside the abdominal cavity, intestines often mal-rotate, and this increases the risk of intestinal obstruction and strangulation. Physiological function of the intestines is usually delayed in infants with gastroschisis and malabsorption is a common early complication. It has an estimated prevalence of about 3 in 10,000 births with a suggested male predilection (Prefumo and Izzi, 2014).

#### Aetiology:

Aetiology is poorly understood with many study authors believing it to be multifactorial involving genetic and environmental factors. Young maternal age is the most commonly known isolated risk factor for gastroschisis. Other risk factors include low BMI, low socioeconomic status, poor antenatal care and the use of recreational drugs during pregnancy. Several hypotheses for the pathogenesis of gastroschisis are reported in the literature with some being more accepted than others. One of the earliest theories proposes that arrested growth of the body wall due to some teratogenic effects results in a defective wall with a lack of proper closure. This theory is still widely accepted despite the fact that it does not explain what type of insults occur or the mechanism by which they affect this small area (Duhamel, 1963). Another theory proposes that gastroschisis occurs as a result of a ruptured amniotic membrane covering the physiological umbilical hernia during the early weeks of gestation or a later herniation through a defect caused by failed closure of the umbilical ring (Shaw, 1975). In essence, this theory calls for the disregard of the differentiation between gastroschisis and omphalocele and proposes that they are both similar in origin. This theory lacks embryological and pathological support and is not widely accepted in the literature. There is a more favourable theory that proposes the origin of gastroschisis as a result of a vascular injury of the omphalomesenteric (vitelline) artery resulting in disruption of the blood supply to right side of the abdominal wall producing infarction and necrosis and therefore weakens the wall (Hoyme *et al.* 1981). One major problem with this theory is that these arteries form a complex network and coalesce to give many branches such as the coeliac and mesenteric arteries, therefore it is hard to explain why a particular branch would be more sensitive to injury rather than others.

A more recent study postulates the origin of gastroschisis as a result of failure of one or more folds responsible for wall closure which leads to the abnormal development process that ends up with a primary intestinal loop herniating into the amniotic cavity instead of the umbilical cord. It shares some aspects of Duhamel 1963 theory who attributed the defect to lack of proper wall closure but differs in providing clearer embryological explanation of the herniation (Feldkamp *et al.* 2007). This theory suggests that gastroschisis occurs before the physiological herniation of the gut into the umbilical cord takes place (6th-11th GW) and it occurs as early as third week post conception.

Unlike omphalocele, gastroschisis is less commonly associated with other anomalies except for intestinal atresia were incidence is about 10% (Stoll *et al.*, 2008).

#### Management

Management consists of antenatal counselling and a multidisciplinary approach. Delivery should take place in a tertiary centre with high level of neonatal care and paediatric surgery. The treatment of choice is surgical repair of the defect. However, preformed Silos can be used for the temporary protection of the bowel prior to operative fascial closure in theatre under general anaesthesia. Preformed silos are manufactured from silicon and provide a closed environment for the bowel, preventing heat and fluid loss that may compromise gut circulation with resultant ischaemia and infarction (Davies *et al*. 2002). Our institution guidelines for the management of gastroschisis include:

Application of preformed silastic silo (spring-loaded, transparent bag) for haemo/thermodynamically stable neonates at the bedside for the staged reduction of gastroschisis, avoiding the need for general anaesthesia and ventilation in the majority of cases. Contraindications for the use of preformed silo include unstable neonate, bowel perforation, bowel necrosis/ischaemia and bowel atresia.

Sequential bowel reduction: bowel to be reduced twice daily or as tolerated.

Defect closure can be done at least 12 hours after full bowel reduction or day 5 if full bowel reduction cannot be achieved.

The prognosis is usually good post-surgical repair with isolated gastroschisis but complications can occur and include malabsorption, motility dysfunction, fistula formation and gastro-oesophageal reflux.

## GENITOURINARY SYSTEM (GUS)

At birth, urinary tract disorders account for 30% to 50% of the structural anomalies affecting the foetus (Cassart *et al.*, 2004). Functioning foetal urinary system is crucial for the production of amniotic fluid and development of foetal lungs, hence evaluation of the urinary system is an important part of prenatal imaging examinations (Chudleigh, 2001).

### Appearance on *f*MRI:

Diagnosing pathologies of the genitourinary tract requires good visualisation of the urinary bladder, ureters and adjacent pelvic organs without being affected by the acoustic shadowing produced by the pelvic bones (Alamo *et al.*, 2010). *f*MRI is not affected by the pelvic bony structures that obstruct prenatal USS signals and therefore some authors consider it to provide superior quality scans of the GUS. It is also thought to be superior to prenatal USS in differentiating between the bladder and other adjacent large abdominal cystic abnormalities (Poutamo *et al.*, 2000). T2-weighting with specific parameters (Table-4) is the best *f*MRI sequence to assess foetal GUS. Echo planner diffusion-weighted imaging (DWI) is used to evaluate kidney function (Hörmann *et al.*, 2006). Foetal kidneys are evaluated in terms of size, location, appearance and the presence of dysplastic changes. The kidneys appear as ovoid structures in the upper abdomen on both sides of the spine with medium signal intensity on T2-weighted images (Figure 5-a) (Chauvin *et al.*, 2012). Sometimes, differentiation of the kidneys from the adjacent bowel loops can be difficult in early second trimester. Perirenal fat appears as a thin edge of increased signal intensity around the kidneys (Figure 5-b) which must be differentiated from perinephric fluid. Hawkins *et al*. (2008) found that perinephric fat was visible in 84% of the cases studied but it was invisible in foetuses diagnosed with Multi Cystic Dysplastic Kidney Disease (MCDK) and autosomal recessive polycystic kidney disease.

Table 4 Common T2-Weighted Parameters Commonly Used in *f*MRI of the GUS.

|  |  |  |
| --- | --- | --- |
| T2-weighted FFE | T2-weighted TFE | DWI |
| Shortest TR | Shortest TR | Shortest TR |
| Shortest TE | Shortest TE | TE = 125 ms |
| Flip angle = 90° | Flip angle = 80° | Flip angle = 90° |
| Slice thickness = 6mm | Slice thickness = 6mm | Slice thickness = 5mm |
| FOV = 300-200 | FOV = 345-295 | FOV = 290 |
| Acquisition time= 22s | Acquisition time= 19s | Acquisition time= 19s |

*FFE: Fast-Field Echo, TFE: Turbo-Field Echo, DWI: Diffusion-Weighted Imaging, TE: Repetition Time, TE: Echo Time.*

*FFE: Fast-Field Echo, TFE: Turbo-Field Echo, DWI: Diffusion-Weighted Imaging, TE: Repetition Time, TE: Echo Time.*

*FFE: Fast-Field Echo, TFE: Turbo-Field Echo, DWI: Diffusion-Weighted Imaging, TE: Repetition Time, TE: Echo Time.*

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*FFE: Fast-Field Echo, TFE: Turbo-Field Echo, DWI: Diffusion-Weighted Imaging, TE: Repetition Time, TE: Echo Time.*

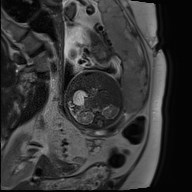
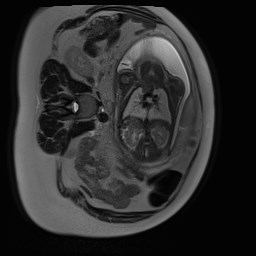


Figure fMRI showing foetal Kidneys. a) Coronal T2-Weighted Image showing foetal Kidneys as intermediate signal intensity structures (white arrows). b) Axial T2-Weighted Image showing hyperintense signal from Renal Pelvis (green arrows) and hyperintense signal from Perinephric Fat (red arrows).

Figure 5 fMRI showing foetal Kidneys. a) Coronal T2-Weighted Image showing foetal Kidneys as intermediate signal intensity structures (white arrows). b) Axial T2-Weighted Image showing hyperintense signal from Renal Pelvis (green arrows) and hyperintense signal from Perinephric Fat (red arrows).

a

b

The mean kidney length increases significantly with advancing gestational age. It increases from 13.54 mm in the 16th GW to reach 43.09 mm by full term. The renal tissue signal intensity to renal pelvis signal intensity (TIS/PEL) decreases with advancing gestational age (Witzani *et al.*, 2006) whilst there is a progressive increase in the ratio between renal cortex signal intensity and medulla signal intensity (Witzani *et al*., 2006). On T1-weighted images, the distinction of the corticomedullary junction is not as clear (Amin *et al.*, 1999). Evaluation of the cortex in terms of its thickness and signal intensity is important to determine in cases of renal dysplasia (Hörmann *et al.*, 2006). Measurement of anteroposterior renal pelvis diameter is best assessed on the axial plane and is considered abnormal if it is more than 7mm in foetuses >22GW.

The kidneys and renal pelvis are easily identified on single-shot fast spin-echo images (Figure 5-b) and they are best visualised on coronal and axial planes. The urinary bladder is also clearly seen on *f*MRI which appears as a fluid filled structure in the foetal pelvis. Due to the small size of the foetal pelvis, the urinary bladder can occupy a large part of the abdomen (Shinmoto *et al.*, 2000). Fluid filled structures such as the urinary bladder and urinary collecting systems appear as hyperintense organs on heavily T2-weighted images (Figure-6) whereas solid organs such as the kidney appears hypointense.

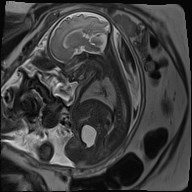


Figure 6 Sagittal T2-Weighted Image showing foetal Urinary Bladder (arrowed).

b

b

b

b

Figure Sagittal T2-Weighted Image showing Male Genitalia a) Scrotum (red arrow) and Penis (green arrow).b

b

b

b

The foetal urinary bladder should be visible by 12 GW. It voids regularly but is never entirely empty there is always a small amount of residual urine. Using *f*MRI T2 weighted sequences that are excellent in depicting fluid-filled structures, the urinary bladder appears as a smooth, uniform thickness ovoid or round structure that arises from the pelvis with uniform hyperintense signal. The umbilical arteries, which are located on both sides of the bladder, and have a hypointense signal on HASTE and T2- weighted images can be used to help establish the identification of the urinary bladder. Bladder wall thickness is best assessed on sagittal or axial planes on *f*MRI and is seen as a dark line around the bladder. Evaluation of the urinary bladder size and wall thickness is important in assessing those urinary tract abnormalities such as urinary flow obstruction disorders in which the bladder will be distended (Chauvin *et al.*, 2012).

Foetal urine appears bright on T2-weighted images and its signal characteristics becomes more intense with increasing gestation (<24 GW). In normal foetuses, hyper-intense signal from foetal urine is visible in the renal collecting system. One indirect marker suggesting renal agenesis is the absence of urine signal in the renal pelvis on T2-weighted images(Hawkins, Dashe and Twickler, 2008; Farhataziz *et al.*, 2005; Poutamo *et al.*, 2000). A case-controlled study by (Hawkins *et al*., 2008) found that renal anomalies including renal agenesis, MCDK (Multi Cystic Dysplastic Kidney) and autosomal recessive polycystic kidney disease have a characteristic absence of a bright signal (signal void) from the renal pelvis and bladder on T2-weighted images. The presence of a bright signal within the foetal bladder could mean that at least one of the kidneys is functioning. The adrenal glands appear as hypointense structures with triangular shapes lying above the kidneys (Trop and Levine, 2001).

Before 24 GW, T1-weighted images have limited value in clearly identifying the presence or absence of foetal kidneys. However, after 24 GW, T1-weighted images maybe of value in identifying the ureters and differentiating them from the adjacent colon. Furthermore, T1-weighting can be helpful in the diagnosis of adrenal hematoma and extra-adrenal neuroblastoma by detecting blood and fat, respectively (Farhataziz *et al.*, 2005).

A study by Cassart *et al.* (2004), in which half-fourier acquisition single-shot turbo spin echo, T2-weighted turbo spin echo and a mixture of T1- and T2-weighted sequences were used for the visualisation of the GUS, showed that *f*MRI modified, added or excluded potential defects in five out of sixteen foetuses. They concluded that *f*MRI could easily identify bilateral ureteric dilatation and differentiate enlarged foetal bladders from megacystic microcolon because of the good visualisation of foetal bowel with *f*MRI.

T2-weighted sequences have the ability to depict high signal intensity from increased water content of the renal parenchyma and this has been suggested as particularly useful in diagnosing cases of recessive polycystic kidney disease (Helin and Persson, 1986). Whilst others (Poutamo *et al.,* 2000) demonstrated that hydronephrotic kidneys were depicted equally by both *f*MRI and prenatal USS and that *f*MRI had no superiority over prenatal USS in imaging enlarged or cystic kidney lesions. In the same study however, *f*MRI could correctly diagnose 20 cases (>83%) in contrast to prenatal USS which could only diagnose 15 of these cases (62%). T2-weighted *f*MRI (axial plane) was more accurate than prenatal USS in cases with suspected renal agenesis or hypoplasia, as the latter misdiagnosed two cases in which the dark structures of the adrenal glands were mistakenly thought to be hypoplastic kidneys. More recently diffusion weighted imaging on *f*MRI has proved useful for detecting functioning renal tissue whether in the renal fossa or ectopic.

Others showed different results again, suggesting *f*MRI was 100% accurate and prenatal USS 66% in a cohort of 18 cases (Abdelazim *et al.*, 2010).

There is no consistency between the numerous small studies published as to either the accuracy of the 2 imaging modalities or the type of pathologies they are superior or inferior for. This is most likely to be due to the small sample sizes and may also reflect the level of experience the different authors had in *f*MRI and prenatal USS.

External Genitalia:

Assessment of the external genitalia is important as some GUS anomalies occur primarily in males while others occur in females for example Triad syndrome and posterior urethral valves occur predominantly in male foetuses while abnormalities such as megacystis-microcolon-intestinal hypoperistalsis syndrome and cloacal malformations occur primarily in females (Berdon *et al.*, 1976; Jaramillo, Lebowitz and Hendren, 1990). Trop and Levine (2001) found that detection of male gender (visualisation of scrotum and penis) and female gender (visualisation of labia) were possible in most of the cases (89%) with a grade of accuracy (Figure-7). However because the *f*MRI examinations assessed were not primarily performed to detect foetal gender, it is suggested that it would have been even easier to detect the gender if the scans were aimed to do so (Trop and Levine, 2001). In some cases with complicated GUS anomalies, *f*MRI can be useful and superior to prenatal USS in visualising the external genitalia. Prenatal USS could not identify the foetal genitalia in a foetus with micropenis, posterior urethral valves and sever hydronephrosis which were all detected by *f*MRI (Alamo *et al.*, 2010). However, in a retrospective study by Shinmoto *et al.* (2000) in which 51 foetuses with different body abnormalities were included, male genitalia were often recognised, but female genitalia were hardly ever detected. One could argue that the *f*MRI examinations were not primarily performed to detect foetal gender. Detection of male genitalia compared to female genitalia is easier on both prenatal USS and *f*MRI.

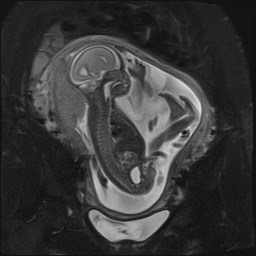


Figure 7 Sagittal T2-Weighted Image showing Male Genitalia a) Scrotum (red arrow) and Penis (green arrow).

Figure Sagittal T2-Weighted Image showing Male Genitalia a) Scrotum (red arrow) and Penis (green arrow).

## Renal and Urinary tract malformations

Congenital anomalies of the kidney and urinary tract (CAKUT) are a group of malformations characterised by structural defects in embryonic kidney and urinary tract development. It is estimated that renal and urinary tract malformations account for almost 30% of all congenital anomalies registered in Europe. They have a prevalence of about 3 per 1,000 births with strong male predilection (Lanzoni *et al.*, 2019). Prenatal detection of these abnormalities is extremely important. Some of them are incompatible with life and can result in complications during pregnancy for both the f0etus and the mother. Furthermore, if some of these abnormalities run undetected prenatally or during early childhood, they may present later in life with renal complications such as hypertension, proteinuria and renal impairment. It is thought that congenital anomalies of the kidneys and the urinary tract are responsible for about 30-50% of all end-stage kidney disease in childhood and adolescence (Seikaly *et al.*, 2003). Prenatal diagnosis of CAKUT has significantly improved overtime due to wider availability and advancement in ultrasonography. CAKUT can occur as an isolated anomaly or multiple anomalies within the genitourinary system or as part of a syndromic pathology. The majority of CAKUT are thought to be caused by defective development of the wolffian duct and/or ureteric bud in the process of embryogenesis. The exact aetiology and pathogenesis of these anomalies is poorly understood. Many authors suggest that both environmental factors and genetic mutations contribute to the development of these anomalies (Nicolaou *et al.*, 2015). Environmental factors included theories about diet contents of proteins and retinoids (Welham *et al.*, 2005), use of some medicines during pregnancy such as angiotensin converting enzyme inhibitors or receptor blockers (medicines widely used to treat hypertension) (Sekine *et al.*, 2009; Schreuder *et al.*, 2011), pre-gestational diabetes mellitus (Parikh *et al.*, 2002; Dart *et al.*, 2015). There is abundance of genes that are reported in the literature to be involved in nephrogenesis and ureter development. Several mutations of these genes have been identified and linked to syndromic and isolated CAKUT. The most widely recognised mutations include Bone Morphogenetic protein 4 (BMP4), SIX2 (Weber *et al.*, 2008), AGTR2 gene (Nishimura *et al.*, 1999; Yosypiv, 2014), PAX2 (Dressler *et al.*, 1993; Favor *et al.*, 1996), TGF2 gene (Lazzarro *et al.*, 1992), SALL1 (Kohlhase *et al.*, 1998).

The following are types of different congenital urinary tract malformations found prenatally; Some of these anomalies are extremely rare. Only those encountered in our study will be discussed further.

Hydronephrosis

Pelvi-ureteric junction (PUJ) obstruction

Renal agenesis

Ectopic or pelvic kidney

Horseshoe kidney

Polycystic kidneys

Renal (simple) cysts

Renal hypoplasia

Renal dysplasia

Duplex kidneys

Duplication of the ureter

Ectopic ureter

Renal tumours

Urethral obstruction (posterior urethral valves)

Bladderexstrophy

### Hydronephrosis

Dilatation of the renal collecting system (renal pelvis and calyces) either physiological or due to urine accumulation secondary to obstruction or blockage. Hydronephrosis is not a distinct disease entity by itself but rather a result of an anomaly or a pathology that disturbs the free flow of urine away from the kidneys. The obstruction is often caused by PUJ (Pelvi-Ureteric Junction) obstruction. Other causes include posterior urethral valves in males, vesico-ureteric junction obstruction, urethral agenesis, ureterocoele and vesico-ureteric reflux. Mild hydronephrosis is sometimes known as pyelectasis (prominence of the renal pelvis) which is a relatively common finding on antenatal imaging. It is usually a physiological dilatation of the collecting system that resolves spontaneously.

There were 3648 cases of congenital hydronephrosis among over 3 million births reported to the European Registration of Congenital Anomalies and Twins (EUROCAT) between the period 1995-2004, giving it a prevalence of about 11 in 10,000 births. More than 70% of these cases were boys (Lanzoni *et al.*, 2019). It can present as an isolated condition or can be associated with other congenital abnormalities. Hydronephrosis is bilateral in about a third of cases. In some cases, the contralateral kidney might be affected by a different abnormality such as being multicystic, ectopic or absent which leads to increased load on the kidney causing its dilatation.

It is divided according to the anteroposterior diameter of the pelvis into:

Mild: 4-7mm in second trimester 7-9mm in third trimester; the dilatation is only in the renal pelvis.

Moderate: 8-10mm in second trimester 10-15mm in third trimester; here the dilatation occurs in the pelvis and calyces.

Severe: >10mm in second trimester >15mm in third trimester: in this stage there will be thinning of the cortex.

#### Management:

Mild hydronephrosis with no identifiable cause will usually resolve spontaneously either in utero or in neonatal period. Otherwise treating the cause will usually resolve hydronephrosis. Complications may include increased risk of infection or reduced renal function. In-utero progressive hydronephrosis and those with anterio-posterior diameter >15mm carry worse prognosis.

### Pelvi-ureteric junction obstruction (PUJ):

PUJ refers to the obstruction to urine flow from the renal pelvis into the proximal ureter. It has an incidence of about 1 in 1,000 to 1,500 births, male to female ratio is 3 to 4:1 and more commonly on the left side (68%) (Karnak *et al.*, 2008; Williams *et al*., 2007). PUJ is the most common cause of antenatal and neonatal hydronephrosis with up to 50% of all hydronephrosis detected antenatally caused by PUJ. The exact aetiology is poorly understood but a number of theories are reported in the literature. The aetiological origins include embryological, anatomical, histological and molecular origins. These origins can be divided into either intrinsic or extrinsic causes. Intrinsic causes include histological and molecular origins. Histological origins can be either an absent musculature of a segment of the ureter resulting in interrupted peristalsis, or muscle fibres malorientation or a congenital narrowing of a ureter segment with high collagen contents resulting in obstruction (Hanna, 1978). The molecular origin describes a faulty intercellular relationship between muscle bundles in PUJ. Extrinsic causes include compression by nearby vasculature (crossing vessels) resulting in an arrested development of a ureter musculature segment, and congenital high insertion of the ureter into the renal pelvis (Pope IV *et al.*, 1999; Hanna, 1978).

Congenital PUJ obstructions were associated with other urologic anomalies in about 20% of cases. Among those, vesico-ureteric reflux was the highest encountered with 7.7% followed by contralateral MCDK, bilateral hydrocele and congenital heart anomalies.

#### Management:

Majority of isolated PUJ obstruction cases do not require intervention and resolve on their own. However, in some cases where the cause is identified or other associated anomalies exist, further investigations, management and follow-up is required. It is important to evaluate the extent of any insult on the kidneys and assess the severity. Corrective surgery such as laparoscopic pyeloplasty maybe required if severely affected. Complications include hydronephrosis, renal impairment and failure, urinary tract infections and urolithiasis (Lowth, 2016; NICE, 2004).

### Renal agenesis

Is the complete absence of one or both kidneys without the presence of any rudimentary tissue. Bilateral renal agenesis occurs in approximately 1 in 10,000 births (Boyd *et al.*, 2011) and <1 in 1,000 births for unilateral agenesis (Jain and Chen, 2019; Westland *et al.*, 2013). Foetal kidneys can be visualised by prenatal USS scan as early as 10-12 GW. Renal agenesis can present in association with other anomalies within the genitourinary tract (CAKUT) or anywhere in the body such as the VACTERL association, trisomy13 and 18, CHARGE association, Turner syndrome or present as an isolated anomaly (Stonebrook *et al*., 2019). In a systematic review of 43 studies on associated anomalies with unilateral renal agenesis, it was found that a third of the patients had associated CAKUT, of which vesicoureteral reflux was the most frequent. Associated anomalies outside the genitourinary tract were found in a third of patients (Westland *et al.*, 2013).

Bilateral renal agenesis is incompatible with life and neonates die shortly after birth due to lung hypoplasia and the absence of renal function. The absence of both kidneys causes severe oligohydramnios or anhydramnios which in turn leads to lung hypoplasia. Furthermore, the lack of surrounding amniotic fluid produces pressure effects on the foetus which causes a classical physical appearance to the foetus. Foetuses often present with broad facial features, wide-set eyes, limb deformities, prominent epicanthal folds. These classical features are commonly known as Potter’s syndrome (Thomas and Smith, 1974).

Unilateral renal agenesis is usually asymptomatic and presents as an incidental finding in most cases. Sometimes, compensatory hypertrophy of the contralateral kidney may be present. Therefore, the presence of a solitary enlarged kidney should always warrant a detailed pelvic US scan and further investigations such as *f*MRI to confirm either the absence, the ectopic presence or the dysplastic appearance of the other kidney. Oligohydramnios and low signal from foetal lungs are usually common *f*MRI findings in cases of renal hypoplasia or agenesis on T2-weighted images. If both kidneys are absent (bilateral agenesis) then the foetal bladder would be not be visualised (Morales Ramos *et al.*, 2007).

#### Management:

Antenatal counselling is very important to help parents take the most appropriate course of action. Genetic testing and chromosomal analysis are also helpful in some cases to help determine the existence of any syndromic gene mutations or defective chromosomes. Most cases with unilateral renal agenesis lead a normal life without any specific treatment needed. Occasionally, a solitary kidney might be associated with higher risk of hypertension, infections and renal failure and therefore regular follow up is needed.

### Ectopic Kidneys

It is a congenital defect characterised by abnormal location of one or both kidneys. It occurs as a result of arrested migration (ascent) of the kidneys to their normal location. It has an incidence of 1 in 3,000 births. An ectopic kidney can either remain in the pelvis near the bladder (pelvic kidney; most common location) or ascends too high in the abdomen (or rarely to chest) or crosses the midline towards the contralateral kidney and sometimes joining it to form what is known as crossed fused ectopia (Hindryckx and De Catte, 2011; N’Guessen *et al.,* 1984). It is asymptomatic in most cases and only found incidentally usually during an antenatal US scan. It can present as an isolated anomaly or in association with other anomalies such as MCDK, vesico-ureteric reflux and PUJ obstruction. Ectopic kidneys can be unilateral or bilateral. Bilateral pelvic kidneys often fuse at the midline but with distinct renal pelvises forming what is commonly referred to as horseshoe kidney. Ectopic kidneys are usually smaller in size and have tortuous ureters. They are more prone to complications such as calculi, obstruction and infection. Ureteropelvic junction obstruction occurs in about one third of patients with an ectopic kidney.

#### Management:

Isolated ectopic kidney often carries a good prognosis. In most cases no treatment is required, and individuals can lead a normal life. In some cases, complications to the ectopic kidney such as calculi, infection and obstruction occur. These warrant further investigations and treatment including corrective surgery or excision (nephrectomy).

### Horseshoe kidney

It refers to the fusion of the two kidneys by a parenchymal or fibrous isthmus at the midline. This fusion usually occurs between the lower poles (90%). Horseshoe kidneys are the most common type of fusion anomaly and they are found in about 1 in 600 births and more common in males; male/female ratio=2:1 (Weizer *et al.*, 2003). The fusion between the two kidneys occurs early in kidney development whilst in the pelvis during the metanephric stage around 4th GW. Normally, the kidneys migrate up into their normal anatomical location inside the abdominal cavity. They also rotate at the same time of their migration. In Horseshoe kidneys, the fused kidneys get trapped by the inferior mesenteric artery preventing their ascent and rotation and they remain in a lower position in the abdomen. Horseshoe kidneys are typically asymptomatic and usually identified incidentally on prenatal USS scan. However, Horseshoe kidneys can be associated with PUJ obstruction, hydronephrosis, urinary tract infection and calculi formation in the neonatal period and later in life. They can also be associated with both genitourinary and non-genitourinary congenital anomalies and also associated with several chromosomal abnormalities. Horseshoe kidneys are three times more common in patients with congenital vertebral anomalies than those without (Mandell *et al.*, 1996) and were found in up to 25% of cases in Edward’s syndrome (Kravtzova *et al.,* 1975). Furthermore, horseshoe kidneys are associated with an increased incidence of renal malignancies particularly Wilms tumour and carcinoma of the renal pelvis (Redman and Berry, 1977; Buntley, 1976).

#### Management:

Horseshoe kidneys on their own are usually asymptomatic, no specific treatment is required, and individuals often lead a healthy life. However, the presence of complications or other malformations warrant further management.

### Multi Cystic Dysplastic Kidney (MCDK):

It is a congenital renal anomaly characterised by the presence of a dysmorphic kidney with multiple non-communicating cysts of variable sizes, kidney enlargement, non-functioning parenchyma and a hypoplastic or atretic ureter. It is the commonest cause of cystic disease in children with a total prevalence of 4.12 in 10,000 births in Europe (Winding *et al.*, 2014). It is more common on the left side and more prevalent in males. The aetiology of MCDK is hypothesised in the literature as the result of abnormal interaction between the ureteric bud and the metanephric mesenchyme or atresia of the ureteric bud (Schreuder *et al*., 2009). Rarely genetic mutations may play a role in familial cases. Other cases are associated with syndromic chromosomal abnormalities (Winyard and Chitty, 2008). MCDK is most commonly a unilateral anomaly but can rarely present as a bilateral anomaly. It is associated with abnormalities of the genitourinary tract in up to 50% of cases, about 40% of them involved the contralateral renal tract. The most common associated genitourinary tract anomaly was contralateral vesico-ureteric reflux (18%) followed by PUJ obstruction (12%) (Atiyeh *et al*., 1992). Isolated uncomplicated unilateral MCDK is often asymptomatic and usually detected incidentally, however, with bilateral MCDK, pregnancies are often complicated with oligohydramnios which may result in foetal demise. A high incidence of urinary tract infection and progression to renal failure has been reported in up to 50% of cases with complex MCDK (Associated with other GUS anomalies) (Feldenberg and Siegel, 2000).

#### Management:

Spontaneous complete involution of MCDK has been shown to occur in up to 60% of patients over a 10 year period (Aslam *et al.*, 2006). Cases with isolated unilateral MCDK are usually asymptomatic and have normal or near normal renal functions. Bilateral MCDK is a serious condition and unfortunately is incompatible with life. Regular follow up with further investigations is required for babies born with MCDK to check for associated abnormalities and renal functions. Complications include vesico-ureteric reflux, urinary tract infection, PUJ obstruction, renal impairment and hypertension.

### Renal cysts

Usuallyreferto solitary simple cystic structures in the kidney. These are an extremely rare foetal developmental anomalies and their incidence increases with advancement in age in adults. No information was found in the literature regarding simple renal cysts detected antenatally. There were some studies conducted on paediatric population and few case reports describing simple renal cysts in infancy (McHugh *et al.*, 1991; Steinhardt *et al*., 1985). These lesions are usually benign and do not require intervention.

## SKELETAL

Evaluation of foetal musculoskeletal system is one of the most challenging aspects of foetal imaging. Prenatal imaging is essential for management and counselling in cases with congenital musculoskeletal disorders and malformations. *f*MRI can provide information about the foetal body in which integrity of different systems are evaluated e.g. depicting atypical swallowing activity and lack of limbs movement might point towards foetal akinesia. Prenatal detection of foetal musculoskeletal abnormalities usually warrants a complete work-up including genetic counselling (Benacerraf *et al*., 1986; Bromley *et al*., 1995; Zelop & Benacerraf 1996; Paladini *et al*., 2010; S. F. Nemec *et al*., 2011).

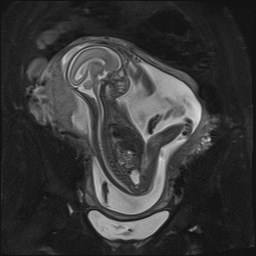
### Appearance on *f*MRI:

Prenatal USS is considered the modality of choice in the assessment and diagnosis of musculoskeletal anomalies. Contribution of USS in the evaluation of these anomalies has been well documented in the literature. It has also long been used to screen for various musculoskeletal disorders e.g. by measuring foetal long bones. Its contribution has increased further with the recent advancements in 3D USS which provides excellent visualisation of the limbs, joints and digits. On the contrary, *f*MRI has not been widely used to image the musculoskeletal system which might explain the lack of experience in its evaluation (S. F. Nemec *et al*., 2011; Khalil *et al*., 2011; Krakow *et al*., 2008; Paladini *et al*., 2010; Schramm *et al*., 2009; Cassart 2010). However, in complex cases in which multiple foetal body systems are affected, *f*MRI is suggested to be beneficial (Nemec *et al.*, 2011).

The foetal skeleton can be visualised by USS as early as 14 GW with femoral and humeral lengths being measured routinely and foetal bone ossification centres can be depicted as early as 9 GW (Tamsel *et al*., 2004; Khalil *et al*., 2011; van Zalen-Sprock *et al*., 1997). Foetal bone growth can be detected by *f*MRI as early as 18-20 GW. Osseous and cartilaginous structures including ossified foetal vertebrae can be seen on EPI sequence depending on the gestational age (Nemec *et al.*, 2013). In both coronal and sagittal planes, foetal bones appear as low signal structures clearly distinguished from the adjacent muscles. Ossifying foetal bones have a characteristic hypo-intense *f*MRI signal from the diaphysis and a hyper-intense signal from the epiphyses. Distinction between muscles and bones becomes difficult in older foetuses, thus modifying EPI sequence parameters is important to obtain good quality images. However, EPI technique has low spatial resolution with low soft tissue contrast and is prone to artefacts which might interfere with anatomical delineation between the surrounding structures (Brugger, Stuhr, *et al*., 2006; Chen & Levine 2001; Nemec *et al*., 2013; S. F. Nemec *et al*., 2011; Brugger, Stuhr, *et al*., 2006).

Thick-slab T2 weighted *f*MRI allows for complete visualisation of the foetal body size and proportions thus can be used to visualise muscle mass and symmetricity which is particularly helpful in cases of suspected IUGR or skeletal dysplasia. One of the advantages that *f*MRI could have over prenatal USS is its ability to evaluate the whole foetal body in relation to the placenta (Figure 6-b) and this is also helpful in cases with suspected IUGR (Weisz *et al.*, 2008; Messerschmidt *et al.*, 2011). It is also helpful in visualising extremities shape and determining their location. This is particularly useful in cases with anomalies of the extremities such as talipes equinovarus (club feet), partial or complete limb absence and limb shortening (Figure 6-b). Dynamic steady-state free precession sequences can be also helpful in the assessment of foetal extremity anomalies and movement disorders. They allow real time depiction of foetal gross motion, limbs motion, swallowing activity and movements of the diaphragm. Focal anomalies affecting feet or hands are thought to be better visualised during their movements using dynamic *f*MRI (Prayer & Brugger 2007; Brugger *et al*., 2006; Nemec *et al*., 2011; Nemec *et al*., 2012). However, unlike prenatal USS, there is lack of *f*MRI diagnostic standards for qualitative foetal movement evaluation, thus dynamic *f*MRI scans must be repeated several times for proper foetal movement assessment (De Vries and Fong, 2006, 2007).

T2-weighted sequences can be used to depict foetal spinal cord and skull anatomy and define the boundaries of the extradural space by delineating the cerebrospinal fluid from the surroundings but are less helpful in visualizing the bony spine (Figure-8-a, b). In that case, another *f*MRI sequence that is thought to be more useful in assessing foetal spine is the Susceptibility-Weighted Imaging (SWI) sequence. It has a high contrast between bones and adjacent musculature allowing excellent delineation between bony structures and surrounding soft tissues (Figure-8-c). However, this sequence requires breath holding techniques due to its long-time of acquisition that makes it more prone to movement artefacts (Robinson *et al.*, 2015). It might be useful though in older foetuses >26wk as their motion will be more restricted by the womb thus reducing movement artefacts (Robinson *et al.*, 2015). A newer, quicker, sequence has recently been shown to overcome some of these difficulties and have potential for imaging the foetal skeleton (Goodall *et al.*, 2021).

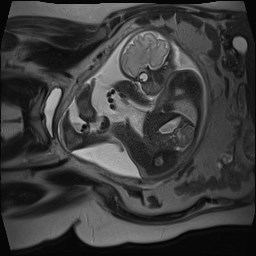


Spinal cord

Skull

CSF

a



Digits

Feet & Toes

Femur

Placenta

b

c

c

c

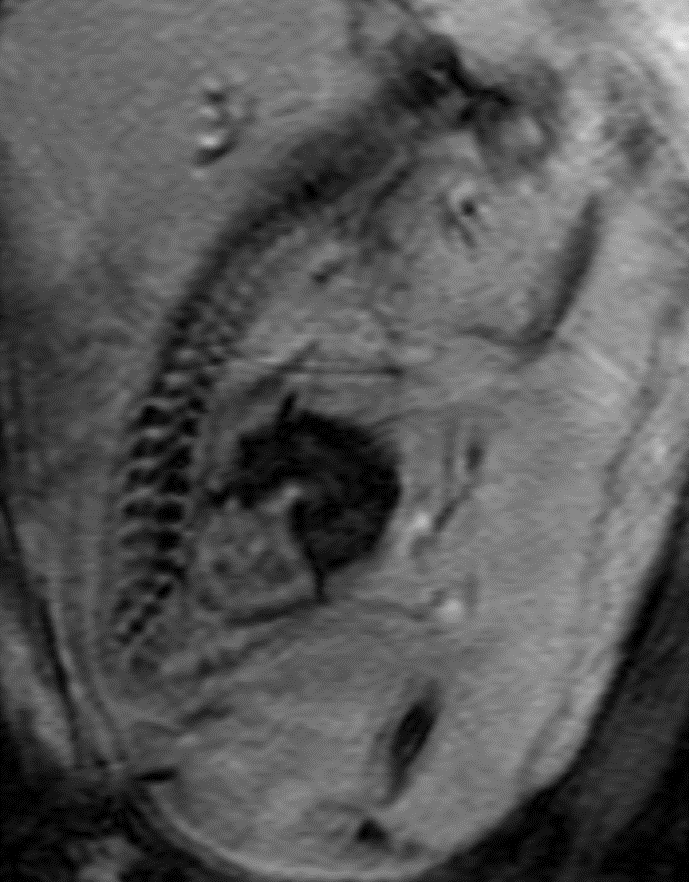
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Figure 8 fMRI of the foetal Musculoskeletal system. a) Sagittal T2-Weighted Image showing anatomical details of the Skull, spinal Cord and Cerebrospinal Fluid (CSF) (arrowed). b) Sagittal T2-Weighted Image foetal body Skeleton, Extremities and the Placenta (arrowed). Foetal long bones such as the femur appear as hypointense dark structures. c) sagittal SW Image showing foetal Vertebrae in anatomical detail as dark hypointense structures along the vertebral column (red arrows).

## Congenital musculoskeletal abnormalities

This section of the introduction will discuss common abnormalities of the musculoskeletal system that were encountered in the study.

### Sacrococcygeal teratoma (SCT)

SCT refers to a rare congenital tumour that arises from the base of the spinal coccyx (commonly known as the tailbone). It is considered the most common perinatal congenital tumour with an estimated incidence of 1:35000 to 1:40000 live births. Approximately 75% of those affected are females with 4:1 female to male ratio (Altman *et al*., 1974). SCT is a germ cell tumour that arises from the embryonic compartment of ectoderm, mesoderm and endoderm. Although its exact embryonic origin remains unclear, it is believed to arise early in embryogenesis from a primitive band of totipotent cells called Hensen’s node in the coccyx with potentials to differentiate into the three germ cell layers (Winderl and Silverman, 1997). SCTs can be classified according to their pathological characteristics or their extent. Pathology based classifications include benign and malignant types. Benign SCTs account approximately for 70% of all cases.

The extent-based classification includes the following:

Type 1: majority of teratoma is external with minimal intrapelvic component; it is the most common type.

Type 2: teratoma present externally with significant intrapelvic component.

Type 3: majority of teratoma is intrapelvic extending to abdomen with apparent external component.

Type 4: teratoma entirely intrapelvic with no external component.

SCTs can be solid or cystic or a mixture of both. Cystic teratomas might be filled with mucoid, serous or sebaceous fluids. Any tissue can be found in this type of tumours including hair, muscle and cartilage as well as epithelial cells from skin, CNS and respiratory tissues (Tuladhar *et al.,* 2000).

These tumours can be isolated or present in association with other congenital anomalies. About 20% of SCTs have associated anomalies; most commonly musculoskeletal malformations such as vertebral anomalies. Detection of these tumours is usually incidental during routine antenatal scans. Intrapelvic teratomas, if not detected antenatally, can present in early childhood with complications produced by their pressure effect on surrounding structures or metastasis (malignant SCTs). Treatment options for these tumours depend on their severity and the existence of associated anomalies. Generally, the gold standard treatment option is surgical excision of the tumour and the coccyx (coccygectomy) with additional chemotherapy for malignant SCTs. Rarely these tumours may cause serious complications while in-utero such as heart failure, hydrops fetalis and polyhydramnios hence interventional treatments such as percutaneous laser therapy, alcohol sclerosis or cyst drainage; or early elective caesarean delivery may be necessary (NICE, 2006). Pressure complications include ureteric obstruction, GI obstructions and compression of underlying nerves. Obstetric complications may include preterm labour and dystocia. The presence of these complications is associated with poor prognosis (NICE, 2006), (Hedrick *et al.*, 2004).

### Scoliosis:

This refers to a rare abnormal lateral curvature or deformity of the spine. It has an estimated incidence of 1-2:1,000 live births in the UK (Wynne Davies, 1975) (Mackel *et al.*, 2018). There are several types of scoliosis that may present in foetal or paediatric population including: congenital scoliosis in which the deformity develops as a result of one or more vertebral malformations and is associated with other congenital anomalies such as heart defects and VACTERL; infantile idiopathic scoliosis in which no cause for the deformity can be found, neuromuscular scoliosis in which the spine lacks muscular support resulting in scoliosis such as seen in Marfan syndrome and muscular dystrophy (Hedequist and Emans, 2004) (Karol, 2019). Only scoliosis with known causes such as congenital and neuromuscular types were mentioned in the literature to be affecting the foetus. There is no established evidence in the literature for the presentation of infantile idiopathic scoliosis during foetal period. This might be due to the level of confidence in diagnosing this type of scoliosis in the antenatal workup. It could be challenging to confirm a diagnosis of idiopathic scoliosis without complete neonatal examination and further investigations.

Scoliosis may progress with advancing age causing and/or aggravating complications. Location and type of scoliosis are two important factors to keep in mind when evaluating scoliosis e.g. thoracic curves are associated with less favourable prognosis and more severe complications. Management of scoliosis depends on the type, degree and existence of associated anomalies. Treatment options are diverse and range from conservative treatment for milder scoliosis to surgical interventions reserved to more severe scoliosis or those caused by vertebral malformations (Mackel *et al.*, 2018) (Burnei *et al.*, 2015) (Weiss and Moramarco, 2016).

### Foetal short long bones and skeletal dysplasia:

Skeletal dysplasia or osteochondrodysplasias refer to disorders with generalised abnormalities of the skeleton. It is an umbrella term that comprises more than 350 different disorders and many of them can present in the foetus. They are rare genetically inherited disorders affecting about 3-4:10,000 births (Lachman, 1994). In general, they can be classified into lethal and non-lethal dysplasias. Antenatal diagnosis of one particular type of these dysplasias is extremely challenging as the imaging findings are not necessarily pathognomonic for a specific type. However, differentiating between lethal and non-lethal disorders is possible and helps to determine the best management option available. The most common type of skeletal dysplasais is called achondroplasia and is caused by mutation in the gene (Fibroblast Growth Factor Receptor) FGFR3 (Bellus *et al.*, 1995) (Manikkam *et al.*, 2018). Other types include osteogenesis imperfecta, achondrogenesis, thanatophoric dysplasia, hypochondroplasia and campomelic dysplasia (Mcmaster *et al.*, 2010).

Foetal short long bones are usually considered signs of skeletal dysplasia. However, short long bones can also present as manifestations of genetic syndromes, foetal growth restrictions, chromosomal abnormalities and in constitutionally small foetuses (Benacerraf *et al*., 1991). In general, congenital limb deformities are usually highly associated with other abnormalities. In a study that included 29 foetuses with upper extremity abnormalities, it was found that 90% of the foetuses (*n*=26) had associated abnormalities in which most of them were structural abnormalities (Nemec *et al.*, 2011).

#### Management:

Management usually takes the multidisciplinary approach involving obstetricians, foetal medicine, neonatologists, clinical geneticists’, neurologists and radiologists. Family counselling and genetic testing is usually recommended to gain accurate information, understand the type of dysplasia and assess risk for future pregnancies. Prognosis for non-lethal dysplasias depend on the type and presence of any associated abnormalities (Mcmaster *et al.*, 2010). Occasionally a specific diagnosis can be made on a pathognomonic sign e.g. Abnormal temporal lobe folding in thanatophoric dysplasia (Fink *et al.*, 2010).

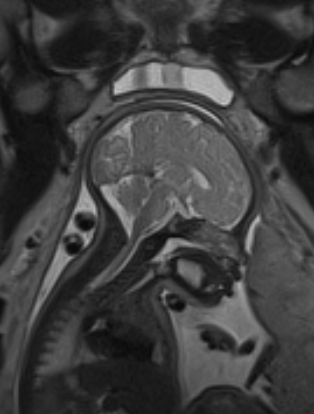
## NECK

The foetal neck is a common site for space occupying lesions and therefore good prenatal imaging is crucial to understanding the type and nature of these lesions and to determine their relationship to the surrounding structures.

### Appearance on *f*MRI:

Assessment of the foetal neck by prenatal imaging includes visualisation of the airways (including larynx, trachea and in a later stage; the oesophagus), thyroid gland, major vessels, muscular layers, subcutaneous fat and skin. The larynx and trachea are normally fluid filled and are best seen on T2-weighted sequences (Figure-9). In older foetuses, further details of the tinier structures in the neck such as the epiglottis and laryngeal folds are more evident. The upper part of the oesophagus is not normally fluid filled and not usually depicted with *f*MRI*.* However, short video clips capturing the swallowing cycle using CINE sequence can be performed to depict the upper part of the oesophagus. The foetal thyroid gland appears as a hyperintense structure on T1-Weighted sequences and normally hardly seen on T2-Weighting. Mostly, T2-Weighted sequences (SSFP) or T1-Weighted flow sensitive sequences (more specific to visualise major vessels) are used to visualise other neck structures (Prayer and Brugger, 2007; Shinmoto *et al.*, 2000).

## 



Spinal Cord

Muscle

Subcutaneous Fat

Trachea

Figure 9 Sagittal T2-Weighted Image showing foetal Neck anatomy (arrowed).

## Foetal neck tumours

These are very rare congenital anomalies affecting the foetal neck. These masses can impair foetal swallowing, cause polyhydramnios, preterm labour and airway obstruction resulting in respiratory distress at birth. Foetal MRI provides useful information that aids the formulation of delivery and management plans by providing excellent visualisation of the neck, pharynx, airway and palate (Tsuchida *et al.*, 1998; Billings *et al.*, 2000; Gorincour *et al.*, 2003). The differential diagnosis of foetal neck masses may include cystic hygroma or lymphangioma, congenital cervical teratoma, haemangioma, rhabdosarcoma and goitre. Cystic hygroma, rhabdomyosarcoma and congenital cervical teratoma were encountered in this study and therefore will be discussed in this section of the introduction.

### Cystic hygroma:

This refers to macrocystic malformations of the lymphatics in the cervico-facial region, most commonly in the posterior triangle of the foetal neck. It is by far the most common type of foetal neck tumours. It is believed to be caused by congenital defects of the lymphatic system that results in blockage to normal lymphatic drainage forming single or multiloculated sac-like masses filled with lymphatic fluid. Cystic hygromas have an estimated incidence of 1-3 per 1000 births with slight male predominance with 4:3 male to female ratio (Kennedy *et al.*, 2001). It can present as an isolated anomaly or in association with syndromic or non-syndromic anomalies. The most common associated syndrome is Turner syndrome followed by Down’s syndrome. Other include trisomy 13, trisomy 18 and other triploidies. Non-syndromic associations include congenital heart defects such as coarctation of aorta and hypoplastic left heart. Complications of cystic hygroma include haemorrhage, rupture, infection and compression effects on surrounding structures such as respiratory difficulties, airway obstruction and dysphagia.

The treatment of choice is surgical excision. Spontaneous resolution was reported in the literature in about 2-9% of cystic hygroma patients (Ninh and Ninh, 1974) (Kennedy *et al.*, 2001). Therefore, timing of surgical excision may be delayed in some patients giving chance for possible spontaneous regression. Other treatment options include sclerosing agents, diathermy and radiation. Prognosis is excellent in most patients.

### Congenital cervical teratoma:

This refers to a very rare congenital tumour arising in the cervical region. They represent about 3% of all teratomas with an estimated incidence of 1:20,000-1:40,000 live births (Brodsky *et al.*, 2017). Although mostly benign, cervical teratomas are associated with high mortality rate due to their compression effects on surrounding anatomy causing airway obstruction. Similar to SCT, cervical teratomas originate from all three embryonic germ cell layers; ectoderm, mesoderm and endoderm and therefore any tissue type can be found in these lesions. They can be mature or immature, multiloculated, cystic, solid or mixed and contain calcification loci in about half of all cases.

This lesion is usually detected during routine USS. However, Approximately 30% of these tumours present with polyhydramnios secondary to foetal swallowing difficulties caused by compression effects by the lesions (Kerner *et al.*, 1998). Management includes a multidisciplinary approach involving obstetricians, neonatologists, paediatric surgeons and radiologists. Timing and place of delivery should be carefully planned. Surgical excision is the treatment of choice. Complications include respiratory distress, airway obstruction, hydrops fetalis and malignant transformation. Prognosis depends largely on the size, location and degree of tracheal compression.

### Rhabdomyosarcoma:

This is a rare cancerous tumour of the soft tissues such as muscles, tendons and connective tissues. it is the most common sarcoma in the paediatric population with the head and neck being the most favoured location. It is characterised by rapid onset and advanced disease. Rhabdomyosarcoma of the head and neck can be classified based on its location into parameningeal and non-parameningeal tumours. Parameningeal rhabdomyosarcoma involves the nasopharynx, nasal cavities, paranasal sinuses, middle ear, infratemporal and pterygopalatine fossae and mastoid. Nonparameningeal rhabdomyosarcoma include all other structures of the head and neck and carries slightly better prognosis (Merks *et al*., 2014). Treatment is usually a combination of chemotherapy, surgery and/or radiotherapy. Prognosis depends on several factors including histological sub-type of tumour, primary site, extent of disease, extent of surgical resection (Reilly *et al*., 2015; Li *et al*., 2018; Gosiengfiao *et al*., 2012). Most of the studies found in the literature focused on the paediatric and adult population with no information regarding the detection of this tumour antenatally. This type of tumours usually presents during the first year of life onwards and this might explain the lack of information in the literature. Furthermore, lack of availability of diagnostic modalities such as *f*MRI might be an additional explanation or lack of recognition of tumour in the antenatal period confusing them with teratomas.

## MISCELLANEOUS

We anticipated to recruit a few hydrops fetalis cases in this study which we intended to include them in the miscellaneous cohort. We suspected other cases to be included in this cohort but in a sporadic fashion (single cases of various anomalies) and we believe their contribution will not be significant. This section of the introduction will briefly discuss pathogenesis, types and current management of hydrops fetalis.

### Hydrops fetalis:

It refers to the accumulation of excess fluid in at least two foetal body cavities or components such as pleural effusion, ascites, pericardial effusion and skin oedema. It may also be associated with polyhydramnios and placental oedema. Hydrops fetalis has an incidence of about 1:1,000 live births and twice and a half more common in males than females (Trainor and Tubman, 2006). It has been traditionally classified into two broad types as immune and non-immune hydrops. Immune hydrops is the rarest and is associated with foeto-maternal blood incompatibility particularly rhesus incompatibility. Non-immune hydrops accounts for the majority of cases and is associated with various aetiological factors. One review reported 14 causes of non-immune hydrops. Some of these causes include Cardiovascular (20%), Idiopathic (19.8%), Lymphatic Dysplasia (15%), Haematologic (9.3%), Chromosomal (9%), Infectious (7%) and Syndromic causes (5.5%) (Bellini *et al.*, 2015). Management depends largely on the underlying aetiology. Proper counselling is crucial to help parents decide whether to continue the pregnancy or opt for termination. In some cases, intervention is possible and treatment options depend on the underlying aetiology and gestational age. Planned delivery in a tertiary centre is advised for optimal resuscitation and neonatal care. Treating foetal arrythmias, intra-uterine foetal transfusion and sometimes surgery are all examples of available treatment options used in selected cases. However, spontaneous resolution is not uncommon and has been reported in the literature (Cameron, 2014; Iskaros *et al*., 1997; Tidy, 2016). The mortality rate is 40% for non-immune hydrops (Trainor and Tubman, 2006).

# Chapter 3

# METHODS

## Patients and study

Retrospective and prospective reviews of *f*MRI and prenatal USS scans were carried out for cases scanned between November 2011 and February 2020 at Sheffield Teaching Hospitals. All *f*MRI examinations were performed at the Royal Hallamshire Hospital radiology department. Most of prenatal USS examinations were performed either locally or in surrounding district general hospitals then were referred to Sheffield Teaching Hospitals for *f*MRI. Some of the USSs were performed in tertiary centres such as Leeds Teaching hospitals and Manchester Royal Infirmary and were referred to Sheffield Teaching Hospitals due to a number of factors including unavailability of appointments, patient’s specific requests and patient’s convenience e.g. live nearer to Sheffield.

All scans included in this study were performed as part of patient’s clinical management protocol. All patients had at least one prenatal USS as part of their clinical care which then indicated the need for a further *f*MRI either due to a foetal pathology or a family history of foetal pathologies.

Participants involved in the prospective part of the study were all invited to take part in this study on the day of their scheduled *f*MRI scan.

Ethics

The retrospective study was approved by Sheffield University Ethics Committee (ref: 007380) and the Sheffield Teaching Hospitals (STH) project registration number is 19026. The prospective study was approved by the Health Research Authority REC Reference 17/EE/0162 and the sponsor was Sheffield Teaching Hospitals NHS Foundation Trust. The standard of care provided by the NHS to all patients was unaffected by the study. This was fully explained (verbally and as a patient information sheets) to the prospective cohort of patients prior to recruitment. Written informed consents were obtained from all participants in this cohort.

All data collected was anonymised and kept strictly confidential at all times on a password protected computer in a locked office in Jessop wing hospital. All participants were given a unique research number as their research ID.

## Data collection

### Prenatal imaging:

For the retrospective cohort, patients with confirmed non-CNS abnormalities were selected from an excel master sheet containing preliminary data (name, D.o.B., hospital number, NHS number, referrer’s details, body region involved with pathology and suspected diagnoses) of all patients scanned from November 2011 to September 2017. A separate Microsoft excel sheet was created with all data collected; including a unique research number, gestational age, date of US scan, date of *f*MRI scan, body region involved, USS report and *f*MRI report for each case.

After the mandatory routine clinical training on PACS, more detailed data was collected via a clinical picture archiving and communication system workstation (PACS) using a clinical software (IMPAX 6.5.2657, Agfa, Belgium) and a Radiology Information System software (CRIS) on an NHS computer. Ideally patients’ hospital numbers were used to search for the cases on PACS but whenever the hospital number was missing or incorrect, patient’s name was used instead.

For the prospective cohort, data was collected immediately during patient’s *f*MRI scan at Royal Hallamshire Hospital Radiology department or on a later time using the same method for the retrospective cohort.

Only the first *f*MRI performed for each pregnancy and the referral prenatal USS were used in this study. No information was obtained from follow up MRI scans or previous prenatal USSs.

### Postnatal outcome:

Postnatal outcome data required included confirmed diagnoses, any postnatal imaging, surgical procedures and findings and post-mortems.

Not all patients included in this study had their full antenatal or postnatal care at Sheffield Teaching Hospitals. Depending on the severity of the findings, patients were counselled regarding their antenatal care. More severe cases that needed tertiary centres care remained in the tertiary hospital system. Those that could be managed locally returned to their local hospitals. In some cases, mothers remained in the tertiary hospital system until their delivery when they were discharged with their babies back to their regional hospitals.

Patients delivered locally were identified by using Jessop’s hospital electronic medical records via Jessop’s Maternity Information System (JMIS). Some of these cases were discharged without any further investigations and were declared to be normal prior to their discharge. Other cases had undergone some investigations (mostly postnatal USS, chest x-rays) during their stay at this hospital. All required data including that of perinatal deaths was collected if present on JMIS at this stage. For patients who had postnatal imaging at Jessops but JMIS did not provide enough or inadequate imaging information then the PACS was used.

Patients who had their continued care transferred to the nearby Children’s Hospital were followed up using Children’s Hospital electronic medical records. All data required was collected if present at this stage. Data for babies who had post-mortem imaging (MRI and x-rays) was collected from PACS.

Patients were subdivided according to place of their continued care (antenatal care, delivery and postnatal follow up) into eight groups. Secure, NHS approved, e-mails were sent to relevant hospitals and the original referring consultants to ask for postnatal outcome data. The same postnatal outcome data required for the local group was also requested for the other groups.

### Technique

Prenatal USS scans were all performed by foetal medicine specialists (clinicians) either locally at Royal Hallamshire Hospital Foetal Medicine Unit or in a tertiary referral unit. The ultrasound machines varied in terms of manufacturer and model but were all used in routine clinical practice at the time.

All *f*MRI examinations were performed using the routine standard clinical protocol on either a 1.5 T MR scanner (Siemens Magnetom Avanto; Erlangen, Germany) or 3T MR scanner (Philips, Eindhoven, Netherlands). Routine sequences used include SSFSE, SSFP, STIR, DWI and T1-weighted sequences. Table-5 summarises the standard sequence parameters used routinely at our institution. Body phased array coils were positioned over the mother’s abdomen in all *f*MRI examinations. All *f*MRI scans included in our study were obtained without the use of sedation or contrast. If tolerated, patients were ideally positioned in the supine position on the MRI scanner, otherwise the left lateral position was adopted, patients were given the choice before entering the scan room.

Table 5 Shows Parameters used for Routine Sequence of fMRI at our Institution.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Sequence | SSFSE | SSFP | STIR | | DWI | | T1-Weighted | |
| TR | 1000.0 ms | 283.5 | 4000 | 4400 ms | | 264 | |
| TE | 91 ms | 1.58 | 118 | 77.0 ms | | 4.76 | |
| FOV | 288 mm | 450 | 300 | 306 mm | | 288 | |
| Matrix | 192🞩192 | 256🞩256 | 256🞩256 | 138🞩138 | | 192🞩192 | |

*SSFSE: Single Shot Fast Spin Echo, SSFP: Steady State Free Precision, STIR: Short Tau Inversion Recovery, DWI: Diffusion Weighted Imaging. TR: Repetition Time, TE: Echo Time, FOV: Field of View.*

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*SSFSE: Single Shot Fast Spin Echo, SSFP: Steady State Free Precision, STIR: Short Tau Inversion Recovery, DWI: Diffusion Weighted Imaging. TR: Repetition Time, TE: Echo Time, FOV: Field of View.*

Figure Distribution of Gestational Age at the Time of fMRI.*SSFSE: Single Shot Fast Spin Echo, SSFP: Steady State Free Precision, STIR: Short Tau Inversion Recovery, DWI: Diffusion Weighted Imaging. TR: Repetition Time, TE: Echo Time, FOV: Field of View.*

*SSFSE: Single Shot Fast Spin Echo, SSFP: Steady State Free Precision, STIR: Short Tau Inversion Recovery, DWI: Diffusion Weighted Imaging. TR: Repetition Time, TE: Echo Time, FOV: Field of View.*

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*SSFSE: Single Shot Fast Spin Echo, SSFP: Steady State Free Precision, STIR: Short Tau Inversion Recovery, DWI: Diffusion Weighted Imaging. TR: Repetition Time, TE: Echo Time, FOV: Field of View.*

### Inclusion and Exclusion criteria:

All Foetuses with confirmed non-CNS abnormalities were included in the study. All patients included in our study were capable of giving informed consents, above 16 years of age and none had contraindications for MRI. These criteria were all required for all participants to be included in the study. Follow up cases, multiple gestations, insufficient data and cases where consent was not given were also excluded from the study.

### First Expert Panel Assessment/Review

Prenatal findings collected from prenatal USS and *f*MRI scans were reviewed and assessed jointly by an expert panel of the principal investigator, a senior Radiologist and Foetal medicine consultant. The panel compared prenatal imaging findings and decided as to the value of *f*MRI in terms diagnosis, management and prognosis using a points-based system (Table 6).

Several meetings were conducted by the first panel experts to discuss and grade the cases as the study progressed. This was achieved via e-mails during the lockdown. Excel sheets with collected data were sent via NHS e-mails to the first panel experts for grading.

Table 6 Criteria used by First Expert Panel to Score each case.

|  |  |
| --- | --- |
| **Criteria** | **Score** |
| Both ultrasound and magnetic resonance gave comparable results and agreed with the final diagnosis. | 1 |
| The diagnosis was not fundamentally changed but magnetic resonance provided extra information that *would not* have affected management or counselling. | 2 |
| The diagnosis was not fundamentally changed but magnetic resonance provided extra information that *could have* affected management or counselling. | 3 |
| The diagnosis was changed on the basis of magnetic resonance imaging. | 4 |
| Any case in which ultrasound provided more information than magnetic resonance. | 5 |
| Magnetic resonance gave incorrect information or uncertain clinical significance that required further clinical investigation or caused unnecessary anxiety. | 6 |

### Second Expert Panel Assessment/Review

Postnatal outcome and prenatal findings of prenatal USS scans and *f*MRIs were compared jointly by an expert panel of the principal investigator, a senior Radiologist and a Neonatal medicine consultant. The panel graded each case in terms of agreement with diagnoses, management and counselling using a points-based system (Table 7).

Grading from 1 to 4 was done on cases with postnatal outcome data based on agreement between *f*MRI and prenatal USS on diagnosis, management and counselling. Grading was achieved by thoroughly reviewing prenatal USS (cause of referral) and *f*MRI reports via the Picture Archiving and Communication System (PACS) or on the excel sheets used for data collection. In the majority of cases, postnatal data provided a definitive final diagnosis but, in a few cases, postnatal outcome data were reviewed via JMIS. In three foetuses definitive diagnoses were challenging and patient information was reviewed on Sheffield Children’s hospital database. Several meetings were conducted by the second panel experts to discuss and grade the cases. This was achieved via e-mails during the lockdown. Excel sheets with collected data were sent via NHS e-mails to the second panel experts for grading.

Table 7 Criteria used by the Second Expert Panel to Score cases with postnatal outcome data.

|  |  |
| --- | --- |
| **Criteria** | Score |
| Imaging agrees with outcome | 1 |
| Imaging missed information without effect on outcome | 2 |
| Imaging missed information that could have changed management or counselling | 3 |
| Imaging was incorrect | 4 |

### Statistical Analysis

Results were recorded in this study as non-parametric values. The results were based on grades as per expert panel (see above). The data is presented in table form and percentage values for each grade. This simple descriptive statistical analysis was chosen to convey clearly to clinicians the difference between USS and *f*MRI and allow comparison with previous published smaller studies which have used the same approach. As a prospective cohort study in a clinical setting with time constraints, compounded by the COVID-19 pandemic, and insufficient published data on the study sample chosen, power calculations for sample size were not appropriate. Post hoc power calculations were performed on the data obtained.

# Chapter 4

# RESULTS

## Study Population

During the time allowed for this study, 421 cases for the retrospective cohort were selected from an internal master database of 1094 cases all scanned between November 2011 and September 2017. A total of 353 cases were included in the retrospective cohort. Sixty-eight cases were excluded: 48 were follow ups, 6 had insufficient data, 13 were twin pregnancies and 1 was an obstetric case.

A total of 134 cases were recruited between September 2017 and February 2020 to form the prospective cohort, of which 128 were included. Six cases were excluded: 3 were follow ups, 1 had no sufficient data and 2 did not consent to participate in the study (one was not approached with the study at the time of *f*MRI scan because of patient’s severe emotional state; patient was extremely worried about her baby’s condition). Table-8 summarises excluded cases in each cohort. All mothers involved in this study were above 18 years of age. Mean GA for the foetuses included was 24.78 weeks. Youngest GA was 15 weeks and eldest was 39 weeks (Figure-10). This represents the distribution of cases when they were referred clinically. The study cohort was subdivided according to GA into two groups: <23 GW and >23 GW. We think GA of 23 GW is a significant time point in pregnancy because of two important factors. First, we predicted that the majority of our study participants will be around that age group based on the need to respond to problems raised at mid-pregnancy (18-21 weeks) anomaly USS programme in the UK. If the recommended two-week window between prenatal USS and *f*MRI is adhered to, that would put *f*MRI time range between 18-23 weeks. Second, the UK governing law of abortion states 24 GW as the key date to determine type (medical or surgical) and logistics (such as self-referral, choosing names, birth and death registrations and choosing health service providers) involved in termination of pregnancy. Also, abortions are usually safer the earlier they are carried out. The decision to have a TOP could be very stressful. Some families may be certain they want to have it, while others might find it more difficult to make that decision and need enough time to consider it. Also, the course of management is usually determined before this date, therefore we choose a cut-off date of 23 GW to give families more time to consider their available options and time for the procedures to be performed. A total of 202 cases were included in <23 GW group and 279 cases were included in >23 GW group.

Table 8 Summarises Excluded cases in each cohort.

|  |  |  |
| --- | --- | --- |
| Reason for exclusion | Prospective Cohort *(n)* | Retrospective Cohort *(n)* |
| Follow Up | **3** | 48 |
| No Data | **1** | 6 |
| Multiple pregnancy | **0** | 13 |
| No consent | **2** | 0 |
| Obstetric | **0** | 1 |
| Total | 6 | 68 |

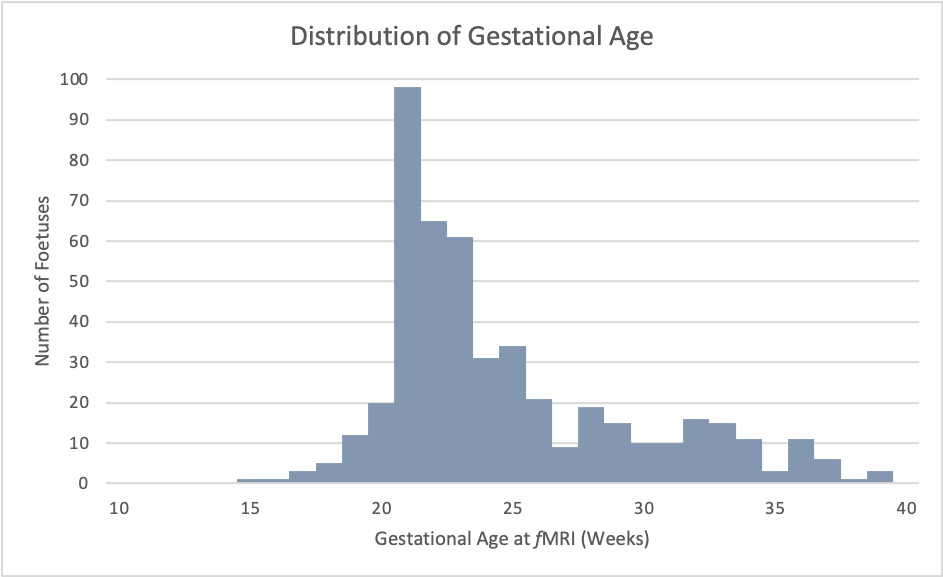


Figure 10 Distribution of Gestational Age at the Time of fMRI.

The study cohort was also divided according to the gap period between prenatal USS and *f*MRI into two groups. First group had their *f*MRI ≤ 2 weeks since their prenatal USS, it contained 426 cases with an average gap period of 6.34 days (range= 0-14 days). The second group had their *f*MRI ≥ 2 weeks since their prenatal USS and it contained 55 cases with an average gap period of 23.21 days (range= 15- 61 days).

Cases were divided according to GA and time delay into:

Group 1: Total of 191 Cases were <23 GW and had <2wks time delay (11 cases were <23 GW and had >2wks time delay).

Group 2: Total of 235 cases were >23 GW and had <2wks time delay (44 cases were >23 GW and had >2wks time delay).

All cases were further subdivided according to body region involved into 6 groups: Chest, Genitourinary, Abdomen, Skeletal, Neck and Miscellaneous. The number of cases in each group is given in Table-9. The decision to which group each case belonged depended on the available postnatal outcome. When the outcome is unavailable then *f*MRI result was used instead. In some cases where postnatal outcome and *f*MRI were normal then the reason for referral and prenatal USS information were used to categorise them.

Table 9 Summarises Subdivision of the Study Cohorts.

|  |  |
| --- | --- |
| Region | Frequency *(n)* |
| Chest | 132 |
| Genitourinary | 142 |
| Abdomen | 128 |
| Skeletal | 43 |
| Neck | 13 |
| Miscellaneous | 23 |
| Total | 481 |

A total of 239 cases had postnatal outcome data collected. 232 cases had their outcome data collected locally. Only one District General Hospital responded with required outcome data for 7 out of 14 patients under their care. Two hundred and four cases (out of 239) with postnatal outcome had their final scoring by the expert panel during the second assessment/review. Postnatal outcome data was not enough for the expert panel to reach a decision and provide a score in 35 out of 239 cases (Figure-11). Postnatal outcome data was collected from a wide range of investigations. Most of the cases had postnatal USS and chest x-rays. Other investigations were used such as CT scans, CT of the pulmonary arteries (CTPA), MRI, abdominal X-rays, limb and spine x-rays, echo, histology, Micturating Cystourethrogram (MCUG), radioactive Dimercaptosuccinic acid scan (DMSA), Barium swallow, skeletal surveys, renal Mercaptuacetyltriglycine scan (MAG3), contrast studies and skin biopsies. Of the 239 cases included 14 had their pregnancies terminated (5.85%), 11 foetuses had intrauterine foetal deaths (4.6%), 27 neonates died (11.29%), 2 cases had intrapartum deaths (<1%) and 1 case had a miscarriage (<1%). Eight cases had post-mortem studies either in the form of radiological examinations such as MRI and X-rays or autopsies and genetic studies. One Pallister-Killian syndrome by genetics, 1 hydrops with a heart defect, 2 CDH cases confirmed by radiological examinations, 1 autosomal recessive polycystic kidney disease, 1 CDH with hydrops case found to have chromosome 4 deletion, CDH and Absent Corpus Collosum in 1 case by post-mortem MRI and post-mortem autopsy confirmed the diagnosis of 1 unilateral renal agenesis but no cause of death was identified.

Figure 1 Summarises Study Population.

Master Database

1094 cases

Master Database

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Master Database

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Second Panel assessment

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Figure Summarises the Study Population.No Data

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Figure Summarises the Study Population.No Data

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## OVERALL RESULTS

### First expert panel Assessment/Review

**Overall***: fMRI provided additional information that could change diagnoses and/or management and counselling in 195 cases (40.5%), provided additional information without affecting management and/or counselling in 113 cases (23%), gave incorrect information that required further clinical investigation in only 1 case and both prenatal USS and fMRI provided similar information in 172 cases (35.7%).*

**First group (*f*MRI within 2 weeks):** *fMRI provided additional information that could change diagnoses and/or management and counselling in 173 cases (40.6%), provided additional information without affecting management and/or counselling in 99 cases (23%), gave incorrect information that required further clinical investigation in only 1 case and both prenatal USS and fMRI provided similar information in 153 cases (36%).*

**Second group (*f*MRI ≥ 2 weeks):** *fMRI provided additional information that could change diagnoses and/or management and counselling in 21 cases (38%), provided additional information without affecting management and/or counselling in 14 cases (25%), did not give incorrect information that required further clinical investigation in any case and both prenatal USS and fMRI provided similar information in 20 cases (36%).*

**First expert panel assessment in 277 cases without postnatal outcome scoring:**

More than half of our patients (n=277) did not have postnatal outcome reference data available (did not have their continued antenatal and/or postnatal care in Sheffield Teaching Hospitals or lost to follow-up) and subsequently no second expert panel scoring (Table-10). Majority were GUS abnormalities (n=84) followed by abdominal abnormalities (n=76) and chest abnormalities (n=63). 36 patients (13%) had >2wks time delay between prenatal USS and *f*MRI while 241 patients (87%) had <2 weeks. First panel scores were only significant in 36% (n=13) of those cases with >2wks time delay (Table-11).

First Expert Panel Assessment as follow:

*fMRI provided similar information to USS in 113 cases (40.7%).*

*fMRI added less important information that could have not changed management and/or counselling in 67 cases (24%).*

*fMRI added valuable information to USS that could have changed management and/or counselling in 53 cases (19%).*

*fMRI fundamentally changed prenatal USS diagnoses in 44 cases (15.8%).*

Table 10 Frequency of cases without Postnatal outcome in each Group.

|  |  |
| --- | --- |
| Region | Frequency *(n)* |
| Chest | 63 |
| Abdomen | 76 |
| GUS | 84 |
| Skeletal | 30 |
| Neck | 7 |
| Miscellaneous | 17 |

Table 11 First Expert Panel assessment of cases without Postnatal outcome.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Body  Region | Chest | Abdomen | GUS | Skeletal | Miscellaneous | Neck | Total |
| Total *(n)* | 63 | 76 | 84 | 30 | 17 | 7 | 277 |
| Similar  *(n)*  *(%)* | 13  *(20.6%)* | 38  *(50%)* | 43  *(51%)* | 9  *(30%)* | 7  *(41%)* | 3  *(42.8%)* | 113  *(40.7%)* |
| Added no Change  *(n)*  *(%)* | 17  *(27%)* | 16  *(21%)* | 21  *(25%)* | 8  *(26.6%)* | 5  *(29%)* | 0 | 67  *(24%)* |
| Altered Mx/Cx  *(n)*  *(%)* | 22  *(35%)* | 8  *(10.5%)* | 13  *(15%)* | 4  *(13%)* | 3  *(17.6%)* | 3  *(42.8%)* | 53  *(19%)* |
| Changed Diagnosis  *(n)*  *(%)* | 11  *(17%)* | 14  *(18%)* | 7  *(8%)* | 9  *(30%)* | 2  *(11.7%)* | 1  *(14%)* | 44  *(15.8%)* |

*Mx: Management*

*Cx: Counselling*

*Mx: Management*

*Cx: Counselling*

*Mx: Management*

*Cx: Counselling*

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### Second Expert Panel Assessment/Review

**Overall***: fMRI agreed with postnatal outcome in 179 cases (87.7%), missed information without effect on outcome in 11 cases (5%), missed information with effect on outcome in 8 cases (4%) and was incorrect in 6 cases (3%). Prenatal USS agreed with postnatal outcome in 141 cases (69%), missed information without effect on outcome in 33 cases (16%), missed information with effect on outcome in 16 cases (7.8%) and was incorrect in 14 cases (6.8%).* Table-12 shows second panel assessment of all cases with postnatal outcome.

**First group (*f*MRI within 2 weeks):** 185 out of 426 (43%) foetuses had postnatal outcome data and scored by second expert panel. *fMRI agreed with postnatal outcome in 162 cases (87.5%), missed information without effect on outcome in 11 cases (6%), missed information with effect on outcome in 8 cases (4%) and was incorrect in 4 cases (2%). Prenatal USS agreed with postnatal outcome in 131 cases (70.8%), missed information without effect on outcome in 28 cases (15%), missed information with effect on outcome in 15 cases (8%) and was incorrect in 11 cases (6%).*

**Second group (*f*MRI ≥ 2 weeks):** 19 out of 55 (34.5%) foetuses had postnatal outcome data and scored by second expert panel. *fMRI agreed with postnatal outcome in 16 cases (84%), missed information with effect on outcome in one case (5%) and was incorrect in 2 cases (10.5%). Prenatal USS agreed with postnatal outcome in 9 cases (47%), missed information without effect on outcome in 5 cases (26%), missed information with effect on outcome in 2 cases (10.5%) and was incorrect in 3 cases (15.7%).*

Table 12 Second Expert Panel Assessment of all cases with postnatal outcome.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Region | Chest | | GUS | | Abdomen | | Skeletal | | Neck | | Miscellaneous | |
| Total *(n)* | 69 | | 58 | | 52 | | 13 | | 6 | | 6 | |
| Scan | USS | *f*MRI | USS | *f*MRI | USS | *f*MRI | USS | *f*MRI | USS | *f*MRI | USS | *f*MRI |
| Agreed  *(n)*  *(%)* | 55  *(79.7%)* | 66  *(95.6%)* | 31  *(53%)* | 44  *(75.8%)* | 36  *(69%)* | 46  *(88%)* | 9  *(69%)* | 12  *(92%)* | 6  *(100%)* | 6  *(100%)* | 4  *(66.6%)* | 5  *(83%)* |
| Missed Info No Effect  *(n)*  *(%)* | 8  *(11.5%)* | 2  *(3%)* | 11  *(19%)* | 5  *(8.6%)* | 10  *(19%)* | 3  *(5.7%)* | 2  *(15%)* | 0 | 0 | 0 | 2  *(33%)* | 1  *(16.6%)* |
| Missed Info with Effect  *(n)*  *(%)* | 5  *(7%)* | 1  *(1%)* | 6  *(10%)* | 5  *(8.6%)* | 4  *(8.7%)* | 1  *(2%)* | 1  *(7.7%)* | 1  *(7.7%)* | 0 | 0 | 0 | 0 |
| Fundamental Change  (*n)*  *(%)* | 1  *(1%)* | 0 | 10  *(17%)* | 4  *(6.8%)* | 2  *(3.8%)* | 2  *(3.8%)* | 1  *(7.7%)* | 0 | 0 | 0 | 0 | 0 |

### Case by case analysis:

Both scans agreed with postnatal outcome as scored by second expert panel in 138 cases (67.6%): 53 chest cases (38.4%), abdomen 35 cases (25%), GUS 31 cases (22.4%), skeletal 9 cases (6.5%), neck 6 cases (4%), Miscellaneous 4 cases (2.9%).

Both scans were incorrect in 5 cases (2.4%): 4 GUS, 1 abdomen.

Both scans missed valuable information in 5 cases (2.4%): 2 GUS, 1 chest, 1 abdomen, 1 skeletal.

Both scans missed less valuable information in 7 cases (3.4%): 3 GUS, 3 abdomen, 1 miscellaneous.

*f*MRI missed less valuable information where prenatal USS provided accurate diagnoses in 2 chest cases <1%.

*f*MRI corrected prenatal USS diagnoses in 7 cases (3.4%): 4 GUS, 1 abdomen, 1 chest and 1 skeletal.

Prenatal USS missed valuable information where *f*MRI provided accurate diagnoses in 9 cases (4.4%): 4 chest, 3 abdomen, 2 GUS. Also missed valuable information in another 2 GUS cases where *f*MRI missed less valuable information.

Prenatal USS missed less valuable information where *f*MRI provided accurate diagnoses in 25 cases (12%): 8 chest, 7 Abdomen, 7 GUS, 2 skeletal, 1 miscellaneous. Also, it missed less valuable information in 1 GUS case, but *f*MRI missed more valuable information.

Prenatal USS provided incorrect diagnoses where *f*MRI missed valuable information in 2 GUS cases <1%.

Prenatal USS corrected *f*MRI in 1 abdomen case <1%.

*Summary*:

*f*MRI was superior to prenatal USS in 21.5% *(n=44)* of cases confirmed postnatally. It changed prenatal USS diagnoses completely in 7 cases: 4 GUS, 1 abdomen, 1 chest, and 1 skeletal cases. *f*MRI was found to be correct postnatally in another 9 cases: 4 chest, 3 abdomen and 2 GUS where prenatal USS missed valuable information that would have changed the course of management and/or counselling. In 24 cases: 8 chest, 7 GUS, 6 abdomen, 2 skeletal and 1 miscellaneous *f*MRI findings were confirmed postnatally whereas prenatal USS missed information but without affecting management and/or counselling. Prenatal USS provided incorrect diagnoses in another 4 GUS cases where *f*MRI provided correct diagnoses but missed valuable information.

### First Expert Panel vs Second Expert Panel

Second panel assessment disagreed with first panel assessment in 14 cases (6.8%) where *f*MRI was believed to be superior to prenatal USS. Nine of those cases where from the GUS cohort. It also disagreed with first panel assessment in 102 cases (49.75%) where prenatal USS was thought to be inferior to *f*MRI. Postnatal outcome and second panel scoring proved that prenatal USS either provided information similar to *f*MRI or missed less valuable information that did not change management or counselling in those patients. The majority of these cases were from the chest cohort 45% (n=46) and almost 70% (n=32) of those were CDH cases in which higher scores were given by the first expert panel due to the added benefit of lung volume measurements by *f*MRI. Table-13 illustrates agreements and disagreements between first and second expert panels.

Table 13 Agreement/Disagreement between First and Second Expert Panels.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Region | *Chest* | | *Abdomen* | | *GUS* | | *Skeletal* | | *Neck* | | *Miscellaneous* | |
| Scan | *fMRI* | *USS* | *fMRI* | *USS* | *fMRI* | *USS* | *fMRI* | *USS* | *fMRI* | *USS* | *fMRI* | *USS* |
| Agree  *(n)* | *67* | *23* | *49* | *29* | *50* | *36* | *12* | *7* | *6* | *4* | *6* | *4* |
| Disagree  *(n)* | *2* | *46* | *3* | *23* | *8* | *22* | *1* | *6* | *0* | *2* | *0* | *2* |

### Diagnostic Accuracy

Definitions:

True positive cases: Cases where scan results are in complete agreement with postnatal outcome.

False positive cases: False positives are defined as those cases found by *f*MRI to be normal and was proved to be correct by postnatal outcome. However, all cases which gave completely different diagnoses to postnatal outcome in this study were scored to be incorrect by the second expert panel regardless of being normal or not. Therefore, only true positive cases were used to calculate the diagnostic accuracy for *f*MRI.

Diagnostic Accuracy for USS: Number of true positive cases divided by the total number of cases.

Diagnostic Accuracy for *fMRI*: Number of true positive cases divided by the total number of cases.

Note: It is only possible to calculate Diagnostic Accuracy for cases which had postnatal outcome. Diagnostic Accuracy was calculated for both scans, overall and according to the time delay between them. To avoid the effect of time delay between the scans on GA, diagnostic accuracy according to GA was only measured for cases with <2wks time delay.

**Overall Diagnostic Accuracy**: *This study found that accurate diagnosis was provided by prenatal USS in 69.6% and by fMRI in 87.7%. The highest diagnostic accuracy for both prenatal USS and fMRI was observed in the neck cohort with 100% correct diagnoses. Followed by the chest cohort with 81% for prenatal USS and 95.6% for fMRI. The lowest diagnostic accuracy was observed for both imaging modalities in the GUS cohort with 53% for prenatal USS and 75.8% for fMRI*. Table-14 shows detailed results of each cohort for the diagnostic accuracies of *fMRI* and prenatal USS.

Table 14 Results of Diagnostic Accuracy for prenatal USS and fMRI.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Region | USS Correct  *(n)* | *f*MRI Correct  *(n)* | *f*MRI Incorrect  *(n)* | Number  Of  Cases | Diagnostic accuracy USS *(%)* | Diagnostic accuracy *f*MRI *(%)* |
| Chest | 56 | 66 | 0 | 69 | 81% | 95.6% |
| Abdomen | 36 | 46 | 2 | 52 | 69% | 88% |
| GUS | 31 | 44 | 4 | 58 | 53% | 75.8% |
| Skeletal | 9 | 12 | 0 | 13 | 69% | 92% |
| Neck | 6 | 6 | 0 | 6 | 100% | 100% |
| Miscellaneous | 4 | 5 | 0 | 6 | 66.6% | 83% |
| Overall | 142 | 179 | 6 | 204 | 69.6% | 87.7% |

**Diagnostic Accuracy for First Group (*fMRI* within 2wks):** *Overall Diagnostic Accuracy was 70.8% for prenatal USS and 87.5% for fMRI in this group. The highest diagnostic accuracy for both scans were in the neck cohort with correct diagnoses in all cases. However, this cohort included only 6 cases with postnatal outcome and due to the small number of cases, this result cannot be considered significant. The second highest accuracy for fMRI was observed in the chest cohort with 95% (USS=82%) followed by Skeletal cohort with 91.6% (USS=66.6%) and abdomen cohort with 87% (USS=67%). The lowest diagnostic accuracies for both scans were in the GUS cohort with 77% for fMRI and 57.6% prenatal USS.*

**Diagnostic Accuracy for Second Group (*fMRI* >2wks):** *Overall Diagnostic Accuracies for both scans in this group were 89% for fMRI and 47% for prenatal USS. The highest accuracy for fMRI was achieved in the chest cohort in this group with 100% (USS=50%) followed by the abdomen cohort with 83% (USS=66.6%). The lowest accuracy for both scans was observed in the GUS cohort in this group with 66.6% for fMRI and 16.6% for prenatal USS.*

**Diagnostic Accuracy for Group 1 (GA<23 GW and time delay ≤2wks):** A total 97 foetuses with GA <23 GW had their *f*MRI ≤2wks**.** *Overall Diagnostic Accuracy for fMRI was 84.5% and 69% for prenatal USS. fMRI had a diagnostic accuracy of 94% in the abdomen cohort (USS=72%), 91% in the chest cohort (USS=80%), 69.6% in the GUS cohort (USS=54.5%), 75% in the skeletal cohort (USS=50%), 100% in the miscellaneous cohort (USS=50%) and 100% for both scans in the neck cohort*. However, miscellaneous and neck cohorts only had 2 and 4 cases with postnatal outcome reference data, respectively.

**Diagnostic Accuracy for Group 2 (GA >23 GW and time delay<2wks):** A total 88 foetuses with GA >23 GW had their *f*MRI >2wks**.** Overall Diagnostic Accuracy for *f*MRI was 92% and 72% for prenatal USS. *f*MRI had a diagnostic accuracy of 100% in the chest cohort (USS=85%), 89% in the GUS cohort (USS=63%), 85.7% in the abdominal cohort (USS=64%), 100% in the skeletal cohort (USS=75%), 75% in the miscellaneous cohort (USS=75%) and 100% for both scans in the neck cohort.

## CHEST

### Overall results:

Total of 132 chest cases were included. CDH was the most frequent chest abnormality with 57 cases (43%) followed by CPAM with 44 cases (33.33%). Table-15 shows detailed description of chest abnormalities and their frequencies in this study. In total, 29 cases (23%) had associated abnormalities. 22 out of all 57 (38.5%) CDH cases had associated abnormalities. Tables-16 and 17 show nature and frequency of associated abnormalities in the chest cohort. Out of the 132 chest cases, 69 cases had postnatal outcome and obtained scores by the second expert panel (52%). 13 babies had neonatal death, 4 had TOP and 1 case had intrauterine death.

Table 15 List Types of Chest abnormalities included in the Study.

|  |  |
| --- | --- |
| Chest Abnormality | Frequency *(n)* |
| CDH | 57 |
| CPAM | 44 |
| Pleural Effusion | 5 |
| Emphysema | 4 |
| Lung Hypoplasia | 1 |
| Lymphatic Malformation | 2 |
| Choroid Plexus Cyst | 1 |
| Eventration | 2 |
| CHAOS | 1 |
| Bronchogenic Cyst | 1 |
| Hiatus Hernia | 1 |
| Mediastinal Teratoma | 1 |
| Ectopia Cordis | 1 |
| Dextrocardia | 2 |
| Abnormal Sternum Ossification | 1 |
| Lung Aplasia | 1 |
| Normal | 7 |
| Total | 132 |

Table 16 Lists Associated Abnormalities with CDH.

|  |  |
| --- | --- |
| Associated Abnormalities | Frequency *(n)* |
| Ipsilateral Pleural Effusion | 9 |
| Bilateral Pleural Effusion | 2 |
| Contralateral Pleural Effusion | 1 |
| Ascites | 2 |
| Left Renal Agenesis | 1 |
| Proximal Bowel Atresia | 1 |
| Lung Aplasia (Contralateral) | 1 |
| Absent Pons | 1 |
| Early Termination of Spinal Cord | 1 |
| Cystic Hygroma | 1 |
| Agenesis of Corpus Collosum | 1 |
| Vertebral Segmentation Abnormalities | 1 |
| Right Renal Agenesis | 1 |
| Left Ureterocoele | 1 |
| PUJ Obstruction with Hydronephrosis | 1 |
| Subcutaneous Oedema | 1 |
| Duplex kidney (Contralateral) | 1 |
| TOF | 1 |
| Hemivertebrae | 1 |
| Partial Agenesis of Corpus Collosum | 1 |
| CPAM | 1 |
| Congenital Heart Disease | 1 |

Table 17 Lists Associated Abnormalities with CPAM.

|  |  |
| --- | --- |
| Associated Abnormalities | Frequency *(n)* |
| Right renal agenesis (confirmed) | 1 |
| Ascites | 1 |
| Subcutaneous Oedema | 1 |
| Hiatus hernia | 1 |
| Pleural Effusion | 1 |
| Hepatic Cyst | 1 |
| CDH (confirmed) | 1 |

### First Expert Panel Assessment/Review:

Table-18 lists grading of different chest abnormalities by the first expert panel.

*fMRI added information that fundamentally changed diagnosis in 21 foetuses (16%)*.

*Changed management and/or counselling in 59 foetuses (44%)*.

*Added information without changing management and/or counselling in 26 cases (20%)*.

*Provided similar information to prenatal USS in 25 cases (19%)*.

*fMRI was unable to identify a lesion seen by USS in 1 miscellaneous case (<1%).*

Table 18 First Expert Panel Grading of the Chest cohort.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Anomaly | CDH | CPAM | Effusion | Emphysema | Miscellaneous | Total |
| Total *(n)* | 57 | 44 | 5 | 4 | 22 | 132 |
| Changed diagnosis  *(n)*  *(%)* | 7  *(12%)* | 9  *(20%)* | 0 | 0 | 5  *(22.7%)* | 21  (*16%)* |
| Changed Mx/Cx  *(n)*  *(%)* | 49  *(86%)* | 3  *(6.8%)* | 0 | 2  *(50%)* | 5  *(22.7%)* | 59  *(44.6%)* |
| Added info without change in Mx/Cx  *(n)*  *(%)* | 0 | 16  *(36%)* | 3  *(60%)* | 1  *(25%)* | 6  *(27%)* | 26  *(19.6%)* |
| Similar  *(n)*  *(%)* | 1  *(1.7%)* | 16  *(36%)* | 2  *(40%)* | 1  *(25%)* | 5  *(22.7%)* | 25  *(19%)* |
| Incorrect  *(n)*  *(%)* | 0 | 0 | 0 | 0 | 1  (4.5%) | 1  (<1%) |

*Mx: Management, Cx: counselling*

*Mx: Management, Cx: counselling*

*Mx: Management, Cx: counselling*

*Mx: Management, Cx: counselling*

### Second Expert Panel Assessment/Review

**Overall:** Table-19 lists grading of different chest abnormalities by the second expert panel.

*fMRI agreed with postnatal outcome in 66 cases (95.6%)*. Prenatal *USS agreed with postnatal outcome in 55 cases (79.7%)*.

*fMRI missed information without effect on outcome in 2 cases (3%)*. Prenatal *USS missed information without effect on outcome in 8 cases (11.5%)*.

*fMRI missed information with effect on outcome in 1 CPAM case (1%)*. Prenatal *USS missed information with effect on outcome in 5 cases (7%)*.

*fMRI was not scored to be incorrect in any cases. Prenatal USS was incorrect in 1 CDH case (1%)*.

**First group (*f*MRI within 2 weeks)**:

*fMRI agreed with postnatal outcome in 60 cases (95%), missed information without effect on outcome in 2 cases (3%), missed information with effect on outcome in 1 case (1.5%) and no incorrect cases. Prenatal USS agreed with postnatal outcome in 52 cases (82%), missed information without effect on outcome in 6 cases (9.5 %), missed information with effect on outcome in 4 cases (6%) and was incorrect in 1 case (1.5%).*

**Second group (*f*MRI ≥ 2 weeks):**

*fMRI agreed with postnatal outcome in all the cases in this group. Prenatal USS agreed with postnatal outcome in 3 cases (50%), missed information without effect on outcome in 2 cases (33%), missed information with effect on outcome in 1 case (16%) and no incorrect diagnosis.*

Table 19 Second Expert Panel Overall Assessment of the Chest cohort.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Anomaly | CDH | | CPAM | | Emphysema | | Effusion | | Miscellaneous | | Total | |
| Total with outcome *(n)* | 34 | | 24 | | 1 | | 0 | | 10 | | 69 | |
| Scan | US*S* | *f*MRI | USS | *f*MRI | USS | *f*MRI | USS | *f*MRI | USS | *f*MRI | USS | *f*MRI |
| Agreed  *(n)*  *(%)* | 29  (85%) | 33  (97%) | 20  (83%) | 22  (91.6%) | 0 | 1  (100%) | 0 | 0 | 7  (70%) | 10  (100%) | 56  (81%) | 66  (95.6%) |
| Missed info no effect  *(n)*  *(%)* | 2  (5.8%) | 1  (3%) | 3  (12.5%) | 1  (4%) | 1  (100%) | 0 | 0 | 0 | 2  (20%) | 0 | 8  (11.6%) | 2  (2.9%) |
| Missed info with effect  *(n)*  *(%)* | 2  (5.8%) | 0 | 1  (4%) | 1  (4%) | 0 | 0 | 0 | 0 | 1  (10%) | 0 | 4  (5.8%) | 1  (1.4%) |
| Incorrect  *(n)*  *(%)* | 1  (3%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1  (1.4%) | 0 |

## ABDOMEN

### Overall results:

Total of 128 cases with abdominal abnormalities were included in this cohort. Abdominal cysts were the most frequent with 47 cases (36.7%), TOF in 24 cases (18.7%), exomphalos in 19 cases (14.8%) and duodenal atresia in 9 cases (7%). Table-20 shows detailed description of abdominal abnormalities with their frequency in this study. Associated abnormalities were found in 37 cases (29%). 10 of 19 (52.6%) exomphalos cases had associated abnormalities. 12 of 24 (50%) TOF cases had associated abnormalities. 7 of 47 (15%) abdominal cysts were associated with other abnormalities. Tables-(21-25) show nature and frequency of associated abnormalities in the abdomen cohort. Out of 128 abdomen cases, 52 had postnatal outcome and obtained scores by the second expert panel (40.6%). 3 babies had neonatal death, 1 case had a miscarriage, 1 still birth and 1 TOP.

Table 20 List Types of Abdominal Abnormalities included in the Study.

|  |  |
| --- | --- |
| Abdominal Anomalies | Frequency *(n)* |
| Exomphalos | 19 |
| Abdominal Cysts | 47 |
| TOF | 23 |
| Laryngeal Atresia | 1 |
| Gastroschisis | 4 |
| Duodenal Atresia | 9 |
| Ascites | 2 |
| Miscellaneous | 18 |
| Situs Inverses | 5 |
| Total | 128 |

Table 21 List Associated Abnormalities with Oesophageal Atresia.

|  |  |
| --- | --- |
| Associated Abnormalities | Frequency *(n)* |
| Fistulous Connection | 11 (2 confirmed postnatally) |
| Large Bladder | 1 |
| Hydronephrosis "Bilateral" | 1 |
| Right Duplex kidney with hydronephrosis and Ureterocoele Laryngeal atresia case | 1 |
| Subcutaneous Oedema (Laryngeal atresia case) | 1 |
| Short Long Bones | 1 |
| Hypoplastic Left Heart and Hepatomegaly | 1 |

Table 22 List Associated Abnormalities with Exomphalos.

|  |  |
| --- | --- |
| Associated Abnormalities | Frequency *(n)* |
| Inguinal Hernia (confirmed postnatally) | 1 |
| Tetralogy of Fallot and Ascites (confirmed postnatally) | 1 |
| Malrotation (confirmed postnatally) | 1 |
| Beckwith Weidermann Syndrome (confirmed postnatally) | 1 |
| Spina Bifida and Chiari II formation | 1 |
| Colonic Atresia (confirmed postnatally) | 1 |
| Abnormal Placenta | 1 |
| Bicornuate Uterus | 1 |
| Renal Agenesis | 1 |
| Abnormal Sacral Development | 1 |
| Nuchal Thickening and abnormal facial profile ?Chromosomal abnormality | 1 |

Table 23 List Associated Abnormalities with Abdominal Cysts.

|  |  |
| --- | --- |
| Associated Abnormalities | Frequency *(n)* |
| Arachnoid Cyst, Partial Agenesis of Corpus Collosum and Heterotopia (?duplication) | 1 |
| Whipped Hands and Parietal Skull Abnormality (abdominal cyst ?nature; resolved) | 1 |
| Left Hydronephrosis (?nature cyst) | 1 |
| Bowel Malposition (?Choledochal cyst) | 1 |
| Ascites and Hepatomegaly (Beckwith Weidermann Syndrome) | 1 |
| Right Renal Agenesis and Two Vessel Cord=1 (?nature cyst) | 1 |

Table 24 List Associated Abnormalities with Gastroschisis.

|  |  |
| --- | --- |
| Associated Abnormalities | Frequency *(n)* |
| Abdominal Cyst | 1 |
| Mediastinal Fluid (pericardial or Pleural effusion) no outcome data | 1 |
| Pulmonary Hypoplasia | 1 |
| Abnormal Placenta | 1 |

Table 25 List Associated Abnormalities with Miscellaneous cases.

|  |  |
| --- | --- |
| Associated Abnormalities | Frequency |
| Left Duplex Kidney with Liver Haemangioma | 1 |
| Polysplenia with Situs Inversus | 1 |
| Short Long Bones with Bilateral Adrenal Haemorrhage | 1 |

### First Expert Panel Assessment/Review

Table-26 lists grading of different abdominal abnormalities by the first expert panel.

*fMRI added information that fundamentally changed diagnosis in 26 foetuses (20%)*.

*Changed management and/or counselling in 15 foetuses (11.7%)*.

*Added information without changing management and/or counselling in 27 cases (21%)*.

*Provided similar information to prenatal USS in 60 cases (46.8%).*

Table 26 First Expert Panel Grading of the Abdominal cohort.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Anomaly | Cysts | Exomphalos | TOF | Gastroschisis | DA | Situs | Miscellaneous | Total |
| Total *(n)* | 47 | 19 | 24 | 4 | 9 | 5 | 20 | 128 |
| Changed diagnosis  *(n)*  *(%)* | 16  *(34%)* | 0 | 3  (12.5%) | 1  (25%) | 0 | *0* | 6  (30%) | 26  (20%) |
| Changed Mx/Cx  *(n)*  *(%)* | *3*  *(6%)* | *2*  *(10.5%)* | 5  (20.8%) | *0* | *2*  *(22%)* | *2*  *(40%)* | 1  (5%) | 15  (11%) |
| Added info without change in Mx/Cx  *(n)*  *(%)* | 10  (21%) | *6*  *(31.5%)* | *6*  *(25%)* | *2*  *(50%)* | *2*  *(22%)* | *0* | 1  (5%) | 27  (20.9%) |
| Similar  *(n)*  *(%)* | *18*  *(38%)* | *11*  *(57.8%)* | *10*  *(41.6%)* | *1*  *(25%)* | *5*  *(55.5%)* | *3*  *(60%)* | 12  (60%) | 60  (46.8%) |
| Incorrect  *(n)* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

*DA: Duodenal atresia, Mx: Management, Cx: Counselling*

*DA: Duodenal atresia, Mx: Management, Cx: Counselling*

*DA: Duodenal atresia, Mx: Management, Cx: Counselling*

*DA: Duodenal atresia, Mx: Management, Cx: Counselling*

### Second Expert Panel Assessment/Review

**Overall:** Table-27 lists grading of different abdominal abnormalities by the second expert panel.

*fMRI agreed with postnatal outcome in 46 cases (88%)*. Prenatal *USS agreed with postnatal outcome in 36 cases (69%)*.

*fMRI missed information without effect on outcome in 3 cases (5.7%)*. Prenatal *USS missed information without effect on outcome in 10 cases (19%).*

*fMRI missed information with effect on outcome in 1 exomphalos case (2%)*. Prenatal *USS missed information with effect on outcome in 4 cases (8.7%)*.

*fMRI was incorrect in 2 cases (3.8%)*. Prenatal *USS was incorrect in 2 abdominal cysts cases (3.8%)*.

**First group (*f*MRI within 2 weeks):**

*fMRI agreed with postnatal outcome in 41 cases (87%), missed information without effect on outcome in 3 cases (6%), missed information with effect on outcome in 1 case (2%) and was incorrect in 2 cases (4%). Prenatal USS agreed with postnatal outcome in 31 cases (65%), missed information without effect on outcome in 10 cases (21%), missed information with effect on outcome in 4 cases (8%) and was incorrect in 2 cases (4%).*

**Second group (*f*MRI ≥ 2 weeks):**

*fMRI agreed with postnatal outcome in 5 cases (83%) and missed information with effect on outcome in 1 case (16%). Prenatal USS agreed with postnatal outcome in 4 cases (66%), missed information without effect on outcome in 1 case (16%) and missed information with effect on outcome in 1 case (16%).*

Table 27 Second Expert Panel assessment of the Abdominal cohort.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Anomaly | Cysts | | Exomphalos | | | TOF | | | DA | | | Gastroschisis | | | Situs | | | Miscellaneous | | | Total | | |
| Total *(n)* | 23 | | 11 | | | 9 | | | 2 | | | 0 | | | 3 | | | 4 | | | 52 | | |
| Scan | US*S* | *f*MRI | USS | *f*MRI | USS | | *f*MRI | US*S* | | *f*MRI | USS | | *f*MRI | USS | | *f*MRI | USS | | *f*MRI | USS | | *f*MRI |
| Agreed  *(n)*  *(%)* | 17  (73.9%) | 21  (91%) | 8  (72.7%) | 10  (90.9%) | 4  (44%) | | 6  (66.6%) | 1  (50%) | | 2  (100%) | 0 | | 0 | 3  (100%) | | 3  (100%) | 3  (75%) | | 4  (100%) | 36  (69%) | | 46  (88%) |
| Missed info no effect  *(n)*  *(%)* | 3  (13%) | 1  (9%) | 2  (18%) | 0 | 3  (33%) | | 2  (22%) | 1  (50%) | | 0 | 0 | | 0 | 0 | | 0 | 1  (25%) | | 0 | 10  (19%) | | 3  (5.7%) |
| Missed info with effect  *(n)*  *(%)* | 1  (4%) | 0 | 1  (9%) | 1  (9%) | 2  (50%) | | 0 | 0 | | 0 | 0 | | 0 | 0 | | 0 | 0 | | 0 | 4  (7.6%) | | 1  (1.9%) |
| Incorrect  *(n)*  *(%)* | 2  (8.6%) | 1 | 0 | 0 | 0 | | 1  (11%) | 0 | | 0 | 0 | | 0 | 0 | | 0 | 0 | | 0 | 2  (3.8%) | | 2  (3.8%) |

*TOF: Tracheooesophageal Fistula, DA: Duodenal Atresia*

*TOF: Tracheooesophageal Fistula, DA: Duodenal Atresia*

*TOF: Tracheooesophageal Fistula, DA: Duodenal Atresia*

*TOF: Tracheooesophageal Fistula, DA: Duodenal Atresia*

## GENITOURINARY TRACT

### Overall results:

A total of 142 cases with genitourinary abnormalities were included in this cohort. MCDK cases were the most frequent with 35 cases (24.6%), unilateral renal agenesis in 24 cases (16.9%), ectopic kidney in 20 cases (14%), urinary tract obstruction in 21 cases (14.7%) and duplex collecting system in 13 cases (9%). Table-28 shows detailed description of genitourinary abnormalities with their frequency in this study. Associated abnormalities were present in 62 cases (43.6%). They were detected in 18 unilateral renal agenesis cases (75%), 12 MCDK cases (34%), 10 ectopic kidney cases (50%), 7 duplex collecting system cases (53.8%), 6 urinary tract obstruction cases (28.5%), 2 bilateral renal agenesis cases (11.7%) and 2 miscellaneous cases (25%). Tables-(29-35) show lists of associated abnormalities and their frequencies in the genitourinary cohort. Out of 142 genitourinary cases, 58 had postnatal outcome and obtained scores by the second expert panel (40.8%). 8 cases had TOP, 5 had neonatal deaths, 4 intrauterine deaths and 1 baby died during delivery (intrapartum death).

Table 28 List Types of Genitourinary Abnormalities included in the Study.

|  |  |
| --- | --- |
| Genitourinary Tract Anomalies | Frequency *(n)* |
| MCDK | 35 |
| Bilateral Renal Agenesis | 17 |
| Unilateral Renal Agenesis | 24 |
| Ectopic Kidneys | 18 |
| Crossed Fused Ectopia | 2 |
| Horseshoe Kidneys | 4 |
| Urinary Tract Obstruction | 21 |
| Duplex Kidneys | 13 |
| Miscellaneous | 8 |
| Total | 142 |

Table 29 List Associated Abnormalities with MCDK.

|  |  |
| --- | --- |
| Associated Abnormality | Frequency *(n)* |
| Hydronephrosis | 5 |
| Ureterocoele | 3 |
| Duplex Kidney | 2 |
| Posterior Urethral Valves | 1 |
| Dilated Bowel | 1 |
| Pleural Effusion | 1 |
| Contralateral Small Kidney | 1 |
| Abnormal Position | 1 |
| Pancreatic Cysts | 1 |
| Bifurcated Bladder | 1 |
| Lipoma | 1 |
| Segmentation Vertebral Anomalies | 1 |
| Lung Collapse | 1 |
| Septate Bladder | 1 |
| Ascites | 1 |
| Scrotal Fluid | 1 |
| TOF | 1 |
| Incomplete Spinal Cord | 1 |
| PUV Obstruction | 1 |
| Large Irregular Bladder | 1 |
| Dilated Urethra | 1 |

Table 30 List Associated Abnormalities with Unilateral Renal Agenesis.

|  |  |
| --- | --- |
| Associated Abnormality | Frequency *(n)* |
| Lung Hypoplasia | 1 |
| Simple Cyst | 1 |
| Ovarian Cyst | 2 |
| MCDK | 2 |
| Polycystic Kidney | 1 |
| Imperforate Anus | 1 |
| Hydronephrosis | 3 |
| Ureterocoele | 2 |
| Long Umbilical Cord | 1 |
| Hypertrophy | 5 |
| Funnel Shaped Stomach + Dilated Oesophagus | 1 |
| Short Forearm with Club Hand | 1 |
| PUJ Obstruction | 1 |
| Megacystis | 1 |
| Small Stomach | 1 |

Table 31 List Associated Abnormalities with Ectopic Kidneys.

|  |  |
| --- | --- |
| Associated Abnormality | Frequency *(n)* |
| Contralateral Hydronephrosis | 1 |
| Ipsilateral Hydronephrosis | 1 |
| Ureterocoele | 3 |
| Small Size | 4 |
| Cats Eye Syndrome (Ventricular Septal Defect; VSD, Hypoplastic Optic Nerve) | 1 |
| MCDK | 1 |
| Cleft Palate (Pierre Robin Syndrome)  Confirmed Genetic Abnormality | 1 |

Table 32 List Associated Abnormalities with Urinary Tract Obstruction.

|  |  |
| --- | --- |
| Associated Abnormality | Frequency *(n)* |
| Ascites (posterior urethral valves confirmed postnatally) | 1 |
| Bilateral Ureterocoele | 4 |
| Dilated Urethra | 1 |

Table 33 List Associated Abnormalities with Duplex Collecting System.

|  |  |
| --- | --- |
| Associated Abnormality | Frequency *(n)* |
| Ureterocoele | 7 |
| Renal Scarring | 1 |

Table 34 List Associated Abnormalities with Bilateral Renal Agenesis.

|  |  |
| --- | --- |
| Associated Abnormality | Frequency *(n)* |
| Renal fossa mass | 1 |
| bell shaped thorax | 1 |

Table 35 List Associated Abnormalities with Horseshoe Kidneys.

|  |  |
| --- | --- |
| Associated Abnormality | Frequency *(n)* |
| MCDK | 2 |
| Macrosomia | 1 |

### First Expert Panel Assessment/Review

Table-36 lists grading of different GUS abnormalities by the first expert panel.

*fMRI added information that fundamentally changed diagnosis in 19 foetuses (13%)*.

*Changed management and/or counselling in 23 foetuses (16%).*

*Added information without changing management and/or counselling in 40 cases (28%)*.

*Provided similar information to prenatal USS in 60 cases (42%)*.

Table 36 First Expert Panel Assessment of the Genitourinary cohort.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Anomaly | MCDK | B/L Agenesis | U/L agenesis | Ectopic | Horseshoe | Obstruction | Duplex | Miscellaneous | Total |
| Total  *(n)* | 35 | 17 | 24 | 20 | 4 | 21 | 13 | 8 | 142 |
| Changed diagnosis  *(n)*  *(%)* | 7  (20)% | *1*  *(5.8%)* | 1  (4%) | 2  (10%) | *0* | *7*  *(33%)* | 0 | 1  (12.5%) | 19  (13%) |
| Changed Mx/Cx  *(n)*  *(%)* | *2*  *(5.7%)* | *3*  *(17.6%)* | 3  (12.5%) | *3*  *(15%)* | *2*  *(50%)* | *6*  *(28.5%)* | 3  (23%) | 1  (12.5%) | 23  (16%) |
| Added info without change in Mx/Cx  *(n)*  *(%)* | 13  (37%) | *4*  *(23.5%)* | *7*  *(29%)* | *8*  *(40%)* | *0* | *3*  *(14%)* | 4  (30.7%) | 1  (12.5%) | 40  (28%) |
| Similar  *(n)*  *(%)* | *13*  *(37%)* | *9*  *(53%)* | *13*  *(54%)* | *7*  *(35%)* | *2*  *(50%)* | *5*  *(23.8%)* | 6  (46%) | 5  (62.5%) | 60  (42%) |
| Incorrect  *(n)* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

MCDK: Multi Cystic Dysplastic Kidneys, B/L: Bilateral, U/L: Unilateral, Mx: Management, Cx: Counselling.

MCDK: Multi Cystic Dysplastic Kidneys, B/L: Bilateral, U/L: Unilateral, Mx: Management, Cx: Counselling.

MCDK: Multi Cystic Dysplastic Kidneys, B/L: Bilateral, U/L: Unilateral, Mx: Management, Cx: Counselling.

MCDK: Multi Cystic Dysplastic Kidneys, B/L: Bilateral, U/L: Unilateral, Mx: Management, Cx: Counselling.

MCDK: Multi Cystic Dysplastic Kidneys, B/L: Bilateral, U/L: Unilateral, Mx: Management, Cx: Counselling.

MCDK: Multi Cystic Dysplastic Kidneys, B/L: Bilateral, U/L: Unilateral, Mx: Management, Cx: Counselling.

MCDK: Multi Cystic Dysplastic Kidneys, B/L: Bilateral, U/L: Unilateral, Mx: Management, Cx: Counselling.

MCDK: Multi Cystic Dysplastic Kidneys, B/L: Bilateral, U/L: Unilateral, Mx: Management, Cx: Counselling.

### Second Expert Panel Assessment/Review

**Overall:** Table-37 lists grading of different GUS abnormalities by the second expert panel.

*fMRI agreed with postnatal outcome in 44 cases (75.8%).* Prenatal *USS agreed with postnatal outcome in 31 cases (53%).*

*fMRI missed information without effect on outcome in 5 (8.6%) cases*. Prenatal *USS missed information without effect on outcome in 11 cases (19%).*

*fMRI missed information with effect on outcome in 5 cases (8.6%).* Prenatal *USS fMRI missed information with effect on outcome in 6 cases (10%)*.

*fMRI was incorrect in 4 cases (6.8%)*. Prenatal *USS was incorrect in 10 cases (17%).*

**First group (*f*MRI within 2 weeks):**

*fMRI agreed with postnatal outcome in 40 cases (77%), missed information without effect on outcome in 5 cases (9.6%), missed information with effect on outcome in 5 cases (9.6%) and was incorrect in 2 cases (3.8%). Prenatal USS agreed with postnatal outcome in 30 cases (57.7%), missed information without effect on outcome in 9 cases (17%), missed information with effect on outcome in 6 cases (11%) and was incorrect in 7 cases (13%).*

**Second group (*f*MRI ≥ 2 weeks):**

*fMRI agreed with postnatal outcome in 4 cases (66%) and was incorrect in 2 cases (33%). USS agreed with postnatal outcome in 1 case (16%), missed information without effect on outcome in 2 cases (33%) and was incorrect in 3 cases (50%).*

Table 37 Second Expert Panel Overall Assessment of the GUS cohort.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Anomaly | MCDK | | B/L Agenesis | | U/L Agenesis | | Ectopic | | Horseshoe | | Obstruction | | Duplex | | Miscellaneous | | Total | | |
| Total *(n)* | 20 | | 2 | | 8 | | 12 | | 3 | | 6 | | 5 | | 2 | | 58 | | |
| Scan | USS | *f*MRI | USS | *f*MRI | USS | *f*MRI | USS | *f*MRI | USS | *f*MRI | USS | *f*MRI | USS | *f*MRI | USS | *f*MRI | USS | *f*MRI |
| Agreed  *(n)*  *(%)* | 9  45% | 15  75% | 2  100% | 2  100% | 5  62.5% | 7  87.5% | 6  50% | 8  66.6% | 1  33% | 1  33% | 4  66.6% | 6  100% | 2  40% | 3  60% | 2  100% | 2  100% | 31  53% | 44  75.8% |
| Missed info no effect  *(n)*  *(%)* | 4  20% | 2  10% | 0 | 0 | 1  12.5% | 0 | 5  41.6% | 2  16.6% | 0 | 0 | 1  16.6% | 0 | 0 | 1  20% | 0 | 0 | 11  18.9% | 5  8.6% |
| Missed info with effect  *(n)*  *(%)* | 1  5% | 1  5% | 0 | 0 | 1  12.5% | 1  12.5% | 0 | 1  8% | 2  66.6% | 2  66.6% | 0 | 0 | 2  40% | 0 | 0 | 0 | 6  10% | 5  8.6% |
| Incorrect  *(n)*  *(%)* | 6  30% | 2  10% | 0 | 0 | 1  12.5% | 0 | 1  8% | 1  8% | 0 | 0 | 1  16.6% | 0 | 1  20% | 1  20% | 0 | 0 | 10  17% | 4  6.8% |

MCDK: Multi Cystic Dysplastic Kidneys, B/L: Bilateral, U/L: Unilateral.

MCDK: Multi Cystic Dysplastic Kidneys, B/L: Bilateral, U/L: Unilateral.

MCDK: Multi Cystic Dysplastic Kidneys, B/L: Bilateral, U/L: Unilateral.

MCDK: Multi Cystic Dysplastic Kidneys, B/L: Bilateral, U/L: Unilateral.

MCDK: Multi Cystic Dysplastic Kidneys, B/L: Bilateral, U/L: Unilateral.

MCDK: Multi Cystic Dysplastic Kidneys, B/L: Bilateral, U/L: Unilateral.

MCDK: Multi Cystic Dysplastic Kidneys, B/L: Bilateral, U/L: Unilateral.

MCDK: Multi Cystic Dysplastic Kidneys, B/L: Bilateral, U/L: Unilateral.

## SKELETAL

### Overall results:

Total of 43 cases with skeletal anomalies were included in this cohort including 12 SCT cases (27.9%), 14 miscellaneous cases (32.5%), 10 skeletal dysplasia cases (23%) and 7 scoliosis cases (16%). Table-38 shows detailed description of the skeletal anomalies with their frequency in this study. Associated abnormalities were present in 16 cases (37%): 5 SCT cases (31%), 5 skeletal dysplasia cases (31%), 3 scoliosis cases (18.7%) and 3 miscellaneous cases (18.7%). Tables-39,40,41,42 list associated abnormalities and their frequency in the skeletal system cohort. Out of 43 skeletal cases, 13 had postnatal outcome and obtained scores by the second expert panel (30%). 2 cases had neonatal deaths, 2 intrauterine deaths and 1 intrapartum death.

Table 38 List Types of Skeletal Abnormalities included in the Study.

|  |  |
| --- | --- |
| Skeletal Anomalies | Frequency *(n)* |
| Sacrococcygeal Teratoma | 12 |
| Skeletal Dysplasia | 10 |
| Scoliosis | 7 |
| Miscellaneous | 14 |
| Total | 43 |

Table 39 Lists Associated Abnormalities with Sacrococcygeal Teratoma.

|  |  |
| --- | --- |
| Associated Abnormality | Frequency *(n)* |
| Neuropathic Bladder and Bowel at 4yrs age (confirmed) | 1 |
| Spinal Dysraphism (confirmed) | 1 |
| Suspected Currarino Syndrome | 1 |
| Subcutaneous Oedema and missing left rib (confirmed) | 1 |
| Bilateral Hydronephrosis | 1 |

Table 40 List Associated Abnormalities with Skeletal Dysplasia.

|  |  |
| --- | --- |
| Associated Abnormality | Frequency *(n)* |
| Lung Hypoplasia | 3 |
| Hydrops | 1 |
| Periventricular Cysts | 1 |
| Club Feet | 1 |
| Subcutaneous Oedema | 2 |

Table 41 List Associated Abnormalities with Scoliosis.

|  |  |
| --- | --- |
| Associated Abnormality | Frequency *(n)* |
| Dextrocardia and Hemivertebra | 1 |
| Segmentation Anomalies | 1 |
| Anal Atresia | 1 |

Table 42 List Associated Abnormalities with Miscellaneous cases.

|  |  |
| --- | --- |
| Associated Abnormality | Frequency (n) |
| Lung Hypoplasia and Subcutaneous Oedema with Amyotrophic Myopathy | 1 |
| Cord Tethering with Diastematomyelia | 1 |
| Cord Tethering with Lipomyelomeningiocele | 1 |

### First Expert Panel Assessment/Review

Table-43 lists grading of different skeletal abnormalities by the first expert panel.

*fMRI added information that fundamentally changed diagnosis in 12 foetuses (28%):* 8 miscellaneous cases (66.6%), 2 SCT cases (16.6%) and 2 scoliosis cases (16.6%).

*Changed management and/or counselling in 7 foetuses (16%):* 3 SCT cases (42.8%), 3 scoliosis cases (42.8%) and 1 skeletal dysplasia case (14%).

*Added information without changing management and/or counselling in 9 cases (21%)*: 4 skeletal dysplasia cases (44%), 2 SCT cases (22%), 2 miscellaneous cases (22%) and 1 scoliosis cases (11%).

*Provided similar information to prenatal USS in 15 cases (34.8%):* 5 SCT cases (33.33%), 5 skeletal dysplasia cases (33%), 4 miscellaneous cases (26.6%) and 1 scoliosis case (6.6%).

Table 43 First Expert Panel assessment of the Skeletal cohort.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Anomaly | SCT | Skeletal Dysplasia | Scoliosis | Miscellaneous | Total |
| Total *(n)* | 12 | 10 | 7 | 14 | 43 |
| Changed diagnosis  *(n)*  *(%)* | 2  (16.6%) | *0* | 2  (28.5%) | 8  (57%) | 12  (27.9%) |
| Changed Mx/Cx  *(n)*  *(%)* | *3*  *(25%)* | *1*  *(10%)* | 3  (42.8%) | 0 | 7  (16%) |
| Added info without change in Mx/Cx  *(n)*  *(%)* | 2  (16.6%) | *4*  *(40%)* | *1*  *(14%)* | 2  (14%) | 9  20.9% |
| Similar  *n)*  *(%)* | *5*  *(41.6%)* | *5*  *(50%)* | *1*  *(14%)* | 4  (28.5%) | 15  34.8% |
| Incorrect  *(n)* | 0 | 0 | 0 | 0 | 0 |

SCT: Sacrococcygeal Teratoma, Mx: Management, Cx: Counselling

### Second Expert Panel Assessment/Review

**Overall:** Table-44 lists grading of different skeletal abnormalities by the second expert panel.

*fMRI agreed with postnatal outcome in 12 cases (92%)*. Prenatal *USS agreed with postnatal outcome in 9 cases (69%)*.

*fMRI did not miss information without effect on outcome*. Prenatal *USS missed information without effect on outcome in 2 cases (15%)*.

*fMRI missed information with effect on outcome in 1 scoliosis case (7.7%). Prenatal USS missed information with effect on outcome in 1 scoliosis case (7.7%)*.

*fMRI was not scored to be incorrect in any skeletal case*. Prenatal *USS was incorrect in 1 SCT case (7.7%).*

**First group (*f*MRI within 2 weeks):**

*fMRI agreed with postnatal outcome in 11 cases (91.6%) and missed information with effect on outcome in 1 case (8%). Prenatal USS agreed with postnatal outcome in 8 cases (66%), missed information without effect on outcome in 2 cases (16%), missed information with effect on outcome in 1 case (8%) and was incorrect in 1 case (8%).*

**Second group (*f*MRI ≥ 2 weeks):**

*Only one case was included in this group and both scans agreed with postnatal outcome.*

Table 44 Second Expert Panel Overall Assessment of the Skeletal cohort.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Anomaly | SCT | | Skeletal Dysplasia | | Scoliosis | | Miscellaneous | | Total | |
| Total *(n)* | 5 | | 4 | | 2 | | 2 | | 13 | |
| Scan | USS | *f*MRI | USS | *f*MRI | USS | *f*MRI | USS | *f*MRI | USS | *f*MRI |
| Agreed  *(n)*  *(%)* | 3  (60%) | 5  (100%) | 3  (75%) | 4  (100%) | 1  (50%) | 1  (50%) | 2  (100%) | 2  (100%) | 9  69% | 12  92% |
| Missed info no effect  *(n)*  *(%)* | 1  (20%) | 0 | 1  (25%) | 0 | 0 | 0 | 0 | 0 | 2  (15%) | 0 |
| Missed info with effect  *(n)*  *(%)* | 0 | 0 | 0 | 0 | 1  (50%) | 1  (50%) | 0 | 0 | 1  (7.6%) | 1  (7.6%) |
| Incorrect  *(n)*  *(%)* | 1  (20%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1  (7.6%) | 0 |

SCT: Sacrococcygeal Teratoma.

SCT: Sacrococcygeal Teratoma.

SCT: Sacrococcygeal Teratoma.

SCT: Sacrococcygeal Teratoma.

SCT: Sacrococcygeal Teratoma.

SCT: Sacrococcygeal Teratoma.

SCT: Sacrococcygeal Teratoma.

SCT: Sacrococcygeal Teratoma.

## NECK

### Overall results:

Total of 13 cases with neck abnormalities were included in this cohort including 3 teratomas (23%), 5 lymphangiomas (38%), 1 cystic hygroma (7.7%), 1 rhabdomyosarcoma (7.7%), 1 Kaposi’s lymphangioma (7.7%) and 2 haemangio-lymphangioma (15%). Table-45 shows a summary of neck abnormalities included in this study. No associated abnormalities were found. Out of 13 neck cases, 6 had postnatal outcome and obtained scores by the second expert panel (46%). 2 babies died: 1 neonatal and 1 intrapartum death.

Table 45 List Types of Neck abnormalities included in the Study.

|  |  |
| --- | --- |
| Neck Anomalies | Frequency |
| Rhabdosarcoma | 1 |
| Teratoma | 3 |
| Kaposi’s Lymphangioma | 1 |
| Haemangio-lymphangioma | 2 |
| Cystic Hygroma | 1 |
| Lymphangioma | 5 |
| Total | 13 |

### First Expert Panel Assessment/Review

*fMRI added information that fundamentally changed diagnosis in 1 lymphangioma case (7.7%).*

*fMRI changed management and/or counselling in 5 foetuses (38%)* including 2 teratoma cases, 2 lymphangioma cases and 1 haemangio-lymphangioma case.

*Added information without changing management and/or counselling in 3 cases (23%)* including 1 rhabdomyosarcoma case, 1 teratoma case and 1 Kaposi’s lymphangioma case.

*Provided similar information to prenatal USS in 4 cases (30.7%)* including 2 lymphangioma cases, 1 haemangio-lymphangioma case and 1 cystic hygroma case.

### Second Expert Panel Assessment/Review

*Both imaging modalities agreed with postnatal outcome in all 6 cases*.

*All cases with postnatal outcome were in the first group in which fMRI was done within 2 weeks.*

## MISCELLANEOUS

### Overall results:

Total of 23 cases with miscellaneous abnormalities were included in this cohort including 12 hydrops cases (52%). The other 11 miscellaneous cases are listed in Table-46. Associated abnormalities were found in 5 hydrops fetalis cases (21.7%). Table-47 lists associated abnormalities with hydrops and their frequency. Out of 23 miscellaneous cases, 6 had postnatal outcome and obtained scores by the second expert panel (26%). 3 babies had neonatal deaths, 2 intrauterine deaths and 1 TOP.

### First Expert Panel Assessment/Review

*fMRI added information that fundamentally changed diagnosis in 2 foetuses (8.7%*) including a foetus referred with increased nuchal thickening and a foetus with difficult USS assessment.

*Changed management and/or counselling in 5 foetuses (21.7%)* including 4 hydrops fetalis cases and 1 probable cytomegalovirus infection case.

*Added information without changing management and/or counselling in 7 cases (30%)* including 4 hydrops cases, 1 micrognathia case, 1 case with history of cleft palate, 1 retroplacental bleed case.

*Provided similar information to prenatal USS in 9 cases (39%)* including 5 hydrops fetalis cases, 1 axillary lymphangioma case, 1 bilateral cleft lips case, 1 IUFD (Intra Uterine Foetal Death) case, 1 case with history of anophthalmia.

### Second Expert Panel Assessment/Review

*fMRI agreed with postnatal outcome in 5 Hydrops fetalis cases (83%). Prenatal USS agreed with postnatal outcome in 4 Hydrops fetalis cases (66.6%)*.

*fMRI missed information without effect on outcome in 1 Bilateral Cleft Lip case (16.6%). USS missed information without effect on outcome in 2 cases (33%)*: 1 Bilateral Cleft Lip case and 1 Hydrops fetalis case.

*All cases with postnatal outcome were in the first group in which fMRI was done within 2 weeks*.

Table 46 List Miscellaneous Abnormalities included in the Study.

|  |  |
| --- | --- |
| Miscellaneous anomalies | Frequency |
| Hydrops | 12 |
| Retroplacental Bleed | 1 |
| Cannot Visualise Foetus on USS - Normal Foetus | 1 |
| Family History of Cleft Palate | 1 |
| Bilateral Cleft Lips and Palate | 1 |
| IUFD (Intra Uterine Foetal Death) | 1 |
| Micrognathia | 1 |
| Family History of Anophthalmia - normal Foetus | 1 |
| Left Axillary Lymphangioma | 1 |
| Family history of Anophthalmia | 1 |
| Family history of Cleft palate | 1 |
| Subtle Abnormalities (Abnormal Brain, poorly filled stomach, Large umbilical Vein) | 1 |
| Total | 23 |

Table 47 List Associated Abnormalities with Hydrops Fetalis.

|  |  |
| --- | --- |
| Associated Abnormality | Frequency |
| Ventriculomegaly, Bowel calcification, Lung Hypoplasia | 1 |
| Pulmonary Hypoplasia | 7 |
| ASD (Atrial Septal Defect) | 1 |
| Villamentous Cord | 1 |
| Hyper Coiled Umbilical Card | 1 |

# Chapter 5

# DISCUSSION

At the time of writing this thesis, this was the largest both retrospective and prospective study to assess the clinical value of *f*MRI in only foetal anomalies of non-CNS origin with and without postnatal confirmation. Similar studies done in the past were either too small to produce significant effects or lacked postnatal confirmation. Also, most of the previous studies included both CNS and non-CNS foetal anomalies. This study confirmed with and without postnatal confirmation that *f*MRI provided valuable diagnostic information to prenatal USS when evaluating foetal non-CNS abnormalities. Prenatal USS remains without a doubt the standard modality in the screening of all foetal abnormalities, but *f*MRI can complement prenatal USS role particularly when it is uncertain or its performance is reduced by other factors.

In this study, only first *f*MRI scans and referral USSs (done by the most experienced operator in a tertiary hospital) were included. In most of the cases, patients had more than one prenatal USS prior to having their first *f*MRI. However, those USSs did not warrant *f*MRI referral at that time. This could be due to many reasons such as inability to visualise any foetal abnormalities at that time either because simply there were not any or inexperienced operator at that scan, some pathologies manifest in later gestational age, change in appearance of pathologies in subsequent scans, involvement of other structures, visualisation of more findings in subsequent scans that may suggest syndromic features.

Therefore, multiple prenatal USSs could have led to the final diagnoses suggested by the referring USS. One could argue that we should perform prenatal USS on little older foetuses when it is clearer to visualise foetal anatomy to provide more information about pathologies thus avoiding *f*MRI referrals however the earlier the information can be obtained the better it is for management and decision making. Parents find any delay between US and MRI difficult and prolonging this time adds to their stress. Whilst this could be true for some cases, the majority of cases would benefit from *f*MRI not only to reach diagnoses but also to provide more valuable information that could determine management plans e.g. in cases with CDH. Furthermore, some pathologies are harder to detect with advancing gestational age as we can see later when we discuss the effect of GA on diagnostic accuracy of both modalities. In many cases, not having a *f*MRI would lead to a serial prenatal USS follow up with more frequent foetal medicine appointments. This is especially important in cases where prenatal USS is uncertain or when less harmful abnormalities mistaken by prenatal USS with more serious pathologies.

The argument could be true for *f*MRI as well. That it might be more useful to perform *f*MRI earlier or later in pregnancy but then we will have the same counter argument as for prenatal USS.

When is the best time to perform *f*MRI in pregnancy is highly controversial. Whilst *f*MRI is not recommended by the MAHRA in the first trimester due to safety concerns, it can be done at second or third trimesters. Our study results showed better results for both imaging techniques in older foetuses with exception to abdominal cohort where they performed better amongst the younger foetuses. Obtaining information late in pregnancy might not be ideal for patients, families and clinicians. Parents could go through significant amount of stress throughout most of their pregnancies and even more stressed if they were aware of other investigations that could be performed which might add important information to what they already had.

Also, this information could be a “game changer” for many cases. Parents as well as clinicians should have enough time to think about management options available. In some cases, such as CDH with significantly low lung volumes, TOP option is recommended. In other cases, the pathway of antenatal routine follow-up, mode of delivery, timing and place of delivery could be significantly decided upon as a result of *f*MRI results. Normally, routine antenatal care for healthy women involves sharing and discussing management plans including mode, place and time of delivery with parents. This should not be different for pregnancies complicated with foetal abnormalities. Prenatal USS and *f*MRI can together help provide them with the opportunity of having less stressful pregnancies.

Finally, by conducting this study which reflects today’s actual clinical practice, we attempt to provide some answers for those arguments.

Overall, this study confirmed the usefulness of *f*MRI as an adjunct to prenatal USS in the imaging of foetal non-CNS abnormalities. The diagnostic accuracy of *f*MRI in detection of overall foetal non-CNS abnormalities was 87.7% compared to 69.6% for prenatal USS. *f*MRI provided 18% more accurate diagnoses than prenatal USS. These values are lower for both scans than that reported by Rodríguez *et al.* (2020) in which diagnostic accuracy was 92% for *f*MRI and 90% for prenatal USS. However, their study included CNS pathologies as well. In fact, the majority of the cases included in their study had CNS pathologies which might explain the higher values in their results. The present study also confirms the added value of *f*MRI in providing additional information to prenatal USS. It added information in 21.5% in which it changed prenatal USS diagnoses or management and/or counselling in 7.8% of the cases. These findings are in line with Amini *et al.* (2011) study in which they found that *f*MRI provided additional information to prenatal USS in 32% of their cases which *f*MRI changed the management in 5% of the cases. *f*MRI had better performance in our study by providing almost 3% more useful information compared to Amini’s *et al.* study, 7.8% and 5%, respectively. However, one limitation of their study was the small size of the study population with only 63 patients with different non-CNS abnormalities. Also, their study only evaluated *f*MRI during the second trimester whereas our study included foetuses in both second and third trimesters. It has been also reported in the literature that *f*MRI contributed to prenatal USS by providing valuable information in which diagnoses or management had been altered in 39% of the cases included in one study (Kul *et al.*, 2012). That study too involved all foetal anomalies in which CNS pathologies accounted for >40% of the cases. However, analysis of their data shows that *f*MRI added information in 27% of foetuses with non-CNS abnormalities which, although slightly higher, is in keeping with our findings.

Our results are lower than those reported by Verburg *et al.* (2015) in their study to investigate the additional value of *f*MRI in the assessment and management of 257 foetuses with abnormal findings on prenatal USS, in which they seen additional findings with *f*MRI in 28% of the cases that changed diagnoses in 21%, prognosis in 19% and perinatal management in 8%. However, similar to Rodríguez *et al.* (2020) study, their higher results might be also explained by the fact that more than 70% (*n*=182) of their cases were CNS pathologies, for which *f*MRI clinical value has been already established (Griffiths *et al.*, 2017). Also, there is a lack of a definite consensus on which additional information to be considered as clinically relevant. It is the clinical relevance of the added information that show some disagreement between our results and that of Verburg *et al.’* (2015). For instance, 11% of their cases were referred for *f*MRI only for assessment of foetal lungs, of which 79% were CDH cases with the main indication for *f*MRI is measurement of total foetal lung volumes to predict survival. Our second expert panel regarded >13% of the added information as less valuable and would not change management and/or diagnoses. There was no scoring category in their study for less valuable or clinically irrelevant information for us to make a full comparison between results.

Time delay between both scans was of less significance to *f*MRI with almost similar results for both first group <2wks time delay and second group >2wks time delay with 87% and 89% accurate diagnoses, respectively. Prenatal USS was more affected by the time delay with 70.8% for the first group (<2kws delay) and 47% for the second group (>2wks delay). It also missed information and gave incorrect diagnoses in higher rate than for the first group. However, the small size *(n=55)* of the second group (>2wks delay) might reduce the significance of our findings.

There are no formal studies in the literature describing the effect of time delay between prenatal USS and *f*MRI on their performance. It has been accepted in the clinical practice today that a limit of 2 weeks should be adhered to. However, time delay will affect GA in that the more the time delay the advanced the GA will be which in turn might affect scan results. Foetuses in the second group in our study had their *f*MRI 2wks or more later after having their prenatal USS which means changes could have occurred between the prenatal USS and *f*MRI that would have been visible if the prenatal USS was done at the time of the *f*MRI. It could be argued that the delay allowed *f*MRI to be better than the USS. Our ideal was to divide the study cohort according to the gap period between the scans in each category sub-cohort from early on in the study. However, after subdividing the cohort into two groups according to the gap period, we found out that there is no significant difference in the overall results between the two groups. Also, the second group with gap period >2 weeks had only a small number of patients *(n=55)*, so it seemed pointless further subdividing them into 6 more groups, compared to the first group *(n=426)* with gap period <2 weeks. Therefore, analysis of our data based on the gap period ended with the overall results and was not implemented to the sub-cohorts (six groups of body areas).

This study also split the cohort into 2 subgroups according to GA and confirmed that *f*MRI provides more diagnostic accuracy when performed on older foetuses. Its diagnostic accuracy increased by > 7% (92%) when performed on Group 2 with GA >23 GW compared to 84.5% for Group 1 with GA <23 GW. Varying GA between the two groups was of less significance on prenatal USS. Advanced GA slightly enhanced prenatal USS diagnostic accuracy by 3% in Group 2 (Group 1=69%, Group 2=72%). *f*MRI might be of more clinical significance when used as an adjunct to prenatal USS in late second or third trimesters. However, this leaves the diagnosis and any management changes to late in pregnancy and is not the preferred choice of many parents and clinicians. In younger GA, the foetus is small and more mobile which can affect image quality on *f*MRI. Higher performance of *f*MRI during late trimesters has been reported in previous studies; *f*MRI provided 83% accurate diagnoses whereas prenatal USS provided 62% in one study that evaluated the benefits of *f*MRI compared to prenatal USS in foetal imaging in 22 pregnancies, all of which except for one were in third trimester (Poutamo *et al.*, 2000). Another study of 32 foetuses between 23 and 38 GW with GI abnormalities described *f*MRI as more informative than prenatal USS during this GA. Evaluating normal foetal anatomy by *f*MRI has also been reported to be superior to prenatal USS during the late stages of the pregnancy (Hubbard and States, 2001). However, Rodrigues *et al.* (2020) found no significant differences in the diagnostic accuracy of *f*MRI either before or after 24 GW.

We believe that the first expert panel assessment in our study reflects the actual clinical practice where foetal medicine experts use scan results alongside with their clinical experience in managing pregnancies complicated with foetal abnormalities. Usually, clinicians have confidence in the results of prenatal scans especially if they have made the referrals themselves. The likelihood of them acting upon the scans is even higher when both scans give similar information. In most cases, it is only possible after delivery to either confirm or refute prenatally suspected diagnoses and clinicians plan the course of management according to the available information prior to delivery. This study confirmed based only on prenatal scan results that *f*MRI could have changed prenatal USS diagnoses or course of management and/or counselling in 40.5% (*n=195)* and provided additional less valuable information in another 23% of the cases included in our study (*n=113)*. Our findings also prove that *f*MRI is usually blindly regarded as a superior technique of imaging than prenatal USS in the clinical practice. Generally, most people feel that MRI must somehow be superior to USS because it is usually more expensive, and the images obtained seem to be more elaborate. It seems that that this feeling is also shared by healthcare professionals. It is true that clinicians regard MRI as the modality of choice (supported by evidence based medical practice) when it comes to imaging certain body structures such as the head, spine, joints, breasts and soft tissues in the adult and paediatric populations but it is also true that they regard other imaging modalities such as CT scans and USS as modalities of choice when it comes to imaging bones, lungs and intra-abdominal organs.

Using MRI to image the foetus on the other hand, has only been around for about thirty years, being used routinely in clinical practice only in the last ten years and is limited only to some parts of the world. Therefore, without established evidence, regarding *f*MRI as superior to prenatal USS in imaging all foetal body structures is a misconception. This misconception was confirmed to be incorrect as shown by the disagreement between our first and second expert panels. Prenatal USS provided similar information to *f*MRI in 50% more cases than it was thought by the first panel. It is true that these results were different for each cohort of the study and it was expected and understandable for some of them to have higher results due to certain functions that *f*MRI provides such as lung volume measurements and DWI but even with that in mind we think the results are still significant. Based on this mismatch between the results of the first and second expert panels, there might be a consequence on the prenatal care provided to the patients in terms of planning optimal course of management and counselling. However, our study was conducted in a single centre and only one Foetal medicine expert included in the first panel and one Neonatal medicine expert in the second panel, although both had more than 15 years’ experience. In the clinical practice, clinicians might view certain information differently and many clinicians view some information as significant but will be viewed as less valuable by others. The first expert panel was blinded to postnatal outcome reference data, and it appears they valued *f*MRI results higher than prenatal USS. This could be due to the above-mentioned misconception, experience or the lack of full understanding of the actual benefits of MRI in imaging the foetus. The second expert panel on the other hand, had access to postnatal outcome reference data necessary for them to score scans. They already had the advantage of knowing the final outcome which might have led them to believe that the need for *f*MRI could have been avoided, thus unjustifiably valued *f*MRI lower than prenatal USS. The need-to-know factor could have played a role here. Clinicians would try to evaluate cases to the best of their abilities to provide optimal healthcare to their patients and to avoid consequences. They need to be certain about their diagnoses by finding supporting information to either confirm or refute their suspicion. Our first expert panel were put in a setting that reflects routine clinical practice where investigations such prenatal USS and *f*MRI are performed to reach diagnoses. They are expected to act upon the results and determine healthcare plans for their patients.

In some cases, where no confident diagnoses can be reached by prenatal USS due to known established difficulties that USS faces such as oligohydramnios, maternal obesity or functional assessments, it is acceptable to reach for the helping hand of *f*MRI. In other cases however, the lack to reach confident diagnoses using prenatal USS alone could be due to lack of experience, in which cases, seeking information from *f*MRI will provide clinicians the confidence they need (two opinions). Problems that might arise are that when *f*MRI results point toward completely different diagnoses. The choice will then be entirely upon the managing clinicians. Theoretically, if clinicians place more confidence on MRI results, then they will be confirming the misconception about MRI. But in routine practice, this conflict between prenatal USS and *f*MRI will usually lead to more scans (USSs and *f*MRI) and further investigations. By conducting this study, we aim to provide statistical data supporting the benefits of *f*MRI when used as an adjunct to prenatal USS in imaging of foetal body structures in a clinical setting.

Time delay between both scans did not significantly affect *f*MRIperformance. It provided valuable information in 40% (similar to overall result) of cases when *f*MRI was performed within 2wks of prenatal USS and was slightly lower than that with 38% when *f*MRI performed after 2wks.

It is expected that all cases referred for *f*MRI are imaged on the supposition that *f*MRI would be of benefit. Routinely, when clinicians need more information regarding a pathology or could not reach diagnoses based on one investigation, they usually request the next available investigation which might provide them the information they seek. Whether or not *f*MRI referrals are all justifiable remains debatable. One might argue that some of the cases included in this study did not need *f*MRI in the first place and reaching confident diagnoses with all information needed could possibly be achieved with prenatal USS alone given different, more experienced and well-trained USS operators at that time. Several published studies in the literature support the added value of *f*MRI when imaging certain foetal pathologies such as CNS abnormalities, CDH and GI abnormalities (Amini *et al.*, 2011, Rodríguez *et al.*, 2020, Griffiths *et al.*, 2017, Ramdass *et al.*, 2021). Referring clinicians have some awareness of the added value of *f*MRI but perhaps not all of them have the full understanding of what foetal structures would benefit most from *f*MRI. Because *f*MRI is relatively new in clinical practice, research conducted in its field is still in its base apart from those looking at its value in imaging foetal CNS and lungs. However, it should be also clear that even just the confirmation of prenatal USS findings by *f*MRI and the exclusion of other pathologies is of clinical relevance as it provides clinicians with sufficient diagnostic confidence to appropriately counsel parents and to prognosticate the future quality of life of the newborns.

The imaging expertise of the persons reporting the scans whether for prenatal US or *f*MRI, is of an important value in determining the results of both scans. Because *f*MRI is only performed in tertiary centres, scans are expected to be reported by more experienced radiologists and comparison of their results with prenatal USS performed by less experienced personnel is not ideal. To avoid this mismatch in expertise, all our study participants had prenatal USSs performed in our tertiary centre prior to *f*MRI. One might argue that the superiority of *f*MRI shown in this study could be due to better imaging expertise of the radiologist reporting *f*MRI compared to the imaging expertise to those reporting prenatal USS. This could be true for a minority of our cases were USS examinations and interpretation could have been performed better e.g. missing a poorly filled stomach or a misdiagnosis of subpulmonary sequestration. USS is highly operator dependent imaging modality and requires skills that take time to acquire and therefore they must be undertaken by well-trained and experienced practitioners and, even then, optimal scans may not be obtained in all cases.

However, all prenatal USS in our study were performed by the most experienced operators with vast experience in the field and unlike *f*MRI, in which all scans were reported by the same radiologist, prenatal USSs were interpreted by many different reporters and no pattern of less accurate reports were observed from any of these reporters. Therefore, it is highly unlikely for the results we have shown in this study to be only due to USS practitioners’ level of expertise. Finally, this study was designed to reflect the actual clinical practice in a tertiary centre, and it reflects the routine healthcare undertaken for patients using this service.

It is difficult to compare experience level between different speciality experts using different scanning methods. However, we believe that development of more robust training programmes on interpretation of obstetric USSs and *f*MRIs will bring imaging interpretation into higher levels of accuracy. These programmes must also ensure that scan interpretation skills get passed to future trainee interpreters.

Before the start of this study, it was thought and anticipated that all the cases will be collected prospectively. In the research proposal for this study, based on experience in the subject, we anticipated to recruit about 400 cases prospectively over 3 years allowed for the study. It became evident during the first year that our anticipation would not be met as we realised that for some unknown reasons less cases with non-CNS abnormalities were referred. Furthermore, it took about ten months to sort study ethics and research passport from the relevant health authorities. This led to the retrospective review. There was no difference whatsoever between collecting data retrospectively or prospectively for this study and that would have not changed the results. Therefore, we decided to collect all the cases present in the master database since November 2011 to September 2017. Meanwhile, the prospective recruitment of the referred cases continued throughout the study.

Gradings of scan results for this study were performed in an expert panel approach in which, along with the principal investigator and a radiologist, a foetal medicine expert was included in the first panel and a neonatologist in the second panel. Scans were reviewed and discussed by these panels until they reached an agreement on scores, therefore eliminating interobserver variations.

Scans were not reviewed by either the same panel (intra-observer variation) or second different panel (interobserver variation) for a second grading. This could be a limitation of this study. Running scan results by a different panel for a second opinion might have changed the results, as clinicians might view information differently and their expertise in the field will have a significant effect.

All follow up cases were excluded from the study and only the initial referral was included. Fifty-one cases had follow-up *f*MRIs (48 retrospective, 3 prospective). Almost all cases had follow-up prenatal USS either as part of their antenatal routine or as clinically indicated. As some conditions evolve during pregnancy, some findings could be either easier or harder to detect on both imaging modalities. Information obtained from imaging at that point of time would indicate the management pathway for each pregnancy which might include more or less follow-up imaging. The majority of our cases did not require follow up *f*MRIs either suggested by the radiologist nor the foetal medicine expert referrer which could mean definite satisfactory information were provided to both. Furthermore, scan results of both modalities would have been affected by the initial results of previous scans. One could argue that follow up prenatal USS results would have been based on *f*MRI, results which is the main reason *f*MRI is performed, to offer a helping hand to prenatal USS. This study was designed to reflect clinical practice.

Multiple pregnancies were also excluded from this study due to the additional complexities of these cases.

Some cases had insufficient data for the first expert panel to reach decisions on definite scores and therefore they had to be excluded. This was different to postnatal outcome data. Cases with insufficient postnatal outcome data were scored by the first panel but they were not scored by the second panel and they were not excluded from the study as we think their result would be of significance.

Generally, recruitment was very successful among the patients, only one mother refused to take part in the study.

## CHEST

The present study confirmed the added value of *f*MRI in evaluating foetal chest abnormalities with an overall diagnostic accuracy of 95.6*%* *(n=66)*, more than fifteen percent higher than prenatal USS (79.7%, *n=55*). Its best diagnostic performance was achieved among older foetuses (>23 GW) with an accuracy that reached 100% (USS=85%). However, both scans’ results were enhanced by the increasing GA. In fact, the highest diagnostic accuracy for prenatal USS was achieved in the chest cohort among the four major cohorts (chest, GUS, abdomen and skeletal). Better performance of *f*MRI in older foetuses has been previously reported in the literature (Levine *et al.*, 2003; Amini *et al.*, 2011; Cannie *et al.*, 2008). Our findings are in agreement with Kul *et al.* study in which they found *f*MRI in total agreement with postnatal outcome data in all 16 cases with chest abnormalities included in their study whereas prenatal USS could only find 11 correct diagnoses (68%). Our findings were slightly lower for *f*MRI of those reported in Rodrigues *et al.* study in which *f*MRI correctly diagnosed 34 out of 37 (92%) but almost similar to their prenatal USS results with 33 correctly diagnosed out of 37 (89%) thoracic pathologies.

*f*MRI provided additional information to prenatal USS in 17% of all chest abnormalities confirmed postnatally that had an effect on patient’s care in 5.8% and corrected prenatal USS in 1.4%. These results are much lower than reported by Rodrigues *et al.* (56.8%with effect on management/prognosis and changed prenatal USS diagnosis in 2.7%) but they have explained their high results of being mainly due to the effect that *f*MRI had on evaluating CDH cases by measuring lung volumes and determining liver location. Our second expert panel did not take this advantage of *f*MRI (lung volumes) into account when assessing our patients which might explain our results for the chest cohort. The neonatologist in the second expert panel did not value the lung volume information, whilst other clinicians, neonatologists and foetal medicine experts use them for prognosis and counselling prior to birth. Lung volumes, whilst predictive of outcome, do not change neonatal management hence this neonatologists grading. The results of Rodrigues *et al*. do correlate to our first expert panel results with 64% extra information added by *f*MRI compared to US, that had an effect (management or counselling) in 44% of cases.

*f*MRI correctly diagnosed 33 out of 34 CDH cases (97%) (prenatal USS=85%) confirmed postnatally and missed information without effect on management and/or counselling in only one case. It was also scored by first expert panel to could have changed diagnoses, management and/or counselling in 98% of all CDH cases included in this study with and without postnatal outcome reference data. The latter high value produced by our first expert panel is mainly due to *f*MRI advantage in measuring lung volumes and evaluating level of liver herniation enabling determination of neonatal prognosis. The role of *f*MRI in evaluating CDH has been well established in the literature. It has the aforementioned advantages in addition to accurately detecting the presence of hernia, depicting herniated intrathoracic abdominal organs, evaluating signal intensity of the lungs and detecting the presence of pulmonary hypoplasia. It also has better tissue contrast allowing for superior characterisation of the surroundings, used to evaluate CDH contents and other thoracic anomalies such as bronchogenic cysts and CPAMs (Levine *et al.*, 2003)(Hubbard and States, 2001) (Jani *et al.*, 2008). *f*MRI was also found to be correct in 22 out of 24 (91.6%) confirmed cases of CPAM (USS=83%). The first expert panel found that *f*MRI could have changed diagnoses, management and/or counselling in 26.8% of all CPAM cases included in the study. CPAM lesions had markedly high signal intensity than remaining normal lung parenchyma on *f*MRI which also showed greater performance than prenatal USS in determining size and cystic type of CPAMs in addition to detecting the presence of feeding vessels.

Also in agreement with our findings, a study by Levin *et al.* that evaluated 74 foetuses with thoracic abnormalitiesincluding 18 CDH, 8 CPAM, 8 pleural effusions, 4 BPS cases all confirmed postnatally, found that *f*MRI provided 38% of additional information to prenatal USS and changed patient’s care in 8%. In their study both scans equally correctly detected the presence of CDH except in one foetus where *f*MRI corrected prenatal USS by detecting an eventration instead of CDH. They used an additional confirmatory prenatal USS in their study which might explain their enhanced results for prenatal USS in providing similar findings in CDH cases. In another study that evaluated the effect of *f*MRI on management of 24 foetuses with complex foetal chest disorders, it was found that *f*MRI directly influenced foetal care in 17% of the cases and provided less valuable information in another 33%. Further supported in a study by Amini *et al.* (2011) that found that *f*MRI added information in all 6 cases of CDH included, correctly verified prenatal USS suspicion of CHAOS in 2 cases and correctly diagnosed a case of CPAM where prenatal USS was uncertain. Hubbard *et al.* (1999)found similar results for *f*MRI in their study of 18 foetuses with suspected chest lesions on prenatal USS, they found that *f*MRI correctly diagnosed 17 pathologies (94%) (prenatal USS= 50%) confirmed postnatally either by surgery or autopsy. They found that *f*MRI correctly diagnosed all CDH, BPS, foregut cyst, lung atresia, tracheal atresia and 8 out of 9 CPAM cases (88%) and misdiagnosed one foetus with BPS as a CPAM.

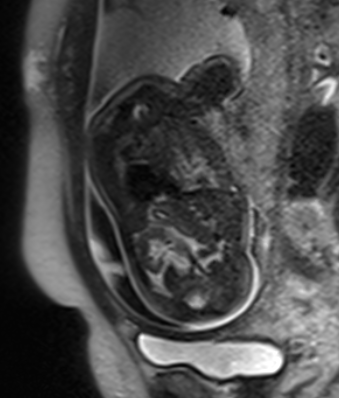
### We found that *f*MRI added information in the following cases:

In one case that died 24 hours after delivery, diagnosed postnatally by chest x-ray and USS with right CDH with mediastinal shift, complex upper thoracic segmentation abnormality, solitary left kidney with pelvic dilatation and hydroureter, *f*MRI correctly detected all the abnormalities. Prenatal USS was correct in identifying the CDH with mediastinal shift and the solitary kidney but provided incorrect information of the presence of cystic area within the chest and could not clearly identify the liver and the stomach which could raise the suspicion of other diagnoses. Measuring the lung volumes alone by *f*MRI would have changed management/counselling according to first expert panel assessment. (Figure-12).

Prenatal USS report did not mention the absence of a left kidney and the presence of proximal bowel atresia in a case confirmed postnatally by USS and chest x-ray to have left CDH, right lung agenesis, solitary right kidney and proximal bowel atresia. All of which were successfully picked up by *f*MRI and was considered by first expert panel to have added important information in addition to lung volumes measurements which could have changed management and/or counselling. Unfortunately, this baby died at operation and the information missed by prenatal USS were considered valuable by the second expert panel. (Figure-13).

In another case, prenatal USS was down scored for missing the contents of the right hemithorax and pointing towards the diagnosis of a right CCAM more likely than a right CDH. This baby died 20 hours after birth and was confirmed to have right CDH and chromosome 4 deletion. *f*MRI provided the correct diagnosis for this case and added valuable information about liver position, contents of right hemithorax, presence of pleural effusions in addition to measurements of lung volumes (fundamental change in diagnosis as per first panel). (Figure-14).

*f*MRI confidently pointed to the correct diagnoses in 2 CDH cases were prenatal USS was also correct but missed some less valuable information. As with all CDH cases *f*MRI always have the advantage over prenatal USS of calculating lung volumes. This was reflected by the first expert panel score as *f*MRI added information with effect on outcome. In these two cases however, it was not only the lung volume that prenatal USS missed but also the exact location, size, contents and existence of any lung tissue. *f*MRI provided the correct diagnoses with detailed anatomical description of the defect with its size, contents and presence of lung tissue with total lung volume allowing for a prediction for one foetus to be in the good prognostic group and the other to be in the worse prognostic group. Fortunately, both babies survived and had their surgical operations for CDH corrections and had normal follow up until 2 years of age (first foetus had further surgery for a recurrent CDH).



Bowel

Heart

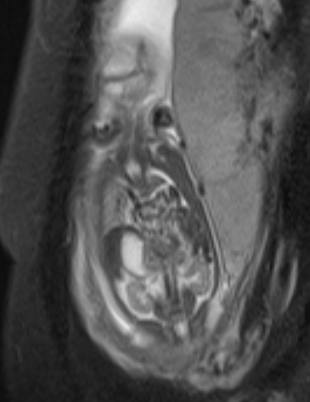
Hydronephrosis

Figure 12 Coronal T2-Weighted Image of a 21 GW foetus with Right Diaphragmatic Hernia containing bowel resulting in Mediastinal shift. Also has Hydronephrosis of a solitary kidney. (Arrowed).



Dilated Obstructed Bowel

Figure 13 Sagittal T1-Weighted Image of 30 GW foetus with Proximal Bowel Atresia (arrowed). No Meconium beyond the obstruction.



Lung

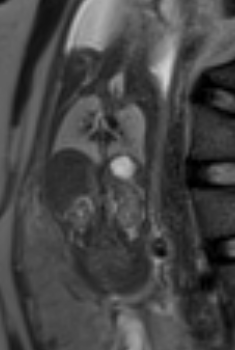
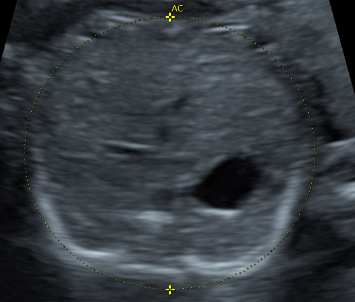
Bowel

Figure 14 Coronal T2-Weighted Image of 23 GW foetus with Right CDH containing Bowel. Left lung appears normal (arrowed).

In one case of hiatus hernia confirmed 2 days postnatally by Barium Swallow, prenatal USS could not identify the correct diagnosis but provided information that pointed towards a CDH diagnosis whereas *f*MRI correctly identified the stomach to be posterior to the mediastinum in the hemithorax midline suggesting a hiatus hernia. However, *f*MRI also suggested a small Morgagni type of CDH as a differential diagnosis, although less likely. The first expert panel thought that *f*MRI added valuable information with effect on outcome. The second panel decided that prenatal USS missed some information but without an impact on outcome.

*f*MRI correctly diagnosed one case of being normal, agreeing with postnatal scans but disagreeing with prenatal USS which suggested the presence of echogenic lungs raising the suspicion of CPAM (fundamental change in diagnosis as per first panel) and leading to unnecessary investigations and anxiety for the family (graded as, prenatal USS missed valuable information that affected management/counselling) (Figure-15).

In 2 CPAM cases *f*MRI was correct but prenatal USS missed some less important information that did not change diagnoses or management. First foetus had bilateral CPAM confirmed postnatally by chest x-ray and CT scan of the chest which was put on watch and wait approach of management. *f*MRI provided correct diagnosis with accurate description of the type, size and location of the pathology with its relation to the surrounding structures and commented on the lung condition. First panel scored this added information as could not have affected management or counselling. Prenatal USS confidently confirmed the presence of CPAM on the left side but was uncertain about the presence of CPAM on the right side. The second foetus (time-delay= >2wks) had a right lower lobe CPAM confirmed postnatally with CT scan of the chest and had lobectomy at 7 months of age. Follow up chest x-ray at 11 months was normal and the baby was alive and healthy with no concerns at 2 years of age. Prenatal USS did not provide information about the remainder of the affected lung (the right upper lobe) and the contralateral lung, all of which was provided in detail by *f*MRI. The first panel thought that both scans were similar despite that *f*MRI had more information than prenatal USS, although would not have an impact on outcome. The second panel scored prenatal USS in having missed less valuable information. This illustrates the variability between clinicians in different specialities.



Bright Echogenic Lung

Normal Lungs

a

b

Figure 15 a) Prenatal USS showing left bright echogenic Lung (arrowed). b) Coronal T2-Weighted Image of 23 GW foetus with normal Lungs (arrowed).

*f*MRI using T2-Weighted images was able to identify a subdiaphragmatic sequestration by its signal characteristics and finding its blood supply which was direct form the aorta. This was confirmed on postnatal USS and remained with no changes at 5 years of age. Prenatal USS could not confirm the diagnosis for sure and was hesitant regarding the origin of the depicted echo-bright lesion. Differentials suggested by prenatal USS were bowel mass and spleen. Therefore, the first panel scored prenatal USS as provided the incorrect diagnosis but the second panel decided that this was only a missed information by prenatal USS without effect on care and that by visualising an echo-bright area in that location would put subdiaphragmatic sequestration automatically in the differentials, and also by looking at the outcome and the way this baby was managed, they did not think that prior finding of this information by prenatal USS would have had an impact on the care provided. Again, this reflects the different clinical approaches in different specialities. Something that has not been highlighted in *f*MRI studies before.

*f*MRI fundamentally changed the diagnosis of prenatal USS from CPAM to Bronchogenic cyst (clinically different conditions with different prognosis and postnatal management) in one case. *f*MRI was scored to have completely changed the diagnosis by the first panel. This case was confirmed to have bronchogenic cyst by chest x-ray at 12 days of age and CT chest at 6 weeks. It was surgically excised at 3 months of age and the baby was alive and well at 3 years of age. *f*MRI could clearly identify the lesion with its relation to the surrounding structures and provided information about lungs condition (Figure-16). Prenatal USS could also visualise the cystic lesion in the lung but it suggested a diagnosis of a CPAM of the macro-cystic type. Either of these diagnoses would have had the same approach of management and counselling. Therefore, the second expert panel saw this as an information missed by prenatal USS without an impact on the course of management or counselling.



Bronchogenic Cyst

Lungs

Figure 16 Coronal T2-Weighted Image of 21 GW foetus with Bronchogenic Cyst and normal lungs (arrowed).

*f*MRI pointed to the correct diagnosis of Emphysema in 1 case in the chest cohort where prenatal USS found some difficulties to confirm the nature of the echogenic appearance of the left lung. This foetus was confirmed to have left upper lobe emphysema by postnatal CT scan of the chest. The first panel thought that *f*MRI added valuable information with effect on outcome. The second panel decided that prenatal USS missed some information but without an impact on outcome. This scenario has been debated in the local multi-disciplinary team meetings numerous times. The paediatric surgeons wish all potential emphysema cases to deliver in the tertiary centre due to the risk of hyperinflation of the emphysematous area. This risk is very low for cases with CPAM and they can deliver in their local hospital.

In a dextrocardia case confirmed postnatally with CTPA and a TOF repaired surgically, prenatal USS failed to suspect the presence of TOF. *f*MRI on the other hand, detected, in addition to dextrocardia, a poorly filled stomach with a degree of polyhydramnios raising the suspicion of TOF (Figure-17). *f*MRI findings were considered by the first panel to “could not have affected the outcome”. Looking at the postnatal outcome and the management course for this baby, the second expert panel found the information missed by prenatal USS was valuable and had a negative impact on the outcome for this baby.



Stomach

Heart

Figure 17 Coronal T2-Weighted Image of a 32 GW with Dextrocardia and TOF with poorly filled stomach (arrowed).

### We found that *f*MRI missed information in the following cases:

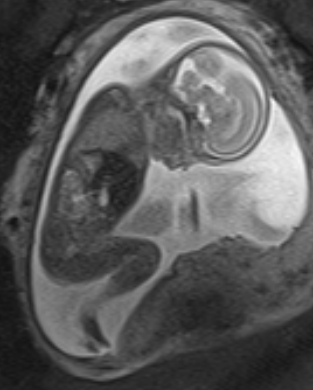
*f*MRI was mildly penalised by the second expert panel for putting a CDH foetus in the good prognostic outcome group by calculating total lung volumes (considered by first panel as valuable information added by *f*MRI that could have affected outcome). Unfortunately, this foetus died shortly after birth and had a post-mortem MRI that confirmed prenatal USS and *f*MRI in the diagnosis of CDH. *f*MRI was considered by the panel to have missed less valuable information without effect on management and counselling. Having a good lung volume alone should not be used as a guarantee of survival. Survival rate for CDH patients depends on many factors; lung volume with good lung expansion being one of them. The author felt it could be more understandable if this information was considered to affect counselling to some extent. If so, then it should have been scored for changing counselling. This will be modified for future studies.

*f*MRI missed less valuable information were prenatal USS was superior in another 2 cases of the chest cohort. The first case was a type 1 CPAM in the right upper lobe confirmed with postnatal USS in which *f*MRI suspected either CPAM or bronchogenic cyst with the latter being more likely (considered by first panel as fundamental change in diagnosis). Prenatal USS on the other hand suspected either CDH or CPAM with the latter being more likely. *f*MRI confidently dismissed the possibility of CDH suspected by prenatal USS. It is unlikely for CPAM to present in the upper lung lobes and it usually prefers the lower lobes and hence the suspicion of bronchogenic cyst was raised. No change in counselling or added investigations were needed for this baby apart from the postnatal USS for confirmation which is the usual pathway for such cases with either diagnosis.

Both prenatal USS and *f*MRI missed valuable information in a left lower CPAM case in which grade 4 reflux of a single kidney was found postnatally. Both scans were successful in detecting the CPAM and the solitary kidney (provided similar information as per first panel) but they missed the urinary reflux. This was a very important finding especially in a baby with a solitary kidney and it did have a big impact on the management course and counselling (in particular) in this case.

### Fundamental change in diagnosis by *f*MRIas per First Expert Panel:

*f*MRI fundamentally changed prenatal USS diagnoses in 11 foetuses according to our first expert panel assessment (without postnatal reference outcome). More than half of them were suspected CDH cases by prenatal USS but found later by *f*MRI to have no evidence of CDH. *f*MRI found both diaphragms to be intact in 6 foetuses with alternative diagnoses of a large mediastinal teratoma in one foetus (proven at surgery), CCAM in another case and to be normal in the remaining 4 foetuses. In one of these foetuses, we were able to gather some but not all postnatal outcome data (data was insufficient for second expert panel to reach a decision). This baby had a postdelivery CT scan which reported the presence of a small CDH with the stomach being up in the chest cavity but we also found a second CT scan done at 2 days of life which revealed the presence of a hiatus hernia which was repaired at Sheffield Children Hospital. At 5 days of age this baby had contrast studies which showed a rotated stomach that lay in the left retro cardiac area. A third CT scan was done at 11 weeks of age that confirmed the presence of CPAM which was surgically resected (lobectomy). The baby was alive and a chest x-ray showed normal lungs with no further concerns at 22 months of age. In another 3 foetuses (one case with >2wks time-delay), prenatal USS identified echogenic lungs or areas within the chest cavity with no specific diagnoses but raising concerns over the existence of some abnormalities. No abnormal signals were detected by *f*MRI in all 3 foetuses and appearances of foetal anatomy were within normal. Prenatal USS suggested the diagnosis of a liver nodule in another foetus where *f*MRI found this appearance as a small wedge-shaped area posterior and separate to the liver with its own blood supply directly from the aorta but remains infra-diaphragmatic which is all consistent with the diagnosis of infra-diaphragmatic pulmonary sequestration (Figure-18). *f*MRI changed the diagnosis suggested by prenatal USS in one foetus from a duplication cyst into right CPAM and small right liver cyst.



Infra-diaphragmatic pulmonary sequestration

Liver

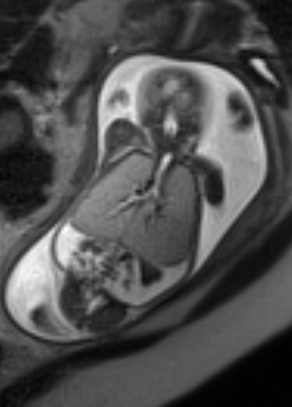
Figure 18 Sagittal T2-Weighted Image of a 21 GW foetus with Infra-diaphragmatic Sequestration posterior and separate to the liver (arrowed).

### *f*MRI addition of valuable information as per First Expert Panel:

*f*MRI added important information that could have changed management and/or counselling according to first expert panel assessment in 22 cases of the chest cohort. More than 80% (n=18) were CDH cases in which *fMRI* added the benefits of lung volume measurements and liver position in all of them (except one with >2wks time-delay). Lung volume measurement alone will automatically put *fMRI* superior to prenatal USS. Prenatal USS was unsure whether the lungs appear normal in 2 foetuses (one case with >2wks time-delay) whereas *fMRI* confirmed them to be normal. *fMRI* also changed the diagnosis of upper lobe CPAM suggested by prenatal USS in one foetus into upper lobe emphysema. Whilst the signal intensity on *f*MRI in this foetus was typical of CPAM, it was unusual for this lesion to occur in the upper lobe. The prenatal diagnosis or suspicion of lobar emphysema is very important as their cases have a tendency to increase and expand post-delivery as the baby breathes hence delivery needs to be in a tertiary referral hospital with access to paediatric surgery. Other pathologies that give this appearance include upper lobe emphysema and less likely CPAM.

*fMRI* also added important findings in another foetus suspected to have Congenital High Airway Obstruction Syndrome (CHAOS) by prenatal USS. Only a small trace of fluid could be seen in this foetus’s stomach on *fMRI* and there was a complete obstruction caused by a soft tissue mass at the level of the larynx (Figure-19). On Movie sequence, this foetus attempted to swallow and oropharynx and nasopharynx fill with fluid but it got expelled back into the amniotic fluid and none of it passed the obstruction confirming complete occlusion.

In the 5 foetuses with suspected pleural effusion in our study there were no postnatal outcome reference data to confirm either scan. Our first expert panel believed that both scans provided similar information in 2 cases (40%) and that *f*MRI added information without affecting patient’s care in 3 cases (60%) mainly by assessing lung volumes, character and morphology of existent lung tissue.



Hyperexpanded Lungs

Trachea

Obstruction

Figure 19 Coronal T2-Weighted Image of a 20 GW foetus with CHAOS. Showing fluid filled airways with hyperexpanded lungs and showing obstruction at the level of larynx (arrowed) CHAOS: Congenital High Airway Obstruction Syndrome.

In the miscellaneous group of the chest cohort, *f*MRI found the correct diagnoses in 10 out of 10 cases (prenatal USS detected 7) that had postnatal outcome reference data and obtained scores by the second expert panel. The information provided by *f*MRI was found to be valuable by the first expert panel and changed diagnoses and could have changed management in 45% of all the cases included in the miscellaneous group with and without postnatal outcome data.

As can be seen by the above discussion there remains debate on grading several of the cases and this reflects clinical practice. Different clinicians have different approaches and would hence grade differently. However, the most important significant grades, i.e. those that change diagnosis as correct or incorrect are not debated. The author believes this is the first study to highlight these clinical differences.

## ABDOMEN

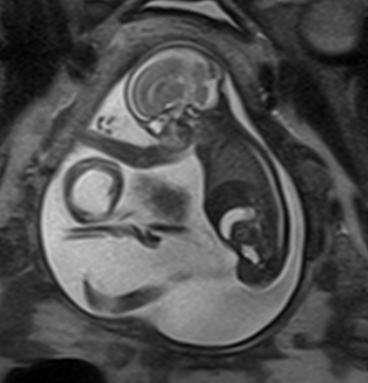
This study confirmed the added clinical value of *f*MRI to prenatal USS in the evaluation of foetal abdominal abnormalities with an overall diagnostic accuracy of 88% compared to 69% for prenatal USS (*n=46 and n=36, respectively)*. 19% more accurate diagnoses were provided by *f*MRI. Interestingly, both scans achieved their best diagnostic accuracy of foetal abdominal abnormalities among younger foetuses (<23 GW) where it reached 94% for *f*MRI and 72% for prenatal USS. They both showed slightly reduced accuracy in foetuses older than 23 GW with 85.7% for *f*MRI and only 64% for prenatal USS. Studies performed to evaluate the use of *f*MRI in foetal abdominal abnormalities are still limited. Most of the studies available in the literature lack the focus on foetal abdominal abnormalities and only report them in a generalised aspect among many other foetal abnormalities. However, our findings are in line with those reported by Rodrigues *et al.* study in which 62 foetal abdominal pathologies were included with diagnostic accuracy for *f*MRI of 88.5% and 85% for prenatal USS. They found no significant difference in relation to GA. Their results showed higher performance of prenatal USS than ours but diagnostic accuracy for *f*MRI were similar. We also found that *f*MRI provided additional information to prenatal USS in 27.7% of all cases with abdominal abnormalities that were confirmed postnatally and had an effect on patient’s care in 8.7% of them. It also corrected prenatal USS diagnosis in 2%. The contribution rate of *f*MRI to prenatal USS in the diagnosis of foetal abdominal abnormalities was reported by Kul *et al.* to be 38% where it also correctly changed prenatal USS diagnoses in 18% in their study which included 16 foetuses with suspected GI abnormalities among other foetal CNS and non-CNS abnormalities.

Our values are less than those reported by Rodrigues *et al.* in which *f*MRI added information that affected perinatal management and prognosis in 27.9% and corrected prenatal USS in 4.9%. Our results are also lower than those reported by Manganaro *et al.* in a study of 38 foetuses with gastrointestinal abnormalities in which they found that *f*MRI provided additional information in 60.6% of cases and corrected prenatal USS in 5.2%. The discrepancies between our results and those reported by previous studies could be explained by the lack of consensus in the definitions of additional, valuable and less valuable information. However, according to our first expert panel assessment, *f*MRI added information to prenatal USS in 32.7% in which it could affect management and counselling in 11.7% of cases included in the study. *f*MRI has been previously described to provide better resolution of the abdominal viscera, clear tissue characterisation, being able to detect bowel calibre and contents (using different *f*MRI sequences i.e. T1 and T2-weighting) and its ability to distinguish between normal and abnormal bowel signal (Veyrac *et al.*, 2005).

The present study found that *f*MRI provided the correct diagnoses in all miscellaneous abdominal abnormalities, situs inversus, duodenal atresia and 91% of abdominal cysts, 90.9% of exomphalos and 66.6% of TOF cases confirmed postnatally. It also added information to prenatal USS in 17% of abdominal cysts, 27% of exomphalos cases, 55% of TOF, 50% of duodenal atresia and 25% of miscellaneous cases. Manganaro *et al.* found that it added information in 50% of abdominal cysts and 80% of bowel dilation (bowel dilation was included in the miscellaneous group of this cohort).

### We found that *f*MRI added information in the following cases:

One case in the abdomen cohort was verified to be normal postnatally agreeing with *f*MRI diagnosis of a normal dilated slightly ectopic gallbladder but disagreeing with prenatal USS suspicion of an upper abdominal cyst (Figure-20). The first expert panel considered *f*MRI findings to “could not have changed the management/counselling in this baby”. One could argue that *f*MRI had fundamentally changed the diagnosis (from abdominal cyst to normal gallbladder) which was later supported by postnatal outcome. Decision by expert panels is subjective and is not always flawless. Decision might differ between experts according to their own clinical experience and management protocols. However, this could be considered as a reflection to the actual everyday clinical practice where it is not uncommon for foetal medicine experts, obstetricians, radiologists and neonatologists to disagree.



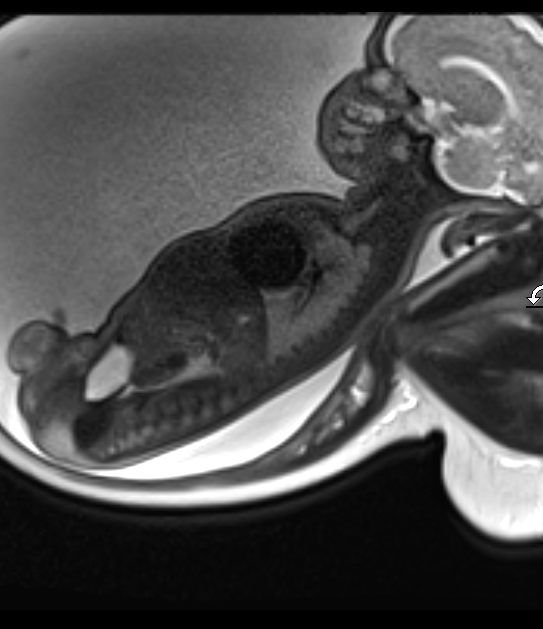
Gallbladder

Figure 20 Sagittal T2-Weighted Image of a 21 GW foetus with normal dilated, slightly ectopic Gallbladder (arrowed).

*f*MRI provided a confident diagnosis of a normal gallbladder which was mistakenly picked up by prenatal USS as a cystic lesion in the abdomen/pelvis region suspecting it to be of a bladder or a ureter origin but also suspecting a gallbladder in its differentials (both scans provided similar information as per first expert panel). Unlike the previous normal gallbladder case where prenatal USS was scored to be incorrect, in this case prenatal USS did provide a diagnosis of normal gallbladder in its differentials but among others which needed further investigations for confirmation and hence scored for missing valuable information instead.

*f*MRI diagnoses of oesophageal atresia in 2 cases were verified postnatally by surgical repair. The upper oesophagus and a partially filled stomach (appeared as a slit-like fluid filled structure below the left lobe of the liver) were clearly seen in one case by *f*MRI. These findings could not be seen on prenatal USS (*f*MRI findings could not have affected outcome as per first expert panel). The stomach bubble was persistently not visible on prenatal USS and in the absence of polyhydramnios, it could not confidently diagnose an oesophageal atresia (prenatal USS missed findings that had an impact on the management course in this baby as seen by second expert panel).

The level of oesophageal atresia, thin sleeve of fluid in the stomach and presence of polyhydramnios were noted by *f*MRI in the second case (Figure-21). Prenatal USS could not visualise the stomach. Together with the finding of polyhydramnios, it suspected the diagnosis of TOF. Both prenatal scans were considered by the first expert panel to have provided similar information. Looking at the confirmation of oesophageal atresia by the postnatal outcome, the second expert panel found that prenatal USS missed information that affected management in this case. Failure to identify the stomach bubble (whether on prenatal USS or *f*MRI) particularly in the presence of polyhydramnios should always raise the suspicion of oesophageal atresia +/- fistula formation. The gold standard treatment option for oesophageal atresia with or without a fistula is the surgical correction of the anomaly. Management and follow up course for this case did not reveal any new concerns and we do not think that prenatal USS could have added any more information to its findings.

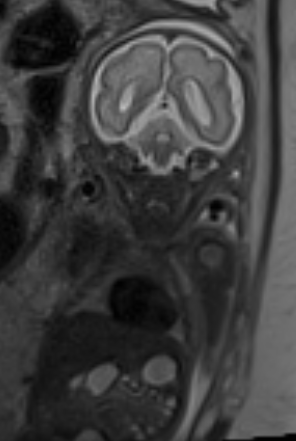


Stomach

Polyhydramnios

Figure 21 Sagittal T2-Weighted Image of a 35 GW foetus with Oesophageal Atresia. Small stomach with thin sleeve of fluid and Polyhydramnios (arrowed).

*f*MRI was correct in 7 cases of the abdominal cohort where prenatal USS missed some information without any effect on outcome. 3 of these cases were suspected abdominal cysts. Interestingly, no cysts were identified on postnatal USS on all 3 cases. This might be due to the spontaneous resolution commonly observed in such cases. *f*MRI could not identify any cystic structure that was seen on prenatal USS in the first foetus. This was considered a fundamental change in diagnosis by the first expert panel. It provided similar information to prenatal USS according to the first expert panel in the second foetus and added information that could have changed management/counselling in the third foetus where a suspicion of duodenal atresia (confirmed postnatally and operated) was more evident by *f*MRI (Figure-22).



Double Bubble Sign

Stomach

Duodenum

Figure 22 Coronal T2-Weighted Image of a 30 GW foetus with Duodenal Atresia. Distended stomach and duodenum making a Double Bubble appearance (arrowed).

*f*MRI was correct in 2 exomphalos cases where prenatal USS missed some information without any effect on outcome. Prenatal USS could not confirm the diagnosis in a foetus with exomphalos. It was unable to clearly visualise the exact location of the defect and its contents with their covering leaving a room for a gastroschisis in the differentials. *f*MRI confidently pointed toward the right diagnosis and provided valuable information about the abdominal wall defect in terms of its size, location and contents with their membrane covering agreeing with postnatal USS. They both provided similar information according to the first expert panel. The defect was surgically repaired soon after birth with no new concerns afterwards. The other exomphalos case was a large defect containing the whole liver as seen by both prenatal USS and *f*MRI. The examination was very challenging for prenatal USS obtaining only suboptimal views of the foetus due to its position and reduced liquor volume. It missed information about the position of the foetal heart in relation to the abdominal wall defect which was seen on *f*MRI to be very close and also failed to recognise an underdeveloped sacrum which was clearly seen by *f*MRI (Figure-23). *f*MRI added information without affecting management/counselling according to first expert panel. However, they both could not visualise the kidneys which have raised the suspicion of their agenesis. Unfortunately, this foetus had a miscarriage and no genetics or follow up have been done.



Exomphalos

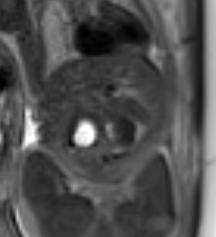
Heart

High end to Spinal Cord

Figure 23 sagittal T2-Weighted Image of a 19 GW foetus with Exomphalos. Extremely curled foetus. Heart appears very close to the defect. There is a high end to the Spinal Cord (arrowed).

*f*MRI was superior to prenatal USS in finding about a dilated pelvicalyceal system in the right kidney in a case with laryngeal atresia. *f*MRI was considered to have added important information that could affect management/counselling. But the second expert panel saw this information as less valuable and did not have an impact on management or counselling as the baby had a preterm delivery at 33 weeks and died after a failed resuscitation attempt.

*f*MRI was also superior to prenatal USS in a case with a small fluid collection over the liver in which *f*MRI gave detailed description of the lesion and provided clearer assessment of the liver and its surroundings and confirmed them to be normal whereas prenatal USS suspected the presence of subdiaphragmatic calcification area with no comment on the liver or its surroundings. The information provided by both scans were considered similar by the first expert panel. It is known that small areas of calcifications are difficult to identify on *f*MRI but in this case there was a dark area visualised over the liver (Figure-24) which was confirmed later by postnatal USS to be a fluid collection over the left lobe of the liver. This fluid collection disappeared in subsequent USSs at 10 weeks and 2 years of age.



Fluid collection

Left lobe of Liver

Figure 24 sagittal T2-Weighted Image of a 31 GW foetus with small fluid collection over the left lobe of the liver (arrowed).

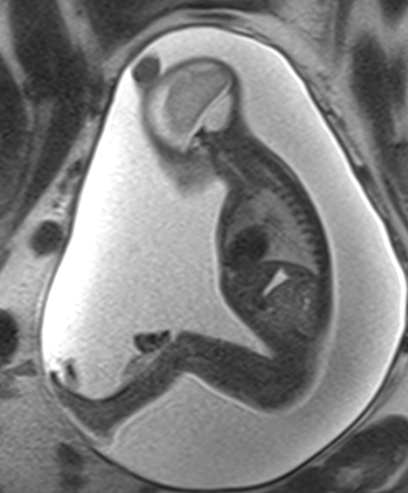
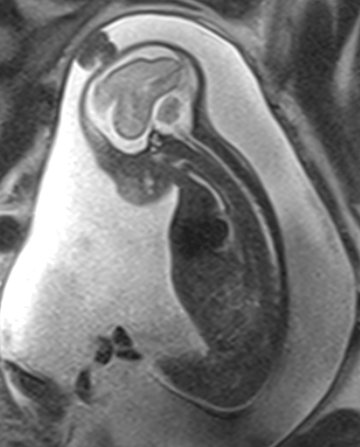
### We found that *f*MRI missed information in the following cases:

Both scans missed less important information that would not have an effect on either management or counselling in 3 cases of the abdomen cohort. The first case was a dilated bowel loop and a mild left pelvicalyceal dilatation confirmed postnatally and followed up until 18 months of age with USS. *f*MRI had the advantage of visualising meconium high signal characteristics on T1-Weighted imaging thus providing detailed anatomy of the bowel but it was unsuccessful in detecting the mild pelvicalyceal dilatation in the left kidney. Prenatal USS was uncertain about the appearance of this abnormality. It pointed toward the lower pole of the right kidney as its origin, although concluded that both kidneys appeared normal (*f*MRI fundamentally changed prenatal USS diagnosis as per first expert panel). In this case the second expert panel decided that whether this information was available or not, this case would have a similar approach of counselling and follow up and therefore did not affect outcome. The other two cases were normal postnatally which was also the most likely diagnosis by prenatal USS and *f*MRI as they both were able to visualise the stomach clearly but they could not confidently exclude the possibility of a TOF. *f*MRI provided extra information about stomach filling, size and foetal swallowing using CINE images (without effect on outcome as per first panel).

Both prenatal USS and *f*MRI missed the presence of a postnatally confirmed colonic atresia in a small pedunculated exomphalos which was surgically repaired and followed up until 5 months of age with no new concerns. Both scans identified the exomphalos prenatally (provided similar information as per first panel). The detection of colonic atresia prenatally would have changed the course of the surgical management and family counselling (as per second panel).

*f*MRI and prenatal USS suspected the presence of a simple fluid-filled cyst most likely to be a choledochal cyst as per *f*MRI or likely to be of a renal origin as per prenatal USS. This was considered a fundamental change in diagnosis by the first expert panel. The second expert panel however, scored both scans to be incorrect as no cyst was to be found on postnatal scan. Abdominal cysts, as mentioned earlier in chapter 2 (page 63-64), do have the tendency in many cases to resolve spontaneously without any intervention. The absence of this cyst postnatally does not necessarily mean that both scans were incorrect and no cyst was there in the first place but may be both scans were correct prenatally and postnatally, and the cyst resolved spontaneously and it could not be identified postnatally.

*f*MRI was confirmed to be incorrect postnatally in 1 abdomen case with TOF where prenatal USS agreed with postnatal outcome. In this case, it was clearly seen on *f*MRI that the foetal stomach is partially filled but the upper oesophagus was also clearly seen and there was no obvious obstruction identified in the visualised oesophageal segment (fundamentally changed prenatal USS diagnosis as per first panel) (Figure-25). The second panel deemed *f*MRI to be incorrect and their comment on the score was that if *f*MRI report mentioned TOF per se then it would have changed the score into agreement with postnatal diagnosis. We agree that the word “TOF” was not mentioned in the report but indication and suspicion of TOF were raised by the report. The diagnosis of TOF was not dismissed by *f*MRI in this case. On the contrary, the report gave a description of a partially filled stomach which always raises the suspicion of TOF and that the whole oesophagus is not seen but only the upper segment which appears patent. The level of atresia might be well beyond the segment seen on *f*MRI and visualising the upper oesophageal segment never excludes the presence of atresia.



Oesophagus

Trachea

Stomach

Polyhydramnios

a

b

Figure 25 Sagittal T2-Weighted Images of a 27 GW foetus with TOF. a) Shows fluid filled Trachea and Upper segment of Oesophagus (arrowed). b) Shows partially filled stomach and Polyhydramnios (arrowed).

### Fundamental change in diagnosis by *f*MRIas per First Expert Panel:

*f*MRI fundamentally changed prenatal USS diagnoses in 14 foetuses. Abdominal cysts were suspected by USS in six cases. *f*MRI found no cystic structures in five of them (three cases with >2wk time-delay) and confirmed the presence of one to be an ovarian cyst and not originated from the lower pole of the right kidney as suggested by USS. Two cases were poorly seen stomachs by prenatal USS which were later found by *f*MRI to be normal (one case with >2wk time-delay). Prenatal USS suspected the presence of adrenal glands enlargement in two cases in which no enlargement of the glands was found by *f*MRI. One foetus with severe growth restriction was suspected by USS to have Bilateral renal agenesis but both kidneys were clearly seen on *f*MRI which was also able to identify an additional diagnosis of gastroschisis which was not suspected by USS. One foetus with suspected exomphalos by prenatal USS was found to have an umbilical artery aneurysm by *f*MRI. Prenatal USS was unable to assess foetal anatomy in one case due to high maternal BMI whereas *f*MRI clearly visualised the foetal anatomy which was normal.

### *f*MRI addition of valuable information as per First Expert Panel:

*f*MRI added two important findings of a TOF and a possible sacral agenesis in a foetus with known cardiac defects and suspected sacral and spine curvature abnormalities by prenatal USS (>2wk time-delay). *f*MRI excluded the presence of TOF in a foetus with polyhydramnios which could not be excluded by prenatal USS, although the stomach was clearly visible. Foetal stomach was not visible by prenatal USS in two cases with polyhydramnios, it was clearly visible fully filled on *f*MRI in one case and partially filled in the other case. Prenatal USS identified the appearance of a double bubble sign in two cases where *f*MRI identified a large stomach, dilated rectum and small sigmoid with no evidence of double bubble sign or GI obstruction in one foetus and a duodeno-jejunal flexure obstruction in the other case. Prenatal USS was unable to clearly assess the spine in a foetus with abdominal cyst whereas *f*MRI clearly visualised the spine and added information about the cyst location which was found to be intra-hepatic. *f*MRI also provided valuable information in a foetus suspected with abdominal situs inversus by prenatal USS with some concerns over the liver, spleen and thymus which all found to be normal by *f*MRI.

## GUS

This study confirmed the added value of *f*MRI in evaluating foetal GUS abnormalities with an overall diagnostic accuracy of 75.8%, almost 22% higher than that of prenatal USS (53%) which reached 26% difference when *f*MRI performance was assessed in the older GA (>23 GW group) where *f*MRI had a diagnostic accuracy of 89% (prenatal USS=63%). Prenatal USS was less affected by the changes in GA. Our findings are in line with those reported by Poutamo *et al.* in their study that compared both scans in the diagnosis of foetal urinary tract abnormalities in 24 foetuses. They found that *f*MRI provided the correct diagnoses in 83% whereas prenatal USS in 62%. Most of the foetuses included in their study were in the third trimester and the mean GA during *f*MRI was 34 GW. They also found that *f*MRI added information to prenatal USS in 36% of their cases and corrected its diagnoses in 33%. In our study however, we found that *f*MRI provided additional information to prenatal USS in 22% in which it altered course of management and counselling in 12 % and corrected its diagnoses in 7%. Amini *et al.* in their study of 17 foetuses with urinary tract anomalies found that *f*MRI provided additional information in 23% leading to change in management in 5% of cases. Our results were also in agreement with those reported by Barseghyan *et al.* study of the role of *f*MRI and prenatal USS in the assessment of foetal urinary tract anomalies that included 39 foetuses in which *f*MRI modified the initial prenatal USS diagnoses and counselling but not management in 36% and added information that resulted in substantial change in management in 3% of cases (Barseghyan *et al.*, 2008). A study by Cassart *et al.* (2004) on the complementary role of *f*MRI after prenatal USS in assessing 16 foetuses with suspected bilateral urinary tract anomalies found that *f*MRI provided additional information that modified prenatal USS diagnoses in 31% of cases.

Different studies report highly variable values and this could be due to the fact that both scanning modalities rely significantly on scanning equipment themselves as well as experience of the radiologists in interpreting the results. Not only that but also the experience of those involved in research field who decide on the additional value of the results provided by the scans.

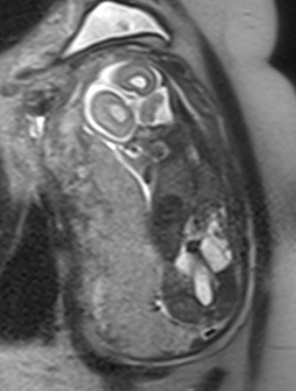
In our study, the highest diagnostic accuracy provided by *f*MRI in assessing foetal GUS abnormalities was achieved in all urinary tract obstructions (USS=66.6%), bilateral renal agenesis (USS=all), miscellaneous cases (USS=all) and 87.5% of unilateral renal agenesis (USS=62.5%), 75% of MCDK (USS=45%), 66.6% of ectopic kidneys (USS=50%), 60% of duplex collecting system (USS=40%) and 33% of horseshoe kidney cases (USS=33%). Some of these results are in agreement with Kajbafzadeh *et al.* comparison of *f*MRI with prenatal USS in detection of foetal urogenital anomalies in 46 foetuses. They reported 100% of *f*MRI sensitivity in detection of ureterocoele, ureteral dilation (all classified as urinary tract obstruction in our study), 94% of PUV and 92% of PUJ obstruction cases. However, our study showed lower accuracy for *f*MRI in detecting MCDK cases (75%) than their finding of 100% *f*MRI sensitivity in detecting MCDK. This discrepancy could be due to their smaller number of MCDK cases included in their study (*n=6)* compared to our study (*n=20)*.

### We found that *f*MRI added information in the following cases:

In a case with posterior urethral valves confirmed postnatally by USS, *f*MRI provided the correct diagnosis with added DWI assessment of the kidneys function (Figure-26). Prenatal USS however, suspected that it is likely to be a reflux nephropathy or partial bladder neck obstruction. The diagnosis was fundamentally changed as seen by the first expert panel. This baby died soon after birth. Chest and abdominal X-rays showed bilateral pneumothorax and ascites. We could not confirm whether this baby had a postmortem.

Two MCDK cases confirmed postnatally, one by postnatal USS and one by DMSA and USS at 2 years of age, *f*MRI was successful by providing the correct diagnoses in both cases and added detailed assessment of renal function with DWI sequence (Figures-27). Prenatal USS was incorrect in both cases. It suggested either vesico-ureteric obstruction in the collecting system or a severe reflux in one case (fundamental change in diagnosis by first expert panel) and was unable to visualise the kidneys suggesting either their absence or non-function in the other one (*f*MRI added information without impact on outcome as per first expert panel).

One complex case with ascites and suspected viral, genetic or chromosomal abnormalities was found to have bilateral renal dysplasia, bilateral hydronephrosis, dilated posterior urethra and PUJ obstruction. *f*MRI successfully gave the correct diagnosis but prenatal USS was incorrect and could not identify any GUS abnormality (fundamental change in diagnosis as per first panel and incorrect diagnosis by prenatal USS as per second expert panel).



Urinary Bladder

Dilated Ureters

Kidneys

a

b

Figure 26 Coronal T2-Weighted Image of a 21 GW foetus with Posterior Urethral Valves resulting in dilated ureters and over-distended bladder (arrowed). b) DW Image showing functioning Kidneys (arrowed).



Left MCDK

Stomach

Figure 27 Coronal T2-Weighted Image of a 24 GW foetus with Left MCDK (arrowed).

A case of bilateral hydronephrosis and hydroureters was confirmed postnatally with MCUG to have bilateral duplex systems and ureterocoeles in bladder and was found 5 years later to have bilateral renal scarring confirmed by USS. *f*MRI provided similar information to postnatal outcome with extra valuable comments on functioning renal parenchyma and the condition of the lungs (*f*MRI findings could not have had an impact on outcome as per first expert panel). Prenatal USS failed to recognise the duplex systems and suspected a vesico-ureteric reflux with a possibility of a cystic kidney (information missed by prenatal USS did have an impact on the management/counselling course in this baby according to second expert panel).

*f*MRI was superior to prenatal USS in another GUS case with left unilateral renal agenesis confirmed with postnatal USS. It could also recognise a hydronephrosis due to PUJ obstruction in the solitary kidney (Figure-28), assessed its function and commented on lung development, morphology and volumes which was all well within the expected for that GA (*f*MRI findings were valuable and could have affected management/counselling as per first expert panel). Prenatal USS on the other hand provided incorrect information in suspecting severe pulmonary hypoplasia carrying very poor prognosis to this foetus causing unnecessary anxiety which affected the course of management/counselling as found by the second expert panel.



Hydronephrosis

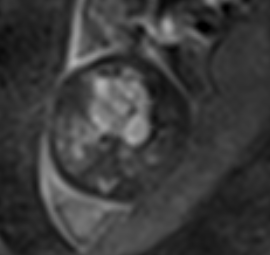
Normal Lung

Figure 28 Coronal T2-Weighted Image of a 33 GW foetus with PUJ obstruction of a solitary kidney resulting in Hydronephrosis. Right Lung appears normal (arrowed).

*f*MRI was successful in finding the correct diagnoses in 7 GUS cases where USS missed some information that was considered less valuable without effect on outcome. 3 of them were MCDK cases. In the first one, prenatal USS could not clearly visualise the contralateral kidney. The renal artery was identified using prenatal doppler USS and therefore agenesis was less likely. The condition of the contralateral kidney remained uncertain which could affect the course of management/counselling and this was the decision of the first expert panel. In the second case, prenatal USS correctly detected the right MCDK but could not be certain of the normality of the contralateral kidney (left). Both scans provided similar information according to the first expert panel. The findings in this foetus were confirmed postnatally with two USSs at 6 weeks, 19 months of age and with DMSA at 3 months. The second expert panel considered the information missed by prenatal USS did not have an impact on management or counselling of this baby.

In the third case, prenatal USS could not identify for certainty the origin of the cystic mass (MCDK) which was confirmed by *f*MRI then postnatally by USS and DAMSA to be from the left kidney, however in an ectopic position (Figure-29). Both scans provided similar information according to first expert panel but missed information without effect on outcome according to second panel.

In a baby with a slightly long, rotated and thin but normal kidney confirmed by *f*MRI and postnatal USS, prenatal USS gave a correct description of the abnormality but also raised the possibility of a duplex collecting system to be responsible for such an appearance. *f*MRI provided additional information without affecting outcome according to first panel whereas prenatal USS missed information without affecting the outcome as per second expert panel assessment.



Left Ectopic MCDK

Right Kidney

Figure 29 Axial T2-Weighted Image of a 21 GW foetus with Left Ectopic MCDK which appears in the midline and a normal Right Kidney (arrowed).

In one case with left unilateral renal agenesis confirmed by postnatal USS agreeing with *f*MRI, prenatal USS was correct for not being able to visualise the absent kidney but it did suspect the presence of a small pelvic kidney on the right side. *f*MRI was considered to have added less valuable information in dismissing the suspicion of an ectopic kidney. Looking at the course of management in this case, the second panel decided that the information missed by prenatal USS did not have an effect on the outcome. In another case, the presence of an ectopic right kidney was confirmed by both postnatal USS and *f*MRI. Prenatal USS however, could not clearly visualise the ectopic kidney and only suspected the presence of some echogenicity in the pelvis that might represent an ectopic renal tissue. This was considered as a fundamental change in diagnosis by the first expert panel but the second panel found the missed information by prenatal USS did not affect neither management or counselling.

Prenatal USS could not identify PUJ obstruction in a dilated collecting system appearance and suspecting a horseshoe kidney instead. *f*MRI suspected a diagnosis of PUJ obstruction which was later confirmed by serial follow up USSs until 3 years of age with no new concerns. This was a fundamental change in diagnosis according to the first expert panel. The information missed by prenatal USS did not have an effect on the management course taken for this baby as decided by the second expert panel.

*f*MRI could not detect a left MCDK in a case confirmed to have a segmentation anomaly, anterior meningocele (by postnatal MRI) and complex urinary anomalies (MCUG at 2 weeks and MRI pelvis at 22 months) and had surgical repair for bifurcated bladder. However, it was successful in detecting all other anomalies in this case except for not detecting the left MCDK and therefore was considered by the second expert panel to not have affected the course of management and/or diagnosis. Prenatal USS scan failed to detect the left MCDK and the abnormal bladder. This led the second panel to score prenatal USS as missed information with effect on management and/or counselling. Also appearances on prenatal USS were suggestive of partial or complete urethral obstruction (*f*MRI fundamentally changed diagnosis of prenatal USS as found by first expert panel).

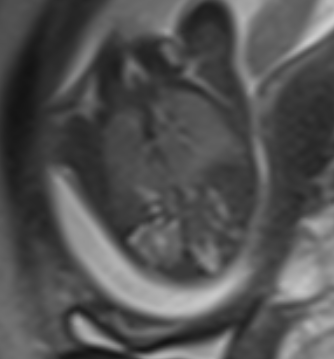
In a case of a duplex system only in the left kidney (unilateral) confirmed by US KUB (Kidney, Ureter and Bladder) at 3 weeks and 6 months of age, both kidneys (bilateral) appeared to be large and to have duplex collecting systems on *f*MRI. For this, *f*MRI was considered by the panel to have missed information without affecting the management and/or counselling. With fairness to *f*MRI, both kidneys were seen as duplex by the first postnatal USS as well (at 1 week of age). Prenatal USS could not reach a confident diagnosis on this case. It was unable to visualise the kidneys clearly. However, it raised the concern about the stomach and oesophagus of this foetus as only a thin rim of fluid was seen in the stomach, thus raising the possibility of a TOF (prenatal USS findings had a negative impact on the management course). *f*MRI dismissed this possibility by clearly visualising a normally small stomach with oesophagus seen along its course and fluid seen in the bowel (*f*MRI added information that could have an impact on management/counselling as per first expert panel). For not clearly visualising the kidneys and the stomach, prenatal USS missed valuable information and caused unnecessary anxiety and led to further confirmatory investigations.

### We found that *f*MRI missed information in the following cases:

Both scans missed some information without an effect on outcome in 3 GUS cases. Both scans were unable to visualise the right kidney in a foetus where the kidney was found on postnatal USS at 2 weeks of age albeit small and ectopic. *f*MRI had the flattened appearance of the right adrenal gland which was more consistent with kidney absence (Figure-30) (first panel found *f*MRI to have added some information without impact on outcome). However, suspicion of an ectopic kidney remained as a possibility in prenatal scanning and having a confirming postnatal USS is the usual course of management in such cases which led the second expert panel to score them only for missing information without an effect on outcome.

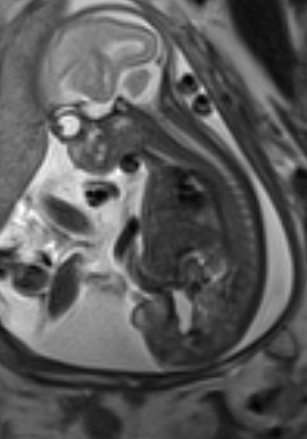
In another case, prenatal scanning suspected the presence of multiple cysts replacing the kidney in the right renal fossa pointing towards a diagnosis of right MCDK without function on DWI sequence (both scans provided similar information as per first expert panel). Postnatal USS at 14 days of age found only some remnants of tissue in the right renal fossa with no cysts which was later confirmed by DMSA at 7 months of age. Regardless of the presence or absence of MCDK the course of management and counselling will be similar.

*f*MRI and prenatal USS could not confirm the presence of a crossed fused ectopia in a foetus with atypical kidneys position appearance on both scans. This diagnosis was also difficult with postnatal imaging and it took multiple USSs postnatally to finally come to the correct diagnosis of crossed fused ectopia. Both prenatal scans were successful in pointing to the atypical position of the right kidney. The left kidney was found by *f*MRI to be located in the midline posterior to the bladder (Figure-31) which could not be seen by prenatal USS (added information that could have affected management/counselling as per first expert panel). One could argue that the information provided by *f*MRI could be the closest possible information to aid a diagnosis of a Crossed Fused Ectopia. Looking at the course of management provided to this case, the panel scored both scans for missing information without an effect on outcome.



Flattened Adrenal Gland

Figure 30 Coronal T2-weighted Image of a 22 GW foetus with small Ectopic Right Kidney, only confirmed postnatally. fMRI visualised a flattened Adrenal gland "pancake sign" pointing to Right Kidney absence (arrowed).



Left Ectopic kidney

Urinary Bladder

Bladder

Figure 31 Sagittal T2-Weighted Image of a 25 GW foetus with Crossed Fused Ectopia. Left Kidney in the midline posterior to the urinary bladder (arrowed).

Both scans missed valuable information that could have affected management and/or counselling in 2 GUS cases. In one case confirmed by DMSA 10 months postnatally to have Horseshoe kidneys. First postnatal USS at 6 weeks was unable to detect the horseshoe kidneys and could only find a size discrepancy between the kidneys with left kidney appearing smaller than the right. Both prenatal scans could not detect a horseshoe abnormality and could only visualise an enlarged left kidney with pelvicalyceal dilatation (found by first expert panel to provide similar information). The other case was a complex urinary tract abnormality confirmed during post-mortem. *f*MRI could only find a pelvic horseshoe kidney, a possible MCDK and only small margins of functioning parenchyma whereas prenatal USS raised the suspicion of an abnormal position with possible MCDK (*f*MRI findings could have affected outcome as per first expert panel). However, both scans failed to depict a detailed anatomical description of this complex abnormality involving the whole urinary tract (both missed valuable information that had an impact on outcome).

One GUS case died at birth and found to have massive bilateral MCDK and cysts in the pancreatic head and body, prenatal USS failed to detect both cystic appearances in the kidneys and in the pancreas, hence provided the incorrect diagnosis. While *f*MRI detected the bilateral MCDK and provided details about their functions using DWI sequence but mistakenly suspected the cysts on the pancreas as a double bubble sign and raised the suspicion of duodenal atresia. This finding had a negative impact on the management course of this baby as per the second expert panel assessment. *f*MRI was found by the first expert panel to have added information that could not have affected outcome in this case.

*f*MRI missed valuable information that affected management and/or counselling in another GUS case where prenatal USS was incorrect. It failed to detect the absence of the right kidney and the presence of multiple small cysts on the left kidney. It did give information about the morphology and function of the left kidney (added information that could not have affected outcome as per first panel). The appearance on prenatal USS was more suggestive of fused kidneys where the scan was unable to clearly see if both kidneys where separate (there was only one kidney as was confirmed by postnatal scans). This baby was delivered with imperforated anus and without renal function and died shortly after birth.

Prenatal USS was superior to *f*MRI in a GUS case confirmed postnatally to be a right pelvic kidney with mild pelvicalyceal dilatation on the left. *f*MRI gave the description of a possible crossed fused ectopia with left pelvicalyceal dilatation and an abnormal position but normal structure to the right kidney (added information without effect on outcome as per first expert panel). *f*MRI findings led the second expert panel to give *f*MRI a low score as it had an impact on management and/or counselling. Prenatal USS on the other hand, could not visualise the right kidney at all and raised the possibility of right kidney agenesis. However, a less likely diagnosis of an ectopic right kidney was also provided and hence the panel decided that missing this information did not change management or counselling.

Both scans were incorrect by providing different diagnoses to the postnatal outcome in 4 GUS cases. Both missed the diagnosis of posterior urethral valves with hydronephrosis and pelvicalyceal dilatation in 1 case. Here, *f*MRI raised the suspicion of PUJ obstruction in a male foetus or Cloacal abnormality in a female foetus. Prenatal USS suspected the diagnosis of large right MCDK with compensating enlargement of the left kidney and to a lesser extent also suspected the presence of a duplex system or a horseshoe kidney. The diagnosis was fundamentally changed by *f*MRI according to the first panel. The correct diagnosis of posterior urethral valves was confirmed postnatally by MCUG at 10 days of life and had resection of the valves with ureterostomy. No new concerns were found on follow up USS apart from pelvicalyceal dilatation. It is important to point out that postnatal USS was also incorrect initially by confirming prenatal USS with a diagnosis of a dysplastic kidney.

They also provided incorrect diagnosis in a case diagnosed postnatally by USS with right dysplastic pelvic kidney. *f*MRI diagnosis was that of a Crossed Fused Ectopia with dilated ureter and no functioning parenchyma. Prenatal USS on the other hand could not fully assess the right kidney to determine whether it is MCDK or a unilateral reflux. *f*MRI findings were considered by the first panel as added information without effect on outcome.

Both scans suspected an abnormal left kidney in 1 GUS case with prenatal USS scan describing it as an enlarged left kidney with echogenic area whereas *f*MRI suspected a left Duplex system with no reflux or obstruction. The information provided by *f*MRI could not have changed management or counselling as seen by the first expert panel. No abnormality was detected in this baby’s GUS on postnatal USS and hence both prenatal scans were incorrect.

In one case with Cat’s Eye syndrome, the right kidney could not be identified by either prenatal USS or *f*MRI and right unilateral renal agenesis was suspected. *f*MRI added to prenatal USS the presence of nuchal thickening, widely spaced eyes and the flattened appearance to the back of both eyes which is consistent with coloboma. This information could not have an impact on outcome according to the first expert panel. Interestingly, the first postnatal USS in the first week of life also could not identify the right kidney. However, the correct diagnosis was only known later to be an ectopic pelvic kidney by USS at 5 weeks and confirmed by DMSA at 20 months.

### Fundamental change in diagnosis by *f*MRIas per First Expert Panel:

*fMRI* fundamentally changed prenatal USS diagnoses in 7 foetuses. It confirmed the presence of the right kidney which was not visible by prenatal USS in a case with polycystic left kidney (Figure-32). It also confirmed both kidneys to be normal in another foetus where prenatal USS had poor views of the kidneys. *fMRI* found no bladder exstrophy in a foetus with family history of this anomaly that was not diagnosed antenatally. *fMRI* found a mild right sided hydronephrosis and hydroureter suggesting vesico-ureteric junction obstruction with normal functions for both kidneys on DWI and a normal stomach in a foetus with concerns raised over the stomach size by prenatal USS which identified it as enlarged but failed to detect any problems with this foetus GUS.

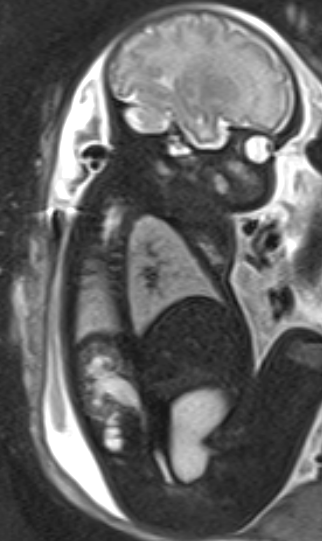
In another case, prenatal USS failed to detect the diagnosis of posterior urethral valves but rather dismissed the possibility of an obstruction and suggested the presence of a reflux as responsible for the appearance on the scan. Bilateral hydronephrosis, dilated ureters and dilated thick-walled bladder were all seen on *f*MRI (Figure-33). These features were consistent with posterior urethral valves given that this foetus was of a male gender. Unfortunately, DWI sequence could not be performed as the mother could not tolerate the scanner and had to leave the scan.

Prenatal USS mistakenly gave the appearance of renal cysts of what was later seen on *fMRI* as a very prominent right renal pelvis with mild dilatation of the pelvicalyceal system consistent with right sided PUJ obstruction but normal amount of functioning renal parenchyma on DWI sequence. It also suspected large bright kidneys and a small cerebellum in a foetus with polyhydramnios and confirmed congenital tricuspid regurgitation in which *fMRI* gave normal appearances of both kidneys and brain. Superiority of *fMRI* over prenatal USS in visualising the foetal brain is well documented in the literature but in this case, visualising the kidneys was also a very important finding according to the first expert panel.



Functioning Right Kidney

Figure 32 Axial DW Image of a 24 GW foetus with left Polycystic Kidney. Image shows a functioning Right Kidney (arrowed).



Hydronephrosis

Dilated Ureter

Urinary Bladder

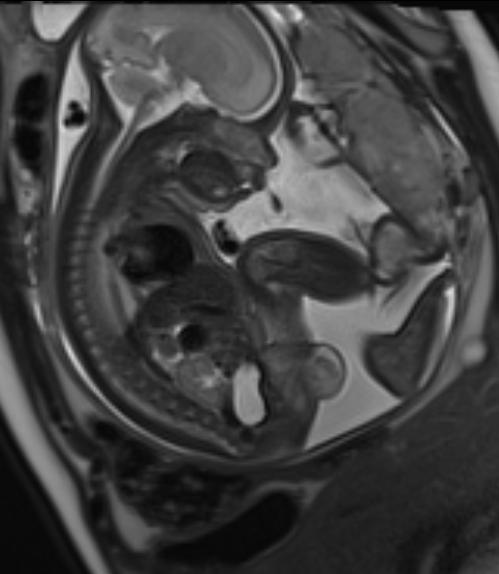
Figure 33 Coronal-Sagittal angle T2-weighted Image of a 34 GW foetus with Posterior Urethral valves. There is a Hydronephrosis, dilated ureter and a distended thick-walled urinary bladder (arrowed).

### *f*MRI addition of valuable information as per First Expert Panel:

*fMRI* added important information that could have changed management and/or counselling according to first expert panel in 13 cases of the GUS cohort. Two of these cases were suspected MCDK by prenatal USS which was later seen on *fMRI* as dilated pelvicalyceal systems suggesting PUJ obstruction. This could be seen as a fundamental change in diagnosis by some, but our first expert panel considered this change as a very important finding that would change management and counselling but not diagnosis. Their argument was that the key finding in this case was the appearance of the kidney (either as dilated pelvicalyceal system or cystic appearance) which prenatal USS was able to detect and both conditions could essentially give the same appearance on both scans.

*fMRI* added the findings of a duplex system with a ureterocoele in a foetus found by prenatal USS to have only a renal pelvis dilatation in the upper limit of normal. *fMRI* was also superior to USS in a foetal scan complicated by high maternal BMI and a severe oligohydramnios where *fMRI* found a structurally normal foetus whereas prenatal USS could not identify clear foetal anatomy.

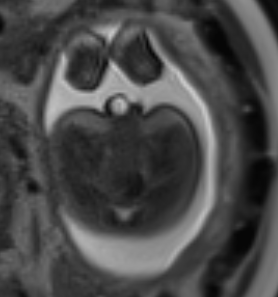
Prenatal USS could not identify the right kidney in a foetus during routine anomaly and subsequent scans and was assumed to be absent but was later found by *f*MRI in the foetal pelvis posterior to the bladder (Figure-34). *fMRI* was also superior to prenatal USS in visualising a female foetus external genitalia, adrenal glands and bladder which were all seen to be structurally normal apart from a simple labial cyst (Figure-35) that was identified by prenatal USS as ambiguous genitalia, suggesting hypertrophy of external female genitalia suspecting a virilising syndrome/adrenal abnormality. Appearance on prenatal USS also suggested partial emptying of the bladder which was seen to be normal on *f*MRI.



Right Ectopic Kidney

Urinary Bladder

Figure 34 Sagittal T2-Weighted Image of a 34 GW foetus with Ectopic Right Kidney found in the pelvis behind the urinary bladder (arrowed).



Labial Cyst

Labia

Figure 35 Axial T2-weighted Image of a 35 GW foetus with Simple Labial Cyst (arrowed).

In another case, prenatal USS could not surely ascertain the origin of a cystic structure appearance in the foetal abdomen/pelvis that appeared separate to the left kidney and pointed towards a diagnosis of a simple cyst. *fMRI* on the other hand, found that this cystic structure appeared closely related to the left kidney which was lower in position than normal (pelvic kidney) and it also had a tubular characteristic and did appear to move towards the bladder suggesting that this was a dilated ureter (pelvic kidney with a dilated ureter).

Both scans agreed on the diagnosis of a right PUJ obstruction with severe pelvicalyceal dilatation in one foetus but *fMRI* gave important findings about the function of the affected kidney (using DWI sequence) which was partially preserved and could also clearly visualise the resultant thinning of the renal parenchyma. In another foetus, *fMRI* confirmed prenatal USS diagnosis of left renal agenesis but it also found an enlargement of the contralateral kidney but with normal structure, morphology and more importantly function (most likely compensating) and it could identify a straight and slightly dilated rectum. According to the clinical experience of our experts, in previous cases with similar scan appearances of the rectum, babies were diagnosed with anal atresia at birth.

*fMRI* was superior to prenatal USS in identifying a tiny amount of renal tissue that had some signal from DWI suggesting function but not enough renal parenchyma for amniotic fluid production and lung development (Figure-36). It also could identify the stomach with tiny amount of fluid which was not visible on prenatal USS. In another similar case, *fMRI* confirmed the absence of any renal tissue and the presence of pulmonary hypoplasia with extremely reduced total lung volume and it could identify the bladder albeit with small amount of fluid. Prenatal USS appearances of this foetus renal system could only confirm the absence of one kidney with poor views of the other one with a tiny possibility of a single kidney and it could not identify the bladder.

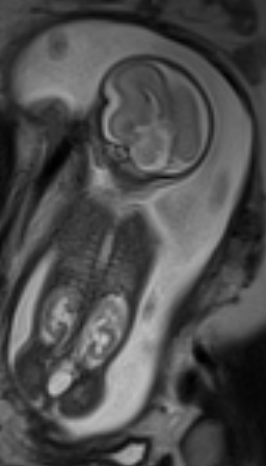
In a foetus with a prominent thick-walled urinary bladder on both scans suggesting bladder outlet obstruction or neurogenic bladder, prenatal USS views were somewhat limited by the advanced GA (37 GW) where the stomach appeared collapsed with prominent large bowel suggesting GI tract narrowing or atresia. The stomach and large bowel were clearly visible on *fMRI* and appeared to be normal.



Functioning Renal Tissue

Figure 36 Axial DW Image of a 21 GW foetus showing tiny amount of functioning Renal tissue (arrowed).

Finally, *fMRI* added an important finding of an ectopic insertion of mildly dilated tortuous ureters (possibly ureterocoele) into the vagina (Figure-37) which was not visible on prenatal USS in a foetus with complex abnormalities in both kidneys including a duplex system with mild pelvicalyceal dilatation on the left and a pelvicalyceal dilatation of the right kidney. In this foetus, *fMRI* could clearly distinguish between an anterior superior fluid filled urinary bladder and a posterior inferior fluid filled vagina.



Hydronephrosis

Dilated Ureter

Fluid Filled Vagina

Figure 37 Coronal T2-Weighted Image of a 28 GW foetus with ectopic insertion of the ureters into the Vagina resulting in Bilateral Hydronephrosis, dilated ureter and a fluid filled Vagina (arrowed).

## SKELETAL

The present study confirmed the added value of *f*MRI in evaluating foetal skeletal abnormalities with an overall diagnostic accuracy of 92% *(n=12),* a twenty three percent higher than prenatal USS with 69% *(n=9).* The diagnostic performance of both scans was best achieved among older foetuses (GA= >23 GW) with an accuracy that reached 100% for *f*MRI and 75% for prenatal USS compared to 75% for *f*MRI and 50% for prenatal USS among the younger foetuses (GA=<23 GW). Both scans’ results were similarly enhanced by the increasing GA with *f*MRI changing prenatal USS diagnoses in 8.3%. However, the significance of these results might be slightly controversial owing to the small size of this cohort which had confirmed postnatal outcome reference data to produce significant results, particularly for the small GA subgroup *(n=4)*. Although, foetal skeletal abnormalities are very rare, we managed to recruit a total number of 43 foetuses with these abnormalities but we were successful to obtain postnatal outcome data only in 13 cases (one of them had >2wks time delay, so was not included in GA analysis). Similarly, most of the studies currently in literature, which are limited, have a small sample size of foetal skeletal abnormalities. Our findings are in disagreement with those reported by Kul *et al.* (2012) study where 12 foetuses with skeletal abnormalities were included in which both scans provided accurate diagnoses similarly in 58% of cases with *f*MRI changed prenatal USS in 8% (the latter is similar to our finding). Also, in Amini *et al.* (2011) study where it included 7 foetuses with musculoskeletal abnormalities, they found no additional information was provided by *f*MRI to prenatal USS and in fact, prenatal USS was found to be superior to *f*MRI in 14% of cases. However, in line with our findings are those reported by Griffiths *et al.* (2006) in their study which evaluated the diagnostic accuracy of *f*MRI 50 foetuses with suspected spinal abnormalities in which *f*MRI had 100% accuracy compared to 80% for prenatal USS and provided additional information in 20% of cases. We found that *f*MRI added information to prenatal USS in 15% of cases (without the change in diagnosis which was 8.3%) but without effect on the course of management and counselling provided for the patients.

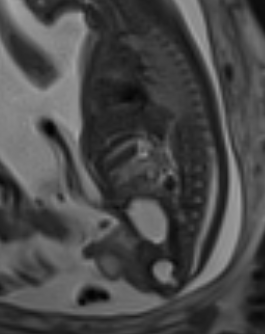
Our first expert panel results found that *f*MRI provided additional information in 65% that could change diagnoses in 28% and change management and/or counselling in 16% of cases.

Assessing foetal musculoskeletal system is usually challenging for both scans especially in younger GA where the foetus usually has enough space to be mobile producing movement artefacts that interfere with scan interpretation. Visualisation of the foetal skeleton is also challenging for both scans. As the foetus grows, the extent and distribution of bone ossification varies from week to week and appearances of skeletal abnormalities that might seem obvious in children are actually subtle in foetuses.

### We found that *f*MRI added information in the following cases:

A baby with Bowel duplication cyst verified postnatally, agreeing with *f*MRI differential diagnoses among Mullerian duct cyst, cystic sacrococcygeal teratoma or anterior meningocele with no significant effect on the surroundings (Figure-38), was picked up as SCT type-4 (internal) by prenatal USS. This was a fundamental change in diagnosis as seen by the first and second panels.

*f*MRI showed slight superiority over prenatal USS in a case with SCT confirmed postnatally by MRI spine at 6 days of life which also detected a spinal dysraphism and was later confirmed by a second MRI spine at 2 years of age. This lesion was surgically resected soon after birth. Postnatally the teratoma gave the appearance on MRI spine of a complex mixed cystic and solid mass below the sacrum without any attachments to the surrounding structures agreeing with *f*MRI. Prenatal USS was not completely certain about the diagnosis of a teratoma and suspected a neural tube defect as a deferential. It could only detect the cystic component of the mass. However, it did define the boundaries and confirm the absence of any apparent communication with the spine or spinal cord. The information added by *f*MRI was considered by the first expert panel to could have an impact on the course of management/counselling on this baby. The second expert panel decided that the information missed by prenatal USS did not have an impact on the final outcome for the baby.



Bowel Duplication Cyst

Rectum

Urinary Bladder

Figure 38 Sagittal T2-Weighted Image of a 25 GW foetus with Bowel Duplication Cyst (arrowed).

### We found that *f*MRI missed information in the following cases:

Both scans missed the finding of a segmentation anomaly that was confirmed postnatally with x-ray spine at 11 weeks. It also confirmed the prenatally suspected scoliosis. *f*MRI could detect a mild scoliosis but was unable to obtain any definitive bone imaging to ascertain the presence or absence of hemivertebra. Prenatal USS was unable to obtain a true alignment of the lumbar/thoracic spine pointing towards a diagnosis of hemivertebra or scoliosis. No hemivertebra was found postnatally. Both scans provided similar information according to the first expert panel and they both missed valuable information with effect on outcome according to the second expert panel.

### Fundamental change in diagnosis by *f*MRIas per First Expert Panel:

*fMRI* fundamentally changed prenatal USS diagnoses in 9 foetuses of the skeletal cohort. It could clearly visualise and evaluate the foetal skeleton in 6 of these foetuses and found them to have normal anatomy in which prenatal USS either suspected an anomaly or could not clearly visualise or confirm normality of foetal anatomy as follows: Prenatal USS was unable to obtain good views of the foetal skeleton and spine in one foetus due to high maternal BMI, foetal size and position and the views that were obtained gave an appearance of a defect with an uncertain nature. It also suspected the presence of an abnormal area in the cervical spine of another foetus suggesting what might be a scoliosis or a bony spur. It also spotted a persistent slight elevation (noted on several prenatal USS) of the spine in the lumbosacral region of another foetus. It suspected the presence of scoliosis in one case, suggested a hemivertebra in another and suspected the presence of a presacral mass of a third foetus. *fMRI* changed the diagnoses of SCT suggested by prenatal USS into myelomeningocele in 2 foetuses and a skin tag in 1 foetus.

### *f*MRI addition of valuable information as per First Expert Panel:

*fMRI* added important information that could have changed management and/or counselling according to first expert panel in 4 cases of the skeletal cohort. SCT was prenatally diagnosed by both scans in two of them. *fMRI* was superior to prenatal USS in providing valuable information regarding the accurate size, shape, attachments, tumour covering, thickening of the membrane covering with detailed description of its weakest part and the condition of the surrounding structures. The diaphragm appeared slightly elevated with no cause found on prenatal USS in one of these two cases in which *fMRI* identified upward displacement of the small bowel and liver by the tumour to be responsible for this elevation (Figure-39). Both scans suspected the diagnosis of scoliosis in one foetus with an appearance of mal-aligned foetal spine. Prenatal USS suspected that a hemivertebra could be responsible for this appearance but no structural vertebral defects were to be found on *fMRI*. In another case, both scans agreed on the presence of hemivertebra but *fMRI* added the presence of scoliosis and a prominent straight rectum suggesting the possibility of anal atresia (Figure-40).

Despite the general feeling that *f*MRI is not good for skeletal anomalies, this study has shown that *f*MRI provides a lot of additional information and not just for the associated abnormalities as suggested by Gilligan *et al.* (2020) but for the skeleton itself. Further development of new sequences will improve the diagnostic accuracy and increase the role of *f*MRI in the skeletal system Goodall *et al.* (2021).



Internal Cystic Component

External Solid Component

Displaced Liver

& Stomach

Figure 39 Sagittal T2-Weighted Image of a 21 GW foetus with Sacrococcygeal Teratoma causing upward displacement of abdominal organs resulting in elevation of the diaphragm (arrowed).



Prominent Straight Rectum

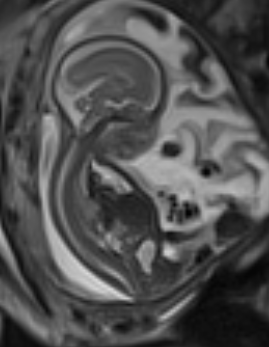
Figure 40 Sagittal T1-Weighted Image of a 21 GW foetus showing a prominent straight rectum raising a possibility of Anal Atresia (arrowed).

## NECK

In this study we found no difference in the diagnostic accuracies of both imaging modalities in foetal neck abnormalities. Both scans provided accurate diagnoses in all of the cases in the neck cohort *(100%, n=6)* that were verified postnatally. No differences in diagnostic accuracy was observed in the different GA groups. However, our first expert panel results showed that *f*MRI provided additional information in 69% that could change diagnoses in 7.7% or patient’s care in 38% of all cases. Our results are in agreement with those reported by Zemet *et al.*(2020) study in which they examined the value of *f*MRI in diagnosing congenital head, neck and face abnormalities in 45 foetuses including 6 foetuses with neck masses. They reported diagnostic accuracies of 100% for *f*MRI and 98% for prenatal USS with correction of prenatal USS diagnoses by *f*MRI in 33% of cases. Our findings are further supported by those reported by Ravelli *et al.*(2019) in which they examined the role of *f*MRI in the imaging of 19 foetal neck masses with a special focus on the evaluation of foetal airway. They found that in diagnosing foetal airway involvement, *f*MRI had a diagnostic accuracy of 89% and demonstrated 100% sensitivity. They also found that 47% of the babies needed respiratory care after delivery, 31% needed EXIT procedures and 15% needed endotracheal intubations. Their results demonstrate the importance of *f*MRI evaluation in such cases in which clinicians (particularly surgeons) need to know specific details about the anatomy of lesions and their relation to the surrounding structures. In our study, no paediatric surgeons were involved in either of our two panels. Despite the similarity between the results of *f*MRI and prenatal USS, we still believe that the use of *f*MRI in conjunction with prenatal USS is important in the evaluation of foetal neck abnormalities.

### Fundamental change in diagnosis by *f*MRIas per First Expert Panel:

*fMRI* fundamentally changed the prenatal USS diagnosis of pericardial effusion into a lymphangioma in one foetus. This was seen as a fluid filled collection in the superior mediastinal area that appeared to originate from the left side of the neck and was consistent with a lymphangioma (Figure-41).



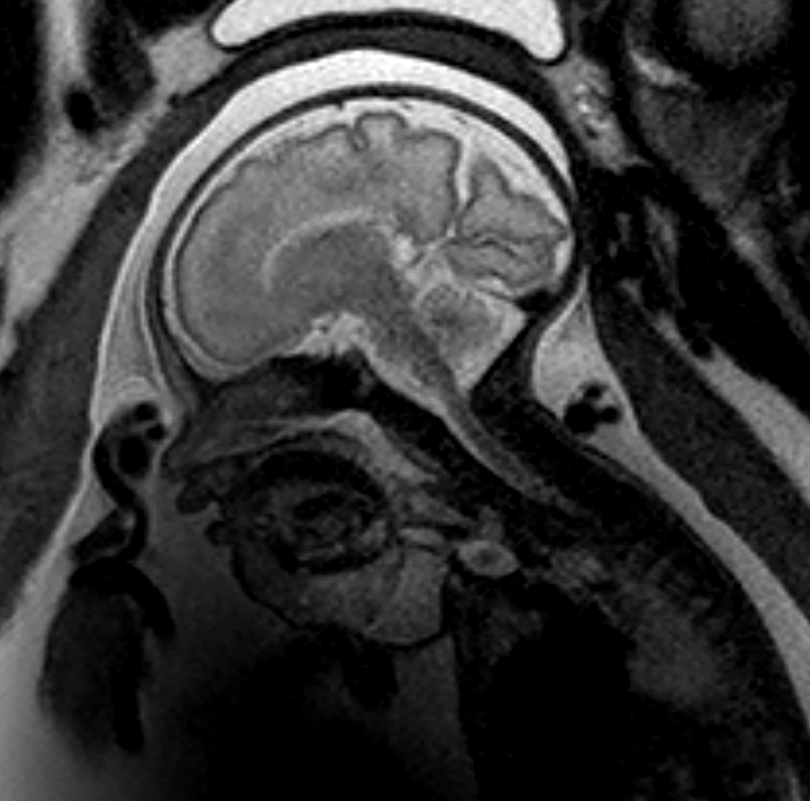
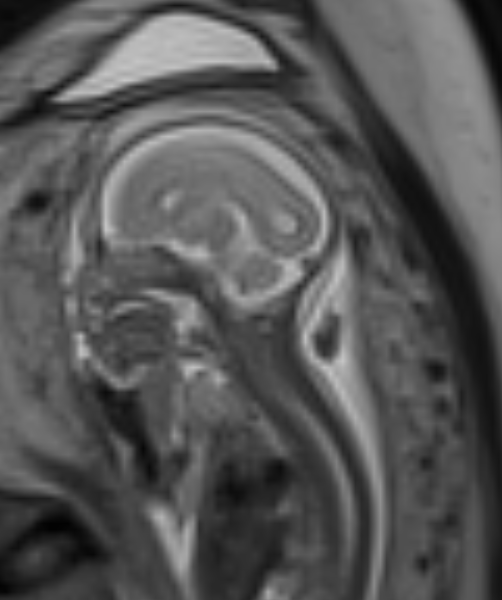
Lymphangioma

Figure 41 Sagittal T2-Weighted Image of a 19 GW foetus with a Lymphangioma (arrowed).

### *f*MRI addition of valuable information as per First Expert Panel:

*fMRI* added important information that could have changed management and/or counselling according to first expert panel in 3 foetuses of the neck cohort. It provided detailed anatomical description of cystic lesions with their relations to the surrounding structures particularly the nearby airways. Compression of the airways were noted in two foetuses (Figure-42 a,b) and bilateral pleural effusions in the third foetus. *f*MRI could also clearly visualise the lesions and by the images provided, the radiologist was able to identify the components of the lesion and possible areas for drainage if required or to allow access for tracheostomy if an airway could not be established.

The cohort here is very small making a generalised conclusion difficult but again *f*MRI had advantages over prenatal USS that were important in clinical management especially at the time of delivery. The addition of a paediatric surgeon to the expert panel should be considered in future studies.



Mass

Pharynx

Mass

Pharynx

Figure 42 fMRI of the Neck a) Sagittal T2-weighted Image of a 21 GW foetus with large Teratoma displacing airways (arrowed). b) Sagittal T2-Weighted Image of a 31 GW foetus with Haemangio-lymphangioma with slight compression of the Trachea (arrowed).

a

b

b

b

b

b

a

a

a

a

## MISCELLANEOUS

Our study results show that *f*MRI had a diagnostic accuracy of 83% *(n=5)* in detecting miscellaneous foetal abnormalities compared to 66.6% *(n=4)* for prenatal USS. It was possible to verify the postnatal diagnoses in only 6 cases, 5 of which were hydrops fetalis cases. In this case, *f*MRI diagnostic accuracy for detecting hydrops fetalis was 100% *(n=5)* compared to 80% *(n=4)* for prenatal USS. *f*MRI was not affected by GA in detecting foetuses with hydrops fetalis but it missed less valuable information in 1 cleft lip case which happened to be >23 GW. On the other hand, prenatal USS missed information about a foetus with hydrops fetalis in the younger GA group and a foetus with cleft lip in the older group but neither information was judged to have affected patient’s care. Our first expert panel assessment showed that *f*MRI added information to prenatal USS in 60% that could change diagnoses in 8.7% and management and/or counselling in 21.7% of cases. In line with our findings are those reported by Kul *et al.* (2012) in which they reported on 12 miscellaneous foetal abnormalities , 5 of which were foetuses with hydrops fetalis, that *f*MRI and prenatal USS provided correct diagnoses in 83% with *f*MRI correcting prenatal USS in 8% of cases. Our findings for this cohort are lower than those reported by Rodríguez *et al.* (2020) who included 96 foetuses with miscellaneous indications for *f*MRI. They found that *f*MRI had 99% diagnostic accuracy compared to 97% for prenatal USS. However, their miscellaneous cohort sample size was >4 times larger than our cohort. Second, indications for *f*MRI in their miscellaneous group varied significantly than the indications in our cohort. They had 47 cases with normal prenatal USS in high risk pregnancies in addition to 9 cases with placental pathologies and they also included 7 foetal musculoskeletal abnormalities in their miscellaneous cohort. The lack of consensus in the definition of miscellaneous abnormalities might explain the varying values between the results. Most of the studies available in the literature do not report on miscellaneous findings with all focus being confined to major body systems.

**We found that *f*MRI added information in the following cases:**

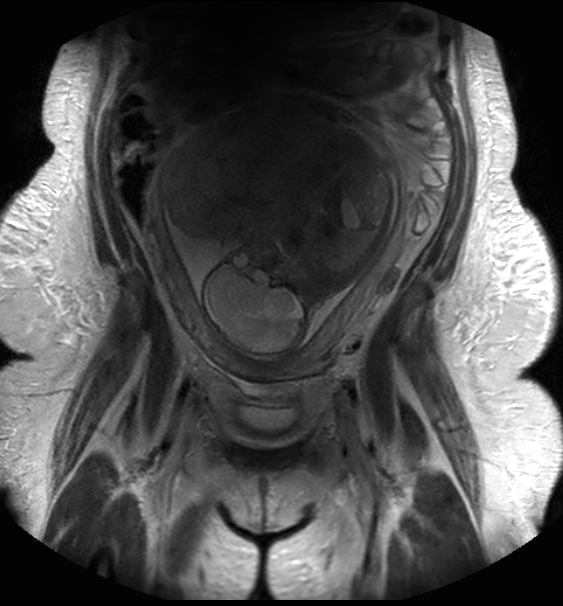
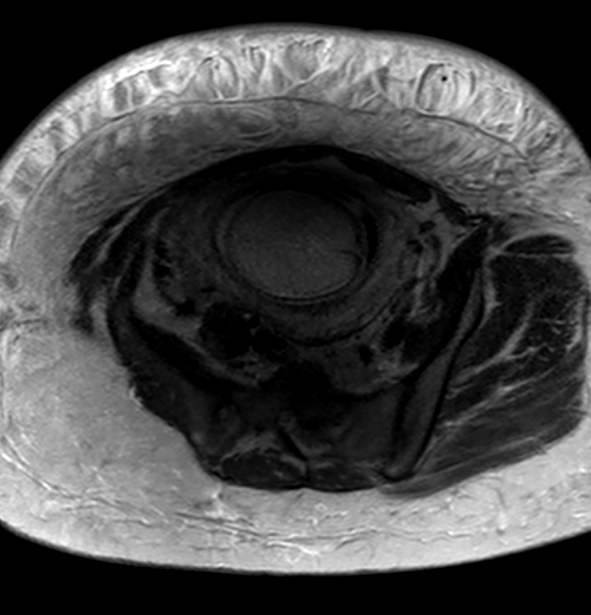
In one case with bilateral pleural effusions in the miscellaneous cohort confirmed with postnatal chest x-ray and echo, treated with pigtails insertion, *f*MRI provided the correct diagnosis. It also detected small trace of ascites and confirmed normal swallowing mechanism in the foetus by CINE images. It provided important information about the condition of the lungs and lung volume. Providing this extra information by *f*MRI has been reflected on the first expert panel decision of being able to change management and/or counselling. Prenatal USS on the other hand did not visualise any ascites and understandably could not comment on the condition or volume of the lung. Missing this information and looking at the course of management this foetus had, made the second expert panel to grade prenatal USS as only for missed information without effect on outcome.

### We found that *f*MRI missed information in the following cases:

Both scans missed less valuable information without effect on management and/or counselling in a case with bilateral Cleft Lip and Palate confirmed postnatally by physical features and examination. *f*MRI was correct about the Cleft Lip but it was technically challenging for it to get good views of the palate which appeared to be intact. Prenatal USS was significantly affected by maternal habitus and foetal position which resulted in extremely degraded images in this case. It was successful in finding both the Cleft lip and palate but with uncertainty. Both scans provided similar information according to the first expert panel.

### Fundamental change in diagnosis by *f*MRIas per First Expert Panel:

*fMRI* fundamentally changed prenatal USS diagnoses in 2 foetuses of the miscellaneous cohort (both had >2wks time delay). It was difficult to assess foetal anatomy by prenatal USS in one of these two foetuses due to maternal oedema and *fMRI* was performed on a 3T scanner with a wider bore than our 1.5T scanner as patient was claustrophobic all foetal anatomy was clearly seen and no maternal ascites was identified apart from abnormal looking subcutaneous fat (Figure-43). The second case was referred with prenatal USS appearance of multiple anomalies including increased nuchal thickening, duplex system, abnormal cerebellum and abnormal foot. *fMRI* found no structural abnormality in this foetus either.



a

a

a

a

b

b

Figure T2-Weighted Images of a 26 weeks GA foetus. Images showing Maternal abnormal Subcutaneous Tissue with no Ascites (arrowed). a) Coronal. b) Axial.b

b

Figure 43 T2-Weighted Images of a 26 GW foetus. Images showing Maternal abnormal Subcutaneous Tissue with no Ascites (arrowed). a) Coronal. b) Axial.

### *f*MRI addition of valuable information as per First Expert Panel:

*fMRI* added important information that could have changed management and/or counselling according to first expert panel in 3 foetuses of the miscellaneous cohort. It added the findings of profuse subcutaneous oedema over the whole foetus and hardly any lung tissue available in a foetus with hydrops in which only ascites was detected by prenatal USS. The second foetus was a suspected CMV infection as a result of a positive CMV IgM and IgG on TORCH screening test. Prenatal USS could only find an echogenic bowel but *fMRI* identified subtle abnormalities that definitely were not normal particularly in foetal brain in addition to a poorly filled stomach. The latter finding alone could easily change management and/or counselling if the poorly filled stomach turns out to be an oesophageal atresia. The third case was a suspected pelvic mass seen behind the bladder with ovarian cyst or dilated large bowel being among prenatal USS differentials. However, appearance of this pelvic mass on *fMRI* (Figure-44) was that of a proteinaceous fluid with haemorrhagic component in a form/shape suggesting a diagnosis of a dilated fluid filled vagina secondary to imperforate hymen (hydrocolpos). Bilateral hydronephrosis due to compression of the ureters by this hydrocolpos was also seen on *fMRI* with added comments about kidneys function with DWI sequence.

Overall conclusions from this group are impossible due to the diverse nature of the pathologies but this study has clearly shown a role for *f*MRI in all cases with abnormalities that are not 100% certain on the prenatal USS.



Vagina

Vagina

Figure Sagittal T2-Weighted Image of a 36 weeks foetus with Hydrocolpos (arrowed).Vagina

Vagina

Figure 44 Sagittal T2-Weighted Image of a 36 GW foetus with Hydrocolpos (arrowed).

# Chapter 6

# CONCLUSION, LIMITATIONS

# and

# FUTURE WORK

This study confirms the added clinical value of *f*MRI to prenatal USS in evaluating foetal non-CNS abnormalities. It has a superior diagnostic accuracy than prenatal USS in evaluating prenatally suspected foetal abnormalities, especially chest, abdomen and GUS abnormalities. The diagnostic performance of both scans is affected by different foetal body regions scanned. However, *f*MRI is less affected, especially when evaluating foetal GUS and abdominal abnormalities. In addition, it provides additional useful information to prenatal USS in all foetal body abnormalities. Therefore, to provide accurate detection of foetal body abnormalities, a combination of prenatal USS and *f*MRI should be used.

**Advantages and Limitation**s

This study has shown the added value of the *f*MRI and also shown the diagnostic accuracy of the *f*MRI in the same cases. This is important to establish so that the clinicians can be confident in the *f*MRI report and use it to determine the clinical care. Many studies compare the 2 scan techniques but do not compare them to the outcome data.

This study was performed in a single centre with over 20years experience in *f*MRI and may not reflect the value of *f*MRI in other less experienced centres.

The panels were comprised of clinicians in the same centre and whilst this reflects the clinical practice in the centre evaluating the value of *f*MRI and prenatal USS in clinical practice is challenging and subjective. Determination of their contribution is based on clinical evaluation of case scenarios and local experience. Therefore, larger panels including a wider range of experts would provide a more robust decision. Ideally the panel will reflect the multidisciplinary team members that could be involved in the patient pathway.

A prospective multicentre study may overcome some of the above limitations but even this is likely to contain bias. An international based study may reduce the bias but would be influenced by the local termination laws that affect when patients are referred for scans, the centres in utero surgery programmes, treatment guidelines and many more factors all of which vary between hospitals and countries.

**FUTURE WORK**

Unfortunately, this study was affected by the pandemic and the lockdowns. The plan was to collect as much postnatal outcome data as possible but reduced clinical access and the need to return to clinical work to provide ‘hands on deck’ for COVID patients meant this was not possible. However, power calculations made for this study (assuming a 10% difference, 10% variability and a two-sided test for 80% power and 5% significance) we needed to include 250 cases. We recruited almost double of what power calculation suggested to overcome any unforeseen problems that might arise during the study. If we assume a difference of 11% in power calculations, then we needed to include 210 cases. We have managed to collect postnatal outcome data for 239 cases with complete datasets of which 204 cases had final decisions by the second expert panel.

Post Hoc Power calculation on the data we collected and analysed gave a 99% power for the whole group. When we further measured power for cases with outcome in each cohort, we had 70% power for chest (69 complete datasets out of 132 cases), 56.7% power for abdomen (52 complete data sets out of 128), 57.7% power for GUS (58 complete data sets out of 142) and 28.7% power for skeletal cohorts. Although power was not reached for these cohorts, the statistical significance is very high. The sample size for the skeletal cohort is very small so might not reach power. Collecting the remaining outcome data is something we plan to do in the future. The data from this study will be used to calculate power for future studies.

We also plan to examine the value of *f*MRI based on gestational age in each cohort of the study to determine its strongest performance among different gestational ages.

This study provided an insight on the different clinical approaches taken in the evaluation of optimal management and counselling pathways of different foetal abnormalities. Therefore, involvement of more experts from different specialties and regions would allow for more accurate evaluation. It has become clear to me that the inclusion of a paediatric surgeon is essential and we should also consider a clinical geneticist. The panel should represent the multidisciplinary team potentially involved in the patient care pathway.

Generally, *f*MRI had high acceptance rate by the patients with only one patient refusing to take part in this study. During the consultations conducted with the patients after having *f*MRI, most of them had a general feeling that having the scan would help in providing more information and diagnostic accuracy about their babies and that would help them take proper actions, although difficult and worrying to some of them. All patients had the opportunity to see the images and have them explained to them along with the opportunity to ask questions. When patients undergo *f*MRI, their speculations sometimes are far worse than the truth and they are inevitably anxious between having the scan and when they are given the results by their referring foetal medicine clinicians. At our hospital, we have a patient consultation room sat up with a computer in the radiology department where patients can be shown the images and have findings explained to them straight after having the scan. This alleviates patients’ stress of uncertainty by immediate reassurance or explanation. In a study that looked at whether radiologists should consult patients immediately after the scans, Vallely and Mills (1990) found that >85% of patients would wish to know the results of the examination immediately. We understand this might not be popular with referring clinicians and they would prefer the results to be communicated with them and they will explain them to patients. In our hospital the referring clinicians are aware and approve of the radiologist discussing the results with the patient and this removes the need for a follow up appointment with the clinicians to receive the results. This effectively streamlines the service and reduces the number of foetal medicine appointments for each patient thus freeing up appointments for new referrals.

Radiologists too might be reluctant to discuss results with patients as they are only temporarily under their care and are not ultimately responsible for their clinical management.

Most of the patients referred to *f*MRI would have been given provisional diagnoses by their clinicians and *f*MRIs were requested to either confirm or refute them. Therefore, patients would have been already aware to an extent of their condition and of what to expect from *f*MRI making consultations with radiologists more straightforward.

We had intended to interview our patients in order to find out the impact of *f*MRI on them. This would have built on previous work done by some of the research team that examined mothers’ experience when having *f*MRI (Reed *et al.,* 2016). If restrictions remain, we will consider skype interviews or send small questionnaires to patients by post in order to continue our evaluation of the impact of *f*MRI on patients.

Finally, combining our study results with analysis for health economics will provide a clearer picture of the cost-effectiveness of *f*MRI when used in adjunct to prenatal USS. in this study, we started the process of analysis for health economics, with the relevant department (ScHARR) in which we provided them with the relevant data needed for the analysis but then all that had to stop during the lockdown last year. This needs to resume.

The work presented confirms the suggestions from smaller mixed case studies that *f*MRI has an important role to play in clinical decision making, a large prospective study would be of value as this is a single centre study that was performed in a centre of excellence with extensive experience of *f*MRI and might not reflect the experience in other centres. It does however reflect clinical practice.

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