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Minimally invasive fetal autopsy using ultrasound: a feasibility study

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KEYWORDS: fetal autopsy; high-frequency linear probe; imaging; postmortem ultrasound

ABSTRACT

Objectives *To evaluate postmortem ultrasound (PM-US) for minimally invasive autopsy, and to demonstrate its feasibility, sensitivity and specificity, as compared with conventional autopsy, in detecting major congenital abnormalities.*

Methods *Over a 19-month study period from 1 March 2012 to 30 September 2013, we recruited from a referral hospital 88 consecutive fetuses, at 11–40 weeks' gestation, which had undergone termination, miscarriage or intrauterine fetal death. We performed PM-US using different transducers and compared the data with those from conventional autopsy. The latter was performed, according to the Societé Francaise de Foetopathologie (France) guidelines, by experienced perinatal pathologists who were blinded to the ultrasound data.*

Results *Complete virtual autopsy by ultrasound was possible in 95.5% of the cases. The sensitivity of PM-US for detecting brain abnormalities was 90.9% (95% CI, 58.7–99.8%) and the specificity was 87.3% (95% CI, 75.5–94.7%). In 20% of cases, a neuropathological examination was not possible due to severe maceration. The sensitivity for detection of thoracic abnormalities was 88.9% (95% CI, 65.3–98.6%) and the specificity was 92.8% (95% CI, 84.1–97.6%), and the sensitivity for detection of abdominal anomalies was 85.7% (95% CI, 57.2–98.2%) and the specificity was 94.6% (95% CI, 86.7–98.5%).*

Conclusion *This pilot study confirms the feasibility of PM-US for virtual autopsy as early as 11 weeks' gestation. This new technique shows high sensitivity and specificity in detecting congenital structural abnormalities as compared with conventional autopsy.* *Copyright © 2014 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Fetal and perinatal deaths due to structural or chromosomal abnormality, late miscarriage or stillbirth are common in obstetric practice, complicating around 1% of pregnancies[1]. Perinatal and neonatal postmortem examination plays an important role, providing important information on the pathological processes involved[2,3]. Even when there is an identifiable clinical cause of death, autopsy findings may modify or correct it, and may inform on the risk of recurrence in cases of fetal abnormality[3,4]. Postmortem examination also provides useful information for clinicians, helping them to understand the causes and effects of diseases as well as the effectiveness and complications of treatment. In addition, postmortem examination can play a crucial role in research and so advance the progress of fetal and pediatric medicine[4].

Despite this, however, increasing numbers of parents decline autopsy. The neonatal postmortem examination consent rate is less than 20% in England and Wales, as reported by the Confidential Enquiry into Maternal and Child Health (CEMACH)[5]. Magnetic resonance imaging (MRI) was proposed as an alternative to conventional perinatal autopsy more than two decades ago[6]. Various studies have examined the role of postmortem MRI as an alternative or complement to conventional autopsy, defined as the gold standard for postmortem evaluation[7–10]. Virtual autopsy is reliable and highly accepted by patients[11]. A prospective validation study on MRI *vs* conventional autopsy demonstrated that it has similar accuracy to that of conventional autopsy

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for detection of cause of death or major pathological abnormality[12]. For small fetuses, high-field (9.4 Tesla) MRI allows an examination as early as 11 weeks' gestation, thanks to the better spatial resolution and better tissue contrast[13]. It is unfortunate that the accessibility of this technique is limited, it being unavailable in some clinical departments.

In this study, we aimed to evaluate a more accessible technique for virtual autopsy, namely, postmortem ultrasound (PM-US), to show its feasibility and to evaluate its sensitivity and specificity for detection of major congenital abnormalities as compared with conventional autopsy.

METHODS

In this prospective validation study, we performed all PM-US examinations at Brugmann University Hospital, Brussels, between 1 March 2012 and 30 September 2013. We selected a sequential population of fetuses for which the parents accepted both conventional and virtual autopsy, giving their written consent. The study had institutional approval.

Fetuses underwent first PM-US and then conventional autopsy. Scans were performed on fresh fetuses 1–4 days after death, bodies being stored in a mortuary at 4°C, or on fetuses preserved in formalin for no more than 4 weeks; we have demonstrated previously on a phantom that formalin does not interfere with the quality of PM-US. All fetuses before 15 weeks' gestation and 22% of fetuses between 15 and 28 weeks (when particular circumstances necessitated longer or better preservation) were preserved in formalin as soon as possible after delivery for better preservation of organ structures, particularly the fetal brain. In the case of miscarriage, the duration of intrauterine retention after death was estimated from the difference between the gestational age at delivery (predicted from early ultrasound or date of last menstrual cycle) and that estimated from the autopsy parameters.

All PM-US examinations were performed by a single operator: a fetal medicine specialist with 10 years' experience in fetal ultrasound but no previous experience in PM-US. The examiner was not blinded to the antenatal clinical details. In order to optimize the ultrasound settings and to identify the best planes, preliminary PM-US examinations were performed on four fetuses which were not included in the study. Examinations were performed using a Voluson E8 (GE Medical Systems, Zipf, Austria) machine, equipped with the following transducers: a high-frequency linear probe, RSP 6-16 (bandwidth, 6–18 MHz, field of view (FOV), 37.4 mm; volume (V), 37.4 mm × 29°; 192 elements) and/or transvaginal probe RIC 6-12 (bandwidth, 5–13 MHz; FOV, 149°; V, 149° × 120°; Wide 195°: V, 195° × 120°; 256 elements) and/or transvaginal probe RIC 5-9 (bandwidth, 4–9 MHz; FOV, 146°: V, 146° × 120°; Wide 179°: V, 179° × 120°; 192 elements). The spatial resolution was less than 1 mm. Ultrasound contrast agents were not used. Two-dimensional (2D) examinations were performed first, in real time, and at least three three-dimensional (3D) volumes (at least one each of the head, the thorax and the abdomen) were acquired using grayscale imaging, for storing data and teaching purposes.

The fetus was placed in a supine position and completely covered by a 5-mm-thick layer of standard ultrasound transmission gel. The probe was placed on the fetal part of interest (Figure 1). The fetal brain was scanned using one of the three probes, depending on the gestational age and size of the skull fontanels. Figure 2 shows different positions of the probes using different acoustic windows. According to our experience, in the first trimester of pregnancy, a single approach, with the linear probe, through the anterior fontanel is sufficient for visualization of the whole brain; however, in the second and third trimesters, a transvaginal probe is needed due to the reduced size of the fontanel, and approaches through the sphenoid, mastoid and posterior fontanels are recommended for visualization of the posterior fossa. We used a high-frequency linear probe for the fetal thorax and abdomen in all cases. In some cases, we had to turn the fetus to a prone position for better visualization of the kidneys and adrenal glands.

Images were interpreted during the 2D evaluation according to ISUOG guidelines[14] for prenatal diagnosis. For evaluation of the fetal brain, we analyzed the supratentorial structures and posterior fossa; for evaluation of the thorax, we analyzed the lungs, four cardiac chambers and great vessels; for evaluation of the abdomen, we analyzed the stomach, spleen, liver, bowel, kidneys, adrenal glands and bladder. As suggested by Thayyil *et al.*[12], we regarded small fetal ventricular bleeds without dilation, small amounts of pleural, pericardial or peritoneal fluid and intestinal hyperechogenicity as postmortem artifacts with no clinical significance. When ultrasound images were not of sufficient quality to allow diagnosis, we classified the minimally invasive autopsy examination as 'non-diagnostic'. Thus, each organ system was classified as either 'abnormal' (with specific diagnosis), 'normal' or 'non-diagnostic'. The total ultrasound scan time was about 15 min per fetus.

Conventional autopsy, defined as a procedure that included open dissection of any body part, was performed according to the guidelines set down by the Societé Francaise de Foetopathologie (SOFFET, France) by one of two experienced perinatal pathologists, each of whom had at least 20 years' experience of perinatal autopsy and was accredited by SOFFET. Pathologists were blinded to the PM-US data, but had available to them a review of the clinical history and all relevant antemortem information, as well as postmortem radiography. The procedure included external examination, open dissection and macroscopic examination, followed by histological sampling of all major organs and removal of the brain, with examination after prolonged fixation. Ancillary investigations, such as genetic and metabolic testing and virology and microbiology sampling, were conducted as needed. One of two specialized pathologists performed the neuropathological examinations. In all cases, placental histopathological

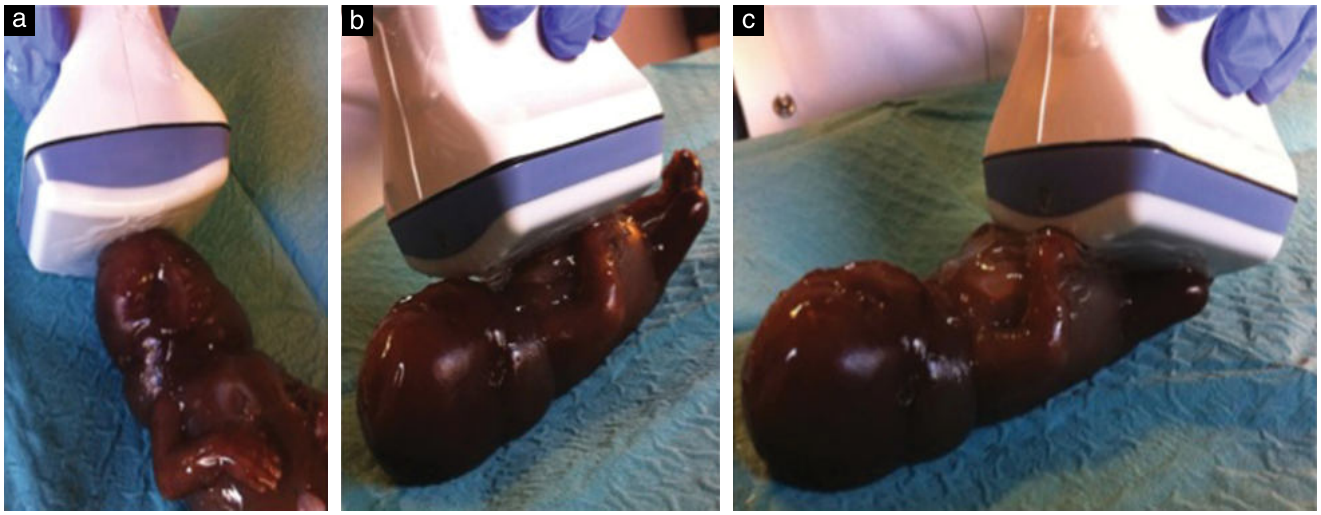

Figure 1 Postmortem ultrasound examination performed with a high-frequency linear probe (RSP 6-16) in a 14-week fetus terminated for Down syndrome and cystic hygroma. In (a) the probe is positioned on the anterior fontanel to image the fetal brain. In (b) and (c) the probe is on the thorax and abdomen, respectively.

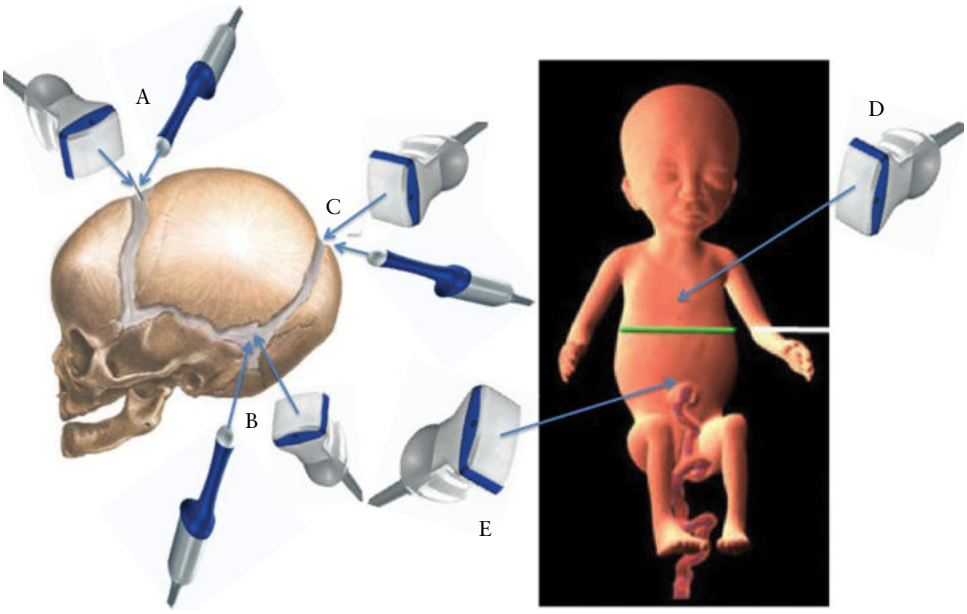

Figure 2 Schematic representation of different approaches for scanning the fetal brain through the anterior fontanel (position A), mastoid fontanel (position B) and posterior fontanel (position C). High-frequency linear probe RSP 6-16 or transvaginal probes RIC 5-9 or RIC 6-12 can be used according to the size of the fontanels and the gestational age. Position D is used for scanning the fetal thorax and position E for scanning the fetal abdomen.

examination was carried out. Cases in which autolysis occurred were classified as non-diagnostic.

Autopsy and PM-US data were entered into the same database. For statistical analysis, we grouped organ structures into three main categories: brain, thorax (including heart and lungs) and abdomen (including gastrointestinal and genitourinary systems).

RESULTS

After exclusion of the four fetuses used for optimization of US settings, the study included 88 fetuses between 11 and 40 gestational weeks (Figure 3). The median gestational age was 21 weeks and the median weight was 702 (range, 7–4020) g. PM-US was performed on fresh fetuses in 53 cases; the median time between delivery and PM-US was 2 days (range, 1 h to 4 days), and that between PM-US and autopsy was 1 day (range, 1 h to 2 days). PM-US was performed on formalin-fixed fetuses in 35 cases. Fifty-eight cases derived from termination of pregnancy (TOP), 15 from miscarriage and 15 from unexplained intrauterine death (IUFD); 15 of the latter 30 were retained *in utero* for between 1 and 4 weeks after death. The indication for TOP was chromosomal abnormality in 15 cases, genetic syndrome in five cases, brain

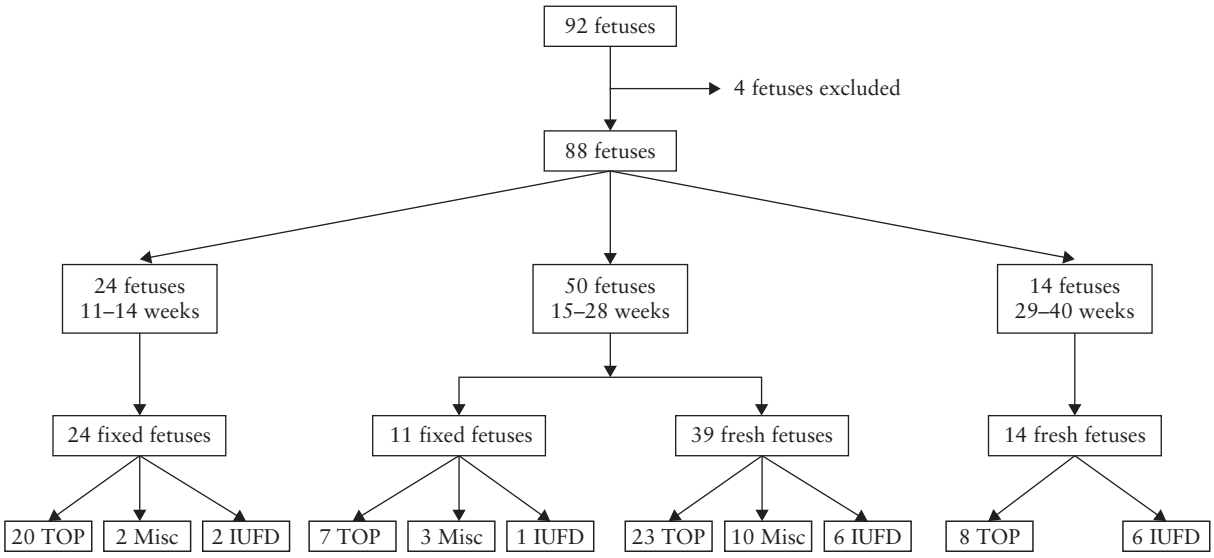

Figure 3 Flowchart summarizing fetuses included in study. IUFD, intrauterine fetal death; Misc, miscarriage; TOP, termination of pregnancy.

abnormality or neural tube defect in 16 cases, skeletal syndrome in seven cases, cardiovascular abnormality in two cases, gastrointestinal or genitourinary abnormalities in five cases, severe intrauterine growth restriction in one case, fetal akinesia deformation syndrome in two cases, anasarca in one case, severe facial anomaly in two cases, early premature rupture of the membranes in one case and severe infection in one case.

During the real-time 2D PM-US examination, complete evaluation of the fetus, with recognition of all organ structures, was possible in 84 (95.5%) cases; in four cases, no brain structure was recognizable and, in two of these cases, the thorax and abdomen could also not be evaluated. The gestational ages of these four fetuses were 13, 14, 18 and 23 weeks, and all had undergone IUFD with a severe degree of maceration. During conventional autopsy, complete neuropathological examination was possible in 66 cases (we excluded five cases with anencephaly and 17 cases in which the brain was not diagnostic due to general autolysis), while a complete pathological examination of the thorax and abdomen was possible in all cases.

Table 1 summarizes the PM-US and conventional autopsy findings and Table 2 gives a detailed description of the main abnormalities identified by conventional autopsy and the ability of PM-US to identify them. Ten of the 11 brain anomalies detected at conventional autopsy were identified at PM-US. One case of ventriculomegaly was not identified at PM-US. The sensitivity of PM-US for detection of brain abnormalities was 90.9% (95% CI, 58.7–99.8%). The specificity was 87.3% (95% CI, 75.5–94.7%) as the following abnormalities were incorrectly suspected at PM-US: Arnold–Chiari malformation in a case at 13 weeks, delayed gyration in a case of trisomy 18 at 25 weeks, and ventriculomegaly, vermian hypoplasia, agenesis of the corpus callosum and microphthalmia in one case each. One case was not diagnostic.

Table 1 Numbers of normal and abnormal diagnoses by postmortem ultrasound (PM-US) compared with conventional autopsy for fetal brain, thorax (including heart and lungs) and abdomen ($n = 88$)

Organ system/ technique	*Normal* (n)	*Abnormal* (n)	*Non-diagnostic* (n)
Brain*			
PM-US	60	19	4
Conventional autopsy	55	11	17†
Thorax			
PM-US	67	19	2
Conventional autopsy	70	18	0
Abdomen			
PM-US	71	15	2
Conventional autopsy	74	14	0

*$n = 83$; five cases showed anencephaly and were not considered for neuropathological examination at conventional autopsy; these data have therefore been omitted from the PM-US data. †Cases in which autolysis occurred.

Concerning the fetal thorax (including heart and lungs), 16 of the 18 malformations were identified at PM-US. The sensitivity was 88.9% (95% CI, 65.3–98.6%), as with PM-US we failed to identify a case of tetralogy of Fallot in a fetus that had undergone IUFD with severe maceration at 24 weeks and a perimembranous interventricular defect in a 15-week fetus terminated for Down syndrome. The specificity was 92.8% (95% CI, 84.1–97.6%); at PM-US, we diagnosed incorrectly the following abnormalities: a case of hydrothorax, a case of cardiomegaly and a hypoplastic aorta; in two cases, PM-US was not diagnostic.

We identified by PM-US 12 of the 14 abdominal malformations. The sensitivity in detecting abdominal abnormalities was 85.7% (95% CI, 57.2–98.2%) as we failed to identify a case of hypoplastic kidneys and a case of horseshoe kidney. The specificity was 94.6% (95% CI, 86.7–98.5%) as we diagnosed incorrectly the following

Table 2 Ability of postmortem ultrasound (PM-US) to identify organ abnormalities in cases in which conventional autopsy was diagnostic and abnormal

	Number of cases with abnormalities identified at:	
Organ system/abnormality	*Conventional autopsy*	*PM-US*
Brain ($n = 66$)		
Corpus callosal agenesis	3	3
Hydrocephaly	1	1
Porencephaly	2	2
Vermian hypoplasia	1	1
Hemimegalencephaly	1	1
Severe hemorrhage	1	1
Holoprosencephaly	1	1
Ventriculomegaly	1	0
Thorax ($n = 88$)		
Pulmonary arterial stenosis	1	1
Truncus arteriosus	1	1
Tetralogy of Fallot	1	0
Interruption of aortic arch	1	1
Diaphragmatic hernia	3	3
Atrioventricular septal defect	3	3
Hypoplastic left heart syndrome	1	1
Cardiomegaly	1	1
Ventricular septal defect	1	0
Dilated right atrium	1	1
Aortic stenosis	1	1
Transposition of the great vessels	1	1
Ectopia cordis	1	1
Mediastinal tumor	1	1
Abdomen ($n = 88$)		
Hypoplastic kidneys	1	0
Horseshoe kidney	2	1
Multicystic kidney	2	2
Hepatomegaly	1	1
Megacystis	1	1
Omphalocele	3	3
Diaphragmatic hernia	3	3
Bowel atresia	1	1

Cases were included for a particular organ system only if results were available for conventional autopsy: examination was possible and conclusive at conventional autopsy in all 88 cases for thorax and abdomen, but in only 66 cases for the brain (excluding five that were not considered for neuropathological examination due to anencephaly and 17 in which the brain was not diagnostic due to advanced autolysis).

abnormalities at PM-US: a case of bowel dilatation and two cases of ascites; one case was not diagnostic.

Table S1 shows the results at PM-US for all 88 fetuses. Figures 4–7 present examples of normal and abnormal PM-US images for fetal brain, thorax, heart and abdomen.

DISCUSSION

Our study demonstrates that virtual autopsy by ultrasound is feasible as early as 11 weeks' gestation. A complete PM-US could be performed in 95% of cases; in four cases, severe maceration due to IUFD did not allow recognition of any fetal brain structures. A conventional neuropathological examination was possible in 80% of the cases, as in 17 cases severe maceration precluded the study. The fetal brain is composed predominantly of water and, once removed from the supporting cerebrospinal fluid and skull, it collapses and structural integrity is sometimes altered. Due to its fragility, it is sometimes hard to investigate the fetal brain with conventional autopsy when fixation and preservation are not optimal, especially in small fetuses, particularly when autolysis occurs. Our study demonstrates that PM-US allows diagnostic information to be obtained in 15% of cases in which conventional neuropathology was not possible. The sensitivity and specificity of PM-US in detecting brain abnormalities were 91% and 87%, respectively.

Conventional autopsy for the abdomen and the thorax was possible in all fetuses. The sensitivity of PM-US in detecting heart and lung abnormalities was 89% and the specificity was 93%, and the sensitivity for detecting abdominal abnormalities was 86% and the specificity was 95%. Thus, minimally invasive autopsy by PM-US could be suitable as an alternative or as a complement to conventional autopsy in the vast majority of cases.

PM-US presents some important advantages, including low cost, wide accessibility, short examination time and safety for the examiner due to lack of toxicity. Formalinization, an important process for preserving brain and soft tissue, does not seem to impact on PM-US image quality, giving an advantage over MRI, which is performed on fresh fetuses. The acquisition of 3D volumes also allows storage of digital data which can be re-examined or sent to another specialist for a second opinion. 3D reconstructions can also be performed and, with tools such as tomographic ultrasound imaging, there is the possibility of analyzing multislice images with a resolution power of 0.5 mm. This tool is particularly useful for teaching purposes, as structural abnormalities can be illustrated compared with the normal appearance of the fetal anatomy much better than is possible using 2D ultrasound (Figures 4–7).

The role of perinatal autopsy in confirming or refuting an antemortem diagnosis is undisputed. Many studies report significant disagreement between the premorbid diagnosis and postmortem examination in at least 10% of cases and additional clinically significant findings which would affect counseling in 14–46% of cases[5,15–20]. This impacts upon both risk of recurrence and the approach to prenatal diagnosis in future pregnancies[17,21]. However, autopsy rates have declined steadily over the years; 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[5]. Since the first report of minimally invasive autopsy in 1990[6], growing interest in imaging techniques has led to an increase in these procedures. A prospective validation study showed that virtual autopsy by MRI has similar accuracy to that of conventional autopsy, with a sensitivity and specificity of more than 95% for detection of major intracranial and non-infective pathological abnormalities[12]. Unfortunately, computed tomography

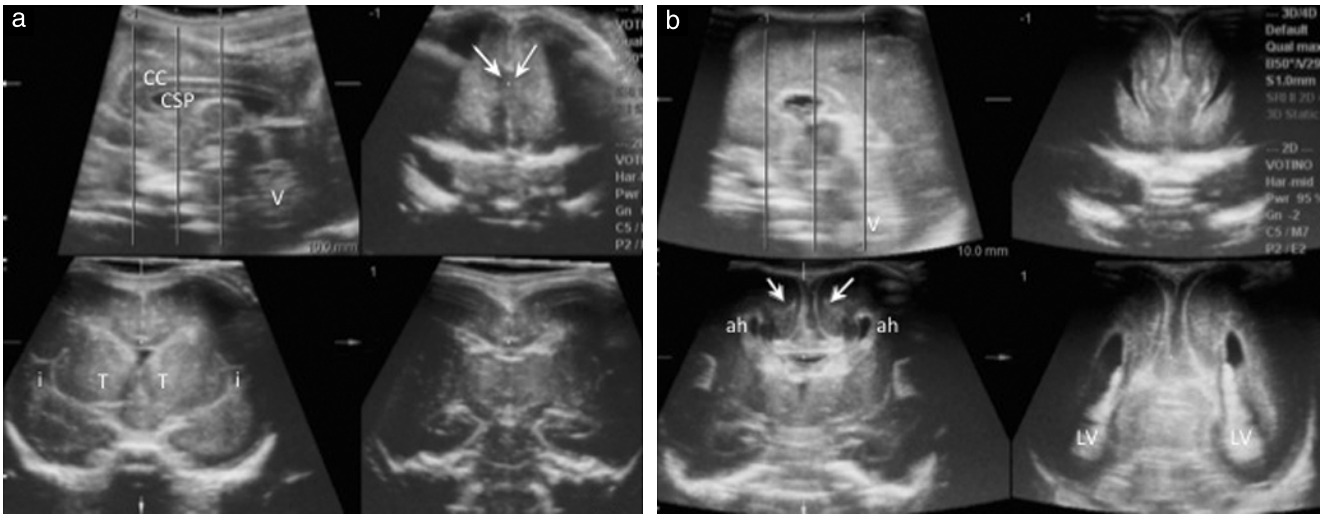

Figure 4 Postmortem ultrasound of fetal brain (tomographic ultrasound imaging of coronal plane). (a) Normal brain from a 22-week fetus, terminated for cystic fibrosis. Images obtained with a transvaginal transducer (RIC 5-9) through the anterior fontanel. In the sagittal plane, can be seen a normal corpus callosum (CC), with normal cavum septi pellucidi (CSP) and vermis of cerebellum (V); in the coronal plane, can be seen a normal midline (arrows), thalami (T) and insulae (i). (b) Corpus callosal agenesis in a 23-week fetus. Images obtained with a linear transducer (RSP 6-16) through the anterior fontanel. In the sagittal plane, the corpus callosum is not visible; in the coronal plane, there is increased separation of the hemispheres with a prominent interhemispheric fissure (arrows). The anterior horns (ah) of the lateral ventricles (LV) are displaced laterally and point superiorly. There is disproportionate enlargement of the occipital horns (colpocephaly) with a teardrop configuration of the lateral ventricles.

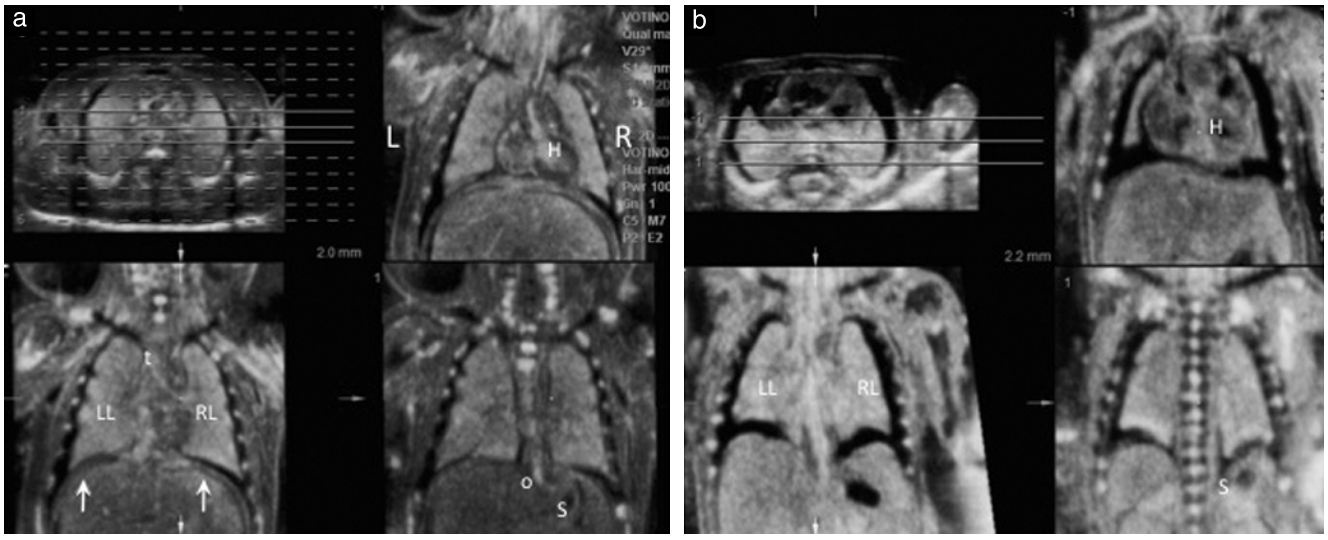

Figure 5 Postmortem ultrasound of fetal thorax and upper part of the abdomen (tomographic ultrasound imaging of coronal plane). Images were obtained using a linear probe (RSP 6-16). (a) Normal fetal thorax in a 14-week fetus terminated for Down syndrome. Cardiac situs is normal and it is easy to identify the stomach (S) on the same side as the heart (H); the diaphragm (arrows) is normal, and the esophagus (o) can be seen entering the stomach; the right (RL) and left (LL) lungs are normally developed and occupy the entire thoracic cavity; also visible is the trachea (t) and its bifurcation. L, left; R, right. (b) A case of hydrothorax and cardiomegaly in a 13-week fetus terminated for trisomy 18 and general anasarca. The increased amount of fluid in the thoracic cavity and cardiomegaly is evident: the fetal heart occupies more than half of the thoracic cavity.

(CT) and/or MRI require special equipment, a dedicated room and trained specialists. Furthermore, though we are unaware of the precise cost of postmortem MRI, it is safe to assume that PM-US will be considerably less expensive, which is perhaps the most important consideration in the present atmosphere of medical cost containment[22]. Further studies are needed to compare PM-MRI with PM-US. Ultrasonography is commonly applied in the field of clinical medicine and its use is expanding globally, but in the field of forensic medicine, especially in external examination and diagnosis of cause of death, it is a relatively new technique. Increasing attempts have been made to apply this technique to cadavers[22–24].

Increasingly, as early fetal ultrasound techniques improve, malformations are detected earlier in pregnancy, and parents in severe cases can be given the option of early TOP. Conventional autopsy might be difficult when fetuses are small, or in the presence of maceration and autolysis, particularly for adequate examination of the brain. The accuracy of conventional

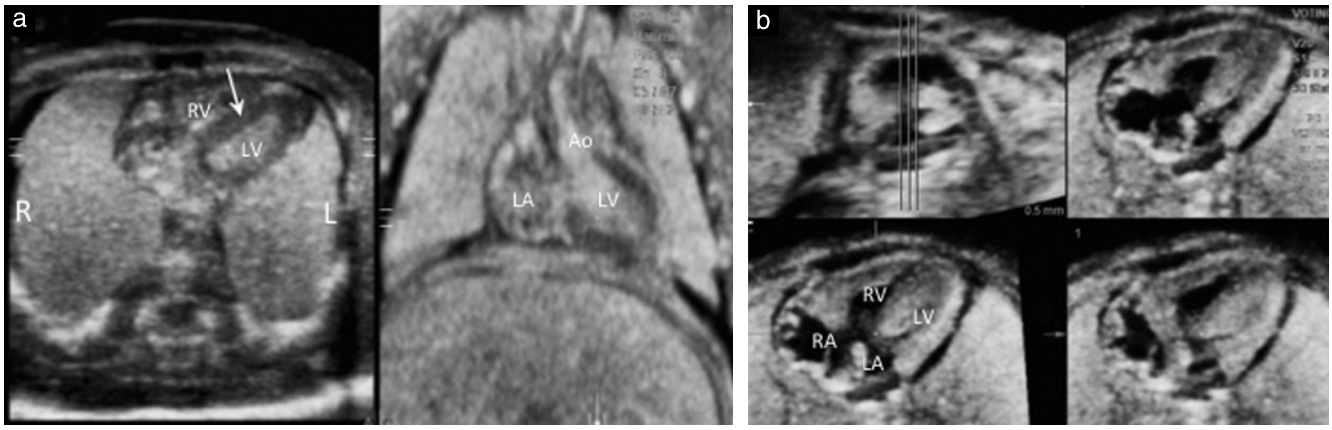

Figure 6 Postmortem ultrasound of fetal heart. Images were obtained using a linear probe (RSP 6-16). (a) Normal fetal heart in a 14-week fetus terminated for cystic hygroma; a normal cardiac axis and normal four-chamber view are visible, and the left ventricle (LV) is on the left side (L) and the right ventricle (RV) on the right side (R); the integrity of the interventricular septum is clear (arrow). The aorta (Ao) arises from the LV and is normally connected with the left atrium (LA). (b) Tomographic ultrasound images in a case of atrioventricular septal defect in a 15-week fetus terminated for Down syndrome. The four-chamber view demonstrates the crux of the heart in which the atrial and ventricular septal defects are located, as well as the single common atrioventricular valve.

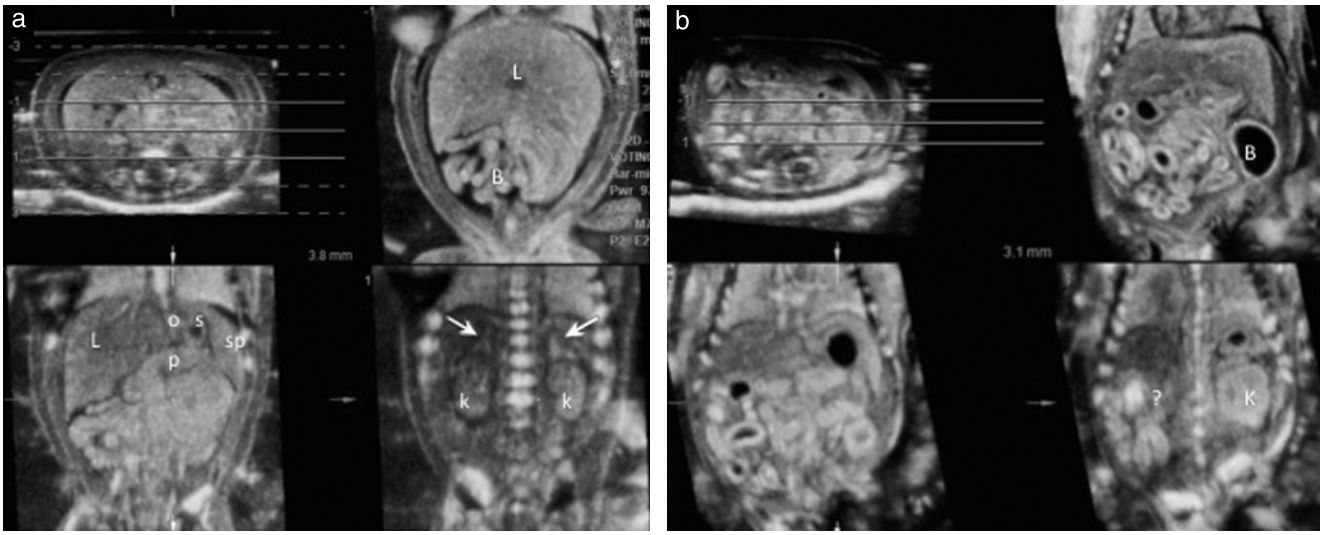

Figure 7 Postmortem ultrasound of fetal abdomen (tomographic ultrasound imaging of coronal plane). Images were obtained using a linear probe (RSP 6-16). (a) Normal abdomen in a 14-week fetus terminated for Down syndrome; visible are the normal liver (L), stomach (s), esophagus (o), pancreas (p), spleen (sp), bowel (B), kidneys (k) and adrenal glands (arrows). (b) A 14-week fetus terminated for multiple anomalies. Bowel dilatation (B) and one dysplastic kidney (K) are evident, with contralateral kidney agenesis (?).

MRI is poor; however, high-field MRI, at 9.4 Tesla, can provide diagnostic information[13,25,26]. A novel study has proposed the use of 'micro-CT' for examination of small fetuses and fetal hearts as early as 7 weeks' gestation[27]. Unfortunately, both high-field MRI and micro-CT are not widely accessible. In contrast, PM-US is easy to perform and available from all clinical departments, and we achieved a good examination of fetal anatomy as early as 11 weeks' gestation.

Of course, our study has some limitations. First, a single fetal medicine specialist performed all the examinations and interobserver variability could not be evaluated in this preliminary study. We suspect that the ability to visualize different organs and structures is an operator-dependent variable. According to our experience, good visualization of the fetal brain in the second and third trimesters can be achieved by choosing the most appropriate probe and the best acoustic window through the different fontanels. When examining the fetal heart, particularly in the third trimester, the ossification of the ribs interferes with optimal visualization of the cardiac structures and so we recommend that an echocardiographer performs this evaluation. Another important limitation of our study is that the examiners performing both virtual and pathological examinations were not blinded to the patients' files. In future research it would be interesting to evaluate the sensitivity of PM-US with the operator blinded to patient data. Interpretation of the images was performed using prenatal ultrasound parameters. However, certain fetal

postmortem physiological alterations should be taken into account; bowel dilatation, reduction of the cisterna magna, and small amounts of pleural, pericardial and abdominal fluid could interfere with the interpretation of images. Specific guidelines for PM-US examination should be drafted in the future.

Our experience in this pilot study suggests that PM-US is feasible and shows high sensitivity in detecting fetal structural abnormalities. It could offer clear advantages over traditional autopsy, particularly when the central nervous system is not amenable to conventional dissection. This new technique could represent a bridge between the prenatal diagnosis and the postmortem examination. Furthermore, thanks to the high-frequency probes used in PM-US, we have learned to recognize better some organs that are not easy to visualize *in utero*; this technique could also prove useful in the education of physicians and sonographers in prenatal ultrasound, by helping them to understand normal sonographic anatomy and to recognize major anomalies.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Details of postmortem ultrasound (PM-US) findings in 88 fetuses