Post-mortem MRI versus conventional autopsy in fetuses and children: a prospective validation study

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Summary

Background Post-mortem MRI is a potential diagnostic alternative to conventional autopsy, but few large prospective studies have compared its accuracy with that of conventional autopsy. We assessed the accuracy of whole-body, post-mortem MRI for detection of major pathological lesions associated with death in a prospective cohort of fetuses and children.

Methods In this prospective validation study, we did pre-autopsy, post-mortem, whole-body MRI at 1·5 T in an unselected population of fetuses (≤24 weeks' or >24 weeks' gestation) and children (aged <16 years) at two UK centres in London between March 1, 2007 and Sept 30, 2011. With conventional autopsy as the diagnostic gold standard, we assessed MRI findings alone, or in conjunction with other minimally invasive post-mortem investigations (minimally invasive autopsy), for accuracy in detection of cause of death or major pathological abnormalities. A radiologist and pathologist who were masked to the autopsy findings indicated whether the minimally invasive autopsy would have been adequate. The primary outcome was concordance rate between minimally invasive and conventional autopsy.

Findings We analysed 400 cases, of which 277 (69%) were fetuses and 123 (31%) were children. Cause of death or major pathological lesion detected by minimally invasive autopsy was concordant with conventional autopsy in 357 (89·3%, 95% CI 85·8–91·9) cases: 175 (94·6%, 90·3–97·0) of 185 fetuses at 24 weeks' gestation or less, 88 (95·7%, 89·3–98·3) of 92 fetuses at more than 24 weeks' gestation, 34 (81·0%, 67·7–90·0) of 42 newborns aged 1 month or younger, 45 (84·9%, 72·9–92·1) of 53 infants aged older than 1 month to 1 year or younger, and 15 (53·6%, 35·8–70·5) of 28 children aged older than 1 year to 16 years or younger. The dedicated radiologist or pathologist review of the minimally invasive autopsy showed that in 165 (41%) cases a full autopsy might not have been needed; in these cases, concordance between autopsy and minimally invasive autopsy was 99·4% (96·6–99·9).

Interpretation Minimally invasive autopsy has accuracy similar to that of conventional autopsy for detection of cause of death or major pathological abnormality after death in fetuses, newborns, and infants, but was less accurate in older children. If undertaken jointly by pathologists and radiologists, minimally invasive autopsy could be an acceptable alternative to conventional autopsy in selected cases.

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Introduction

Autopsy can confirm or augment antemortem findings, provide information for accurate counselling about recurrence risk and implications for other family members, advance medical research, and provide disease-specific mortality statistics.[1,2] Despite the recognised value of the procedure, rates of non-forensic autopsy have fallen worldwide.[3] In the UK between 2000, and 2007, consent rates for fetal autopsy declined from 55% to 45%, and rates for neonatal autopsy declined from 28% to 21%, despite increases of more than 90% and 80%, respectively, in the number of parents offered autopsy.[4] Parental objection was the main cause for conventional autopsy not being done.[4]

Initial reports suggesting the effectiveness of post-mortem MRI were published more than a decade ago.[5] Since then, various studies[6–9] have examined the use of post-mortem MRI as an alternative or adjunct to conventional autopsy. Minimally invasive, post-mortem MRI is more acceptable to parents and next of kin than conventional autopsy,[10,11] and consequently, some UK health-care providers now offer post-mortem MRI, with a death certificate based on MRI findings accepted as a medicolegal document.[12] However, evidence for the accuracy of post-mortem MRI is scarce. Published studies[8,9,13,14] have been small or retrospective with no adequate masking of MRI and autopsy reports, and are mainly based on fetal brain imaging. A systematic review and meta-analysis[15] of the existing scientific literature concluded that data were insufficient to support or refute the accuracy of post-mortem MRI as an alternative to conventional autopsy.

To address this issue, we assessed the accuracy of whole-body, post-mortem MRI, with and without other minimally invasive ancillary investigations, for detection of major pathological lesions that either contributed to, or were responsible for, death in a large prospective cohort of fetuses and children.

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See Online for appendix

Methods

Study design and population

In this prospective validation study, we undertook whole-body, post-mortem MRI at Great Ormond Street Hospital for Children and University College London Hospital (both London, UK) between March 1, 2007 and Sept 30, 2011, in a sequential population of fetuses (≤24 weeks' or >24 weeks' gestation) and children (aged ≤16 years) for whom parental consent for conventional autopsy was available. Eligible cases were undergoing conventional autopsy. We excluded cases with no available consent or for which MRI could not be done before autopsy. We obtained informed parental consent for consented autopsies. Research consent in legally mandated Her Majesty's coronial autopsies is complex because of various legal, ethical, and logistical issues; therefore, we developed an effective prospective telephone consenting model, which has been previously reported.[16,17] The study had institutional approval (reference 04/Q0508/41).

Procedures

The study protocol has been previously published.[18] All bodies were stored in a mortuary at 4°C for 1–6 days before MRI. We mainly used high-resolution, T2-weighted, three-dimensional (3D) sequences to improve tissue characterisation of organs, and did not use any exogenous contrast agents (appendix). Total MRI scan time was about 90 min in fetuses and 60 min in children. Scans were done as soon as practically possible; in most cases, this was 1–7 days after death. One of two MRI radiographers (both with 12 years' MRI experience) or one neonatologist (1 year of MRI experience) did all post-mortem MRI scans. Most scans were done out-of-hours (between 6 pm and 8 am) with no disturbance to the clinical service.

Image interpretation was done for the nervous, cardiovascular, pulmonary and abdominal, and musculoskeletal body systems. A specialist paediatric radiologist reported each system (four radiologists per case) masked to the clinical details and autopsy findings. Each report was entered into a Microsoft Access database (Version 12), with predefined drop-down menus of categorical variables (based on standard autopsy reporting).[18] One of three neuroradiologists (WKC, RSG, DES) reported on the nervous system, one cardiac radiologist (AMT) reported on the cardiovascular system, one of two body radiologists (OO, CMO) reported on the pulmonary and abdominal systems, and one musculoskeletal radiologist (ACM) reported on the musculoskeletal system. All radiologists were

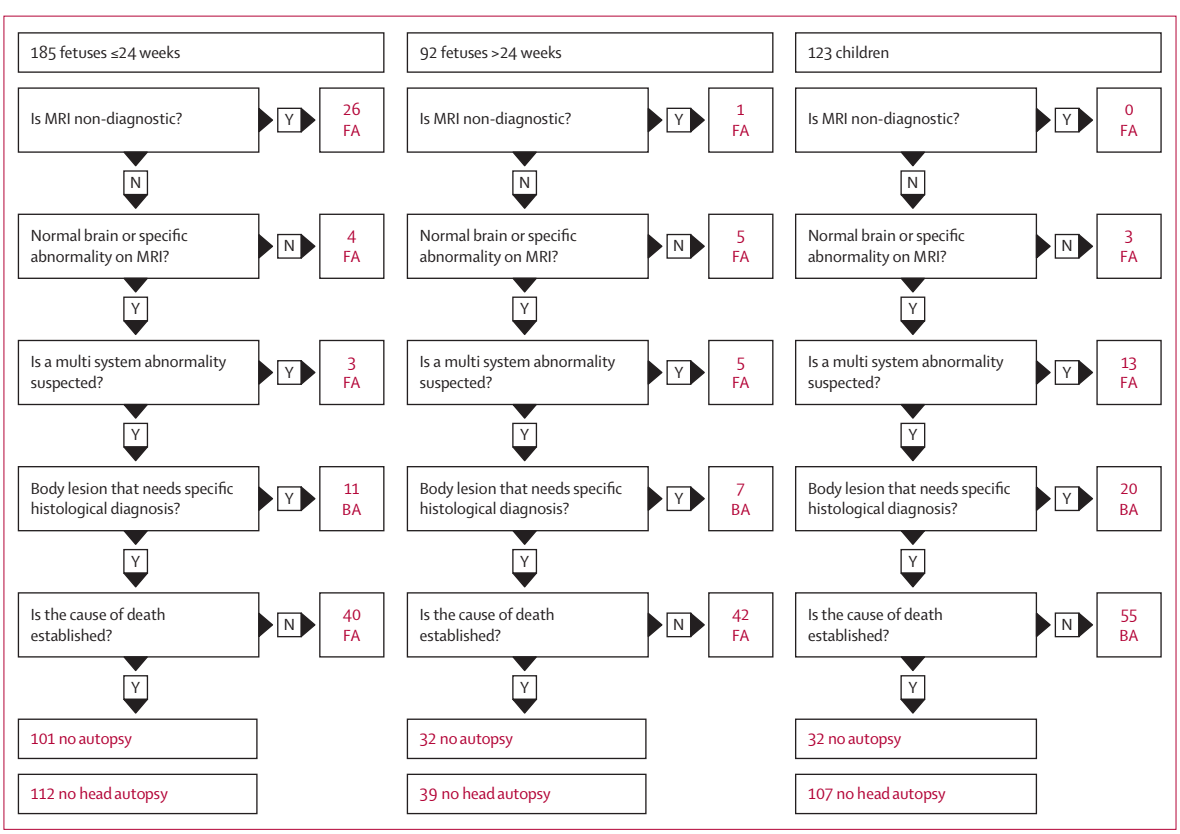


***Figure 1*: Predefined criteria to predict whether a full or partial conventional post-mortem examination was needed on the basis of the minimally invasive assessment**
FA=full autopsy. BA=body autopsy. Y=yes. N=no.

accredited by the Royal College of Radiologists (London, UK) and had at least 8 years of clinical reporting experience. We regarded small fetal ventricular bleeds without dilation; retinal detachment with collapsed eyeballs; small amounts of pleural, pericardial, or peritoneal fluid; and air in the liver or biliary tree as post-mortem MRI artifacts or intrapartum artifacts with no clinical significance,[12] and hence did not include them in the analysis.

We defined minimally invasive autopsy as a post-mortem investigation with no incisions or dissection, but with post-mortem blood sampling via needle puncture. This procedure included a review of the cases' clinical history and a summary of the relevant ante-mortem information, external examination, post-mortem MRI and other post-mortem imaging, genetic and metabolic tests (antemortem or post-mortem blood sampling), and examination of the placenta or placental tissue.[19] The minimally invasive procedure did not include histological tissue sampling by percutaneous biopsy. If MRI was of non-diagnostic quality and the ancillary investigations could not be obtained, we deemed minimally invasive autopsy as non-diagnostic. Before the study started, a radiologist (AMT) and a pathologist (NJS) defined a set of general best-guess criteria to predict whether a full or partial conventional post mortem could be avoided on the basis of minimally invasive assessment (figure 1). We applied these criteria to the reports for minimally invasive autopsy once the study was complete.

We defined conventional autopsy as a procedure that included open dissection of any body part and ancillary post-mortem investigations, but with exclusion of post-mortem MRI. One of seven perinatal or paediatric pathologists did conventional autopsy as part of routine clinical practice according to national guidelines[20] and the Kennedy protocol,[21] masked to the MRI findings. Briefly this procedure included a review of clinical history and all relevant antemortem information, post-mortem radiography; external examination; open dissection; and macroscopic examination, followed by histological sampling of all major organs; removal of the brain with examination after fixation; and ancillary investigations, such as genetic and metabolic testing and virology and microbiology sampling. Routine microbiology samples were obtained from cardiac blood, cerebrospinal fluid, the lung, and the spleen, with additional samples when specifically indicated. Placental histopathological examination was done in all fetal autopsies. All pathologists undertaking conventional autopsy had at least 8 years' experience of perinatal or paediatric autopsies and were accredited by the Royal College of Pathologists (London, UK). Autopsy data were entered into the same database, but with different entry forms with data masked to the MRI dataset.

Statistical analysis

Before data unmasking (ie, before comparisons were made between data for minimally invasive and conventional autopsy), a pathologist, radiologist, and neonatologist reviewed all the MRI scans alone, and minimally invasive autopsy and pathology reports separately, in random order and several weeks apart, to define a cause of death or the most clinically important pathological abnormality for each case.

Primary outcome was concordance (yes or no), which we summarised as the proportion of cases for which minimally invasive autopsy (index test) identified the same cause of death or major pathological change as conventional autopsy (gold standard). Secondary outcomes were the proportion of cases in which all incidental pathological lesions were correctly identified, irrespective of whether they contributed to death, expressed as the proportion of undetected pathological lesions (false negatives) and apparent overcalls (false positives). We did subgroup analysis on the basis of age (fetuses ≤24 weeks' or >24 weeks' gestation, and children

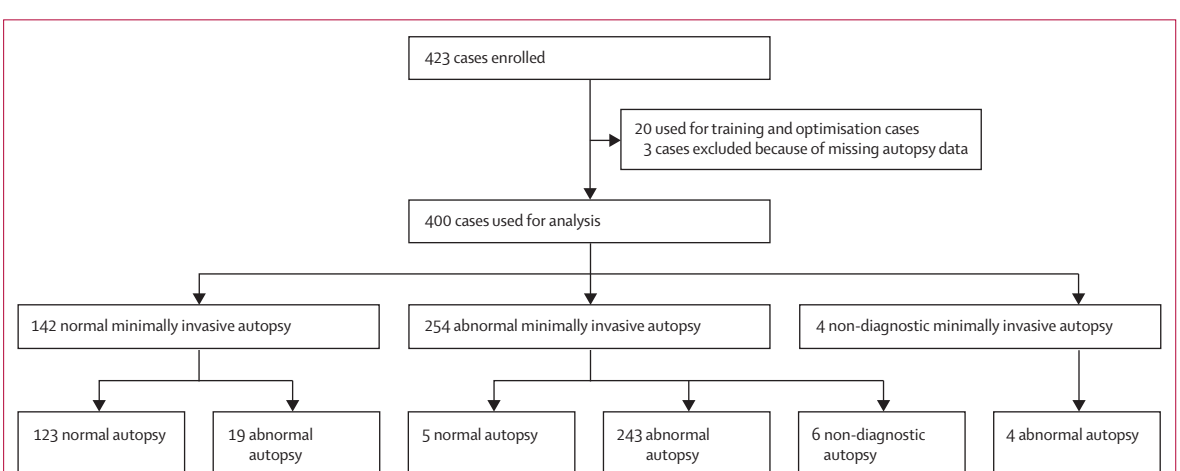


Figure 2: **Study profile**

	Fetuses ≤24 weeks (n=185)	Fetuses >24 weeks (n=92)	Children (n=123)	Total (n=400)
Brain or spinal cord	32 (17%)	31 (34%)	50 (4%)	113 (28%)
Intracranial bleed	2	6	21	29
Anencephaly	0	1	0	1
Callosal agenesis	2	2	0	4
Cerebellar fossa cyst	1	0	0	1
Other brain malformations	6	2	2	10
Cortical maldevelopment	1	0	0	1
Dandy-walker variant	2	0	0	2
Microlissencephaly	0	1	0	1
Ventriculomegaly	2	2	0	4
Neural-tube defect	12	1	0	13
Porencephaly	0	0	1	1
Precocious gyration	1	0	0	1
Schizencephaly	1	1	1	3
Dysplasia of dentate nucleus	0	1	0	1
Ischaemic injury	0	10	15	25
Acquired brain damage	0	1	0	1
Haemangioma	0	0	1	1
Cerebral infarction	0	1	0	1
Chloroma	0	1	0	1
Complex neuropathological changes	0	0	1	1
Diffuse brain injury	0	1	7	8
Infective brain lesion	1	0	0	1
Reduced white matter	0	0	1	1
Tumour	1	0	0	1
Heart	20 (11%)	5 (5%)	22 (18%)	47 (12%)
Major congenital heart disease	16	3	8	27
Minor congenital heart disease	3	1	2	6
Myocarditis	0	0	8	8
Other	1	1	4	6
Lungs	35 (19%)	16 (17%)	62 (50%)	113 (28%)
Abnormal lobation	2	0	0	2
Absent nostrils	1	0	0	1
Congenital diaphragmatic hernia	2	0	0	2
Absent lungs	0	1	0	1
Pulmonary hypoplasia	11	2	3	16
Subglottic stenosis	0	0	1	1
Tracheo-oesophageal fistula	2	0	2	4
Aspiration or haemorrhage	0	7	16	23
Infection	15	2	20	37
Chronic lung disease	0	0	2	2
Hyaline membrane disease	0	0	3	3

(Continues in next column)

	Fetuses ≤24 weeks (n=185)	Fetuses >24 weeks (n=92)	Children (n=123)	Total (n=400)
(Continued from previous column)				
Pleural effusion	1	3	3	7
Pulmonary congestion and oedema	0	1	8	9
Pulmonary hypertension	0	0	2	2
Pulmonary interstitial emphysema	0	0	1	1
Hydrops	1	0	0	1
Traumatic chest-wall injury	0	0	1	1
Abdomen	36 (20%)	17 (19%)	17 (14%)	70 (18%)
Abdominal-wall defects	5	1	1	7
Absent visceral organs	0	1	0	1
Cloacal extrophy	1	0	0	1
Duodenal atresia	0	1	0	1
Liver haemangioma	1	0	0	1
Situs inversus	2	0	0	2
Urogenital fistula	0	1	0	1
Acute intraabdominal abnormality	0	0	2	2
Intestinal atresia or obstruction	2	1	1	4
Malrotation	2	0	2	4
Meckels diverticulum	1	1	0	2
Adrenal haemorrhage	2	3	3	8
Hepatic necrosis	0	0	2	2
Hepatosplenomegaly	1	1	0	2
Necrotising enterocolitis	0	0	2	2
Periportal abnormality	0	2	0	2
Small adrenals	1	0	0	1
Splenomegaly	0	1	0	1
Subcapsular haematoma	1	0	0	1
Sacrococyygeal teratoma	0	1	0	1
Viral inclusions	1	1	0	2
Dilated renal pelvis	1	0	0	1
Focal non-specific renal lesion	1	0	0	1
Obstructive uropathy	3	0	1	4
Renal malformations	11	2	3	16
Musculoskeletal system	28 (15%)	6 (7%)	13 (11%)	47 (12%)
Sirenomelia	1	0	0	1
Arthrogyposis	5	1	1	7
Cleft palate	3	1	0	4
Cleft vertebrae	1	0	0	1
Variation in size of muscle fibre	0	1	0	1
Missing metatarsals	1	0	0	1
Vertebral abnormality	4	2	0	6

(Continues in next column)

	Fetuses ≤24 weeks (n=185)	Fetuses >24 weeks (n=92)	Children (n=123)	Total (n=400)
(Continued from previous column)				
Vertebral defect	0	1	0	1
Fracture	0	0	9	9
Skeletal dysplasia	12	0	1	13
Other	1	0	2	3
Type of pathology				
Congenital	64 (35%)	12 (13%)	13 (11%)	89 (22%)
Infective or inflammatory	46 (25%)	5 (5%)	32 (26%)	83 (21%)
Vascular	11 (6%)	21 (23%)	5 (4%)	37 (9%)
Anatomical*	8 (4%)	1 (1%)	6 (5%)	15 (4%)
Traumatic†	0	0	15 (12%)	15 (4%)
Genetic or chromosomal	6 (3%)	6 (7%)	1 (<1%)	13 (3%)
Other	1 (<1%)	5 (5%)	9 (7%)	15 (4%)

Data are n (%) or n. Total number of abnormalities is more than the number of cases because some cases had more than one abnormality. *Structural defects. †Non-accidental injuries.

Table 1: **Pathological abnormalities identified at conventional autopsy**

	Fetuses ≤24 weeks (n=185)	Fetuses >24 weeks (n=92)	Children (n=123)	Total (n=400)
Minimally invasive autopsy *vs* conventional autopsy				
Concordant	175 (94·6, 90·3–97·0)	88 (95·7%, 89·3–98·3)	94 (76·4%, 68·2–83·1)	357 (89·3%, 85·8–91·9)
Non-diagnostic*	9 (5%)	1 (1%)	0	10 (3%)
Discordant	1 (<1%)	3 (3%)	29 (24%)	33 (8%)
Apparent false-positives	1 (<1%)	2 (2%)	3 (2%)	6 (2%)
Callosal agenesis	1	0	0	1
Ischaemic brain injury	0	2	1	3
Lungs (drowning)	0	0	1	1
Skull fracture†	0	0	1	1
Undetected abnormality	0	1 (1%)	26 (21%)	27 (7%)
Lungs (aspiration)	0	0	1	1
Pulmonary haemorrhage	0	0	1	1
Metabolic (steatosis)	0	0	1	1
Sepsis‡	0	1	23	24
MRI alone *vs* conventional autopsy				
Concordant	79 (42·7%, 35·8–49·9)	58 (63·0%, 52·8–72·2)	85 (69·1%, 60·5–76·6)	222 (55·5%, 50·6–60·3)
Non diagnostic§	64 (35%)	4 (4%)	4 (3%)	72 (18%)
Discordant	42 (23%)	30 (33%)	34 (27%)	106 (27%)
Apparent false-positives	2 (1%)	2 (2%)	2 (2%)	6 (2%)
Callosal agenesis	1	0	0	1
Ischaemic brain injury	0	2	1	3
Lungs (drowning)	0	0	1	1
Dilated renal pelvis	1	0	0	1
Undetected abnormality	40 (22%)	28 (30%)	32 (26%)	100 (25%)
Genetic syndrome	2	4	0	6
Haematological	0	2	0	2
Lungs (aspiration)	0	0	1	1
Pulmonary haemorrhage	0	0	1	1
Metabolic (steatosis)	0	0	1	1
Athrogryposis	2	0	1	3
Fracture	0	0	1	1
Cleft palate	1	0	0	1
Skeletal dysplasia	1	0	0	1
Placental	34	21	3	58
Sepsis	0	1	24	25

Data are n (%, 95% CI), n (%), or n. *Cases for which no diagnostic information could be obtained from minimally invasive autopsy or pathology, or both. †X-ray radiograph. ‡Sepsis was of the lungs (n=11), heart (7), heart and lungs (1), gut (1), or was disseminated (3). §Cases for which diagnostic information could not be obtained from MRI scans of any one of the organ systems (brain, heart, chest and abdomen, or musculoskeletal) or pathology, or both.

Table 2: **Concordance for detection of major pathological abnormalities related to death**

≤16 years) and cause (infective *vs* non-infective). 400 cases were needed to determine primary outcome within 5% with 95% confidence if concordance was only 50%. If concordance was 90%, primary outcome was estimable to within 3% for 400 cases. We used exact logistic regression methods in STATA (version 11.1) to examine associations, and Fisher exact test to compare concordance between subgroups.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study. All authors approved the final version of the manuscript submitted for publication.

Results

Figure 2 shows the study profile. We enrolled 423 cases. We used the first 20 cases for MRI optimisation and radiologist training, and excluded three cases because of missing autopsy data (figure 2). Of the remaining 400 cases, 277 (69%) were fetuses (185 [67%] ≤24 weeks' and 92 [33%] >24 weeks' gestation) and 123 (31%) were children (42 [34%] aged ≤1 month, 53 [43%] >1 month to ≤12 months, 28 [23%] >12 months to ≤16 years). 170 (61%) of the fetal cases were due to unexplained intrauterine death and 107 (39%) to medical terminations of pregnancy (mifepristone followed by misoprostol, or gemeprost) for fetal abnormality; feticide by intracardiac injection of potassium chloride was done for terminations of more than 21 weeks. HM Coroners requested autopsies for six (2%) fetuses and 102 (83%) children. Mean time between death or delivery and post-mortem MRI was 4·5 (SD 2·5) days. Table 1 shows major lesions identified at autopsy.

Minimally invasive autopsy and conventional autopsy identified the same cause of death or major pathological lesion in 357 (89·3%, 95% CI 85·8–91·9) of cases (table 2). Concordance was significantly higher for fetuses (263 [94·9%] of 277, 91·7–97·0) than for children

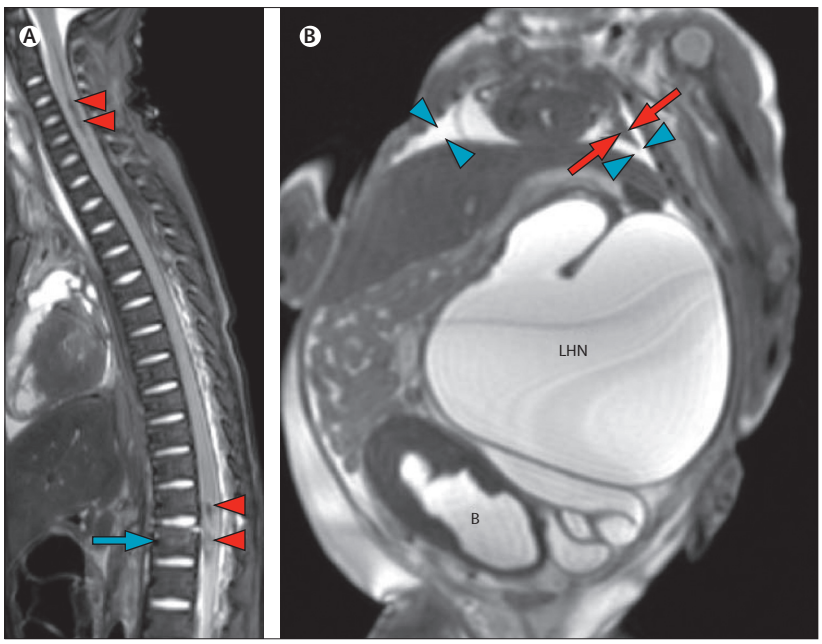


***Figure 3*: Pathological abnormalities on post-mortem MRI**
(A) Sagittal T2-weighted turbo-spin echo image (echo time [TE] 11 ms, repetition time [TR] 3000 ms, flip angle 170°, slice thickness 3 mm) of spinal cord of an infant after an unexplained death, which shows haemorrhage in the cervical cord and just above the conus (red triangles). There are signal abnormalities in the L1 vertebral body with reduction in vertebral body height, consistent with bone trauma at the level of cord injury (blue arrow), suggesting non-accidental injury. These findings were confirmed at autopsy. (B) Coronal three-dimensional T2-weighted whole-body image (constructive interference steady state; TE 2·3 ms, TR 5·2 ms, flip angle 54°, voxel size 0·4 x 0·4 x 0·4 mm) a 21-week-old fetus after termination of pregnancy for bilateral cystic kidneys. Massive hydronephrosis (LHN) and thickened bladder (B) suggestive of posterior urethral valve is seen. Lungs are hypoplastic (red arrows) with bilateral pleural effusions (blue triangles). See appendix for 18 concordant MRI abnormalities.

(difference 18·5%, 95% CI 11·1–27·0; p<0·0001; table 2). The lower concordance in children than fetuses was mainly because of undetected sepsis affecting the lungs, the heart, or both, the intestine, or because of disseminated sepsis (table 2, figure 3, appendix). Concordance in fetuses delivered after termination of pregnancy (99 [92·5%] of 107, 95 CI 85·9–96·2) was similar to that for unexplained intrauterine deaths (164 [96·5%] of 170, 92·5–98·4; difference –4%, 1·4–10·8; p=0·17). Minimally invasive autopsy was concordant in 34 (81·0%, 66·7–90·0) of 42 children younger than 1 month, 45 (84·9%, 72·9–92·1) of 53 aged 1–12 months, and 15 (53·6%, 35·8–70·5) of 28 younger than 12 months to 16 years. Concordance in children decreased with increasing age (0·5% per week, 95% CI 0·1–0·9; p=0·005); however after adjustment for infection, this association was not noted. No association of the referral pattern (HM coronial autopsies in unexplained fetal or childhood deaths) with concordance was noted with logistic regression analysis.

MRI alone had lower concordance with conventional autopsy than minimally invasive autopsy (difference 33·8%, 95% CI 27·9–39·3; p<0·0001, table 2). Sensitivity for detection of infection was lower than that for non-infection, particularly in children (table 3). If infection were a presumptive diagnosis when minimally invasive autopsy does not detect the cause of death in children, 117 (95%) infective deaths would be detected; however, 43 (35%) would have been wrongly diagnosed as infective death. Hence, the overall concordance in children would reduce to 58%. Poor accuracy of MRI for detection of lung infections accounted for most missed infective deaths (table 3).

The dedicated radiologist and pathologist review of minimally invasive autopsy with our predefined criteria (figure 1), suggested that in 165 (41%) of 400 cases, the most commonly occurring abnormality or cause of death could be accurately identified without a full conventional autopsy (figures 1, 4). Concordance in this subgroup was 99·4% (table 3), with only one discordant case, an apparent false-positive brain lesion (callosal agenesis; table 2). In 258 (65%) cases, the minimally invasive autopsy criteria suggested that opening of the head for formal brain autopsy was unnecessary (figure 1). Neuropathological examination provided clinically important new information in only two of these cases (figures 1, 4). A full or body autopsy was recommended to identify cause of death in 144 (52%) fetuses and 91 (74%) children (figures 1, 4), for which conventional autopsy provided new information in four (3%) and 30 (33%) cases, respectively (figure 4). Potentially, targeted tissue sampling alone without opening of the body could have been sufficient in 18 (13%) fetuses and 75 (82%) children who were recommended to have a full autopsy (figure 4).

Minimally invasive autopsy did not detect pathological lesions (related or unrelated to death) in 70 (18%) of 400 cases (appendix). Undetected fetal pathological abnormalities were mainly in the lungs and heart, of which both were reported mostly in those at 24 weeks' gestation or less (appendix). Corpus callosum agenesis (n=1) and intestinal obstruction (n=1) were undetected in two fetuses (appendix). Specific diagnosis of skeletal dysplasia (n=1) and renal dysplasia (n=1) needed additional histological confirmation. In children, the main undetected abnormalities were pneumonia (20 [16%]), and myocarditis (8 [7%]). One cerebral pathology—Dandy-Walker variant—was undetected (appendix). No structural heart disease was missed in this population (appendix).

We recorded pathological abnormalities identified by MRI, but not confirmed at autopsy, in 79 (20%) cases (appendix). These overcalls were mainly due to brain lesions, mostly related to hypoxic-ischaemic injury, agenesis of corpus callosum, minor ventricular bleeds, and other cerebral malformations (appendix). Cardiac lesions were overcalled in 13 (3%) cases, and lung lesions in 17 (4%) cases (appendix). In one case, a fracture was reported on skull radiograph, but this finding was unconfirmed at autopsy (appendix). We noted non-diagnostic cerebral MRI or autopsies mainly in the fetuses of 24 weeks' gestation or less (appendix).

	FP	TP	FN	TN	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Positive likelihood ratio	Negative likelihood ratio
Detection of major pathological abnormality or cause of death in all cases										
Fetuses ≤24 weeks (n=176)	1 (<1%)	131 (74%)	0	44 (25%)	99·6% (96·5–100)	97·8% (88·4–99·6)	99·2% (95·8–99·9)	98·9% (90·1–99·9)	44·8% (6·5–311·4)	0·004% (0·001–0·06)
Fetuses >24 weeks (n=91)	2 (2%)	47 (52%)	2 (2%)	40 (44%)	95·9% (86·3–98·9)	95·2% (84·2–98·7)	95·9% (86·3–98·9)	95·2% (84·2–98·7)	20·1% (5·2–77·9)	0·043% (0·011–0·167)
Children (n=123)	3 (2%)	56 (46%)	25 (20%)	39 (32%)	69·1% (58·4–78·1)	92·9% (81·0–97·5)	94·9% (86·1–98·3)	60·9% (48·7–71·9)	9·7% (3·2–29·1)	0·33% (0·24–0·47)
Overall (n=390)	6 (2%)	234 (60%)	27 (7%)	123 (32%)	89·7% (85·4–92·8)	95·3% (90·2–97·9)	97·5% (94·7–98·9)	82·0% (75·1–87·3)	19·2% (8·8–42·2)	0·11% (0·08–0·155)
Detection of major pathological abnormality or cause of death when conventional autopsy was regarded as not needed										
Fetuses ≤24 weeks (n=101)	1 (1%)	97 (96%)	0	3 (3%)	99·5% (95·3–99·9)	75·0% (30·1–95·4)	99·9% (94·4–99·8)	85·7% (35·6–98·5)	3·9% (0·73–21·7)	0·007% (0–0·12)
Fetuses >24 weeks (n=32)	0	32 (100%)	0	0	98·5% (86·8–99·8)	50·0% (5·5–94·5)	98·5% (86·8–99·8)	50·0% (5·5–94·5)	1·9% (0·28–13·99)	0·031% (0·001–0·901)
Children (n=32)	0	31 (97%)	0	1 (3%)	98·4% (86·5–99·8)	66·7% (12·9–96·4)	98·4% (86·5–99·8)	66·7% (12·9–96·4)	2·95% (0·31–28·4)	0·024% (0·001–0·466)
Overall (n=165)	1 (<1%)	160 (97%)	0	4 (2%)	99·7% (97·1–100)	80·0% (37·6–96·4)	99·4% (96·6–99·9)	88·9% (43·1–98·8)	4·98% (0·86–28·8)	0·004% (0–0·064)
Detection of non-infective pathological abnormality										
Fetuses ≤24 weeks (n=176)	0	86 (49%)	0	90 (51%)	99·4% (94·7–99·9)	99·4% (94·9–99·9)	99·4% (94·7–99·9)	99·4% (94·9–99·9)	179·9% (11·3–2855·5)	0·006 (0–0·09)
Fetuses >24 weeks (n=91)	2 (2%)	43 (47%)	1 (1%)	45 (50%)	97·7% (88·2–99·6)	95·7% (85·8–98·8)	95·6% (85·5–98·8)	97·8% (88·7–99·6)	22·9% (5·9–89·2)	0·02% (0·003–0·16)
Children (n=123)	3 (2%)	48 (39%)	3 (2%)	69 (56%)	94·1% (84·1–98·0)	95·8% (88·5–98·6)	94·1% (84·1–97·9)	95·8% (88·5–98·6)	22·6% (7·4–68·5)	0·06% (0·02–0·18)
Overall (n=390)	5 (1%)	177 (45%)	4 (1%)	204 (53%)	97·8% (94·5–99·1)	97·6% (94·5–99·0)	97·3% (93·7–98·8)	98·1% (95·2–99·2)	40·9% (17·2–97·2)	0·02% (0·008–0·06)
For detection of infective pathological abnormality										
Fetuses ≤24 weeks (n=176)	0	46 (26%)	0	130 (74%)	98·9% (90·5–99·9)	99·6% (96·4–100)	98·9% (90·5–99·9)	99·6% (96·4–100)	258·2% (16·7–4106·7)	0·01% (0·001–0·17)
Fetuses >24 weeks (n=91)	0	4 (4%)	1 (1%)	86 (95%)	80·0% (37·6–96·4)	99·4% (94·7–99·9)	88·9% (43·1–98·8)	98·9% (93·8–99·8)	138·4% (8·4–2272·1)	0·20% (0·04–1·16)
Children (n=123)	0	8 (7%)	22 (18%)	93 (76%)	26·7% (14·2–44·4)	100% (95·8–100)	100% (67·6–100)	80·9% (72·7–87·0)	49·9% (2·9–842·8)	0·74% (0·59–0·92)
Overall (n=390)	0	58 (15%)	23 (6%)	309 (79%)	71·6% (61·0–80·3)	99·8% (98·5–100)	99·1% (92·3–99·9)	93·1% (89·8–95·3)	443·2% (27·7–7094·4)	0·28% (0·20–0·40)

Data are n (%) or % (95% CI), unless otherwise indicated. We excluded non-diagnostic cases from analysis. FP=false positive. TP=true positive. FN=false negative. TN=true negative.

***Table 3*: Diagnostic accuracy of minimally invasive autopsy**

Post-mortem MRI detected clinically important lesions in 13 (30%) of the 43 cases in which neuropathology was inadequate because of autolysis (figure 5). However, when post-mortem MRI was non-diagnostic, formal neuropathological examination detected no abnormal cerebral lesions. Ancillary post-mortem investigations provided additional clinically important information that would not have been obtained by MRI alone in 108 (38·9%, 95% CI 33·4–44·8) fetuses and 12 (9·8%, 5·7–16·3) children. This information was obtained from the placenta (77 [28%] fetuses and three [2%] children), radiographs (15 [5%] and six [5%]), genetic or chromosomal testing (13 [5%] and two [2%]), external examination (six [2%] and one [<1%]) and haematological tests (two [<1%] and 0).

Discussion

Our results show that minimally invasive autopsy had similar accuracy to conventional autopsy for detection of cause of death or major pathological abnormality. The lower concordance in children than fetuses was mainly due to undetected pneumonia and myocarditis. Minimally invasive autopsy had a sensitivity and specificity of more than 95% for detection of major intracranial and non-infective pathological abnormalities. Furthermore, in the cases for which a pathologist and radiologist jointly predicted that full autopsy was unnecessary, the concordance rate for cause of death or major pathology was almost 100%. Thus, minimally invasive autopsy could be a suitable alternative to conventional autopsy for detection of

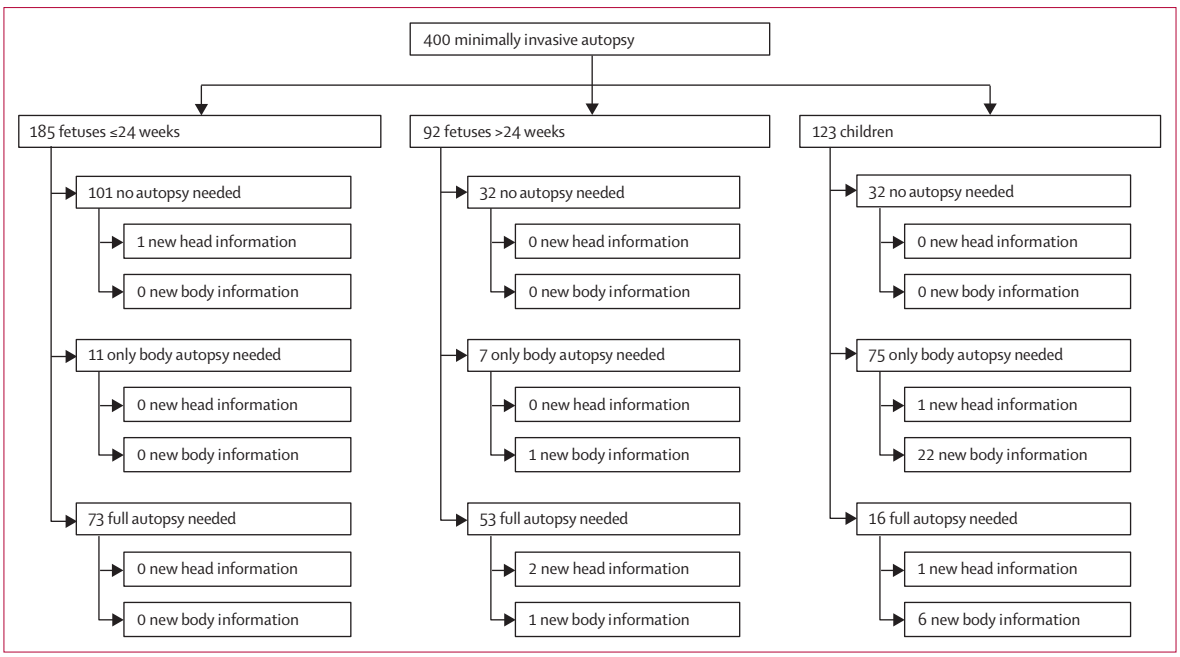
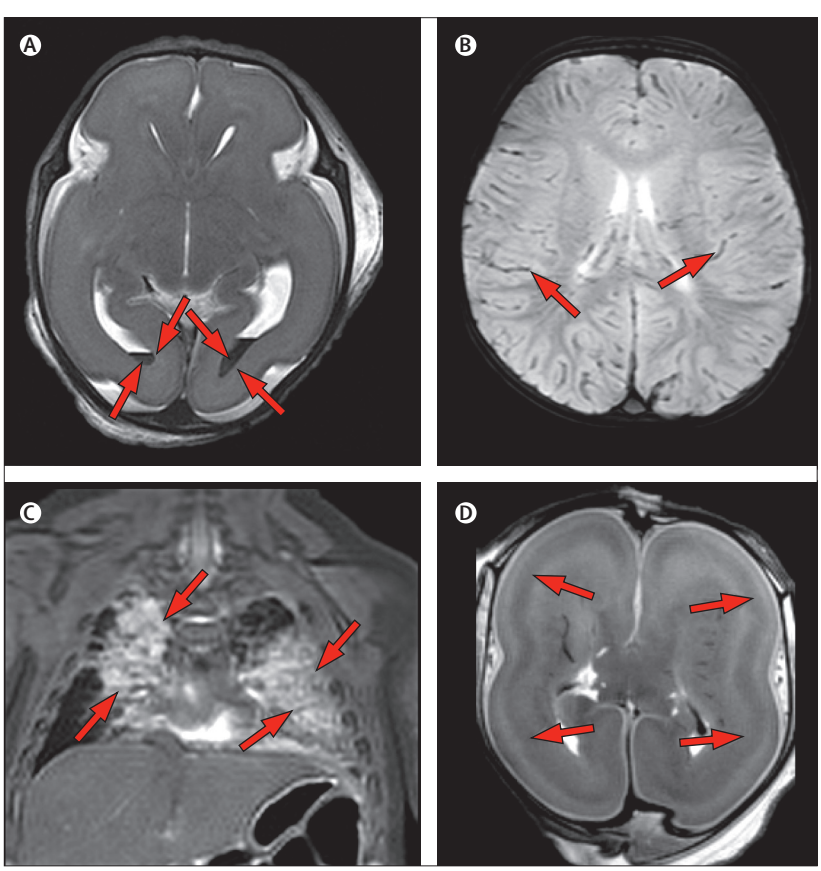


Figure 4: **Results of categorisation based on predefined criteria after minimally invasive autopsy**
Probable additional benefit of full or partial autopsy for detection of major pathological abnormalities or cause of death compared with full standard autopsy. Full standard autopsy was done in all cases.



cause of death or major pathological lesions in selected cases for which an invasive post-mortem examination is unacceptable.

The role of autopsy is not only limited to detection of cause of death or major pathology; other pathological lesions detected at autopsy often have an important role in advancing of medical research and knowledge, and at times, in answering of specific antemortem questions.[1] Our findings suggest that minimally invasive autopsy

Figure 5: **Artifacts and apparent false-positives on post-mortem MRI**
(A) Intraventricular haemorrhage (red arrows) in the occipital horns of a fetus on three-dimensional (3D) T2-weighted axial image of brain (constructive interference steady state [CISS]; echo time [TE] 5·1 ms, repetition time [TR] 10·2 ms, flip angle 70°, voxel size 0·6 × 0·6 × 0·6 mm). Intraventricular haemorrhage is often seen on MRI scans of fetuses in the absence of any intracranial pathological abnormality, and is often not reported at autopsy, suggesting blood staining of cerebrospinal fluid during or after death. (B) Normal appearance on axial gradient-echo brain image (T2-star [T2*] weighted) of an infant (TE 26 ms, TR 800 ms, flip angle 20°, slice thickness 5 mm) due to clots in cortical and intramedullary veins seen in almost all post-mortem cases (red arrows), except for liquefied fetal brains. (C) T2-weighted double-echo short inversion recovery (DeSTIR) axial brain image (TE 16 ms, TR 5460 ms, inversion time [TI] 130 ms, flip angle 150°, slice thickness 2·5 mm) showing a lissencephaly in a 22-week-old fetus. The pregnancy was terminated for ventriculomegaly. The thin outer cortical layer of grey matter is separated from a layer of arrested neurons (red arrows) by normal white matter (the cell sparse zone). The shallow vertically orientated Sylvian fissures give the brain a figure of eight appearance. Brain was completely autolysed and hence neuropathological examination was uninformative. Post-mortem genetic testing showed deletion of chromosome 17p13.3 (Miller-Dieker syndrome). (D) 3D T2-weighted (CISS; TE 5·1 ms, TR 10·2 ms, flip angle 70°, voxel size 0·6 × 0·6 × 0·6 mm) post-mortem MRI (coronal plane) of a 3-month-old infant after a sudden unexpected death, showing extensive consolidation of the lungs (false-positive). Histological examination of lungs was normal.

detects all clinically relevant pathological lesions, irrespective of contribution to death, in roughly 90% of fetuses, and 60% of children. Apparent overcalls of pathological lesions were mainly related to ischaemic brain injury, and lung abnormalities.

Within individual organ systems, post-mortem MRI was most accurate for detection of cerebral, cardiac, and renal abnormalities, with the exception of ischaemic brain injury and myocarditis. MRI could not differentiate between antemortem ischaemic brain injury and post-mortem autolytic cerebral changes; the latter of which was present to a varying extent in all cases examined. Abdominal MRI findings were at times non-specific, for example, gut dilatation was present in many cases as a post-mortem change and also in association with bowel obstruction. Lung imaging was inaccurate for diagnosis of any pulmonary abnormality, except major structural lesions, for example diaphragmatic hernia. This finding is supported by results from a large autopsy study[22] of infant deaths, reporting that pulmonary histological findings correlate poorly with macroscopic features of the lungs at autopsy. By contrast, histological brain abnormalities are unlikely when clinical history and macroscopic examination are normal.[23] Although needle biopsies (either blind or image guided) can be challenging to undertake in fetuses and children,[12,24] we have previously shown that visceral tissues can be accurately sampled with a laparoscope.[25] Therefore, post-mortem MRI followed by targeted laparoscopic post-mortem examination might detect most clinically significant pathological abnormalities with little disruption to the body.[12,25] Autolysis can often affect the diagnostic accuracy of fetal neuropathological changes, hence, we use the term apparent overcalls, because whether such lesions identified by post-mortem MRI were present is impossible to determine with certainty.[26] Overcalls in this study could represent subtle cerebral[26] or cardiac lesions undetected at autopsy.

The detection rates for our major MRI findings are greater than those in previous publications,[6–9] particularly for cardiac anomalies (panel). Use of 3D MRI, high-resolution, isotropic images; involvement of specialist radiologists; and skewed age distribution, mainly in the perinatal age group, probably accounts for our increased diagnostic yield. Overall, concordance between minimally invasive autopsy findings and conventional autopsy was highest in fetuses and gradually decreased with increasing age in the paediatric population; the concordance in children is similar to that (57%) from a large prospective adult study.[28] This finding is expected, and is almost certainly related to the changing pattern of underlying pathological changes associated with autopsy across this age range, from mostly structural anomalies in fetuses to mostly infective causes in infancy and older children. By contrast with adults,[11,28–30] post-mortem CT has poor differentiation of visceral tissue in fetuses and children and is of little value, except in skeletal injuries and dysplasias.[12]

Panel: Research in context

Systematic review

We searched Medline from Jan 1, 1980, to July 1, 2012, for studies comparing whole-body post-mortem MRI with conventional autopsy in fetuses and children. We used search terms "post-mortem magnetic resonance imaging", "minimally invasive autopsy", "virtual autopsy", and "autopsy imaging". We excluded case reports, studies of adult autopsies, studies in which the imaging was limited to one body part only, or those in which conventional autopsy was not done. Six small studies,[5,9,10,12,14,27] with 20, ten, 26, 26, 44, and 19 cases, respectively, compared whole-body post-mortem MRI with conventional autopsy in fetuses. Although two[10,33] of the fetal studies had a few newborn infants, no studies were available of whole-body post-mortem MRI in children.

Interpretation

Our findings suggest that minimally invasive autopsy (MRI with other ancillary post-mortem investigations) has similar accuracy to conventional autopsy in fetuses for identification of cause of death or major pathological abnormality. The accuracy is lower in children, mainly because of missed infections of the lungs or heart. However, in a predefined group of children, the concordance of minimally invasive autopsy and conventional autopsy was very high. Therefore, minimally invasive autopsy including post-mortem MRI could be an acceptable alternative to conventional autopsy in fetuses and a selective subgroup of children.

Our study has limitations. First, the study was done in two large tertiary university hospitals with optimum scanning and reporting conditions; although methodologically robust, the results might not be directly transferable to less specialist settings. Nevertheless, post-mortem MRI can be done in most hospitals, with image reporting by specialist radiologists at tertiary centres. Alternatively, bodies could be transported to regional centres for minimally invasive autopsy; however, such an approach might be more suitable in the UK where fetal and paediatric autopsies are done only at regional centres, which are likely to have the necessary specialist radiology expertise.[20,29] Second, we included only cases with consent for conventional autopsy, thus the study population might be unrepresentative of the cases for which conventional autopsy was declined. Third, we did not assess the economic aspects of post-mortem MRI. Although minimally invasive autopsy can be less expensive than conventional autopsy,[31] the overall cost of post-mortem services might rise because parents who decide against autopsy might want a minimally invasive autopsy, which paradoxically increases the workload for both pathologists and radiologists. Fourth, the accuracy of conventional MRI in small fetuses was poor because many images were non-diagnostic. In these cases, use of high-field MRI (eg, 9·4 T) could provide diagnostic quality information.[32] Fifth, although this study is large, rare pathological abnormalities undetectable by minimally invasive autopsy might not have been represented.

This study has important implications for the way perinatal and paediatric autopsies are likely to be done in the future. Concerns about falling autopsy rates have been raised since the early 1970s; however, attempts to

improve these rates have been unsuccessful and non-forensic autopsies have become almost non-existent.[3] Minimally invasive autopsy could increase the uptake of post-mortem examination if adequate resources are allocated.[10] The UK Department of Health has commissioned a report of how to establish a national service for minimally invasive post-mortem.[33] Importantly, post-mortem MRI could change the autopsy procedure—eg, opening of the cranium for microscopic brain examination might not be needed when brain MRI is normal. In fetuses at 24 weeks' gestation or less, conventional neuropathological examination can be uninformative because of autolysis; hence, routine pre-autopsy cerebral MRI might be needed to obtain the best post-mortem information. Close engagement of parents is important in such a process, and contrary to popular belief, bereaved parents often view this involvement positively.[16] Future studies should examine the clinical, psychological, epidemiological, and economic effect of minimally invasive autopsy.

Contributors

ST managed the study, developed the study protocol, designed the database, recruited cases, did MRI, analysed the data, and wrote the first draft of the final manuscript. AMT (chief investigator) led the study, developed the study protocol, reported cardiac MRI, assisted in data analysis and interpretation, contributed to writing and editing of the manuscript, and had overall responsibility for the study. NJS provided input into the pathological aspects of the study, assisted case recruitment from Great Ormond Street Hospital for Children NHS Foundation Trust, contributed to protocol development, classified the MRI and pathology data along with AMT, and contributed to writing of the manuscript. LSC provided input into the fetal aspects and NJR into the neonatal aspects of the study; both contributed to protocol development. RJS assisted recruitment cases from University College Hospital NHS foundation Trust. AW advised on the study design, and supervised the final data analysis. WKC, RSG, and DES reported the brain and spinal cord MRI, CMO and OO interpreted chest and abdomen MRI, and ACO interpreted musculoskeletal MRI. SA assisted collection and cleaning of data. AB, EDV, and EBC advised on MRI sequence optimisation, and EBC contributed to drafting of the manuscript. WN and RJ did MRI scans. All authors have critically reviewed the manuscript on the scientific content and have approved the final version of the manuscript submitted for publication.

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Conflicts of interest

We declare that we have no conflicts of interest.

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References

1 Burton JL, Underwood J. Clinical, educational, and epidemiological value of autopsy. *Lancet* 2007; **369:** 1471–80.

2 Shojania KG, Burton EC, McDonald KM, Goldman L. Changes in rates of autopsy-detected diagnostic errors over time: a systematic review. *JAMA* 2003; **289:** 2849–56.

3 Shojania KG, Burton EC. The vanishing nonforensic autopsy. *N Engl J Med* 2008; **358:** 873–75.

4 Confidential Enquiry into Maternal and Child Health (CEMACH). Perinatal mortality 2007. London, UK: CEMACH, 2009.

5 Brookes JA, Hall-Craggs MA, Sams VR, Lees WRC. Non-invasive perinatal necropsy by magnetic resonance imaging. *Lancet* 1996; **348:** 1139–41.

6 Cohen MC, Paley MN, Griffiths PD, Whitby EHC. Less invasive autopsy: benefits and limitations of the use of magnetic resonance imaging in the perinatal postmortem. *Pediatr Dev Pathol* 2008; **11:** 1–9.

7 Whitby E, Variend S, Rutter S, et al. Corroboration of in utero MRI using post-mortem MRI and autopsy in foetuses with CNS abnormalities. *Clin Radiol* 2004; **59:** 1114–20.

8 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.

9 Breeze AC, Jessop FA, Set PA, et al. Minimally-invasive fetal autopsy using magnetic resonance imaging and percutaneous organ biopsies: clinical value and comparison to conventional autopsy. *Ultrasound Obstet Gynecol* 2011; **37:** 317–23.

10 Cannie M, Votino C, Moerman P, et al. Acceptance, reliability and confidence of diagnosis of fetal and neonatal virtuopsy compared with conventional autopsy: a prospective study. *Ultrasound Obstet Gynecol* 2012; **39:** 659–65.

11 Wichmann D, Obbelode F, Vogel H, et al. Virtual autopsy as an alternative to traditional medical autopsy in the intensive care unit: a prospective cohort study. *Ann Intern Med* 2012; **156:** 123–30.

12 Thayyil S. Less invasive autopsy: an evidenced based approach. *Arch Dis Child* 2011; **96:** 681–87.

13 Woodward PJ, Sohaey R, Harris DP, et al. Postmortem fetal MR imaging: comparison with findings at autopsy. *AJR Am J Roentgenol* 1997; **168:** 41–46.

14 Huisman TA, Wisser J, Stallmach T, Krestin GP, Huch R, Kubik-Huch RAC. MR autopsy in fetuses. *Fetal Diagn Ther* 2002; **17:** 58–64.

15 Thayyil S, Chandrasekaran M, Chitty LS, et al. Diagnostic accuracy of post-mortem magnetic resonance imaging in fetuses, children and adults: a systematic review. *Eur J Radiol* 2010; **75:** e142–48.

16 Thayyil S, Robertson NJ, Scales A, et al. Prospective parental consent for autopsy research following sudden unexpected childhood deaths: a successful model. *Arch Dis Child* 2009; **94:** 354–58.

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

18 Thayyil S, Sebire NJ, Chitty LS, Wade A, Olsen O, Gunny RS, et al. Post mortem magnetic resonance imaging in the fetus, infant and child: a comparative study with conventional autopsy (MaRIAS Protocol). *BMC Pediatr* 2011; **11:** 120.

19 Rutty GN, Brogdon G, Dedouit F, et al. Terminology used in publications for post-mortem cross-sectional imaging. *Int J Legal Med* 2012; published online Oct 18. DOI:10.1007/s00414-012-0782-7.

20 Royal College of Paediatrics and Child Health. Guidleines for autopsy investigation of fetal and perinatal death. Sept, 2002. http://www.rcpath.org/Resources/RCPath/Migrated%20Resources/Documents/A/appendix_6.pdf (accessed Jan 10, 2013).

21 The Royal College of Pathologists and The Royal College of Paediatrics and Child Health. Sudden unexpected death in infancy: a multi-agency protocol for care and investigation. Sept, 2004. http://www.rcpath.org/NR/rdonlyres/30213EB6-451B-4830-A7FD-4EEFF0420260/0/SUDIreportforweb.pdf (accessed Jan 10, 2013).

22 Weber MA, Pryce JW, Ashworth MT, Malone M, Sebire NJ. Histological examination in sudden unexpected death in infancy: evidence base for histological sampling. *J Clin Pathol* 2012; **65:** 58–63.

23 Pryce JW, Paine SM, Weber MA, Harding B, Jacques TS, Sebire NJ. Role of routine neuropathological examination for determining cause of death in sudden unexpected deaths in infancy (SUDI). *J Clin Pathol* 2012; **65:** 257–61.

24 Breeze AC, Jessop FA, Whitehead AL, et al. Feasibility of percutaneous organ biopsy as part of a minimally invasive perinatal autopsy. *Virchows Arch* 2008; **452:** 201–07.

25 Sebire NJ, Weber MA, Thayyil S, Mushtaq I, Taylor A, Chitty LS. Minimally invasive perinatal autopsies using magnetic resonance imaging and endoscopic postmortem examination ("keyhole autopsy"): feasibility and initial experience. *J Matern Fetal Neonatal Med* 2012; **25:** 513–18.

26 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.

27 Alderliesten ME, Peringa J, van der Hulst VP, Blaauwgeers HL, van Lith JMC. Perinatal mortality: clinical value of postmortem magnetic resonance imaging compared with autopsy in routine obstetric practice. *BJOG* 2003; **110:** 378–82.

28 Roberts IS, Benamore RE, Benbow EW, et al. Post-mortem imaging as an alternative to autopsy in the diagnosis of adult deaths: a validation study. *Lancet* 2012; **379:** 136–42.

29 Votino C, Cannie M, Segers V, et al. Virtual autopsy by computed tomographic angiography of the fetal heart: a feasibility study. *Ultrasound Obstet Gynecol* 2012; **39:** 679–84.

30 Ross SG, Thali MJ, Bolliger S, Germerott T, Ruder TD, Flach PM. Sudden death after chest pain: feasibility of virtual autopsy with postmortem CT angiography and biopsy. *Radiol* 2012; **264:** 250–59.

31 Weustink AC, Hunink MG, van Dijke CF, Renken NS, Krestin GP, Oosterhuis JW. Minimally invasive autopsy: an alternative to conventional autopsy? *Radiol* 2009; **250:** 897–904.

32 Thayyil S, Cleary JO, Sebire NJ, et al. Post-mortem examination of human fetuses: a comparison of whole-body high-field MRI at 9·4 T with conventional MRI and invasive autopsy. *Lancet* 2009; **374:** 467–75.

33 NHS Implementation Sub-Group of the Department of Health Post Mortem, Forensic, and Disaster Imaging Group. Can cross-sectional imaging as an adjunct and/or alternative to the invasive autopsy be implemented within the NHS? August, 2012. http://www.dh.gov.uk/health/2012/10/less-invasive-autopsy/ (accessed Oct 30, 2012).

Webappendix

Typical post-mortem MRI sequences

Sequence	Voxel size	Scan time	Averages
Brain imaging			
3 D CISS	0·6x0·6x0·6 mm	13·5 min	4
3D Flash T_1–weighted	1x1x1 mm	5·4 min	3
2D Destir T_2–weighted	0·4x0·4x0·4 mm	13·5 min	6
Gradiant echo (T_2*)	0·5x0·4x4 mm	6·3 min	4
Spine imaging			
2D T_2–weighted Turbo Spin Echo (children)	1x1x3 mm	5·4 min	3
3D CISS (fetus)	0·6x0·6x1 mm	4·2 min	8
3D T_1–weighted Flash	0·6x0·6x1 mm	3·5 min	10
Body imaging			
3D T_2–weighted Turbo Spin Echo	0·8x0·8x0·8 mm	6·2 min	2
3D T_1–weighted VIBE	0·8x0·8x0·8 mm	5·5 min	8
3D CISS (cardiac sequence)	0·6x0·6x0·6 mm	29 min	10

CISS: Constructive Interference Steady State (CISS is a T_2–weighted MRI sequence); FLASH: Fast Low Angle Shot; DESTIR: Dual Echo Short T_1 Inversion Recovery; VIBE: Volumetric Interpolated Breath-hold Examination

Further pathologies seen on post-mortem MRI

Figure 1. A. Axial T_2-weighted image of the brain in a 2-year-old child showing a bleed in the caudate nuclei (*) and intraventricular blood (arrows), secondary to middle cerebral artery aneurysm rupture. B. Axial T2-weighted image of the brain in an 8-month-old child showing parenchymal bleed (*) secondary non-accidental injury

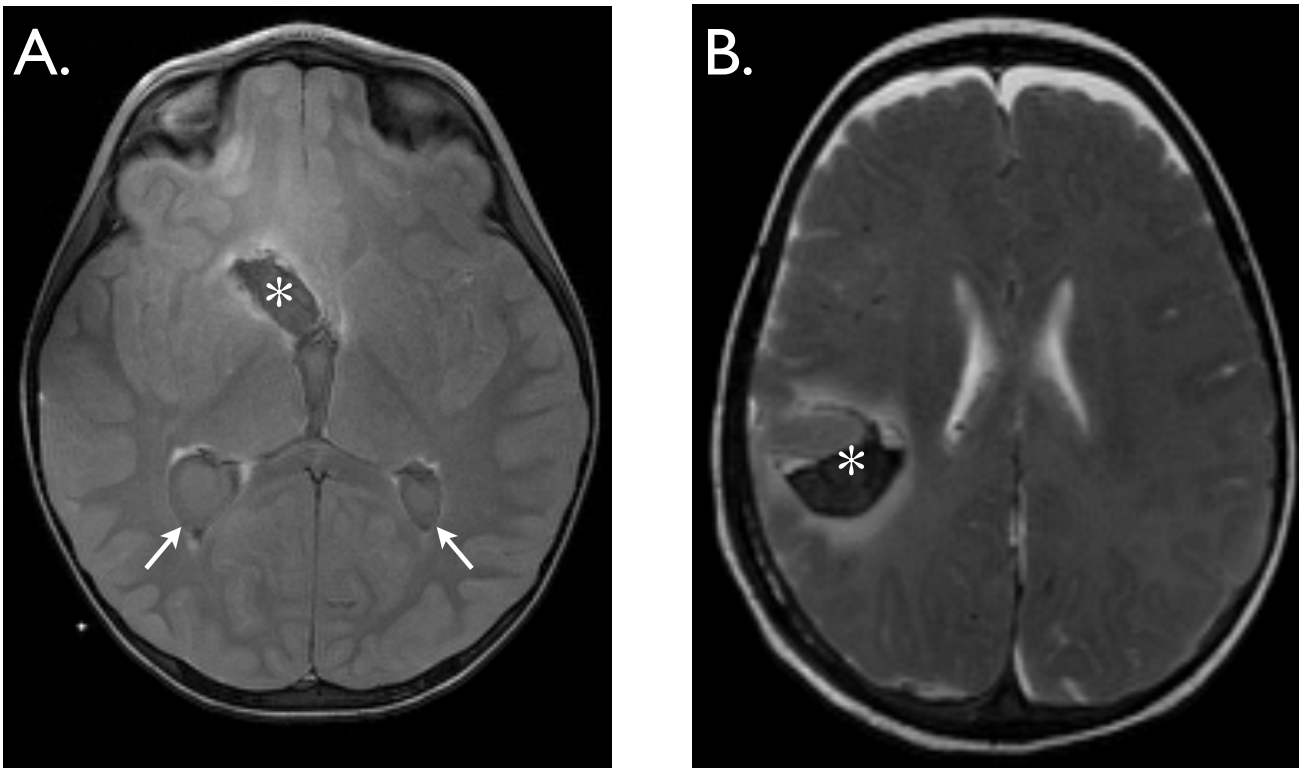


Figure 2. Axial (A) and coronal (B) T_2-weighted images of the brain in a 5-year-old child showing a capillary haemangioma with calcification (white arrows) and underlying white matter disease (red arrows).

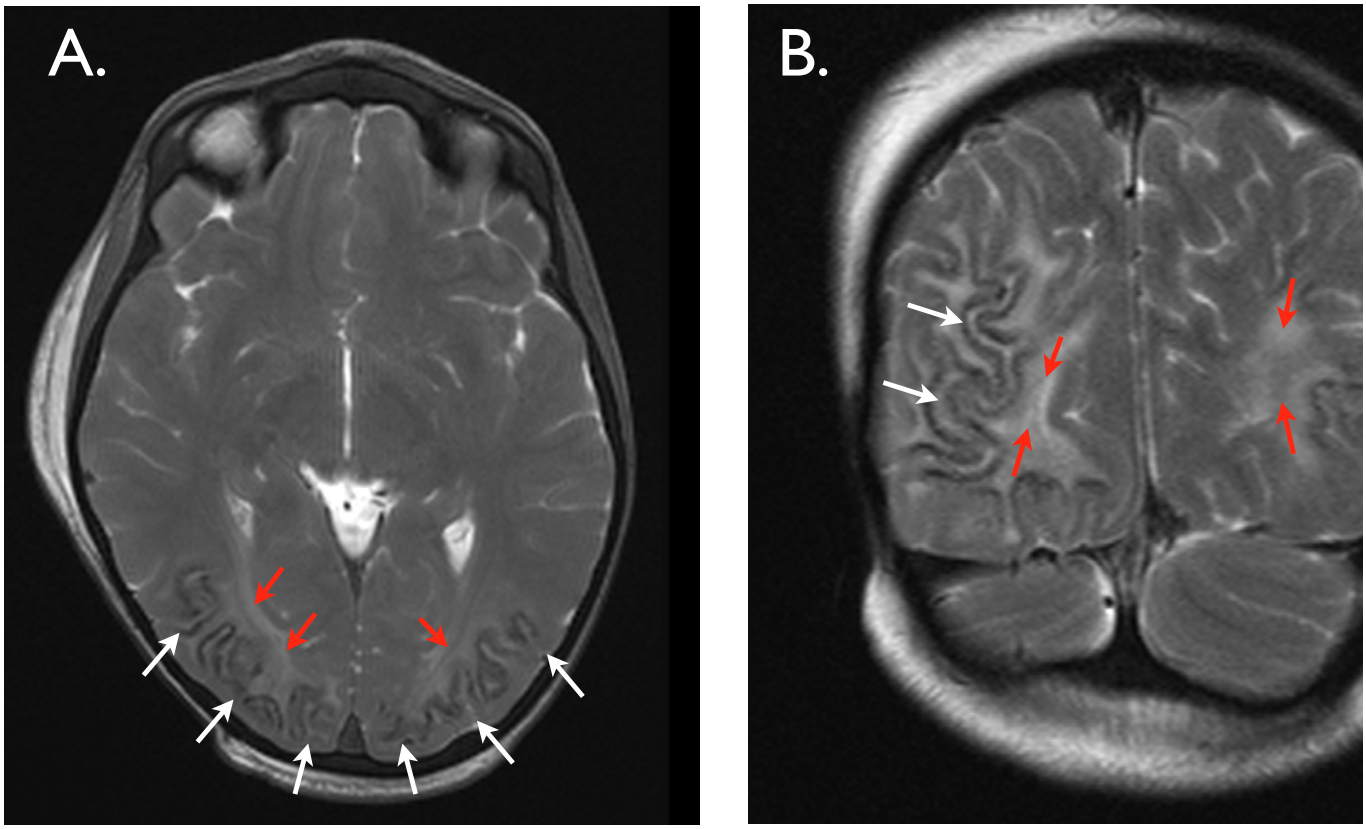


Figure 3. Axial T_2-weighted image of the brain in a 31-week-old fetus showing brain microlissencephaly.

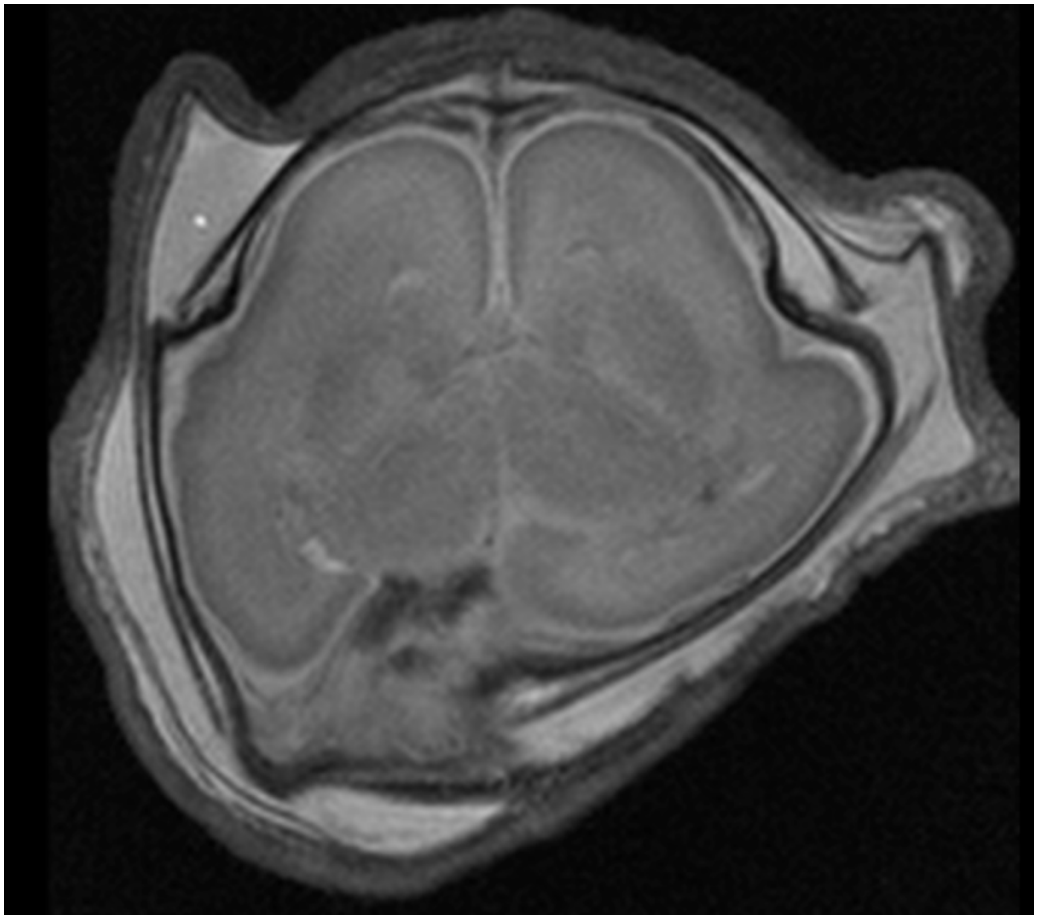


Figure 4. Right oblique view of a 3D volume-rendered reconstruction of the face in a 16-week-old fetus showing a cleft lip (arrows). Cleft palate also present – not shown.

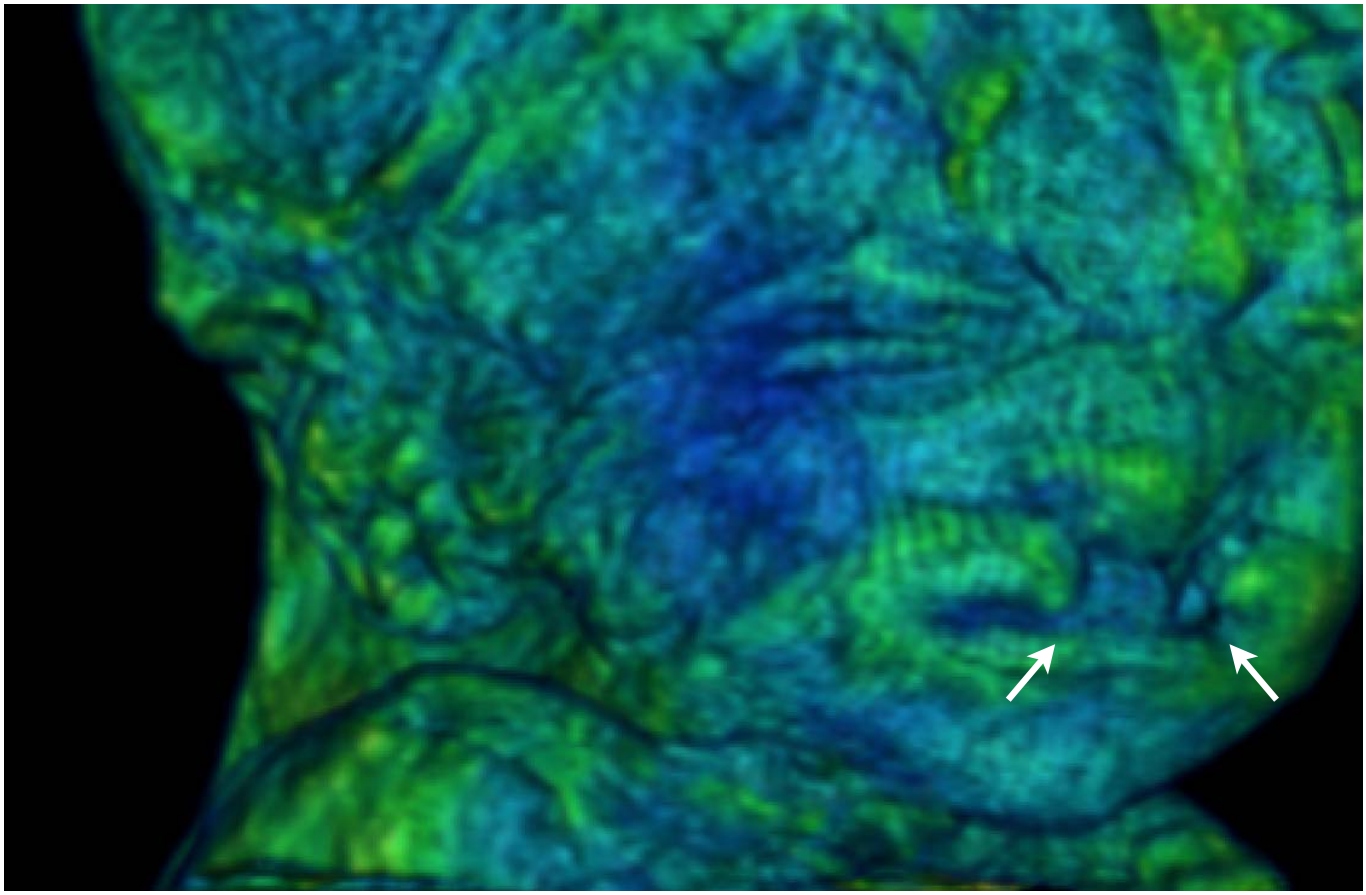


Figure 5. Axial T_2-weighted image of the heart in a 21-week-old fetus showing an unbalanced atrioventricular defect (AVSD), with small right ventricle (RV). Common atrium (*) and left ventricle (LV).

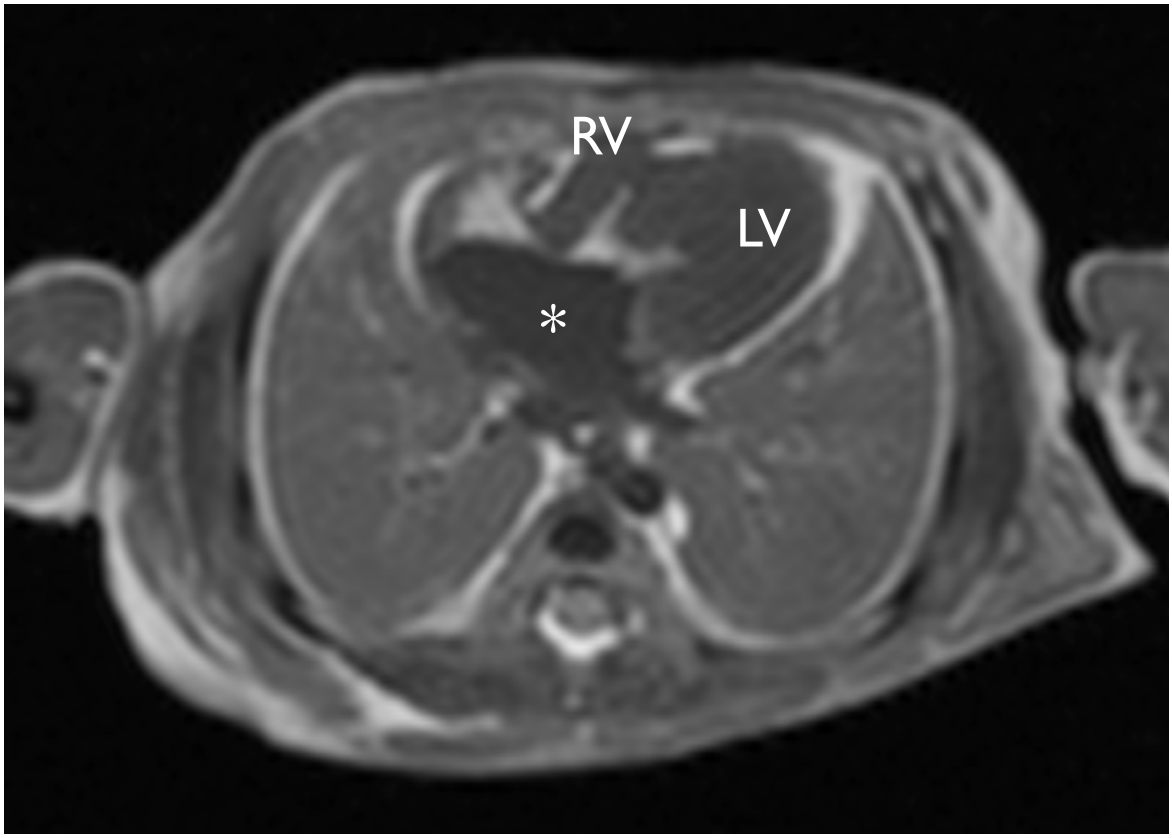


Figure 6. Axial T_2-weighted image of the heart in a 29-week-old fetus showing a massive cardiac teratoma (*). This is displacing the main structures of the heart posteriorly. Right ventricle (RV) and left ventricle (LV).

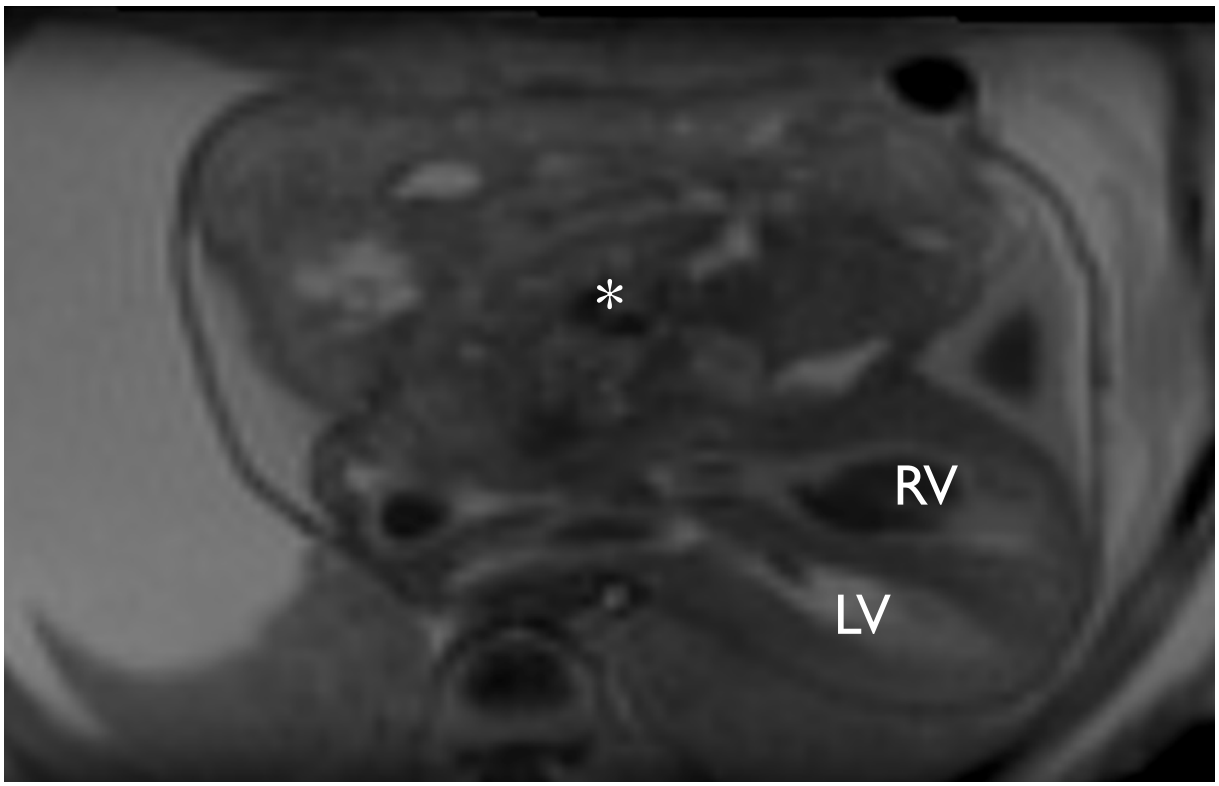


Figure 7. Long-axis T_2-weighted image of the heart showing a ventricular septal defect (VSD) (*) and overriding aorta (Ao) in a 5-month-old child with pulmonary atresia, VSD and aortopulmonary collaterals. Right ventricle (RV), left ventricle (LV) and left atrium (LA). Note separation of blood in the aorta – plasma (white).

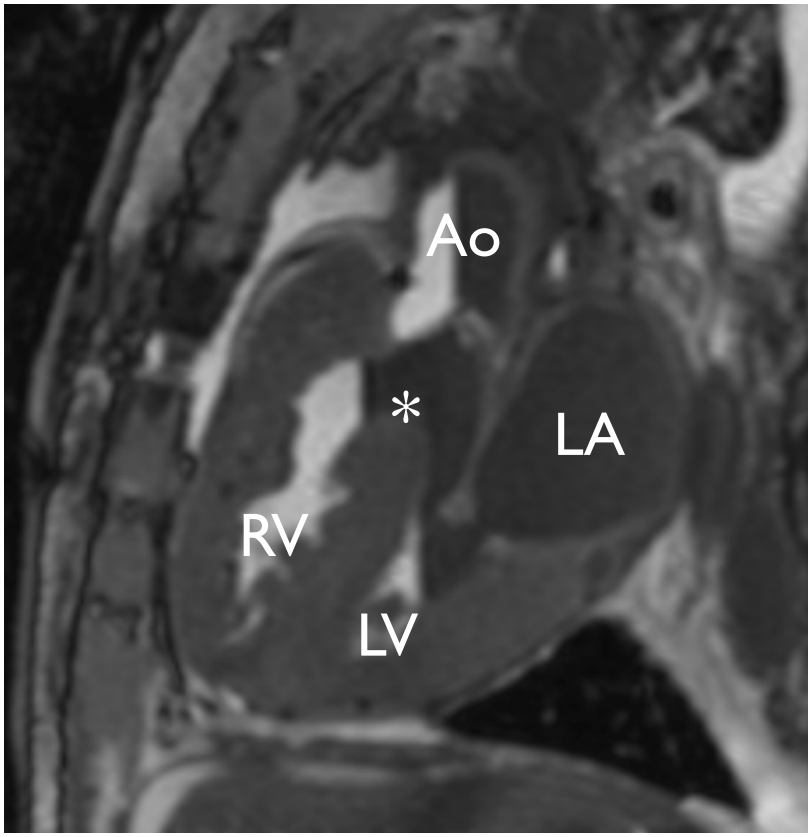


Figure 8. A. Coronal T_2-weighted image of the chest and abdomen in a 22-week-old fetus showing left-sided diaphragmatic hernia. Small bowel seen in the left chest (*). B. Sagittal T_2-weighted image of the left lung in a 4-month-old child showing chronic lung disease.

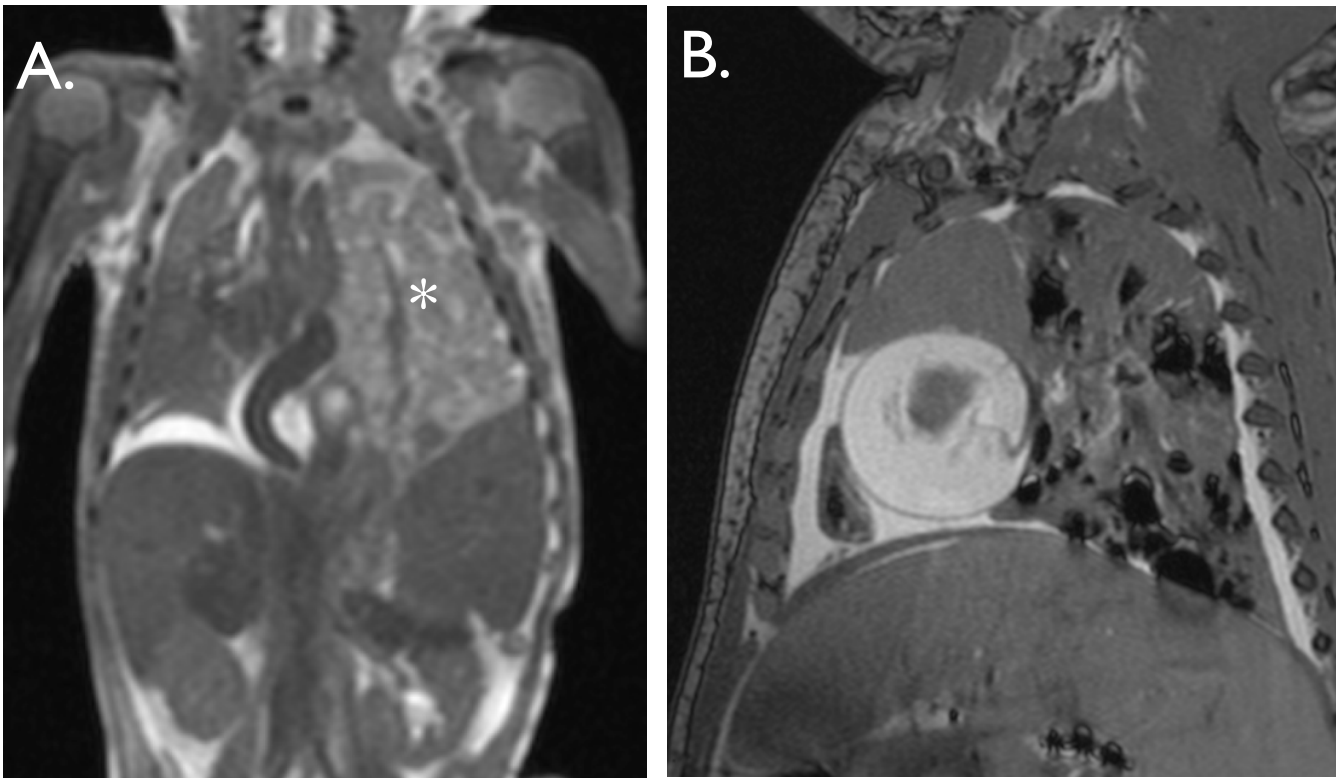


Figure 9. Coronal T_1-weighted image of the whole body in a 34-week-old fetus showing bilateral lung hypoplasia (arrows).

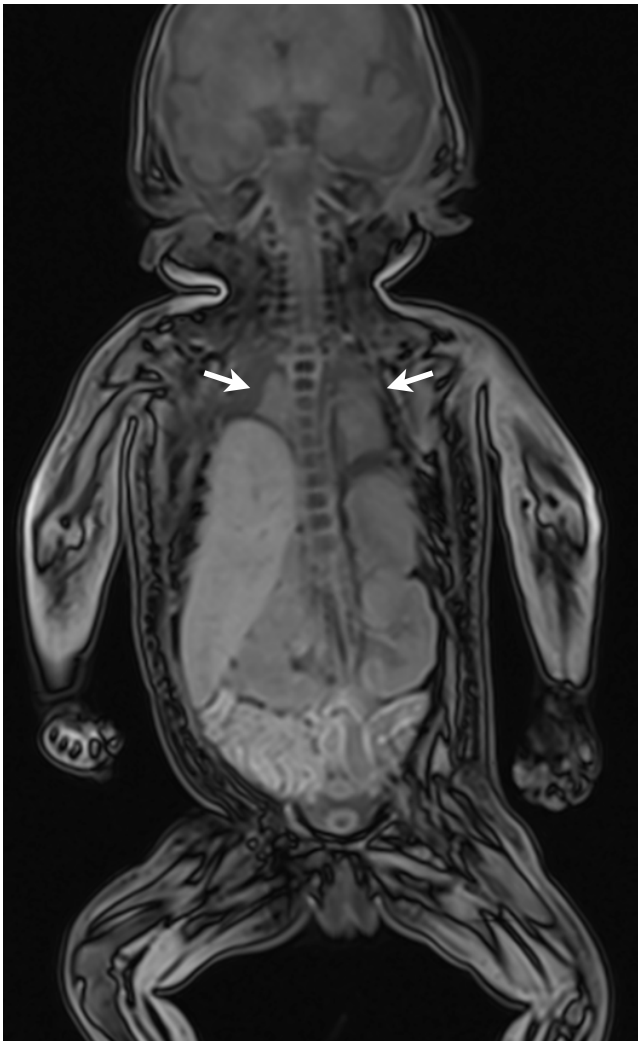


Figure 10. A. Coronal T_2-weighted image of the chest and abdomen in a 29-week-old fetus showing bilateral renal dysplasia (*). B. Coronal T2-weighted image of the chest and abdomen in a 4-day-old neonate showing left adrenal haemorrhage (arrow). C. Sagittal T2-weighted image of the chest and abdomen in a 19-week-old fetus showing abdominal exompholos.

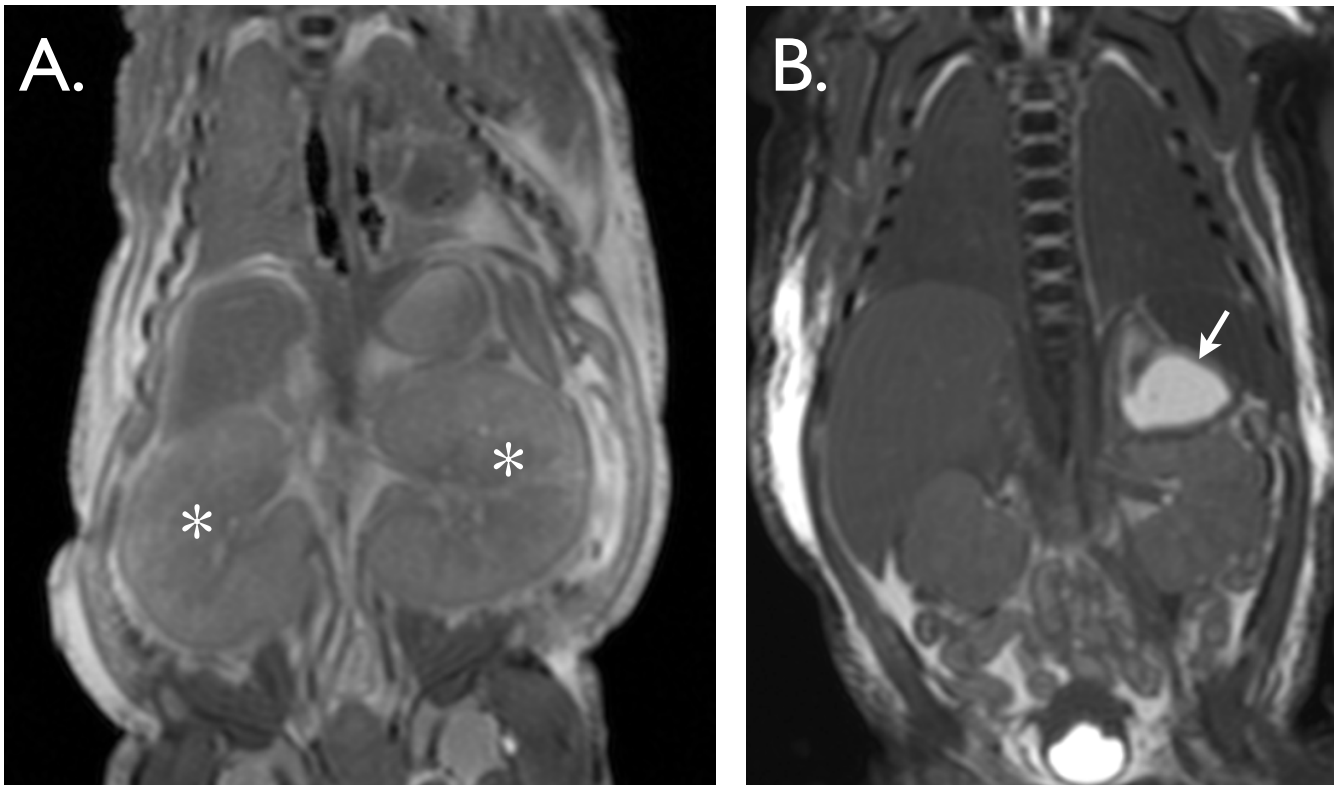


Figure 11. A. Double-oblique T_2-weighted image of the left femur in an 18-week-old fetus showing thanatophoric dysplasia-like osteochondrodysplasia. B. Double-oblique T2-weighted image of the right humerus in a 27-week-old preterm neonate showing a mid-shaft fracture (arrow)

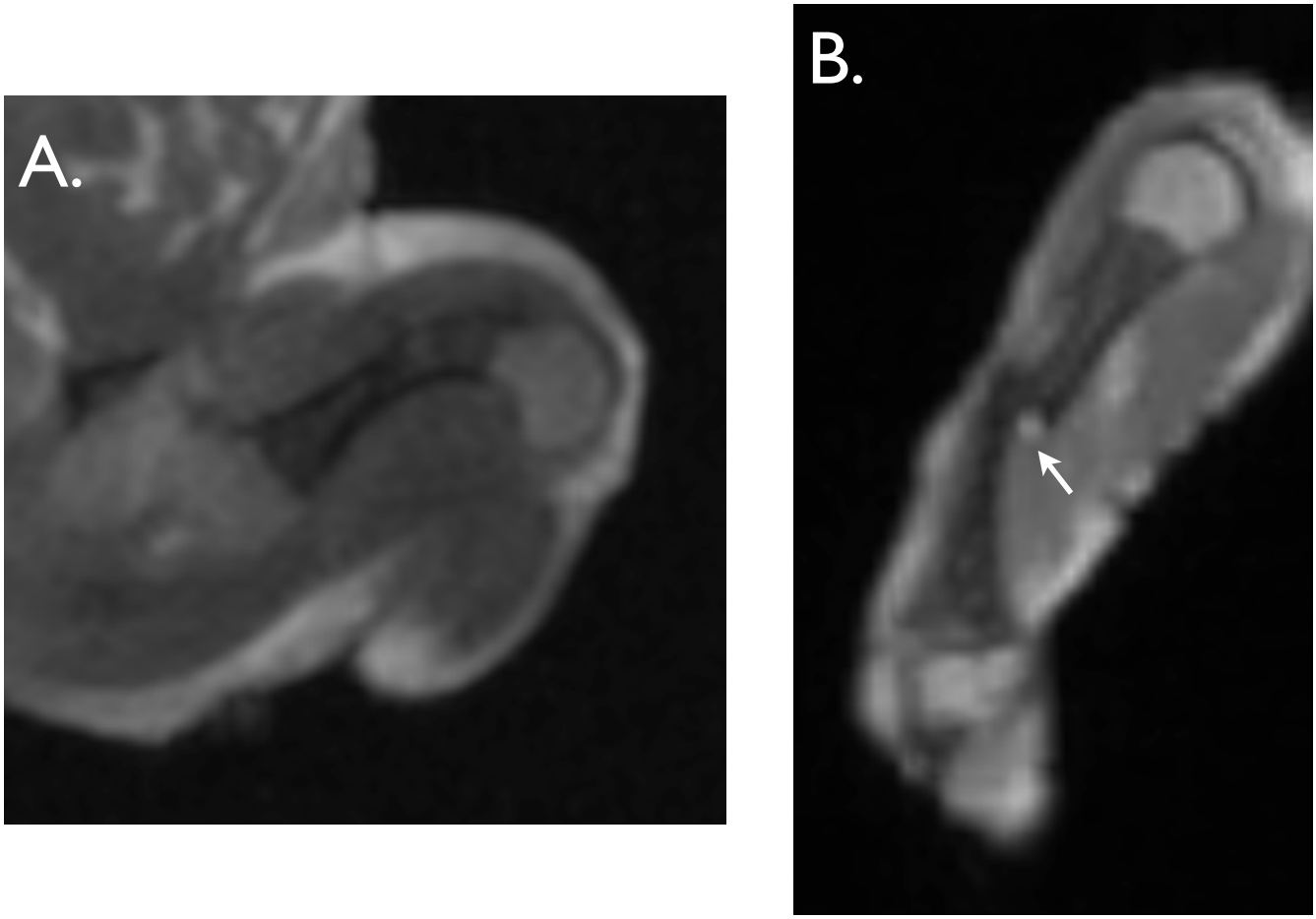
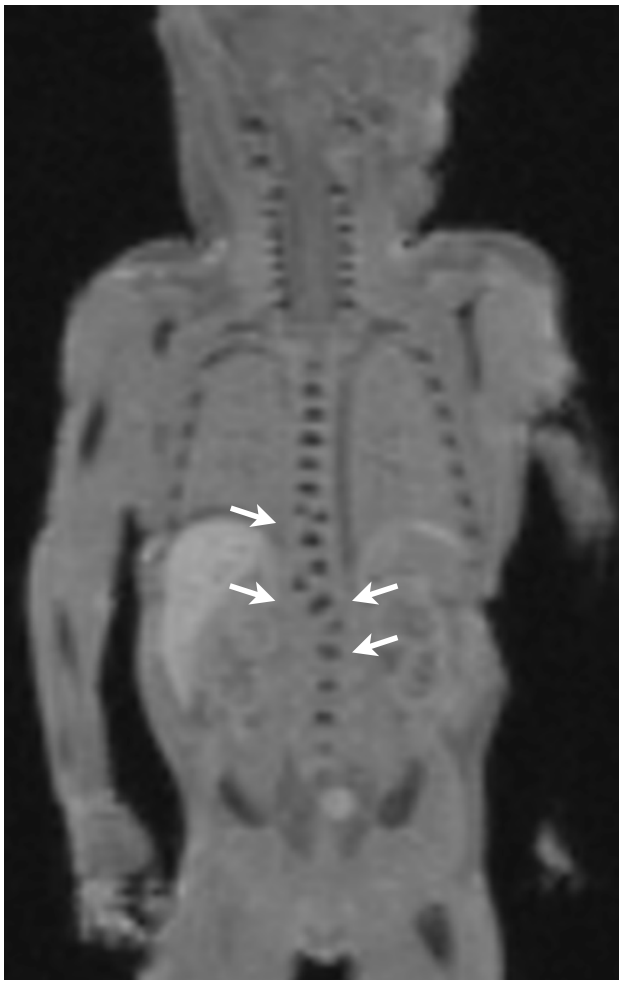


Figure 12. Coronal T_1-weighted image of the spine in a 19-week-old fetus showing vertebral anomalies (arrows). Case also had complex congenital heart disease – not shown.



Pathologies (with or without relation to death) undetected by minimally invasive autopsy

	Fetus ≤24 weeks (n=185)	Fetus >24 weeks (n=92)	Children (n=123)	Total (n=400)
All pathologies detected	161 (87·0) [81·4–91·1]	86 (93·5) [86·5–97·0]	73 (59·3) [5·5–67·6]	326 (81·5) [77·4–85·0]
Non diagnostic	9 (4·9)	1 (1·1)	0	10 (2·5)
Some pathology undetected	15 (8·1) [5·0–12·9]	5 (5·4) [2·3–12·1]	50 (40·7) [32·4–49·5]	70 (17·5) [14·1–21·5]
Abdomen	**3 (1·6)**	**2 (2·2)**	**5 (4·1)**	**10 (2·5)**
Adrenal bleed	1 (0·5)	1 (1·1)	1 (0·8)	3 (0·8)
Intestinal obstruction	0	1 (1·1)	0	1 (0·3)
Liver haemangioma	1 (0·5)	0	0	1 (0·3)
Liver infective focus	0	0	2 (1·6)	2 (0·5)
Steatosis	0	0	1 (0·8)	1 (0·3)
Subcapsular hematoma	1 (0·5)	0	0	1 (0·3)
Meckel's Diverticulum	0	0	1 (0·8)	1 (0·3)
Musculoskeletal	**1 (0·5)**	**0**	**0**	**1 (0·3)**
Skeletal dysplasia–specific diagnosis	1 (0·5)	0	0	1 (0·3)
Brain	**1 (0·5)**	**0**	**1 (0·8)**	**2 (0·5)**
Callosal agenesis	1 (0·5)	0	0	1 (0·3)
Dandy-Walker variant	0	0	1 (0·8)	1 (0·3)
Heart	**3 (1·6)**	**1 (1·1)**	**6 (4·9)**	**10 (2·5)**
Myocardial infarction	0	1 (1.1)	0	1 (0.3)
Myocarditis	0	0	6 (4·9)	6 (1·5)
Tetralogy of Fallot	2 (1·1)	0	0	2 (0·5)
Ventricular septal defect	1 (0·5)	0	0	1 (0·3)
Lungs	**6 (3·2)**	**2 (2·2)**	**33 (26·8)**	**41 (10·3)**
Aspiration	0	2 (2·2)	4 (3·3)	6 (1·5)
Haemorrhage	0	0	6 (4·9)	6 (1·5)
Pulmonary oedema	0	0	1 (0·8)	1 (0·3)
Hyaline membrane disease	0	0	1 (0·8)	1 (0·3)
Hypoplasia	3 (1·6)	0	0	3 (0·8)
Pneumonia	2 (1·1)	0	18 (14·6)	20 (5·0)
Pulmonary hypertension	0	0	1 (0·8)	1 (0·3)
Tracheo oesophageal fistula	1 (0·5)	0	2 (1·6)	3 (0·8)
Renal	**1 (0·5)**	**0**	**0**	**1 (0·3)**
Renal dysplasia	1 (0·5)	0	0	1 (0·3)
Multiple pathologies	**0**	**0**	**5 (4·1)**	**5 (1·3)**
Myocarditis and pulmonary oedema	0	0	1 (0·8)	1 (0·3)
Myocarditis and pneumonia	0	0	1 (0·8)	1 (0·3)
Pulmonary haemorrhage and steatosis	0	0	1 (0·8)	1 (0·3)
Pneumonia and necrotizing enterocolitis	0	0	1 (0·8)	1 (0·3)
Multi-organ failure (lung, liver)	0	0	1 (0·8)	1 (0·3)

Data are number (%); 95% Confidence intervals in square brackets

Apparent false-positives (with or without relation to death) by minimally invasive autopsy

	Fetus ≤24 weeks (n=185)	Fetus >24 weeks (n=92)	Children (n=123)	Total (n=400)
No apparent false positives	152 (82·2) [76·0–87·0]	67 (72·8) [63·0–80·9]	92 (74·8) [66·5–81·6]	311 (77·8) [73·4–81·6]
Non diagnostic	9 (4·9)	1 (1·1)	0	10 (2·5)
Apparent false-positives	24 (13·0) [8·9–18·6]	24 (26·1) [18·2–35·9]	31 (25·2) [18·4–33·5]	79 (19·8) [16·1–23·9]
Abdomen	**1 (0·5)**	**3 (3·3)**	**4 (3·3)**	**8 (2·0)**
Adrenal bleed	0	1 (1·1)	0	1 (0·3)
Intestinal obstruction	1 (0·5)	2 (2·2)	4 (3·3)	7 (1·8)
Musculoskeletal	**0**	**0**	**1 (0·8)**	**1 (0·3)**
Bone skull fracture	0	0	1 (0·8)	1 (0·3)
Brain	**18 (9·7)**	**11 (12·0)**	**10 (8·1)**	**39 (9·8)**
Colossal agenesis	9 (4·9)	0	0	9 (2·3)
Cerebellitis	0	0	1 (0·8)	1 (0·3)
Encephalitis	0	0	1 (0·8)	1 (0·3)
Ischemic injury	0	8 (8·7)	7 (5·7)	15 (3·8)
Malformation	1 (0·5)	1 (1·1)	0	2 (0·5)
Lissencephaly	1 (0·5)	0	0	1 (0·3)
Minor bleed	5 (2·7)	1 (1·1)	1 (0·8)	7 (1·8)
Schizencephaly	1 (0·5)	0	0	1 (0·3)
Spinal dysraphism	0	1 (1·1)	0	1 (0·3)
Vermis hypoplasia	1 (0·5)	0	0	1 (0·3)
Genetic	**0**	**1 (1·1)**	**0**	**1 (0·3)**
Heart	**4 (2·2)**	**6 (6·5)**	**2 (1·6)**	**12 (3·0)**
Aortic valvular stenosis	1 (0·5)	0	0	1 (0·3)
Atrial septal defect	0	0	2	2 (0·5)
Coarctation of aorta	0	1 (1·1)	0	1 (0·3)
Cortriatrum	0	1 (1·1)	0	1 (0·3)
Anomalous pulmonary venous drainage	1 (0·5)	1 (1·1)	0	2 (0·6)
Ventricular septal defect	2 (1·1)	3 (3·3)	0	5 (1·3)
Lungs	**0**	**2 (2·2)**	**14 (11·4)**	**16 (4·0)**
Aspiration	0	0	1 (0·8)	1 (0·3)
Consolidation	0	0	10 (8·1)	10 (2·5)
Drowning	0	0	1 (0·8)	1 (0·3)
Hypoplasia	0	1 (1·1)	0	1 (0·3)
Non specific lesion	0	1 (1·1)	2 (1·6)	3 (0·8)
Multiple pathologies	**1 (0·5)**	**1 (1·1)**	**0**	**2 (0·5)**
Heart lesion/minor cerebral bleed	1 (0·5)	0	0	1 (0·3)
Lung lesion/adrenal bleed	0	1 (1·1)	0	1 (0·3)

Data are number (%); 95% Confidence intervals in square brackets