OBSTETRICS

Postmortem microfocus computed tomography for early gestation fetuses: a validation study against conventional autopsy

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BACKGROUND: Perinatal autopsy provides useful clinical information in up to 40% of cases. However, there is a substantial unmet clinical need with regards to postmortem investigation of early gestation fetal loss for parents for whom standard autopsy is either not available or not acceptable. Parents dislike the invasive nature of autopsy, but current clinical imaging techniques do not provide high-enough imaging resolution in small fetuses. We hypothesized that microfocus computed tomography, which is a rapid high-resolution imaging technique, could give accurate diagnostic imaging after early gestation fetal loss.

OBJECTIVE: The objective of the study was to evaluate the diagnostic accuracy of microfocus computed tomography for noninvasive human fetal autopsy for early gestation fetuses, with the use of conventional autopsy as the reference standard.

STUDY DESIGN: We compared iodinated whole body microfocus computed tomography in 20 prospectively recruited fetuses (11–21 weeks gestation from 2 centers) with conventional autopsy in a double-blinded manner for a main diagnosis and findings in specific body organs. Fetuses were prepared with 10% formalin/potassium tri-iodide. Images were acquired with a microfocus computed tomography scanner with size-appropriate parameters. Images were evaluated independently by 2 pediatric radiologists, who were blinded to formal perinatal autopsy results, across 40 individual indices to reach consensus. The primary outcome was agreement between microfocus computed tomography and conventional autopsy for overall diagnosis.

RESULTS: Postmortem whole body fetal microfocus computed tomography gave noninvasive autopsy in minutes, at a mean resolution of 27μm, with high diagnostic accuracy in fetuses at <22 weeks gestation. Autopsy demonstrated that 13 of 20 fetuses had structural abnormalities, 12 of which were also identified by microfocus computed tomography (92.3%). Overall, microfocus computed tomography agreed with overall autopsy findings in 35 of 38 diagnoses (15 true positive, 18 true negative; sensitivity 93.8% [95% confidence interval, 71.7–98.9%], specificity 100% [95% confidence interval, 82.4–100%]), with 100% agreement for body imaging diagnoses. Furthermore, after removal of nondiagnostic indices, there was agreement for 700 of 718 individual body organ indices that were assessed on microfocus computed tomography and autopsy (agreement, 97.5%; 95% confidence interval, 96.1–98.4%), with no overall differences between fetuses at ≤14 or >14 weeks gestation (agreement, 97.2% and 97.9%, respectively). Within first-trimester fetal loss cases (<14 weeks gestation), microfocus computed tomography analysis yielded significantly fewer nondiagnostic indices than autopsy examination (22/440 vs 48/348, respectively; $P<.001$).

CONCLUSION: Postmortem whole-body fetal microfocus computed tomography gives noninvasive, detailed anatomic examinations that are achieved in minutes at high resolution. Microfocus computed tomography may be preferable to magnetic resonance imaging in early gestation fetuses and may offer an acceptable method of examination after fetal loss for parents who decline invasive autopsy. This will facilitate autopsy and subsequent discussions between medical professionals who are involved in patient care and counselling for future pregnancies.

Key words: autopsy, microfocus computed tomography, postmortem, termination of pregnancy

Fetal loss is a common event that impacts a million women each year in the United States,[1] and there is a growing Western trend to postponing pregnancy, despite an increased risk of fetal death with advancing maternal age.[2] Perinatal autopsy provides diagnostic information regarding fetal anomalies, which are the causes of intrauterine fetal death, and influences the management of future pregnancies and living relatives.[3-5] Although perinatal autopsy is an important source of epidemiologic data regarding developmental abnormalities and complications of pregnancy and labor, most parents decline standard invasive perinatal autopsy,[6-8] mainly because of its invasive nature.[7-12]

Postmortem magnetic resonance imaging can be offered as part of a less invasive approach[13,14]; however, although postmortem magnetic resonance imaging has high diagnostic accuracy in fetuses (approximately 94% concordance with autopsy),[14] it does not provide adequate high-resolution imaging in early gestation loss (<500 g bodyweight or <18 weeks gestation),[15,16] even at higher field strengths.[17] Furthermore, after the use of modern high-resolution ultrasound scanning[18-24] and in the era of cell-free DNA testing,[25-48] earlier antenatal

Cite this article as: Hutchinson JC, Kang X, Shelmerdine SC, et al. Postmortem microfocus computed tomography for early gestation fetuses: a validation study against conventional autopsy. Am J Obstet Gynecol 2018;218:445.e1-12.

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2018.01.040

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AJOG at a Glance

Research question: Why was this study conducted?

To evaluate the diagnostic accuracy of microfocus computed tomography as a high-resolution imaging technique for noninvasive autopsy after early gestational fetal loss.

Key Findings

Microfocus computed tomography shows high levels of agreement with conventional autopsy across multiple organ systems in fetal loss or termination of pregnancy (700/718 indices; agreement, 97.5%; 95% confidence interval, 96.6–98.4%).

What does this add to what is known?

The study shows that microfocus computed tomography can provide noninvasive high-resolution imaging 3-dimensional volumes of fetal anatomy that facilitate autopsy and subsequent discussions between medical professionals who are involved in patient care and counselling for future pregnancies.

diagnoses of congenital malformations are being made, subsequently leading to terminations of pregnancy at earlier gestations.[49,50] The combination of limited fetal size and tissue breakdown after in-utero death (termed *maceration*) makes conventional fetal autopsy challenging at lower gestations and fetal bodyweights, in addition to the issue of availability of specialist fetal postmortem examination.[3,51] Availability of high-quality clinical imaging techniques for first- and early second-trimester perinatal postmortem use would realize the parents' need for noninvasive investigation with high diagnostic accuracy and may improve access to a specialist's opinion.

Microfocus computed tomography (micro CT) is an attractive alternative technique in terms of resolution, cost, speed, and accessibility. Micro CT has been used previously to phenotype animal models of disease,[52-54] in maxillofacial research,[55] in archeology,[56] and for nondestructive testing of components within industry. Recently, 3-dimensional imaging of human tissue at histologic resolution has been shown to be possible,[57,58] and feasibility for postmortem imaging of ex-vivo organs and whole fetuses has been demonstrated.[59-61]

In this study, we evaluated the diagnostic accuracy of micro CT for noninvasive human fetal autopsy for early gestation fetuses using conventional autopsy as the reference standard.

Materials and Methods

Case selection

This study was performed as part of an ethically approved larger study that investigated minimally invasive autopsy techniques and novel methods of postmortem imaging (ethical approval numbers CE13/LO/1494 and CE2015/81). All samples were handled in accordance with the Human Tissue Act (2004). Fully informed, written parental consent for conventional autopsy, imaging, and the use of tissue for research was obtained in all cases; all material was handled in accordance with parental instructions. Twenty cases (11–21 weeks gestation; median, 14 weeks gestation) were recruited prospectively from 2 centers that regularly performed postmortem perinatal imaging for formal perinatal autopsy examination between June 2015 and September 2016. The trial conforms to the Standards for Reporting Diagnostic accuracy studies (STARD) statement.[62]

Tissue preparation

After being sampled for cytogenetic investigations (where necessary), fetuses were immersed at room temperature in a solution of 10% formalin (to prevent tissue degradation) and potassium triiodide (I_2KI/Lugol's iodine, to impart tissue contrast), with a total iodine content of 63.25 mg/mL (iodine mass, 2.49×10^{-4} mol/mL), in a 1:1 ratio for 72 hours before imaging. Before being scanned, the specimens were removed from the iodine solution, rinsed in water to remove excess surface iodine, and dried with gauze. Specimens were secured with foam supports (Parafilm M; Bemis, Oshkosh, WI) and carbon fiber rods to ensure mechanical stability during micro CT examination. After micro CT examination, fetuses were deiodinated with the use of sodium thiosulfate pentahydrate dissolved in water (4% wt/vol) for at least 12 hours before autopsy. Fetuses were further fixed in 10% formalin to prevent tissue degradation before autopsy examination when needed.

Micro CT examination

Micro CT images of the specimens were acquired with an micro CT scanner with a multimetal target (XT H 225 ST; Nikon Metrology, Tring, UK). X-ray energies and beam current were 80–110 kV and 87–180 μA, respectively. Exposure times were from 250–354 msec, with the number of projections optimized for the size of the specimen (number of pixels covered within area of interest×1.5) and 1 x-ray frame per projection. When possible, each fetus was scanned 3 times (approximately 19 minutes each; total scan time approximately 57 minutes), to provide 1 overview whole body dataset at lower magnification followed by 2 higher-magnification scans of the brain, and thorax and abdomen. Projection images were reconstructed with modified Feldkamp filtered back-projection algorithms with proprietary software (CTPro3D; Nikon Metrology, Tring, UK) and postprocessed with VG Studio MAX (version 3.0; Volume Graphics GmbH, Heidelberg, Germany). Isotropic voxel sizes varied according to specimen size and magnification achieved and ranged from 7.4–51.0 μm.