



Tissue pathway for histopathological examination of the placenta

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NICE has accredited the process used by the Royal College of Pathologists to produce its tissue pathways. Accreditation is valid for five years from 25 July 2017. More information on accreditation can be viewed at www.nice.org.uk/accreditation.

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

Foreword

The tissue pathways published by the Royal College of Pathologists (RCPATH) are guidelines that should assist pathologists in providing a high standard of care for patients. Guidelines are systematically developed statements to assist the decisions of practitioners and patients about appropriate healthcare for specific clinical circumstances and are based on the best available evidence at the time the document was prepared. This guideline has 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 guideline may therefore be required to report a specimen in a way that maximises benefit to the patient. In these circumstances, pathologists should be able to justify any variation.

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

The following stakeholders were contacted to consult on this document:

- The British and Irish Paediatric Pathology Association (BRIPPA)
- The Royal College of Obstetricians and Gynaecologists (RCOG)
- The Royal College of Midwives (RCM)
- Sands (Stillbirth and Neonatal Death Society).

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

The information used to develop this tissue pathway was obtained by undertaking a systematic search of the medical literature, previous recommendations of the RCPATH, RCOG and local guidelines, and protocols from perinatal pathology units in the UK. Key terms searched included placenta, clinical complications, guidelines, stillbirth, fetal growth restriction, examination, workload, reports, monochorionic, histopathology, pathology, medico-legal, post mortem, outcomes, pregnancy, twins and consensus, and dates searched were between January 1997 and April 2022. Published evidence was evaluated using modified SIGN guidance (see Appendix D). The level of evidence was grade B, C or D, or met the Good Practice Point (GPP) criteria. Consensus of evidence in this tissue pathway was achieved by expert review. Gaps in the evidence will be identified by College Fellows via feedback received from consultation.

Implementation of the tissue pathway to its full extent may require some local organisational changes, as the delivery of placental pathology services varies widely between hospitals. It is desirable that placental pathology services should be available to all maternity units in the UK although service constraints put this at risk.

A formal revision cycle for all tissue pathways takes place on a five-yearly basis. However, each year, the College will ask the author(s) of the tissue pathways, in conjunction with the relevant subspecialty adviser to the College, to consider whether or not the document needs to be updated or revised. A full consultation process will be undertaken if major revisions are required. If minor revisions 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 pathway and the full revised version (incorporating the changes) will replace the existing version on the publications page of the College website. All changes will be documented in the data control section on the front page of the relevant pathway.

The pathway was reviewed by the Clinical Effectiveness team, Working Group on Cancer Services and Lay Advisory Group. It will be placed on the College website for a full consultation

with the membership from 28 July to 25 August 2022. All comments received from the Working Group, Lay Advisory Group and membership were addressed by the authors to the satisfaction of the Chair of the Working Group and Clinical Lead for Guideline Review (Cellular Pathology).

This pathway was developed without external funding to the writing group. The College requires the authors of tissue pathways to provide a list of potential conflicts of interest; these are monitored by the Clinical Effectiveness team and are available on request. The authors have declared no conflicts of interest.

1 General introduction

Histopathological examination of the placenta following a pregnancy affected by medical complications, pregnancy loss or neonatal death may provide an explanation of why this occurred. This explanation can be beneficial to the patient to understand and make sense of what has happened. It may also provide information relevant to the management of the associated infant and/or subsequent pregnancies and be of use to serious incident reviews and other audits of patient care.¹⁻⁵

This document is intended as a guide to good practice. It also attempts to provide information that might be useful when dealing with placentas from different pregnancy complications. Where possible, references are provided, but it is inevitable that some criteria are based on UK best practice rather than on published evidence, as the latter is often non-existent or sparse. It is recommended that laboratories adopt the approaches indicated in this tissue pathway to provide compassionate and equitable care for mothers and babies across the UK. In addition, the document is not intended as a replacement for standard current textbooks but highlights the principles of handling and reporting placental specimens. Further reading is highlighted in section 9.

This tissue pathway aims to provide guidance on the range of indications for referral of a placenta for histopathological examination and minimum standards for examination and histological reporting of placentas by pathologists undertaking placental examinations. Variations to the standard pathway for singleton placentas, relating to pregnancies from multiple gestations, are also included. Please note that products of conception (1st trimester) have been included in the tissue pathways for gynaecological pathology.

[Level of evidence C.]

1.1 Target users of this guideline

This pathway will be of use to consultants and trainees in paediatric and perinatal pathology, general histopathologists with an interest in placental pathology, biomedical scientists and advanced practitioners, obstetricians and midwives, and those commissioning perinatal pathology services.

2 Generic considerations

2.1 Staffing and workload

Pathologists should:

- participate in audits
- participate in the RCPATH Continuing Professional Development (CPD) scheme
- participate in relevant external quality assessment (EQA) including the Perinatal Pathology section of the Paediatric Pathology EQA organised by BRIPPA and

undertaken by all subspecialist paediatric and perinatal pathologists. General pathologists undertaking perinatal autopsies or paediatric surgical pathology, in addition to placental pathology, should participate in this scheme

- have access to adequate current publications (online) and textbooks, for reference
- have access to specialist referral opinions on a local/regional network or national basis. For general pathologists, this will usually mean access to a subspecialist perinatal pathologist at a regional centre.

2.2 Laboratory facilities and generic laboratory requirements

Placental examination should be undertaken in an appropriate laboratory environment. Provision should be made for macroscopic and microscopic photography as placentas from pregnancy losses may be discussed at local perinatal mortality meetings and visual information may assist the discussion. If injection studies are to be undertaken on monochorionic twin placentas, appropriate equipment and dyes should be available.

The laboratory should:

- be equipped to allow the recommended technical procedures to be performed safely
- be enrolled with the UK Accreditation Service (UKAS)
- participate in the UK National External Quality Assurance Scheme (UKNEQAS) for cellular pathology technique
- participate in the UKNEQAS for immunocytochemistry
- have access to light microscopy and common special stains
- have access to immunohistochemistry
- have access to genetics services
- have access to microbiology and virology services
- have access to photographic equipment.

Reports should be held on a secure electronic database that has facilities to search and retrieve specific data items and that is indexed according to SNOMED codes. It is acknowledged that existing laboratory information systems may not meet this standard; however, the ability to store data in this way is recommended when laboratory systems are replaced or upgraded.

Workload data should be recorded in a format that helps determine which resources should be used and which, if applicable, is suitable for mapping to healthcare resource groups.

3 General issues

3.1 Staffing and workload

In hospitals with specialist(s) in perinatal pathology, placental examination may be undertaken by the specialist. In some departments, placental examination is undertaken as part of a general rota but undertaken by those with an interest in placental/perinatal pathology with suitable experience and competency. In either circumstance, there must be a sufficient number of pathologists to provide cover and to conform to the College's guidance on staffing and workload levels.^{6,7}

3.2 Specimen submission

The indications for referring placentas for histopathological examination are given (for more information see Appendix A).^{8–12} These are: all placentas from stillbirths (antepartum or intrapartum),¹³ placentas from miscarriages (14+0–23+6 completed weeks' gestation), infants with fetal growth restriction (defined as birthweight below 3rd centile or drop in fetal growth velocity of >2 quartiles or >50 percentiles),^{10,11,14,15} preterm birth (less than 32+0 completed weeks' gestation),^{14,15} and cases of severe fetal distress (defined as pH<7.05 or Base Excess \geq -12 or scalp lactate >4.8 mmol/l),⁸ abnormal umbilical artery Dopplers (absent or reversed end-diastolic flow), fetal hydrops, early-onset (<32 weeks' gestation) severe pre-eclampsia requiring iatrogenic delivery, Caesarean peripartum hysterectomy for morbidly adherent placenta, severe maternal sepsis requiring adult intensive care admission and/or fetal sepsis requiring ventilation or level 3 Neonatal Intensive Care Units (NICU) admission (following swab taken from the placenta for microbiology at delivery),¹⁶ massive placental abruption with retroplacental clot, and monochorionic twins with twin-to-twin transfusion syndrome (TTTS).¹⁷

Full details of the patient (mother), clinical consultant and date of delivery must be provided on the request form. As a minimum, the gestational age, birth weight, birthweight centile, sex of the baby and the indication for referral must be stated. Details of previous pregnancy complications and relevant maternal disease should also be provided. A placental referral proforma for use by clinicians, such as that shown in Appendix B, should be used.

The specimen container must be labelled with the patient details. Placentas may be submitted to the laboratory fresh or formalin fixed, as per local protocols. If submitted in formalin, the container should be of sufficient size to minimise distortion of the specimen and formalin should be of adequate volume to cover the specimen entirely to ensure proper fixation. Any samples for cytogenetic testing, or, where appropriate, microarray or whole genome sequencing, should be taken before fixation following appropriate ethical guidance and consent. The specimen should not otherwise be disrupted before receipt in the histopathology laboratory unless this has been agreed on previously with the receiving pathologist.

Submission of the unfixed placenta may be preferable for identification of macroscopic changes in complicated monochorionic twin placentas. However, formalin fixation is preferred for risk reduction in potential transmission of infection or where there is a risk of congenital infection being transmitted to a clinically vulnerable member of staff. For adequate fixation, the placenta must be placed in a container of adequate size and containing at least three times the tissue volume of formalin with a fixation period of 48 hours.

[Level of evidence – B, C, D and GPP.]

3.3 Specimen dissection and block selection

Sampling of the placenta for histology should be undertaken from sufficient areas to provide a representation of the pathology present.^{8,16,18} Each cassette must have a unique identifying number or letter. A record of the number of pieces of tissue in each cassette is desirable for audit purposes. Specific details of dissection and block selection relating to singleton and multiple pregnancy placentas are detailed in sections 4–6.

It may be appropriate in some clinical situations for the placenta to be retained bagged, labelled and refrigerated on the labour ward for a week, in case the baby or mother develops significant complications that placental examination may help to explain or for which it may help to direct treatment.¹⁹

[Level of evidence – C, D and GPP.]

3.4 Embedding options

Local procedures for processing and embedding tissue samples should be followed. There are no specific requirements for general placental tissue. Samples from the maternal surface, searching for spiral arteries in the decidua, may be embedded either 'on edge' or with the decidual face downwards, depending on local preference and experience.

3.5 Sectioning

Tissue sections should be produced as per local protocols.

3.6 Staining

In the vast majority of cases, a single haematoxylin and eosin-stained section of each tissue block is sufficient for diagnosis. It is essential that the sections produced include the fetal and maternal surface of the placenta and that sections of umbilical cord include the complete circumference of the cord.

3.7 Further investigations

Additional stains are usually not required. In individual cases, consideration may be given to the use of special stains, immunohistochemistry, genetic analysis, electron microscopy and microbiological samples. Commonly employed special stains include Gram for bacteria, PAS for fungi and Perls' stain for haemosiderin (to distinguish from meconium pigment in the fetal surface). Immunostaining for cytomegalovirus, toxoplasma, CD3, CD68 and parvovirus B19 should be available to all pathology departments undertaking placental histopathology reporting. Access to SARS-CoV-2 antibody staining should be available when required. Genetic testing may be indicated if the placenta is being examined following fetal death, or where post mortem has been declined and there is a clinical indication (e.g. severe fetal growth restriction [FGR] or congenital malformations). Samples should only be sent for genetic analysis if there is documented parental consent. Electron microscopy is rarely indicated but may be considered in cases of death due to fetal hydrops when post mortem is declined.

3.8 Report content

A minimum dataset for placenta histopathology reports is given (see Appendix C). In general, the report should include as a minimum: the patient details, the clinical history (summarised or directly transcribed from the request form), a macroscopic description of the umbilical cord, membranes, fetal, maternal, and cut surfaces of the placenta, and a microscopic description of the umbilical cord, membranes, fetal placental surface, villous parenchyma and maternal decidua.^{18,20–22}

The report should conclude with a diagnosis or list of pathological findings and a clinicopathological comment to assist the clinician in interpreting the significance of the findings. Diagnostic coding (e.g. SNOMED) of the findings is recommended.

[Level of evidence – D and GPP.]

4 Specific considerations for singleton placenta

4.1 Dissection and macroscopic description^{5,9,10}

The following measurements should be made in all cases:

- maximum linear dimensions of the placental disc in two perpendicular planes (to nearest 10 mm)

- thickness of disc (to nearest 5 mm)
- length of umbilical cord (to nearest 10 mm) and approximate diameter (to nearest 1 mm)
- weight of placental disc following removal of cord and membranes (to nearest gram) and whether this is fresh or fixed.

There should be a systematic description of the umbilical cord, membranes, fetal and maternal surface, and parenchyma. The site of the cord insertion and number of umbilical cord vessels should be recorded. The degree of coiling of the umbilical cord may also be described, either qualitatively or numerically (e.g. *n* coils per 100 mm). The presence and site of true knots in the umbilical cord should be recorded and an assessment should be made about whether the knot appears to have occluded flow in the cord vessels. It may be helpful to record the appearance photographically. The appearance of the placental membranes (translucency, colour, insertion) and the fetal placental surface (colour, vascular congestion/thrombosis) should be described. The presence and extent of macroscopic pathology in the placental parenchyma should be described giving a percentage of the total placental volume, and an attempt should be made to assess whether the membranes and parenchyma have been received in their entirety or whether they are incomplete.

Major lesions, particularly in placentas from pregnancy losses, should be recorded photographically. If the placenta is examined in the fresh state, consideration should be given to sampling the placenta for genetic testing or virology, if clinically indicated. Genetic analysis should only be undertaken if parental consent has been obtained.

4.2 Sampling for histology

Histological sampling is indicated in the majority of situations. It is recommended that the following samples are taken as a minimum:

- two transverse sections of umbilical cord
- one roll of membranes (to include the rupture site)
- a minimum of two full thickness blocks of the placental parenchyma (away from the placental edge) to include the fetal and maternal surfaces
- additional blocks depending on the clinical indications for the examination and macroscopic findings.¹⁸

Representative samples of macroscopic lesions should be taken as necessary. In cases of severe FGR or early-onset severe pre-eclampsia (<32 weeks' gestation with iatrogenic delivery), additional small samples may be taken from the maternal surface to attempt to identify maternal vascular pathology.^{8,18}

Macroscopic examination/macroscopic examination with tissue blocks taken and not examined microscopically (block only cases) or storage of placentas with no formal examination in pathology departments are no longer recommended practices.

4.3 Report content

See section 3.8 for general comments.

The histological report should reflect the specific clinical situation detailed on the request form. Key elements to note include: the presence, severity and extent of acute inflammation in the cord, membranes and/or fetal surface, the villous development in relation to the stated gestation and evidence of villous ischaemia, and the presence of infarction, chronic inflammation and other parenchymal disease. In cases of FGR and maternal preeclampsia, the decidua should be examined for the presence of maternal vascular disease.^{8,18,21,22}

[Level of evidence – D and GPP.]

5 Specific considerations for dichorionic twin placentas

5.1 Specimen submission

Dichorionic twin placentas should only be referred for examination if they meet the essential criteria for examination listed (see Appendix A). Examination to confirm chorionicity only is of limited clinical value and may be undertaken in the delivery suite by an appropriately trained and competent midwife or doctor.⁸

5.2 Dissection and macroscopic description

For dichorionic twin placentas, the aim of the examination is to look for pathologies associated with the essential referring criteria and confirm chorionicity. A dichorionic dividing membrane will have four thin layers and is usually tethered to the placental surface with an identifiable chorionic ridge. Monochorionic dividing membranes have two thin layers and will be more mobile and lack a chorionic ridge. Dichorionic placentas can often be easily separated into two discs along the twin vascular territories with minimal traction. It should be described whether the placental discs are separate or joined. Otherwise, examination assesses the same features as for a singleton pregnancy for each part of the placenta.

5.3 Sampling for histology

The pathologist may wish to include a roll of the dividing membrane or a T-block from the insertion of the dividing membrane into the placental surface as histological confirmation of chorionicity. Otherwise, the rationale for sampling is the same as for two singleton placentas.

5.4 Report content

Apart from a description of the dividing membrane, the report should follow the same format as for two singleton placentas.

The conclusion or diagnosis should indicate the chorionicity of the placenta. Other relevant pathology should be listed and a clinicopathological comment added as necessary.

[Level of evidence – GPP.]

6 Specific considerations for monochorionic placentas

6.1 Specimen submission

Monochorionic pregnancies are subject to a number of additional pathological disorders not seen in singleton or dichorionic twin placentas.^{15,23} Rates of complications are also significantly higher. They may be subject to medical intervention during pregnancy to treat the complications. Monochorionic placentas should be referred if they meet the essential referring criteria (see Appendix A).

6.2 Dissection and macroscopic description

In general, it is necessary to approach the monochorionic twin placenta as a single entity in terms of weight, measurements, and description – the obvious exception being the umbilical cords, which are described separately.

The fetal surface is of particular interest and usually carries connections between the two fetal circulations. The description of the fetal surface should include the site and distance between the insertion of the two umbilical cords and the relative shares of the placental disc. An assessment of the vasculature in the chorionic plate should be made and a description made of the vascular anastomoses (AA, VV, AV).¹⁷ Identification of anastomoses may be facilitated by injection of the vasculature in unfixed placentas. A simple method involves injecting a 1% agar solution, coloured with four tissue-marking dyes, into an artery and the vein of each umbilical cord, after removal of excess blood from superficial vessels.¹⁷ The resulting preparation can be photographed and is suitable for histological examination. Injection studies are particularly helpful if the pregnancy has been complicated by growth discordance or TTTS. Other methods for placental injection to determine vascular anastomoses have been described.²⁴ These methods are not suitable for formalin-fixed placentas.

If the placenta has been subject to laser coagulation for TTTS, the presence of laser sites and completeness of interruption of interfetal vascular anastomoses should be recorded.

6.3 Sampling for histology

In cases where histological examination is undertaken, the approach to histological sampling is the same as for singleton placentas, except that in complicated monochorionic pregnancies samples should be taken from the areas supplying each twin for comparison. A roll of the dividing membrane is also usually taken.

6.4 Report content

The description of the placenta should include detail of its fetal surface, including the site and distance between the insertion of the umbilical cords, the sharing of the placental disc, and interfetal anastomoses and their direction (arteriovenous [deep] anastomoses only).

The histological report should include a description of the dividing membrane and compare the appearance of parenchymal samples from the areas supplying each twin. Otherwise, the description follows the same lines as for singleton placentas.

A clinicopathological comment on the contribution of the placental findings to the observed clinical complications (if any) should be given.

Placentas from higher multiple pregnancies (e.g. triplets) should be processed according to the essential referring criteria (Appendix A).

[Level of evidence – D and GPP.]

7 Criteria for audit

As recommended by the RCPATH as key performance indicators (see [Key performance indicators – proposals for implementation](#), July 2013).

Implementation of this tissue pathway may be monitored by audit of:

- completeness of adherence to referral criteria
 - standard: less than 10% of referred placentas fall outside the local referral criteria
- completeness of recording of standard measurements
 - standard: placental trimmed weight, measurements in three planes and umbilical cord length recorded in all cases
- adherence to minimum histological sampling guidance

- standard: a minimum of two sections of umbilical cord, one section of membranes and two full thickness samples of placenta taken in all cases submitted for histology
- turnaround time for reports
 - standard: 75% of placental histology reports issued within 30 working days of receipt.

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Appendix A Indications for referral of placentas for pathological examination

Referral of placenta for examination is **essential** for singletons or multiples as indicated below:

- stillbirth (ante partum or intra partum)
- miscarriage (14+0–23+6 completed weeks' gestation)
- severe fetal distress defined as: pH <7.05 or Base Excess \geq -12 or scalp lactate >4.8mmol/l
- preterm birth (less than 32+0 weeks' gestation)
- fetal growth restriction defined as: birthweight below 3rd centile or drop in fetal growth velocity of >2 quartiles or >50 percentiles
- abnormal umbilical artery Dopplers (absent or reversed end diastolic flow)
- fetal hydrops
- early-onset (<32 weeks) severe pre-eclampsia requiring iatrogenic delivery
- caesarean peripartum hysterectomy for morbidly adherent placenta
- severe maternal sepsis requiring adult intensive care admission and/or fetal sepsis requiring ventilation or level 3 NICU admission (following swab taken from the placenta for microbiology at delivery)
- massive placental abruption with retroplacental clot
- mono chorionic twins with TTTS.

Referral is **not** indicated in the following conditions as histopathological examination is unlikely to provide useful information:

- cholestasis of pregnancy
- 'gritty' placenta
- pruritis of pregnancy
- maternal diabetes with normal pregnancy outcome
- hepatitis B, HIV, etc
- other maternal disease with normal pregnancy outcome
- placenta praevia
- post-partum haemorrhage
- polyhydramnios
- rhesus negative mother with no fetal hydrops
- history of maternal Group B streptococcus
- maternal coagulopathy
- maternal substance abuse
- uncomplicated twin pregnancy
- congenital anomaly
- common aneuploidies
- low grade pyrexia in labour
- history of previous molar pregnancy
- normal pregnancy

- accessory lobe
- uncomplicated velamentous cord.

Consultant request: If there are queries, examination may be possible following discussion with your receiving consultant pathologist.

Appendix B Sample request form for placental examination

Pathology placenta examination request form

Patient label / details Patient name: NHS/CHI number: Address:	Laboratory number: (Lab use only)
--	-----------------------------------

Send placenta and this request form to:
 Department of Histopathology,
 xxxx,xxxxxx,xxxxx,xxxxx XX01 8XX

GESTATION:	(essential, if not supplied the placenta will be returned)
Birth weight centile:	GAP <input type="checkbox"/> Intergrowth <input type="checkbox"/> Other <input type="checkbox"/>
INDICATION(S) for examination (essential, if not supplied the placenta will be returned)	

CLINICAL DETAILS:

Consultant obstetrician:	Livebirth (Y/N):
Date of delivery:	Birth weight/s:
Gravidity: (total number of pregnancies) Parity: (total number of live births post 24 weeks)	Sex:

Stillbirth		Preterm birth <32 weeks	
Miscarriage (14+1–23+6 weeks)		<32-week-onset severe PET	
FGR <3rd centile or drop in growth velocity >50 percentiles		Severe sepsis with maternal ITU admission and/or fetal sepsis requiring ventilation or level 3 NICU (placental swabs taken at delivery)	
Fetal hydrops		Massive placental abruption with retroplacental clot	
UA Dopplers (absent /reversed end diastolic flow)		Severe fetal distress pH<7.05 / BE ≥-12/ scalp lactate >4.8 mmol	
Monochorionic twins with TTTS		Caesarean peripartum hysterectomy for morbidly adherent placenta	

Twin A: sex _____ cord clamps _____
 Twin B: sex _____ cord clamps _____

Any other information: e.g. maternal smoking, BMI, medications, viral infections during pregnancy, mode of delivery, Rhesus status, significant maternal co-morbidities	HIGH RISK: (blood borne infections) <input type="checkbox"/>
	URGENT: <input type="checkbox"/>

Person completing the request form:

Name: (print)	Hospital:
Full contact number:	Date:

Appendix C Minimum dataset for placenta histopathology reports

Clinical information:

- Gestational age (weeks):
- Birthweight (grams):
- Birthweight centile:
- Sex of baby:
- Indications for referral from the essential criteria:
- Consultant obstetrician and referring unit:

Macroscopic description:

- Cord: insertion, length, diameter, spiral index, number of vessels, focal lesions, discolouration
- Membranes: completeness, type of insertion, generalised or localised macroscopic lesions/changes
- Placental disc (following removal of the cord and membranes): Size given in three dimensions, completeness, weight (g), any pathological changes affecting the chorionic plate including the chorionic plate vessels, any sub-chorionic lesions, lesions/defects involving the maternal surface, any lesions seen on cut sections and the percentage of the parenchyma that the lesions occupy
- (For twins, description of the dividing membrane, presence or absence of chorionic ridge, presence or absence of vascular anastomoses, and approximate percentage of the vascular territories of the twins).

Microscopic description:

- Description of the cord including number of vessels
- Description of the membranes including any inflammatory pathology, vasculopathy, meconium, etc.
- Placenta sections: comment on the chorionic plate, villous maturation, focal or generalised lesions and severity of any inflammatory lesions (use of special stains and immunohistochemistry may be required for infective agents for example). Comment on the basal decidua (inflammation, vasculopathy, etc.).

Clinicopathological correlation or comment:

- The fetal/placental weight ratio (if relevant)
- The placental weight centile (standard charts are available for placenta weight centiles and fetal placental ratio in most placenta textbooks; see section 9, Further Reading)
- A brief summary of findings and the clinical correlation and state if the pathological findings have been reported to have a significant risk of recurrence in subsequent pregnancies.

Appendix D 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	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 cancer type or 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 cancer type.
Grade B	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 cancer type or Extrapolation evidence from studies described in A.
Grade C	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 cancer type or Extrapolation evidence from studies described in B.
Grade D	Non-analytic studies such as case reports, case series or expert opinion or Extrapolation evidence from studies described in C.
Good practice point (GPP)	Recommended best practice based on the clinical experience of the authors of the writing group.

Appendix E AGREE II guideline monitoring sheet

The tissue pathways of the Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines. The sections of this tissue pathway 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	Introduction
2 The health question(s) covered by the guideline is (are) specifically described	Introduction
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword
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	Introduction
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
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	Foreword and Introduction
12 There is an explicit link between the recommendations and the supporting evidence	2–6
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	2–6
16 The different options for management of the condition or health issue are clearly presented	2–6
17 Key recommendations are easily identifiable	2–6
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	Appendices A–C
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	7
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