The Royal College of Pathologists
Pathology: the science behind the cure

Tissue pathways for gynaecological pathology

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NICE has accredited the process used by the Royal College of Pathologists to produce its cancer datasets. 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 enable pathologists to deal with routine surgical specimens in a consistent manner and to a high standard. This ensures that accurate diagnostic and prognostic information is available to clinicians for optimal patient care and ensures appropriate management for specific clinical circumstances. 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 provide a clear rationale for 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:

- British Association of Gynaecological Pathologists
- British Gynaecological Cancer Society
- British Society for Colposcopy and Cervical Pathology.

The information used to develop this tissue pathway was obtained by undertaking a systematic search of PubMed database. Key terms searched included gynaecological pathology, biopsy, resection, grossing, morphology and immunohistochemistry (IHC). The dates searched were between 1 January 2015 and May 2022. Published evidence was evaluated using modified SIGN guidance (see Appendix D). Consensus of evidence in the guideline was achieved by expert review. Gaps in the evidence will be identified by College members via feedback received during consultation.

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

A formal revision cycle for all tissue pathways takes place on a five-yearly basis. However, each year the College will ask the authors of the tissue pathways, in conjunction with the relevant subspecialty adviser to the College, to consider whether 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 pathways and the full revised version (incorporating the changes) will replace the existing version on the College website. All changes will be documented in the data control section of the relevant pathway.

This tissue pathway has been reviewed by the Clinical Effectiveness team, Working Group on Cancer Services and Lay Advisory Group. It was placed on the College website for consultation with the membership from 1 November 2022 to 29 November 2022. All comments received from the stakeholders and membership were addressed by the authors to the satisfaction of the Chair of the Working Group and the Clinical Lead for Guideline Review.

This tissue 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 of this document have declared that there are no conflicts of interest.

1 Introduction

The previous version of this guideline, *Tissue Pathway for Gynaecological Pathology*, was published in 2015. It has now been revised to ensure that recommendations are up to date, that terminology complies with recommendations in the 2020 revision of the WHO classification of female genital tumours,[1] and that the document complies with the revised format of the tissue pathway series.

This document provides guidance on the handling of specimens and reporting of tissue specimens from the vulva, vagina, cervix, endometrium, uterus and adnexa, and relates primarily to those biopsies taken for the investigation of benign or pre-neoplastic conditions at these anatomical sites. The specimens described in this guideline are currently reported by most histopathology departments in the UK.

The purpose of this guideline is to promote a uniform good practice of specimen handling and reporting in histopathology departments and to assist cellular pathologists in providing a high standard of care for patients in the reporting of benign and pre-neoplastic gynaecological specimens. The tissue pathways are important as they provide a consistent approach to managing this range of pathological specimens and highlight the use of ancillary techniques when appropriate.

There is very little literature on the handling of samples resected for benign and non-neoplastic conditions, but a good overview and clear guidance can be found in several standard gynaecological pathology reference books.[2,3] The tissue pathway should be used in conjunction with the datasets on gynaecological cancers.[4–8]

1.1 Target users of this guideline

The primary users of the tissue pathway documents are trainee and consultant cellular pathologists. The recommendations will also be of value to biomedical science advanced practitioners who currently deal with this range of specimens in some histopathology laboratories in the UK, histology laboratory managers, users of gynaecological pathology services and service commissioners.

2 Generic issues relating to staffing, workload and facilities

The following recommendations should be met for a general level of acceptable practice.

- The diagnostic laboratory should have sufficient pathologists, biomedical scientists and clerical staff to cover all of its functions. In general, staffing levels will follow RCPath workload guidelines.
- Pathologists and advanced practitioners should:
  - participate in audits
  - participate in the RCPath Continuing Professional Development (CPD) scheme
  - participate in relevant external quality assessment (EQA) schemes of a general or specialist nature
  - via their pathology department, have standard gynaecological pathology texts available for reference
  - have access to specialist referral opinions on a local, regional or national basis. This need will be influenced by the local level of expertise.
- The laboratory should:
  - be equipped to allow the recommended technical procedures to be performed safely

  - be accredited by or awaiting accreditation by UK Accreditation Service (UKAS) or equivalent
  - participate in the UK National External Quality Assurance Scheme (UK NEQAS) for cellular pathology technique
  - participate in the UK NEQAS for IHC and fluorescent in-situ hybridisation (if these techniques are used in the diagnostic pathway).
- 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 Systematised Nomenclature of Medicine Clinical Terms (SNOMED) T, M and P codes or SNOMED-CT. It is acknowledged that existing laboratory information systems (LIMS) may not meet this standard; however, the ability to store data in this way should be considered when laboratory systems are replaced or upgraded.
- Compliance must be met with the RCPath *Key Assurance Indicators for Pathology Services*[9] to ensure that cellular pathology turnaround times are monitored and audited against locally agreed turnaround times to support patient pathways.
- Workload data should be recorded in a format that facilitates the determination of the resources involved.

3 General principles

3.1 Specimen submission

Most specimens are received fixed in 10% neutral buffered formalin. They may vary in size from small biopsies to larger excisional biopsies and resection specimens. Fresh specimens received for frozen sections should be fixed in 10% neutral buffered formalin after frozen section examination is complete.

3.2 Specimen photography and specimen dissection

Routine photography of all specimens is not encouraged. Photographs of certain specimens such as obstetric hysterectomy specimens and specimens from failed sterilisation are recommended as they may have clinicopathological and medicolegal implications. Specimens may also be photographed for teaching and for reference to blocks taken.

As a general principle, careful handling of vulval and cervical specimens is recommended to prevent surface trauma and disruption or loss of surface epithelium. If small biopsy specimens, including punch excisions, are bisected, the laboratory staff may need to be alerted to avoid rough trimming during levelling of the paraffin block to preserve diagnostic material.

Routine inking of margins is not recommended. Use of ink for margins is left to individual practice.

3.2.1 Biopsies

It is important to examine the contents of the container and the under-surface of the lid carefully to ensure that any stray fragments of tissue are recovered. In small biopsies, the numbers of fragments, maximum dimension of largest fragment, colour and texture of all fragments (mucoid, granular, friable) should be recorded. If fragments are very small, adequate precautions, such as placing between layers of foam, should be taken to avert tissue loss during processing. All the material submitted must be processed for histological examination.

3.2.2 Larger specimens

The method of handling larger specimens depends on a number of factors, including the size of the specimen, whether the lesion can be seen and whether it is thought to be an

inflammatory, benign neoplastic or premalignant lesion. It is recommended that a judgement be made on each individual case, taking these variables into account. Consideration should be given to inking the margins to allow more accurate assessment of lesional clearance. A block index should be always maintained. Resection margins and areas of interest should be recorded. Description should be sufficiently clear that another pathologist can understand the purpose and site of each block.

3.3 Embedding

Intact biopsies should be orientated carefully and embedded on edge, with the epithelial surface perpendicular to the face of the block to be cut by the microtome. The flat, cut face of any sliced specimens must be embedded downwards to ensure that this face is cut by the microtome.

3.4 Sectioning and staining

A single haematoxylin and eosin (H&E)-stained section representing a full face of each block is adequate for the initial microscopic examination of larger specimens but small fragmented biopsies and punch biopsies should be sectioned as recommended for the individual site. Depending on the histological findings, additional levels may be requested.

3.5 Case consultations

It is good practice to consult on cases with colleagues. Departments may choose to designate a time and day for such consults. This allows sharing of experience and provides a learning opportunity for trainees and advanced practitioners. It is recommended that a record of the consultation should be maintained in the LIMS, or other secure system as approved by host institution. Incidence of concordance, discordance, need for additional work (levels, IHC) etc. may be a part of this record. This process can be audited as a part of quality assurance procedures. Documentation on the reporting of names of all pathologists seeing any particular case is not needed. Double reporting is recommended only when mandated by RCPath cancer datasets or other relevant guidelines. It is recommended that policy for double reporting is documented in departmental standard operating procedures (SOPs).

3.6 Standardised format and canned reports

Specimens arising from the cervical screening programme should be reported in a standardised format.[10] Use of a standardised format for other specimens and canned reports can be helpful. This is an individual or departmental decision.

3.7 Ancillary tests

IHC has been included in individual segments of this guidance and as appendices. Molecular tests have not been included as they are used predominantly when a diagnosis of malignancy is made.

4 Vulval and vaginal biopsies

4.1 Vulval and vaginal epithelial biopsies

General principles are followed with regards to specimen handling and processing. Three levels are recommended for small biopsies.

4.1.1 Macroscopic handling

The diameter of punch biopsies should be recorded. Although small punch biopsies may be processed whole, punch biopsies with a diameter of >5 mm may be bisected.

If ellipse excisions for non-neoplastic conditions are wider than 3 mm, they may be bisected longitudinally and both halves processed. It must be appreciated that a histological section along the longitudinal axis may not accurately reflect the nearest peripheral margin. Wider/larger ellipses that include a well-defined lesion should be cut transversely, perpendicular to the long axis of the ellipse, to include the nearest resection margins. If appropriate, the entire specimen should be processed in 2–3 mm serial transverse sections. The sections should be placed in separate cassettes. The blocks containing the end slices should be noted (these will usually be the first and last blocks in the sequence). It may be appropriate to ink the resection margins if the clinician has orientated the specimen, or to assess the clearance margin.

4.1.2 Further investigations

Where appropriate, the following histochemical stains may be requested:

- PAS(D) or Grocott stains for the identification of fungal hyphae and spores
- Elastic van Gieson (EVG) to help confirm lichen sclerosus – the zone of homogenised dermal collagen does not usually contain elastic fibres in contrast to the mid and lower dermis where there is an increase in elastic fibres.

[Level of evidence – GPP.]

IHC p16 can be used in the correct context to confirm a high-grade human papillomavirus (HPV)-associated intraepthelial neoplasia – vulval (VIN) or vaginal (VaIN) (VIN 2/3 or VaIN 2/3) – and to differentiate HPV-associated lesions from mimics.[11]

[Level of evidence – C.]

Aberrant or mutation type (henceforth referred to as aberrant) p53 expression may assist in the diagnosis of differentiated VIN, as may loss of GATA3 expression.[12]

[Level of evidence – C.]

Primary vulvar Paget's disease usually expresses CK7, carcinoembryonic antigen (CEA), CAM5.2, epithelial membrane antigen and GCDFP15. CK20, oestrogen receptor (ER) and progesterone receptor (PR) are usually negative. Secondary vulvar Paget's disease shows a similar immunophenotype to the primary tumour (typically CK20, uroplakin and p63 positive in urothelial carcinoma and CK20, CDX2 and CEA positive in colorectal carcinoma).[13] Pagetoid melanoma is distinguished by the expression of S100 and melanoma markers, and pagetoid VIN by expression of p63, p16 and high molecular weight cytokeratin.

[Level of evidence – C.]

4.1.3 Report content

VIN should be documented as HPV associated or HPV independent.[1] Use of p16 or, if not available, HPV in-situ hybridisation (HPV ISH) is recommended. P16 IHC is available in most UK laboratories. HPV-associated premalignant lesions of the vulva and vagina should be graded. The WHO[1] recommends a two-tier grading system: LSIL (low-grade squamous intraepithelial lesion that includes HPV-related changes and VIN1/VaIN1), and HSIL (high-grade squamous intraepithelial lesion, including VIN2, VIN3, VaIN2, VaIN3).[1] In the UK, the terms LSIL and HSIL are not widely accepted, and VIN/VaIN terminology can be used.

Differentiated VIN is not graded but is automatically regarded as high grade.

HPVI precursors other than differentiated VIN are increasingly recognised. These are p16 negative and show wild type p53 expression.[14]

Resection margins of premalignant lesions must be assessed in excision specimens and documented in the pathology report.

If an invasive component is present, pathologists should use the RCPath cancer dataset for the histopathological reporting of vulval carcinomas.[4]

Pathology reports should try to classify non-neoplastic epithelial diseases of the vulva, e.g. lichen sclerosus, squamous hyperplasia, lichen planus and other vulvar dermatoses according to the International Society for the Vulvovaginal Disease's 2011 terminology as this aids clinical correlation.[15]

4.2 Vulval and vaginal soft tissue lesions

4.2.1 Macroscopic handling

Lesions are usually submitted intact but large, more deeply sited, soft tissue lesions may be submitted in fragments. If appropriate, excision margins can be inked. Larger fragments may need bisection or slicing so that the tissue can be accommodated in a standard cassette. Myxoid, oedematous, haemorrhagic or necrotic areas should be well sampled. Any attached, macroscopically uninvolved tissue must be sampled and examined carefully to identify infiltration/invasion. Where the surgeon has orientated a specimen, excision margins should be sampled.

4.2.2 Further investigations

IHC is of relatively limited value because of considerable immunophenotypic overlap between vulvovaginal mesenchymal lesions. However, a judiciously chosen immunohistochemical panel may be useful, which may include ER, PR, smooth muscle actin (SMA), CD34, desmin, h-caldesmon, CD99, S100 and HMGA2.[16]

[Level of evidence – C.]

Given the overlapping morphology and immunophenotype and the relative rarity of the various mesenchymal lesions at this site, seeking a specialist opinion should be considered.

4.3 Vulval and vaginal cysts

4.3.1 Macroscopic handling

Where possible, the cyst wall should be embedded with the cyst wall and lining perpendicular to the face of the block. If submitted intact, the size of the cyst and the external appearance of the capsule should be recorded. If the clinician orientates the specimen or a neoplasm is suspected, it may be prudent to ink the external surface/cyst capsule to assess the status of the excision margins. In some cases, an ellipse of overlying surface epithelium may be attached. The cyst contents should be noted, as should the wall thickness and the presence of solid and/or papillary areas. These should be preferentially sampled.

Very small cysts can be processed whole. Small cysts may need to be bisected and representative tissue sections of larger cysts should be processed.

4.3.2 Report content

In the vulva, diagnoses include a range of cystic lesions specific to the female genital tract, such as Bartholin’s gland cysts, mucous cysts of the vulva, and cysts that arise in anogenital mammary-like glands, as well as epidermal inclusion cysts and cysts arising in local skin adnexal structures. Common vaginal cysts include Mullerian cysts, epidermal inclusion cysts, Gartner’s duct (mesonephric) cysts, Bartholin’s gland cysts and endometriotic cysts. Although accurate classification is usually possible, it is typically of little clinical significance in benign non-neoplastic lesions. If appropriate, the status of the resection margins should be documented.

Neoplastic, cystic adnexal tumours or rare neoplastic lesions of Bartholin's gland may require IHC and referral for expert opinion.

[Level of evidence – C.]

5 Cervix

5.1 Cervical biopsy (NOS), punch, loop, cone and wedge biopsy

5.1.1 Specimen types

Cervical biopsies (including punch biopsies) are usually carried out as a diagnostic procedure, after an abnormal cervical cytology result. They are colposcopically directed and may be up to several millimetres long and 2–4 mm in diameter. They may be mounted for optimal orientation.

[Level of evidence – D.]

Cervical loop (large loop excision of the transformation zone/LLETZ) and, rarely, cone biopsies are carried out for women with abnormal cytology as part of the 'see and treat' strategy or following a positive punch biopsy.

5.1.2 Macroscopic handling

For cervical biopsies (NOS) and punch biopsies, the number of fragments and the largest dimension of each fragment should be recorded. The colour and texture (mucoid, granular, friable) should be documented.

Cervical loop and cone biopsies (including LLETZ) are roughly conical in shape when received intact.

On most occasions, the specimen is received intact. However, it may be received open at one end (U-shape) or in some instances submitted as multiple specimens/loops.

The specimen(s) should be measured in three dimensions: the antero-posterior, lateral and thickness or depth. A flat/opened loop biopsy must also be measured in three dimensions and care must be taken to provide a clear statement of exactly what is being measured.

If multiple fragments are submitted, the number of pieces is noted and all pieces are measured in three dimensions unless very small when the maximum dimension is sufficient. The colour, consistency and presence of any surface lesions should be recorded. Opening or probing an intact loop or cone biopsy may damage the surface epithelium and must be avoided.

With the updating of the NHS Cervical Screening Programme's colposcopy guideline in September 2021,[17] follow up of individuals over the age of 50 years who have cervical intraepithelial neoplasia (CIN)3 at the deep lateral or endocervical margins, and in whom satisfactory screening samples and colposcopy cannot be guaranteed, repeat excision has been mandated to obtain clear margins. The guideline also states that individuals under the age of 50 with high-grade cervical intraepithelial neoplasia (HGCIN) (CIN2+) on LLETZ or loop specimens at the deep lateral and/or endocervical canal margin do not need to have extra levels or the end blocks turned to assess excisional completion. This implies that macroscopic handling of loops is different in the different age groups.

The most commonly used method is sometimes referred to as 'book-ending' or 'bread slicing' (Figure 1). It is appropriate for individuals 49 years and under. The loop/cone biopsies are sliced serially at 2–3 mm intervals, from one edge to the other in a sagittal and parasagittal plane (beginning at the 3 or 9 o'clock edge), perpendicular to the transverse axis of the external os (see Figures 2–3). In fragmented specimens, the epithelial surface is identified and the specimen is sliced parallel to this surface. This results in a crescendo–decrescendo pattern in

most instances. The slices are laid in sequential, individually designated cassettes to ensure that the sequential faces of consecutive slices are blocked and cut for histology to enable measurement of the third dimension of cervical tumours when necessary. The slices are embedded such that there are no apposing faces except for one end slice and its adjacent slice.

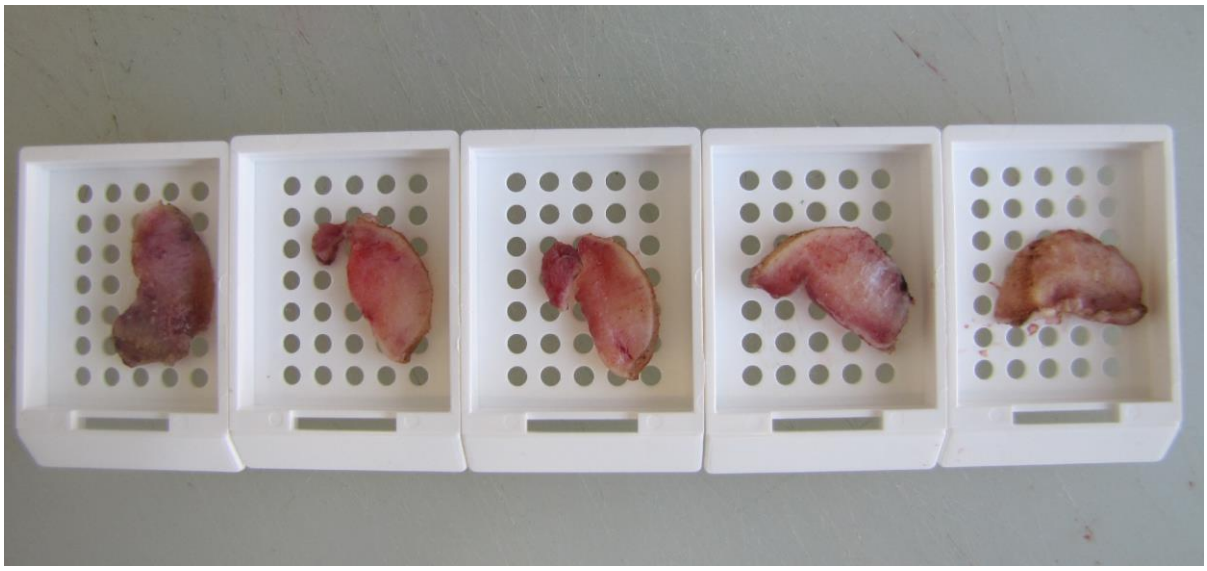

Figure 1. The loop has been 'breadsliced' in 5 slices, approximately 3 mm per slice. Each slice has been placed in one cassette.

The procedure for blocking a loop is to place the surface to be cut face down in the cassette, or, if preferred, to embed the outer (curved) surface of the first and last (edge) slices of the loop, with the outer edge face down for sectioning. The laboratory SOP must identify which approach is used. Each subsequent slice should be placed in a sequential cassette, with cut faces orientated similarly. Each slice of tissue should be placed in a separate cassette and more than one slice (which can be in two pieces) of tissue should not be placed in one cassette. The whole loop excision must be submitted in all cases. In case of 'U' shaped (torn at one edge) or fragmented loops, the ectocervical surface can be a help to orientation. The whole specimen should be sliced at 2–3 mm intervals and blocked sequentially.

In individuals aged 50 and over, the blocks need to be sliced perpendicular to the excision plane to demonstrate the status of the deep lateral margin.

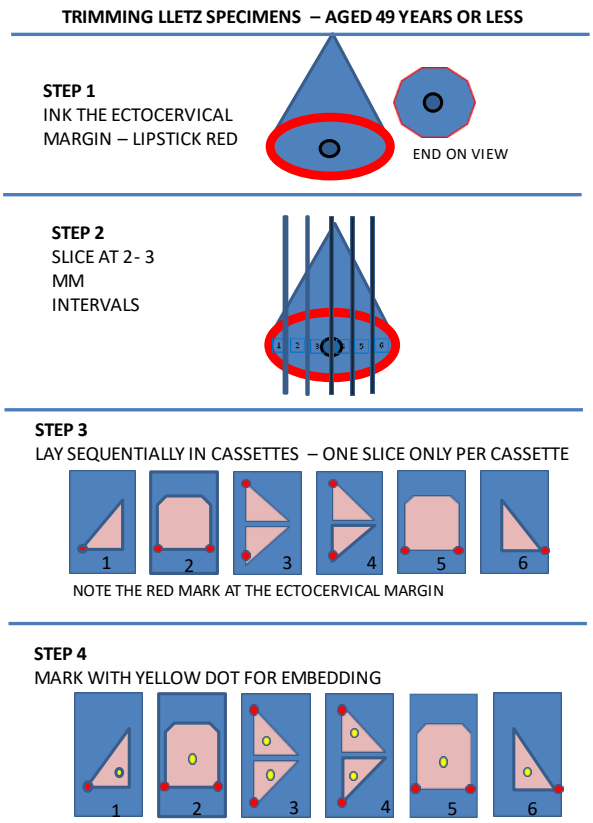

Figure 2. Trimming LLETZ specimens – aged 49 years or less. Reproduced with permission from Dr William Boyle and Dr Jason Wong.

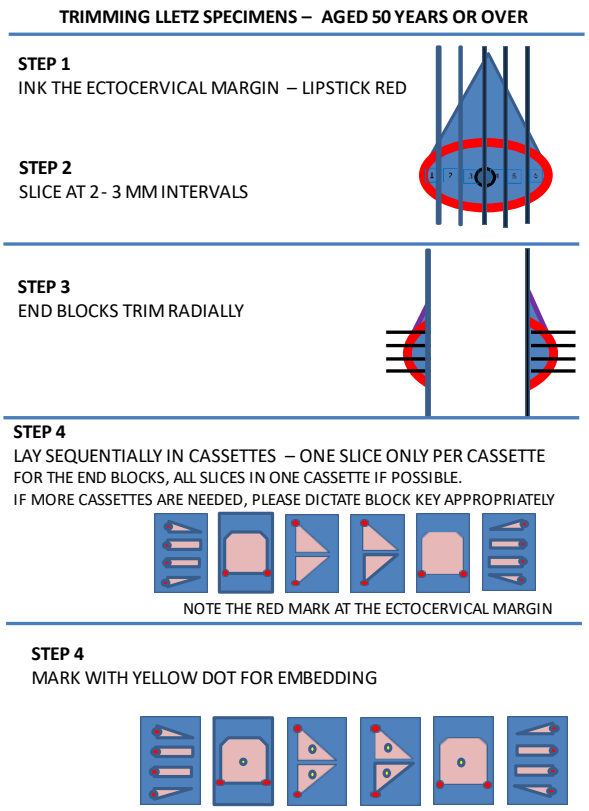

Figure 3. Trimming LLETZ specimens – aged 50 years or over. Reproduced with permission from Dr William Boyle and Dr Jason Wong.

For cervical biopsies (including punch biopsies), three levels should be examined initially. Further levels should be examined if there is a suggestion of an abnormality appearing in the initial levels or if a high-grade abnormality is expected from the cytology and or colposcopy and is not present in the initial 3 levels.

[Level of evidence – D.]

For cervical loop and cone biopsies, a single level full face section from each block is sufficient for initial examination. Further levels may be of value if there are histological features where this may help to clarify the issue, or if there is a need to help correlate with a suggested abnormality based on the cytology report.

[Level of evidence – D.]

If the surface epithelium or squamocolumnar junction is missing, or there is a discrepancy between the histological and cytological findings, a single further level is usually adequate.[10]

[Level of evidence – D.]

If invasive disease is suspected based on the cytological, colposcopic or histological features, further levels must be examined.

5.1.3 Report content[16]

An adequate biopsy for histopathology reporting should: include the transformation zone; be greater than 2 mm in maximum dimensions, intact and not so fragmented as to interfere with reliable interpretation; lack crush artefacts; be adequately fixed and processed; be well orientated; and be well stained. A cervical biopsy must not be classified as inadequate if it shows an abnormality.

A cervical biopsy taken as a result of cytology showing squamous dyskaryosis must be called inadequate if it does not contain squamous epithelium and shows no abnormality. A cervical biopsy taken as a result of cytology showing a borderline endocervical abnormality or glandular neoplasia (endocervical) must be called inadequate if it does not contain any endocervical tissue and shows no abnormality.

Proforma for reporting cervical biopsies and loops are recommended (Appendix A).

5.1.4 Further investigations

p16 immunostaining can be used in the correct context to confirm a high-grade HPV-associated lesion, to assess margins of a loop/cone, to differentiate between metaplastic and neoplastic changes and to assist in the differentiation between atrophy and CIN.[18]

[Level of evidence – C.]

5.2 Manchester repair

5.2.1 Macroscopic handling

Manchester repair is performed for uterine prolapse, and comprises the amputated cervix, usually with one or two triangular pieces of tissue from the anterior and posterior vaginal walls. The cervix is sampled according to the recommended protocols for cervical sampling in a non-malignant hysterectomy specimen, i.e. two midline blocks of cervix, one each from the anterior and posterior cervical lips at the level of the endocervical canal. If possible, block vaginal mucosa tissue in continuity with the cervix.

If there is a history of current abnormal cytology, the specimen is handled as a loop/LLETZ.

5.2.2 Report content

- The report should incorporate the macroscopic description of the specimen.
- If CIN or cervical glandular intraepithelial neoplasia (CGIN) is identified, this must be graded and reported according to the dataset referenced above.

5.3 Endocervical polypectomy

5.3.1 Macroscopic handling

Most endocervical polyps are asymptomatic and identified incidentally at the time of smear taking. They are usually removed by avulsion.

Larger polyps may be removed by excision. The maximum dimension is recorded if submitted as a single polyp. If multiple fragments are sent, measure the size of the smallest and largest. If the fragments are very disrupted and friable, their aggregated size is measured.

If a single large polyp >5 mm is submitted, the polyp is sliced longitudinally parallel to the axis of the stalk and processed completely. If multiple fragments are sent, all fragments are sampled.

5.3.2 Report content

The report should mention lack of CIN or CGIN. In the case or larger or recurrent polyps, diagnosis of adenosarcoma should be considered.

6 Endometrial specimens

6.1 Curettings, pipelle biopsies and transcervical resection of the endometrium specimens

6.1.1 Macroscopic handling

The specimen must be accompanied by a fully completed request form including information about:

- the menstrual status (the last menstrual period [LMP] should be provided for people with pre-menopausal and perimenopausal status)
- any relevant history of hormone treatment or use of tamoxifen in patients with breast carcinoma
- previous endometrial ablation
- endometrial thickness
- presence of intrauterine contraceptive device, where applicable.

The colour and texture of the specimen should be described. A semi-quantitative estimate of the volume by measurement in three dimensions in millimetres or by the maximum dimension is recommended. All the tissue submitted must be processed for histological examination.

6.1.2 Report content

A comment about the adequacy of the sample is appropriate. The adequacy of a sample depends not only on the quantity of material submitted but also on the clinical setting. A scanty specimen may contain sufficient material for assessment in a post-menopausal person with an endometrial thickness of <4 mm and therefore represent an adequate sample. A sample of similar quantity in a pre- or post-menopausal person with thickened endometrium is inadequate. It has been suggested that a specimen is labelled as ‘inadequate’ in the absence of endometrial tissue or ‘not assessable’ where only minimal endometrial tissue was present.[18] This allows the clinician to assess whether the endometrial cavity has been entered but does not alter clinical management.

- The report should indicate the phase of the menstrual cycle and correlate this with the LMP and any other clinical information provided.
- The presence of non-endometrial tissue may be important as the identification of adipose tissue or tissue of bowel wall origin is suggestive of uterine perforation. If only adipose tissue is seen, derivation from a lipoleiomyoma is a possibility. The finding of these tissues should be conveyed to the clinical team as a matter of urgency.
- The presence of cervical tissue should be recorded.
- Endometrial hyperplasia should be classified as hyperplasia with or without cytological atypia.[1]
- Proliferative activity in endometrial samples from post-menopausal women should be reported, as this finding indicates ongoing oestrogenic stimulation. The oestrogenic stimulation may be exogenous, i.e. as a result of hormone replacement therapy/hormone administration or due to endogenous oestrogen production, which may result from an increased body mass index or an ovarian tumour such as a fibroma or granulosa cell tumour.
- Use of canned or template reporting should be considered by individuals and departments. A useful template is provided in the Canadian Consensus-based and evidence-based guidelines[19] and may be adapted for individual or departmental use.

7 Uterus

7.1 Macroscopic handling

Hysterectomy (with or without cervix and the adnexa) may be performed for a wide range of clinical conditions including uterovaginal prolapse, fibroids, adenomyosis, endometriosis, dysfunctional uterine bleeding, persistently abnormal cervical cytology (± previous cervical biopsy/LLETZ) and, in some cases, for obstetric complications. If performed for malignancy, the relevant RCPath cancer datasets must be used.

The uterine serosa represents a barrier for fixative permeation, so the hysterectomy specimen should be promptly sliced and placed in a container with adequate amount of fixative to ensure proper fixation of the endometrium. The slicing may be sagittal or coronal depending on local preference. Surgeons should be educated and encouraged to slice the uterus if there is likely to be a delay in receiving the specimen in the laboratory.

The reason for the hysterectomy should be provided on the clinical request form and any relevant clinical information that may affect histological interpretation should be disclosed. Such information includes prior endometrial ablation, pre-operative treatment with hormones, tamoxifen or uterine embolisation, which can significantly alter the morphology of fibroids. History of rapid growth of a fibroid, especially in a post-menopausal woman, is important.[20] Hysteroscopic/transcervical endometrial resection also changes the appearances of the endometrium and myometrium and may be associated with uterine wall perforation. A patient's cervical screening history may be pertinent if the patient has had previous loop/LLETZ biopsies for CIN and/or if there is persisting abnormal cytology.

Laparoscopic hysterectomies may be submitted as morcellated specimens. There should be a previous endometrial sample to exclude any endometrial abnormality. This procedure should not be performed if there is a history of atypical endometrial hyperplasia or gynaecological neoplasia.

If the hysterectomy is performed for an obstetric complication, the clinician must specify at what stage of the delivery the uterus was removed, what the indication for the hysterectomy was (intractable intra-partum/post-partum haemorrhage, uterine rupture, abnormal placental implantation) and if there is a history of a previous Caesarean section. If relevant, the condition of the newborn should be available.

The specimen should be orientated using the following anatomical landmarks:

- the posterior peritoneal reflection that extends lower on the surface of the pouch of Douglas in comparison with the anterior peritoneal reflection
- the ovaries, sited posterior to the fallopian tubes.

The weight of the uterus can be recorded if desired. Although it is standard practice to measure the uterus in millimetres in three dimensions, the dimensions and weight of the uterus are variable and are related to age, parity, body mass index, phase of the menstrual cycle and other associated pathological processes (fibroids, adenomyosis, etc.) and are therefore of limited clinical significance. The length of the vaginal cuff where it is longest may be recorded. It is more important to record the specimen components and the presence of any developmental abnormalities such as arcuate, bicornuate, didelphys or unicornuate uterus or any focal abnormality.

The absence of a cervix must be noted in subtotal hysterectomy specimens as young patients who undergo this procedure will still require cervical smears as part of the National Cervical Screening Programme. The submission of both intact adnexa must be confirmed when a risk-reducing (prophylactic) hysterectomy is carried out for a family history of ovarian cancer.

Surgical or traumatic lesions and serosal abnormalities, e.g. adhesions or endometriosis, should be described. If the uterus has been perforated, the presence and location of the perforation must be recorded. Interruptions in the fallopian tubes as a result of prior tubal ligation should be recorded and sterilisation clips that are present in the fallopian tubes should be described. If a vaginal cuff is attached, this is usually asymmetrical; the cuff should be measured in millimetres where it is longest.

[Level of evidence – C.]

Note recent or past Caesarean section sites in hysterectomies performed for obstetric complications. A recent Caesarean section usually takes the form of a transverse incision through the anterior lower uterine segment. Rarely, a vertical, classical surgical incision through the uterine body may be performed. If uterine rupture is identified, the site should be clearly and carefully described, as should abnormal sites of placental implantation. There may be medicolegal issues associated with obstetric hysterectomies and photographic images of these specimens are recommended. It is advisable to enquire about the patient's clinical status. If there is an association with maternal death, it is best to send the specimen to the pathologist performing the post mortem or, at the very least, to liaise with them.

Morcellated specimens are submitted in multiple pieces, but it may be possible to identify endometrial, endocervical or serosal surfaces and fibroid-derived fragments. The preoperative introduction of intrauterine methylene blue is an easy, cheap, harmless and quick method to reduce the time spent on macroscopic examination,[21] as it allows identification of the endometrial lining.

If the hysterectomy has been done for persistent abnormal cervical cytology or if a cervical lesion is suspected, the cervix should be amputated and dissected in the same way as a LLETZ or cone biopsy (see section 5.1.2 above).

There are several ways of opening the uterus, depending on the preference and experience of the pathologist. Some pathologists prefer to open the uterus in the sagittal plane while others open it coronally along the lateral borders and between the cornua. The method of opening may be affected if the uterus is markedly distorted, e.g. by multiple fibroids. Opening should be adjusted to optimally expose the uterine cavity. Gentle probing of the uterus may be necessary to aid the identification and orientation of the cavity. Whatever the method of opening, the uterine cavity should be exposed for inspection. The myometrium can then be examined by multiple parasagittal or horizontal incisions.

The appearance of the cervix should be described, and notes made if there is scarring as a result of previous loop/LLETZ biopsies and if any polyps are present.

The appearance of the endometrium (cystic, granular, irregular) should be noted. The endometrial thickness in millimetres should be recorded. If endometrial polyps are present, the number, size, location and appearance of the polyp(s) should be noted. The presence and location of an intrauterine device, if present, should be noted. When fibroids are present, their number (an estimate is acceptable if numerous), size (usually of the largest and smallest fibroid if they are multiple), location (submucosal, intramural or subserosal), outline (discrete or poorly defined), texture (firm, soft, gritty), colour and appearance (whorled, cystic, presence of fatty, calcified or myxoid areas) should be recorded. It is important to note the presence of necrosis. Haemorrhage, if present, may be focal/spotty or widespread and may be associated with necrosis.

7.2 Block selection

7.2.1 Cervix

If the cervix is grossly normal, one representative block is taken from the anterior and the posterior cervical lips, including the transformation zone. The entire transformation zone must be sampled if there is a recent history of CIN or CGIN or if the most recent cervical cytology sample was abnormal.

Endometrium: if no focal abnormality is seen, two blocks – one each of the full thickness of the anterior and posterior uterine walls – are submitted. Any focal abnormality should be completely sampled. There is a small but definite risk of carcinoma even with a pre-operative diagnosis of non-atypical hyperplasia.[22] There is no evidence in the literature on block taking for hysterectomy for endometrial hyperplasia. Based on author practice, a minimum of four blocks each from the corpus, isthmus and cornua is recommended. If hyperplasia is not identified at microscopy in a patient with a prior biopsy diagnosis of hyperplasia, the remaining endometrium will need to be sampled. When there is a preoperative diagnosis of atypical hyperplasia, specimens should be handled in the same way as hysterectomy for endometrial adenocarcinoma.

[Level of evidence – D.]

7.2.2 Myometrium

Fibroids/leiomyomas (note that the term ‘fibroid’ should only be used for the macroscopic description) are common and leiomyosarcomas are rare, so the majority of uterine smooth muscle tumours are likely to be benign. When fibroids appear typical on gross examination, minimal sampling, usually one block of the largest fibroid and one or two others selected at random, will suffice. More extensive sampling is required if clinical information is provided that suggests unusually rapid growth or abnormal radiological appearances, particularly in post-menopausal status. The presence of softening, haemorrhage, cystic degeneration or variation in colour should prompt more extensive sampling. The junction with myometrium should be sampled.

7.2.3 Adnexa

See sections 9 and 10.

7.2.4 Block selection in specific situations

Morcellated hysterectomy: attempts should be made to sample the cervical, endometrial and serosal surfaces and any focal lesions such as polyps or fibroids. This may be easier, if pre- or intraoperative injection of methylene blue was done.[23]

Obstetric hysterectomy: several blocks of the fresh Caesarean section site should be taken, as should the edges of a traumatic rupture. Ragged, haemorrhagic tissue lining the uterine cavity may represent retained, adherent placental tissue and should be sampled thoroughly. In cases of placenta praevia, accreta and increta, the interface between the placenta and adjacent myometrium should also be sampled.

Prophylactic hysterectomy for Lynch syndrome: in the absence of a macroscopic lesion in the endometrium, the entire endometrium including the lower uterine segment and cornua should be submitted for histological examination. The myometrium does not have to be submitted in its entirety. The adnexa should be handled according to the sectioning and extensively examining the fimbriated end (SEE-FIM) protocol for risk-reducing (prophylactic) bilateral salpingo-oophorectomy specimens.[6,24]

[Level of evidence – C.]

7.2 Further investigations

ABPASD is helpful in differentiating between oedema and myxoid change in leiomyomas and in the diagnosis of myxoid smooth muscle tumours. SMA, desmin, CD10 and h-caldesmon may be helpful to differentiate endometrial stromal from smooth muscle lesions, although there may be immunophenotypic overlap.

p53 and Ki67 immunostaining of stretches of cytologically atypical epithelium in the fallopian tube or endometrial cavity, especially on the surface of polyps, can be helpful to confirm serous tubal intra-epithelial carcinoma (STIC) or serous endometrial intra-epithelial carcinoma.[6,24]

[Level of evidence – C.]

7.3 Report content

- Cervix: report CIN and CGIN if present and assess excision margins.
- Endometrium: if the hysterectomy was performed for hyperplasia, comment on the presence of residual/persistent hyperplasia. Report on polyps if these are present and the effects of hormonal therapy.
- Myometrium: comment on presence or absence of adenomyosis. If leiomyomas are present, assess and comment on the following features if appropriate:
  - recognised variants including cellular, epithelioid, mitotically active, myxoid, dissecting/cotyledonoid, hydropic, apoplectic and lipomatous leiomyomas, also leiomyoma with bizarre nuclei
  - degenerative changes (hyaline, hydropic, including perinodular hydropic and red degeneration)
  - unusual growth patterns (dissecting or intravenous growth patterns)
  - junction with normal myometrium
  - mitotic activity as number of mitoses/10HPF; 1HPF = 0.1734 mm^2, if increased
  - necrosis (coagulative or ischaemic/infarct type)
  - nuclear atypia (severity, distribution – diffuse or localised)
  - lymphovascular involvement.
- Uterine serosa: report on endometriosis or endosalpingiosis if present.
- Obstetric hysterectomy: report on the state of any tears/rupture, the Caesarean section site, the site of placental implantation (note if this is ectopic, i.e. in the fallopian tube, cervix or on the serosa), the presence of placenta praevia, the state of the placental bed and on infiltration of the myometrium by placenta accreta, increta or percreta. The identification of subinvolutional changes in placental bed vessels may be the cause of post-partum bleeding.

8 Myomectomy and morcellation specimens

8.1 Macroscopic handling

Myomectomies may be performed laparoscopically, hysteroscopically or during the course of laparotomy. One or more fibroids may be resected, and usually submitted intact if removed at laparotomy. If removed laparoscopically or hysteroscopically, the fibroids may be submitted as disrupted fragments or morcellated specimens.

All relevant clinical information that may affect histological interpretation should be provided. Such information includes prior endometrial ablation, pre-operative treatment with hormones, tamoxifen or uterine embolisation, all of which can significantly alter the morphology of fibroids.

Intact myomectomy specimens should be measured. In the presence of multiple fibroids, a range with measurement of smallest and largest is sufficient. The presence of a smooth serosal surface should be noted and suggests a subserosal origin. The fibroid(s) should be sliced at 5–10 mm intervals and the cut surfaces examined and described. Fragmented or morcellated specimens should be measured and a semi-quantitative estimate of the volume should be provided by measurement in three dimensions in millimetres. Fragmented or morcellated specimens must also be sliced. The cut surface should be described. If slicing reveals any difference to the typical macroscopic appearance of a white, whorled cut surface, this must be noted. Sampling should be undertaken as recommended for fibroids at hysterectomy. In pre-menopausal women with no unusual history or imaging findings, up to three representative blocks of morcellated or fragmented specimens will suffice. If there is any abnormality in appearance or unusual clinical/imaging history, there must be more extensive sampling. Where possible, the blocks should include the interface between the normal myometrium and the fibroid. In any instance, when the appearance on histology is not that of a typical benign leiomyoma or the common benign variants, further tissue should be sampled.

8.2 Report content

Leiomyomas (and their variants) should be reported in a similar manner to leiomyomas that are identified in hysterectomy specimens (see section 7.3 above). Diagnosis of a leiomyoma with bizarre nuclei may not be possible on a morcellated specimen and it is advised that more tissue is sampled. The report carries a caveat that the lesion needs complete removal to be confident of the diagnosis.

9 Ovary

9.1 Oophorectomy, ovarian cystectomy, ovarian biopsy

9.1.1 Macroscopic handling

Non-neoplastic ovaries may be removed as part of a total abdominal hysterectomy and bilateral or unilateral salpingo-oophorectomy for uterine, pelvic, ovarian or tubal disease. Ovaries, usually with the attached fallopian tube, may be removed without the uterus for pelvic pain (often due to pelvic inflammatory disease or adhesions), cysts, mass lesions, endometriosis and torsion/oedema or as a prophylactic measure in women with breast cancer (BRCA) gene mutations. Wedge biopsies may be undertaken to investigate infertility, polycystic ovarian disease or for other specific clinical indications. Cystectomy is performed for clinically and radiologically benign cysts and to preserve fertility.

9.1.2 Specimen dissection and block selection

Avoid excessive handling of the surface to prevent abrasion of the delicate covering mesothelium. Measure the ovary in three dimensions and describe the appearance of the ovarian surface – any capsular breaches/tears, surface papillary or solid projections must be recorded and measured.

Slice small post-menopausal ovaries in the coronal/longitudinal plane, or serially in the parasagittal plane in prophylactic salpingo-oophorectomy specimens. Note any cysts; measure their size in three dimensions, record their internal structure (unilocular, multilocular, solid or papillary areas) and describe their contents (watery, serous, mucoid, gelatinous, blood-stained, altered blood ('chocolate'-like material). Physiological cysts may measure up to 20 mm in diameter. For cysts with complex internal structures, solid or papillary areas, follow the guidelines in the *Dataset for Histopathological Reporting of Carcinomas and Borderline Tumours of the Ovaries, Fallopian Tubes and Peritoneum*.[7] Thin-walled cysts are sampled by

rolling up the wall to give a ‘Swiss roll’ block. Sample and describe para-ovarian cysts in the same way. Block the cyst wall, solid, soft or papillary areas in endometriotic cysts to exclude/document atypia, hyperplasia or tumour. In dermoid cysts, there may be hair or sebum in the cyst lumen, with bone and teeth in the cyst lining and wall. Take blocks from the nodule protruding into the cyst cavity (Rokitansky protuberance), when visible, and cyst wall.

One block is sufficient for a normal ovary. The block should include cortex, medulla and hilum. Several blocks may be needed for otherwise normal ovaries larger than 25 mm in the greatest dimension. Block papillary and solid areas to identify possible borderline tumours.[8] One block per centimetre of solid or papillary area is recommended.

[Level of evidence – D.]

If the ovary contains a solid tumour or tumour component on slicing, measure the maximum dimensions of the solid component, and describe its colour and appearance (whorled, calcified, haemorrhagic, yellow). Try to identify residual ovary if possible.

Block the entire wedge biopsy specimens and ensure a vertical section through the cortex, medulla and capsule. Small samples can be bisected along their long axis. Take multiple blocks from larger samples at right angles to the long axis of the specimen.

Block the whole ovary (and fallopian tube) in patients with BRCA mutations who have prophylactic salpingo-oophorectomies according to the SEE-FIM protocol to identify any microscopic tumours or precursor lesions.[24]

[Level of evidence – C.]

9.2 Further investigations

A reticulin stain may be helpful to identify the structure of the ovary in infarcted/torted specimens. IHC may be required to characterise ovarian tumours.[1]

9.3 Report content

Oophorectomy for pelvic pain: fibrous capsular adhesions may be present as a result of endometriosis or past pelvic inflammatory disease. Note the presence of inflammation and evidence of old/recent bleeding. Two of three features: organising blood, endometrial-type stroma and endometrioid epithelium are required for a diagnosis of endometriosis. Occasionally stromal endometriosis, i.e. endometriosis that consists only of endometrial-type stroma and no endometrial glands, is seen.

Oophorectomy for venous infarction/torsion: there may only be minimal viable ovarian tissue for assessment. If the architecture of a neoplasm is identified, it may not be possible to determine its nature if the ovary is completely infarcted.

Wedge biopsy for infertility: note the presence of primordial follicles and signs of previous ovulation, such as corpora albicantia and lutea. Record the finding of dysmorphic follicles, inflammation and fibrous capsular thickening with abnormal cystic follicles in polycystic ovaries.

Oophorectomy for ovarian cyst(s): record the nature of functional cysts, the presence of Müllerianosis or endometriosis. If there is a benign ovarian epithelial tumour, this should be classified according to the 2020 WHO classification of female genital tract tumours.[1] Atypically proliferative/borderline ovarian tumour and cancers should be reported according to the *Dataset for Histopathological Reporting of Carcinomas and Borderline Tumours of the Ovaries, Fallopian Tubes and Peritoneum*.[7]

10 Fallopian tube

10.1 Macroscopic handling

Short segments of the fallopian tube are most commonly resected as part of a sterilisation procedure, and either a segment or the entire fallopian tube may be excised for hydrosalpinx, pelvic inflammatory disease, endometriosis or ectopic pregnancy. The laterality of the tubes (or segments of tube) should be indicated ('left' and 'right') by the clinician to enable subsequent exploration of the correct site if necessary.

Fallopian tubes may be submitted with an excised ovary, or with total abdominal hysterectomy and oophorectomy specimens for a range of benign and malignant conditions.

Fallopian tubes also accompany oophorectomy specimens when risk reducing surgery is performed.

10.2 Specimen dissection and block selection

SEE-FIM is the optimal way to examine normal appearing fallopian tubes in the setting of risk reduction for pelvic neoplasia in women with genetic syndromes (Figure 4).[6,24] It may not be practical to use this protocol for all fallopian tube specimens taken for benign conditions, given the low risk of diagnosing significant lesions.[25] We recognise the value in sampling the fimbrial end of tubes and encourage sampling the fimbrial end, with or without a transverse section, as an opportunity to identify precursor lesions and occult cancer in the general population.[26] This does not apply to sterilisation specimens, where a transverse section is mandated.

[Level of evidence – D.]

10.2.1 Tubal segment for sterilisation

Measure the length and diameter of the tube segment in millimetres and note if the fimbrial end is included. Submit at least one transverse slice of each fallopian tube to confirm the presence of fallopian tube in full cross-sectional profile. Consider taking two cross sections to optimise identification of a full face.

10.2.2 Salpingectomy for sterilisation

Measure the length and maximum diameter of the tube in millimetres and describe the appearances of the fallopian tube and fimbrial end. Document any macroscopic abnormality. Note any serosal abnormality (adhesions, haemorrhage, adherent cysts) and evidence of previous surgery, including indications of past sterilisation such as the presence of Filshie/Hulka clips or device, e.g. Essure system. Take at least one block (one or two cross sections) of each fallopian tube to confirm a full cross-sectional profile.

10.2.3 Failed sterilisation

Measure the length and maximum diameter of the tube in millimetres. If the tube is distorted, it may not be possible to obtain accurate macroscopic dimensions. It may be helpful to photograph the specimen(s), including patient details, date and time as the subsequent findings may have medicolegal implications. Note the presence of fimbriae and any other signs of previous surgery, such as suture material, devices or clips. Note the position of any clips, devices or suture material. Block the whole tube (levels may be necessary) to identify possible recanalisation. Where there is gross distortion, it may be necessary to take longitudinal blocks.

10.2.4 Salpingectomy for ectopic pregnancy

Record the length and maximum diameter in millimetres of the tube. Note any areas of rupture and describe the contents of the tube. Sample the dilated portion of the tube or implantation site on the surface of the tube. Also sample the non-dilated tube, usually the isthmic end, to document pre-existing inflammation or structural abnormality. Separately submitted blood clots

in the specimen container may contain products of conception (POC) and should also sampled. Document whether any fetal tissue is present. Follow HTA guidance regarding handling and disposal of pregnancy remains. A standard operating procedure must be place that details the method of sensitive disposal of specimens containing fetal tissue/parts.[27]

10.2.5 Risk-reducing (prophylactic) salpingo-oophorectomy for inherited/familial cancers

See section 9 above. Follow the SEE-FIM protocol and process all tissue, i.e. after fixation, the distal 20 mm of the fallopian tube (infundibulum and fimbria) is processed longitudinally in sections of approximately 2 mm thickness and the remaining tube is processed as 2 mm cross sections (Figure 2).

[Level of evidence – C.]

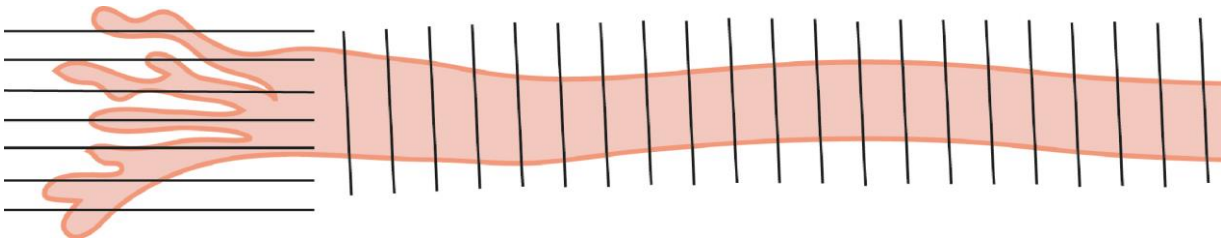

Figure 4. The fallopian tube should be completely sampled. The fimbrial end is sampled in slices 2–3 mm thick and the slices are oriented perpendicularly. The rest of the tube is sampled in tranverse, parallel slices 2–3 mm thick. This maximises the visualisation of tubal epithelium. Diagram copied from the *Dataset for Histopathological Reporting of Carcinomas and Borderline Tumours of the Ovaries, Fallopian Tubes and Peritoneum*.[7]

10.3 Report content

10.3.1 Tube segment or salpingectomy for sterilisation

Confirm that fallopian tube is present and a complete cross-sectional profile of the fallopian tube is seen. Report any abnormalities.

10.3.2 Failed sterilisation

Confirm that a complete cross-sectional profile of the fallopian tube is identified. Identify and document evidence of previous surgery, including the presence and position of clips or device. Note if recanalisation is present; this may require additional levels.

10.3.3 Salpingectomy for ectopic pregnancy

The identification of a placental implantation site, villi or fetal parts confirms an ectopic gestation. Document any pre-existing pathology that may have predisposed to the development of an ectopic pregnancy, e.g. pelvic inflammatory disease, tubal diverticulum or endometriosis. The presence of an implantation site confirms tubal pregnancy; the presence of villi alone is suggestive but not diagnostic of the same. In practice, the presence of chorionic villi is considered evidence of a tubal pregnancy. HTA guidance must be followed for disposal of tissue in an ectopic pregnancy.[27]

10.3.4 Salpingectomy for pelvic inflammatory disease

Record the presence of inflammation (acute, subacute, chronic, xanthogranulomatous). If present, report on the presence of plical fibrosis, fusion, simplification and salpingitis isthmica nodosa. Exclude malakoplakia and other causes of granulomatous inflammation. Histochemical stains can be performed to identify specific microorganisms but in most instances the clinician would have submitted material for microbiological testing.

10.3.5 Salpingectomy for other reasons

Document any significant incidental findings such as epithelial metaplasia, endometriosis or STIC, if present.

10.3.6 Risk-reducing (prophylactic) salpingo-oophorectomy for inherited/familial ovarian cancer and Lynch syndrome

Record the presence of STIC or carcinoma using the *Dataset for Histopathological Reporting of Carcinomas and Borderline Tumours of the Ovaries, Fallopian Tubes and Peritoneum*.[7]

[Level of evidence – C.]

11 Products of conception (pregnancy remains, pregnancy loss)

11.1 Purpose of pathologic examination

Examination of POC is required for documentation of (intrauterine/ectopic) pregnancy, exclusion of gestational trophoblastic disease (GTD) and confirmation of suspected or unsuspected fetal anomalies (if possible).

11.2 Specimen submission

Most specimens are submitted to the laboratory fixed in formalin. In some situations, e.g. if the patient has a history of recurrent miscarriages, fresh specimens may be submitted because karyotyping will be required in addition to routine histopathology. The request for karyotyping should be clearly indicated on the request form and the laboratory should have standard operating procedures in place to facilitate the transfer of some of the fresh tissue to a genetics department.

[Level of evidence – D.]

All specimens must be accompanied by a fully completed request form with clinical information, optimally including ultrasound appearance, gestational age, history of previous trophoblastic disease, serum human chorionic gonadotrophin (hCG) level and date of delivery in cases of post-partum haemorrhage.

POC are sometimes sent in a length of stockinette or in the receptacle of a suction device. If the specimen is bulky, it may be preferable to open the stockinette to ensure adequate overnight fixation prior to specimen sampling.

11.3 Types of specimens received

Specimens submitted include POC/retained POC, ectopic pregnancy and, very rarely, tissue originating from medical termination of pregnancy (MTOP) and suction termination of pregnancy (STOP).

Tissue from MTOP or STOP is not usually submitted for histopathological examination if a viable pregnancy is confirmed and fetal parts have been identified on prior ultrasound examination. When an abnormality is seen on the ultrasound scan or this is a non-viable/failing pregnancy, histological examination of the tissue is advised.[28,29]

[Level of evidence – D.]

11.4 Specimen dissection and block selection

Estimate the volume or measure the specimen in three dimensions. Describe the colour and consistency. Comment on whether spongy placental tissue and/or a gestational sac is present. Measure the maximum dimension of the gestational sac, if present, and describe the contents. Glistening membranous tissue may include the implantation site and should be sampled. Look for vesicles suggestive of trophoblastic disease. Measure the maximum vesicle diameter in

millimetres. Comment on the presence of fetal parts. If identified, measure the foot length of the foetus. Avoid sampling fetal tissue. There is no uniform or evidence-based practice to deal with unintentionally sampled fetal tissue. It is recommended that departmental SOPs reflect departmental practice.

11.4.1 Sampling for miscarriage/abortion

Determination of the number of sections to submit for microscopic examination is based on the index of suspicion for underlying pathology.

[Level of evidence – D.]

In a therapeutic abortion in which no macroscopic abnormalities are noted, one cassette, which includes villous tissue and a small portion of decidua with an implantation site, is usually adequate. In a spontaneous abortion, at least two cassettes should be submitted.

However, as the clinical indication is not always provided on the request form, depending on the local protocol, 1–2 blocks (containing sufficient villous tissue) must be examined, and further blocks may be required if the initial section has failed to confirm intrauterine pregnancy or there is a suspicion of trophoblastic disease or malignancy. The threshold for additional sampling should be low to avoid missing a GTD.[30]

In the absence of chorionic villi, trophoblast or fetal tissue, the possibility of an ectopic pregnancy should be considered. Additional tissue should be submitted to ensure the diagnosis of an intrauterine pregnancy is not missed. There is variation in practice in the amount of additional tissue sampled.

[Level of evidence – D.]

11.4.2 Sampling for suspected molar pregnancy

If there is clinical suspicion of molar pregnancy, vesicles are identified macroscopically. If the histological differential diagnosis is villous dysmorphism/abnormal villous morphology and partial hydatidiform mole, then four blocks should be sampled upfront. This is especially important in cases of partial mole, as only a small percentage of villi may be abnormal. In all cases of hydatidiform mole, usually four blocks are sufficient to establish a diagnosis. Extensive sampling and/or sampling of the entire tissue is not required in the cases where sufficient molar villi are identified in the initial sections. When atypical or pleomorphic villi are identified, the specimen should not be discarded until a specialist opinion has been received from the supraregional trophoblastic disease unit.

11.5 Report content

Comment on presence and appearance of chorionic villi (normal, sclerotic, oedematous). If placental membranes or microscopic fetal tissue are present, this should be reported. If villi are absent, the presence of placental implantation site trophoblasts or fetal tissue confirms an intrauterine pregnancy. If gestational endometrium or decidua are present but no placental implantation site or trophoblast is identified, then an ectopic pregnancy should be suspected. Mechanisms should be in place for quick communication of results to the ward and/or clinician. If there are scanty or no villi, the report should note the scanty sample, suggest an inability to rule out GTD and suggest monitoring serum HCG return to normal. If no villi or implantation site is identified and only nests and sheets of atypical extravillous trophoblast are identified, further blocks must be taken to exclude GTD.

It is unusual to see smooth muscle in these specimens but, if present, it should be commented upon. The presence of smooth muscle may be due to a submucosal leiomyoma but, if deep curettage has been performed, there is a possibility of developing subsequent intrauterine adhesions.[31]

If GTD is identified, i.e. partial or complete hydatidiform mole, choriocarcinoma, placental site or epithelioid trophoblastic tumour, the pathological features should be described and clearly reported and the information should be communicated to the ward and/or clinician urgently if the diagnosis is unexpected.

A diagnosis of GTD will result in reflex referral of the patient to one of three national centres for the investigation, treatment and follow-up of patients with trophoblastic disease. These centres are based at Charing Cross Hospital (London), Weston Park Hospital (Sheffield) and Ninewells Hospital (Dundee). Central review of diagnostic material will take place and laboratories should document despatch of the material required for review. This should include all the H&E slides and one representative block, including villi and at least some decidua. Once the diagnosis of GTD is confirmed, it is likely that this material will be archived in the centres and will be returned only in exceptional circumstances.

11.6 Further investigations

Immunohistochemical studies may be necessary, depending on H&E appearances.

p57KIP2 helps in confirming a diagnosis of complete hydatidiform mole;[32,33] however, it cannot be used to differentiate between partial hydatidiform mole and villous dysmorphism secondary to non-molar aneuploidy gestation and hydropic abortus. Further use of ancillary techniques is noted in Appendix C.

[Level of evidence – B.]

11.7 Specimen disposal

An SOP must be in place that details the method of sensitive disposal of specimens containing fetal tissue/parts.[34]

12 Criteria for audit

The following are recommended by the RCPath as Key assurance indicators (see *Key Assurance Indicators for Pathology Services*, November 2019) and key performance indicators (see *Key Performance Indicators – Proposals for Implementation*, July 2013):

- cancer resections should be reported using a template or proforma, including items listed in the English COSD, which are, by definition, core data items in RCPath cancer datasets. English trusts were required to implement the structured recording of core pathology data in the COSD
  - standard: 95% of reports must contain structured data.
- histopathology cases must be reported, confirmed and authorised within seven and ten calendar days of the procedure
  - standard: 80% of cases must be reported within seven calendar days and 90% within ten calendar days.

12.1 Staffing and workload

Periodic reviews should be performed on the numbers and types of specimens reported by each pathologist, and on compliance with EQA and RCPath CPD.

12.2 Timeliness of report

Confirmation of compliance with *Key Assurance Indicators for Pathology Services* is required by an annual (as a minimum) audit of performance against locally agreed turnaround times and targets (Key Assurance Indicator 18: Turnaround times linked to patient pathways).

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Appendix A Cervical biopsy reporting proforma

Macro
Number of pieces:
Size of pieces (one dimension only): …mm

Micro
Cervical screening sample: Yes/No
Adequate: Yes/No
If no Please state reason (may be multiple)
No transformation zone
No endocervical tissue
Too small/fragmented
Artefact (specify) ……

Number of levels examined:

Transformation zone: Present/Absent
HPV-related changes: Present/Absent
CIN: Present/Absent

Grade: 1/2/3/ungradable (state why ungradable, favour high or low grade if possible)

Crypt involvement: Present/Absent
High grade CGIN: Present/Absent
SMILE: Present/Absent
Invasion: Present/Absent

p16 performed: Yes/No
If yes, please give indication and result: ……

Identified for MDT: Yes/No
If yes, please give indication: ……

Mismatch with cytology/high grade CGIN/invasive carcinoma/interesting case/other (specify) …….

May need to include
Screening cytology results/colposcopic findings are not provided. Please determine if the case is required for discussion at the multidisciplinary meeting.

Diagnosis:

Cervical biopsy:

Codes
M76720 HPV
M74006/7/8 CIN1/2/3
M81402 CGIN
M80703 SQUAMOUS CELL CARCINOMA
CPMDT
M81403 ADENOCARCINOMA

Appendix B Loop/LLETZ reporting proforma

Macro
This is a LLETZ specimen/cold knife cone/other.
This specimen was received in …… piece(s).
This measures … mm x … mm x … mm (in depth).
The cervical os is complete/incomplete.
A lesion is seen (describe and measure the lesion)/no lesion is seen.
The specimen is serially sliced and embedded in … blocks (give the block numbers). The end slices are present in … (give block numbers).

Micro
The loop was examined in …… slices.

These do (not) include the cervical transformation zone.

There is CIN1/CIN2/CIN3 (delete as appropriate) in …… slices/there is no evidence of CIN.

HPV related changes: Present/Absent
Extension into crypts: Present/Absent
High grade CGIN: Present/Absent
SMILE: Present/Absent
Stromal invasion: Present/Absent (if present, use cervical cancer reporting proforma)

Excision margins (delete as appropriate):
Endocervical margin – clear/involved by CIN (grade)/CGIN
Ectocervical margin – clear/involved by CIN (grade)/CGIN
Deep radial margin – clear/involved by CIN (grade)/CGIN

Any other features: chronic cervicitis/tuboendometrioid metaplasia/endometriosis/microglandular hyperplasia/none/other (specify) …….

p16 performed: Yes/No
If yes, please give indication and result:

Correlation of histology with cytology (or recent biopsy): Yes/No

Identified for MDT (delete as appropriate):
Mismatch with cytology
High grade CGIN
Invasive carcinoma
Interesting case
Other (specify) …….

May need to include
Screening cytology results/colposcopic findings are not provided/please determine if the case is required for discussion at the multidisciplinary meeting

Diagnosis:

Cervical LLETZ specimen:

Codes
M76720 HPV
M74006/7/8 CIN1/2/3
M81402 CGIN
M80703 SQUAMOUS CELL CARCINOMA
CPMDT
M81403 ADENOCARCINOMA

Appendix C Ancillary tests in gestational trophoblastic disease

p57KIP2 helps confirm a diagnosis of complete hydatidiform mole; however, it cannot be used to differentiate between partial hydatidiform mole and villous dysmorphism secondary to non-molar aneuploidy gestation and hydropic abortus.

p57KIP2 is a cyclin-dependent kinase inhibitor that is paternally imprinted and maternally expressed. Complete moles lack maternal genes and have androgenetic diploidy; therefore, p57KIP2 expression in villous cytotrophoblast and villous mesenchymal cells is absent or minimal. Normal syncytiotrophoblast does not usually express p57KIP2 (negative control) while nuclear positivity is seen in decidua and extravillous trophoblast (positive control) in all specimens, including complete hydatidiform mole. In partial hydatidiform mole, non-molar aneuploidy gestation and hydropic abortus (all of which contain maternal genes) villous cytotrophoblast and villous mesenchymal cells are positive for p57KIP2. Molecular genotyping is the gold standard test for differentiating these lesions but can only be performed in a limited number of cases. Ki-67 and hCG immunostaining have no role in diagnosis or sub-typing of molar pregnancy.

All trophoblastic cell lineages express cytokeratins (AE1/3, CAM 5.2), inhibin, GATA-3[35] and CD10. Human placental lactogen (hPL), MelCAM, β-hCG, PLAP and p63 can assist in the identification of particular trophoblastic populations.

Trophoblastic tumours (choriocarcinoma [CC], placental site trophoblastic tumour [PSTT] and epithelioid trophoblastic tumour [ETT]) all express cytokeratins (AE1/3, CAM 5.2), inhibin, GATA-3 and CD10. PSTT expresses hPL, MelCAM focal β-hCG and is p63 negative, whereas ETT is positive for p63 and PLAP and is usually negative for hPL. Choriocarcinoma is positive for β-hCG and other trophoblastic markers.

Trophoblastic tumours/tumour-like lesions	**Cell Types**	**IHC**
Choriocarcinoma (CC)	Cytotrophoblast, syncytiotrophoblast and villous intermediate trophoblast	Cytokeratins (AE1/3, CAM 5.2), inhibin, GATA-3 and CD10 Diffusely positive for hCG, hPL and SALL4 in syncytiotrophoblast; Ki-67 proliferation index >70%
Placental site trophoblastic tumour (PSTT)	Implantation site intermediate trophoblast	Cytokeratins (AE1/3, CAM 5.2), inhibin, GATA-3 and CD10 hPL and MCAM; scattered multinuclear cells positive for hCG. Ki-67 usually >10%
Epithelioid trophoblastic tumour (ETT)	Chorion leave type intermediate trophoblast	Cytokeratins (AE1/3, CAM 5.2), inhibin, GATA-3 and CD10. Diffuse positivity for p63 and PLAP. Ki-67 usually >10%
Exaggerated Placental site (EPS)	Implantation site intermediate trophoblast	Cytokeratins (AE1/3, CAM 5.2), inhibin, GATA-3 and CD10 hPL and MCAM; scattered multinuclear cells positive for hCG. Ki-67 usually <1%
Placental site nodule (PSN) and atypical placental site nodule	Chorion leave type intermediate trophoblast	Cytokeratins (AE1/3, CAM 5.2), inhibin, GATA-3 and CD10. Diffuse positivity for p63 and PLAP. Ki-67 usually <5% for PSN and <10% for APSN

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 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	2−11
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	2−11
16 The different options for management of the condition or health issue are clearly presented	2−11
17 Key recommendations are easily identifiable	2−11
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	2−11
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	12
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