Post-mortem examination of human fetuses: a comparison of whole-body high-field MRI at 9·4 T with conventional MRI and invasive autopsy

Sudhin Thayyil, Jon O Cleary, Neil J Sebire, Rosemary J Scott, Kling Chong, Roxanna Gunny, Catherine M Owens, Oystein E Olsen, Amaka C Offiah, Harold G Parks, Lyn S Chitty, Anthony N Price, Tarek A Yousry, Nicola J Robertson, Mark F Lythgoe, Andrew M Taylor

Summary

Background **Conventional whole-body MRI at 1·5 T does not provide adequate image quality of small fetuses, thus reducing its potential for use as an alternative to invasive autopsy. High-field whole-body MRI at 9·4 T provides good images of small animals. We therefore compared the diagnostic usefulness of high-field MRI with conventional MRI for post-mortem examination of human fetuses.**

Methods **We did whole-body MRI at 9·4 T and 1·5 T on 18 fetuses of less than 22 weeks' gestation, using three-dimensional T_2-weighted fast-spin echo sequences, before doing invasive autopsy. Images obtained with MRI for each system were compared with the findings of invasive autopsy in a blinded manner. Tissue contrast of 14 different regions was compared on 1·5 T and 9·4 T images that were provided by paediatric radiologists separately and in a random order, and image quality was scored on a four-point scale. The primary endpoint was diagnostic accuracy.**

Findings **Spatial resolution, tissue contrast, and image quality of all organ systems were much better with high-field MRI than with conventional MRI. All structural abnormalities that were detected with invasive autopsy and internal examination of visceral organs were also detected with high-field MRI, whereas conventional MRI was not diagnostically useful in 14 (78%) cases.**

Interpretation **Whole-body high-field MRI is a feasible option for post-mortem examination of human fetuses, and can provide good tissue characterisation even in small fetuses (5 g). The use of MRI at 9·4 T might be helpful in the development of a minimally invasive perinatal autopsy system.**

Funding **Department of Health Policy Research Programme, British Heart Foundation, National Institute of Health Research, Higher Education Funding Council for England, Biotechnology and Biological Sciences Research Council, Engineering and Physical Sciences Research Council, Great Ormond Street Hospital, University College London (UCL) Institute of Child Health, UCL Hospital, and UCL.**

Introduction

Despite the technological advances in antenatal diagnosis and screening, the role of perinatal autopsy in confirmation or refuting an antemortem diagnosis is undisputed.[1,2] With improvements in technology and increased use of early fetal ultrasound, malformations are detected early in pregnancy. When parents choose to terminate a pregnancy, post-mortem examination has an important role in confirmation of the diagnosis to inform discussion of recurrence risks and in the quality assurance of ultrasound screening programmes.[3,4]

However, conventional invasive autopsy might be difficult when fetuses are small, or maceration and autolysis are present, particularly for adequate examination of the brain and heart. This difficulty is compounded by an increase in the number of parents requesting a rapid return of internal organs to the body for burial; thus extended fixation for optimum examination of brain tissue is often not possible.[5] Furthermore, despite an increase in the rates of terminations of pregnancy, a substantial reduction in the rate of perinatal autopsies has been reported in the past decade.[6,7] The rates of traditional autopsy done after termination of pregnancy are 50–67% because for a substantial proportion of parents the traditional fetal autopsy is unacceptable.[6,7] Therefore, on the basis of these factors, the development of methods of assessment that have reduced invasiveness is important.

Although conventional whole-body MRI at 1·5 T was proposed as an alternative to perinatal autopsy more than a decade ago,[8] it has not become widely acceptable. The results of the first post-mortem MRI studies in fetuses suggested high sensitivity (100%) and specificity (92%) for imaging the brain, when compared with conventional autopsy.[8,9] However, the results from subsequent studies suggest that in up to 40% of cases the agreement between the findings of post-mortem MRI and autopsy are poor for the brain and spinal cord.[10,11] Moreover, accuracy of conventional post-mortem MRI at 1·5 T for other fetal organs, particularly the heart, is poor.[1,11–13]

We can do virtual histological examination using high-field MRI, particularly of the heart and brain in transgenic small animals[14,15] and in excised human

Lancet 2009; 374: 467–75

See **Comment** page 432

Centre for Cardiovascular Imaging, University College London (UCL) Institute of Child Health and Great Ormond Street Hospital for Children, London, UK (S Thayyil MD, A M Taylor MD)**; Department of Medical Physics and Bioengineering, UCL, London, UK** (J O Cleary BSc)**; Centre for Advanced Biomedical Imaging, Department of Medicine and UCL Institute of Child Health, London, UK** (J O Cleary, A N Price PhD, M F Lythgoe PhD)**; Department of Histopathology, UCL Institute of Child Health and Great Ormond Street Hospital for Children, London, UK** (N J Sebire MD)**; Department of Histopathology, UCL Hospital, London, UK** (R J Scott FRCPath)**; Department of Radiology, Great Ormond Street Hospital for Children, London, UK** (K Chong MD, R Gunny FRCR, C M Owens FRCR, O E Olsen PhD, A C Offiah PhD)**; UCL Institute of Neurology, Queens Square, London, UK** (H G Parks PhD, Prof T A Yousry MD)**; Clinical Molecular Genetics Unit, UCL Institute of Child Health, London, UK** (L S Chitty PhD)**; and UCL Institute of Women's Health, London, UK** (S Thayyil, L S Chitty, N J Robertson PhD)

Correspondence to:
Dr Sudhin Thayyil, Centre for Cardiovascular Imaging, University College London Institute of Child Health and Great Ormond Street Hospital, 30 Guilford Street, London WC1N 1EH, UK
s.thayyil@ich.ucl.ac.uk

tissues,[16,17] with an accuracy that might be equal to that of conventional light microscopy.[18] Moreover, because MRI is not invasive, it is not associated with the risk of tissue destruction or other artifacts that are produced during the process of tissue sectioning for histological examination.[14] For these reasons, we postulate that high-field (9·4 T) post-mortem MRI of fetuses would enable us to improve the signal to noise ratio, spatial resolution, and tissue contrast, thereby ultimately improving the diagnostic usefulness of post-mortem MRI in small fetuses compared with conventional MRI at 1·5 T.

	Conventional (1·5 T) MRI	High-field (9·4 T) MRI
Volume coil	Head	Rapid 39 mm, 72 mm, or 150 mm
Effective echo time (ms)	360	120
Relaxation time (ms)	3500	500
Echo train length	169	8
Field of view (mm)	125×200×64	100×50×50
Matrix (data points)	160×252×80	512×256×256
Voxel dimensions (mm)	0·8×0·8×0·8	0·2×0·2×0·2
Acquisitions (n)	10	1
Scan time (min)	≤50	≤70
Flip angle	90°/120°	90°/180°

Table 1: **Typical MRI variables for three-dimensional (isotropic) T_2-weighted fast-spin echo sequence**

Methods

Study population and procedures

The local research ethics committee approved the study. As stipulated by the research ethics committee (reference 04Q050841), we obtained parental consent for MRI.

We prospectively studied 20 consecutive fetuses of less than 22 weeks' gestation that were referred for conventional autopsy to Great Ormond Street Hospital for Children or University College London Hospital (both London, UK). Fetuses were kept in the mortuary at 4°C until immediately before MRI was done. Whole-body MRI was done in a 1·5 T scanner (Avanto, Siemens Medical Systems, Erlangen, Germany) and in one of two 9·4 T scanners (VNMRS, Varian, Palo Alto, CA, USA) with bore diameters of 20 cm and 30 cm. We used a three-dimensional T_2-weighted fast-spin echo sequence for whole-body MRI, with conventional and high-field scanners. Sequences at both field strengths were optimised for image quality for whole-body MRI, with a scan time of less than 2 h (table 1).

	High-field (9·4 T) MRI	Conventional (1·5 T) MRI	Invasive autopsy	Final diagnosis
Group A: fetuses obtained after termination of pregnancies (clinical details; gestational age; weight)				
Case 1: skeletal dysplasia (figure 3); 22 weeks; 400 g	Post-mortem IVH, and normal brain, all internal organs, and cartilaginous junction	Post-mortem IVH; normal brain, liver, spleen, kidneys, cartilaginous junction; non-diagnostic for other organs	All internal organs and cartilaginous junction normal	Skeletal dysplasia NOS
Case 2: myelomeningocele (figure 1); 19 weeks; 270 g	Post-mortem IVH, lumbosacral myelomeningocele, Chiari 2, frontoparietal germinal matrix bleed, all other internal organs normal	Post-mortem IVH, lumbosacral myelomeningocele, Chiari 2, frontoparietal germinal matrix bleed; normal liver, spleen, kidneys; non-diagnostic for other organs	Lumbosacral myelomeningocele, Chiari 2, normal internal organs	Lumbosacral myelomeningocele, Chiari 2
Case 3: right congenital diaphragmatic hernia, coarctation of aorta (figure 2); 16 weeks; 64 g	Post-mortem IVH, haematoma in choroid plexus and pons, large PDA, LV much smaller than RV, small aortic arch, no coarctation, pulmonary hypoplasia	Not done	Formal neuropathological examination normal, however unable to assess corpus callosum; large PDA, LV much smaller than RV, small aortic arch, no coarctation, pulmonary hypoplasia	Right congenital diaphragmatic hernia, small aortic arch, no coarctation of aorta, LV much smaller than RV, pulmonary hypoplasia
Case 4: fixed flexion deformity of limbs; probably progressive genetic disorder; 12 weeks; 16 g	Normal brain and internal organs	Too small to generate MRI signal	Normal brain and internal organs	Fixed flexion deformity of limbs undetermined
Case 5: cystic hygroma; 15 weeks+4 days; 20 g	No gross brain abnormalities, pleural and pericardial effusion, pulmonary hypoplasia, no cystic hygroma	Non-diagnostic for all organs	Severely macerated fetus, brain autolysed, formal neuropathological examination not possible, pulmonary hypoplasia, no cystic hygroma	Turner syndrome, pulmonary hypoplasia, no cystic hygroma
Group B: spontaneous miscarriages and unexplained intrauterine fetal deaths (time from death to delivery)				
n=4; <1 week	Normal brain and internal organs in 4 (100%)	Non-diagnostic images in 4 cases	Formal neuropathological examination not possible because of autolysis; other organs normal	Unexplained IUD in 3 cases chorioamnionitis in 1 cases
n=8; 2–7 weeks	Normal brain in 4 (50%), normal internal organs in 2 (25%), non-diagnostic images in 2 (25%)	Non-diagnostic images in 7 cases; fetus too small to generate MRI signal in 1 case	Formal neuropathological examination not possible because of autolysis; other organs normal	Unexplained IUD in 8 cases

IVH=intraventricular haemorrhage. NOS=not otherwise specified. PDA=patent ductus arteriosus. LV=left ventricle. RV=right ventricle. IUD=intrauterine death.

Table 2: **Comparison of high-field (9·4 T) MRI, conventional (1·5 T) MRI, and invasive autopsy**

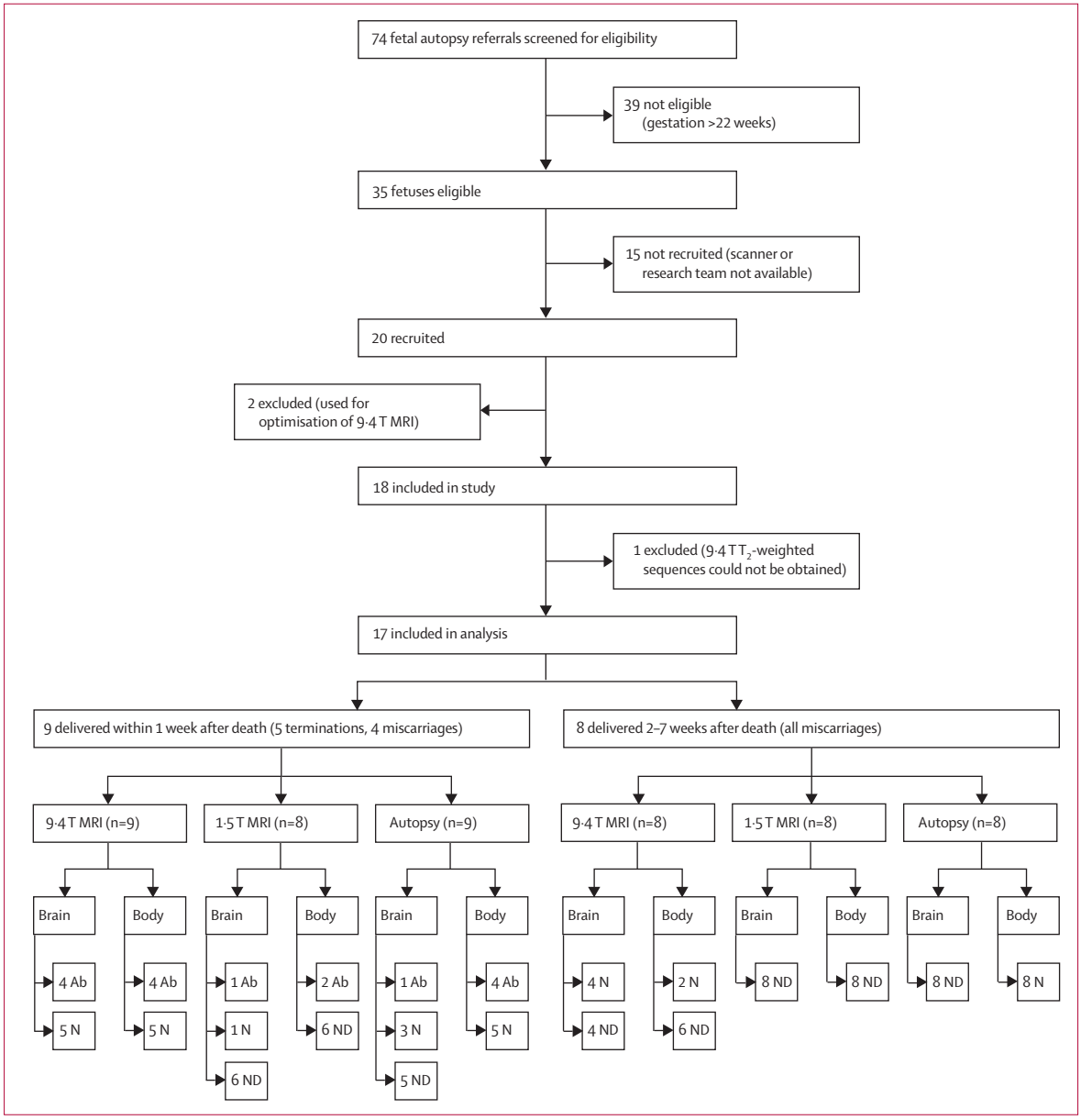

Figure 1: **Study profile**
Ab=abnormal. N=normal. ND=non-diagnostic.

A team of four paediatric radiologists (specialising in neurology, cardiology, chest and abdomen, and musculoskeletal system) provided images at 1·5 T and 9·4 T separately and in a random order, unaware of the unique identifiers of each case. Predefined variables, similar to those reported for clinical autopsy, including relevant negative variables were recorded for each system in one Microsoft Access database (version 2003). Each organ system was reported as abnormal (with actual diagnosis), normal, or not diagnostic. Additionally, the quality of the images at 1·5 T and 9·4 T were also interpreted according to a previously reported four-point quality rating scale for MRI—ie, poor, moderate, good, and excellent.[19]

Mean signal intensity in 14 regions of interest (2–3 regions per organ system) were calculated with ImageJ (version 1.40) by one operator (ST) with 2 years of experience in image processing. Size and position of these regions were equivalent for images at 1·5 T and 9·4 T. Tissue contrast was calculated with the formula[20]

$$\frac{\text{Signal intensity of area A} - \text{signal intensity of area B}}{\text{Signal intensity of area A} + \text{signal intensity of area B}}$$

In accordance with the guidelines of the Royal College of Pathologists, London, UK, conventional autopsy was done by one of four perinatal pathologists, with support

from a specialist paediatric cardiac pathologist and a paediatric neuropathologist if appropriate. For miscarriages, the duration of intrauterine retention after death was estimated from the difference between gestational age at delivery (predicted with early ultrasound or date of last menstrual cycle), and the autopsy parameters.[21] We inputted autopsy data into the same database, unaware of the MRI report. Microsoft Office database was split into one back end (data tables) and several front ends (data entry forms). Access of each radiologist or pathologist was restricted to their own front ends, which had separate passwords to log in. Only ST had access to the whole database, and therefore the pathologist and radiologist were mutually unaware of their reports.

We defined minimally invasive autopsy as an autopsy process that includes information from all non-invasive post-mortem investigations. These investigations include external examination of the fetus, placental histopathology, cytogenetic investigations, post-mortem radiography, and MRI, and exclude invasive dissection, and macroscopic or microscopic examination of visceral organs. Conventional (or invasive) autopsy included all invasive and non-invasive post-mortem investigations, but did not include information from MRI.

Statistical analysis

The primary endpoint was diagnostic accuracy and the secondary endpoint was image quality. We compared all data with the Mann-Whitney *U* test. A p value of less than 0·05 was taken to be significant. Data were analysed with SPSS (version 16.0 for Mac).

Role of the funding source

The study sponsors had no role in the design or conduct of the study, gathering, analysis, interpretation of the data, or writing of the report. All the authors had access to the data and had final responsibility for the decision to submit the report for publication. The report was read and approved by the Department of Health before submission.

Results

We obtained the optimum sequences for high-field MRI from two cases that were not included in further analyses. In one case, T_2-weighted images could not be obtained

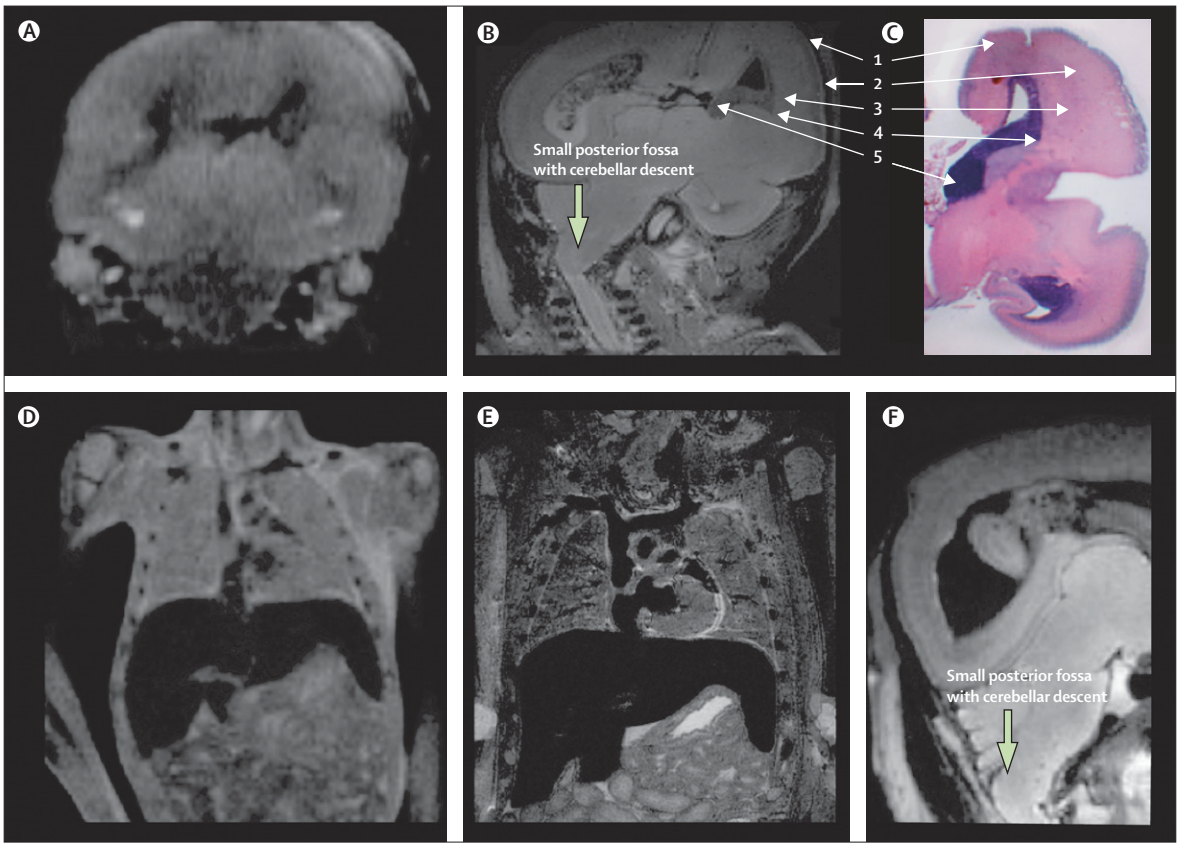

Figure 2: **MRI at 1·5 T and 9·4 T, and histopathological examination of a fetus with myelomeningocele terminated at 19 weeks' gestation**
(A) Three-dimensional T_2-weighted turbo-spin echo of head in coronal plane with MRI at 1·5 T. (B) Three-dimensional T_2-weighted turbo-spin echo of head in coronal plane with MRI at 9·4 T. (C) Histopathological examination of the brain showing a healthy multilayered cortex (1=cortical plate; 2=subplate; 3=intermediate zone; 4=subventricular zone; 5=ganglionic eminence). (D) Three-dimensional T_2-weighted turbo-spin echo of the body in coronal plane with MRI 1·5 T. (E) Three-dimensional T_2-weighted turbo-spin echo of body in coronal plane with MRI 9·4 T. (F) Sagital view showing the cerebellar descent and Chiari-2 malformation with MRI at 9·4 T. Features of Chiari 2 and myelomeningocele were seen with MRI at 1·5 T and 9·4 T, and at autopsy.

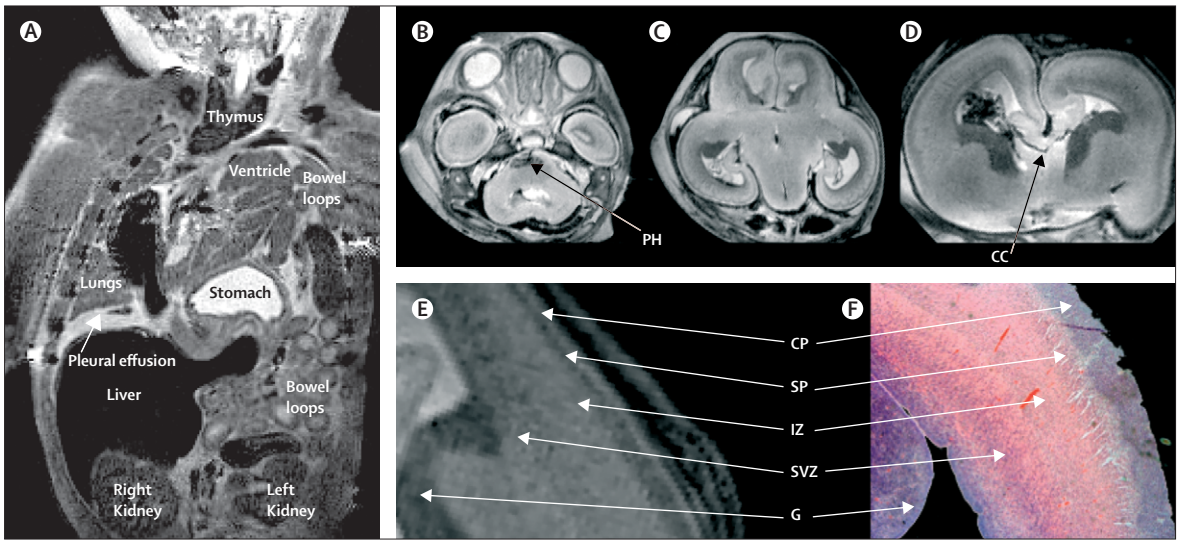

Figure 3: **High-field (9·4 T) MRI of a fetus with congenital diaphragmatic hernia and coarctation of the aorta terminated at 16 weeks' gestation (weight 64 g)**
(A) Coronal view of the chest and abdomen, showing left congenital diaphragmatic hernia with stomach, intestine, and spleen in right chest. Right ventricle shows substantial hypertrophy, and lungs are hypoplastic. Left ventricle was very small. No coarctation was seen, however the arch was small. (B) and (C) are axial views of the brain showing a pontine haematoma (PH). (D) Coronal view showing early normal development of corpus callosum (CC). (E) MRI at 9·4 T and (F) histology showing multilayered cortex. Corpus callosum could not be assessed at autopsy because of the poor preservation of brain. Formal neuropathological examination that was done by a paediatric neuropathologist showed a healthy brain, and no haematoma was seen. Results of a cardiac examination by a paediatric cardiac pathologist were in complete agreement with the MRI findings. CP=cortical plate. SP=subplate. IZ=intermediate zone. SVZ=subventricular zone. G=ganglionic eminence and ventricular zone.

at 9·4 T. Table 2 shows the results for the remaining 17 cases. Conventional MRI at 1·5 T could not be done in three cases because the fetuses were small. Figure 1 shows the study profile.

The median gestation of the fetuses was 16 weeks (range 11–22) and median weight was 59 g (5–400). All scans were done within 24 h of arrival of the fetus at the mortuary. Median time between delivery and MRI was 4 days (2–8), and that between MRI and autopsy was 1 day (0–5). Five cases were terminations of pregnancies, and 12 were unexplained intrauterine deaths, of which eight (67%) were retained in utero for more than 1 week after death. Four (24%) fetuses were fresh (ie, no evidence of maceration) and 13 (76%) were macerated or mummified when examined at the time of autopsy.

Figures 2–4 show the diagnostic accuracy of MRI. With MRI at 9·4 T, diagnostic images were obtained in all cases of termination of pregnancy and unexplained intrauterine deaths when the intrauterine retention period was less than 1 week (n=9). When the intrauterine retention period was more than 1 week (n=8), diagnostic images of the brain were obtained in four (50%) cases, and those of other visceral organs were obtained in two (25%) cases. With MRI at 1·5 T, diagnostic images of the brain and spinal cord were obtained in only two (14%) of 14 cases, whereas those of all the other internal organs were not diagnostic. With conventional autopsy, diagnostic information for the brain was obtained in four (24%) of 17 cases, and all of the remaining internal organs. Table 3 shows a comparison of the three methods of assessment.

For all cases, routine conventional autopsy of the brain did not provide any additional information to that obtained with 9·4 T MRI (table 3). In 13 cases in which formal autopsy of the brain was non-diagnostic because of autolysis, high-field MRI provided diagnostic information about the brain and spinal cord in nine (69%) fetuses. Furthermore, in all cases in which the

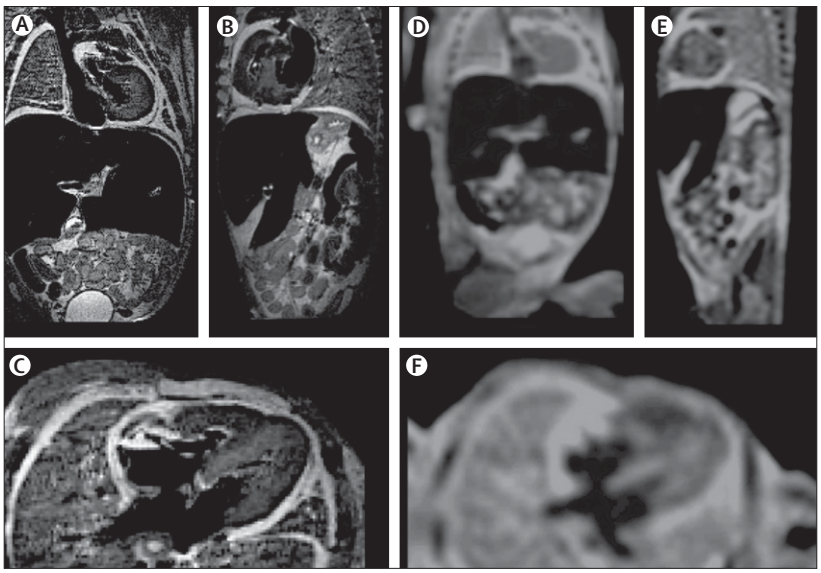

Figure 4: **Fetus with skeletal dysplasia terminated at 22 weeks' gestation**
(A) Coronal, (B) sagital, and (C) axial images obtained with three-dimensional T_2-weighted MRI at 9·4 T. (D) Coronal, (E) sagital, and (F) axial images obtained with three-dimensional T_2-weighted MRI at 1·5 T. Images at 9·4 T showed healthy cartilage and internal organs.

	Time between death to delivery (week)	Brain			Body		
		9·4 T	1·5 T	Autopsy	9·4 T	1·5 T	Autopsy
Case 1	≤1	Normal	Normal	Normal	Abnormal	Abnormal	Abnormal
Case 2	≤1	Abnormal	Abnormal	Abnormal	Abnormal	Abnormal	Abnormal
Case 3	≤1	Normal	Not done	Normal	Abnormal	Not done	Abnormal
Case 4	≤1	Normal	Non-diagnostic	Normal	Normal	Non-diagnostic	Normal
Case 5	≤1	Normal	Non-diagnostic	Non-diagnostic	Abnormal	Non-diagnostic	Abnormal
Case 6	≤1	Normal	Non-diagnostic	Non-diagnostic	Normal	Non-diagnostic	Normal
Case 7	≤1	Normal	Non-diagnostic	Non-diagnostic	Normal	Non-diagnostic	Normal
Case 8	≤1	Normal	Non-diagnostic	Non-diagnostic	Normal	Non-diagnostic	Normal
Case 9	≤1	Normal	Non-diagnostic	Non-diagnostic	Normal	Non-diagnostic	Normal
Case 10	>1	Normal	Non-diagnostic	Non-diagnostic	Normal	Non-diagnostic	Normal
Case 11	>1	Normal	Non-diagnostic	Non-diagnostic	Normal	Non-diagnostic	Normal
Case 12	>1	Normal	Non-diagnostic	Non-diagnostic	Non-diagnostic	Non-diagnostic	Normal
Case 13	>1	Normal	Non-diagnostic	Non-diagnostic	Non-diagnostic	Non-diagnostic	Normal
Case 14	>1	Non-diagnostic	Non-diagnostic	Non-diagnostic	Non-diagnostic	Non-diagnostic	Normal
Case 15	>1	Non-diagnostic	Non-diagnostic	Non-diagnostic	Non-diagnostic	Non-diagnostic	Normal
Case 16	>1	Non-diagnostic	Non-diagnostic	Non-diagnostic	Non-diagnostic	Non-diagnostic	Normal
Case 17	>1	Non-diagnostic	Non-diagnostic	Non-diagnostic	Non-diagnostic	Non-diagnostic	Normal

Table 3: **Comparison of diagnoses obtained with MRI at 9·4 T and 1·5 T, and invasive autopsy for cases 1–17**

	9·4 T MRI	1·5 T MRI	p value*
Brain	3·0 (1·6–3·8)	2·0 (1·0–1·5)	0·0042
Heart	3·5 (2·8–4)	1·0 (1·0–1·0)	0·0012
Chest and abdomen	4·0 (2·7–4)	1·0 (1·0–1·0)	0·0012
Musculoskeletal system	4·0 (2·7–4)	1·0 (1·0–1·0)	0·0011

Data are median (IQR). *Mann-Whitney *U* test.

Table 4: **Comparison of image quality scores obtained with MRI at 9·4 T and 1·5 T**

intrauterine retention period was less than 1 week, conventional autopsy did not provide any additional information to that obtained with MRI at 9·4 T.

Table 4 shows that for brain, heart, chest, abdomen, and musculoskeletal system, median image quality scores with MRI at 9·4 T were significantly better than those with conventional MRI at 1·5 T. Tissue contrast between different organs and tissues was much higher with MRI at 9·4 T than at 1·5 T (figure 5; table 5).

Mean image quality scores were significantly better with fresh fetuses (n=4) than with macerated stillbirths (n=13) for brain (4·0 [SE 0] versus 2·1 [0·9], p=0·0011), heart (4·0 [0] versus 2·8 [1·2], p=0·0445), and chest and abdomen (4·0 [0] versus 2·7 [1·2]; p=0·0445). No significant difference was noted in the image quality scores for the musculoskeletal system between fresh fetuses and macerated stillbirths (3·5 [0·6] and 3·2 [1·2], p=0·9624), indicating that maceration did not have any relevance in this system.

Seven structural abnormalities were diagnosed during antenatal ultrasonography in five fetuses (cases 1–5), and the pregnancies were subsequently terminated (figures 2–4). High-field (9·4 T) MRI and conventional autopsy were used to confirm five of these abnormalities and refute two (table 2, cases 3 and 5). Five additional malformations, which were not detected with antenatal ultrasonography, were diagnosed in three fetuses (cases 2, 3, and 5) from terminated pregnancies. These abnormalities were detected with high-field MRI and with conventional autopsy.

Discussion

High-field (9·4 T) MRI provided greater spatial resolution, higher tissue contrast, and better diagnostic information than did conventional (1·5 T) MRI. High-field MRI (and ancillary non-invasive post-mortem investigations) provided all the information that could be obtained with invasive autopsy for all internal organs in cases in which the intrauterine retention period was less than 1 week. Moreover, clinically useful information about the brain could be obtained even in cases in which maceration and autolysis prevented formal neuropathological examination. Conversely, conventional MRI was not diagnostic in most of these small fetuses.

Several researchers have reported that conventional MRI has poor diagnostic usefulness in small fetuses, particularly for organs other than the brain;[11,13,22] our data support this finding. Images with conventional MRI can be acquired with an in-plane resolution of 0·4 mm×0·4 mm;[9] however, the slice thickness might be 1 mm or 2 mm, thus introducing partial volume effects and preventing accurate analysis, particularly for organ systems other than the brain. Image quality might be improved if the coil is weighted with bags of saline;[23] however, the fundamental necessity

for increased image resolution is not changed. Theoretically, achievement of resolutions of up to 0·4 mm×0·4 mm×0·4 mm is possible by sequence optimisation of signal to noise and the acquisition of multiple averages with conventional MRI; however, long scanning times (up to 24 h) would be needed and would not be acceptable in the clinical setting. The increased diagnostic usefulness of MRI at 9·4 T is mainly because high-field isotropic three-dimensional images can be created, within clinically acceptable scan times.

One potential limitation associated with the use of MRI alone, irrespective of the field strength, is the absence of tissue availability for histological or ancillary diagnosis. Although histological examination is an integral part of perinatal autopsy, the usefulness of routine histological examination of all visceral organs is unclear when pregnancies are terminated because of fetal malformations.[4,24,25] Thus, for those women undergoing termination of pregnancy—ie, the fetuses for which high-field MRI provided the best image quality and diagnostic information—MRI might be the most appropriate first-line examination because the fetuses are least likely to have undergone changes that are secondary to maceration; structural abnormalities are the most likely findings; and histopathological examination has the least to offer.[4,24,25] Furthermore, for those organs in which histological examination might be important (lungs and kidneys), tissue could be obtained with image-guided percutaneous biopsies, without the need for open dissection of the body.[26] However, such an approach requires confirmation of diagnostic usefulness.

The other limitation is the rate of positive findings with MRI that are not identified during conventional autopsy, particularly intraventricular haemorrhage, germinal matrix bleeds, and haematomas in the brain, which might represent false-positive findings. Autopsy is the gold standard for post-mortem assessment of fetuses; however pathological lesions detected with post-mortem MRI of the brain, specifically the posterior fossa, without correlation with autopsy findings are increasingly reported.[8,27] Pathologists and radiologists should be aware of the potential for these false-positive findings[28] so that parents can be counselled appropriately.

All non-invasive post-mortem investigations including MRI are part of a minimally invasive autopsy process and should be thought of as a service provision provided by perinatal pathologists, in conjunction with specialist radiologists.[29] Two separate large studies in which the accuracy of conventional MRI at 1·5 T is being examined in children and adults are now in progress in the UK.[29] In the future, specialist pathologists might be able to offer a two-stage post-mortem process to parents, whereby an MRI at 9·4 T plus information from all other non-invasive tests with or without percutaneous biopsy is done first and then, if needed, a targeted internal examination of the body is done. Alternatively, this form of autopsy might be offered to parents who refuse conventional autopsy. Both these approaches would require close involvement and engagement of parents in the post-mortem process. Contrary to popular belief, we have noted that parents do wish to be closely involved

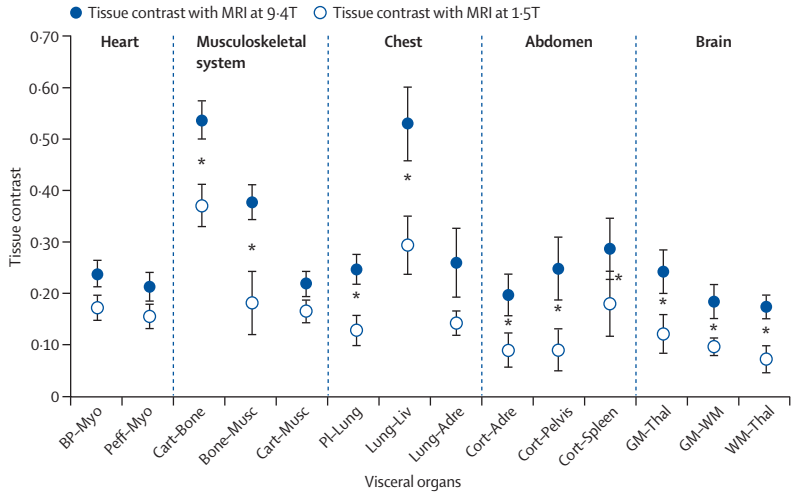

Figure 5: **Tissue contrast of visceral organs with MRI at 9·4 T and 1·5 T**
Squares represent mean values, and error bars represent SE. BP=blood pool in right ventricle. Myo=myocardium. Peff=pericardial effusion. Cart=cartilage (head of humerus). Bone=humeral metaphysis. Musc=muscle (upper arm). Pl=pleural effusion. Liv=liver. Adre=adrenal. Cort=renal cortex. Pelvis=renal pelvis. GM=germinal matrix. WM=white matter (periventricular region). Thal=thalamus. *p<0·05 (Mann-Whitney *U* test).

	Tissue contrast at 1·5 T	Tissue contrast at 9·4 T	*p value
Heart			
Right ventricular blood pool and ventricular wall	0·17 (0·02)	0·24 (0·02)	0·0513
Pericardial effusion and ventricular wall	0·15 (0·02)	0·21 (0·03)	0·0254
Musculoskeletal system			
Cartilage and bone	0·37 (0·09)	0·54 (0·04)	0·0019
Bone and muscle	0·18 (0·06)	0·38 (0·03)	0·0058
Cartilage and muscle	0·17 (0·02)	0·22 (0·02)	0·0513
Chest and abdomen			
Pleural effusion and lung parenchyma	0·12 (0·02)	0·25 (0·03)	0·0011
Lung and liver	0·29 (0·05)	0·53 (0·07)	0·0288
Lung and adrenal	0·14 (0·02)	0·26 (0·07)	0·4909
Renal cortex and adrenal	0·09 (0·03)	0·20 (0·04)	0·0121
Renal cortex and renal pelvis	0·09 (0·04)	0·25 (0·06)	0·0095
Renal cortex and spleen	0·17 (0·06)	0·29 (0·06)	0·0121
Brain			
Germinal matrix and thalamus	0·12 (0·03)	0·24 (0·04)	0·0004
Germinal matrix and periventricular white matter	0·09 (0·02)	0·18 (0·03)	0·0513
Periventricular white matter and thalamus	0·07 (0·02)	0·17 (0·02)	0·0029

Data are mean (SE). *Mann Whitney *U* test.

Table 5: **Tissue contrast with MRI at 1·5 T and 9·4 T with three-dimensional turbo spin echo sequences**

in the post-mortem process and research; this involvement might perhaps lead to a largely beneficial effect on their bereavement process.[30] Such an approach might increase the autopsy rates and bring back post-mortem research in the UK. The data presented in our study might be one step towards such a process. Although high-field MRI scanning capabilities are not available at all hospitals in the UK, they would be accessible in tertiary centres that undertake perinatal autopsy. Furthermore, costs for post-mortem MRI done at 9·4 T are similar to those at 1·5 T.

High-field MRI is at an experimental stage, and is being actively researched. Even though resolution of up to 18 μm is achievable with MRI at 9·4 T, scan times of more than 18 h might be needed, therefore reducing applicability for routine examination of human fetuses. Several rapid acquisition methods and high-field MRI staining techniques to increase image quality (eg, addition of gadolinium-diethylenetriaminopenta-acetic acid) have been developed for virtual autopsy of small animal embryos in the past few years.[14] Once these methods are adapted for use in human fetuses, three-dimensional virtual magnetic resonance microscopy might be possible and would greatly enhance our understanding of early normal and abnormal organ development in human fetuses.

Post-mortem whole-body MRI at 9·4 T is a feasible option for examination of small human fetuses, and can be done within clinically acceptable scanning times. This method might be a satisfactory alternative to conventional autopsy in small human fetuses.

Contributors

ST, KC, RG, CMO, OEO, TAY, NJR, ACO, HGP, MFL, JOC, ANP, and AMT made substantial contributions to study conception and design; data gathering, analysis, and interpretation. ST, CMO, TAY, NJR, and AMT contributed to drafting the report and figures, and intellectual content. ACO participated in drafting and editing the report. RJS made substantial contributions to the acquisition of data (doing many of the autopsies), and original study design for the Department of Health MRI autopsy study; and contributed comments for revision of the drafts of the report. NJS made substantial contributions to study design, data acquisition and analysis, and writing the report. OEO, MFL, JOC, and ANP participated in revising the report for intellectual content. LSC contributed to study design, interpretation of the data, and preparation of the report. All authors have approved the final version of the report.

MaRIAS (Magnetic Resonance Imaging Autopsy Study) Collaborative group

Alan Bainbridge (Medical Physics, University College London [UCL], London, UK), Jocelyn Brookes (Cardiac MRI, UCL), Lyn S Chitty (Fetal Medicine, UCL), Kling Chong (Paediatric Neuroradiology, Great Ormond Street Hospital [GOSH], London, UK), Andrew Cook (Cardiac Morphology, GOSH), Enrico de Vita (Medical Physics, UCL), Brian Harding (Paediatric Neuropathology, GOSH), Tom Jacques (Paediatric Neuropathology, GOSH), Rod Jones (Cardiovascular Imaging, GOSH), Mark F Lythgoe (High-Field Imaging, Centre for Advanced Biomedical Imaging, UCL), Wendy Norman (Cardiovascular Imaging, GOSH), Amaka C Offiah (Paediatric Musculoskeletal MRI, GOSH), Oystein E Olsen (Paediatric Chest and Abdomen Imaging, GOSH), Catherine M Owens (Paediatric Chest and Abdomen Imaging, GOSH), Nicola J Robertson (Neonatology, UCL), Tony Risdon (Paediatric Forensic Pathology, GOSH), Neil J Sebire (Perinatal and Paediatric Pathology, GOSH), Dawn Saunders (Paediatric Neuroradiology, GOSH), Angie Scales (Family Liaison Sister), Silvia Schievano (Medical Engineering, GOSH), Rosemary J Scott (Perinatal pathology, UCL Hospital), Andrew M Taylor (principal investigator, Centre for Cardiac Imaging, GOSH), Sudhin Thayyil (Centre for Cardiac Imaging, GOSH), Angie Wade (Paediatric Epidemiology and Biostatistics, UCL Institute of Child Health), Jolene Skordis-Worrall (Health Economics and Financing Program, London School of Hygiene and Tropical Medicine, London, UK).

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

We are indebted to Alistair Parker (UK Department of Health, London, UK), who has guided us through the process of this project. The work for this project was funded by the UK Department of Health (0550004) and the British Heart Foundation, London (CI/05/010). AMT is funded by the National Institute of Health Research, London (SRF/08/01/018). ST is funded by the UK Department of Health. NJR and NJS are funded by Higher Education Funding Council for England, Bristol, UK. MFL is funded by the British Heart Foundation, ANP is funded by Biotechnology and Biological Sciences Research Council, Swindon, UK, and JOC by the Engineering and Physical Sciences Research Council, Swindon. This work was undertaken at Great Ormond Street Hospital, Institute of Child Health, University College London Hospital, and University College London. University College London Hospital and University College London received a proportion of the funding from the UK Department of Health's National Institute of Health Research Biomedical Research Centres funding scheme.

References

1 Burton JL, Underwood J. Clinical, educational, and epidemiological value of autopsy. *Lancet* 2007; **369:** 1471–80.
2 The Lancet. Ensuring autopsy lives on. *Lancet* 2007; **369:** 1404.
3 Picone O, Levaillant JM, Hirt R, Frydman R, Boulvain M, Senat MV. Correlation between referral ultrasound with suspected foetal anomalies and autopsy examination in two prenatal diagnosis centres. Impact of the routine use of 3D/4D scan. *Prenat Diagn* 2008; **28:** 191–96.
4 Sankar VH, Phadke SR. Clinical utility of fetal autopsy and comparison with prenatal ultrasound findings. *J Perinatol* 2006; **26:** 224–29.
5 The Lancet. Autopsy at the crossroads. *Lancet* 2006; **367:** 1460.
6 Dickinson JE, Prime DK, Charles AK. The role of autopsy following pregnancy termination for fetal abnormality. *Aust N Z J Obstet Gynaecol* 2007; **47:** 445–49.
7 Khong TY, Tanner AR. Foetal and neonatal autopsy rates and use of tissue for research: the influence of 'organ retention' controversy and new consent process. *J Paediatr Child Health* 2006; **42:** 366–69.
8 Brookes JAS, Hall-Craggs MA, Sams VR, Lees WR. Non-invasive perinatal necropsy by magnetic resonance imaging. *Lancet* 1996; **348:** 1139–41.
9 Griffiths PD, Variend D, Evans M, et al. Postmortem MR imaging of the fetal and stillborn central nervous system. *AJNR Am J Neuroradiol* 2003; **24:** 22–27.
10 Cohen MC, Paley MN, Griffiths PD, Whitby EH. Less invasive autopsy: benefits and limitations of the use of magnetic resonance imaging in the perinatal postmortem. *Pediatr Dev Pathol* 2008; **11:** 1–9.
11 Breeze AC, Cross JJ, Hackett GA, et al. Use of a confidence scale in reporting postmortem fetal magnetic resonance imaging. *Ultrasound Obstet Gynecol* 2006; **28:** 918–24.
12 Griffiths PD, Paley MNJ, Whitby EH. Post-mortem MRI as an adjunct to fetal or neonatal autopsy. *Lancet* 2005; **365:** 1271–73.
13 Alderliesten ME, Peringa J, van der Hulst VP, Blaauwgeers HL, van Lith JM. Perinatal mortality: clinical value of postmortem magnetic resonance imaging compared with autopsy in routine obstetric practice. *BJOG* 2003; **110:** 378–82.
14 Driehuys B, Nouls J, Badea A, et al. Small animal imaging with magnetic resonance microscopy. *Ilar J* 2008; **49:** 35–53.
15 Schneider JE, Bamforth SD, Farthing CR, Clarke K, Neubauer S, Bhattacharya S. Rapid identification and 3D reconstruction of complex cardiac malformations in transgenic mouse embryos using fast gradient echo sequence magnetic resonance imaging. *J Mol Cell Cardiol* 2003; **35:** 217–22.

16 Scholtes F, Adriaensens P, Storme L, et al. Correlation of postmortem 9·4 Tesla magnetic resonance imaging and immunohistopathology of the human thoracic spinal cord 7 months after traumatic cervical spine injury. *Neurosurgery* 2006; **59:** 671–78.

17 Beuls EA, Vanormelingen L, van Aalst J, et al. In vitro high-field magnetic resonance imaging-documented anatomy of a fetal myelomeningocele at 20 weeks' gestation. A contribution to the rationale of intrauterine surgical repair of spina bifida. *J Neurosurg* 2003; **98:** 210–14.

18 Petiet AE, Kaufman MH, Goddeeris MM, Brandenburg J, Elmore SA, Johnson GA. High-resolution magnetic resonance histology of the embryonic and neonatal mouse: a 4D atlas and morphologic database. *Proc Natl Acad Sci USA* 2008; **105:** 12331–36.

19 Wyttenbach R, Gianella S, Alerci M, Braghetti A, Cozzi L, Gallino A. Prospective blinded evaluation of Gd-DOTA- versus Gd-BOPTA-enhanced peripheral MR angiography, as compared with digital subtraction angiography. *Radiology* 2003; **227:** 261–69.

20 McRobbie DW, Moore EA, Graves MJ, Prince MR, eds. MRI from picture to proton. 2nd edn. Cambridge: Cambridge University Press; 2007: 66–67.

21 Maroun LL, Graem N. Autopsy standards of body parameters and fresh organ weights in nonmacerated and macerated human fetuses. *Pediatr Dev Pathol* 2005; **8:** 204–17.

22 Thayyil S, Schievano S, Robertson NJ, et al. A semi-automated method for non-invasive internal organ weight estimation by post-mortem magnetic resonance imaging in fetuses, newborns and children. *Eur J Radiol* 2009; published online Sept 2. DOI:10.1016/j.ejrad.2008.07.013.

23 Whitby EH, Paley MN, Cohen M, Griffiths PD. Postmortem MR imaging of the fetus: an adjunct or a replacement for conventional autopsy? *Semin Fetal Neonatal Med* 2005; **10:** 475–83.

24 Corabian P, Scott NA, Lane C, Guyon G. Guidelines for investigating stillbirths: an update of a systematic review. *J Obstet Gynaecol Can* 2007; **29:** 560–67.

25 Curry CJ. Pregnancy loss, stillbirth, and neonatal death. A guide for the pediatrician. *Pediatr Clin North Am* 1992; **39:** 157–92.

26 Aghayev E, Ebert LC, Christe A, et al. CT data-based navigation for post-mortem biopsy—a feasibility study. *J Forensic Leg Med* 2008; **15:** 382–87.

27 Lavanya T, Cohen M, Gandhi SV, Farrell T, Whitby EH. A case of a Dandy-Walker variant: the importance of a multidisciplinary team approach using complementary techniques to obtain accurate diagnostic information. *Br J Radiol* 2008; **81:** e242–45.

28 O'Donnell C, Woodford N. Post-mortem radiology—a new sub-speciality? *Clin Radiol* 2008; **63:** 1189–94.

29 Thayyil S, Robertson NJ, Scales A, et al. MaRIAS (Magnetic Resonance Imaging Autopsy Study) Collaborative Group. Prospective parental consent for autopsy research following sudden unexpected childhood deaths: a successful model. *Arch Dis Child* 2009; **94:** 354–58.

30 Thayyil S, Robertson NJ, Scales A, Sebire NJ, Taylor AM. Parental consent for research and sudden infant death. *Lancet* 2008; **372:** 715.