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REVIEW

PRENATAL DIAGNOSIS WILEY

Less-invasive autopsy for early pregnancy loss

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Abstract

Autopsy investigations provide valuable information regarding fetal death that can assist in the parental bereavement process, and influence future pregnancies, but conventional autopsy is often declined by parents because of its invasive approach. This has led to the development of less-invasive autopsy investigations based on imaging technology to provide a more accessible and acceptable choice for parents when investigating their loss. Whilst the development and use of more conventional clinical imaging techniques (radiographs, CT, MRI, US) are well described in the literature for fetuses over 20 weeks of gestational age, these investigations have limited diagnostic accuracy in imaging smaller fetuses. Techniques such as ultra-high-field MRI (>3T) and micro-focus computed tomography have been shown to have higher diagnostic accuracy whilst still being acceptable to parents. By further developing and increasing the availability of these more innovative imaging techniques, parents will be provided with a greater choice of acceptable options to investigate their loss, which may in turn increase their uptake. We provide a narrative review focussing on the development of high-resolution, non-invasive imaging techniques to evaluate early gestational pregnancy loss.

Key points

What's already known about this topic?

- Autopsy investigations provide valuable information regarding fetal death that can help parental bereavement and influence future pregnancies.
- Conventional invasive autopsy is often declined by parents.
- Less-invasive autopsy investigations provide a wider and more acceptable choice for parents.

What does this review add?

- Conventional clinical imaging techniques (radiographs, CT, MRI, US) have limited accuracy in imaging smaller fetuses below 20 weeks of gestational age.
- High-field MRI and micro-CT are the most useful post-mortem imaging techniques following early pregnancy fetal loss.

This review has not been published at any conferences.

- More widespread availability of these techniques will help parents access the most appropriate and acceptable investigations following pregnancy loss.

1 | INTRODUCTION

Pregnancy loss is a common event with an estimated 23 million miscarriages (<24 weeks gestation) and nearly 2 million stillbirths (>24 weeks gestation) occurring worldwide every year.[1,2] These numbers are increasing and could be far higher as many women may not present to the health services and data is therefore often based on approximate estimates.[3–5]

Any pregnancy loss can be traumatic for the family and can lead to prolonged grief, depression, anxiety, and post-traumatic stress, with effects possibly lasting for several years.[6–10] Alongside this, miscarriage is little understood by both the general public and healthcare professionals and has been recognised as an under investigated area of medicine.[1,11] Compounding these issues around awareness, parents often believe that they are somehow at fault, which can stop them seeking help and support from healthcare professionals, preventing the true number of miscarriages in the community to be identified.[4,12] In this traumatic context, the delivery of information and its reception by the couple is particularly challenging. Therefore, providing support and a supportive environment where families can make an informed and appropriate choice for themselves is key.

Investigating the possible causes of pregnancy loss has multiple advantages including guiding future pregnancies and advancing medical knowledge,[13–15] but helping bereaved parents understand the implications of their choices at this difficult time can be extremely challenging.[16] Staff training is key to imparting complex information at this difficult time, and experience and guidance in this area for the staff is important to clearly convey key complex information.[14,17] This training should come in differing formats including formal courses, case discussions, and involvement in multidisciplinary meetings to raise awareness of the impact autopsy, and alternative less invasive investigations can make.[17,18]

2 | HISTORICAL BACKGROUND

Conventional autopsy (CA) is the traditional reference standard investigation into pregnancy loss and consists of multiple investigations also called feto-placental examination including a review of the clinical history, an external examination with photography, internal macroscopic examination and histological analysis, tissue sampling for genetic testing and macroscopic/microscopic examination of the placenta.[15,19] Together these investigations provide new clinical information in 40%–70% of cases, depending on the clinical question to be answered.[15,20–22]

Most perinatal and fetal autopsies are carried out with parental consent for diagnostic purposes, rather than being directed by the coroner/medical examiner for forensic purposes. Involving parents in the decision-making process is essential to increase uptake rates and provide care for the families.[13,23] Some parents choose conventional autopsy as the "reference standard" or maximum level of investigation possible as they wish to be sure they have excluded all possible causes for their loss,[15,24] but this may not be appropriate for all cases: there remains a significant proportion of pregnancy losses where the cause is still 'undetermined' despite full investigation.[15,25,26] Others decline all autopsy investigations as they wish to avoid 'further harm' to their child and are not prepared to undergo a more mental turmoil at this challenging time but can later regret this decision.[14,16,24,27,28]

Parents choose to investigate their loss for multiple reasons, including to understand their child's death more fully,[29] the recurrence risk of future pregnancies,[30] to advance scientific knowledge,[31] for a degree of 'closure' after their loss[32] and to rule out self-blame[15,24]

However, autopsy uptake has been declining for many years[10,17,22,33–37] with parental reasons for declining including wishing to protect the baby, practical aspects over transfer to a specialist hospital, misconceptions regarding the benefits of autopsy, poor communication between families and healthcare professionals, uncertainty about the value of the procedure, a mistrust of the hospital system, religious and personal beliefs, and the invasiveness of the procedure.[10,14,38,39] Added to this, there is now a relatively small number of specialist paediatric pathologists (relative to the number of deaths to be investigated[40]), meaning that access to specialist paediatric pathology services in the UK is becoming less accessible.

To challenge the declining consent rate, less-invasive autopsy (LIA) techniques, such as laparoscopic examination of the internal organs through smaller incisions or imaging techniques alone, have been developed in recent years, providing a greater and more acceptable choice to parents.[10,13,14,27,28,37,39,41–44] Significant challenges remain in identifying the cause of fetal demise <20 weeks gestational age (GA) or <500 g, as routine imaging techniques (magnetic resonance imaging (MRI), computed tomography (CT), ultrasound, radiographs) cannot provide sufficient resolution, tissue contrast, or soft tissue detail.[41,45–49] It should also be noted that identifying abnormalities in early gestation through CA also remains challenging.[47,48,50–57] Several terms are commonly used to describe the different post-mortem approaches towards diagnosis, and it is important to understand the investigations each term refers to and what can be achieved (Table 1).

In this narrative review article, we aim to focus on the development of high-resolution, non-invasive imaging techniques to identify the possible causes of early pregnancy loss in this challenging area. We defined up to 20 weeks as "early" gestation but clarified it according to the published literature. Articles published in the last

TABLE 1 Four terms used to describe the different post-mortem investigational approaches.

Key terminology				
Term	**Explanation**	**Includes**	**Histology**	**Genetics**
Conventional autopsy	Collection of investigations and gold standard for identifying the cause of fetal demise	Review of the clinical history, external examination with photographs, internal macroscopic examination and placental examination	Yes, all target organs as recommended in guidelines of the Royal College of Pathologists	Tissue samples from target organs for genetic testing
Less-invasive autopsy	Umbrella term including any autopsy procedure (CA or imaging) that is performed with smaller, less or no incisions than CA	Minimally invasive autopsy, non-invasive autopsy and placental examination	Yes, most organs with focal biopsy via minimally invasive autopsy approach	Tissue samples from target organs for genetic testing
Minimally invasive autopsy	Combination of imaging investigations, utilizes smaller incisions than for CA	Laparoscopic or image-guided needle-biopsy approach and placental examination	Yes, most organs with focal biopsy	Tissue samples from target organs for genetic testing
Non-invasive autopsy	Imaging only, no incisions required	External examination, placental examination and all non-invasive imaging investigations	No histology available	No genetic testing available

15 years were identified in December 2022. As there is no definitive gestation related to many of the investigations described, we aim to include 20 weeks, but will identify specific gestations where the literature allows. Articles were identified in December 2022 through a search of MEDLINE and PubMed using a Boolean search strategy with word variations relating to 'autopsy', 'conventional', less-invasive', minimally invasive', 'non-invasive', 'imaging', 'early gestation', and 'fetus'.

3 | CONVENTIONAL CLINICAL IMAGING TECHNIQUES

3.1 | Post-mortem radiographs

Fetal post mortem radiographs (PMXR) are cheap, quick, widely available, easy to perform, and largely used to estimate gestational age and assess the developing skeleton.[47] As most skeletal dysplasias and abnormalities are now typically identified through ante-natal ultrasound,[58] PMXR of all fetuses has been shown to add diagnostically useful information in less than 1% of routine cases.[59] Whilst PMXR is diagnostic in suspected skeletal dysplasia, improvements in antenatal diagnosis mean that these abnormalities are being detected earlier at earlier gestations, when the bones are less ossified, and therefore PMXR are less discriminatory.[60–62]

3.2 | Post-mortem computed tomography

Post-mortem computed tomography (PMCT) is also widely available, cheap, and quick to perform[47,63] but the combination of small size and poor soft-tissue contrast limits its diagnostic ability in small fetuses.[56,64,65] Although PMCT angiography can increase the soft tissue contrast, large validation studies are still required.[56,66,67] PMCT can also provide information on dysplasia imaging through 3D reconstructions, but with limited additional diagnostic utility due to limited ossification at early gestation negating this advantage in early pregnancy.[56]

3.3 | Post-mortem magnetic resonance imaging (1.5 and 3T)

Post-mortem magnetic resonance imaging (PMMRI) is widely available and provides excellent soft-tissue information. However, due to the increasing clinical pressures combined with the time required to perform detailed PMMRI (approx. 60 min),[52,68] there is often difficulty in accessing these scanners for post-mortem imaging.

The main challenge for PMMRI at field strengths below 3T is the low spatial resolution and subsequent difficulty in visualising structures in <20 weeks GA due to poor tissue contrast and low signal-to-noise.[41,45,52–54,69] PMMRI at 3T field strength provides fewer non-diagnostic scans than 1.5T for fetuses <20 weeks GA through better image contrast, with higher sensitivity (34.6% vs. 17.3%)), specificity (65.1% vs. 45.3%), and concordance (55.1% vs. 36.1%) with CA.[52] Field strengths above 3T have reported further improvement for fetuses <20 weeks gestation.[49,57,70] Soft tissue contrast and signal-to-noise ratio (SNR) can be improved through immersion of smaller fetuses in a Gadolinium/formaldehyde solution prior to scanning at 3T, but this technique has not been optimised for clinical use.[50] Overall, conventional PMMRI has limited diagnostic accuracy below 20 weeks gestation.[41,52,71,72]

3.4 | Post-mortem ultrasound

Post-mortem ultrasound (PMUS) may be a suitable alternative when cross-sectional imaging techniques are less available. It can provide information on a wide array of body systems including the head, neck, spine, cardiac and vascular imaging, thorax and abdomen, musculoskeletal and soft tissue malformations.[73]

It may also be better understood by parents when consenting for post-mortem imaging having already undergone ante-natal ultrasound scanning and is also unaffected by tissue fixation.[61,72,74–77] PMUS also has the advantage of being able to direct needle biopsies for tissue sampling.[47,73,78–81] However, PMUS is operator-dependent, requiring specialist training to develop the skills and experience to accurately identify possible causes of pregnancy loss in these smaller fetuses.[47,51,61,74]

A high-resolution linear or curvilinear probe is advised given the small fetal size. The loss of normal live tissue rigidity can lead to slumping and difficulty maintaining contact with the ultrasound probe, and so a 'water bath' technique has been described, where the whole fetus is fully immersed within a cold, still water bath with a gel stabilising pad.[74] Alternatively, ultrasound transmission gel can be used to generate a stand-off, although cleaning the body afterwards is more challenging and may lead to fungal growth in residual gel.[61]

Although relatively high sensitivities and specificities have been reported from multiple studies (ranging from 73% to 97%, similar to 1.5T PMMR), most studies have found lower diagnostic rates and higher yield of non-diagnostic imaging in fetuses below 20 weeks gestation.[51,61,72,75,76]

4 | HIGHER RESOLUTION IMAGING

More advanced post-mortem imaging techniques including High-field (HF) PMMRI and Micro-focus Computed Tomography (micro-CT) imaging[50,71,82,83] have been developed for early fetal loss, primarily to address the combined issues of poor resolution, and low signal and contrast-to-noise ratios.[41,46,49,55,57,61,71,72,82,84–88]

4.1 | Micro-focus computed tomography

Micro-CT provides non-invasive micron-level resolution imaging (Figure 1), with increased spatial resolution as fetal size decreases (Figure 2), making it ideal for early GA pregnancy loss and providing isotropic datasets which can be reconstructed for visualisation in different planes.[41,57,83–85,88–95]

To provide adequate soft tissue contrast, however, an exogenous contrast agent is required, typically potassium tri-iodide (I_2KI), which stains the soft tissue through cellular diffusion.[46,83,85] Sufficient time must be allowed for complete diffusion, which can take several days or weeks and is dependent on the size of the fetus (Figure 3).[83,85,89,96,97]

One downside is that concentrated I_2KI may result in tissue distortion, although this can be minimised by using a buffered solution.[46,71,85,86,98] Endovascular staining using various contrast agents has also been investigated[99–101] and may offer opportunities to iodinate larger fetuses in a reduced timeframe in the future.[46]

Iodination can cause visible darkening of the fetus, which should be discussed with parents during the consent process and may be initially undesirable but can be partially reversed by sodium thiosulphate solution (Figure 4).[46,83] This does not necessarily remove the iodine from all body tissues; however, in many cases, it is sufficient to just de-stain the skin for cosmetic purposes prior to returning the body to the parents.

Micro-CT has shown a high level of agreement with CA across multiple organ systems for 11 and 21 weeks GA of 21 fetuses, with overall sensitivities and specificities of 93.8% and 100%. Although non-diagnostic rates were higher for <14 weeks GA than above (12% vs. 4.7%), there were fewer non-diagnostic indices <14 weeks GA, with higher positive predictive values, 97.3% versus 85.7%.[88]

A large study analysing 268 micro-CT scans (GA 11–24 weeks) demonstrated that sensitivity and specificity were 92.3% and 98%, respectively, for fetuses up to 24 weeks GA, and pathologists deemed invasive autopsy unnecessary in 86.9% of cases.[84]

Maceration, the breakdown of tissue structure due to immersion within a fluid filled cavity (amniotic fluid) combined with autolysis following fetal demise, is a major challenge in identifying the cause of early pregnancy loss both through imaging and CA.[25,70,79,103] Through the late diagnosis of a miscarriage and a delay between fetal demise, identifying pregnancy loss and delivery of the fetus, it is exposed to an often unknown intra-uterine retention time. Maceration affects many early pregnancy losses and can affect the accuracy of PMUS even within 48 h, with between 25% and 40% of scans becoming non-diagnostic due to severe maceration.[51,72,78,79,104–106] Equally, in-utero maceration deteriorates image quality for micro-CT, yet high quality is still possible in over 95% of cases despite the presence of a range of maceration states.[102]

Micro-CT can also be used as an adjunct to CA providing high resolution imaging of excised organs, for example, of the kidney,[107] brain[92] and heart.[57,93,94,108] Diagnostic accuracy of ex-vivo imaging is also high, for example, for congenital heart disease equal to CA and superior for smaller specimens[108] and has been used to assess cardiac anatomy between 8—13 weeks GA to validate prenatal diagnosis following TOP for cardiac anomalies.[57]

One practical limitation of micro-CT is that due to the high-resolution of the technique, the data files are large (approximately 50 GB per clinical patient) requiring large provision of storage for clinical use relative to other suitable techniques (ultra-high-field PMMRI <1GB per patient).[83,85]

Overall, due to the relative higher-resolution, low cost, and quick scan times, micro-CT has clear advantages[71] and is an excellent alternative to CA.[48,57,84] It can be used to create detailed scale 3D models or augmented virtual reality to aid parental counselling and

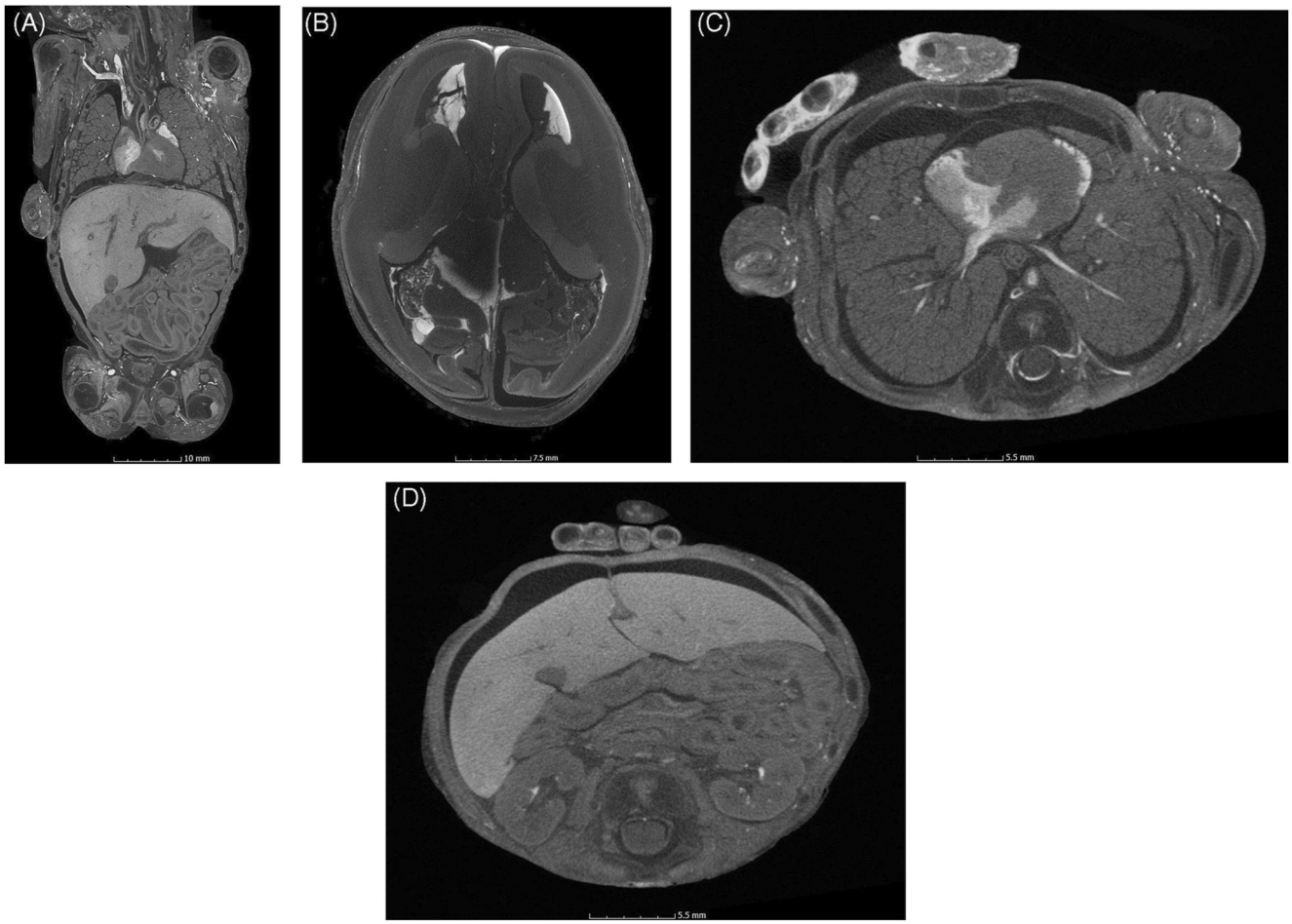

FIGURE 1 Coronal post-mortem iodinated micro-CT image of a 15-week gestation fetus, resolution 60 μm (A), axial images at the level of the ventricles of the brain (B), and heart (C) and the liver (D) demonstrating the high-resolution imaging micro-CT provides for early gestation pregnancy losses. Figure adapted from Shelmerdine et al. 2020 with permission.[48]

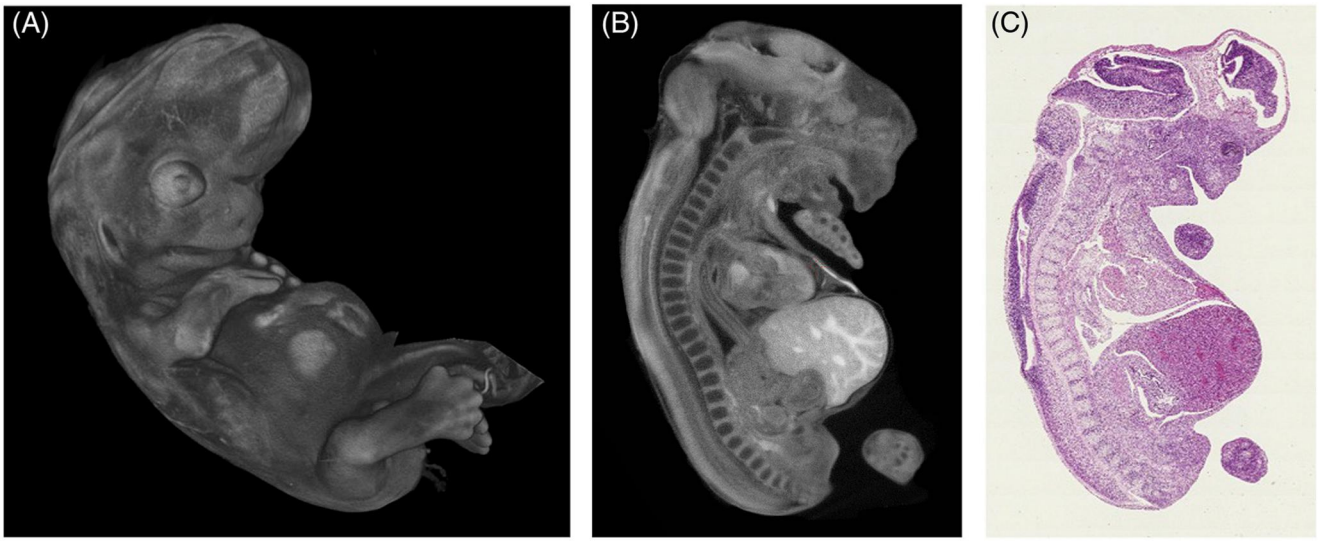

FIGURE 2 (A) Volume rendered a 3-dimensional image of a 7-week gestation embryo demonstrating early eyelid and external ear development along with individual digits of the hand and toe notches. (B) A sagittal post-mortem micro-CT of the same embryo at 9.7 μm with (C) corresponding histopathological section stained with haematoxylin and eosin staining demonstrating the equivalent internal detail attainable with both micro-CT and histopathology. Figure adapted from Shelmerdine et al. 2018 with permission.[91]

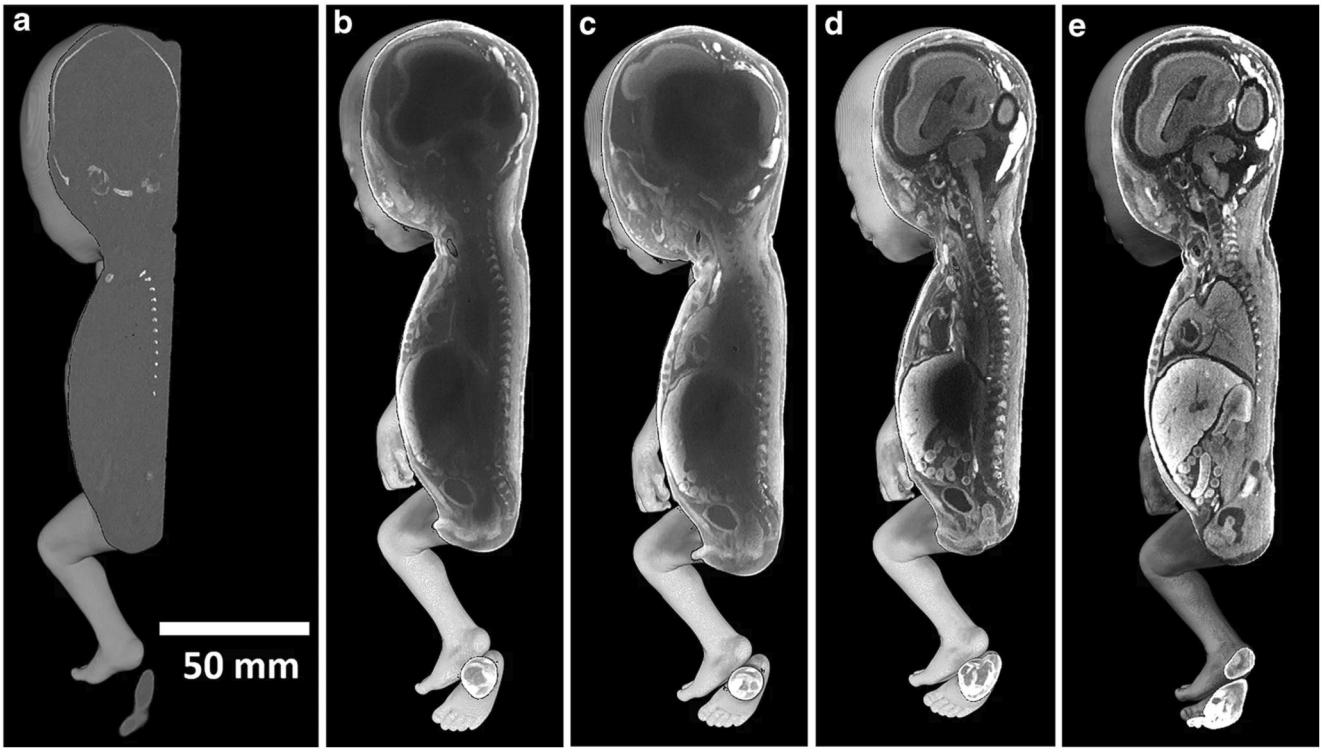

FIGURE 3 Iodination of the fetus occurs as an iodine solution diffuses towards the interior of the fetus over time as demonstrated by (A) pre-iodination, (B-D) progressive iodination seen with iodination from the external surface of the fetus towards the centre, until (E) full iodination occurs. Figure adapted from Docter et al. 2022 with permission.[46]

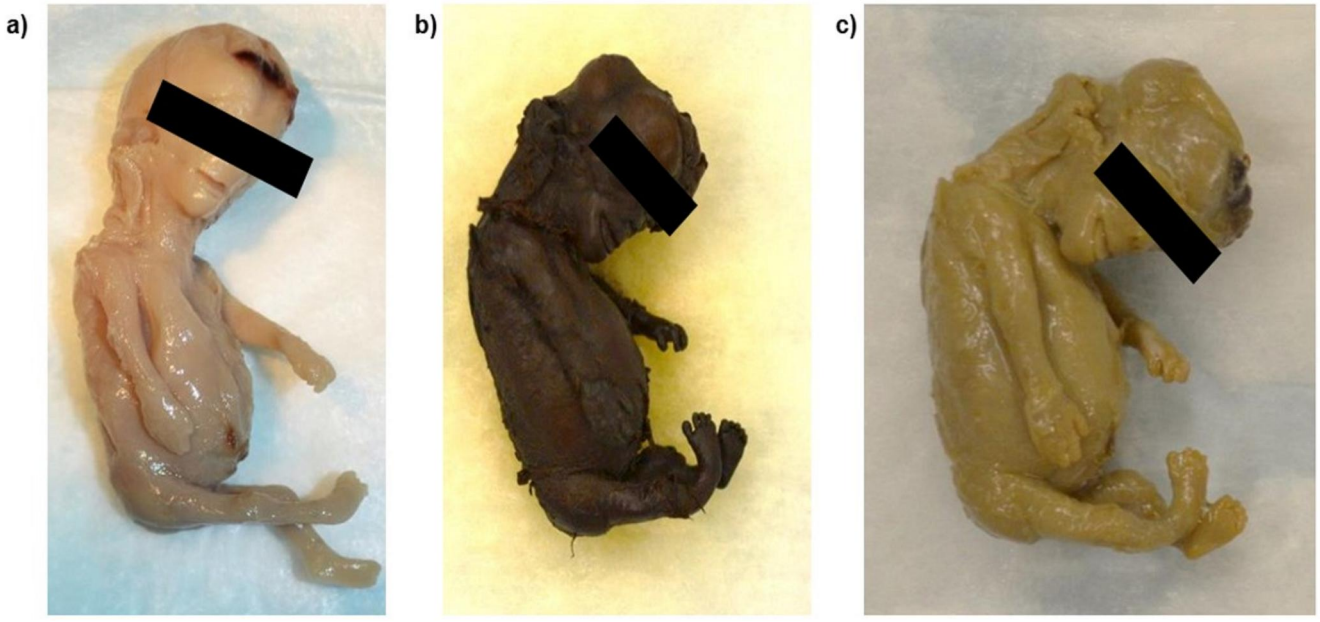

FIGURE 4 A 14- week gestation fetus (A) having been refrigerated post-delivery, (B) following immersion in a mixture of potassium tri-iodide solution and 10% formalin to achieve fixation and full iodination where the skin is stained a darker shade, and (C) following immersion in thiosulphate solution prior to being returned to the parents, where the skin colour is returned to close to its original colour.

education of congenital anomalies/fetal development,[41,57,83–85,88–95,109] with a range of fetal gestations scanning from 6 weeks[87] to 24 weeks[84] with relatively short scanning times.[83]

4.2 | Ultra-high-field post-mortem magnetic resonance imaging

Despite the numerous studies and multiple technical advances in recent years, the main disadvantage for PMMRI is the low image quality below <20 weeks GA or 300 g.[49,70,110] To overcome this, HF-MRI (7T and above) offers a significant increase in the SNR which can either improve the resolution or decrease the scan time, whilst also offering superior soft tissue contrast, whilst reducing the complexity of introducing an exogenous contrast agent.[55,70,85,110–112]

HF-MRI images are able to accurately identify anatomical structures, particularly of the heart, below 20 weeks GA[49] albeit with a lower resolution than seen with micro-CT (137 μm in HF-MRI vs. 22 μm in micro-CT),[71] whilst a high concordance between HF-MRI and CA is seen for a range of anatomical structures with sensitivity (94.6%), specificity (97.6%) and positive and negative predictive values respectively (93% and 98.2%).[112] One study comparing CA with 9.4 and 1.5T PMMRI of the brain demonstrated that CA provided no additional information to that of HF-MRI and where CA was non-diagnostic, HF-MRI could provide diagnostic information in 69% of cases.[70] HF-MRI provided greater spatial resolution, higher tissue contrast and better diagnostic information than 1.5T and was equivalent to CA when there was minimal maceration.[70]

Micro-CT can also provide increased SNR and CNR than HF-PMMRI (7T) for human fetal scanning (4 fetuses, 13–18 weeks GA, 17–137 g) with a greater ability to identify anatomical structures in micro-CT (Figure 5).[7,1]

HF-MRI typically takes longer scanning times (>18 h), making it difficult to implement in a clinical setting,[47,55,70,83] and may be more expensive than Micro-CT (400 Euros per patient in comparison to 200 Euros for micro-CT).[71] Most HF-MRI scanners have a small-bore size (16–30 cm diameter), thus limiting the field-of-view, to smaller fetuses.[55] The smaller the fetus, the more likely micro-CT would be a better imaging modality, as even higher spatial resolution should be possible by positioning the fetus closer to the X-ray source,[71,83] whilst also maintaining shorter scanning times.[55]

Overall, as with micro-CT, most HF-MRI scanners are research based with limited clinical availability[41,55,61,70]; Relative to HF-MRI, micro-CT provides greater cost efficiencies and higher resolution.[71]

5 | AUTOPSY IN ADDITION TO LIA

Whilst LIA techniques are proven to provide answers to parents, it is important to identify whether any additional yield would be possible from completing an invasive autopsy.[113] Shelmerdine et al., demonstrated that when there was concordance between PMMRI and prenatal ultrasound, additional clinically significant information was found at autopsy in only 4.5% (2/44) of cases, where autopsy found additional brain abnormalities after prenatal ultrasound and PMMRI reported only ventriculomegaly.[113]

6 | TISSUE SAMPLING FOLLOWING EARLY PREGNANCY LOSS

Laparoscopic autopsy allows evaluation and tissue sampling of all internal organs via a smaller incision than that employed in CA; thus, it is more cosmetically acceptable to parents.[13,28,39] It has been shown to be useful in fetuses as early 15 weeks of GA but is more difficult with smaller fetuses.[47,81] It also provides similar tissue sampling success (>80%) when compared with more invasive approaches and comparable results to CA in identifying a cause of death.[81] Ultrasound-guided needle biopsy of organs is also a feasible method of tissue sampling, providing biopsy rates of around 85% organ success, and improved accuracy compared to 'blind' tissue sampling (76% vs. <52%),.[80] The INTACT approach, tissue biopsy through the umbilicus, is particularly appealing as it combines tissue sampling without making an incision, leaving the fetus cosmetically intact, although not all organs (brain, thyroid, thymus) could be sampled by this approach.[80] Ultrasound guided tissue sampling at post-mortem has obvious implications for the developing world, for example, for microbiological assessment in infectious outbreaks in children.[114]

7 | CHALLENGES FOR IMPLEMENTATION

Although post-mortem imaging guidance can be used to optimise perinatal investigation and pregnancy loss,[82] and has been embedded within specific autopsy protocols from the UK Royal College of Pathologists for infants and second/third trimester pregnancies, there is currently no specific guidance available for the first trimester loss. A stepwise approach has been suggested for fetal post-mortem examination with imaging used to triage further investigations,[41] whilst further advice is offered for fetuses <500 g when more specialised investigations are available (HF-MRI and micro-CT) (Figures 6 and 7).[47] The developing role of imaging means that new guidelines and referral pathways would be welcome and are likely to support investment and raise awareness for post-mortem investigations following early pregnancy loss.[82]

8 | FUTURE DIRECTIONS/OTHER DEVELOPMENTS

Major challenges for the implementation of both micro-CT and HF-MRI for investigating early pregnancy loss are the lack of availability for both scanning techniques within a clinical setting, along with

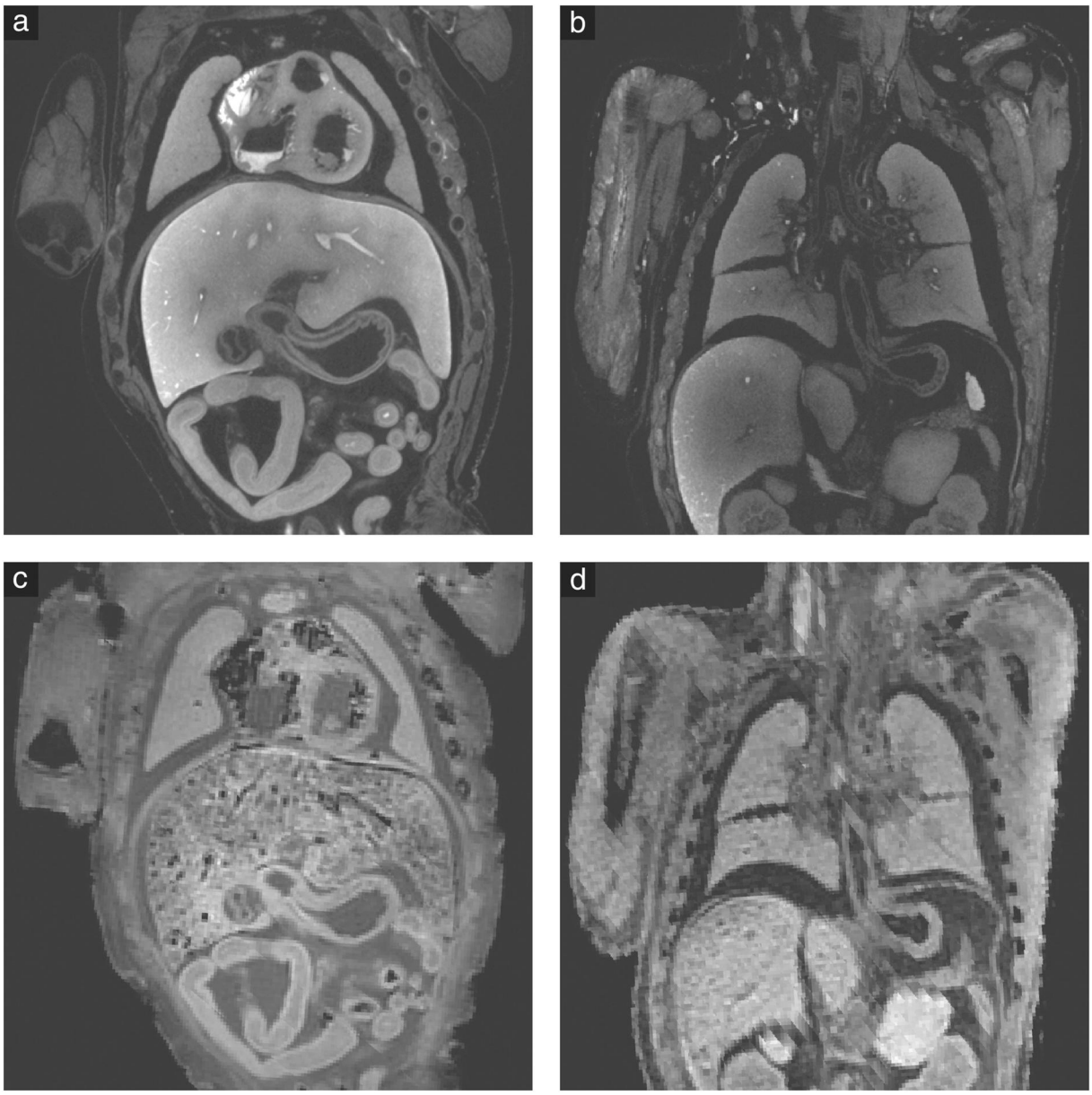

FIGURE 5 Coronal slices demonstrating the high-resolution imaging possible of internal anatomy including liver and stomach (A, C) and primary bronchi and lungs (B, D) for both micro-CT (A, B) and high-field magnetic resonance imaging (MRI) 7T (C) and 3T (D). Figure adapted from Dawood et al. 2021 with permission.[71]

staff training in image acquisition and interpretation. Limited funding for these types of services in specific jurisdictions will further limit clinical experience and patient access. Alongside this, referrers and parents should be educated on the benefits of post-mortem investigations and what these innovative techniques can yield. Similarly, national guidance is required to determine their economic role in the wider service provision at a time of acute shortage of paediatric pathologists.

A detailed health economic assessment is needed, weighing up the costs of scanning against the benefit of helping the grieving process, and a potential reduction in the future burden of mental health issues and ongoing pregnancy losses.[82] Important features of this process include providing the information in sensitive, easily understood terms according to the families personal situation, with time spent answering questions to ensure parents can make decisions that they do not later regret, whilst providing unbiased support in the decision-making process.[14,18,30,115]

9 | CONCLUSIONS

LIA investigations are preferred by parents for a variety of reasons, and through greater provision and choice there will be uptake in parental consent. Micro-CT and HF-MRI offer superior post-mortem image quality for early pregnancy loss through increased resolution and CNR when compared to more established NIA techniques.

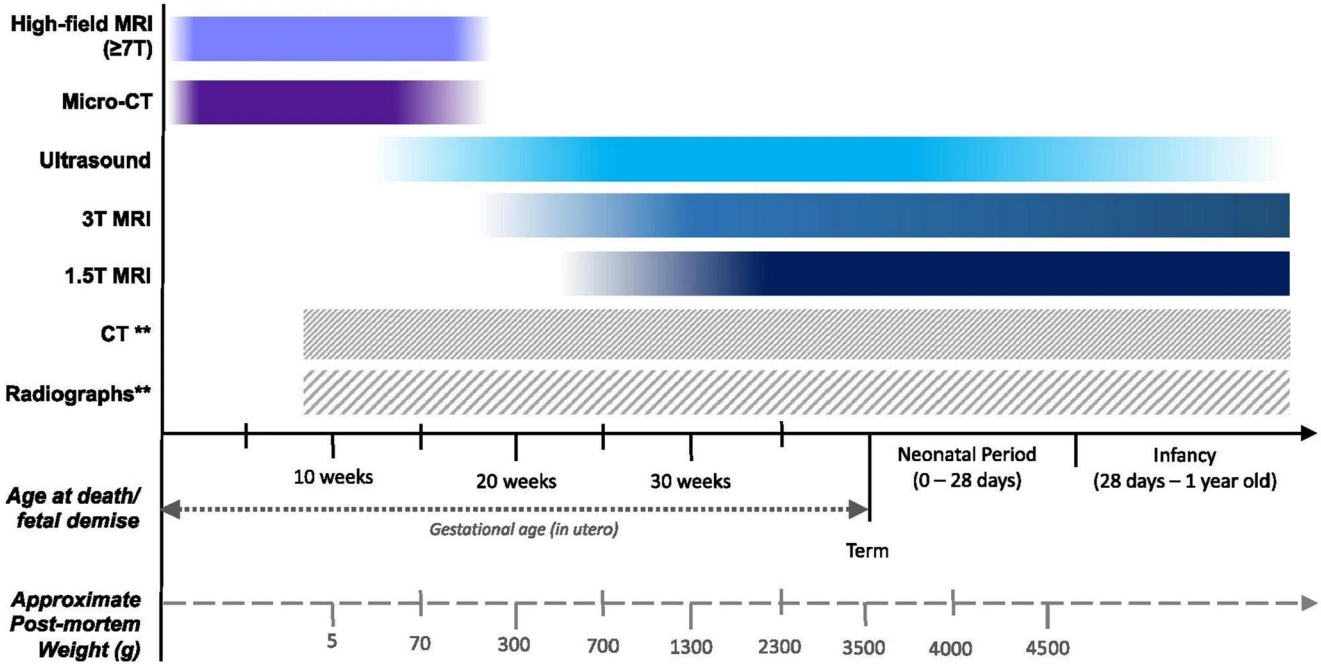

FIGURE 6 Demonstration of when micro-CT and high-field magnetic resonance imaging (MRI) can provide superior imaging for early gestation fetuses relative to other imaging modalities. Figure adapted from Shelmerdine et al. 2021 with permission.[63]

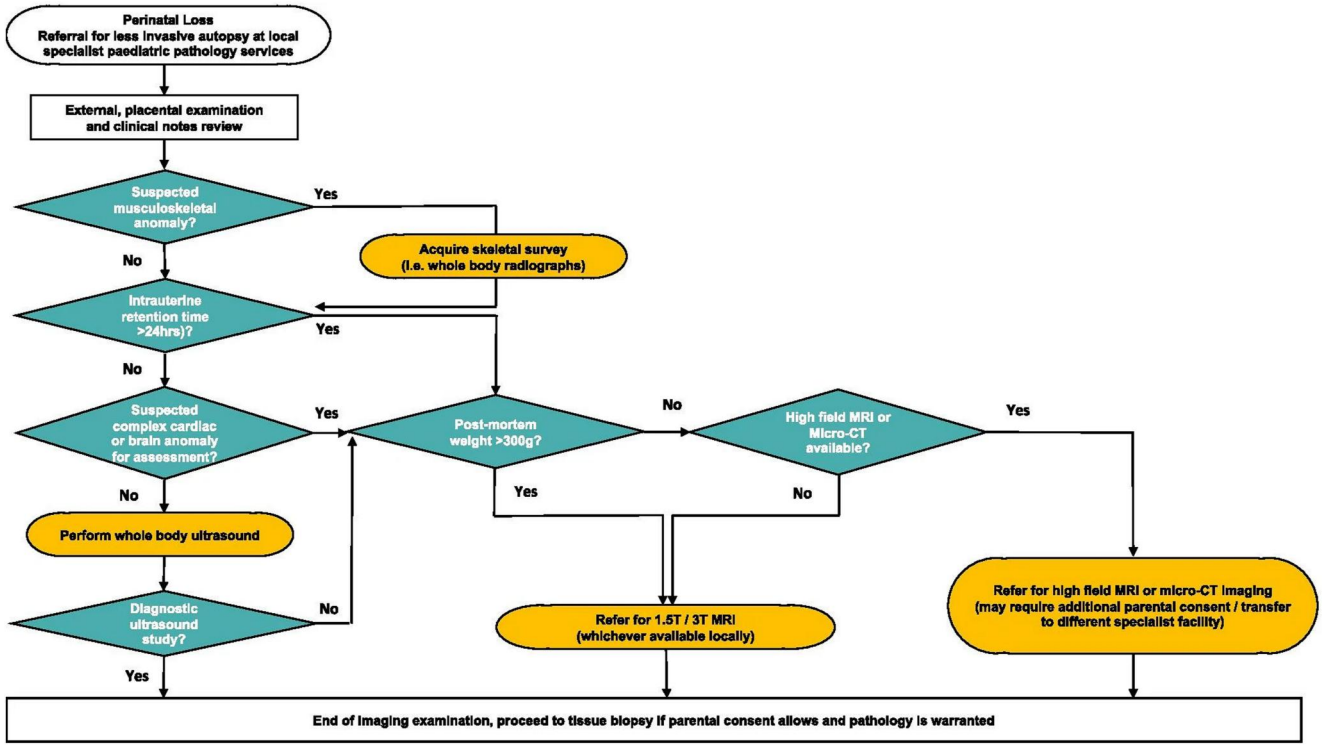

FIGURE 7 Step-wise flowchart for non-invasive investigation of perinatal loss including options for micro-CT and high-field magnetic resonance imaging (MRI). Figure adapted from Shelmerdine et al. 2021 with permission.[63]

Wider adoption of these investigations will increase the societal awareness surrounding miscarriage and reduce the emotional cost for parents by investigating their loss in a more acceptable personalised manner.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

ETHICS STATEMENT

No ethical consent was required for this review article.

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