Investigating perinatal death: a review of the options when autopsy consent is refused

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Autopsy remains the best method of investigating perinatal deaths. Recent years have, however, seen a decline in autopsy rates. This review looks at some of the options available for investigating perinatal deaths when the family decline to give consent for standard autopsy.

The information provided by perinatal autopsy has important implications both for families and for maintaining standards of care, and remains the best method of investigating fetal loss, stillbirth, and neonatal death. There has been a gradual fall in autopsy rates in recent years, and the reasons for this probably include changing cultural and societal views towards death, the body of the deceased, and the autopsy procedure itself and a decline in healthcare professionals’ understanding of the value of the autopsy. The recent controversies surrounding the issue of organ retention are also likely to have had an impact. Nonetheless, recent national figures show autopsy rates for stillbirths of 58% and neonatal deaths of 41%, which are considerably higher than those for adults and reflect a continuing recognition of the important benefits of the procedure in the perinatal period.

The standard perinatal autopsy allows identification of a huge range of fetal and neonatal disorders. The focus of the investigation is tailored to the particular clinical circumstances, but the basic methods available in all cases include:

- External examination of the baby
- Examination of the internal organs
- Examination of the placenta and cord
- Imaging
- Supplementary laboratory investigations such as microbiology and cytogenetics
- Metabolic studies

Although internal organ examination represents only one step in the process, its importance lies in the fact there is currently no other way of reliably obtaining the detailed and crucial information it provides. This comes in particular from:

- Internal organ weights. These allow accurate assessment of intrauterine growth restriction, organomegaly syndromes—for example, diabetes—and disordered growth of individual organs.
- Detailed macroscopic and histological examination of internal organs. Clearly, direct macroscopic examination of the organs permits detection of major malformations, iatrogenic disease, etc. The diagnosis of infection, assessment of hypoxic injury (particularly of the brain), and identification of many types of malformation/dysplasia and metabolic disease are largely dependent on histology. A combination of macroscopic (cerebral gyral pattern) and histological (lung, kidney) appearances is used to aid assessment of gestational age.

Clearly, for many of those families not willing to give consent to a standard autopsy their major objection is to this invasive step of internal organ examination. However, this should not necessarily preclude any postmortem investigation as other options are available, and, although none can replace the standard autopsy, they may provide useful information. In addition to limiting the autopsy to particular organs or body cavities, these options include the non-invasive components of the standard postmortem examination (external and placental examination and radiology) and other methods for assessing internal organ morphology, such as magnetic resonance imaging (MRI) and needle biopsy. The aim of this article is to review the potential benefits of these non-invasive or less invasive methods of investigation.

EXTERNAL EXAMINATION

Many non-pathologists are unaware of the importance of detailed external examination after perinatal loss. In addition to assessment of gestational age from basic external measurements and identification of dysmorphic features, a large range of other features can be evaluated. These include: nutritional status—for example, growth restriction or macrosomia; degree of autolysis (timing of intrauterine death); odour (presence of infection); soft tissue oedema (generalised, localised); pallor—for example, fetomaternal bleeding; the presence of meconium staining, jaundice, petechiae; traumatic and other iatrogenic lesions. If a perinatal pathologist or clinical geneticist is not immediately available, abnormalities can be photographed for later review.

PLACENTA AND UMBILICAL CORD

These structures are of course part of the conceptus and it is often overlooked that examining them can help to establish the sequence of events leading to perinatal death. For example, it may show the cause (and give an estimate of the time of onset) of hypoxic/ ischaemic insults. There may be evidence of
ascending or haematogenous infection, and specific organ-
isms can be identified using special staining techniques, 
imunohistochemistry, and in situ hybridisation. Assessment of 
chorionicity is clearly important in multiple pregnancy. 
Histological examination of the placenta may give the first 
clue to an underlying inborn error of metabolism.7 Fibroblasts 
prepared from placental tissue can be used for metabolic 
studies as well as cytogenetic investigations, and provide a 
source of DNA for molecular biological studies.

Therefore after perinatal death (and also when infants are 
born alive but in poor condition), the placenta and cord 
should wherever possible be sent for pathological examina-
tion. Increasingly, the findings are required to resolve issues 
rised during medicolegal investigation.

RADIOGRAPHY

Many pathology departments providing a perinatal pathology 
service now have dedicated x ray cabinets for radiography. 
This allows a variety of skeletal and soft tissue abnormalities 
to be identified, many of which are not readily detectable by 
any other method (table 1).

The appearance of ossification centres and measurement of 
long bone lengths can give a rough guide to gestational age, 
particularly after 24 weeks gestation, and this is helpful 
when the more precise information available from internal 
examination (cerebral gyral development, organ histology) is 
not available.5 7 8 Refinements to these methods have been 
suggested in recent papers9 10 and require further evaluation.

Table 1 summarises the findings from reported series of 
fetal and infant postmortem radiography. Most reports are 
largely descriptive and all except one hospital based. The 
proportion of cases with radiological abnormalities varies 
considerably from series to series, depending partly on the 
degree of case selection and also on whether non-skeletal 
abnormalities are included. In several reports,11 17–19 an 
attempt is made to quantify the clinical value of the 
examination, but only Olsen et al20 attempt to provide 
reproducible criteria (in their series, the degree to which 
the abnormality specifically informs the cause of death). Four 
papers have compared cases with and without external 
malformations,15 17–20; not surprisingly more skeletal abnorm-
ations occur in the former group, and Grisom and Driscoll12 
and Cremin and Draper14 recommend restricting radiography 
to these cases.

Table 1 Information provided by postmortem radiology

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
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<tbody>
<tr>
<td>Gestational age assessment</td>
<td></td>
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<tr>
<td>Skeletal malformation</td>
<td></td>
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<tr>
<td>(a) Dysplasia</td>
<td></td>
</tr>
<tr>
<td>(b) Dysostoses (eg defects of limbs, ribs, vertebrae)</td>
<td></td>
</tr>
<tr>
<td>Skeletal trauma (birth, other)</td>
<td></td>
</tr>
<tr>
<td>Other bone disease (eg infection, metabolic bone disease of prematurity)</td>
<td></td>
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<tr>
<td>Extraskeletal mineralisation, for example</td>
<td></td>
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<tr>
<td>– Insipissated intestinal contents (secondary to obstruction)</td>
<td></td>
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<tr>
<td>– Hepatic calcification (hypoxia, infection, etc)</td>
<td></td>
</tr>
<tr>
<td>– Mecumum peritonitis</td>
<td></td>
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<tr>
<td>– Idiopathic arterial calcification of infancy</td>
<td></td>
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<tr>
<td>Abnormal gas accumulations, for example</td>
<td></td>
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<tr>
<td>– Body cavities</td>
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<td>– Pulmonary interstitial emphysema</td>
<td></td>
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<td>– Surgical emphysema</td>
<td></td>
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<tr>
<td>– Intravascular</td>
<td></td>
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<tr>
<td>Necrotising enterocelitis</td>
<td></td>
</tr>
<tr>
<td>Positioning of cannulae, drains, etc</td>
<td></td>
</tr>
<tr>
<td>Additional information from contrast radiography</td>
<td></td>
</tr>
<tr>
<td>Definitive record of skeletal morphology</td>
<td></td>
</tr>
</tbody>
</table>

However, the autopsy rates (where stated) in table 2 are 
very high (100% in many), and only one paper has tried to 
specifically assess the value of radiography when internal 
organ examination is declined: Winter and Sandin20 reported 
that the radiograph “aided assessment” in six of 100 cases 
where there was both no autopsy and no external malforma-
tion. Clearly, if malformations are noted externally, radi-
ographs can show the type and extent of any associated 
skeletal abnormality; for many skeletal dysplasias radiology 
is the single most important diagnostic investigation.11 12 But 
even if there are no external dysmorphic features, when 
autopsy is declined, radiography will exclude most skeletal 
abnormalities and (as table 1 suggests) may provide 
important clues to the underlying disease processes. As an 
example, vertebral body anomalies are associated with 
malformations of other organs such as the heart.21 In their 
study of 137 consecutive perinatal autopsies, Gronvall and 
Graem22 noted “major” radiological abnormalities in 12 (9%), 
including anomalies of spinal vertebral bodies in eight cases, 
of which five had malformations of other internal organs; 
only three of the eight showed external dysmorphism.

To conclude, consent for radiography should be sought in 
all cases where standard autopsy is declined.

CONTRAST RADIOGRAPHY

This technique has been used to show a variety of internal 
malformations, particularly those involving the heart and 
vessels.12 15 19 20–22 Although it is time consuming and presents 
challenges in execution and interpretation (and because of 
this is perhaps underused), it should be considered when full 
autopsy is declined and malformation is suspected, particu-
larly when other imaging modalities such as MRI are not 
available.

ULTRASOUND AND COMPUTED TOMOGRAPHY

Scanning

Although ultrasound is widely used in life, particularly for 
the assessment of neonatal central nervous system pathology, 
there have been few studies of its use after death. In a 
descriptive report of perinatal cases, Furness et al23 noted the 
potential for delineating internal anatomy and guiding needle biopsy. Farina et al24 recently reported their experience 
using a combination of ultrasound and ultrasound guided 
needle biopsy in 100 adult autopsies and claim an 83% concordance rate with standard autopsy for the cause of 
death; or main pathological diagnosis; the value of this 
approach after perinatal death remains to be fully evaluated.

There do not appear to have been any systematic studies of 
the use of computed tomography scanning as an alternative 
to standard perinatal (or adult) autopsy.

MRI

MRI produces high resolution images of internal organs and 
is therefore potentially valuable in postmortem investigation. 
Four prospective studies have correlated MRI and standard 
perinatal autopsy findings.

The feasibility of the method was shown by Ros et al25 in 
examinations of three stillbirths, one neonatal death, and 
two adult deaths. Brookes et al26 examined a series of 20 cases 
including miscarriages, terminations for malformation, still-
births, and neonatal deaths. They detected a variety of macroscopic lesions, and highlighted the potential advan-
tages of MRI in delineating major abnormalities of the 
central nervous system in situ when, for example, autolytic 
softening has made routine autopsy examination technically 
difficult. Although MRI and standard autopsy were said to be 
“of similar clinical significance” in 18 of the 20 cases (90%), 
the validity of this claim is doubtful because it is based on the 
incorrect assumption that MRI and standard autopsy provide
the same level of diagnostic information. For example, a report of negative findings at standard autopsy means that infection, hypoxic injury, organ dysplasia, and metabolic disease have been excluded, but negative findings at MRI do not allow similar conclusions to be drawn.

The other two studies focused on the identification of malformations. Woodward et al.37 examined 26 consecutive fetuses and neonates. All underwent standard autopsy, which showed 47 major and 11 minor malformations (‘‘minor’’ included anomalies such as horseshoe kidney and annular pancreas). MRI films were reviewed independently by three radiologists, all of whom identified 37 of the major malformations (detection rate 79%) and one of the minor malformations (detection rate 91%). One radiologist had a detection rate of 91% for the major malformations. Four major anomalies not identified by any of the reviewers were hypoplastic left heart, tetralogy of Fallot, ileocaecal valve atresia, and oesophageal atresia. Six false positive MRI diagnoses were made. The potential benefits of MRI in detecting and guided biopsy of macroscopic abnormalities of the central nervous system were noted.

In the most recent study,10 10 consecutive fetuses were examined after termination of pregnancy for malformation. MRI and autopsy both confirmed the major antenatal ultrasound findings that had prompted the decision to terminate the pregnancy. Autopsy provided additional information in six cases, which informed risk counselling in two. Two other recent small series (n < 10) have compared MRI and autopsy in adult deaths.13–14

These studies suggest that MRI has a potential role in confirming, detecting, or excluding major malformations and other relatively large structural abnormalities, and may be particularly helpful in assessing malformations of the central nervous system. Identifying cardiovascular anomalies has proved problematic,35 36 although improvements may come through technical advances such as three dimensional MRI.37–39 However, as postmortem MRI does not identify all malformations and does not detect the changes at a histological level that are the hallmark of many perinatal diseases (infection, hypoxia, organ dysplasia, metabolic disease, etc), it cannot be used as a substitute for standard autopsy. Its value in assessing cases when there is an advanced degree of autolysis/maceration (a common situation) is also unknown. definitive assessment of the value of MRI awaits studies comparing it with standard autopsy in large series that include the full spectrum of perinatal disease, perhaps in combination with needle biopsy of internal organs. Of course, the availability of MRI services is another important consideration: many departments are simply not in a position to offer this facility after death.

### LIMITED AUTOPSY AND LAPAROSCOPIC AUTOPSY

Families may be willing to give consent to standard autopsy that is restricted to certain parts of the body. For example, examination of the thoracic contents will allow confirmation of cardiovascular malformations or the presence of pneumonia or other lung disease. Specific diagnostic concerns can therefore be resolved in this way, but it always has to be borne in mind that pathological processes in the perinatal period (such as malformation) very often involve multiple organ systems.

An alternative approach used in adult postmortem investigation is the use of endoscopes or laparoscopes. In addition to case reports, a small number of centres have described their experience with this technique in autopsy series.40–42 When standard autopsy consent is withheld, it allows detection and guided biopsy of macroscopic abnormalities visible within body cavities or hollow viscera. There are no reports of its use in the perinatal period, and clearly there are technical issues to be considered, but there may be potential benefit in selected cases of perinatal loss.

### SKIN BIOPSY, NEEDLE BIOPSY, AND ASPIRATION OF BODY FLUIDS

Fibroblasts cultured from skin and placenta can be used for cytogenetic and metabolic studies. Many units now have protocols for handling the tissue samples, which should be refrigerated (not frozen) if there is likely to be a delay in their despatch—for example, over a weekend.

Trucut biopsies or open biopsies through small incisions, particularly from large accessible organs such as liver or lungs, may allow diagnostic histological or metabolic studies; this can be combined with aspiration of blood, cerebrospinal fluid, urine, or other fluids for microbiological and metabolic investigations.43–45 However, reported series of such ‘‘needle autopsies’’ do not include perinatal deaths, where a more widespread sampling of internal organs for histological examination would be required to adequately assess gestational age, infection, dysplasia, etc. Given the small size of many of the organs, the practicality and value of this approach (perhaps in combination with MRI) remains to be evaluated, but biopsy of individual organs clearly has a role in selected cases.

Where there is a strong clinical suspicion of metabolic disease, the case should be discussed with a metabolic physician or appropriate laboratory staff to obtain advice on

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**Table 2  Studies of perinatal postmortem radiography**

<table>
<thead>
<tr>
<th>Study</th>
<th>Case selection</th>
<th>Autopsy rate</th>
<th>Case mix</th>
<th>Radiographs with abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ryan &amp; Kozlowski et al</td>
<td>109 autopsy</td>
<td>Not stated</td>
<td>SB, NND</td>
<td>Skeletal 17%</td>
</tr>
<tr>
<td>Foote et al</td>
<td>2500 autopsy</td>
<td>Not stated</td>
<td>SB, NND</td>
<td>18%</td>
</tr>
<tr>
<td>Griscam &amp; Driscoll</td>
<td>Series A (unselected): 238 cases</td>
<td>Not stated</td>
<td>Fetal (20 weeks-term), NND</td>
<td>18% (series A), 75% (series B)</td>
</tr>
<tr>
<td>Cremin &amp; Draper</td>
<td>100 autopsy</td>
<td>89%</td>
<td>SB, NND</td>
<td>Not stated</td>
</tr>
<tr>
<td>Winter &amp; Sandin</td>
<td>489 autopsy</td>
<td>77%</td>
<td>SB, NND</td>
<td>Soft tissue 21%, skeletal 18%, “useful or diagnostic” 16%</td>
</tr>
<tr>
<td>Seppersen et al</td>
<td>514 autopsy</td>
<td>100%</td>
<td>SB, NND</td>
<td>30%</td>
</tr>
<tr>
<td>de la Fuente et al</td>
<td>234 autopsy</td>
<td>100%</td>
<td>Fetal (14 weeks-term), NND</td>
<td>21%, “essential” 2.1%</td>
</tr>
<tr>
<td>Kalifa et al</td>
<td>400 autopsy</td>
<td>Not stated</td>
<td>Fetal (11 weeks-term)</td>
<td>“Valuable for diagnosis” 13.5%, “additional information” 34.5%</td>
</tr>
<tr>
<td>Gronwall &amp; Graem</td>
<td>137 autopsy</td>
<td>100%</td>
<td>Fetal (8 weeks-term), NND</td>
<td>59%, “major” 9%</td>
</tr>
<tr>
<td>Olsen et al</td>
<td>542 autopsy</td>
<td>100%</td>
<td>Fetal (16 weeks-term), NND</td>
<td>30%, “vital” 3.1%</td>
</tr>
</tbody>
</table>

SB, Stillbirth; NND, neonatal death.
the locally preferred tissue or fluid samples. As a minimum, the following are suggested: **blood (spots on Guthrie card for acylcarnitines; frozen plasma; frozen EDTA sample for DNA); frozen urine; frozen liver and muscle; skin for fibroblast culture.**

**CONCLUSIONS**

- Standard autopsy provides the only means of fully investigating fetal loss, stillbirth, and neonatal death, and it is a family’s right to have the opportunity to give consent.
- Restricting the autopsy to particular body cavities or organs limits the information available but allows specific questions to be addressed and may be more acceptable to some families.
- When families do not wish to give consent for any direct macroscopic and histological examination of the internal organs, valuable information for counselling andaudit may be obtained from external examination, placental/cord examination, radiology, and, in selected cases, MRI, tissue biopsy, and aspiration of body fluids.
- Radiology should be undertaken if possible in all cases where full autopsy is declined, and is particularly important when there is obvious or suspected malformation.
- MRI can detect some malformations and other macroscopic lesions. It cannot, however, function as a substitute for standard autopsy.
- If the clinical history suggests a possible metabolic disease, tissue and fluid samples may allow diagnosis.
- If in doubt, discuss the case with a perinatal pathologist!

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