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Stillbirth and intrauterine fetal death: role of routine histological organ sampling to determine cause of death

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KEYWORDS:
autopsy; histology; miscarriage; sampling; stillbirth

ABSTRACT

Objectives
Guidelines for the investigation of intrauterine death and sudden unexpected death in infancy (SUDI) recommend, based on expert opinion, autopsy procedures and tissue sampling strategies for histological analysis. Although stillbirth is much more common than SUDI, there have been no large-scale studies published which evaluate the usefulness of histological evaluation of specific organs in stillbirth for determining cause of death. Our aim was to evaluate the use of macroscopic and microscopic assessment of internal organs to determine cause of intrauterine death.

Methods
As part of a larger study evaluating several aspects of autopsy findings in intrauterine death, a dedicated database was used to collate antenatal and postmortem examination details for cases of intrauterine death examined between 2005 and 2013 at two tertiary specialist centers in London, UK. Histological findings for all organs were examined in relation to the final cause of death, as determined by objective criteria.

Results
Among 1064 intrauterine deaths, the majority (>80%) of cases had internal organs that were normal on both macroscopic and microscopic examination. There was no case in which histological cardiac examination provided the cause of death when the macroscopic appearance of the heart was normal. Microscopic examination of lung tissue revealed 13 (1%) cases with

histological abnormalities that provided the cause of death when the macroscopic appearance was normal, but there was only one (0.1%) case in which the diagnosis would not have been apparent on placental examination: a case of congenital cytomegalovirus infection. There was no case in which microscopic examination of macroscopically normal liver, kidneys, adrenals, spleen,

thymus, intestines, pancreas, brain or thyroid provided the cause of death.

Conclusion
In this large series of autopsies in cases of intrauterine death, only around 1% of cases demonstrated histological abnormalities which provided the cause of death when the internal organs appeared normal macroscopically. There was no case in which routine histological examination of most tissues provided diagnostically useful information that was not apparent from other examinations, such as placental pathology. There is little benefit, purely in terms of determining cause of death, in obtaining tissue from most macroscopically normal organs for routine histological examination.

INTRODUCTION

The UK Royal College of Pathologists' guidelines suggest that a wide range of fetal organs should be sampled routinely for histological examination in autopsies carried out for investigation of intrauterine fetal death (IUFD)/stillbirth1. Such guidance is based on expert opinion rather than on demonstrable efficacy from published data. Similarly, the Kennedy Guidelines for the investigation of sudden unexpected death in infancy (SUDI) recommends autopsy procedures and guides pathologists regarding which tissue should be obtained for histological analysis2. Recent data have confirmed the value of routine sampling in SUDI autopsies, but suggest that more limited or targeted sampling would not reduce identification of cause of death3. Stillbirth is much more common than SUDI and yet there have been no large-scale studies evaluating the usefulness of routine histological evaluation of specific organs in determining the cause of death in these cases4.

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 ORIGINAL PAPER

Histological organ sampling and cause of intrauterine death

Routine organ sampling may theoretically lead to detection of specific disease; however, commonly reported causes of death in utero include fetal growth restriction, ascending genital tract infection and 'unexplained', none of which rely particularly on histological analysis of

fetal internal organ tissue for their detection5 10.It may be argued that any ‘exclusion’ diagnosis, such as ‘unexplained’ requires additional and extensive testing, but the decision to perform such investigations is based on the likelihood of tests providing contributory diagnostic information. The aim of this study, therefore, was to evaluate the usefulness of macroscopic and microscopic assessment of internal organs to determine the cause of intrauterine death.

METHODS

As part of a larger study evaluating several aspects of autopsy findings in intrauterine deaths, a customized Microsoft Access Autopsy Database (Microsoft Corp., Redmond, WA, USA) was used to collate antenatal and postmortem examination details for stillbirths (=
24 weeks’ gestation) and second-trimester IUFDs (intrauterine deaths =
23 weeks’ gestation, subdivided into early IUFD (<
20 weeks) and late IUFD (20–23 weeks). Cases were included from Great Ormond Street Hospital and St George’s Hospital, London for the period 2005–2013, with details recorded according to predefined criteria11. Data retrieved for this study included macroscopic and microscopic (histological) features of all organs and tissues examined, as determined by the pathologist at the time of autopsy.

Macroscopic and microscopic examination findings of major organs were categorized into four groups as follows: normal; abnormal but did not contribute to death (e.g. non-specific congestion); abnormal and potentially contributed to death (e.g. mild inflammatory changes); and abnormal and definitive cause of death (documentation of a definite disease process on histological examination,

e.g. cytomegalovirus (CMV) inclusions). Cases in which consent was not provided for specific macroscopic and/or microscopic examination were categorized as ‘not examined’. In some instances, organs were reported as being ‘too autolyzed’ for adequate examination and thus were categorized as such. If an organ was abnormal macroscopically and the microscopic examination provided no additional diagnostic information, such findings were not regarded as having contributed significantly to the cause of death.
Data were analyzed through queries and statistical tests run using Microsoft Access and Microsoft Excel (Microsoft Corp.), GraphPad Prism (GraphPad Software Inc., San Diego, CA, USA) and Stats Direct (StatsDirect Ltd., Altrincham, UK). Comparison of distributions and proportions were carried out using the Mann–Whitney U-test and chi-square test, respectively, as appropriate, with P <
0.05 being considered statistically significant.
The study was approved by the local research ethics committee.

RESULTS

There were 1064 intrauterine deaths in the total study population, including 425 IUFDs (246 early (< 20 weeks' gestation) and 179 late (20–23 weeks)) and 639 stillbirths. In almost all cases, histological examination of internal organs did not provide additional information that was useful in determining the cause of death.

In the majority (81%) of cases, the macroscopic appearance of the heart was normal (Table 1, Figure 1). Stillbirths had the greatest proportion of macroscopic heart abnormalities, but almost all (99%) were minor changes and not the definitive cause of death. Only one case, a stillbirth, had a macroscopic cardiac abnormality that provided the definitive cause of death. Heart histology was also normal in the majority (89%) of cases. Stillbirths had the greatest proportion of microscopic heart abnormalities, but again almost all (98%) were minor abnormalities and were not a definitive cause of death. Only one heart had a microscopic abnormality that provided a definitive cause of death but this was also abnormal macroscopically: Ebstein's anomaly of the tricuspid valve with dilated right atrium. Thus, there was no case in this series in which cardiac histological examination provided the cause of death when the macroscopic appearance was normal.

The majority (79%) of cases had normal macroscopic appearance of the lungs (Table 2, Figure 2) and almost all (98%) abnormalities were minor changes and not the definitive cause of death. In only three cases did the lungs have a macroscopic abnormality that provided a definitive cause of death. Stillbirths had the greatest proportion of microscopic abnormalities of the lungs, but almost all (97%) were minor abnormalities and not the definitive cause of death. In 21 cases there were microscopic abnormalities of the lungs that provided a definitive cause of death. However, most of these (n = 18; 86%) were cases of pneumonia indicating ascending infection; 15 of these cases also had the placenta submitted for examination, all of which demonstrated chorioamnionitis and/or funisitis, hence in these cases lung histology was not required for diagnosis of ascending infection as the cause of death. There were also two cases of CMV infection; only one of these had the placenta submitted for examination and this did not show CMV inclusions. There was one case of cystic pulmonary airway malformation with macroscopically abnormal lung. Therefore, at least 18 (86%) of the 21 cases could have had cause of death identified on placental or macroscopic examination. In 13 (1.2%) cases with macroscopically normal lungs there was abnormal lung histology which provided the cause of death; however, there was only one case in the entire series (0.1%) in which the diagnosis would not have been apparent on placental examination, the single case of congenital CMV infection in which CMV inclusions were not identified in the placental sections.

The majority (86%) of cases had a normal macroscopic appearance of the liver. Stillbirths had the greatest proportion of macroscopic abnormalities of the liver but almost all (99%) were minor changes and not the

598
Man et al.
Table
1
Categorization of results of macroscopic and histological examination of the heart in cases of intrauterine death

Category of finding	Histological findings when Macroscopic findings Early IUFD	Late IUFD	Stillbirth	All	Histological findings macroscopic findings normal Early IUFD	Late IUFD	Stillbirth	All
Normal	234 (95)	153 (85)	480 (75)	867 (81)	240 (98)	160 (89)	547 (85)	947 (89)
Abn, not CoD	4 (2)	13 (7)	104 (16)	121 (11)	0 (0)	5 (3)	41 (6)	46 (4)
Abn, potential CoD	2(<1)	3 (2)	26 (4)	31 (3)	0 (0)	0 (0)	13 (2)	13 (1)
Abn, CoD	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	1 (<1)	1 (<1)
Not examined	4 (2)	10 (6)	28 (4)	42 (4)	4 (2)	12 (7)	32 (5)	48 (5)
Too autolyzed	2 (<1)	0 (0)	0 (0)	2 (<1)	2 (<1)	2 (1)	5 (1)	9 (1)
Total	246	179	639	1064	246	179	639	1064

0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 1 (1) 0 (0) 0 (0) 0 (0) 0 (0) 1 (1) 0 (0) 0 (0) 0 (0) 0 (0) 5 (1) 1 (1) 0 (0) 0 (0) 0 (0) 234 153 480

Data are given as n (%) or n. Early intrauterine fetal death (IUFD) was defined as intrauterine death < 20 weeks, late IUFD was death at 20–23 weeks and stillbirth was death = 24 weeks. Abn, not CoD, abnormal but not cause of death; Abn, potential CoD, abnormal and potentially contributing to death; Abn, CoD, abnormal and definitive cause of death.

Percent of cases

100
90
80
70
60
50
40
30
20
10
0

Normal Abn, not CoD Abn, potential CoD Abn, CoD N/E Autolyzed
Histology

Figure
1
Bar chart of categorized histological findings of the heart when macroscopic heart examination was normal, following early intrauterine fetal death (IUFD) (< 20 weeks,

), late IUFD (20–23
weeks,) or stillbirth (=
24 weeks,

). Histological findings were
categorized as: normal; abnormal but not cause of death (Abn, not
CoD); abnormal and potentially contributing to death (Abn,
potential CoD); abnormal and definitive cause of death (Abn,
CoD); not examined (N/E); or autolyzed.

definitive cause of death. There was only one case of
liver macroscopic abnormality providing the cause of
death. The majority (82%) of liver histology was normal.
Stillbirths had the greatest proportion of microscopic
abnormalities of the liver but almost all (99%) were minor
abnormalities and not the definitive cause of death. There
was only one case in which microscopic examination of
the liver provided the definitive cause of death; however,
in this case the diagnosis would have been made by
examination of the lung and/or the brain (abscesses with
multiple gram-positive bacilli; infection).

The majority of cases had both normal macroscopic
and normal microscopic appearance of the kidneys. Only

two cases had a normal macroscopic appearance and
an abnormal histological appearance which was related
to the cause of death. In both cases there was renal
fetal vascular thrombosis. However, both also showed
extensive placental fetal thrombotic vasculopathy and the
underlying diagnosis would have been identified without
fetal histological sampling.

The majority (61%) of cases had a normal macroscopic
appearance of the brain (Table 3, Figure 3). Stillbirths had
the greatest proportion of macroscopic abnormalities of
the brain, but almost all (98%) were minor changes and
not the definitive cause of death. In six cases, the brain
had macroscopic abnormalities that provided a definitive
cause of death. The majority (57%) of cases had normal
brain histology, but a considerable proportion showed
histological abnormalities. Stillbirths had the greatest
proportion of microscopic abnormalities of the brain,
but almost all (99%) of these were minor abnormalities
and not the definitive cause of death. There were three
cases in which histological examination of the brain
provided a definitive cause of death: a case of massive
subdural and subarachnoid hemorrhage with focal
white-matter cortical hemorrhage; a case of germinal
matrix and periventricular white-matter hemorrhage with
microscopic fresh hemorrhage in the white matter; and a
case of fibrinopurulent leptomeningitis and purulent ventriculitis
with gram-positive organisms present. However,
in this case abnormalities were also present on histology
of both lung and liver and the cases of intracerebral
hemorrhage could have been visualized on postmortem
imaging. The majority of cases had both normal macroscopic
and normal microscopic appearance of the brain.
There was no case in which the macroscopic appearance
was normal with the microscopic examination providing
definitive cause of death. Note that, for the purposes
of this study, minor histological changes indicating a
possible hypoxic–ischemic process, but without further
specific changes to indicate an underlying cause, were
categorized as abnormal but not providing the cause
of death.

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Histological organ sampling and cause of intrauterine death

Table
2
Categorization of results of macroscopic and histological examination of the lungs in cases of intrauterine death

Category of finding	Macroscopic findings			Histological findings			Histological findings when macroscopic findings normal		
	Early IUFD	Late IUFD	Stillbirth	All	Early IUFD	Late IUFD	Stillbirth	All	Early IUFD	Late IUFD	Stillbirth
Normal	235 (96)	159 (89)	448 (70)	842 (79)	198 (80)	100 (56)	198 (31)	496 (47)	196 (83)	96 (60)	172 (38)
Abn, not CoD	1 (< 1)	6 (3)	136 (21)	143 (13)	25 (10)	24 (13)	323 (51)	372 (35)	25 (11)	23 (14)	216 (48)
Abn, potential CoD	4 (2)	3 (2)	25 (4)	32 (3)	14 (6)	32 (18)	72 (11)	118 (11)	13 (6)	28 (18)	50 (11)
CoD											
Abn, CoD	0 (0)	1 (< 1)	2 (< 1)	3 (< 1)	2 (< 1)	8 (4)	11 (2)	21 (2)	1 (< 1)	7 (4)	5 (1)
Not examined	5 (2)	10 (6)	28 (4)	43 (4)	5 (2)	11 (6)	32 (5)	48 (5)	0 (0)	2 (1)	2 (< 1)
Too autolyzed	1 (< 1)	0 (0)	0 (0)	1 (< 1)	2 (< 1)	4 (2)	3 (< 1)	9 (< 1)	0 (0)	3 (2)	3 (< 1)
Total	246	179	639	1064	246	179	639	1064	235	159	448

Data are given as n (%) or n. Early intrauterine fetal death (IUFD) was defined as intrauterine death < 20 weeks, late IUFD was death at 20–23 weeks and stillbirth was death = 24 weeks. Abn, not CoD, abnormal but not cause of death; Abn, potential CoD, abnormal and potentially contributing to death; Abn, CoD, abnormal and definitive cause of death.

Percent of cases

90

80

70

60

50

40

30

20

10

0

Normal Abn, Abn, Abn, N/E Autolyzed
not CoD potential CoD
CoD

Histology

Figure
2
Bar chart of categorized histological findings of lungs when macroscopic lung examination was normal, following early intrauterine fetal death (IUFD) (<
20 weeks,

), late IUFD (20–23
weeks,
) or stillbirth (=
24 weeks,
). Histological findings were categorized as: normal; abnormal but not cause of death (Abn, not CoD); abnormal and potentially contributing to death (Abn, potential CoD); abnormal and definitive cause of death (Abn, CoD); not examined (N/E); or autolyzed. In a minority of cases of IUFD, lung histology demonstrated pneumonia associated with ascending infection or cytomegalovirus infection. There was no case in which histological examination of macroscopically normal adrenals, spleen, thymus, intestines, pancreas or thyroid provided the cause of death.

DISCUSSION

The findings of this large study provide data regarding the clinical utility of macroscopic and microscopic examination for determining the cause of intrauterine death at postmortem examination. The majority of cases

had normal macroscopic and microscopic appearance of the internal organs; this is unsurprising, since with contemporary practice almost all pregnancies undergo detailed sonographic screening for detection of structural anomalies, and hence major anomalies would have been identified or pregnancies terminated prior to presentation with unexpected intrauterine death. Cases of stillbirth showed a greater proportion of macroscopic or microscopic abnormalities than did second-trimester IUFDs, but almost all were non-specific changes that did not provide a cause of death.

In this series of >
1000 autopsies in cases of intrauterine death, there were only 13 (1%) cases in which routine histological sampling of a macroscopically normal organ provided the cause of death and there was no case in which histological examination of the spleen, adrenal glands, thyroid, thymus, intestine or pancreas provided diagnostically useful information. The diagnostic role of routine tissue sampling for the investigation of intrauterine death based on standard histological evaluation in contemporary clinical practice

in developed countries is limited. Furthermore, the vast majority of those cases which did show histological abnormalities could have had the correct cause of death diagnosed without microscopic examination of the fetal organs, based on less invasive investigations such as placental examination. Indeed, initial published data, albeit from a relatively small study12, indicate that non-invasive investigation after death based on postmortem magnetic resonance imaging, together with investigations such as placental histology, external fetal examination and cytogenetics, provide information equivalent to that of a complete invasive autopsy in around 95% of cases of fetal death and termination of pregnancy. Similarly, a review of intrauterine deaths beyond 20 weeks of gestation reported that the most valuable test to help determine the cause of death was examination of the placenta13, and placental examination potentially identifies the cause in many perinatal deaths14.

The strengths of this study are the large number of cases examined and the predefined objective criteria used to standardize classification and reporting. However, a

Ultrasound Obstet Gynecol 2016; 48: 596–601.

600
Man et al.
Table
3
Categorization of results of macroscopic and histological examination of the brain in cases of intrauterine death

Macroscopic findings	Histological findings			Histological findings when macroscopic findings normal			
Category of finding	Early IUFD	Late IUFD	Stillbirth	All	Early IUFD	Late IUFD	Stillbirth	All
Normal	185 (75)	124 (69)	339 (53)	648 (61)	184 (75)	126 (70)	298 (47)	608 (57)
	168 (91)	107 (86)	222 (65)					
Abn, not CoD	16 (7)	25 (14)	200 (31)	241 (23)	10 (4)	23 (13)	206 (32)	239 (22)
	4 (2)	11 (9)	82 (24)					
Abn, potential CoD	5 (2)	6 (3)	35 (5)	46 (4)	3 (1)	7 (4)	52 (8)	62 (6)
	0 (0)	2 (2)	17 (5)					
Abn, CoD	0 (0)	0 (0)	6 (1)	6 (1)	0 (0)	0 (0)	3 (< 1)	3 (< 1)
	0 (0)	0 (0)	0 (0)					
Not examined	15 (6)	13 (7)	49 (8)	77 (7)	23 (9)	16 (9)	64 (10)	103 (10)
	3 (2)	3 (2)	9 (3)					
Too autolyzed	25 (10)	11 (6)	10 (2)	46 (4)	26 (11)	7 (4)	16 (3)	49 (5)
	10 (5)	1 (1)	9 (3)					
Total	246	179	639	1064	246	179	639	1064
	185	124	339					

Data are given as n (%) or n. Early intrauterine fetal death (IUFD) was defined as intrauterine death < 20 weeks, late IUFD was death at 20–23 weeks and stillbirth was death = 24 weeks. Abn, not CoD, abnormal but not cause of death; Abn, potential CoD, abnormal and potentially contributing to death; Abn, CoD, abnormal and definitive cause of death.

Percent of cases

100
90
80
70

60
50
40
30
20
10
0

Normal Abn, Abn, Abn, N/E Autolyzed
not CoD potential CoD
CoD
Histology

Figure
3
Bar chart of categorized histological findings of the brain when macroscopic brain examination was normal, following early intrauterine fetal death (IUFD) (<
20 weeks,

), late IUFD
(20–23 weeks,) or stillbirth (=
24 weeks,

). Histological
findings were categorized as: normal; abnormal but not cause of death (Abn, not CoD); abnormal and potentially contributing to death (Abn, potential CoD); abnormal and definitive cause of death (Abn, CoD); not examined (N/E); or autolyzed. There was no case in which histological examination of a macroscopically normal brain provided a definitive cause of death.

weakness, as with any autopsy study, is the lack of any objective gold standard regarding cause of death. Furthermore, it should be highlighted that these data apply strictly to cases presenting with intrauterine death in current clinical practice. Almost all such cases will have undergone routine antenatal screening for aneuploidy and ultrasound screening for fetal abnormality. Therefore, these conclusions are not likely to be representative of autopsy practice for terminations of pregnancy for fetal abnormality or in healthcare systems in which antenatal

care is less structured or based on a different model. Furthermore, it should be emphasized that here we have highlighted findings which influence directly the cause of death. The presence of certain histological abnormalities, although insufficient to indicate a cause of death, may still be of importance for research studies and other applications, since they may provide indicators regarding underlying mechanisms.

Nevertheless, our main findings suggest that, for most intrauterine deaths, if fetal organs are macroscopically normal and the placenta is available for histological examination, there is limited benefit, in terms of determining cause of death, from obtaining tissue from a range of internal organs for routine histological examination. This contrasts with the situation in SUDI, in which histological examination of heart, lungs, liver and kidney is the single most useful investigation for determination of cause of death, even when such organs appear normal macroscopically3. This discordance is because the underlying causes of death differ in SUDI

compared with death in utero: localized and systemic infection and metabolic disease are causes of death for which tissue diagnosis is essential in SUDI, whereas many cases of intrauterine death are likely to be a consequence of functional placental abnormalities, for which visceral markers have not yet been identified.

While here we have focused on the stratification of histological abnormalities by their immediate relevance to cause of death, in some scenarios, combinations of non-fatal histological abnormalities may imply a mode of death. Examples include increased fat deposition within fetal adrenal glands and various degrees of thymic involution, which may be associated with fetal physio

logical ‘stress’15, meconium staining of placental membranes and fetal skin associated with fetal distress in preterm gestations18,19, and eosinophilic neurones in association with prenatal hypoxia20,21. However, the significance of these findings for future patient management in cases of intrauterine death remains undetermined.

Finally, it should be noted that these data are retrospective, and based on routine histological examination of

Ultrasound Obstet Gynecol 2016; 48: 596–601.

hematoxylin and eosin-stained sections. The lack of utility of such a process to currently determine the cause or mechanism of death does not necessarily indicate absence of value of tissue sampling in this scenario. On the contrary, it is likely that with development of novel laboratory tests based on genomic, metagenomic, proteomic and metabolomic techniques, the requirement for tissue sampling for ancillary investigations may increase. However, the subsequent handling and use of such tissue may be different from those in current practice. In order to improve our understanding of the mechanisms of intrauterine death, and to provide appropriate, scientifically valid information for patients and parents, investigation after death should be based on evidence, and must focus on developing aspects which will allow improved diagnostic accuracy.

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