



Guidelines on autopsy practice: Neonatal death

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For full details on our accreditation visit: www.nice.org.uk/accreditation.

Foreword

The autopsy guidelines published by the Royal College of Pathologists (RCPATH) are guidelines that enable pathologists to deal with non-forensic consent and coroners' post-mortem examinations in a consistent manner and to a high standard. They may contain some distressing information and as such are not intended for a lay audience.

The guidelines are systematically developed statements to assist the decisions of practitioners and are based on the best available evidence at the time the document was prepared. Given that much autopsy work is single observer and one-time only in reality, it has to be recognised that there is no reviewable standard that is mandated beyond that of the FRCPATH Part 2 exam or the Certificate of Higher Autopsy Training (CHAT). Nevertheless, much of this can be reviewed against ante-mortem imaging and other data. These guidelines have been developed to cover most common circumstances. However, we recognise that guidelines cannot anticipate every pathological specimen type and clinical scenario. Occasional variation from the practice recommended in this document may therefore be required to report a specimen in a way that maximises benefit to pathologists, the coroner and the deceased's family.

There is a general requirement from the General Medical Council (GMC) to have continuing professional development in all practice areas and this will naturally encompass autopsy practice. Those wishing to develop expertise/specialise in pathology are encouraged to seek appropriate educational opportunities and participate in the relevant external quality assurance scheme.

The guidelines themselves constitute the tools for implementation and dissemination of good practice.

The following stakeholders were contacted to consult on this document:

- Human Tissue Authority (HTA) and its Histopathology Working Group, which includes representatives from the Association of Anatomical Pathology Technology, the Institute of Biomedical Science, the Coroners' Society of England and Wales, the Home Office Forensic Science Regulation Unit and Forensic Pathology Unit, and the British Medical Association
- British and Irish Paediatric Pathology Association
- Sands (Stillbirth and Neonatal Death Charity)
- Royal College of Obstetricians and Gynaecologists
- British Association of Perinatal Medicine.

The information used to develop this document was derived from current medical literature. As far as possible, this guideline is based on published evidence, but where this does not exist it represents custom and practice, and is based on the substantial clinical experience of the authors and colleagues. All evidence included in this guideline has been graded using modified SIGN guidance (see Appendix B).

No major organisational changes or cost implications have been identified that would hinder the implementation of the guidelines.

A formal revision cycle for all guidelines takes place on a five-year cycle. The College will ask the authors of the guideline to consider whether or not the guideline needs to be revised. A full consultation process will be undertaken if major revisions are required. If minor revisions or changes are required, an abridged consultation process will be undertaken whereby a short note of the proposed changes will be placed on the College website for two weeks for members' attention. If members do not object to the changes, the changes will be incorporated into the guideline and the full revised version (incorporating the changes) will replace the existing version on the College website.

The guideline has been reviewed by the Clinical Effectiveness department, Death Investigations Group and Lay Governance Group and was placed on the College website for consultation with the membership from 6 March to 3 April 2018. All comments received from the membership were addressed by the authors to the satisfaction of the Clinical Lead for Guideline Review.

The guideline was developed without external funding to the writing group. The College requires the authors of guidelines to provide a list of potential conflicts of interest; these are monitored by the Clinical Effectiveness department and are available on request. The authors of this document have declared that there are no conflicts of interest.

1 Introduction

Post-mortem examination of a baby following a neonatal death may provide a cause of death or, at the least, provide a partial explanation of the death.¹⁻³ Autopsy is the single most useful investigation and provides information that changes or significantly adds to the clinical information in nearly half of cases.^{4,5} The autopsy is also a valuable audit of clinical care and may facilitate learning from adverse events.

These guidelines have been created to assist the pathologist undertaking autopsies in cases of neonatal death (death within the first 28 days of birth). It provides practical technical advice on performing the autopsy, guidance on the use of additional investigations and minimum standards for the content of the autopsy report. It is intended as a guide to reasonable practice, rather than a policy statement. If followed, the output from the autopsy should be sufficient to provide useful feedback to the family, to the clinicians involved in the case and for local and national audit. Where possible, references are provided, but it is inevitable that many of the suggestions are based on common UK practice rather than on published evidence, as the latter is often non-existent or sparse. Many pathologists have adopted approaches based on their own experience, evidence and resources, which may differ from these guidelines but which achieve the same outcome. This document does not aim to change such approaches. In addition, the document is not intended as a replacement for standard textbooks, but highlights the principles of undertaking and reporting perinatal autopsies. For detailed guidance on undertaking the autopsy in specific circumstances, the reader is referred to the 'Further reading' list in section 18.

In England, Wales and Northern Ireland, autopsy facilities and procedures must be covered by appropriate licences (issued by the HTA) and consent procedures must be compliant with the relevant HTA *Code of Practice*.⁶ Separate legislation applies in Scotland that does not impose a system of licensing.

Many cases will be performed on the instruction of a coroner/procurator fiscal and are therefore also governed by the appropriate regulations.

Many of the aetiological and pathogenetic factors that are important in intrapartum stillbirth are clearly also relevant to neonatal death, and thus, there is considerable overlap in the approach to these two situations (see *Guidelines on Autopsy Practice: Third Trimester Antepartum and Intrapartum Stillbirth*).⁷

1.1 Target users of these guidelines

The target primary users of these guidelines are UK consultant and trainee perinatal/paediatric pathologists and general histopathologists with an interest in perinatal pathology. The recommendations will also be of value to pathologists working outside the UK, obstetricians, neonatal paediatricians, anatomical pathology technicians working in a paediatric/perinatal mortuary and bereavement midwives.

2 The role of the autopsy

The role of the autopsy is:

- to establish factors (in utero, intra- and post-partum) contributing to death and, if possible, the immediate cause of death
- to identify concomitant diseases, particularly those with implications for subsequent pregnancies (e.g. growth restriction, malformation, maternal diabetes)
- to confirm or exclude iatrogenic disease, including both birth trauma and complications of neonatal management
- to provide information for audit purposes (e.g. cranial ultrasound).

3 Pathology encountered at autopsy

- Effects of hypoxia (occurring ante-, intra- or post-partum), in particular hypoxic-ischaemic encephalopathy.
- Growth restriction: symmetric, asymmetric (nutritional).
- Infection (predominantly septicaemia, pneumonia, meningitis): acquired in utero or post-partum, including infections complicating invasive neonatal management.
- Congenital malformation.
- Neurodevelopmental/neuromuscular disease.
- Pulmonary hypoplasia.
- Complications of prematurity, including:
 - hyaline membrane disease and its sequelae
 - central nervous system (CNS) disease (germinal matrix haemorrhage, white matter infarction/periventricular leukomalacia)
 - necrotising enterocolitis, etc.
- Iatrogenic disease:
 - birth trauma: cranial, extracranial
 - due to neonatal management: intubation/ventilation, chest drains, vascular access, medication, etc.
- Blood loss (in utero/neonatal, external/internal).
- Hydrops.
- Effects of maternal disease e.g. diabetes, hypertension/pre-eclampsia.
- Metabolic disease e.g. urea cycle defect, fatty acid oxidation defect.
- Placental and umbilical cord disease (see *Guidelines on Autopsy Practice: Third Trimester Antepartum and Intrapartum Stillbirth*).⁷

4 Specific health and safety aspects

The pathologist needs to know the results of the antenatal infection screens.

Appropriate precautions should be in place to reduce the risk of accidental transmission of infections such as HIV and hepatitis C.

5 Authorisation for autopsy

Since a baby dying in the neonatal period has, by definition, been born alive, consideration should be given to whether the death should be referred to the coroner (in England, Wales and Northern Ireland) or procurator fiscal (in Scotland). In other countries, local rules for referral to the legal authorities should be followed.

5.1 Legal (coronial/fiscal) autopsy

There is a legal requirement to refer any deaths that fall under their jurisdiction to the local coroner/procurator fiscal.⁸ These include any death where a death certificate cannot be issued by a medical practitioner (i.e. the cause of death is unknown or uncertain) or if the death may have been the result of an accident (including medical) or malicious act.

If the coroner/procurator fiscal determines that an autopsy is necessary, he/she will instruct a pathologist to undertake it on his/her behalf. As such, the autopsy must be performed in line with the Coroner's Rules⁹ or other relevant legislation. The resulting report is the property of the coroner/procurator fiscal and should not be released to any other party without express authorisation.

5.2 Consented autopsy

Deaths falling outside the Coroner's/Procurator Fiscal's jurisdiction may undergo a consented autopsy and this may be appropriate where there are unanswered clinical questions, despite a clear cause of death.

Consented autopsy examination may only be performed with the informed consent of the parents or, in the unlikely event of their absence, by a person in a qualifying relationship as defined by the HTA *Code of Practice (Code A: Guiding Principles and the Fundamental Principle of Consent)*.⁶ In Scotland, consent should be given by the nearest relative as defined in section 50 of the Human Tissue (Scotland) Act 2006.

In England, Wales and Northern Ireland, the consent process should be compliant with the requirements of the HTA's *Code of Practice. Code A: Guiding Principles and the Fundamental Principle of Consent*.⁶

Similar but separate regulations apply in Scotland under the Human Tissue (Scotland) Act 2006.

The autopsy consent form should be compliant with the model Consent Form for Perinatal Post Mortem developed by Sands, the Stillbirth and Neonatal Death Charity, in consultation with the HTA.¹⁰ In Scotland the authorisation form 'Authorisation for the Hospital Post-Mortem Examination of a Child Under 12 Years of Age' should be used.

The pathologist performing the autopsy must see the completed consent form, either as a physical copy or electronically, before commencing the autopsy. Any limitations on the scope of the autopsy must be complied with.

Any concerns about the validity of the consent should be resolved before commencing the autopsy.

[Level of evidence – D].

6 Clinical information relevant to the autopsy

A detailed summary of the obstetric and neonatal history (e.g. neonatal discharge summary) should normally be supplied to the pathologist before the post mortem. If this is not possible, the neonatal and obstetric hospital notes should be made available (where relevant). Alternatively, a structured request form may be employed (see Appendix A).

Information required is as per *Guidelines on Autopsy Practice: Third Trimester Antepartum and Intrapartum Stillbirth*,⁷ as well as:

- condition at birth (cord pH, Apgar scores, etc.)
- clinical course following delivery, including methods of resuscitation and intensive care (including use of chest drains and vascular cannulas)
- main postnatal problems
- results of relevant investigations
- events leading up to death
- clinical cause of death.

[Level of evidence – GPP.]

7 The autopsy procedure

- Requires availability of appropriately sized instruments; balances for weighing body (i.e. up to approximately 6 kg) and organs (to nearest 0.1 g); charts of normal values (baby and placenta).
- Whole body X-ray for gestational assessment, malformation, etc. recommended in all cases; mandatory for suspected skeletal dysplasia. If available, this may be replaced by other imaging modalities e.g. computed tomography (CT), magnetic resonance imaging (MRI).
- Photography recommended in all cases, essential to document external and internal abnormalities. Digital photography and secure storage preferred.
- Routine external body measurements (at least: body weight, crown–rump length, crown–heel length, foot length, occipitofrontal circumference).
- Detailed external examination, including: nutritional status/soft tissue and muscle bulk; presence of oedema (localised/generalised), pallor, meconium staining, jaundice or dysmorphism; evidence of trauma, siting of chest drains and vascular cannulae and other iatrogenic lesions. Report should include a description of external morphology mentioning specifically: fontanelles, eyes, ears, nose, patency of choanae, palatal fusion, spine, limbs, digits, palmar creases, external genitalia, patency of anus, umbilical cord.
- Longitudinal skin incision on front of body (typically T- or Y-shaped); measurement of fat thickness over sternum (if appropriate).
- CNS examination:
 - median posterior or transverse scalp incision
 - skull incisions to allow assessment of falx and venous sinuses
 - assessment of falcine and tentorial injury and meningeal haemorrhage
 - examination for skull fracture or occipital osteodiastasis
 - exclusion of spinal injury by posterior approach

- if suspected CNS malformation (including ventriculomegaly), examination of posterior fossa structures by posterior approach
- observation of gyral pattern to assist gestational assessment
- consider removal under water
- consider referring the whole CNS for neuropathological examination in appropriate cases. This may include sampling peripheral nervous tissue (nerve root, peripheral nerve, muscle, etc.). Consulting the neuropathology team may be helpful if there is doubt about sampling.

[Level of evidence – GPP.]

- Detailed systematic examination of other internal organs, including:
 - identification of pneumothorax (consider chest incision under water)
 - positioning of chest drains
 - umbilical arteries and vein, ductus venosus (exclude trauma/thrombosis secondary to cannulation, document position of cannula tips and evidence of vascular trauma)
 - in situ examination of the heart and great vessels with sequential segmental analysis of malformations
 - thoracic and abdominal organs removed in continuity or in blocks (if the latter, care is needed to assess structures [normal and abnormal] crossing diaphragm)
 - weights of all major organs including thymus.

[Level of evidence – GPP.]

- Detailed examination of placenta and umbilical cord (as per *Guidelines on Autopsy Practice: Third Trimester Antepartum and Intrapartum Stillbirth*)⁷ can be helpful in assessing aetiology and time of onset of infection or hypoxic-ischaemic encephalopathy; this may be of benefit in resolving issues of medicolegal interest. Placentas should be sent for examination when a baby is born preterm and/or in poor condition (and requires admission to the neonatal intensive care unit), or when there is evidence of infection, growth restriction, hydrops or other significant abnormalities. Some units have mechanisms in place to allow short-term storage of placentas so that they can be retrieved if infants become unwell in the neonatal period.

[Level of evidence – C.]

Note: Ward staff should be asked to leave cannulas, drains, etc. in situ as far as possible, to allow assessment of their internal disposition. They can be cut flush with the skin if necessary.

8 Limited autopsy

Where consent for a full autopsy is not given, limited examination may be of value e.g. examination confined to the brain and spinal cord in neuromuscular cases.¹¹ Parents should be aware that limiting the post-mortem examination may limit the available information and not give a full diagnostic picture.

Forms of limited examination include:

- autopsy limited to one or more body cavities
- open or needle biopsy of specific internal organs (if feasible)
- external examination of the body with X-ray, photography and genetics (if indicated)

- placental examination only for early neonatal deaths (if available) with genetic testing (if indicated)¹²
- imaging (CT, MRI – if available) alone or with targeted biopsies.¹³

[Level of evidence – C and D.]

9 Specific significant organ systems

None.

10 Organ retention

Short-term retention of organs to allow fixation for sampling or further examination does not require specific consent, provided the organs are reunited with the body before release for burial/cremation, as this is not regarded as retention by the HTA, but as part of the post-mortem process.

Specific consent should be sought for long-term retention beyond the release of the body, for the purpose of examining the organs. Consider retention for extracranial organs with congenital malformations (particularly heart) if input is not available on site at the time from a perinatal pathologist or cardiac morphologist, and the abnormality cannot be satisfactorily recorded by photography. If prolonged retention is necessary, the parents should be given the option of delaying the release of the body until the organ can be repatriated.

When the brain is to be retained for macroscopic and histological assessment, submersion for a minimum of 2–3 days in 20% formalin ($\pm 5\%$ acetic acid) will usually produce sufficient fixation to allow adequate sectioning and block sampling, to allow the brain to be returned to the body before release for funeral. Longer fixation may be necessary in some complex neuropathology cases. If there is doubt, consult the local neuropathology team.

The consent form must be carefully checked for consistency with respect to tissue retention and achieving the aims of the autopsy. Consent for permanent archiving of tissues blocks and slides should be included on the post-mortem consent form and should be encouraged as the norm since this is generally in the best medical interest of the family.

[Level of evidence – GPP.]

11 Histological examination

Blocks should be taken as appropriate, but at full autopsy may include:¹⁴

- thymus
- heart (including papillary muscle and interventricular septum)
- trachea/thyroid
- lungs (at least two from each lung)
- small and large intestine
- liver
- pancreas
- adrenal gland

- kidney (x 2)
- costochondral junction (assessment of growth plate and bone marrow); bone histology mandatory for suspected skeletal dysplasia
- brain: when systematically assessing hypoxic-ischaemic injury, blocks should, if possible, include:
 - cerebral cortex and periventricular white matter (each cerebral lobe)
 - deep grey matter (thalamus, basal ganglia)
 - hippocampus
 - midbrain (inferior colliculi)
 - pons
 - medulla (inferior olives)
 - cerebellum with dentate nucleus
 - sampling may by necessity be more restricted if there is advanced autolysis, but this should not be a problem in neonatal autopsies. In cases of malformation, appropriate extensive sampling should be undertaken. Consulting the neuropathology team may be helpful if there is doubt about sampling.
- other organ lesions as indicated by history or macroscopic findings
- if available:
 - placenta (at least three full-thickness blocks, plus focal lesions)
 - membrane roll
 - cord (at least two transverse sections).

[Level of evidence – D.]

A record of the samples taken should be kept and tissue blocks and slides should be traceable within the laboratory, in line with the requirements of HTA and the UK Accreditation Service.

12 Toxicology

- Consider for in-hospital deaths if there are concerns about drug dosage, etc.
- Advisable for out-of-hospital deaths.
- Samples may include blood, stomach contents, urine, or other tissues or fluids. If in doubt, specialist advice should be sought.

13 Other relevant samples (as indicated by history and macroscopic findings)

- Bacteriology:
 - lung (swab/tissue)
 - blood (swab/formal culture)
 - other e.g. cerebrospinal fluid, as dictated by clinical history or macroscopic findings.
- Genetics (DNA microarray preferred if available):
 - skin/muscle/cardiac blood

- placenta
- samples recommended by local genetics department
- advise retention of frozen tissue sample (liver/lung/other) as future DNA resource.
- Samples for virology, biochemistry, haematology and electron microscopy.
- In particular, with sudden unexpected neonatal death the possibility of metabolic disease should be considered and appropriate samples would include:
 - blood
 - blood spots (Guthrie card)
 - skin (for fibroblast culture i.e. not frozen)
 - urine
 - tissue for freezing (liver, muscle, etc. as indicated)
 - for details on investigation of metabolic disorders, consult the Neonatal Metabolic Biochemistry Network website¹⁵
 - these samples should be taken as soon as possible after death to reduce deterioration.

[Level of evidence – D.]

14 Imaging

Imaging-based post-mortem examination should never be undertaken without an expert external examination of the body having first been performed by an appropriately trained and experienced person. Imaging modalities, in addition to X-ray, which may be of value include MRI¹³ and CT scan.

The role of MRI in perinatal autopsies has been investigated.¹³ MRI can give useful information, particularly on structural malformations; however, its accuracy is poor for detecting infection and hypoxic-ischaemic brain injury – two of the major pathologies frequently encountered. Targeted biopsies may overcome this, but neither MRI imaging nor the equipment and skills needed to take endoscopic biopsies at post-mortem examination are widely available.

15 Autopsy report¹⁴

Units may choose, if resources allow, to issue a provisional report giving details of the macroscopic findings shortly after the examination of the body, followed by a final report when all histology and other tests have been completed. Alternatively, only a single, final report may be produced.

The report should include the following sections:

- demographic and identification data
- details of autopsy consent and limitations
- body weight and centile (crude or customised)
- body measurements
- list of main findings
- clinicopathological summary (final report)

- summary of clinical history
- systematic description of external and internal findings and placental examination (if available)
- organ weights with relevant reference values and ratios
- details of ancillary tests taken (and results in final report)
- histology (final report)
- list of histology tissue blocks (final report).

[Level of evidence – GPP.]

15.1 Clinicopathological summary

This should include:

- an assessment of organ development relative to gestation and age at death
- a summary of the major findings
- a discussion of the aetiology/pathogenesis of these findings and the timing/sequence of events leading to death (recognising that neonatal deaths are frequently multifactorial and may not be attributable to a single cause of death)
- explicit statements about the presence/absence of malformation and infection and, where appropriate, growth restriction and trauma (negative findings are helpful and may be crucial)
- concordance or discordance of findings with the clinical history and prenatal testing (if appropriate)
- identification of those cases with an increased risk of recurrence (including malformation syndromes, growth restriction and maternal diabetes).

[Level of evidence – GPP.]

Feedback to the referring clinicians may be enhanced by the pathologist attending local perinatal mortality MDT meetings to present and discuss the post-mortem findings.

16 Criteria for audit

The following standards are suggested criteria that might be used in periodic reviews to ensure post-mortem reports meet national standards:

- supporting documentation:
 - standards: supporting documentation was submitted with the body in 95% of cases (note it is recommended that an autopsy should not be commenced in the absence of clinical information – missing information should be obtained before starting)
 - standards: 95% of submitted information is satisfactory, good or excellent
 - standards: a correctly completed autopsy consent form, meeting national requirements, is submitted with 95% of non-coronial cases (note an autopsy must not be commenced unless the pathologist has seen a physical copy of the consent form and it is correctly completed)

- autopsy report:
 - standards: 100% of autopsy reports must include all of the sections detailed in section 15 (above)
 - standards: in 100% of autopsy reports the information documented is satisfactory, good or excellent
 - standards: in 100% of autopsy reports the clinicopathological summary is clear and concise and, when appropriate, contains the information detailed above.

A template for coronial autopsy audit can be found on the College website (www.rcpath.org/profession/clinical-effectiveness/quality-improvement/clinical-audit-templates.html).

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18 Further reading

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Appendix A Specimen autopsy request form

Clinical Information for Fetal / Perinatal Post Mortem

Please attach **Mother's** sticker here
Family name.....
First name
D.o.B.: / /
Reg no.....
Consultant.....

Please attach **Baby's** sticker here
Family name.....
First name
D.o.B.: / /
Reg no.....
Consultant.....

Ethnic origin _____ Father's ethnic origin (if known) _____ Baby's sex: M/F
Referring hospital _____ Ward _____
Hospital of birth (if different) _____

RELEVANT HISTORY:

Maternal height: _____ cm
Booking weight: _____ kg
Consanguinity: Y/N

Previous pregnancies: G: _____ P: _____
date gestation delivery sex outcome
1. _____
2. _____
3. _____
4. _____
5. _____

THIS PREGNANCY: booked / unbooked LMP _____ EDD _____ BMI _____
Gestation: by dates: _____/40 by scan: _____/40 weeks Blood group: _____, Rh D pos / neg
HBsAg: pos / neg Antibodies: _____
Serum screening results: _____ Medications : _____
Abnormal USS findings: _____

Antenatal diagnostic procedures / results: _____

Karyotype: _____

threatened abortion: no / yes when _____	severe anaemia: no / yes
antepartum haemorrhage: no / yes when _____	infection risk: low / high reason _____
hypertension: no/yes max b.p. _____	maternal pyrexia: no / yes when _____
pre-eclampsia: no/ yes when _____	other problem _____

LABOUR: onset: spont. / medical/ none IOL for: IUD / TOP / other _____ Fetocide: y / n date _____

Presentation: vertex / breech / other _____ Liquor volume: normal / reduced / increased; colour _____

Rupture of membranes: date _____ time _____ Augmentation (Syntocinon): yes / no

1st stage: __ h __ min 2nd stage: __ h __ min Fetal heart last heard (S/B): date _____ time _____

Fetal distress: yes / no specify _____

Delivery: spontaneous / assisted (forceps/ventouse) / CS (elective/emergency) date _____ time _____
Death: date _____ time _____

Baby: Birth weight _____ g Apgars: 1st min _____ 5th min _____ 10th min _____

ABNORMALITIES NOTED: nil / _____

For live-born infants:

RESUSCITATION: nil / mucus extraction / oxygen / mask / intubation / other _____
_____ Surfactant: yes / no

NEONATAL PROBLEMS:

1. _____
2. _____
3. _____
4. _____
5. _____

PROCEDURES:

1. _____
2. _____
3. _____
4. _____
5. _____

BRIEF SUMMARY OF LATER SYMPTOMS / TREATMENTS AND MAJOR INVESTIGATIONS (including CPAP/ventilation, IV therapy, fits, episodes of collapse, pneumonia, pneumothorax, bleeding problems, type of feeding etc.; If complex course, please send photocopy of relevant pages of notes):

SUSPECTED CAUSE(S) OF DEATH:

DEATH REGISTERED AS: livebirth / stillbirth / not registered (miscarriage)

BRIEF SUMMARY OF MAIN HISTORY / SPECIAL POINTS TO BE NOTED AT POST MORTEM:

Referring doctor / midwife: _____ Contact no. / bleep no. _____

ALL BABIES AND PLACENTAS SHOULD BE SENT FRESH IN LEAKPROOF, OPAQUE CONTAINERS UNLESS THERE IS AN INFECTIOUS HAZARD (in this case phone to discuss whether the specimen should be fixed in 10% formalin before transportation)

It is essential to send the placenta with a fetus / infant.

ALL SPECIMENS MUST BE CLEARLY LABELLED AND ACCOMPANIED WITH A COMPLETED REQUEST AND CONSENT FORM

Appendix B Summary table – Explanation of grades of evidence
(modified from Palmer K *et al. BMJ* 2008;337:1832)

Grade (level) of evidence	Nature of evidence
Grade A	<p>At least one high-quality meta-analysis, systematic review of randomised controlled trials or a randomised controlled trial with a very low risk of bias and directly attributable to the target population</p> <p>or</p> <p>A body of evidence demonstrating consistency of results and comprising mainly well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias, directly applicable to the target population.</p>
Grade B	<p>A body of evidence demonstrating consistency of results and comprising mainly high-quality systematic reviews of case-control or cohort studies and high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relation is causal and which are directly applicable to the target population</p> <p>or</p> <p>Extrapolation evidence from studies described in A.</p>
Grade C	<p>A body of evidence demonstrating consistency of results and including well-conducted case-control or cohort studies and high-quality case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal and which are directly applicable to the target population</p> <p>or</p> <p>Extrapolation evidence from studies described in B.</p>
Grade D	<p>Non-analytic studies such as case reports, case series or expert opinion</p> <p>or</p> <p>Extrapolation evidence from studies described in C.</p>
Good practice point (GPP)	<p>Recommended best practice based on the clinical experience of the authors of the writing group.</p>

Appendix C AGREE II compliance monitoring sheet

The guidelines of the Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines. The sections of this autopsy guideline that indicate compliance with each of the AGREE II standards are indicated in the table.

AGREE II standard	Section of guideline
Scope and purpose	
1 The overall objective(s) of the guideline is (are) specifically described	Foreword, 1
2 The health question(s) covered by the guideline is (are) specifically described	Foreword, 1
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword, 1
Stakeholder involvement	
4 The guideline development group includes individuals from all the relevant professional groups	Foreword
5 The views and preferences of the target population (patients, public, etc.) have been sought	Foreword
6 The target users of the guideline are clearly defined	1
Rigour of development	
7 Systematic methods were used to search for evidence	Foreword
8 The criteria for selecting the evidence are clearly described	Foreword
9 The strengths and limitations of the body of evidence are clearly described	Foreword, 1
10 The methods for formulating the recommendations are clearly described	Foreword
11 The health benefits, side effects and risks have been considered in formulating the recommendations	n/a
12 There is an explicit link between the recommendations and the supporting evidence	5–15
13 The guideline has been externally reviewed by experts prior to its publication	Foreword
14 A procedure for updating the guideline is provided	Foreword
Clarity of presentation	
15 The recommendations are specific and unambiguous	2–15
16 The different options for management of the condition or health issue are clearly presented	Foreword, 7, 8, 14
17 Key recommendations are easily identifiable	2–15
Applicability	
18 The guideline describes facilitators and barriers to its application	Foreword
19 The guideline provides advice and/or tools on how the recommendations can be put into practice	Foreword
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	16
Editorial independence	
22 The views of the funding body have not influenced the content of the guideline	Foreword
23 Competing interest of guideline development group members have been recorded and addressed	Foreword