

Pediatric Radiology

3-dimensional (3-D) versus 2-dimensional (2-D) post-mortem ultrasound: Feasibility in perinatal death investigation --Manuscript Draft--

Manuscript Number:	PRAD-D-20-00199R1	
Full Title:	3-dimensional (3-D) versus 2-dimensional (2-D) post-mortem ultrasound: Feasibility in perinatal death investigation	
Article Type:	Technical Innovation	
Funding Information:	Medical Research Council (GB) (MR/R002118/1)	Dr Susan Cheng Shelmerdine
	Royal College of Radiologists	Dr Susan Cheng Shelmerdine
	Research Councils UK (GB) (MR/R002118/1)	Dr Susan Cheng Shelmerdine
	National Institute for Health Research (GB) (NIHR-CDF-2017-10-037)	Dr Owen J Arthurs
Abstract:	<p>3-D/4-D ultrasound techniques in antenatal screening are commonplace, but not routinely used for perinatal post-mortem ultrasound. In this technical innovation, we performed both 2-D and 3-D post-mortem ultrasound on 11 fetuses (mean gestation: 23 weeks; range: 15 – 32 weeks) to determine if there was any benefit in 3-D methods over conventional 2-D ultrasound. In 1 case of osteogenesis imperfecta, both 2-D and 3-D ultrasound were non-diagnostic due to small foetal size. Of the remaining 10 fetuses, 7 were normal at imaging and autopsy; and 3 had abnormalities detected on both 2-D and 3-D ultrasound. There were no false positive diagnoses by 2-D or 3-D ultrasound. Whilst 3-D post-mortem ultrasound was a feasible technique, it did not provide additional information over 2-D ultrasound. Routine 3-D post-mortem ultrasound cannot therefore be routinely recommended based on our findings.</p>	
Corresponding Author:	Susan Cheng Shelmerdine, MBBS BSc MRCS FRCR Great Ormond Street Hospital For Children NHS Trust UNITED KINGDOM	
Corresponding Author Secondary Information:		
Corresponding Author's Institution:	Great Ormond Street Hospital For Children NHS Trust	
Corresponding Author's Secondary Institution:		
First Author:	Susan Cheng Shelmerdine, MBBS BSc MRCS FRCR	
First Author Secondary Information:		
Order of Authors:	Susan Cheng Shelmerdine, MBBS BSc MRCS FRCR	
	Neil J Sebire	
	Owen J Arthurs	
Order of Authors Secondary Information:		
Author Comments:	<p>Dear Dr Oystein Olsen and members of the Editorial Board,</p> <p>Thank you for inviting us to resubmit our attached manuscript entitled " 3D versus 2D post-mortem ultrasound: Feasibility and additional value in perinatal death investigation" for publication as a technical innovation article in Pediatric Radiology.</p> <p>We had previously submitted this as an original article on 27 January 2020, however given our small cohort and heterogenous population it was advised that we reproduce our article for the technical innovation. The previously suggested changes by the authors, including removal of abbreviations and acronyms as well as addition of keywords within the text and reformatting of reference list has now been implemented.</p>	

This work was supported by the Guy Sebag research grant, awarded by the ESPR in 2017. The funds from the grant supported the use of a 3D ultrasound machine which we used to acquire the images and results presented in this paper. A preliminary version of this work was presented as an oral presentation at the ESPR annual conference in Helsinki, June 2019. The manuscript has not been published, and is not being considered for publication elsewhere. The authors have no conflicts of interest to disclose.

Yours sincerely,

Dr. Susan Shelmerdine
Paediatric Radiology Research Fellow
On behalf of all authors

Title:

3-~~dimensional (3-D)D~~ versus 2-~~dimensional (2-D)D~~ post-mortem ultrasound: Feasibility ~~and additional value~~ in perinatal death investigation

Short Title:

3-~~dimensional~~D versus 2-~~dimensional~~D perinatal post-mortem ultrasound

Authors:

Susan C Shelmerdine, 1, 2, 3

Neil J Sebire 2, 3, 4

Owen J Arthurs 1, 2, 3

Affiliations:

1 Department of Clinical Radiology, Great Ormond Street Hospital for Children, London, UK

2 UCL Great Ormond Street Institute of Child Health, Great Ormond Street Hospital for Children, London, UK.

3 Great Ormond Street Hospital NIHR Biomedical Research Centre

4 Department of Histopathology, Great Ormond Street Hospital for Children, London, UK

Corresponding Author:

Dr. Susan Shelmerdine

Paediatric Radiology Research Fellow

Department of Clinical Radiology, Great Ormond Street Hospital for Children, London, UK

Email: susan.shelmerdine@gosh.nhs.uk

Telephone: +44 (0) 207405 9200

Type of manuscript: Technical Innovation

Formatted: No underline, Font color: Auto, French (France)

Field Code Changed

Formatted: French (France)

Formatted: French (France)

Abstract

3-D/4-D ultrasound techniques in antenatal screening are commonplace, but not routinely used for perinatal post-mortem ultrasound. In this technical innovation, we performed both 2-D and 3-D post-mortem ultrasound on 11 fetuses (mean gestation: 23 weeks; range: 15 – 32 weeks) to determine if there was any benefit in 3-D methods over conventional 2-D ultrasound. In 1 case of osteogenesis imperfecta, both 2-D and 3-D ultrasound were non-diagnostic due to small foetal size. Of the remaining 10 fetuses, 7 were normal at imaging and autopsy; and 3 had abnormalities detected on both 2-D and 3-D ultrasound. There were no false positive diagnoses by 2-D or 3-D ultrasound. Whilst 3-D post-mortem ultrasound was a feasible technique, it did not provide additional information over 2-D ultrasound. Routine 3-D post-mortem ultrasound cannot therefore be routinely recommended based on our findings.

3D/4D ultrasound techniques in antenatal screening are commonplace, but not routinely used for perinatal post-mortem ultrasound. In this technical innovation, we performed both 2D and 3D post-mortem ultrasound on 11 fetuses (mean: 23 weeks gestation; range: 15 – 32 weeks) to determine if there was any additional value in 3D methods over conventional 2D ultrasound. In 4/11 (36.4%) cases abnormalities were identified at autopsy, of which 3/4 (75%) were identified on both 2D and 3D ultrasound. In one case, both 2D and 3D methods were non-diagnostic. There were no false positive diagnoses by 2D or 3D ultrasound. Whilst 3D post-mortem ultrasound is a feasible technique, it did not provide additional information over 2D ultrasound. Further evaluation in a larger study group is needed.

Keywords:

Ultrasound, autopsy, perinatal, post-mortem, pathology

Declarations:**Funding information:**

This work was supported by the European Society of Paediatric Radiology (ESPR) 2017 Guy Sebag Research Grant. SCS is supported by a RCUK/ UKRI Innovation Fellowship and Medical Research Council (MRC) Clinical Research Training Fellowship (Grant Ref: MR/R002118/1). This award is jointly funded by the Royal College of Radiologists (RCR). OJA is funded by a National Institute for Health Research (NIHR) Career Development Fellowship (NIHR-CDF-2017-10-037).

This article presents independent research funded by the MRC, RCR, NIHR and the views expressed are those of the author(s) and not necessarily those of the NHS, MRC, RCR, the NIHR or the Department of Health & Social Care.

Conflicts of interest:

None of the authors have conflicts to declare

Ethics approval:

Ethical approval was granted for this single centre, prospective cohort study (IRAS ID:13195; REC reference: 13/LO/1494). All parents signed written consent allowing for post-mortem imaging to be conducted as part of the autopsy.

Consent to participate and publication:

All patients included in this article have a signed parental consent form for use of imaging for research/ audit/ educational purposes.

Availability of data and material:

All relevant clinical information is already provided within the manuscript. Additional information is available from the corresponding author upon reasonable request.

Code availability:

Not applicable

Authors' contributions:

SCS performed the data collection, analysis and primary write up of the manuscript. NJS and OJA conceived the idea of the research project. All authors have had an input in reviewing and editing the final draft of this manuscript

Title:

3-dimensional (3-D) versus 2-dimensional (2-D) post-mortem ultrasound: Feasibility in perinatal death investigation

Short Title:

3-dimensional versus 2-dimensional perinatal post-mortem ultrasound

Authors:

Susan C Shelmerdine, 1, 2, 3

Neil J Sebire 2, 3, 4

Owen J Arthurs 1, 2, 3

Affiliations:

1 Department of Clinical Radiology, Great Ormond Street Hospital for Children, London, UK

2 UCL Great Ormond Street Institute of Child Health, Great Ormond Street Hospital for Children, London, UK.

3 Great Ormond Street Hospital NIHR Biomedical Research Centre

4 Department of Histopathology, Great Ormond Street Hospital for Children, London, UK

Corresponding Author:

Dr. Susan Shelmerdine

Paediatric Radiology Research Fellow

Department of Clinical Radiology, Great Ormond Street Hospital for Children, London, UK

Email: susan.shelmerdine@gosh.nhs.uk

Telephone: +44 (0) 207405 9200

Type of manuscript: Technical Innovation

Abstract

3-D/4-D ultrasound techniques in antenatal screening are commonplace, but not routinely used for perinatal post-mortem ultrasound. In this technical innovation, we performed both 2-D and 3-D post-mortem ultrasound on 11 fetuses (mean gestation: 23 weeks; range: 15 – 32 weeks) to determine if there was any benefit in 3-D methods over conventional 2-D ultrasound. In 1 case of osteogenesis imperfecta, both 2-D and 3-D ultrasound were non-diagnostic due to small foetal size. Of the remaining 10 fetuses, 7 were normal at imaging and autopsy; and 3 had abnormalities detected on both 2-D and 3-D ultrasound. There were no false positive diagnoses by 2-D or 3-D ultrasound. Whilst 3-D post-mortem ultrasound was a feasible technique, it did not provide additional information over 2-D ultrasound. Routine 3-D post-mortem ultrasound cannot therefore be routinely recommended based on our findings.

Keywords:

Ultrasound, autopsy, perinatal, post-mortem, pathology

Declarations:**Funding information:**

This work was supported by the European Society of Paediatric Radiology (ESPR) 2017 Guy Sebag Research Grant. SCS is supported by a RCUK/ UKRI Innovation Fellowship and Medical Research Council (MRC) Clinical Research Training Fellowship (Grant Ref: MR/R002118/1). This award is jointly funded by the Royal College of Radiologists (RCR). OJA is funded by a National Institute for Health Research (NIHR) Career Development Fellowship (NIHR-CDF-2017-10-037).

This article presents independent research funded by the MRC, RCR, NIHR and the views expressed are those of the author(s) and not necessarily those of the NHS, MRC, RCR, the NIHR or the Department of Health & Social Care.

Conflicts of interest:

None of the authors have conflicts to declare

Ethics approval:

Ethical approval was granted for this single centre, prospective cohort study (IRAS ID:13195; REC reference: 13/LO/1494). All parents signed written consent allowing for post-mortem imaging to be conducted as part of the autopsy.

Consent to participate and publication:

All patients included in this article have a signed parental consent form for use of imaging for research/ audit/ educational purposes.

Availability of data and material:

All relevant clinical information is already provided within the manuscript. Additional information is available from the corresponding author upon reasonable request.

Code availability:

Not applicable

Authors' contributions:

SCS performed the data collection, analysis and primary write up of the manuscript. NJS and OJA conceived the idea of the research project. All authors have had an input in reviewing and editing the final draft of this manuscript

3-dimensional (3-D) versus 2-dimensional (2-D) post-mortem ultrasound:

Feasibility in perinatal death investigation

3D versus 2D post-mortem ultrasound: Feasibility and additional value in perinatal death investigation.

Formatted: Font: 14 pt, Bold

Formatted: Centered

Formatted: Font: 14 pt

Abstract

3-D/4-D ultrasound techniques in antenatal screening are commonplace, but not routinely used for perinatal post-mortem ultrasound. In this technical innovation, we performed both 2-D and 3-D post-mortem ultrasound on 11 fetuses (mean gestation: 23 weeks; range: 15 – 32 weeks) to determine if there was any benefit in 3-D methods over conventional 2-D ultrasound. In 1 case of osteogenesis imperfecta, both 2-D and 3-D ultrasound were non-diagnostic due to small foetal size. Of the remaining 10 fetuses, 7 were normal at imaging and autopsy; and 3 had abnormalities detected on both 2-D and 3-D ultrasound. There were no false positive diagnoses by 2-D or 3-D ultrasound. Whilst 3-D post-mortem ultrasound was a feasible technique, it did not provide additional information over 2-D ultrasound. Routine 3-D post-mortem ultrasound cannot therefore be routinely recommended based on our findings.

~~3D/4D ultrasound techniques in antenatal screening are commonplace, but not routinely used for perinatal post-mortem ultrasound. In this technical innovation, we performed both 2D and 3D post-mortem ultrasound on 11 fetuses (mean: 23 weeks gestation; range: 15–32 weeks) to determine if there was any additional value in 3D methods over conventional 2D ultrasound. In 4/11 (36.4%) cases abnormalities were identified at autopsy, of which 3/4 (75%) were identified on both 2D and 3D ultrasound. In one case, both 2D and 3D methods were non-diagnostic. There were no false positive diagnoses by 2D or 3D ultrasound. Whilst 3D post-mortem ultrasound is a feasible technique, it did not provide additional information over 2D ultrasound. Further evaluation in a larger study group is needed.~~

Keywords:

Ultrasound, autopsy, perinatal, post-mortem, pathology

Introduction

Post-mortem ultrasound is a feasible imaging tool in the investigation of perinatal and fetal deaths [1] with sensitivity and specificity rates for whole body diagnoses as 73.3% (95% CI: 59.9% to 83.5%) and 96.6% (95% CI: 92.6% to 98.4%) respectively [2]. Articles describing the usage of perinatal post-mortem ultrasound [3] have typically performed 2-dimensional (2-D) acquisitions (i.e. a series of multiple single planes through the fetal body), with only one study [4] describing additional acquisitions of 3-dimensional (3-D) imaging volumes, primarily for educational rather than diagnostic purposes. Acquiring 3-D volume imaging datasets could allow the operator to reconstruct a variety of standard and oblique anatomical planes using specialised computer software, and may provide additional benefits over the conventional 2-D method. For instance, it has been shown that complex congenital cardiac anomalies are poorly detected at post-mortem ultrasound [2], due to a variety of factors one of which includes difficulty acquiring standard sectional planes particularly if there is foetal maceration, which could be mitigated by availability of 3-D imaging. The same is true for the accurate assessment of midline congenital neurological abnormalities, which can be difficult to assess in the standard sagittal plane used for live neonates given loss of tissue elasticity and 'slumping' in the post-mortem state [1].

In this report we aimed to test the feasibility of performing perinatal 3-dimensional (3-D) post-mortem ultrasound at a range of different gestations, and assess whether this technique can provide additional information over our conventional 2-dimensional (2-D) PMUS imaging.

Description of Innovation

Ethical approval was granted for this single centre, prospective cohort study (IRAS ID:13195; REC reference: 13/LO/1494). Eleven consecutive, unselected fetuses/foetuses were prospectively included over a 6-month study period (1 July 2018 – 1 December 2018). No inclusion or exclusion criteria were applied. Of these 6/11 (54.5%) were male. The mean gestation age was 23 weeks (range 15-32 weeks) and mean body weight was 469g (47-1375g). Six fetuses/foetuses (54.5%) were stillborn, 5/11 (45.4%) were terminations of pregnancy (1 for foetal hydrops, 2 for oligohydramnios, 1 for suspected absent corpus callosum, 1 for bladder outlet obstruction). There was an average time between fetal/foetal delivery and ultrasound examination of 5 days (range 1 – 18 days), and average time between ultrasound examination and autopsy or post-mortem MRI was 13 days (1 – 36 days).

The 2-D ultrasound examinations were first performed, followed by 3-D ultrasound imaging by the same operator - a paediatric radiology research fellow (4 years post-mortem imaging; 6 years paediatric radiology experience), according to published guidelines [1, 5]. All ultrasound examinations were performed on machines used only for post-mortem imaging, based in the hospital mortuary. The imaging was performed with the foetus submerged in a cold water bath (approximately 5°C) to ensure maximal sonographic wave transmission from probe to body surface [1].

The 2-D imaging was performed on a UGEO HM70A (Samsung Medison, Gangwon, Republic of Korea) scanner, equipped with a high frequency linear transducer, model L7-16 (bandwidth, 7-16MHz). The 3-D PMUS imaging was performed on a Voluson E8 (GE Medical Systems, Zipf, Austria) scanner, equipped with a 3D/4D wide band convex volume transducer, model RAB4-8-D (bandwidth, 2-8 MHz; field of view 70°: V, 70° × 85°; Wide). 3-D volume acquisitions were taken of the head, thorax and abdomen for all cases/foetuses.

The total scanning and image interpretation time per fetus/foetus was approximately 20 minutes for 2-D ultrasound, and with an additional 30 minutes for 3-D ultrasound. Whilst acquisition of images for 3-D ultrasound were more rapid (taking only approximately 5 minutes), additional time was required to review the different imaging planes and to create diagnostic post-processed images for PACS storage. The findings from the 2-D and 3-D examinations were inserted into a predefined report template, in Microsoft Excel (Microsoft, Seattle, USA) for five anatomical regions: brain, spine, cardiac, thorax and abdomen, as outlined previously [1][6]. For each field, the radiologist allocated either a 'normal' or 'abnormal' label, with further description of the abnormality and organ involved within the body area if abnormal [1][6].

Where parents provided consent for autopsy, these findings were used as the reference standard against the ultrasound findings. All invasive ('full') autopsies were performed according to Royal College of Pathologists autopsy guidelines [6, 7], minimally invasive autopsy methods were performed using laparoscopic guided internal examination techniques [8], and all non-invasive autopsies received a whole body post-mortem MRI examination co-reported by two paediatric radiologists (with 10 and 4 years of paediatric post-mortem imaging experience each). The MRI techniques have also been previously published [9].

Post-mortem Ultrasound Findings

In one foetus, a 15 week gestation foetus with osteogenesis imperfecta (OI), weighing only 47g, both the 2-D and 3-D ultrasound were non-diagnostic due to small foetal size.

For the remaining 10 foetuses, 7 had/11 cases (63.6%) there were no abnormalities identified at autopsy or at 2-D or 3-D ultrasound (i.e. no false positive ~~cases~~). An example of normal foetal anatomy at 2-D and 3-D ultrasound is shown in Figure 1. In 3/4/11 (36.4%) cases/foetuses, abnormalities were identified at autopsy including foetal hydrops, bladder outlet obstruction and/ partial agenesis of the corpus callosum ~~and osteogenesis imperfecta (OI).~~

Both 2-D and 3-D ultrasound imaging were able to identify all three 3/4 (75%) of these diagnoses. The 3-D technique did not demonstrate additional findings that were not seen at 2-D ultrasound for any cases (Figures 2+ – 43). In one case of a 15 week gestation fetus with OI, osteogenesis, weighing only 47g, both 2D and 3D ultrasound were non diagnostic due to small patient size.

Discussion

3-D post-mortem ultrasound imaging is a feasible technique but did not provide additional information over the conventional 2-D imaging in this small cohort. Based on these preliminary findings, there is insufficient evidence to recommend routine usage of 3-D ultrasound volume acquisitions in addition to 2-D ultrasound imaging, particularly given the additional scanning time, cost of equipment and software.

Larger cohort studies from antenatal (i.e. intra-uterine) fetal imaging have reported some benefits of 3-D ultrasound imaging over 2-D techniques, although the size of improvement is variable. Merz et al [10] reviewed over 3000 second and third trimester pregnancies and found that 3-D ultrasound identified 42/1012 (4.2%) congenital malformations which were not seen on 2-D ultrasound. Xu et al [11] corroborate these findings, and found that 3-D ultrasound identified 9/61 (14.8%) additional diagnoses not seen on 2-D imaging alone. Possible reasons why 3-D ultrasound may have offered a benefit for obstetric over post-mortem fetal imaging may be because the additional information seen in-utero is already possible by external examination and plain radiography at perinatal autopsy, without the need for ultrasound. Pathologies such as skeletal dysplasias, cleft palates, neural tube defects, dysmorphic features (e.g. unusual facial appearances, isolated limb anomalies,

polydactyly) can all be assessed by inspecting the ~~fetus~~foetus after delivery, compared to during pregnancy when imaging with 3-D surface rendering and multiplanar reconstructions are more helpful.

Despite this, larger studies ~~covering a greater variety of~~foetuses with ~~of~~ congenital anomalies could identify whether there are specific clinical situations where 3-D ultrasound could be helpful. These may include ~~eases~~ situations where the fetal head has been distorted by extraction. In such cases, post-mortem intracranial imaging is typically difficult due to sutural laxity causing overlapping skull bones, deformed cranial features and a reduced ability to obtain a satisfactory sonographic window via the fontanelles [1]. A 3-D volume, possibly using a micro-convex volume transducer, could help provide multiplanar views of the brain. This has been shown to be useful in utero, particularly for midline structures such as the corpus callosum [12] which can sometimes be difficult to identify at 2-D ultrasound. It may also prove beneficial in the identification and characterisation of complex congenital cardiac diseases, a particularly challenging diagnosis for post-mortem ultrasound. Previous studies assessing the benefit of 3-D versus 2-D fetal echocardiography have found that the addition of 3-D volumes was helpful in assessing the anatomical relationship of the main outflow tracts and their diameters [13], as well as informing the cardiac anatomy for parental counselling in foetuses with double outlet right ventricle [14]. Unfortunately it was not possible to assess this benefit in our cohort, given the lack of any cases with cardiac anomalies.

As with all studies, ours had several limitations - the main one relates to our small sample size, with only a few ~~foetuses~~foetuses with structural abnormalities. A larger sample size ~~with greater variety of~~ different congenital pathologies would have allowed us to better assess whether certain clinical scenarios or anomalies are better suited for additional 3-D ultrasound review. Secondly, we acknowledge the highly operator dependent nature of sonography. Our ultrasound examinations were performed by an experienced paediatric radiologist at a tertiary centre, who already regularly performs 2-D ultrasound in a variety of live and post-mortem paediatric settings. It may be that this experience with 2-D imaging reduced the potential of finding ~~an added value~~ any benefit for of 3-D methods which may not be the case for ~~other~~ less experienced operators.

Finally our 2-D and 3-D imaging were performed on different ultrasound machines with transducers of differing bandwidths. This could have conferred an advantage for the 2-D ultrasound technique given the higher frequency of the linear probe which is better suited to smaller ~~patient~~ foetal sizes. This was determined by the

availability of ultrasound equipment and transducers at the time of the study. Future work using a single ultrasound scanner with both 2-D and 3-D capabilities would be better suited in accurately assessing the true ~~added value~~benefit of the 3-D method.

In conclusion, this study has found that 3-D ultrasound imaging did not provide useful additional information over performing 2-D ultrasound alone. ~~Future sLarger studies~~studies covering with a wider variety of perinatal pathologies ~~could help us~~are warranted to better understand whether there may be a role for 3-D post-mortem ultrasound for specific abnormalities ~~or clinical scenarios~~.

Figure Captions

Fig 1, Normal abdominal appearances in a 24 week gestational aged female foetus. (a) 2-D PMUS imaging of the abdomen, at the level of the adrenal glands in transverse view and (b) sagittal 2-D panoramic imaging of the thorax and abdomen. (c) 3-D PMUS of the abdomen was acquired in the sagittal view (top left corner) with axial (top right), coronal reconstructions (bottom left) and volume rendered image of the anterior abdominal wall (bottom right). With a 3-D volumetric acquisition of the abdomen, it is possible to reconstruct axial views through the adrenal glands (white arrows) and also identify the thoracolumbar vertebral appearances (dashed arrows).

Formatted: Font: Bold, Not Highlight

Formatted: Not Highlight

Fig 24 Foetal hydrops in a 22 week gestational aged female foetus. (a, b) 2-D PMUS imaging of the thorax and (c) abdomen in transverse views show bilateral large pleural effusions and ascites. (db) 3-D PMUS of the thorax and (ee) abdomen, acquired in transverse views (top left corner) with sagittal (top right), coronal (bottom left) and volume rendered reconstructions (bottom right) demonstrate the same abnormalities.

Fig 32 Bladder outlet obstruction secondary to scaphoid megalourethra in a 20 week gestational aged male foetus. (a) 2-D PMUS imaging of the upper abdomen, taken with foetus in a water bath, demonstrates a large left suprarenal septated cyst (asterisk), while (b) transverse and (c) sagittal views of the pelvis demonstrate a distended urinary bladder (white arrow), and dilated penile urethra (dashed arrow). (db) The 3-D PMUS of the abdomen, acquired in sagittal view (top left corner) with axial (top right), coronal (bottom left) and volume rendered (bottom right) views show the same key findings.

Fig 43 Partial agenesis of the corpus callosum in a 20 week gestational aged male fetus. (a) 2-D PMUS imaging of the brain in coronal, (b) trans-temporal and (c) sagittal views shows some callosal tissue anteriorly (white arrow), although it was difficult to visualise posteriorly. (db) 3-D PMUS imaging acquired in the coronal and (ee) sagittal planes with resultant multiplanar reconstructions showed similar appearances as the 2-D PMUS.

References

1. Shelmerdine SC, Sebire NJ, Arthurs OJ (2019) Perinatal post mortem ultrasound (PMUS): a practical approach. Insights into imaging [Mar 18;10\(1\):35](#). doi:10.1186/s13244-019-0723-9
2. Shelmerdine S, Langan D, Sebire NJ, Arthurs O (2019) Diagnostic accuracy of perinatal post-mortem ultrasound (PMUS): a systematic review. *BMJ Paediatrics Open* 3(1):e000566. doi: 10.1136/bmjpo-2019-000566
3. Prodhomme O, Baud C, Saguintaah M, Béchard-Sevette N, Bolivar J, David S, Taleb-Arrada I, Couture A (2015) Comparison of postmortem ultrasound and X-Ray with autopsy in fetal death: Retrospective study of 169 cases. *Journal of Forensic Radiology and Imaging* 3:120-130. doi:10.1016/j.jofri.2015.04.002
4. Votino C, Cos Sanchez T, Bessieres B, Segers V, Kadhim H, Razavi F, Condorelli M, Votino R, D'Ambrosio V, Jani J (2018) Minimally invasive fetal autopsy using ultrasound: a feasibility study. *Ultrasound in Obstetrics and Gynecology* 52(6):776-783. doi: 10.1002/uog.14642
5. Shelmerdine SC, Sebire NJ, Arthurs OJ (2019) Perinatal post-mortem ultrasound (PMUS): radiological-pathological correlation. *Insights into imaging* 10(1):81. doi:10.1186/s13244-019-0762-2
6. ~~The Royal College of Pathologists RCo~~ (2017) Guidelines on autopsy practice: Fetal autopsy (2nd trimester fetal loss and termination of pregnancy for congenital anomaly). In: ~~Osborn M, Lowe J (eds). The Royal College of Pathologists, The Royal College of Pathologists. Available at: <https://www.rcpath.org/uploads/assets/b20ea503-7799-433c-99160653762f896c/Fetal-autopsy-2nd-trimester-fetal-loss-and-termination-of-pregnancy-for-congenital-anomaly.pdf>; Accessed on 1 March 2020~~
7. ~~The Royal College of Pathologists TRCo~~ (2017) Guidelines on autopsy practice: Third trimester antepartum and intrapartum stillbirth. Available at: <https://www.rcpath.org/uploads/assets/0e55a233-5fe6-4965-b85f4fa7c9971742/Guidelines-on-autopsy-practice-Third-trimester-antepartum-and-intrapartum-stillbirth.pdf>; Accessed on 1 March 2020 In: ~~Osborn M, Lowe J (eds), The Royal College of Pathologists.~~
8. Hutchinson JC, Shelmerdine SC, Lewis C, Parmenter J, Simcock IC, Ward L, Ashworth MT, Chitty LS, Arthurs OJ, Sebire NJ (2019) Minimally invasive perinatal and pediatric autopsy with laparoscopically assisted tissue sampling: feasibility and experience of the MinImAL procedure. *Ultrasound Obstet Gynecol* 54:661-669. doi:10.1002/uog.20211

Formatted: Line spacing: 1.5 lines

Formatted: Line spacing: 1.5 lines

Formatted: Line spacing: 1.5 lines

Formatted: Line spacing: 1.5 lines

Formatted: Line spacing: 1.5 lines

Formatted: Line spacing: 1.5 lines

Formatted: Line spacing: 1.5 lines

Formatted: Line spacing: 1.5 lines

9. Norman W, Jawad N, Jones R, Taylor AM, Arthurs OJ (2016) Perinatal and paediatric post-mortem magnetic resonance imaging (PMMR): sequences and technique. *Br J Radiol* 89 (1062):20151028. [doi:10.1259/bjr.20151028](https://doi.org/10.1259/bjr.20151028)
10. Merz E, Welter C (2005) 2D and 3D Ultrasound in the evaluation of normal and abnormal fetal anatomy in the second and third trimesters in a level III center. *Ultraschall Med. Feb; 26(1):9-16.* [doi:10.1055/s-2004-813947](https://doi.org/10.1055/s-2004-813947); *in der Medizin (Stuttgart, Germany : 1980) 26:9-16.*
11. Xu HX, Zhang QP, Lu MD, Xiao XT (2002) Comparison of two-dimensional and three-dimensional sonography in evaluating fetal malformations. *J Clin Ultrasound. 30(9):515-25.* [doi:10.1002/jcu.1019](https://doi.org/10.1002/jcu.1019) *Journal of clinical ultrasound : JCU 30:515-525.*
12. Li Y, Tao GW, Pan MZ, Shao GR (2018) Comparison of traditional 2D and 3D Omniview technique in detection of fetus corpus callosum. *Medical ultrasonography 20 (4):493-497.* [doi: 10.11152/mu-1555](https://doi.org/10.11152/mu-1555)
13. Huang C, Zhao B, Lv S, Mao Y, Guo Q, Pan M, Wang B, Peng X, Chen R (2019) Smart-planes fetal heart (S-planes FH) software to quantitative evaluate the fetal great arteries. *J Matern Fetal Neonatal Med:1-9.* [doi:10.1080/14767058.2019.1651279](https://doi.org/10.1080/14767058.2019.1651279)
14. Karmegaraj B, Kumar S, Srimurugan B, Sudhakar A, Simpson JM, Vaidyanathan B (2020) 3D/4D spatiotemporal image correlation (STIC) fetal echocardiography provides incremental benefit in predicting the postnatal surgical approach in double outlet right ventricle. *Ultrasound Obstet Gynecol. Feb 5.* [doi: 10.1002/uog.21988](https://doi.org/10.1002/uog.21988) [Epub ahead of print]

Formatted: Line spacing: 1.5 lines

Formatted: German (Germany)

Formatted: German (Germany)

Formatted: Line spacing: 1.5 lines

Formatted: Line spacing: 1.5 lines

Formatted: Line spacing: 1.5 lines

Formatted: Line spacing: 1.5 lines

3-dimensional (3-D) versus 2-dimensional (2-D) post-mortem ultrasound: Feasibility in perinatal death investigation

Abstract

3-D/4-D ultrasound techniques in antenatal screening are commonplace, but not routinely used for perinatal post-mortem ultrasound. In this technical innovation, we performed both 2-D and 3-D post-mortem ultrasound on 11 fetuses (mean gestation: 23 weeks; range: 15 – 32 weeks) to determine if there was any benefit in 3-D methods over conventional 2-D ultrasound. In 1 case of osteogenesis imperfecta, both 2-D and 3-D ultrasound were non-diagnostic due to small foetal size. Of the remaining 10 fetuses, 7 were normal at imaging and autopsy; and 3 had abnormalities detected on both 2-D and 3-D ultrasound. There were no false positive diagnoses by 2-D or 3-D ultrasound. Whilst 3-D post-mortem ultrasound was a feasible technique, it did not provide additional information over 2-D ultrasound. Routine 3-D post-mortem ultrasound cannot therefore be routinely recommended based on our findings.

Keywords:

Ultrasound, autopsy, perinatal, post-mortem, pathology

Introduction

Post-mortem ultrasound is a feasible imaging tool in the investigation of perinatal and fetal deaths [1] with sensitivity and specificity rates for whole body diagnoses as 73.3% (95% CI: 59.9% to 83.5%) and 96.6% (95% CI: 92.6% to 98.4%) respectively [2]. Articles describing the usage of perinatal post-mortem ultrasound [3] have typically performed 2-dimensional (2-D) acquisitions (i.e. a series of multiple single planes through the fetal body), with only one study [4] describing additional acquisitions of 3-dimensional (3-D) imaging volumes, primarily for educational rather than diagnostic purposes. Acquiring 3-D volume imaging datasets could allow the operator to reconstruct a variety of standard and oblique anatomical planes using specialised computer software, and may provide additional benefits over the conventional 2-D method. For instance, it has been shown that complex congenital cardiac anomalies are poorly detected at post-mortem ultrasound [2], due to a variety of factors one of which includes difficulty acquiring standard sectional planes particularly if there is foetal maceration, which could be mitigated by availability of 3-D imaging. The same is true for the accurate assessment of midline congenital neurological abnormalities, which can be difficult to assess in the standard sagittal plane used for live neonates given loss of tissue elasticity and ‘slumping’ in the post-mortem state [1].

In this report we aimed to test the feasibility of performing perinatal 3-dimensional (3-D) post-mortem ultrasound at a range of different gestations, and assess whether this technique can provide additional information over our conventional 2-dimensional (2-D) PMUS imaging.

Description of Innovation

Ethical approval was granted for this single centre, prospective cohort study (IRAS ID:13195; REC reference: 13/LO/1494). Eleven consecutive, unselected fetuses were prospectively included over a 6-month study period (1 July 2018 – 1 December 2018). No inclusion or exclusion criteria were applied. Of these 6/11 (54.5%) were male. The mean gestation age was 23 weeks (range 15-32 weeks) and mean body weight was 469g (47-1375g). Six fetuses (54.5%) were stillborn, 5/11 (45.4%) were terminations of pregnancy (1 for foetal hydrops, 2 for oligohydramnios, 1 for suspected absent corpus callosum, 1 for bladder outlet obstruction). There was an average time between foetal delivery and ultrasound examination of 5 days (range 1 – 18 days), and average time between ultrasound examination and autopsy or post-mortem MRI was 13 days (1 – 36 days).

The 2-D ultrasound examinations were first performed, followed by 3-D ultrasound imaging by the same operator - a paediatric radiology research fellow (4 years post-mortem imaging; 6 years paediatric radiology experience), according to published guidelines [1, 5]. All ultrasound examinations were performed on machines used only for post-mortem imaging, based in the hospital mortuary. The imaging was performed with the foetus submerged in a cold water bath (approximately 5°C) to ensure maximal sonographic wave transmission from probe to body surface [1].

The 2-D imaging was performed on a UGEO HM70A (Samsung Medison, Gangwon, Republic of Korea) scanner, equipped with a high frequency linear transducer, model L7-16 (bandwidth, 7-16MHz). The 3-D PMUS imaging was performed on a Voluson E8 (GE Medical Systems, Zipf, Austria) scanner, equipped with a 3D/4D wide band convex volume transducer, model RAB4-8-D (bandwidth, 2-8 MHz; field of view 70°: V, 70° × 85°; Wide). 3-D volume acquisitions were taken of the head, thorax and abdomen for all foetuses.

The total scanning and image interpretation time per foetus was approximately 20 minutes for 2-D ultrasound, and 30 minutes for 3-D ultrasound. Whilst acquisition of images for 3-D ultrasound were more rapid (taking only approximately 5 minutes), additional time was required to review the different imaging planes and to create diagnostic post-processed images for PACS storage. The findings from the 2-D and 3-D examinations were inserted into a predefined report template, for five anatomical regions: brain, spine, cardiac, thorax and abdomen, as outlined previously[1]. For each field, the radiologist allocated either a 'normal' or 'abnormal' label, with further description of the abnormality and organ involved within the body area if abnormal[1].

Where parents provided consent for autopsy, these findings were used as the reference standard against the ultrasound findings. All invasive ('full') autopsies were performed according to Royal College of Pathologists autopsy guidelines[6, 7], minimally invasive autopsy methods were performed using laparoscopic guided internal examination techniques [8], and all non-invasive autopsies received a whole body post-mortem MRI examination co-reported by two paediatric radiologists (with 10 and 4 years of paediatric post-mortem imaging experience each). The MRI techniques have also been previously published [9].

Post-mortem Ultrasound Findings

In one foetus, a 15 week gestation foetus with osteogenesis imperfecta (OI), weighing only 47g, both the 2-D and 3-D ultrasound were non-diagnostic due to small foetal size.

For the remaining 10 foetuses, 7 had no abnormalities identified at autopsy or at 2-D or 3-D ultrasound (i.e. no false positives). An example of normal foetal anatomy at 2-D and 3-D ultrasound is shown in Figure 1. In 3 foetuses, abnormalities were identified at autopsy including foetal hydrops, bladder outlet obstruction and partial agenesis of the corpus callosum. Both 2-D and 3-D ultrasound imaging were able to identify all three of these diagnoses. The 3-D technique did not demonstrate additional findings that were not seen at 2-D ultrasound for any cases (Figures 2 – 4).

Discussion

3-D post-mortem ultrasound imaging is a feasible technique but did not provide additional information over the conventional 2-D imaging in this small cohort. Based on these preliminary findings, there is insufficient evidence to recommend routine usage of 3-D ultrasound volume acquisitions in addition to 2-D ultrasound imaging, particularly given the additional scanning time, cost of equipment and software.

Larger cohort studies from antenatal (i.e. intra-uterine) fetal imaging have reported some benefits of 3-D ultrasound imaging over 2-D techniques, although the size of improvement is variable. Merz et al [10] reviewed over 3000 second and third trimester pregnancies and found that 3-D ultrasound identified 42/1012 (4.2%) congenital malformations which were not seen on 2-D ultrasound. Xu et al [11] corroborate these findings, and found that 3-D ultrasound identified 9/61 (14.8%) additional diagnoses not seen on 2-D imaging alone. Possible reasons why 3-D ultrasound may have offered a benefit for obstetric over post-mortem fetal imaging may be because the additional information seen in-utero is already possible by external examination and plain radiography at perinatal autopsy, without the need for ultrasound. Pathologies such as skeletal dysplasias, cleft palates, neural tube defects, dysmorphic features (e.g. unusual facial appearances, isolated limb anomalies, polydactyly) can all be assessed by inspecting the foetus after delivery, compared to during pregnancy when imaging with 3-D surface rendering and multiplanar reconstructions are more helpful.

Despite this, larger studies of foetuses with congenital anomalies could identify whether there are specific clinical situations where 3-D ultrasound could be helpful. These may include situations where the fetal head has

been distorted by extraction. In such cases, post-mortem intracranial imaging is typically difficult due to sutural laxity causing overlapping skull bones, deformed cranial features and a reduced ability to obtain a satisfactory sonographic window via the fontanelles [1]. A 3-D volume, possibly using a micro-convex volume transducer, could help provide multiplanar views of the brain. This has been shown to be useful in utero, particularly for midline structures such as the corpus callosum [12] which can sometimes be difficult to identify at 2-D ultrasound. It may also prove beneficial in the identification and characterisation of complex congenital cardiac diseases, a particularly challenging diagnosis for post-mortem ultrasound. Previous studies assessing the benefit of 3-D versus 2-D fetal echocardiography have found that the addition of 3-D volumes was helpful in assessing the anatomical relationship of the main outflow tracts and their diameters [13], as well as informing the cardiac anatomy for parental counselling in foetuses with double outlet right ventricle [14]. Unfortunately it was not possible to assess this benefit in our cohort, given the lack of any cases with cardiac anomalies.

As with all studies, ours had several limitations - the main one relates to our small sample size, with only a few foetuses with structural abnormalities. A larger sample size of different congenital pathologies would have allowed us to better assess whether certain clinical scenarios or anomalies are better suited for additional 3-D ultrasound review. Secondly, we acknowledge the highly operator dependent nature of sonography. Our ultrasound examinations were performed by an experienced paediatric radiologist at a tertiary centre, who already regularly performs 2-D ultrasound in a variety of live and post-mortem paediatric settings. It may be that this experience with 2-D imaging reduced the potential of finding any benefit for 3-D methods which may not be the case for less experienced operators.

Finally our 2-D and 3-D imaging were performed on different ultrasound machines with transducers of differing bandwidths. This could have conferred an advantage for the 2-D ultrasound technique given the higher frequency of the linear probe which is better suited to smaller foetal sizes. This was determined by the availability of ultrasound equipment and transducers at the time of the study. Future work using a single ultrasound scanner with both 2-D and 3-D capabilities would be better suited in accurately assessing the true benefit of the 3-D method.

In conclusion, this study has found that 3-D ultrasound imaging did not provide useful additional information over performing 2-D ultrasound alone. Future studies covering a wider variety of perinatal pathologies could

help us better understand whether there may be a role for 3-D post-mortem ultrasound for specific abnormalities.

Figure Captions

Fig 1 Normal abdominal appearances in a 24 week gestational aged female foetus. (a) 2-D PMUS imaging of the abdomen, at the level of the adrenal glands in transverse view and (b) sagittal 2-D panoramic imaging of the thorax and abdomen. (c) 3-D PMUS of the abdomen was acquired in the sagittal view (top left corner) with axial (top right), coronal reconstructions (bottom left) and volume rendered image of the anterior abdominal wall (bottom right). With a 3-D volumetric acquisition of the abdomen, it is possible to reconstruct axial views through the adrenal glands (white arrows) and also identify the thoracolumbar vertebral appearances (dashed arrows).

Fig 2 Foetal hydrops in a 22 week gestational aged female foetus. (a, b) 2-D PMUS imaging of the thorax and (c) abdomen in transverse views show bilateral large pleural effusions and ascites. (d) 3-D PMUS of the thorax and (e) abdomen, acquired in transverse views (top left corner) with sagittal (top right), coronal (bottom left) and volume rendered reconstructions (bottom right) demonstrate the same abnormalities.

Fig 3 Bladder outlet obstruction secondary to scaphoid megalourethra in a 20 week gestational aged male foetus. (a) 2-D PMUS imaging of the upper abdomen, taken with foetus in a water bath, demonstrates a large left suprarenal septated cyst (asterisk), while (b) transverse and (c) sagittal views of the pelvis demonstrate a distended urinary bladder (white arrow), and dilated penile urethra (dashed arrow). (d) The 3-D PMUS of the abdomen, acquired in sagittal view (top left corner) with axial (top right), coronal (bottom left) and volume rendered (bottom right) views show the same key findings.

Fig 4 Partial agenesis of the corpus callosum in a 20 week gestational aged male foetus. (a) 2-D PMUS imaging of the brain in coronal, (b) trans-temporal and (c) sagittal views shows some callosal tissue anteriorly (white arrow), although it was difficult to visualise posteriorly. (d) 3-D PMUS imaging acquired in the coronal and (e) sagittal planes with resultant multiplanar reconstructions showed similar appearances as the 2-D PMUS.

References

1. Shelmerdine SC, Sebire NJ, Arthurs OJ (2019) Perinatal post mortem ultrasound (PMUS): a practical approach. *Insights into imaging* Mar 18;10 (1):35. doi:10.1186/s13244-019-0723-9
2. Shelmerdine S, Langan D, Sebire NJ, Arthurs O (2019) Diagnostic accuracy of perinatal post-mortem ultrasound (PMUS): a systematic review. *BMJ Paediatr Open* 3(1):e000566. doi: 10.1136/bmjpo-2019-000566
3. Prodhomme O, Baud C, Saguintaah M, Béchard-Sevette N, Bolivar J, David S, Taleb-Arrada I, Couture A (2015) Comparison of postmortem ultrasound and X-Ray with autopsy in fetal death: Retrospective study of 169 cases. *Journal of Forensic Radiology and Imaging* 3:120-130. doi:10.1016/j.jofri.2015.04.002
4. Votino C, Cos Sanchez T, Bessieres B, Segers V, Kadhim H, Razavi F, Condorelli M, Votino R, D'Ambrosio V, Jani J (2018) Minimally invasive fetal autopsy using ultrasound: a feasibility study. *Ultrasound in Obstetrics and Gynecology* 52(6):776-783. doi: 10.1002/uog.14642
5. Shelmerdine SC, Sebire NJ, Arthurs OJ (2019) Perinatal post-mortem ultrasound (PMUS): radiological-pathological correlation. *Insights into imaging* 10(1):81. doi:10.1186/s13244-019-0762-2
6. The Royal College of Pathologists (2017) Guidelines on autopsy practice: Fetal autopsy (2nd trimester fetal loss and termination of pregnancy for congenital anomaly). Available at: <https://www.rcpath.org/uploads/assets/b20ea503-7799-433c-99160653762f896c/Fetal-autopsy-2nd-trimester-fetal-loss-and-termination-of-pregnancy-for-congenital-anomaly.pdf>; Accessed on 1 March 2020
7. The Royal College of Pathologists (2017) Guidelines on autopsy practice: Third trimester antepartum and intrapartum stillbirth. Available at: <https://www.rcpath.org/uploads/assets/0e55a233-5fe6-4965-b85f4fa7c9971742/Guidelines-on-autopsy-practice-Third-trimester-antepartum-and-intrapartum-stillbirth.pdf>; Accessed on 1 March 2020
8. Hutchinson JC, Shelmerdine SC, Lewis C, Parmenter J, Simcock IC, Ward L, Ashworth MT, Chitty LS, Arthurs OJ, Sebire NJ (2019) Minimally invasive perinatal and pediatric autopsy with laparoscopically assisted tissue sampling: feasibility and experience of the MinImAL procedure. *Ultrasound Obstet Gynecol* 54:661-669. doi:10.1002/uog.20211
9. Norman W, Jawad N, Jones R, Taylor AM, Arthurs OJ (2016) Perinatal and paediatric post-mortem magnetic resonance imaging (PMMR): sequences and technique. *Br J Radiol* 89 (1062):20151028. doi:10.1259/bjr.20151028

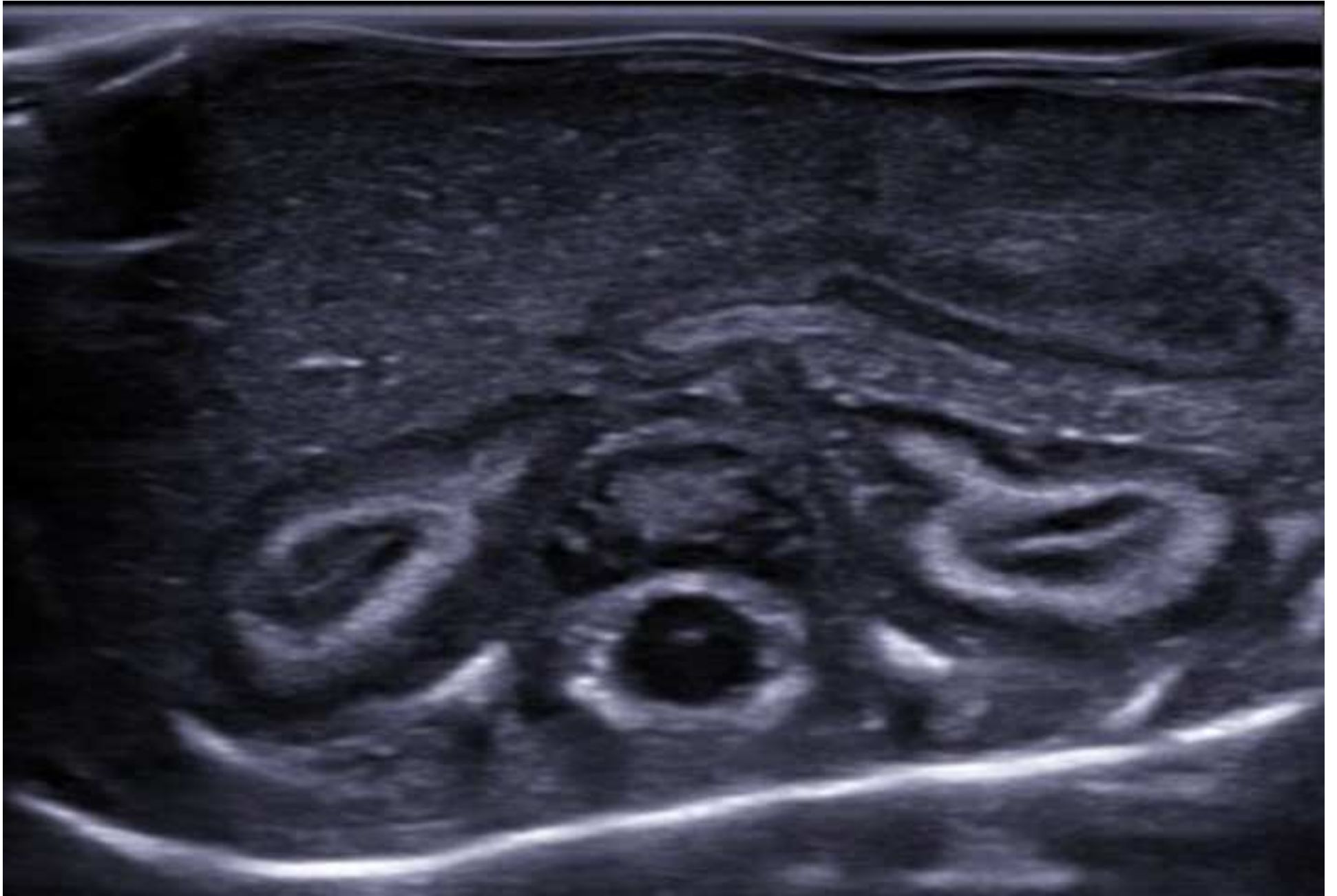
10. Merz E, Welter C (2005) 2D and 3D Ultrasound in the evaluation of normal and abnormal fetal anatomy in the second and third trimesters in a level III center. *Ultraschall Med.* Feb; 26(1):9-16. doi:10.1055/s-2004-813947
11. Xu HX, Zhang QP, Lu MD, Xiao XT (2002) Comparison of two-dimensional and three-dimensional sonography in evaluating fetal malformations. *J Clin Ultrasound.* 30(9):515-25. doi:10.1002/jcu.1019
12. Li Y, Tao GW, Pan MZ, Shao GR (2018) Comparison of traditional 2D and 3D Omniview technique in detection of fetus corpus callosum. *Medical ultrasonography* 20 (4):493-497. doi: 10.11152/mu-1555
13. Huang C, Zhao B, Lv S, Mao Y, Guo Q, Pan M, Wang B, Peng X, Chen R (2019) Smart-planes fetal heart (S-planes FH) software to quantitative evaluate the fetal great arteries. *J Matern Fetal Neonatal Med*:1-9. doi:10.1080/14767058.2019.1651279
14. Karmegaraj B, Kumar S, Srimurugan B, Sudhakar A, Simpson JM, Vaidyanathan B (2020) 3D/4D spatiotemporal image correlation (STIC) fetal echocardiography provides incremental benefit in predicting the postnatal surgical approach in double outlet right ventricle. *Ultrasound Obstet Gynecol.* Feb 5. doi: 10.1002/uog.21988 [Epub ahead of print]

Table 1:

Demographic and imaging findings for all cases included in this study. *M = male, F = female, IUD = intrauterine death, TOP = termination of pregnancy, MIA = minimally invasive autopsy (i.e. laparoscopic assisted internal autopsy examination)*

Foetus	Gestation (weeks)	Gender	Mode of Demise	Antenatal history	2-D Ultrasound	3-D Ultrasound	Autopsy Type	Autopsy Results (foetal findings)	Autopsy Results (placental findings)
1	24	M	IUD	Dichorionic, diamniotic twin pregnancy.	Unremarkable	Unremarkable	MRI / External examination	No major congenital malformations	Acute funisitis and chorioamnionitis
2	24	F	IUD	Dichorionic, diamniotic twin pregnancy.	Unremarkable	Unremarkable	MRI / External examination	No major congenital malformations	Acute funisitis and chorioamnionitis
3	24	M	TOP	Oligohydramnios (secondary to spontaneous rupture of membranes)	Unremarkable	Unremarkable	MIA	No major congenital malformations	Normal
4	20	F	TOP	Oligohydramnios (low grade vaginal bleeding throughout pregnancy)	Unremarkable	Unremarkable	MRI / External examination	No major congenital malformations	Mild chorioamnionitis with large placental haematoma
5	20	M	TOP	Prenatal ultrasound at 20 weeks showed total absence of corpus callosum, small interhemispheric cysts.	Partial absence of the corpus callosum	As per 2-D Ultrasound findings	MIA + Micro-CT imaging	Partial absence of the corpus callosum with small interhemispheric cyst	Normal
6	20	M	TOP	Prenatal ultrasound at 18 weeks showed oligohydramnios, talipes, thickened nuchal fold. Bladder was enlarged and there was a large ventricular septal defect.	Hypoplastic left ventricle, large right atrium. Septal defects difficult to visualise. Left suprarenal cyst. Distended urethra and bladder, bilateral dilated kidneys.	As per 2-D Ultrasound findings	Full	Megalourethra with obstructive uropathy. Microscopic renal cystic dysplasia. Left adrenal gland is necrotic. Associated talipes and positional hand deformities on external assessment.	Normal placenta, single umbilical artery.

					Thickened soft tissue folds along left side of neck.				
7	22	F	IUD	Spontaneous rupture of membranes at 18 weeks gestation. Anomaly ultrasound at 20 weeks showed fetal hydrops, ascites, skin oedema.	Hydropic foetus (large pleural effusions, pericardial effusion, ascites, hypoplastic lungs)	As per 2-D Ultrasound findings	Full	Hydropic foetus, hypoplastic lungs (secondary to hydrops), normal heart. Cause for hydrops not determined.	Stromal villous haemorrhage
8	32	M	IUD	Unremarkable pregnancy. IUD confirmed on prenatal ultrasound, labour induced at 32 weeks gestation.	Unremarkable	Unremarkable	Full	No major congenital malformations	Normal
9	22	M	IUD	Recurrent maternal urinary tract infections during pregnancy. Spontaneous labour with rupture of membranes. Foetus delivered without heartbeat.	Unremarkable	Unremarkable	Full	No major congenital malformations	Acute subchorionitis
10	25	F	IUD	Unremarkable pregnancy.	Unremarkable	Unremarkable	Full	No major congenital malformations	Normal
11	15	F	TOP	Hydropic foetus. Shortened long bones. Suspected skeletal dysplasia.	Non-diagnostic	Non-diagnostic	MIA	Macerated foetus. Post-mortem skeletal survey demonstrated features typical of osteogenesis imperfecta (OI)	Normal



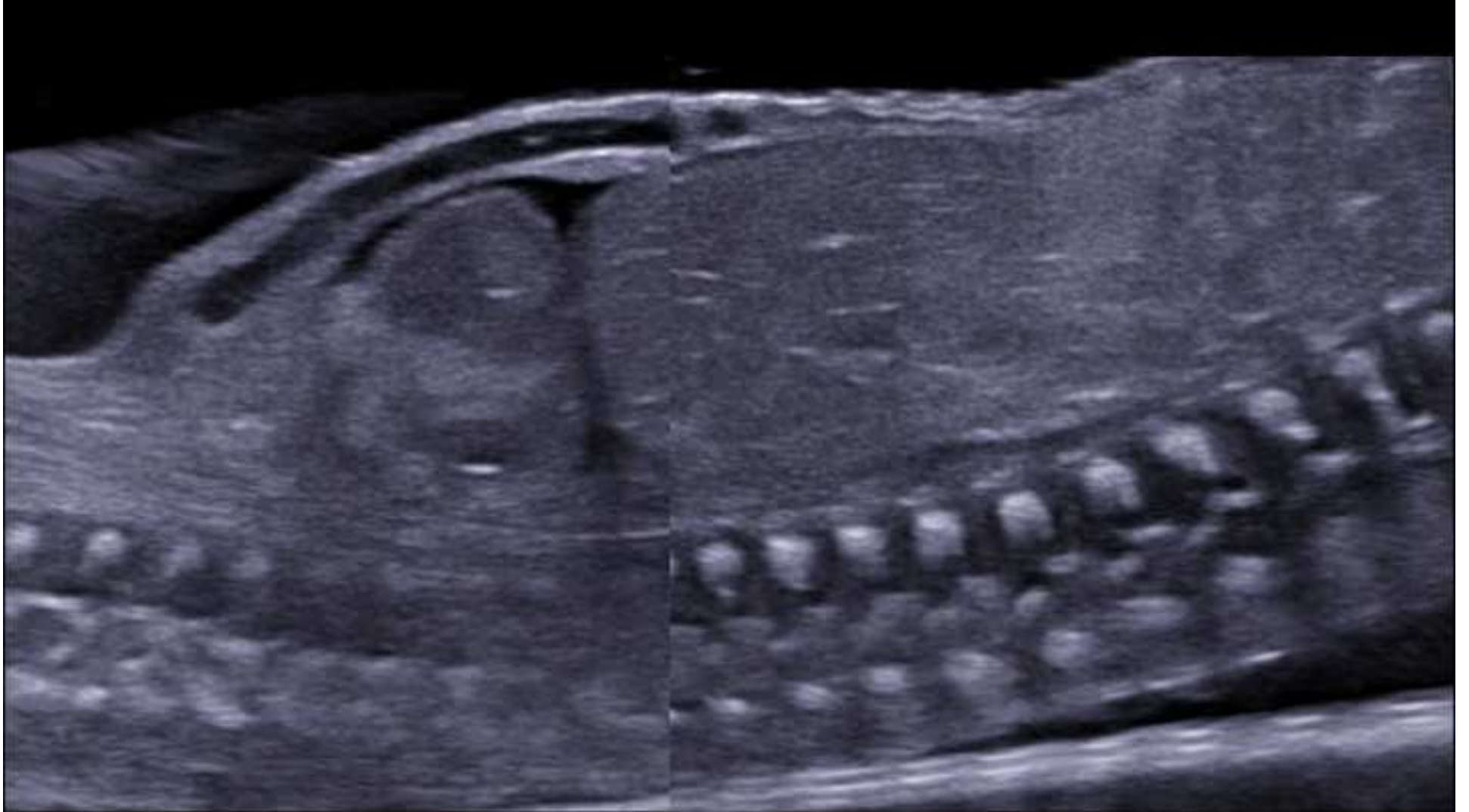
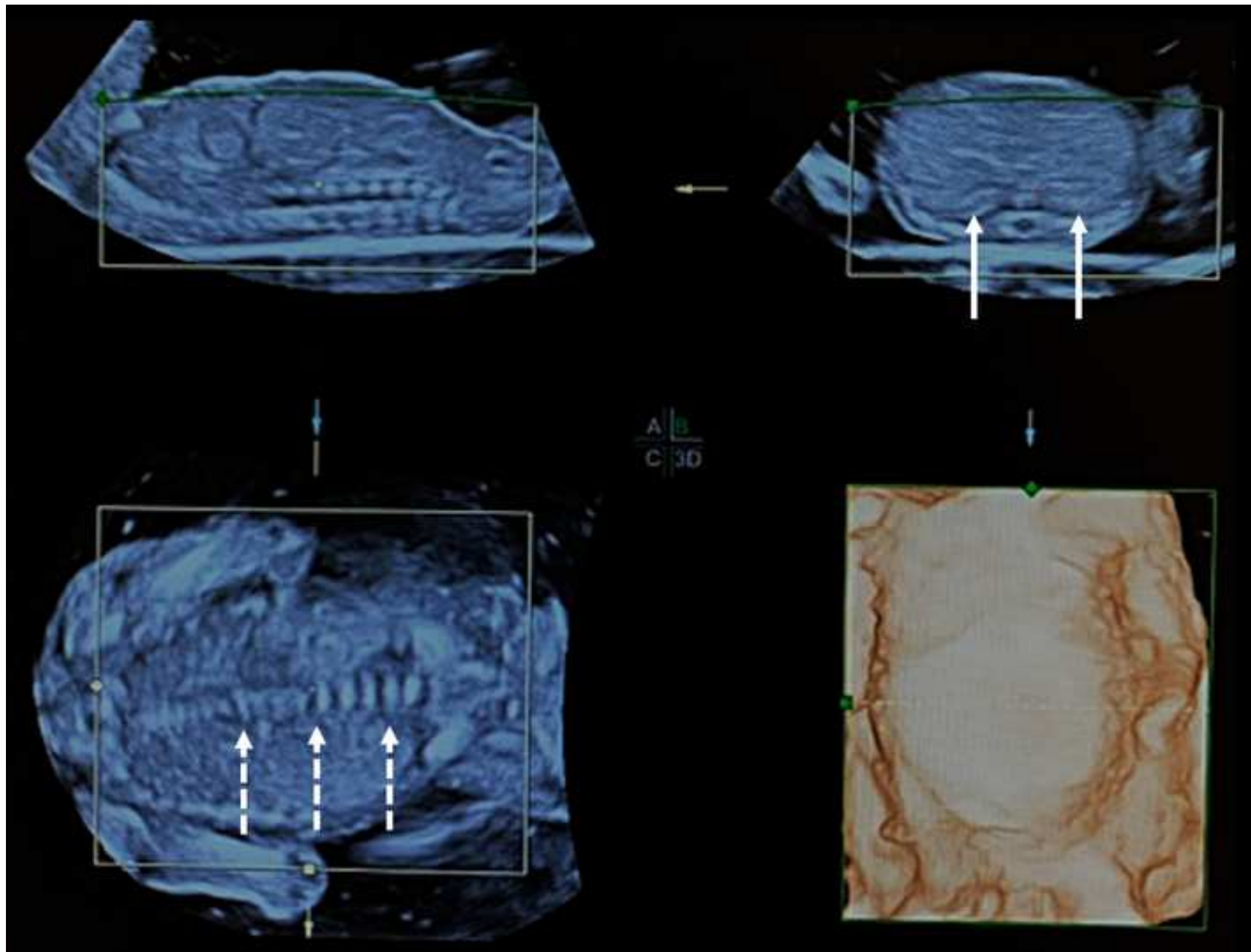
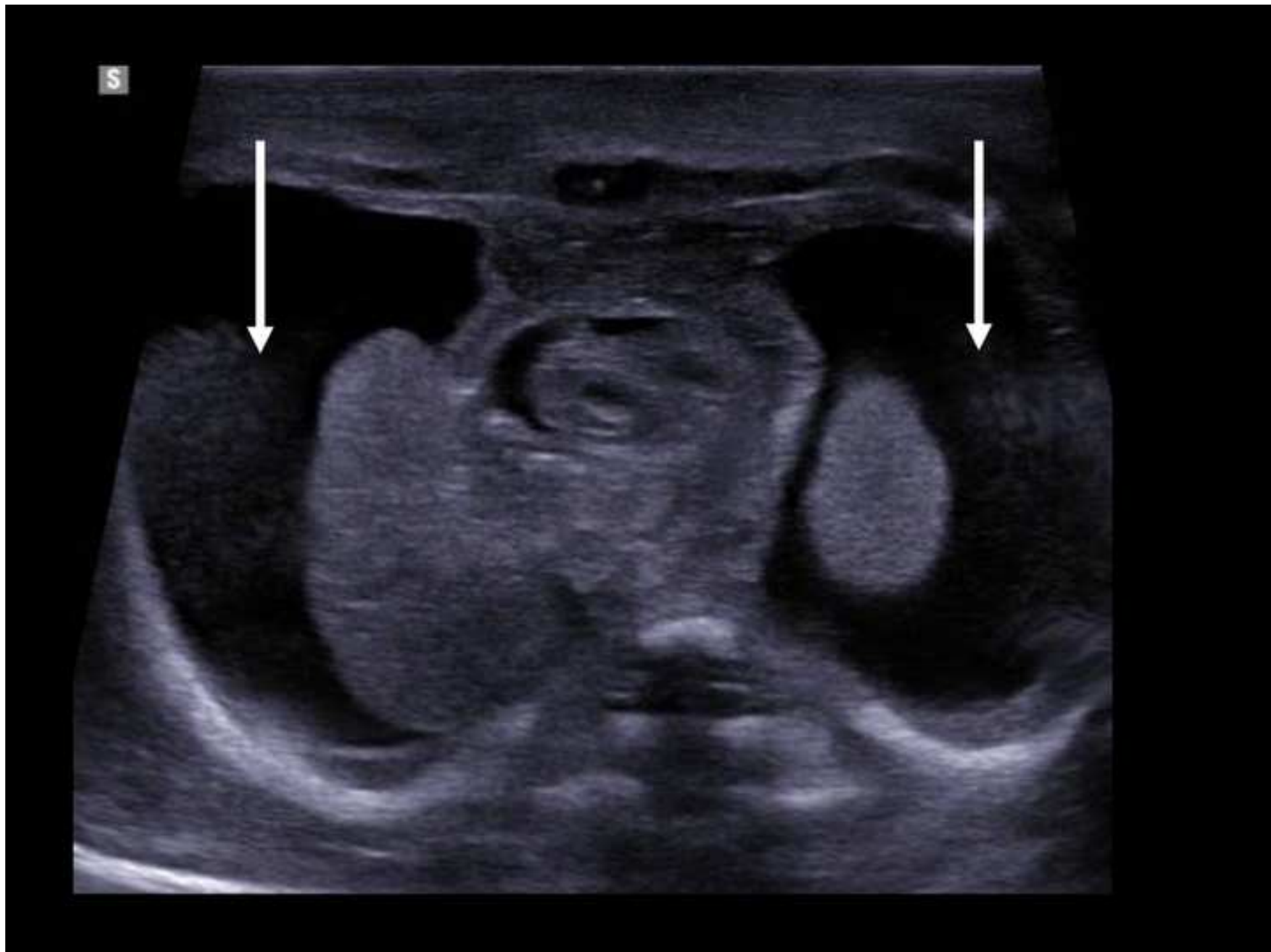
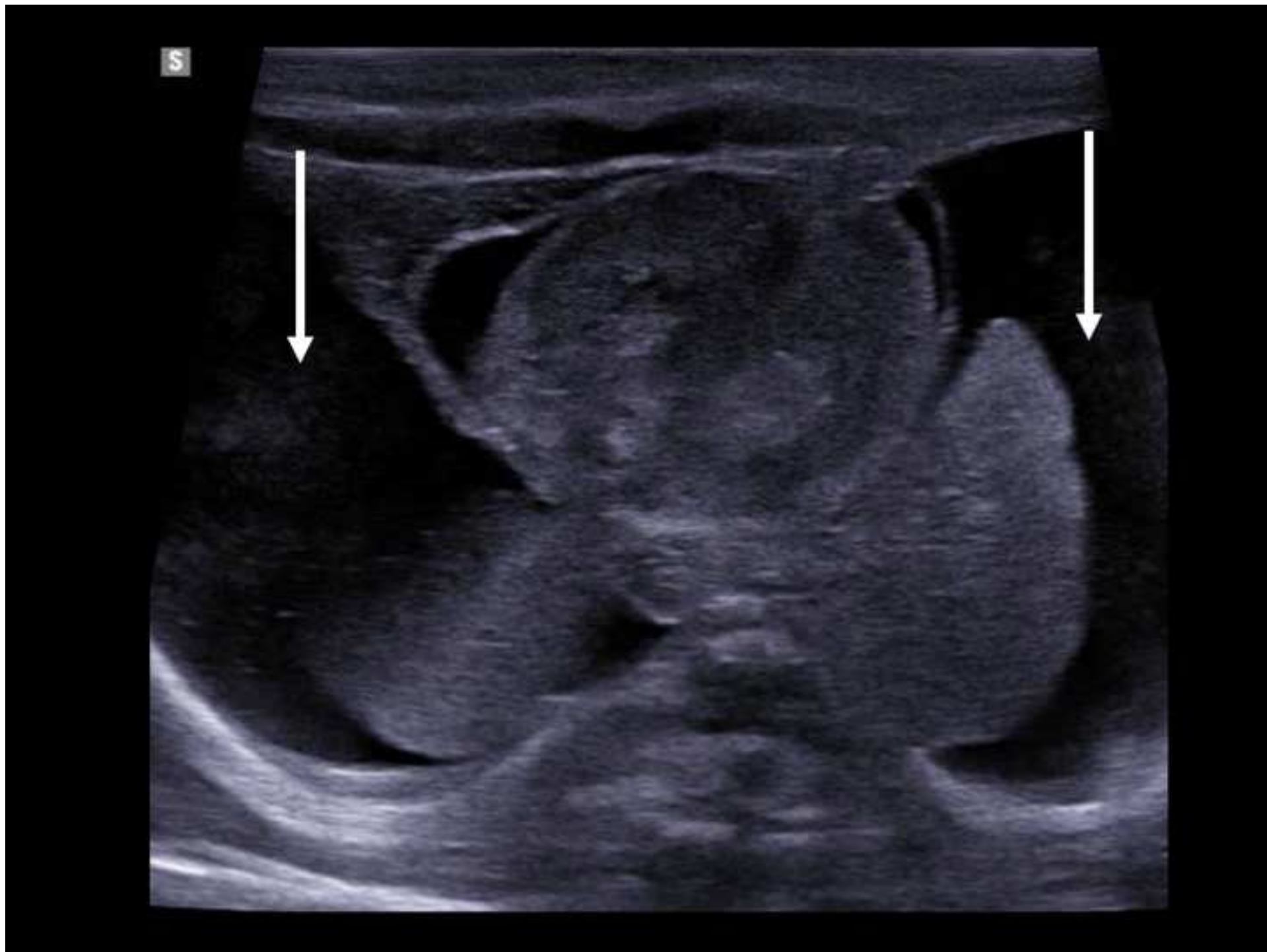


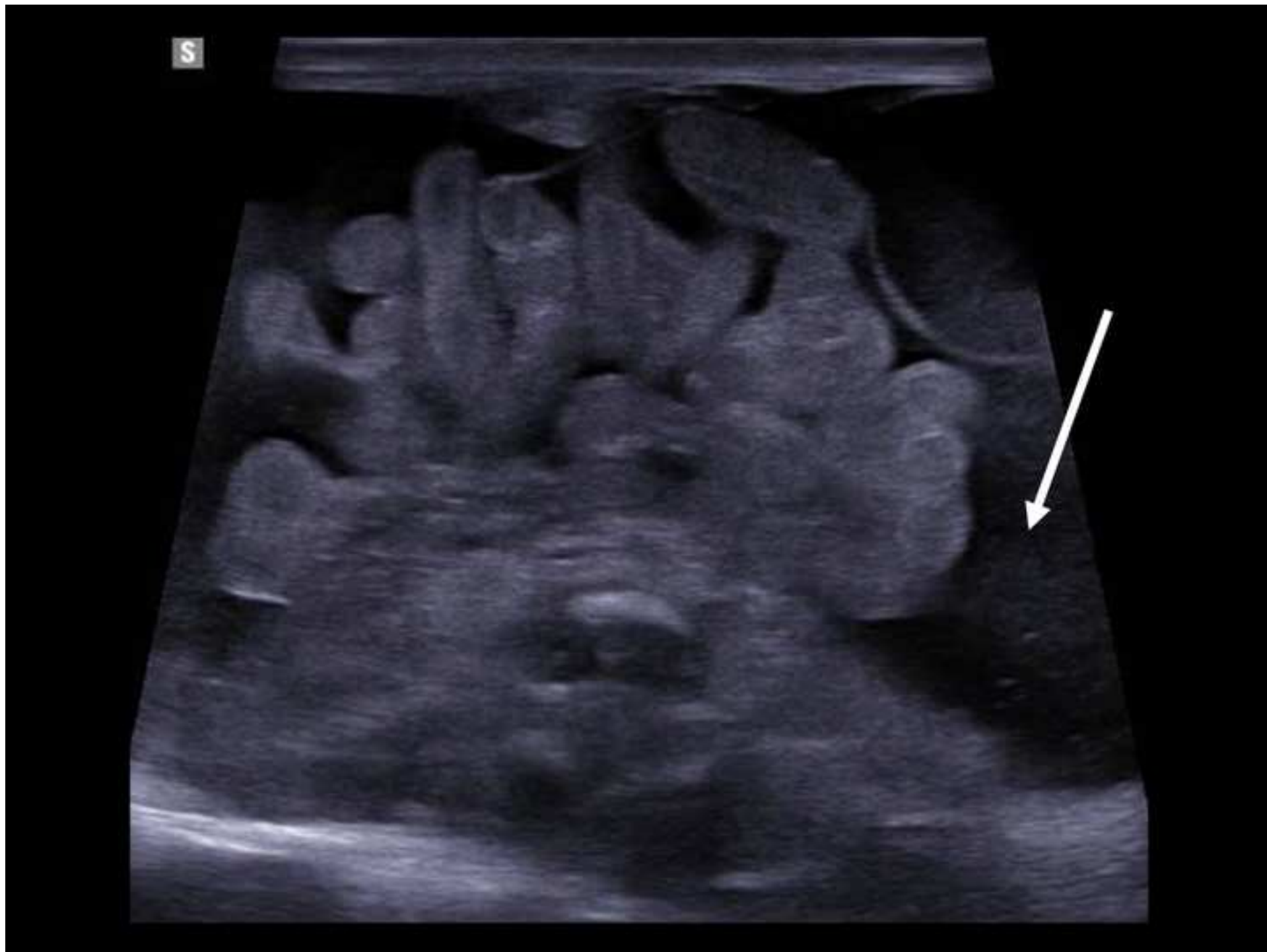
Figure 1c

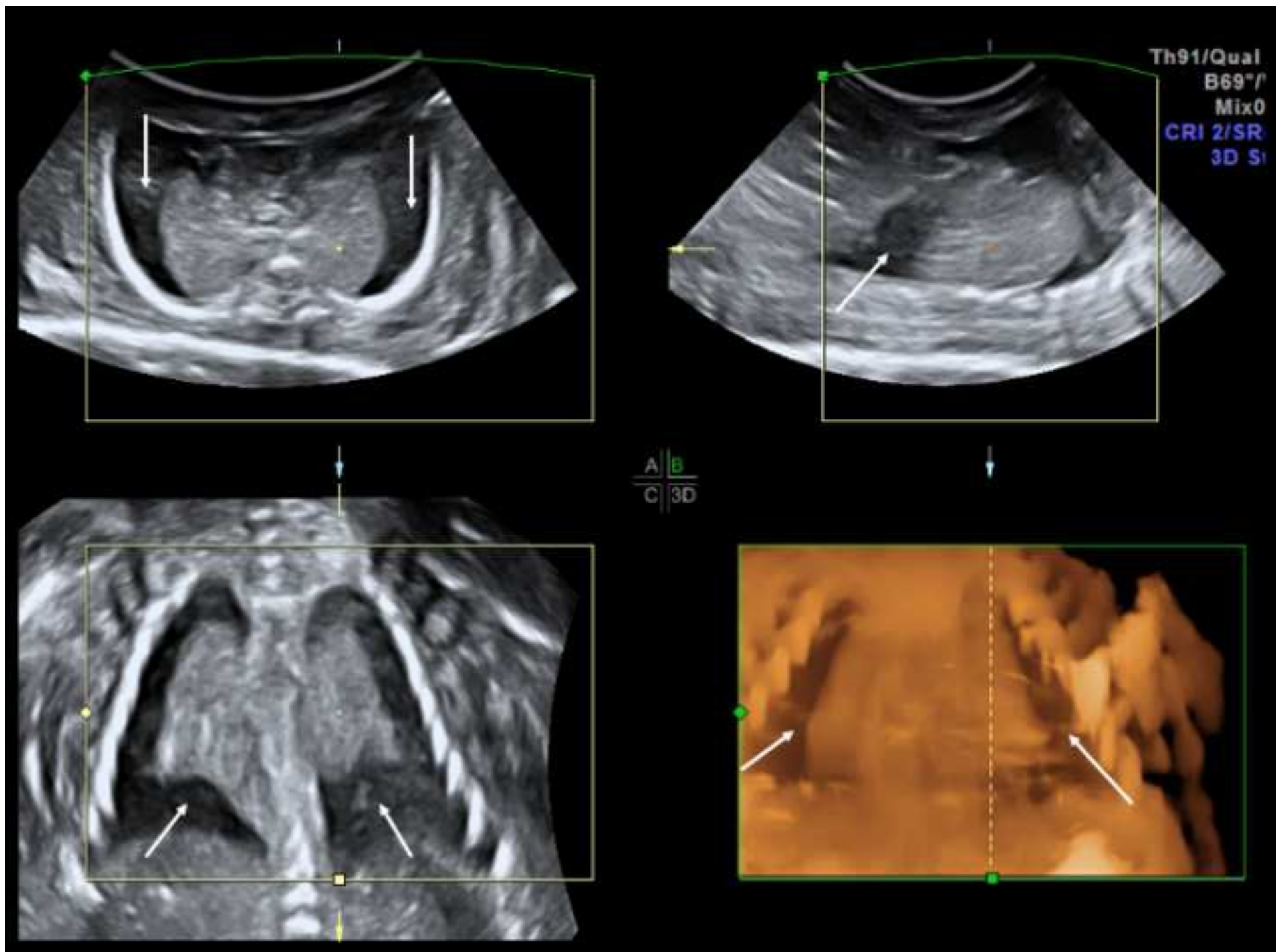
[Click here to access/download;Figure;Figure 1c.tiff](#)











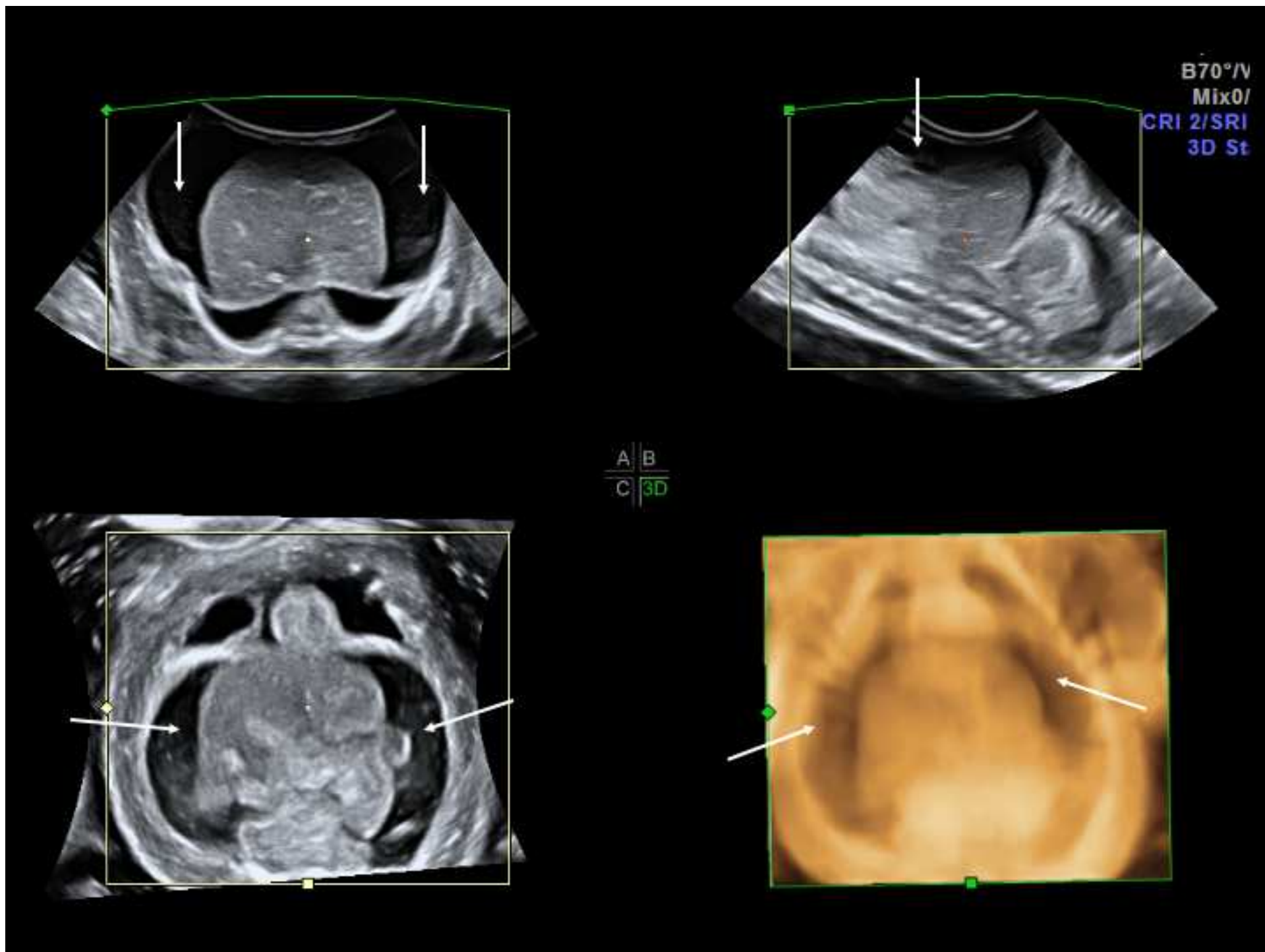
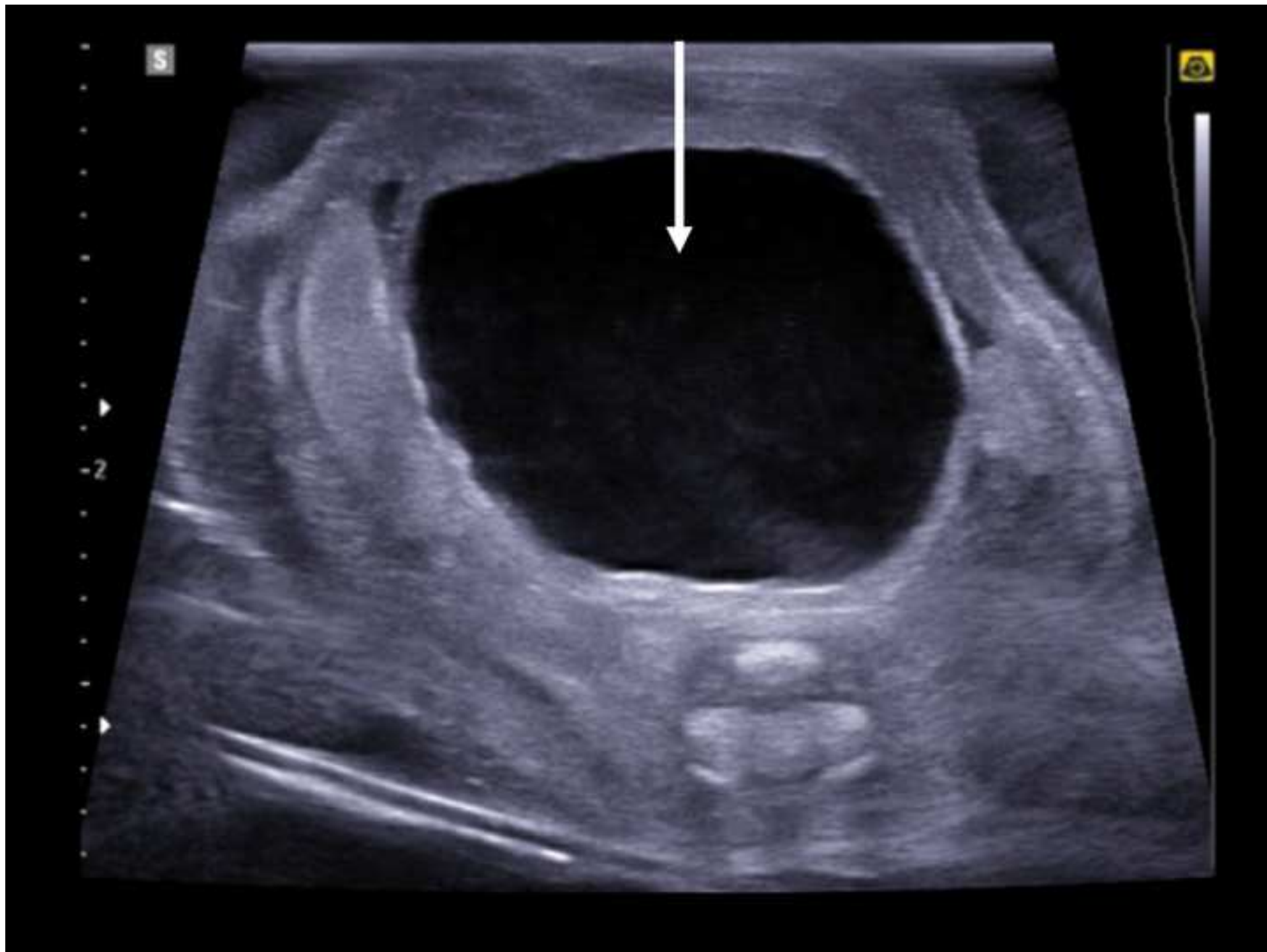




Figure 3b





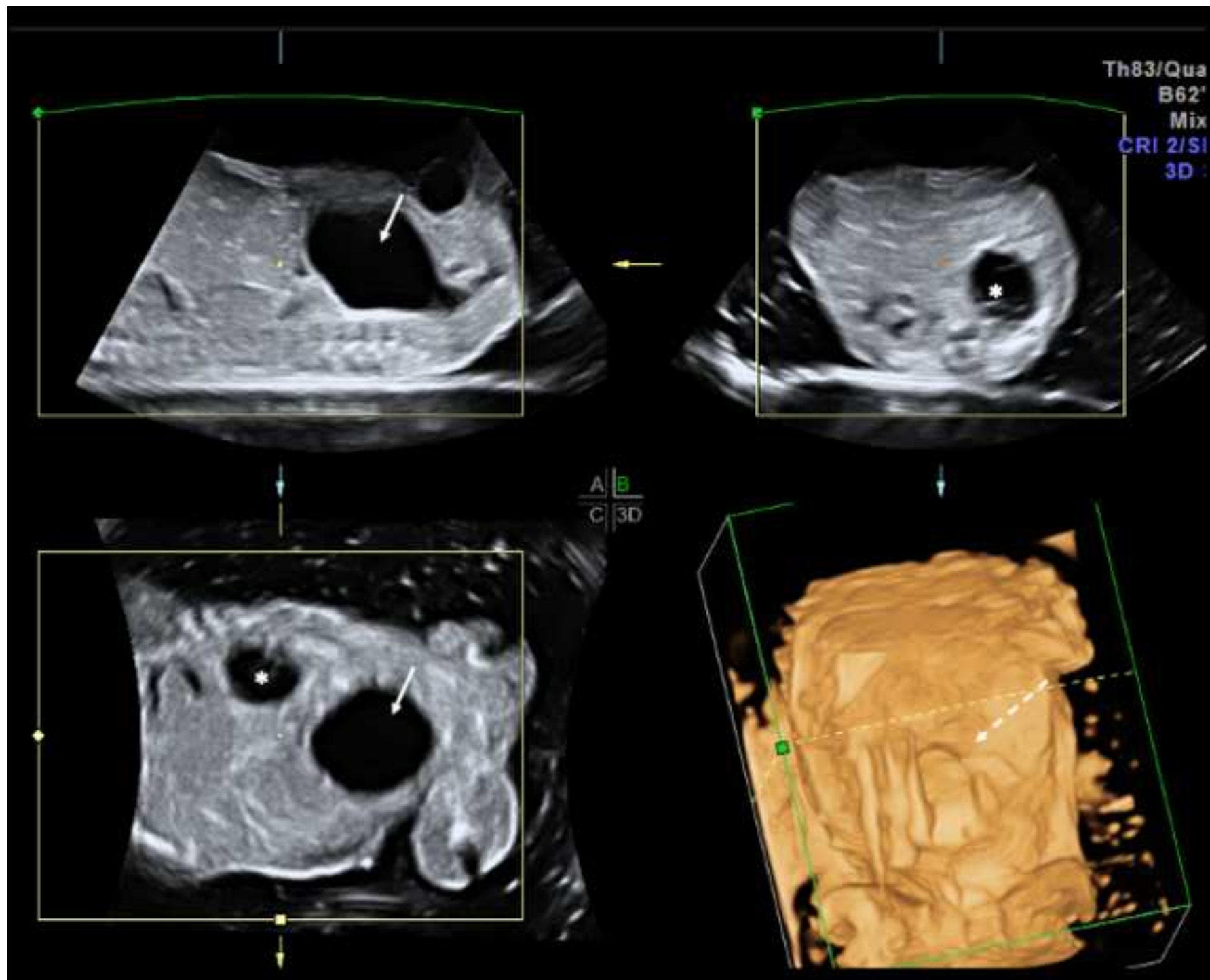
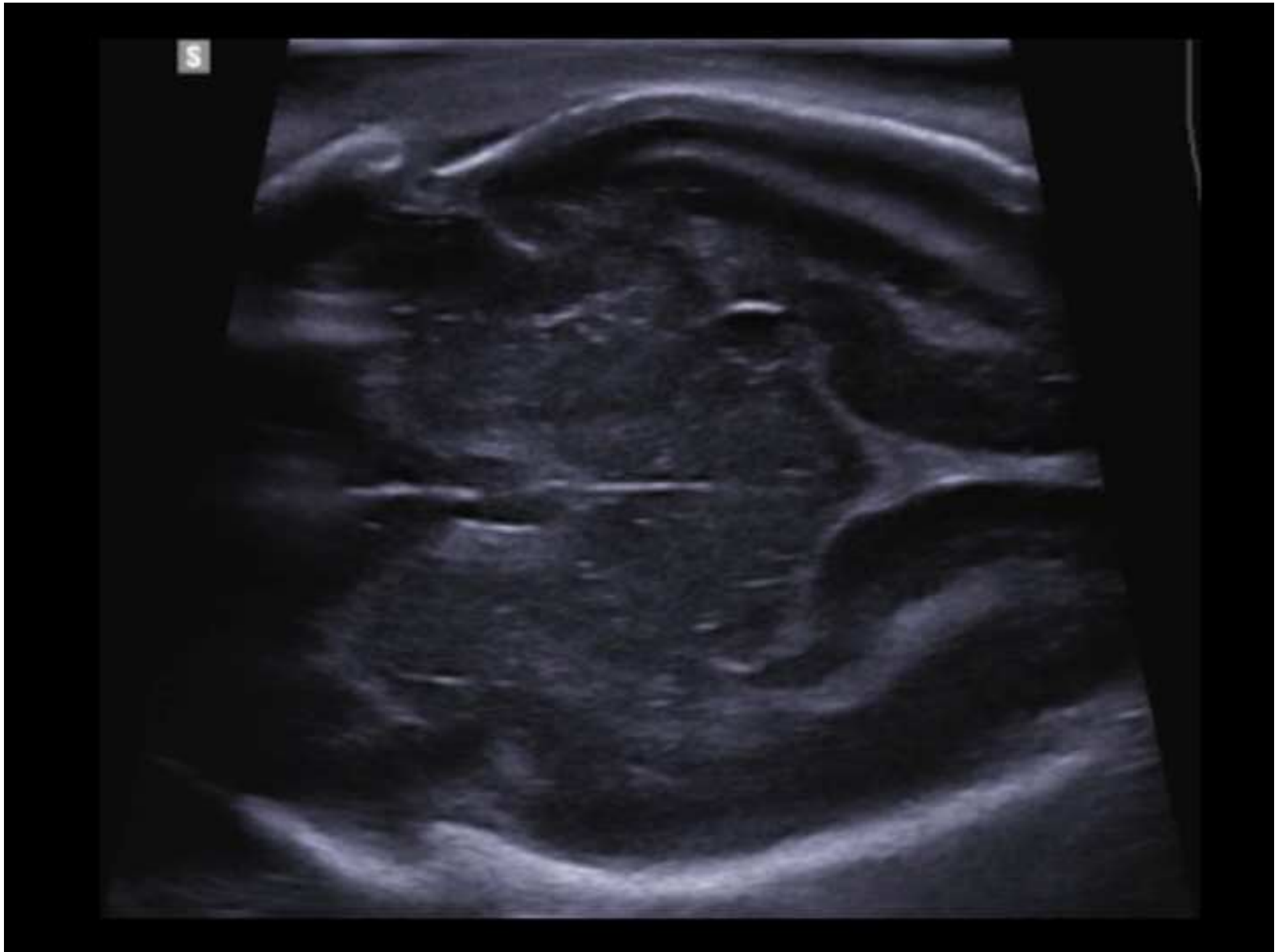


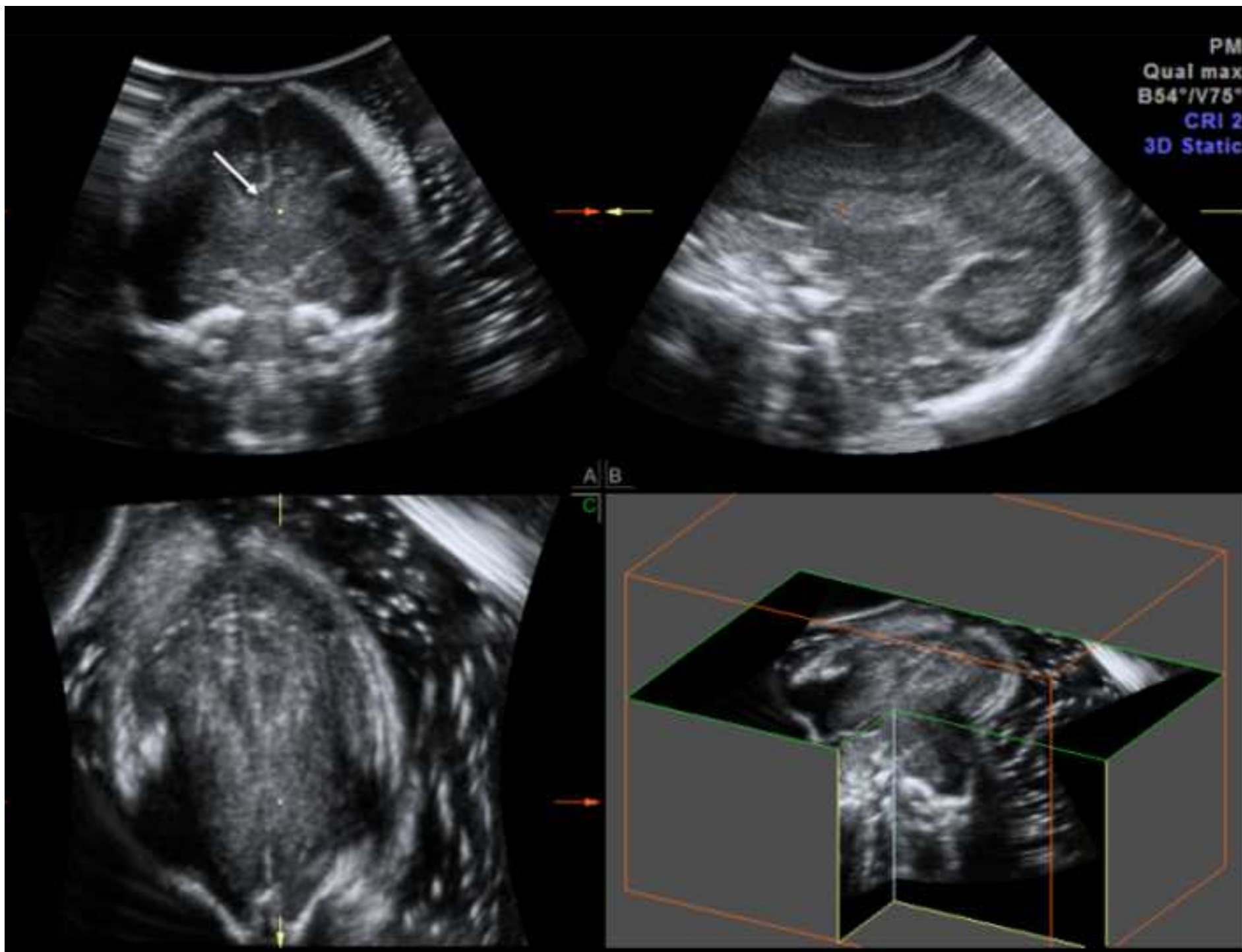
Figure 4a

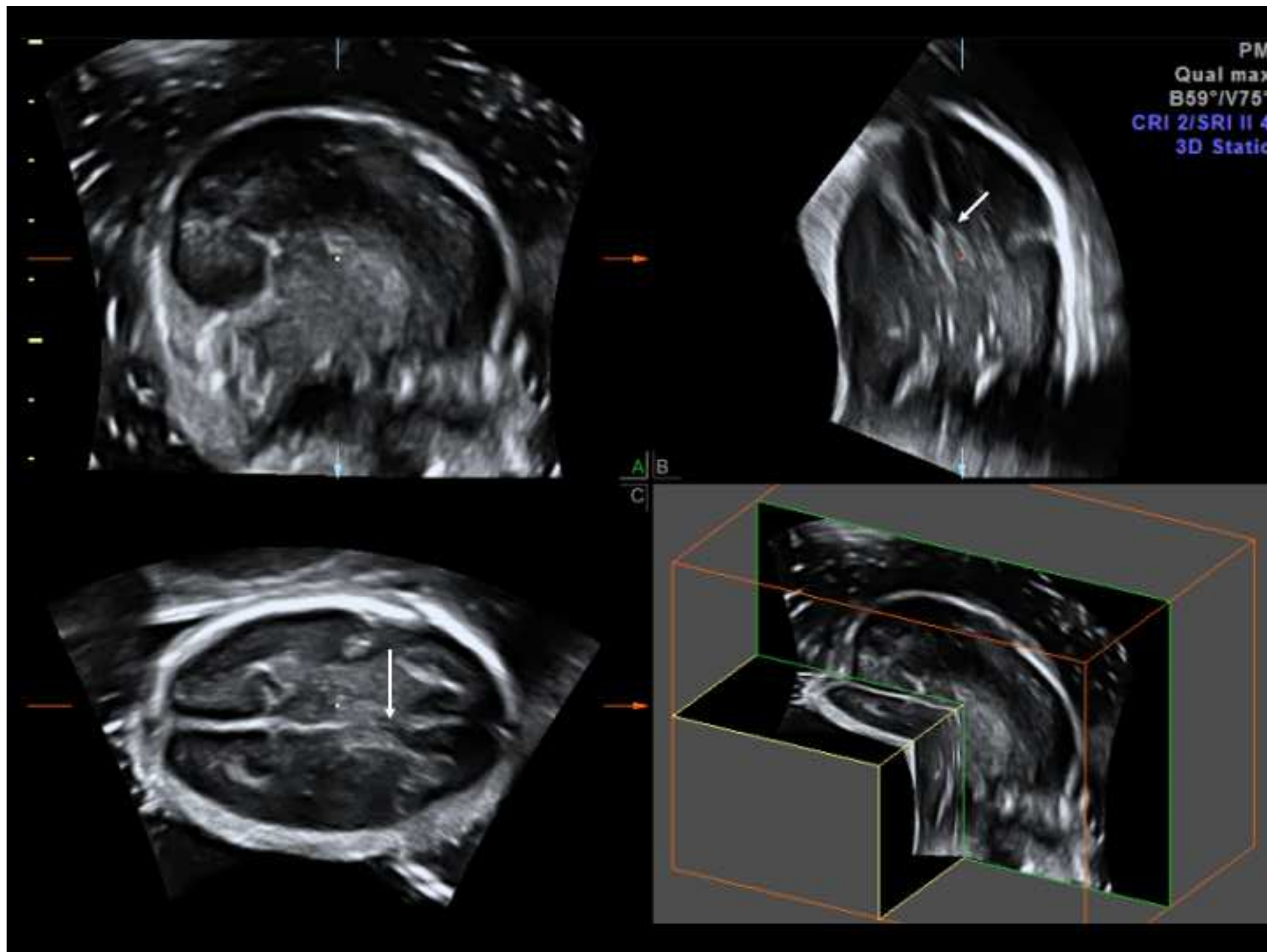
[Click here to access/download;Figure;Figure 4a.tiff](#)

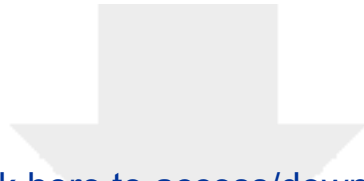








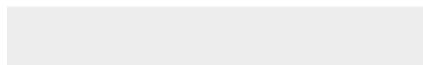


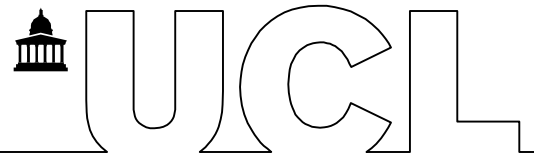


Click here to access/download

Conflict of Interest Form

COI form 3D PMUS paper.pdf





27th August 2020

Editor, Pediatric Radiology

Dear Dr Oystein Olsen,

Re: Submission ID: PRAD-D-20-00199

Thank you for considering our manuscript entitled “ 3-dimensional (3-D) versus 2-dimensional (2-D) post-mortem ultrasound: Feasibility in perinatal death investigation” for publication in *Pediatric Radiology* as a Technical Innovation paper.

We are grateful for your thorough reading of our paper and have addressed the reviewer and editorial comments, with our responses (in bold text) below and made amendments to our article as suggested.

Reviewer #1:

1. In the discussion, please explain why it takes 30 minutes for 3D ultrasound vs 20 minutes for 2D ultrasound. Is this amount of time all acquisition time (which I would have assumed it would be faster for 3D with single acquisitions per body station)? Does the 30 vs 20 min time difference include post-acquisition processing time?

The additional time for the 3-D ultrasound is due to the lengthy image post-processing time. Whilst it only takes a matter of 5 minutes to acquire a volume of each foetal body region (i.e. head, thorax, abdomen), the reconstruction and creation of meaningful and interpretable images for recording in our PACS system and for interpretation requires additional time. This is in contrast to the 2-D ultrasound acquisition where the operator is acquiring and interpreting the imaging as they perform the study. We have now explained this more fully in our methodological description.

2. I suggest including a table of each subject with gestational age, gender, pre-autopsy presumed cause of death (and how it was made, e.g. ultrasound, x-ray, etc), 2D postmortem ultrasound findings, 3D postmortem ultrasound findings, and autopsy findings.

We have now included a single table in this revised submission detailing the 11 fetuses in this study.

3. In the body of the results, I would make it explicit that the 1 case that did not detect an abnormality (i.e. the 25% "false negative") was the OI case but it was due to patient being too small. In all patients where you were able to do an ultrasound, it sounds like you were able to distinguish normal from abnormal. It was only in the case that you couldn't scan that ultrasound was not helpful.

This is correct. We have amended this in the results section to reiterate that the one case we could not diagnose was due to non-diagnostic imaging, and small foetal size and amended our abstract to fit this rewording.

4. I suggest abandoning percentages with such small sample size. Just list it out: 10 patients scanned, 7 normal, 3 abnormal, concordant autopsy. 1 patient not scanned due to OI.

We have now removed all percentages from our results in the main manuscript and listed the abnormalities out of 10 (not 11 cases).

5. For readers like me that are not familiar with the topic, I suggest including another table listing common diagnoses that you think post-mortem ultrasound should be able to detect. Clearly abnormalities that result in fluid accumulation are accessible. This table should be based on existing literature, the results of your study, and your expert opinion.

Thank you for this suggestion. We have published a very comprehensive review of our post-mortem ultrasound technique, template reporting (including specific anatomy and areas for review) and potential abnormalities for perinatal losses in a separate pictorial review/ guidance document within the journal 'Insights into Imaging' as a two part, open access series.

We have now included this as a reference in our manuscript to guide readers who are interested in learning more about postmortem ultrasound imaging. As this is only a short technical innovation article, it may be quite lengthy to incorporate all possible details. If, however, the editor feels it would be helpful to reproduce these tables, we can seek the necessary permissions from the original journal for reproduction.

6. In the figures, you included the 3 abnormal cases. That's great. I suggest also including 1 normal case with annotations showing the level of detail that one can achieve with postnatal ultrasound.

We have now included an additional image of a normal foetus in Figure 1 to demonstrate the normal appearances seen at ultrasound. The previous figures have been renumbered accordingly.

7. Does your report template only include 5 fields, brain, spine, cardiac, thorax, abdomen? Or does it include subcategories (e.g. liver, bladder, etc.)? If subcategories are included, I suggest describing your template in detail in a table or appendix, so that readers have a sense of what your survey covers. Perhaps this information could be tied into my suggestion #5, helping the readers understand what diagnoses you are looking for in each anatomic region.

Thank you for this suggestion. Please see our response above to point 5. Our template is for just the 5 body regions, however if there is any abnormality within any of these areas, we would expand to include positive and negative findings per body organ within these regions.

Reviewer #2:

8. Thank you for this article. I applaud the authors for reporting a "negative" observation. Certainly the use of 3D ultrasound is not new in pediatrics and fetal imaging. In the last 10-15 years it has become apparent that 3D provides very few benefits with regard to accuracy and sensitivity. It like most advanced visualization techniques is helpful in presenting anatomy to non-imagers who might better understand the findings if presented in 3D or multiple planes. If a benefit has been shown it would be in complex disease that may be difficult to understand with a single plane, such as congenital heart disease. This being said and certainly agreed upon by the authors, the report lacks sufficient specificity and power to provide scientific guidance. Given the sample of 11 and the variety of pathology presented it is hard to justify the conclusion that 3D is either beneficial or not. I agree with the authors that the technique is feasible. If the report were to focus on a specific pathology it may be more valuable.

Thank you for these comments. We agree with the reviewer's advice. In our conclusion we have now reworded our suggestion for future larger studies, to include a recommendation for studies covering a wider range of positive pathologies to understand what specific conditions the 3-D technique may be helpful. It is true that for some congenital cardiac malformations, a 3-D volume may be helpful to reconstruct different planes (as is the case in intrauterine/prenatal imaging). In post-mortem fetal cardiac ultrasound we suffer from poor diagnostic 2-D accuracy results given the lack

of circulation to aid diagnosis and collapse of the cardiac chambers with presence of thrombus. It would be interesting to know whether 3-D imaging may be helpful in these circumstances. This issue has been added to our discussion.

Editor:

9. Title cannot have acronyms (2-D, 3-D; also please note the hyphens)

This has been amended in the title. The hyphenation has been amended in the abstract and throughout the document.

10. Title page: fix the phone number

This has been amended

11. I would have removed all mention of 'additional value' from title and objective description, because how can such a broad term be defined based on n=11?

The term 'added value' has been removed from the title and abstract and manuscript.

12. In my opinion the study has not been convincingly justified. To me there is not obvious benefit of 3-D US, which is why we never use it clinically although we could easily do so. Therefore, rather than stating the obvious theoretical benefits, which pathological entities in particular would you say might be more precisely detected and described by 3-D US? Could you add this to Introduction?

Thank you for the suggestion. We believe there may be some benefit in complex congenital cardiac or neurological diseases and have now added this to our introduction to build a more convincing case.

13. How cold is a 'cold water bath'?

We have added this detail to the description (approximately 5 degrees Celsius)

14. We don't need to know which spreadsheet what used, that is too much detail

This detail has been removed.

15. But we would like to know how the scans were done

A full description of the image acquisition parameters and methodology are provided under subheading 'description of innovation', third paragraph. We explain the 2-D and 3-D scanners used, bandwidth of the transducers and the body parts we acquired for the acquisition.

16. Essentially, you have only looked at n=4 since 7/11 were entirely normal anatomically. Why have you not added any description of normal anatomy at 2-D v 3-D? Wouldn't that be of some interest? E.g. luminal volumes, femoral lengths?

As per suggestion of reviewer 1, we have now included an additional figure (Figure 1) of normal anatomy seen at 2-D ultrasound and 3-D ultrasound.

In post-mortem imaging (regardless of CT/MRI or ultrasound) we are mainly looking to confirm antenatally detected anomalies or congenital anomalies (and associated pathologies) that may have been missed. We do not routinely measure femoral lengths (already done on skeletal radiographs prior to cross-sectional imaging), nor any luminal volumes, organ volumes etc. unless these are obviously abnormal or cause for concern has been raised. Therefore our main priority is in identification of major structural anomalies, so if none is apparent then we do not have anything further to comment upon and do not record this level of detail.

17. Are dead foetuses 'patients'?

We have removed the term patients/cases in our manuscript and only use the term foetuses for consistency.

18. Recommending larger studies seems completely futile to me. What is the point if there isn't even some theoretical possibility of any diagnostic benefit? If you think there are possible advantages, then what are those, and why?

We have removed suggestion of conducting further larger studies, given that 3-D imaging did not identify anything that was missed by 2-D. In keeping with reviewer 2 we suggest studies focussing on a wider range of pathologies, where the 3-D imaging may be helpful for reconstructing different imaging planes for better visualisation of complex anatomy.

19. Legend fig 3: male or female?

This is a male foetus, we have added this detail.

20. Figure should as a general rule not be composite. I would accept the MPR/VR grids, but I think 1a, 2a and 3a should be split.

We have now split figures for 1a, 2a and 3a into separate files and provide the new files with this submission. The figure legends have also been amended accordingly to the new numbering and split images.

We hope that you will now find our revised work in a more publishable state.

Thank you once again for your time and help.

Yours sincerely,

Dr. Susan Shelmerdine

Paediatric Radiology Research Fellow

On behalf of all authors