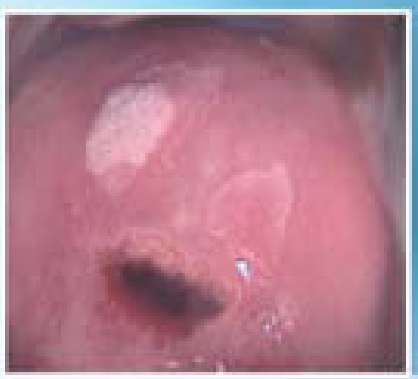

SECOND EDITION

Colposcopy

A Practical Guide

Mahmood Shafi
Saloney Nazeer

CAMBRIDGE Medicine

Colposcopy

A Practical Guide

Second Edition

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This book is dedicated to the love and support of our respective parents – Mohammed Shafi, Alam Begum Shafi; Mohammed Akhtar Khan and Nusrat Akhtar.

Contents

Foreword

Since colposcopy was described first by Hinselmann in 1925, many books have been written to help doctors understand and learn the technique. Each has dealt with the subject in its own way and over the years, as knowledge has evolved, these texts have recognized the need to include not only a description of colposcopic features and pattern recognition, but an understanding of the aetiology of cervical cancer and the principles behind the management of women with cervical problems.

The authors are both experts in their respective fields and in this second edition they have produced well-structured and informative text that will be of immense value to trainees and established colposcopists alike by allowing them to have a greater appreciation of the rationale behind colposcopy and its role in the management of cervical disease and prevention of cervical cancer.

Joe Jordan
Past President of International Federation for Cervical Pathology and Colposcopy (IFCPC); European Federation for Colposcopy (EFC); British Society for Colposcopy and Cervical Pathology (BSCCP)

Preface

This book is aimed as a practical guide for those involved with colposcopy. All the chapters have been updated including the latest nomenclature, staging, classification and treatment guidelines, which are evidence based. There are also additional sections on HPV vaccination and applicability of HPV-based technologies in clinical practice. The manual is aimed at trainees and trainers wanting concise information in relation to the practice of colposcopy. Professions allied to medicine and nurses will also find the book helpful in understanding the principles in relation to colposcopy. It is anticipated that the guide will be applicable to both UK and international healthcare professionals. The chapters provide clear guidance in the core areas. For those requiring further information, the suggested reading list will provide additional and detailed information relevant to colposcopy and the various topics covered in the chapters.

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Glossary of terms

AGC	Atypical glandular cells
AIS	Adenocarcinoma in situ
ALO	Actinomyces-like organisms
ASC-H	Atypical squamous cells, cannot exclude HSIL
ASC-US	Atypical squamous cells of undetermined significance
ATZ	Atypical transformation zone
BSCCP	British Society for Colposcopy and Cervical Pathology
BV	Bacterial vaginosis
CCI	Clinico–colposcopic index
CGIN	Cervical glandular intraepithelial neoplasia
CIN	Cervical intraepithelial neoplasia
CIS	Carcinoma in situ
CT	Computed tomographic scan
CTZ	Congenital transformation zone
CO_2	Carbon dioxide
DNA	Deoxyribonucleic acid
DES	Diethylstilboestrol
ECC	Endocervical curettage
EFC	European Federation of Colposcopy
EMPD	Extramammary Paget's disease
FIGO	Federation Internationale de Gynecologie et d'Obstetrique
FNA	Fine-needle aspiration
5FU	5-Fluorouracil
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
hrHPV	High-risk human papilloma virus
HSIL	High-grade squamous intraepithelial lesion
HSV	Herpes simplex virus
IFCPC	International Federation for Cervical Pathology and Colposcopy
ISSVD	International Society for the Study of Vulvovaginal Disease
IUCD	Intrauterine contraceptive device
IVU	Intravenous urogram
LBC	Liquid-based cytology
LCR	Ligase chain reaction
LEEP	Loop electrosurgical excision procedure
LLETZ	Large loop excision of the transformation zone
LS	Lichen sclerosus
LSIL	Low-grade squamous intraepithelial lesion
MRI	Magnetic resonance imaging
NETZ	Needle excision of transformation zone
NOS	Not otherwise specified
OR	Odds ratio
Pap smear	Papanicolaou smear
PCR	Polymerase chain reaction
PET	Positron emission tomography
PID	Pelvic inflammatory disease
QA	Quality assurance
SCC	Squamous cell carcinoma
SCJ	Squamocolumnar junction
SIL	Squamous intraepithelial lesion
STD	Sexually transmitted disease
SWETZ	Straight-wire excision of transformation zone
TBS	The Bethesda System
TNM	Tumor, node, metastasis
TZ	Transformation zone
VaIN	Vaginal intraepithelial neoplasia
VIN	Vulvar intraepithelial neoplasia
VLP	Virus-like particle
WHO	World Health Organization

Chapter 1

Basic principles of colposcopy

Atypical cervical cytology or positive test for high-risk human papilloma virus (hrHPV), especially if it is persistent, may indicate the presence of abnormality on the cervix. Naked eye visualization will only detect invasive disease but cannot differentiate preinvasive disease from the normal cervix. In this situation colposcopic examination is important.

Indications for colposcopy

Ideally all women with abnormal cervical cytology and/or positive hrHPV should undergo colposcopic assessment to identify those with and those without any clinically visible lesions. This allows clinical verification of the cervical cytology and hrHPV report. In those with an atypical lesion, the colposcope can aid diagnosis and management as appropriate. In those women where no atypical lesions are visualized, they can have a less stringent follow-up schedule often in the community setting.

Indications for colposcopy:

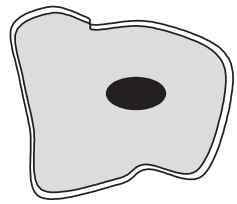
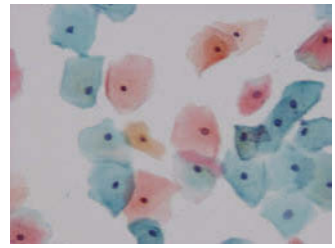
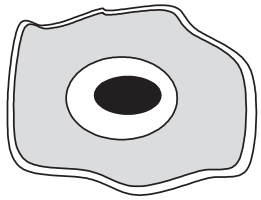
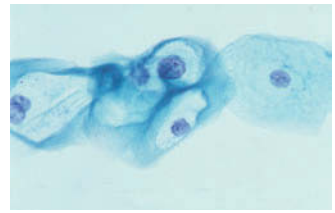
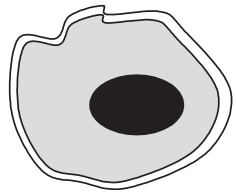
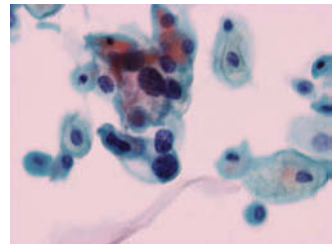
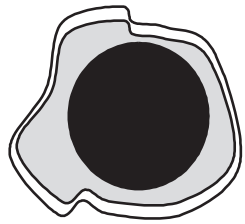
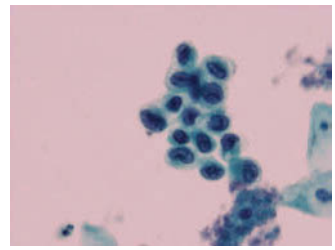
- Borderline (atypical squamous cells of undetermined significance, ASC-US) nuclear abnormalities on three occasions or single ASC-US with positive hrHPV test as triage.
- Mildly dyskaryotic cytology (low-grade squamous intraepithelial lesion, LSIL) with positive hrHPV test as triage if available. If HPV testing is not available, then referral after two consecutive mildly dyskaryotic cytology samples (LSIL) is acceptable practice.
- Moderate or severe dyskaryosis (high-grade squamous intraepithelial lesion, HSIL), with or without hrHPV status.
- Cytology suggestive of malignancy.
- Glandular abnormalities, irrespective of severity.
- Any degree of cytological abnormality or hrHPV positivity in women who have previously undergone treatment for cervical intraepithelial neoplasia (CIN).
- Repeated (three consecutive) unsatisfactory cervical cytology reports.
- Post-coital bleeding after age 40 if cancer suspected.
- Intermenstrual bleeding or persistent vaginal discharge if cancer suspected.
- Suspicious cervix suggestive of malignancy regardless of the cytology report. This may include an abnormal feeling cervix on bimanual examination.
- Lesions affecting the cervix e.g. condyloma acuminata which may have associated preinvasive or invasive disease.
- Repeated inflammatory cervical cytology.

Dyskaryosis or dysplasia on a cervical cytology sample refers to disproportionate nuclear enlargement in the cell in comparison to the amount of cytoplasm present. Dyskaryotic cells have abnormal chromatin content and distribution and may have abnormality in the nuclear shape.

Prior to the colposcopic examination, a relevant medical history should be obtained, ideally using a proforma designed specifically for the colposcopy clinic. Information should be obtained in relation to menstruation, contraception, pregnancies, smoking, previous cervical cytology, symptoms, previous treatments, and date of last menstrual period. A detailed explanation should be given to the patient with regards to the colposcopic examination. Written information should be given prior to the visit to the colposcopy department.

The colposcope is a binocular microscope that allows magnification and illumination of the cervix. By applying various stains to the cervix, abnormalities can be identified. These include benign, precancerous, and malignant changes. Its primary use is to evaluate abnormal cervical cytology as an aid to diagnosis. It can then be used to guide further management.

All colposcopes follow similar principles. They provide magnification between 6- and 40-fold. Low and

Fig 1.1 Normal cells contain plentiful cytoplasm and regular nucleus.		
Fig 1.2 Koilocytosis, which may occur in all grades of cytological abnormality as perinuclear vacuolation.		
Fig 1.3 Increased nuclear size in relation to cytoplasm consistent with low-grade changes (mild dyskaryosis).		
Fig 1.4 High-grade dyskaryosis (moderate or severe dyskaryosis) – note the considerably increased nuclear/cytoplasm ratio.		

medium magnification is used for initial assessment; high magnification (20-fold plus) is used to detect the finer detail of vascular patterns. A green filter allows better visualisation of vasculature on the cervix.

Colposcopy is best carried out on days 10–14 of the menstrual cycle when the cervical mucus is clear and not tenacious. Colposcopic assessment is difficult when there is significant vaginal bleeding. If the woman is menstruating, the procedure should be postponed. If the presenting symptoms were of vaginal bleeding in the presence of a suspicious looking cervix, then the woman should be seen irrespective of bleeding status to rule out the possibility of invasive disease. Common sense needs to prevail in scheduling the appointment. Women taking the oral contraceptive pill can continue with this to allow colposcopic assessment to take place for the convenience of the woman and the clinic.

How to choose a colposcope

There are a variety of colposcopes available. Only by trialling some of these colposcopes will the correct decision be made in terms of choosing the right colposcopic equipment for your particular environment. Some of the criteria that should be assessed are:

- Cost – can vary considerably. Affordability is one of the most important factors in decision making.
- Optical quality – the better the optics, the better the colposcopic image. This relates to brightness, clarity, and an evenly illuminated image.
- Zoom magnification – there should be a good range of magnifications available. Most have a stepped magnification although some have a continuously variable mechanism.
- Design should allow the colposcopic arm to be counter-balanced to ensure smooth movement and stability in usage.
- Eyepiece – should feel comfortable in usage. Many have diopter adjustment for visual correction of myopia (short sightedness) and hypermetropia (long sightedness).
- Focal length – usually fixed, although in some may be variable to a degree, which allows the colposcopist to be optimally positioned for the procedure.
- Illumination – should have good even light with facility for green filter. The bulb should be easily changeable.
- Fixtures – can be free standing, wall, ceiling or chair mounted depending on the clinical environment. Size and maneuvrability may be important if the colposcope is to be used in more than one setting.
- Operating environment – make sure that colposcope will function given the clinic air temperature and humidity level.
- Optional accessories:
  - Display facilities – by attaching to a monitor, live images can be displayed for education and teaching functions. Otherwise a teaching arm is useful.
  - Recording facilities – documentation is becoming increasingly important and digital formats are ideal for this purpose. One can either use still or video formats.

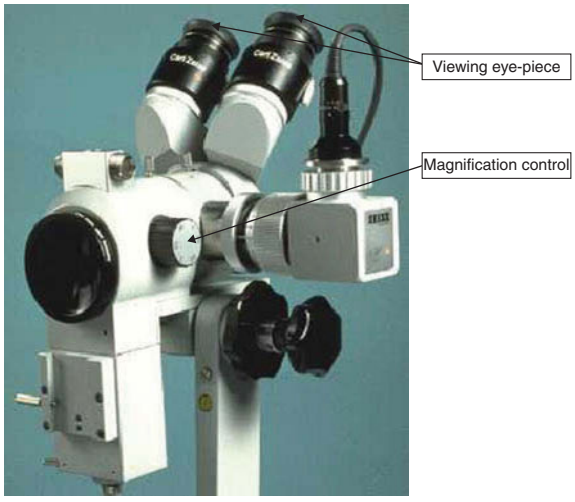


Fig 1.5 Colposcope.

The following instruments should be available

- Examination gloves.
- Cervical sampling devices – cervical brushes (e.g. cytobrush, cervex brush), spatulae (e.g. Ayre's, Aylebury's, or plastic spatula).
- Container for liquid-based cytology; glass slides (plus fixative) for traditional cytology.
- Bivalve speculum of varying size and lubricant.
- Three small pots containing saline, acetic acid (3–5%), and Lugol's iodine.
- Cotton wool balls.
- Sponge holding forceps.
- Cotton-tip and jumbo swabs.
- Endocervical canal specula.
- Biopsy forceps and pots with fixative for specimens.
- Haemostatic solutions/substances – e.g. monsel's solution (ferrous subsulphate) dried to a thick paste or silver nitrate sticks.

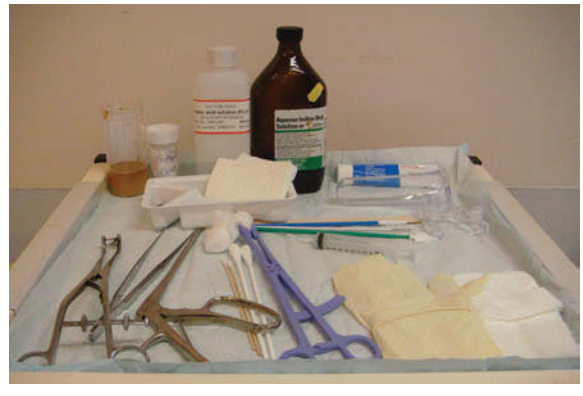


Fig 1.6 Colposcopy trolley.

Technique of colposcopy

Patients should be examined in warm relaxed surroundings having been fully informed about the procedure. The woman is helped onto the couch in the lithotomy position. Leg supports should be comfortable and the couch adjusted appropriately. External genitalia should be assessed for any obvious abnormalities. A suitably sized speculum is used to expose the cervix. If the vaginal sidewalls obstruct the view, they can be displaced by using the finger of an examination glove (or a condom) placed over the speculum blades.

If required a cervical cytology sample is taken but if the woman is presenting with cytological abnormality, this should be avoided as it can cause unnecessary bleeding and interference with the colposcopic examination. A variety of sampling devices are available.

Liquid-based cytology relies on the sampler being either immersed or agitated in fixative fluid (rinse using a vigorous swirling motion and then push the brush into the bottom of the vial at least ten times forcing the bristles apart). The cervical brushes are ideal for this purpose because some of these have detachable ends. Certain plastic spatulas also have detachable ends for this purpose. To obtain the cytology sample, the Cervex brush is rotated clockwise five times after being applied to the cervix. Where sampling of the endocervix is important, then a cytobrush should be used additionally. If a Papanicolaou smear (Pap smear) is required, then this may be obtained by the use of wooden/plastic spatulae or cervical brushes.

If a cervical cytology sample is required, this should be taken before the application of acetic acid. Occasionally, if one forgets and acetic acid is applied before taking the cervical sample, then this should be annotated on the cytology request form.

The cervix and upper vagina are examined at low magnification. Any excess mucus or blood should be removed using a dry or saline-soaked cotton wool ball. Presence of gross lesions and leukoplakia should be identified. The green filter should be used to assess the vascular pattern (low to high power). Benign lesions

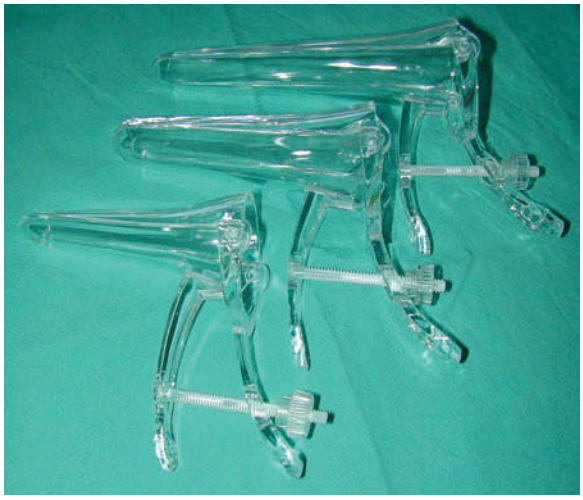


Fig 1.7 Variety of speculae in large, medium, and small size. Bivalve with screw and lever for opening speculum.

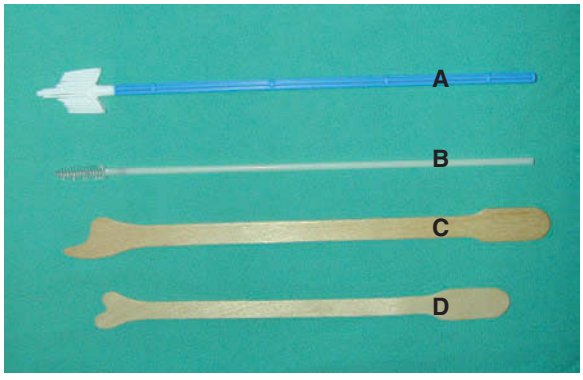


Fig 1.8 Various sampling devices for taking cervical cytology – cervex brush (A), cytobrush (B), Aylesbury spatula (C), Ayres spatula (D).

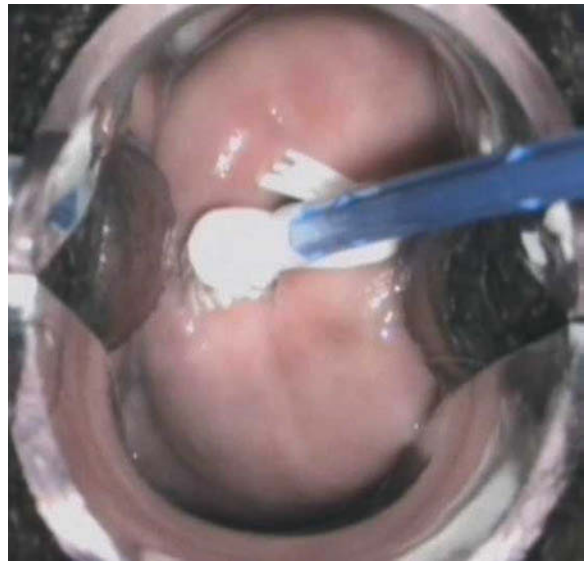


Fig 1.9 Cervex brush being used for cytology sample taking.

that are visualized should be noted. These include Nabothian follicles, cervical polyps, warts, cysts etc.

Acetic acid (3–5%) is gently applied to the cervix with saturated cotton wool balls on sponge forceps or a jumbo swab, or by using a spray or syringe. Unnecessary abrasion should be avoided. The acetic acid is left in contact with the cervix for 10 seconds.

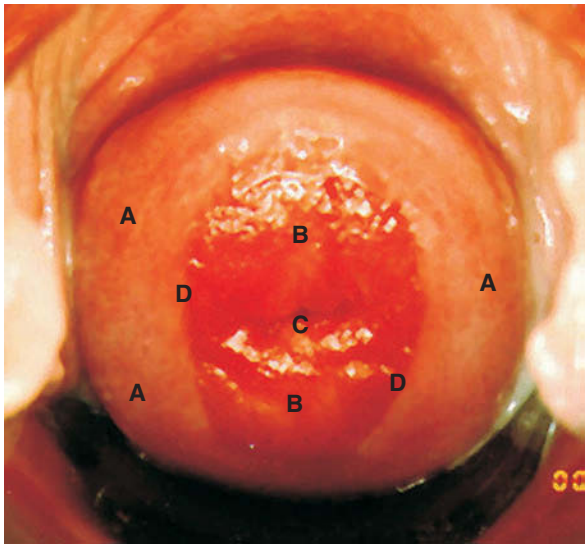


Fig 1.10 Normal cervix with ectropion squamous epithelium (A) surrounds columnar epithelium (B) and cervical canal (C). Junction between the two types of epithelia is the SCJ (D).

Following acetic acid application, any remaining mucus may be removed easily. Further acetic acid is applied as necessary. The cervical landmarks and any atypical areas should be mentally mapped. If image recording facilities are available, then these should be used liberally and stored either digitally or in print format. Lugol's iodine (1% iodine, 2% potassium iodide, 97% distilled water) may be used to further delineate atypical epithelium that contains little or no glycogen and therefore fails to take up the iodine stain. Normal squamous epithelium turns mahogany brown with Lugol's iodine. Columnar epithelium also contains little or no glycogen and fails to take up the stain. This is referred to as 'Schiller's test'. A positive Schiller's test refers to non-staining (i.e. iodine negative) and vice versa. Any excess solutions are removed from the vagina prior to removal of the speculum. The vagina should be examined as the speculum is removed. Immediately following assessment, the findings are recorded, ideally in a standard format.

- Was the squamocolumnar junction visible?
- Was there any acetowhite epithelium? If yes, document its site and size in graphic format (see Chapters 2 and 4).
- Assess the degree of change (see Chapter 4).

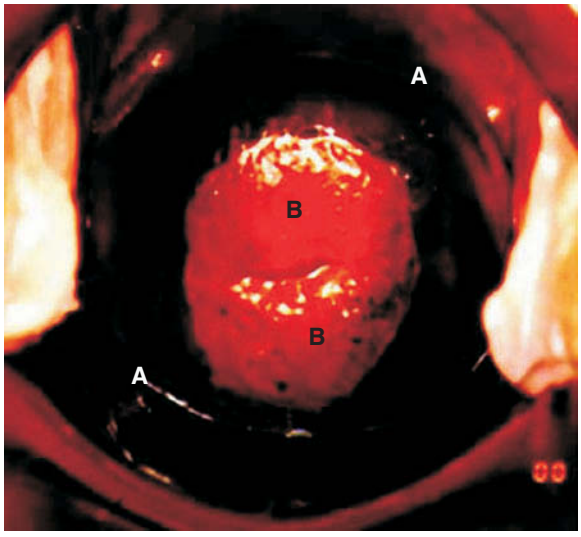


Fig 1.11 Normal cervix with application of Lugol's iodine. Columnar epithelium (B) with minimal stain surrounded by glycogenated normal squamous epithelium (A), which stains darkly.

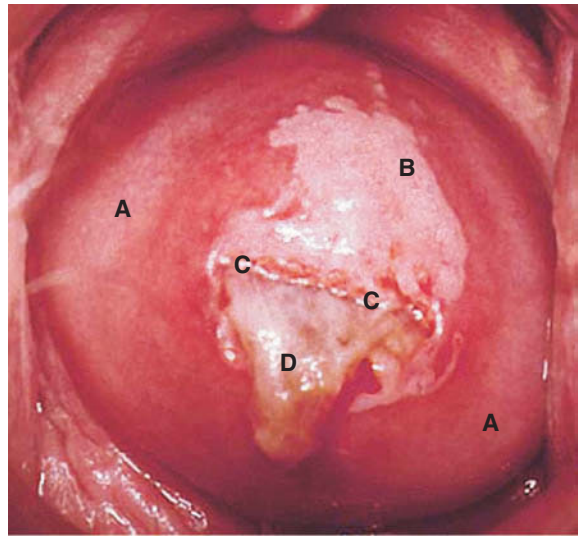


Fig 1.12 Cervix following application of acetic acid. Squamous epithelium (A), acetowhite changes with sharp border (B), cervical canal and SCJ (C), cervical mucus – viscid following acetic acid application (D).

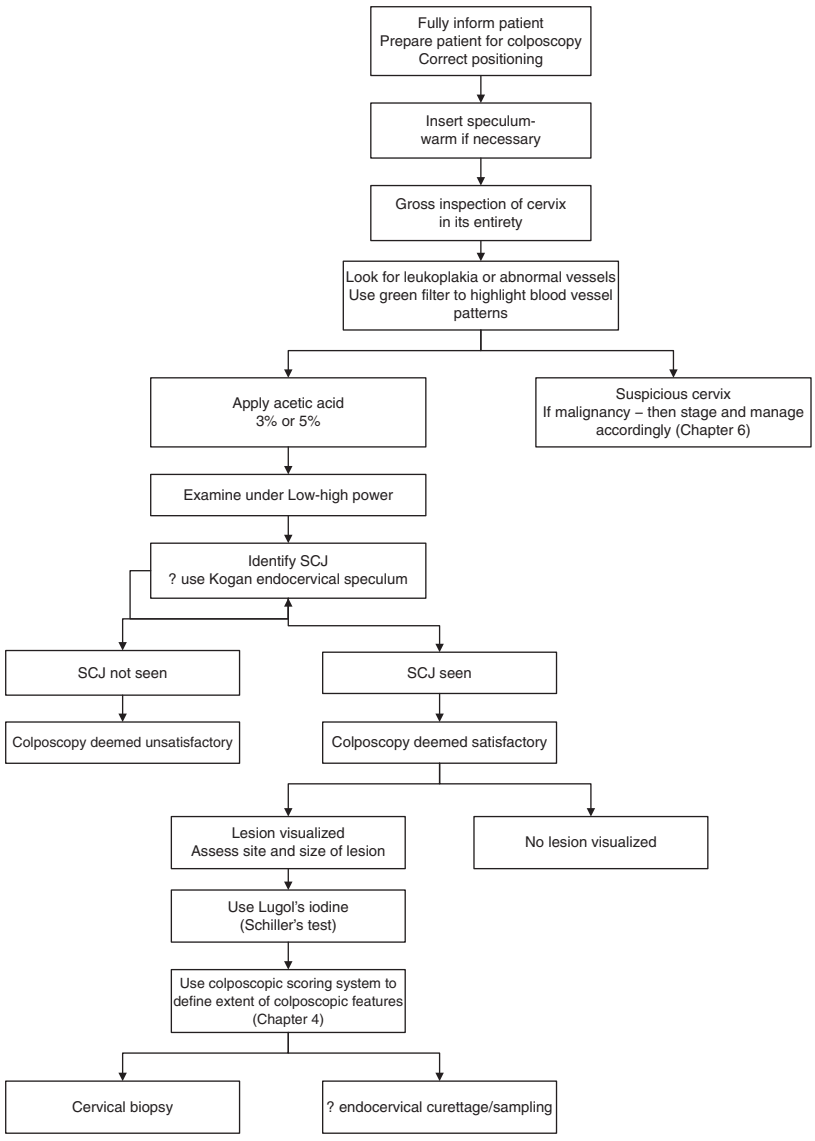


Fig 1.13 Colposcopy flowchart.

Learning points

- Colposcopy is appropriate in women with cytological abnormality.
- Women attending for colposcopy should be adequately informed and counseled.
- Dedicated facilities for colposcopy are ideal with appropriate back-up facilities.
- There needs to be good communication channels between the cytology, colposcopy, and histopathology services.
- Saline, acetic acid, and Lugol's iodine are used sequentially and changes on the cervix noted.
- Accurate documentation is necessary and this can be facilitated with the use of a proforma.
- Digital image storage is recommended or other form of image capture.

Chapter 2

The normal cervix and colposcopic appearance

A detailed knowledge of the normal appearance of the cervix is important prior to looking for colposcopic abnormalities. The size and shape of the cervix shows considerable variation amongst individuals and at different stages of an individual's life. Puberty and pregnancy in particular have significant effects on the cervix. Menopause may cause atrophic changes, which may lead to specific changes that may cause difficulties with screening and colposcopy.

In the adult, the cervix measures 2.5–3 cm in length. In the nulliparous, the external cervical os is circular whereas the multiparous cervix is slit-like in the transverse dimension. The cervix contains two types of epithelia, the stratified squamous, which lines the vaginal portion (ectocervix), and the simple columnar lining the cervical canal (endocervix), which is flattened in the anteroposterior dimension.

The understanding of the appearance and the relationship of the different epithelia types is described.

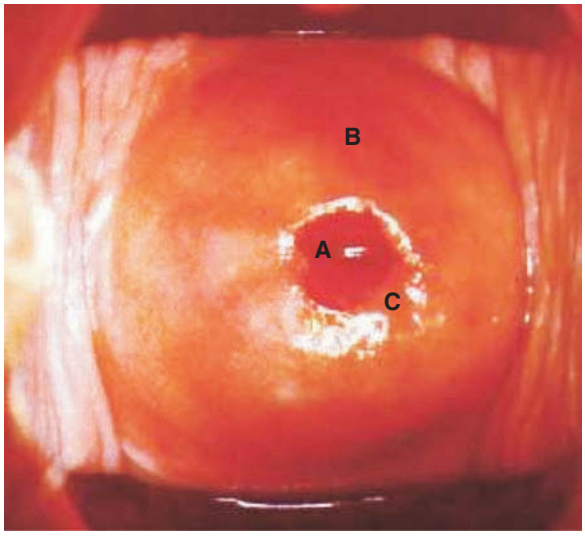


Fig 2.1 Normal nulliparous cervix. Columnar epithelium (A) surrounded by squamous epithelium (B). Border between two epithelial types is the SCJ (C).

Squamous epithelium

Two types of squamous epithelia may be present – original or transformed. The original squamous epithelium is a featureless smooth, pink epithelium originally established on the cervix and vagina. Squamous epithelium is similar to that found in the rest of the vagina and is multilayered. The epithelium does not stain white after the application of a dilute solution of acetic acid and stains brown after the application of Lugol's iodine.

In the transformed squamous epithelium, gland openings may be visualized on colposcopic assessment. If these gland openings become blocked for various reasons, then Nabothian follicles could be present.

Columnar epithelium

Columnar epithelium is a single-layer, mucus-producing epithelium that extends between the endometrium cranially and either the original squamous epithelium or the metaplastic (transformed) squamous epithelium caudally. Columnar epithelium is normally present in the endocervix and may be present on the ectocervix (ectopy) or, on rare occasions, in the vagina. The epithelium appears red and velvety, contrasting with the pink squamous epithelium. Each villi that

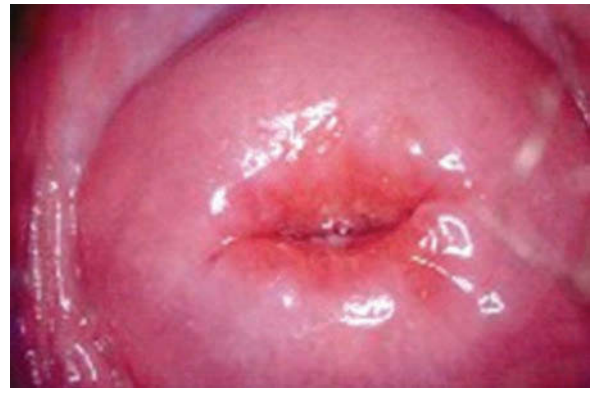


Fig 2.2 Normal cervix in parous woman. Cervical os appears slit-like.

gives it a characteristic appearance has a central blood supply.

At colposcopy the area has a typical grape-like structure. Application of acetic acid causes columnar epithelium to turn white and the villi become less distinct. As the epithelium is thin with blood vessels just below, contact bleeding may occur.

Squamocolumnar junction

The squamocolumnar junction (SCJ) of the cervix is defined as the border between the stratified squamous epithelium and the mucin-secreting columnar epithelium of the endocervix. Two types of SCJ are described:

> The *original* SCJ – site where the native squamous and columnar epithelia meet each other. This is present from birth. The exact location of the SCJ varies between individuals and at various stages in an individual's life.

At the time of menarche, both the cervix and uterus enlarge. This enlargement causes an eversion of the cervix so that more of the columnar epithelium is visible on the vaginal surface of the cervix. As the environment in the vagina is different from the endocervix, especially high acidity, the epithelium undergoes a process of transformation – metaplasia – and eventually is replaced by the stratified multilayered squamous epithelium. This gives rise to an acquired or *new* SCJ.

The *new* SCJ is at the junction of the metaplastic area and the columnar epithelium. This is an important landmark and is relevant for the full assessment of the transformation zone (TZ).

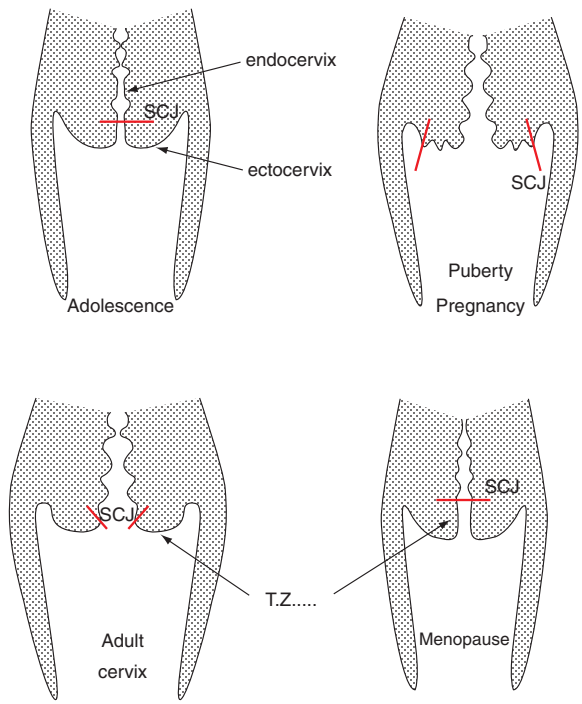


Fig 2.3 The apparent migration of the SCJ secondary to hormonal influence.

Metaplasia

This is the physiological replacement of one type of mature epithelium by another equally mature type of epithelium. In the cervix, squamous metaplasia is the replacement of the mucin-secreting columnar epithelium by a stratified squamous epithelium. Varying stages from immature to mature metaplasia may be recognized on colposcopic assessment. The metaplastic process is irreversible and maximal during times of high estrogenic stimulation. These occur mainly during adolescence, whilst taking the combined oral contraceptive, and during the first pregnancy. It is important not to confuse the immature metaplastic process with abnormality.

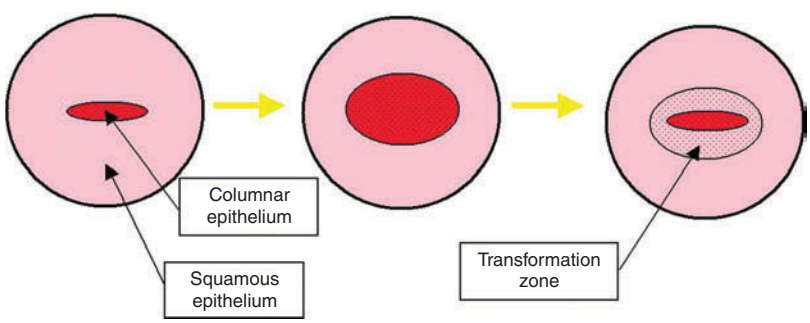


Fig 2.4 Process of metaplasia.

Colposcopic features suggestive of metaplastic change:

- Smooth surface with fine, uniform-caliber vessels
- Mild acetowhite change
- Negative or partial positivity with Lugol's iodine

The transformation zone

The transformation zone (TZ) is the area between the original squamous and columnar epithelium within which varying degrees of maturity may be identified. The TZ is of variable shape and size. At different stages of maturity the metaplastic epithelium may stain slightly white after the application of acetic acid and partially brown after the application of Lugol's iodine. Components of a normal TZ may be islands of columnar epithelium surrounded by metaplastic squamous epithelium, cleft openings and Nabothian cysts.

There are three types of TZ:

- A type 1 TZ is completely ectocervical and fully visible, and may be small or large.
- A type 2 TZ has an endocervical component, is fully visible, and may have an ectocervical component that may be small or large.
- A type 3 TZ has an endocervical component that is not fully visible and may have an ectocervical component that may be small or large.

In a small percentage of women the TZ may extend caudally onto the upper vagina, usually with an anterior and posterior triangle or tongue; it may contain a fine regular mosaic pattern of blood vessels and stain partially or wholly negative after the application of Lugol's iodine.

Ectropion

This relates to the eversion of the columnar epithelium so that it is visible in the vaginal portion of the cervix. Although a physiological phenomenon, it can cause confusion in colposcopic assessment, especially if large and fragile. Ectropions can cause symptoms of vaginal discharge (excess mucin secretion) or postcoital bleeding (contact bleeding from fragile thin columnar epithelium). Cervical ectropion does not warrant any treatment unless there are related symptoms. Before undertaking treatment it is advisable to rule out an infectious cause such as chlamydia. If ablative treatment is undertaken, it is important to have a normal cervical cytology history and even biopsy if there is clinical suspicion. Cryocautery is the commonest method of treating ectropion as it can be conducted in clinic without recourse to anesthesia and has relatively high success rates. An alternative method is diathermy ablation for which local anesthesia is recommended. If necessary, treatment can be repeated in those with continuing symptoms.

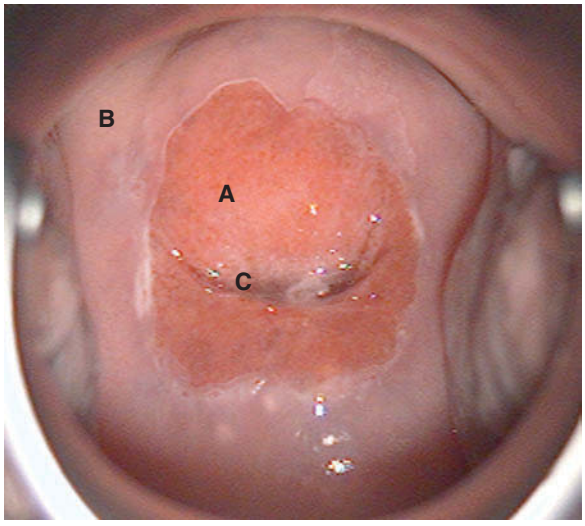


Fig 2.5 Normal cervix with cervical ectropion. Columnar epithelium (A) and squamous epithelium (B), cervical canal (C).

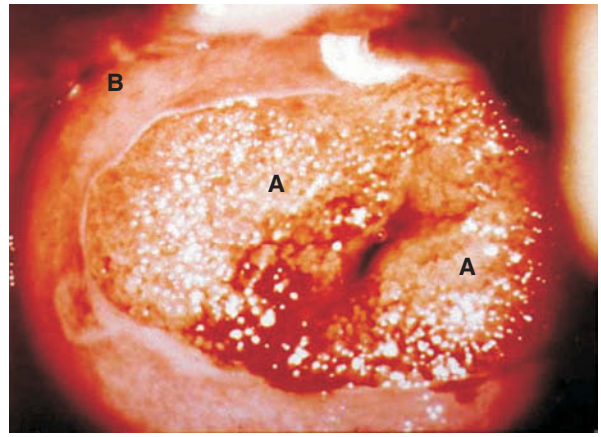


Fig 2.6 Large cervical ectropion. Large area of columnar epithelium (A) exposed and surrounded by squamous epithelium (B).

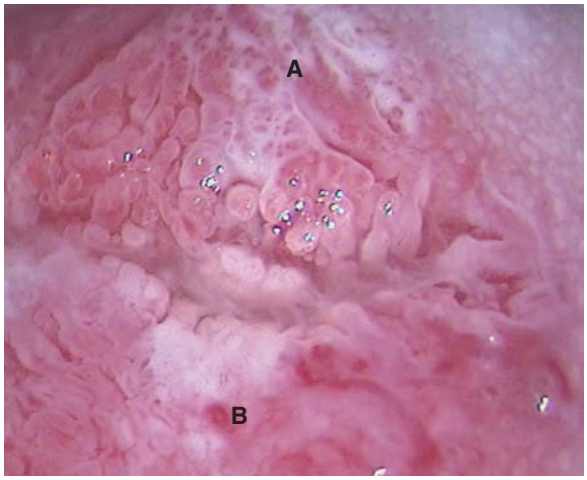


Fig 2.7 Metaplastic changes (A) within the TZ. Gland openings (B).

Pathophysiology at different stages in a woman's life

At birth, most females will have some degree of mucin-secreting columnar epithelium present on the vaginal portion of the cervix. At about one year of age, the cervix begins to elongate and causes the SCJ to move towards the external os.

After menarche, a cervical ectropion is present by the eversion of the columnar epithelium onto the vaginal portion of the cervix. This undergoes physiologic metaplasia to squamous epithelium. These changes are maximal under the age of 20 and during first pregnancy.

At the menopause, there is inversion of the cervix. This makes access to the TZ difficult. Cervical cytology and colposcopy is more likely to be unsatisfactory as the area of concern may be within the endocervix to varying degrees. A short course of estrogen may reverse these changes allowing better cytological and colposcopic assessment.

Learning points

- Recognition of normality and its variations is important for colposcopy.
- The cervix is dynamic, undergoing changes from fetus until old age.
- Metaplasia and the replacement of columnar by squamous epithelium is a normal, irreversible, physiological process.
- Sampling from the TZ by cytology and its assessment by colposcopy varies according to the age of the woman.
- Columnar epithelium is single layered and allows visualization of vasculature beneath the epithelium (appears red).
- Squamous epithelium is multilayered and appears pink on examination.
- Recognition of the TZ and its varying stages of metaplasia is important for colposcopic practice.

Chapter

3 Natural history of cervical carcinoma, HPV, and vaccination

Cervical cancer is the third commonest female cancer worldwide, with breast and colorectal cancer occurring more often. It accounts for 10% of the cancers in women worldwide and is the most commonly diagnosed cancer among women in Southern Africa and Central America. There is a seven-fold variation in the incidence of cervical cancer between the different regions of the world. Cervical cancer is potentially the most preventable major form of cancer, given the prolonged phased natural history of precancerous stage. Those countries that have introduced organized cervical screening programs have seen significant falls in the incidence and mortality associated with cervical cancer. Coverage rates of the at-risk population need to be high (>80%) in order to achieve the desired effect; however, a much greater effect on control of this disease in these countries was achieved even prior to introduction of formal screening programs. This was attributable to health education and empowerment of women leading to increased awareness amongst populations, regular check-ups and availability of appropriate management services. In developing countries, similar efforts could help bring down the high rates of cervical cancer by devoting more resources to educational programs.

Within Europe there is a variation in incidence of cervical cancer depending on the availability and implementation of the cervical screening and management program. Across Europe, cervical cancer is the fifth most common cancer in women. In the UK, cervical cancer is now the eleventh most common cancer in women and accounts for 2% of all female cancers. The estimated lifetime risk of a female developing cervical cancer is 1 in 136 in the UK.

There are many risk factors associated with cervical cancer but many of these are surrogates for sexual activity. The risk factors include:

- Human papilloma virus (HPV) infection – recognizably the most important etiological risk factor. Evidence linking HPV with cervical cancer is extremely strong and satisfies virtually all the epidemiological criteria for causality – namely strength, consistency and specificity of

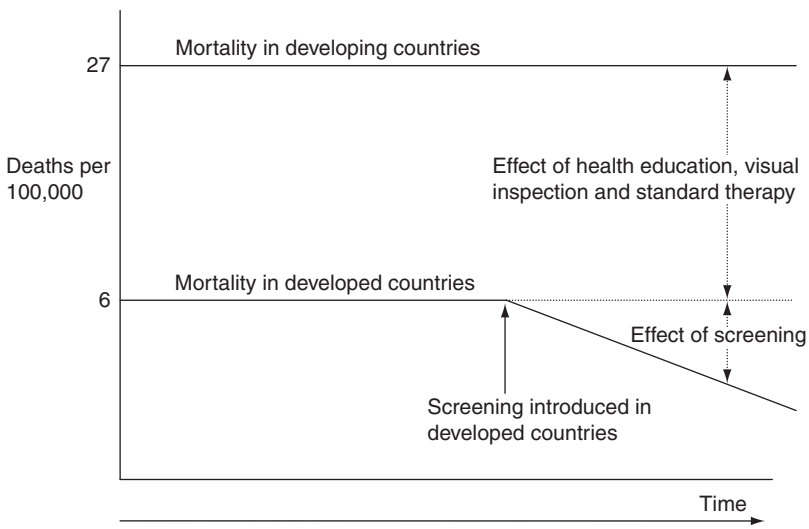


Fig 3.1

association, temporality of events, biological gradient, plausibility, and experimental evidence. Whilst exposure is important, it is the persistence of HPV that is related to the development of CIN and invasive cervical disease (see below).

- Early onset of sexual activity – generally taken as age 16 or younger.
- Multiple sexual partners (self or of the partner) – this relates to the exposure to high-risk oncogenic HPV. The prevalence of HPV approaches 100% in women involved in unprotected sex with multiple partners.
- Low socioeconomic status – this may relate to many other factors that are inter-related; however, it has been shown that women from a low socioeconomic social class have three times increased risk of developing cervical cancer, irrespective of other associated risk factors.
- Tobacco smoking – there is evidence that smoking increases risk of invasive cervical cancer and also interacts with HPV in carcinogenic effect. The increased risk for smokers is around two-fold, with the highest risk in those with long-term and high-intensity use. Smoking does not appear to be associated with increased risk for adenocarcinoma.
- Use of oral contraceptive pill – a long-term follow-up study of women using oral contraceptive pill found a relative risk of death from cervical cancer of 2.5 among current and recent users (within 10 years) compared to never users. A three-fold increased risk for invasive squamous cell cervical cancer was found for women who were HPV positive and had used oral contraception for five or more years.
- Other sexually transmitted infections – namely, herpes simplex virus, Chlamydia, and bacterial vaginosis. No direct causal link has been established with any of these infections; however, evidence is emerging suggesting a catalytic role of these agents with HPV in progression of dysplastic changes.
- Immunocompromise – organ transplant patients, Lupus disease and human immunodeficiency virus (HIV) infection. In these women the increased risk may be five-fold. Treatment for HIV infection will ameliorate its effect. All these women are also at higher risk of residual/recurrent disease after treatment.
- Malnutrition – the weight of evidence, albeit inconclusive, from several contradictory studies indicates that consumption of fruit and vegetables and some associated micronutrients (beta-carotene, vitamin C, and folate) are protective against invasive cancer.
- Multiparity – again a controversial role. Multiparity may be indicative of sexual activity and tissue damage rather than having direct causative role.

Natural history

It has been estimated that the mean time from detectable cytologic abnormality to development of invasive cancer may take as long as 15–20 years. Thus, progression of CIN to invasive cancer, although it can be swift, is usually a slow process.

Many CIN lesions will regress over time. The regression rate depends, amongst other factors, mainly upon the grade of CIN and the age of the woman. Regression is much more common in women under 30 years than those above 30 years of age. Taken together, in the absence of intervention, roughly one-third of early precursor lesions disappear spontaneously, one-third persist, and one-third progress to CIN III or invasive cancer.

The progressive potential of cervical intraepithelial neoplasia varies according to grade of abnormality. In high-grade lesions (CIN II & III), the lesions have definite progressive potential that can be lowered dramatically by treatment of this precancerous phase. In those that are treated, even though their cervical cytology may revert to normal, they remain at increased risk for the development of invasive cervical cancer compared to the general population without cytological abnormality. In those women with abnormal cervical cytology following treatment for CIN, the risk is 25–30 times the background rate for the development of cervical cancer. Women with lesser abnormalities such as CIN I have an unknown but low malignant risk. Management of women with these disorders depends on other variables such as age and compliance to cytological surveillance programs. Women who are immunocompromised are at particular risk for the progression of preinvasive lesions to the malignant phase.

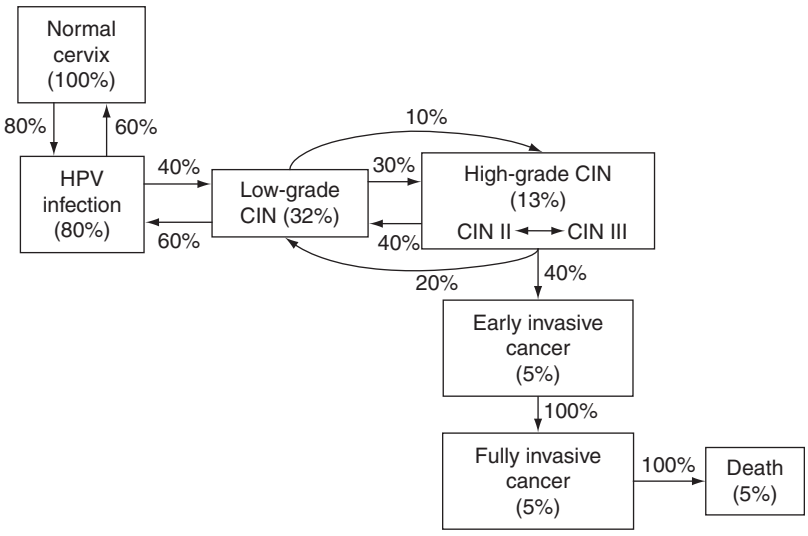


Fig 3.2 Flow representation of natural history of CIN – the percentages given are estimates of what might happen over a lifetime in the absence of screening, vaccination, and treatment (adapted from P Sasieni, Cancer Research, UK).

In those women with hrHPV infection, they are more likely to develop preinvasive disease and then develop the invasive form. Most of the HPV infections are transient, about 60–80%, depending on the age, clear spontaneously within 1–2 years. The rest would result in CIN lesions. Most of the women with HPV positive cytology who develop CIN lesions are still able to clear the virus in 2–3 years and will subsequently have regressive CIN; however, above 30 years the regression rate is much lower. Among women with persistent infection, CIN lesions can develop within 2–4 years. The progression rate of CIN in women with hrHPV positive test, cytologically normal or abnormal cervical sample is about 5% per year. In women above 30 years with positive hrHPV, cytologically normal cervical sample the risk of developing CIN III is 116 times higher than women with a negative hrHPV cytologically normal cervical sample.

Determinants of disease progression or regression

The development of minor cervical cytological abnormality is common in young women. The majority of these will be a transient phase and will regress back to normal over time. Most of the risk factors listed earlier are potential determinants of progression rather than prime etiological agents. Those women with persistent high-risk oncogenic HPV infection and those with repeated exposure to infections remain at risk for disease progression. Women who are exposed to tobacco smoking are more likely to have disease persistence or progression compared to non-smokers or those that cease smoking. Women who are immunocompromised are likewise more likely to have disease progression. It has been established that the age of the host, >30 years, is an independent determinant of oncogenic progression.

The size of lesion and grade of abnormality is related to malignant potential. High-grade intraepithelial disease and large lesions have significantly higher malignant potential compared with low-grade and small lesions. The tumor biology may vary and different cancer types will have a different natural history.

Human papilloma virus

Whilst HPV is present in virtually all cervical tumors, most HPV infections will not progress to CIN or cancer. The invasive disease does not develop unless there is persistence of HPV deoxyribonucleic acid (DNA) and it has been proposed as the first ever identified 'necessary cause' of a human cancer. Out of the >150 known HPV genotypes, 30 are known to infect the genital tract. Out of these, 20 have been identified as carcinogenic with types 16 and 18 found most commonly in malignant lesions.

The common types are classified according to their oncogenic potential as follows:

Low risk: 6, 11, 26, 40, 42, 53, 54, 55, 57, 66, 73, 82, 83, 84
High risk: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73, 82

Both high- and low-risk HPV infections in women occur mostly in adolescent age groups (16–24 years). Reported incidences from different countries have been 10–30%. The incidence drops to about 5% above the age of 30 years. Most of these HPV infections are transient and clear spontaneously within 1–2 years.

Testing for the hrHPV types is becoming clinical practice in the triage of minor cytological abnormalities (borderline/ASC-US and mild dyskaryosis/LSIL). A number of different diagnostic kits are available that test for the hrHPV types using differing technologies including some that are able to genotype. These hrHPV tests can be performed either serially or as co-testing with cervical cytology. The consistency of tests for hrHPV is higher when compared with cytology. It also has clinical applicability in 'test of cure' following treatment for CIN. Testing for HPV in the primary screening setting is being actively studied where it can detect prevalent disease as well as predict risk.

HPV vaccination

HPV is a necessary cause for cervical cancer. It is additionally associated with other genital tract cancers including the vagina, vulva, anus, penis, as well as oropharynx and tonsils. HPV 16 is the main causative agent at these various sites, with other oncogenic types contributing particularly to cervical cancer risk. HPV enters the basal layer through microabrasions at the surface of the epithelium. In approximately 90%, HPV clearance occurs within three years of infection. When there is viral persistence, then precancerous and cancerous changes can occur. The natural antibody response is mainly type-specific as compared to the cross-protection achieved with vaccination.

The currently available vaccines (Gardasil® and Cervarix®) consist of virus-like particles (VLPs) of HPV 16 and 18 that together cause about 70% of the worldwide occurring cases of cervical cancer. Gardasil contains, in addition, VLPs of HPV types 6 and 11 that induce the majority (90%) of genital warts. Both vaccines have an excellent safety profile. There are ongoing studies looking at using a vaccine with nine HPV types, seven of which are oncogenic.

Currently available HPV vaccines

	Quadrivalent vaccine	Bivalent vaccine
Manufacturer & trade name	Merck, Gardasil®	GlaxoSmithKline, Cervarix®
HPV genotypes	6, 11, 16, 18	16, 18
Adjuvant	Proprietary Aluminum	Proprietary Aluminum plus Monophosphoryl Lipid A
Schedule: 3 IM doses at	0, 2, 6 months	0, 1, 6 months
Age range	9–26 27–45 (FDA)	10–25 recommended >10

The current vaccines do not provide a therapeutic effect against prevalent infections hence vaccination is most cost-effective when given before exposure, i.e. before the sexual debut. In the UK, this is offered to girls aged 12–13 through the schools. Unlike natural exposure, HPV vaccination invariably induces seroconversion with noticeably far higher titers of antibody levels. These antibody levels remain high for at least 10 years, which is the current duration of study. It is likely that the protection will remain high for much longer, but these long-term studies are ongoing.

A reduction of cervical cancer rates may only be expected in 20–30 years, but a 25% decrease in abnormal cervical cytology tests in women aged <30 and associated colposcopy referral may be expected within a few years, just as an up to 70% diminishment in excisional treatments for high-grade disease. Furthermore, additional gain can be expected from a reduction of vulvar, vaginal, and anal cancers and their precursors, which are also partly caused by HPV 16 and 18. There will also be a beneficial effect on the incidence of oropharyngeal and oral cavity cancers as the immunity is systemic. For the benefit to be maximized, there is a need for high coverage of the at risk population (80% or greater). Vaccinated women should still attend cervical screening programs, otherwise the incidence of cervical cancer could even double since up to 30% of all cervical cancer cases are caused by non-vaccine types.

Learning points

- There are multiple risk factors for cervical cancers, many of these being surrogates for sexual activity.
- The process of cervical cancer development is generally slow, allowing screening to take place and intervention to alter the natural history.
- Non-invasive changes on the cervix may change over time, allowing for conservative management approaches in certain situations.
- Persistence of high-risk oncogenic HPV infection appears to be important for the pathogenesis of cervical cancer.
- Education and general healthcare provision has a significant impact on the incidence of cervical cancer.
- Countries with planned population-based screening programs have seen the largest effect on cervical cancer incidence and mortality.
- HPV vaccination is available, which provides protection against cervical intraepithelial neoplasia (and anticipated protection against cervical cancer).
- The HPV vaccine has beneficial protection against other anogenital and oropharyngeal cancers.

Chapter 4

Colposcopic appearance of CIN

Assessment of women presenting with abnormal cervical cytology and the selection of those requiring treatment relies on colposcopic assessment of the cervical TZ. Colposcopy remains subjective, and expertise in recognizing differing patterns and their corresponding histological abnormalities is dependent upon a period of apprenticeship. Differentiation of normal and abnormal colposcopic findings and their relative importance is of great significance in the management of women with abnormal cervical cytology or those suspected of invasive disease. Recognizing what is normal is an essential prerequisite before being able to recognize abnormality.

The two sites of possible colposcopic abnormality reside within the epithelia and the vasculature of the cervix, therefore knowledge of the appearances of the three types of normal epithelia and their relationship is of considerable importance. These epithelia are:

- Squamous
- Columnar
- Metaplastic

The TZ is variable in width and configuration and contains columnar and squamous metaplastic epithelium of varying maturity. The use of the green filter aids the recognition of vascular patterns.

Atypical transformation zone

The atypical transformation zone (ATZ) is the area of the cervix whose limits define cervical intraepithelial neoplasia. The TZ is a dynamic region of the epithelium and deviation to abnormality occurs within the unstable metaplastic epithelium; however, there is no one feature that defines a distinct histological abnormality and it is the overall appearance that is important. Any condition that causes increased cellular division, abnormal cellular metabolism, or increased vascularisation can produce atypical colposcopic findings in cervical epithelium.

There are various characteristics of the ATZ and these will be discussed individually. Scoring systems in common usage will be discussed as well as a clinico–colposcopic index (CCI) that takes into account the patient characteristics as well as known prognostic colposcopic factors to predict the degree of abnormality of the TZ.

Cytological and histological parameters (nomenclature) of CIN

The original cytological classification introduced by Papanicolaou has been largely replaced worldwide. The currently used cytological terminology in the UK was proposed by the British Society for Clinical Cytology in 1987, where the appearances of the cells are classified into mild, moderate, and severe dyskaryosis, with borderline nuclear abnormalities used for changes that fall short of dyskaryosis. 'Severe dyskaryosis ?invasive disease' may be used as may '?glandular neoplasia' in those cases where the dyskaryosis appears to be in glandular cells. The National Cancer Institute of the United States developed The Bethesda system (TBS) in 1988, which was modified in 2001. This classifies abnormalities as atypical squamous or glandular cells of undetermined significance (ASC-US), atypical squamous cells but cannot exclude HSIL (ASC-H), low grade squamous intraepithelial lesions, LSIL (encompassing HPV and CIN I) and high-grade squamous intraepithelial lesions, HSIL (encompassing CIN II and CIN III). The various abnormalities can co-exist but management is dictated by the worst histological diagnosis. Irrespective of the terminology used, there is debate as to whether CIN is a continuum.

The histogenetic classification of cervical precancerous lesions, which reflects the depth of epithelial involvement, was first introduced by the World Health Organization (WHO). In 1967, CIN classification was

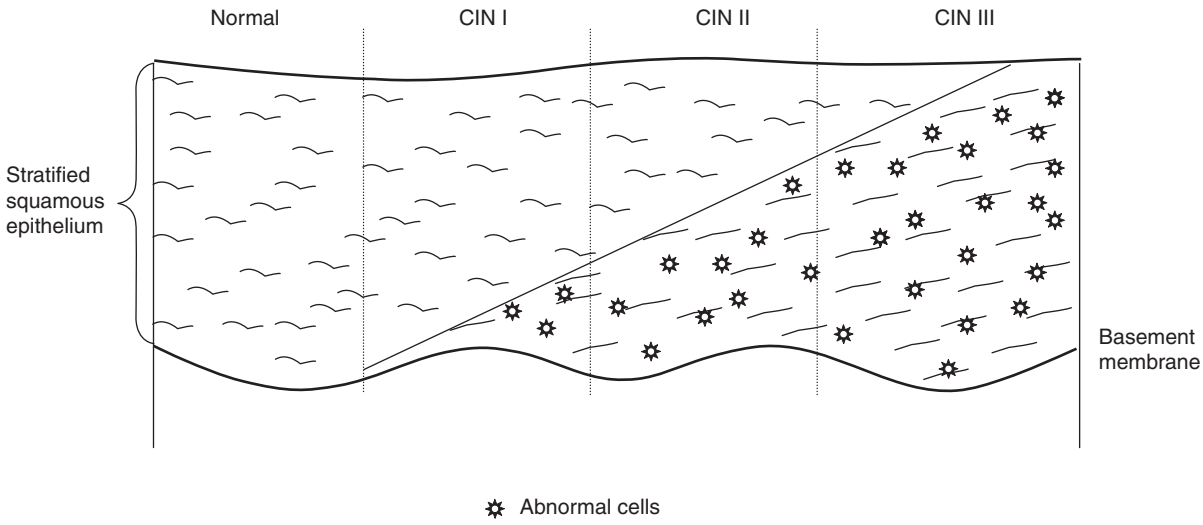


Fig 4.1 CIN is graded on the proportion of epithelium containing abnormal cells (original by G Teale, Australia).

introduced by Richart where CIN I, II, and III corresponds to mild, moderate and severe dysplasia/carcinoma in situ (CIS) of WHO classification, respectively. In 1990 a revised classification was suggested by Richart, with high-grade lesions (CIN II/III) likely to be true cancer precursors and low-grade lesions (CIN I / HPV) with unknown or low progressive potential. In actual practice the WHO and the three-tier CIN classifications are used universally.

Colposcopic parameters and their relative importance

An important element of colposcopy is to view the cervix prior to application of acetic acid. This can be aided by gently cleansing the area with saline and using the green filter to accentuate any vascular patterns. Epithelial alterations to note are leukoplakia and acetowhite epithelium. The vascular changes include punctation, mosaic, and atypical vessels.

Leukoplakia

Leukoplakia is visible without application of acetic acid even to the naked eye. It appears as a white area of thickened epithelium, which maybe patchy or cover large areas of cervix and sometimes extends onto the vagina. Histologically it denotes hyperkeratosis or parakeratosis. Its main significance is that it may obscure visualization of the TZ. Biopsy should always be done.

Acetowhite epithelium

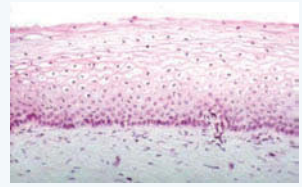
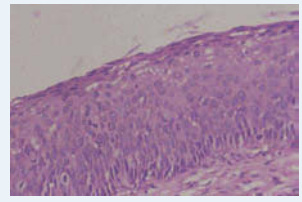
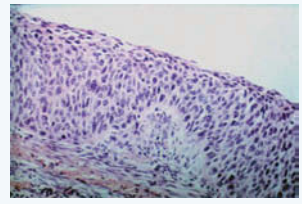
After the application of a dilute solution of 3–5% acetic acid, areas of high nuclear density appear white. Although this may occur in cases of immature metaplasia, generally the denser the acetowhite change, the faster the change becomes apparent, and the increased length of time the epithelium holds the change, the more severe the lesion may be. Dense acetowhite change within columnar epithelium may indicate glandular disease.

Acetowhite epithelium is not diagnostic for CIN. Other conditions that display acetowhiteness are:

- HPV related changes
- Mixture of CIN and HPV
- Columnar epithelium
- Immature squamous metaplasia
- Healing or regenerating epithelium
- Congenital TZ
- Inflammation
- Adenocarcinoma in situ or Adenocarcinoma
- Invasive squamous cell carcinoma (SCC)

In general the more intense and sustained the acetowhite change, the more significant the lesion. The margins may be well defined but appear indistinct or fuzzy, particularly with HPV-related lesions. The size of the lesion can be a good predictor of histological grade of the precancerous lesion. This can either be assessed by the number of quadrants involved with acetowhite change or by the lesion surface area. A large lesion

Classification systems of cervical intraepithelial neoplasia compared

CIN classification	WHO classification	The Bethesda System classification*	Squamous intraepithelial neoplasia (SIL) classification	Histology
CIN I	Mild dysplasia	Low-grade CIN	Low-grade SIL (LSIL)	Abnormal cells occupy basal third of the epithelium  Fig 4.2
CIN II	Moderate dysplasia	High-grade CIN	High-grade SIL (HSIL)	Abnormal cells occupy 1/3–2/3 of epithelium  Fig 4.3
CIN III	Severe dysplasia / carcinoma in situ	High-grade CIN	High-grade SIL (HSIL)	Abnormal cells occupy >2/3 of epithelium  Fig 4.4

*Within The Bethesda System Classification, low-grade CIN incorporates wart virus infection.

would be greater than 1 cm^2. Despite the correlation of histological grade of CIN with lesion size, CIN III may occur as a small focus and CIN I may be extensive.

Iodine negativity

After the application of Lugol's iodine, mature squamous epithelium, which contains glycogen, will stain a deep brown. Iodine-negative areas may represent immature metaplasia, cervical intraepithelial neoplasia, or low estrogen states (i.e. atrophy). A speckled appearance in an area with slight acetowhite change may represent immature metaplasia or low-grade intraepithelial neoplasia. Complete iodine negativity, a yellow staining in an area that has appeared strongly

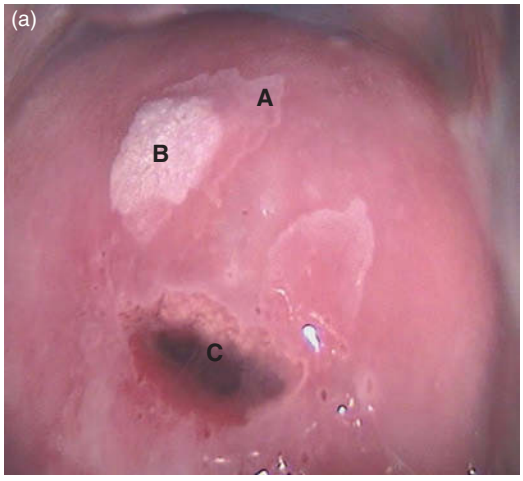


Fig 4.5a Low-grade CIN (A), HPV lesion (B), cervical canal (C).

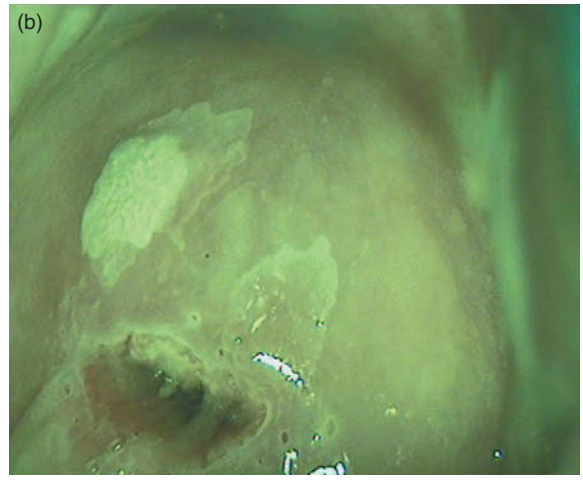


Fig 4.5b Same lesion as in 4.5(a) but with green filter applied.

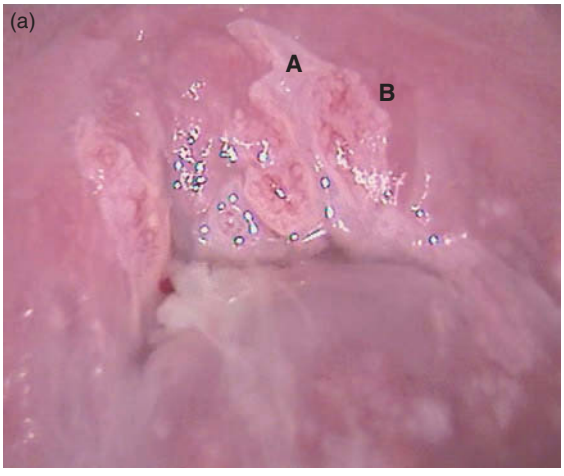


Fig 4.6a Minor colposcopic changes consistent with low-grade CIN (A). Border between atypical area and normal squamous epithelium is fairly indistinct (B).

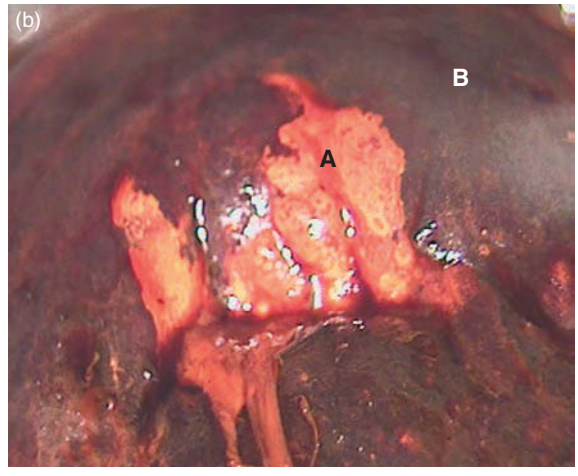


Fig 4.6b Similar lesion as 4.6(a) after application of Lugol's iodine. Atycical area (A)fails to stain and is termed schiller's test posivive. Normal squamous epithelium stains a dark brown color (B).

acetowhite, is highly suggestive of high-grade intraepithelial neoplasia. The use of Lugol's iodine is useful particularly for the beginner in delineating any abnormalities.

Vascular patterns

The three identifiable vascular patterns are:

- *Mosaic*
  A focal colposcopic appearance in which the new vessel formation appears as a rectangular pattern like a mosaic. The smaller the mosaic, the more likely the lesion is to be of low grade or metaplasia. The coarser, wider, and more irregular the mosaic, the more likely the lesion is to be of higher grade.

  Often referred to as 'crazy-paving' pattern when the capillaries are seen parallel to the surface. In its minimal form it shows fine caliber vessels surrounding small areas of regular size and shape. In its maximal development the mosaic shows coarser, more hyperemic, more superficial vessels surrounding irregular fields, so that the intercapillary distance is increased. Often combinations of mosaic and punctation patterns intermingle.
- *Punctation*
  A focal colposcopic pattern in which capillaries appear in a stippled pattern. The finer the punctation

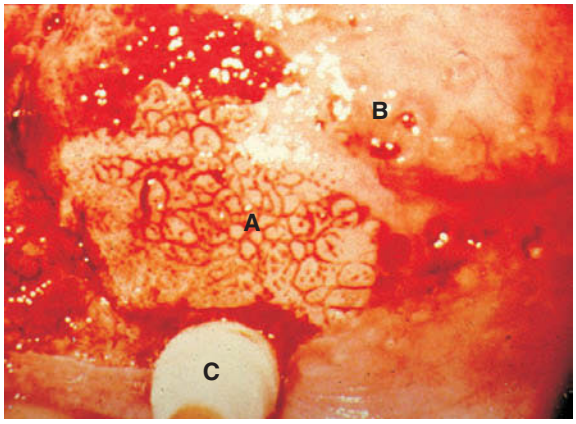


Fig 4.7 CIN II with mosaic. Mosaic and punctation of various coarseness (A), gland opening (B), cotton bud manipulating cervix (C).

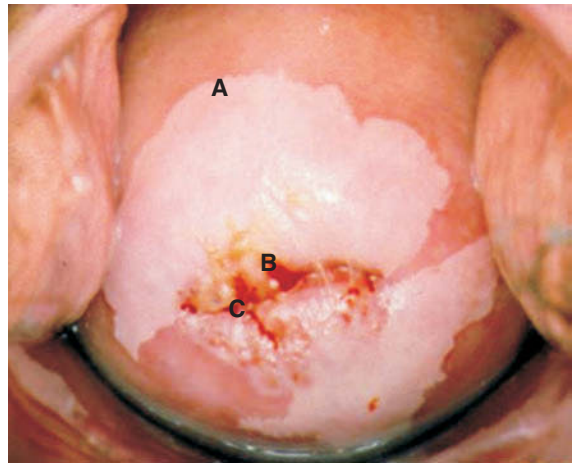


Fig 4.8 High-grade CIN. Acetowhite change with sharp border (A), SCJ (B), cervical canal (C)

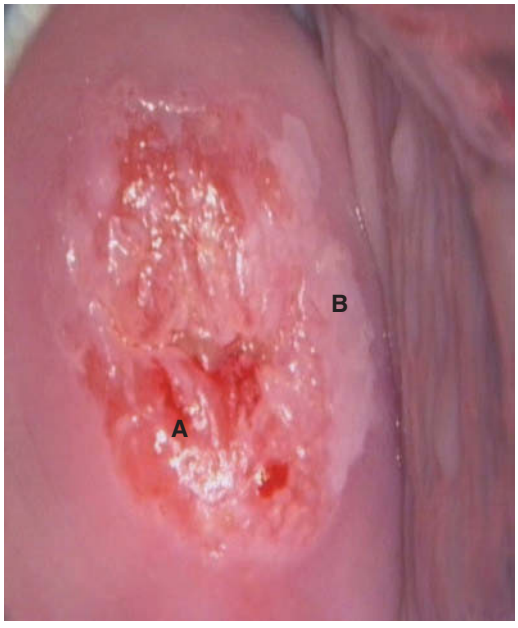


Fig 4.9 Metaplasia (A) seen in various stages with associated high-grade CIN (B).

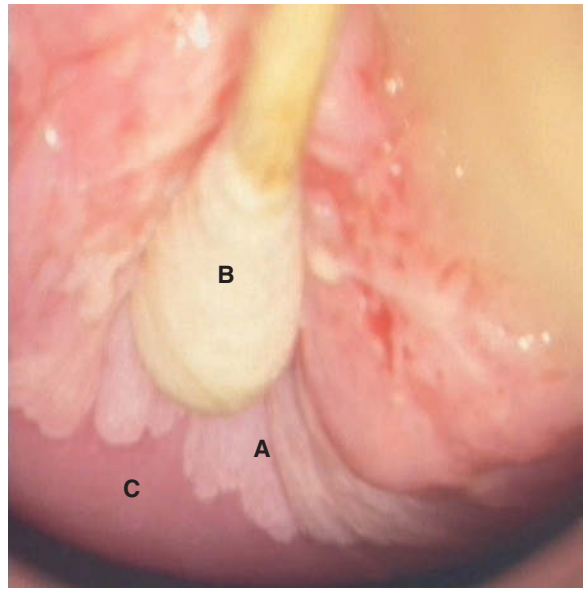


Fig 4.10 CIN (A) extending posteriorly. Exposure is helped by a small cotton-tipped swab (B) with normal squamous epithelium (C) at periphery of cervix.

appearance, the more likely the lesion is to be of low grade or metaplasia. The coarser the punctation, the more likely the lesion is to be of higher grade.

Basic unit of the punctation pattern is the single, looped capillary within the stromal papilla, coursing obliquely or perpendicularly towards the surface of the epithelium, seen end-on as a dot. In its minimal development it is fine with closely spaced capillaries of narrow caliber forming regular patterns. Higher degrees of abnormality display capillaries with increased caliber and irregular spacing, even-coiled (corkscrew) vessels.

- *Atypical vessels*
  A focal abnormal colposcopic pattern in which the blood vessel pattern appears not as punctation or mosaic or as the finely branching capillaries of a normal epithelium, but rather as irregular vessels with an abrupt and interrupted course appearing as commas, corkscrew capillaries, or spaghetti-like

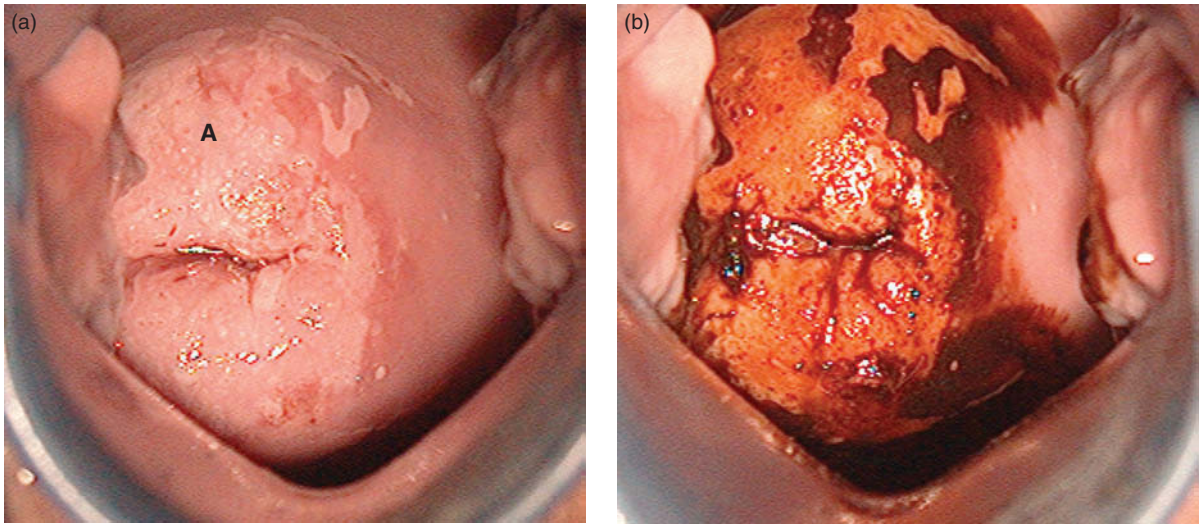


Fig 4.11 High-grade CIN (A) with acetic acid application and following Lugol's iodine application.

forms. Lesions, especially those with invasive changes, have new vessels that are formed often demonstrating gross variation in caliber, branching and arrangement. The intercapillary distance is much greater than is found in normal epithelium.

Colposcopic features suggestive of low-grade disease (minor change)

- A smooth surface with an irregular outer border.
- Slight acetowhite change, slow to appear, and quick to disappear.
- Mild, often speckled iodine partial positivity.
- Fine punctation and fine regular mosaic.

Colposcopic features suggestive of high-grade disease (major change)

- A generally smooth surface with a sharp outer border.
- Dense acetowhite change, that appears early and is slow to resolve; it may be oyster white.
- Iodine negativity, a yellow appearance in a previously dense white epithelium.
- Coarse punctation and wide irregular mosaics of differing size.
- Dense acetowhite change within columnar epithelium may indicate glandular disease.

Colposcopic features suggestive of invasive cancer

- Irregular surface, erosion, or ulceration.
- Dense acetowhite change.
- Wide irregular punctation and mosaic.
- Atypical vessels.

Grading systems

A variety of formal grading schemes have been suggested. All of these are dependent upon a subjective assessment of the colposcopic features. Any grading system should be simple to use and practical in a clinical setting. With adequate training and a systematic approach to colposcopic assessment, it is possible to categorize many lesions affecting the cervix and thereby differentiate between significant as opposed to insignificant lesions.

One of these grading systems analysed data collected prospectively. Of the clinical variables, the referral cervical cytology and smoking status were statistically the most significant predictors of histological grade. From this data a CCI has been devised that is practical to use within a clinical setting and which is weighted to take into account the prognostic importance of index cytology and smoking status. Using this type of CCI, a score can be derived for each individual patient, taking into account the important prognostic factors.

Clinico-colposcopic index – CCI (Shafi–Nazeer index)

	Score		
Variable	**Zero points**	**One point**	**Two points**
Index cytology	Low grade	–	High grade
Smoking status	No	–	Yes
Age	≤30 years	>30 years	–
Acetowhitening	Slight	Marked	–
Surface area of lesion	≤1 cm^2	>1 cm^2	–
Intercapillary distance	≤350μ (fine or no mosaic/punctation)	>350μ (coarse mosaic/punctation)	–
Focality of lesion	Unifocal or multifocal	Annular	–
Surface pattern	Smooth	Irregular	–

For each individual patient, a maximum score of 10 can be achieved. The higher the score, the more significant the lesion.

CCI score	Likely histological abnormality
0–2	Insignificant lesions
3–5	Mixed histological pattern, often CIN I or II
6–10	Generally high-grade disease

Vaginal extension of CIN

In a minority of patients, there may be extension of the CIN onto the vaginal vault. The colposcopic appearances are similar and the abnormality can be delineated with the use of Lugol's iodine. Atypical epithelium will not take up the iodine stain.

Endocervical extension of TZ

In some patients, particularly after the menopause, the upper limit of the TZ and any CIN present may extend beyond the colposcopic visual limit. Use of an endocervical speculum may help in visualization of the lower 1 cm of the cervical canal but can be difficult. Excision biopsy, indicated as colposcopic diagnosis, cannot be relied upon if the TZ is not fully visualized.

Miscellaneous findings

Condylomata – These may occur within or without the TZ and indicate infection with HPV.

Keratosis – A focal colposcopic pattern in which hyperkeratosis is present and that appears as an elevated white plaque. The white change is present before the application of acetic acid and may preclude adequate visualization of the underlying transformation zone.

Erosion – A true erosion represents an area of denuded epithelium. It may have been caused by trauma and may be an indication that the surface epithelium is vulnerable and possibly abnormal.

Inflammation – These can produce significant cervical changes particularly hyperemia. Confusion may occur in differentiating inflammatory changes from CIN or invasive disease. If there is doubt, then appropriate biopsies should be undertaken.

Atrophy – An epithelial change due to a low estrogen state.

Polyps – Enlargement of columnar villi to form polyps. These are usually benign.

Retention cysts.

Deciduosis – A change identified in pregnancy.

Unsatisfactory colposcopy

A colposcopic examination is considered unsatisfactory when the SCJ cannot be visualized in its entirety. Examination can also be unsatisfactory if there is trauma, severe inflammation, or atrophy – conditions that may preclude full colposcopic assessment.

2011 IFCPC colposcopic terminology of the cervix			
General assessment		• Adequate/inadequate for the reason: (i.e. cervix obscured by inflammation, bleeding, scar) • SCJ visibility: completely visible, partially visible, not visible TZ types 1, 2, 3	
Normal colposcopic findings		Original squamous epithelium: • Mature • Atrophic Columnar epithelium • Ectopy Metaplastic squamous epithelium • Nabothian cysts • Crypt (gland) openings Deciduosis in pregnancy	
Abnormal colposcopic findings	**General principles**	**Location of the lesion**: inside or outside of the TZ, location of the lesion by clock position **Size of the lesion**: number of cervical quadrants the lesion covers, size of the lesion in percentage of the cervix	
	Grade 1 (Minor)	Thin acetowhite epithelium Irregular, geographic border	Fine mosaic Fine punctation
	Grade 2 (Major)	Dense acetowhite epithelium Rapid appearance of acetowhitening Cuffed crypt (gland) openings	Coarse mosaic Coarse punctation Sharp border Inner border sign Ridge sign
	Non-specific	Leukoplakia (keratosis, hyperkeratosis), erosion Lugol's staining (Schiller's test): stained/non-stained	
Suspicious for invasion		Atypical vessels **Additional signs**: fragile vessels, irregular surface, exophytic lesion, necrosis, ulceration (necrotic), tumor/gross neoplasm	
Miscellaneous finding		Congenital TZ Condyloma Polyp (ectocervical/endocervical) Inflammation	Stenosis Congenital anomaly Post treatment consequence Endometriosis

2011 IFCPC colposcopic terminology of the cervix – addendum	
Excision treatment types	Excision type 1, 2, 3
Excision specimen dimensions	**Length** – the distance from the distal/external margin to the proximal/internal margin **Thickness** – the distance from the stromal margin to the surface of the excised specimen **Circumference** (optional) – the perimeter of the excised specimen

Nomenclature

The International Federation for Cervical Pathology and Colposcopy (IFCPC) agreed an international revised nomenclature in 2011. This is reproduced in table format.

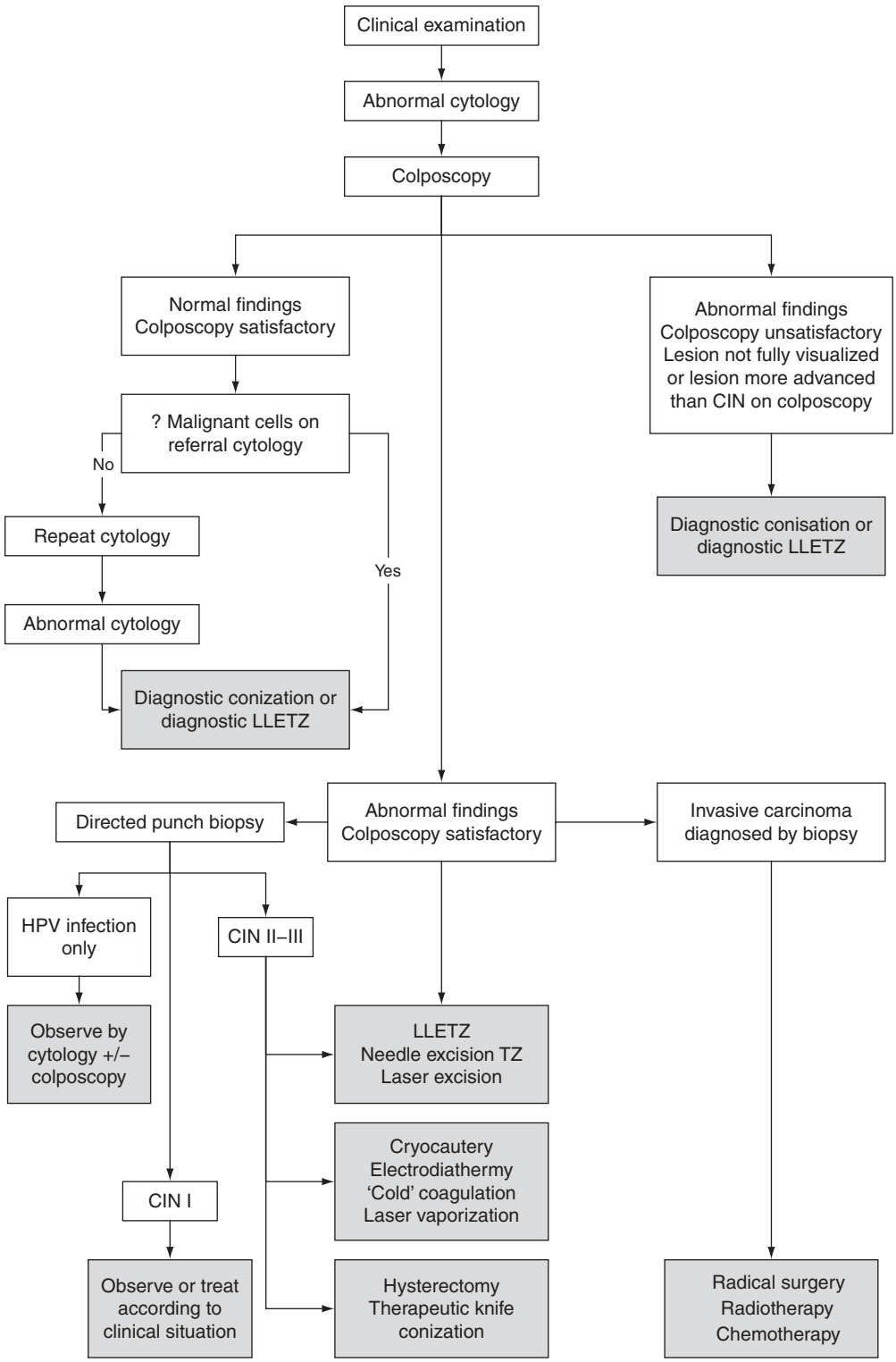


Fig 4.12 Colposcopy flowchart for management.

Summary

Colposcopy requires careful evaluation of the TZ. This allows assessment of the distribution of any lesion present including extension to the vaginal vault or endocervix. It aids exclusion of invasive disease and allows characterization between the differing grades of lesion. Colposcopy aids outpatient management of CIN.

Learning points

- Acetowhite change and assessment of vascular pattern is important for diagnostic colposcopy.
- Many epithelial types display acetowhite change and not just CIN.
- The more intense the acetowhite change and the coarser the mosaic/punctation, the more likely the presence of high-grade CIN.
- Use of a scoring system can aid diagnostic colposcopy.
- Atypical vessels and surface irregularity may indicate an invasive process.

Chapter 5

Colposcopic directed biopsies

When a patient is colposcoped and noted to have an abnormality, it often requires confirmation by taking a suitable biopsy. Biopsy is always necessary if the planned intervention is destructive; however, it may not be required if an excisional technique is to be employed. The type of biopsy depends on the clinical situation, degree of abnormality, and need to exclude invasive or glandular disease.

Punch biopsy

In most clinical situations where invasive or glandular disease is not suspected, punch biopsies will usually suffice. Multiple biopsies from the atypical TZ give greater diagnostic accuracy than a single biopsy. The most severe areas (densely acetowhite, coarse mosaicism, coarse punctation, or with abnormal vessels) of the lesion should be included in the biopsy taking. The biopsies can be sent for histopathological assessment separately labeled as this would affect the clinical management of the patient.

Punch biopsy forceps come in several shapes but all remove a small piece of tissue approximately 3.5 mm diameter. Usually no anesthetic is required; however, the patient's consent is important. The biopsy forceps need to be sharp and able to remove the tissue without distortion. To biopsy a lesion on the margin of the external os, the fixed part of the forceps should be inside the cervical canal and the mobile part outside. If more than one biopsy is required, the posterior lip should be sampled first in order to avoid impairment of vision because of bleeding. If the lesion lies on the ectocervix, it may be difficult to get a good biopsy sample but with manipulation this is usually possible.

The biopsy should be carefully handled to prevent trauma to, or loss of, the covering epithelium. The crater from the biopsy on the cervix usually requires no treatment. If bleeding persists, it can be sealed by a variety of techniques including vaginal tampon, silver nitrate, Monsel's solution, diathermy or other coagulating process. The patient is advised to expect a vaginal discharge of variable intensity and duration.

Wedge biopsy

In those women where invasive disease is suspected, a punch biopsy may be inadequate to confidently exclude this possibility. A suitably large biopsy consisting of either a wedge of tissue or cone biopsy needs to be taken. Wedge biopsy is useful when a diagnosis is required without removing too much cervical tissue. A half-moon incision is made with a scalpel over the most suspicious area, including both epithelial surfaces and the SCJ. There is a potential for bleeding with this procedure. Suitable haemostatic techniques should be employed, either by cautery or suturing the edges with an absorbable material. The procedure can be undertaken under local or general anesthesia. A wedge biopsy is not designed to be curative,

Fig 5.1 Punch biopsy forceps. Some have rotating mechanism for head manipulation. Handle 'squeeze' mechanism for biopsy.

Fig 5.2 Biopsy forceps detail. These need to be sharp and appropriately sized for suitable biopsies.

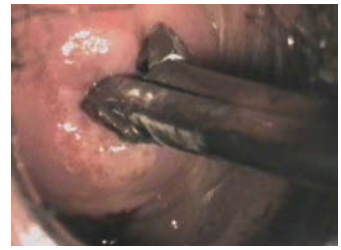


Fig 5.3 Cervical biopsy being performed.

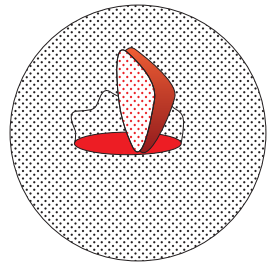


Fig 5.4 Wedge biopsy taken from ATZ. Normal and abnormal epithelium included.

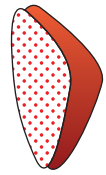


Fig 5.5 Excised wedge removed and sent for histological assessment.

whereas a suitably tailored cone biopsy may be. A wedge biopsy is preferred in pregnant women where malignancy is suspected.

Cone biopsy

A suitably tailored cone biopsy may be used both for diagnostic and therapeutic purposes. Cone biopsy can provide a suitably large biopsy for diagnosis in the following situations:

- Suspected malignancy.
- Glandular abnormality of the endocervical portion.
- Dysplasia is found on cytology and/or endocervical curettage but colposcopy is unsatisfactory.
- Colposcopy evaluation is negative but cytology is persistently positive.
- Upper limit of an apparent lesion is not visible.

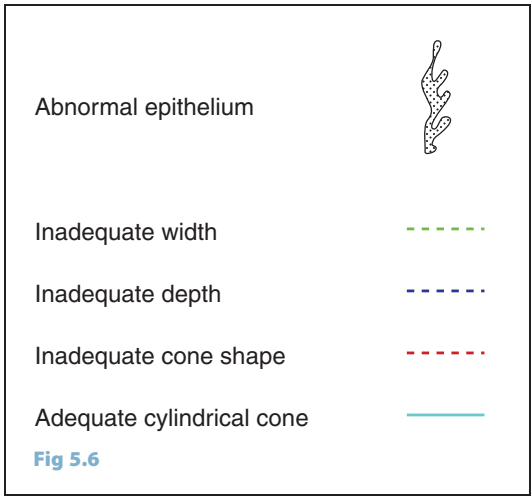


Fig 5.6

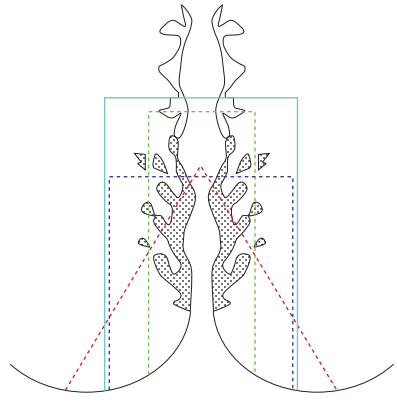


Fig 5.7

In early invasive disease or for those with completely excised squamous/glandular abnormality, no further treatment may be needed.

Cone biopsies can be undertaken with general or local anesthesia, depending on the choice of technique. A variety of cutting techniques can be deployed including knife (scalpel), diathermy or CO_2 laser in cutting mode. The latter two methods can also be used to seal the base of the cone biopsy and provide adequate haemostasis. If a knife is used, the base may be sealed using a pack with Monsel's or the cervical surface sutured. Whichever technique is used, it is important to try and maintain cervical anatomy, as this can be important in the follow-up. Size of the cone biopsy (width and length) affects complication rates. The length of the cone is associated with bleeding complications (primary and secondary) as well cervical stenosis. The width is important for adequate excision of abnormality. The shape will dictate the volume of tissue excised.

Endocervical curettage

In women where it is difficult to assess the endocervical canal in its entirety but there is suspicion of a lesion residing within the canal based on abnormal glandular cells on the cytology sample or the lesion is extending into the endocervical canal, an endocervical curettage (ECC) can be useful; however, the use and indications of ECC remain controversial.

When indicated, the canal should be curetted using a sharp spoon-shaped or grooved instrument. No anesthesia is required. To obtain an adequate sample the canal should be curetted circumferentially, using short, firm strokes to scrape the epithelium off its base of dense stromal tissue. The criticism of the procedure is with regards to the blind nature of the sample, also the fact that the scrapings are too superficial to give an adequate histological assessment, especially about microinvasion, and may miss disease in the crypts. Moreover, studies have shown sampling with an endocervical brush to be equally informative/efficient, if not more.

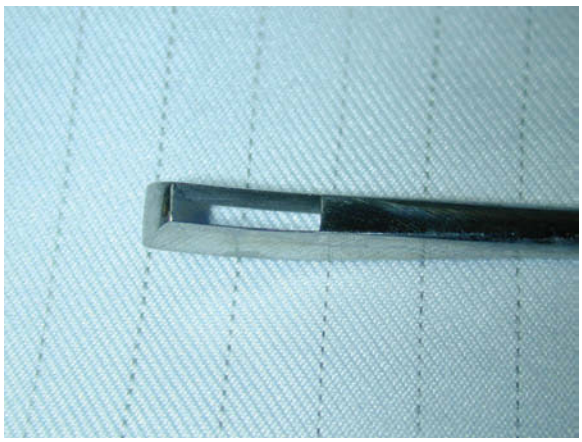


Fig 5.8 Endocervical curette.

Fixation

Any tissue removed should be immersed in solution of either formalin or Bouins. The choice of fixative is laboratory dependent. Once immersed, the tissue is allowed to fix and solidify over the course of 4–6 hours. After this period of time, it may be removed and trimmed in the laboratory for appropriate histological slide formation, which is stained using Haematoxylin and Eosin prior to assessment by histopathologists. If an excisional biopsy has been taken the dimensions of the specimen and margins should be commented on. The following core data should be available from the histological report:

- Size, state, and nature of the specimen. Mention if there is surgical trauma or coagulation artifact.
- All grades of squamous and/or glandular intraepithelial lesions should be reported and invasive lesions classified and graded.
- Koilocytosis.
- Loop or cone biopsies – has the abnormal squamous epithelium been completely excised (often impossible when loop biopsies received in several pieces).
- Punch biopsy showing CGIN must state that the possibility of invasion cannot be excluded from the biopsy.
- Microinvasive carcinoma cannot be diagnosed on punch or wedge biopsy. A loop or cone containing the entire invasive and intraepithelial lesion is required with disease-free margins to make this diagnosis.
- Microinvasive carcinoma must have the measurements of the invasive lesion reported and indication of Federation Internationale de Gynecologie et d'Obstetrique (FIGO) stage.
- Invasive lesions should have measurements made, margins assessed, and indicate type of tumor, differentiation, and the presence or absence of vascular permeation.

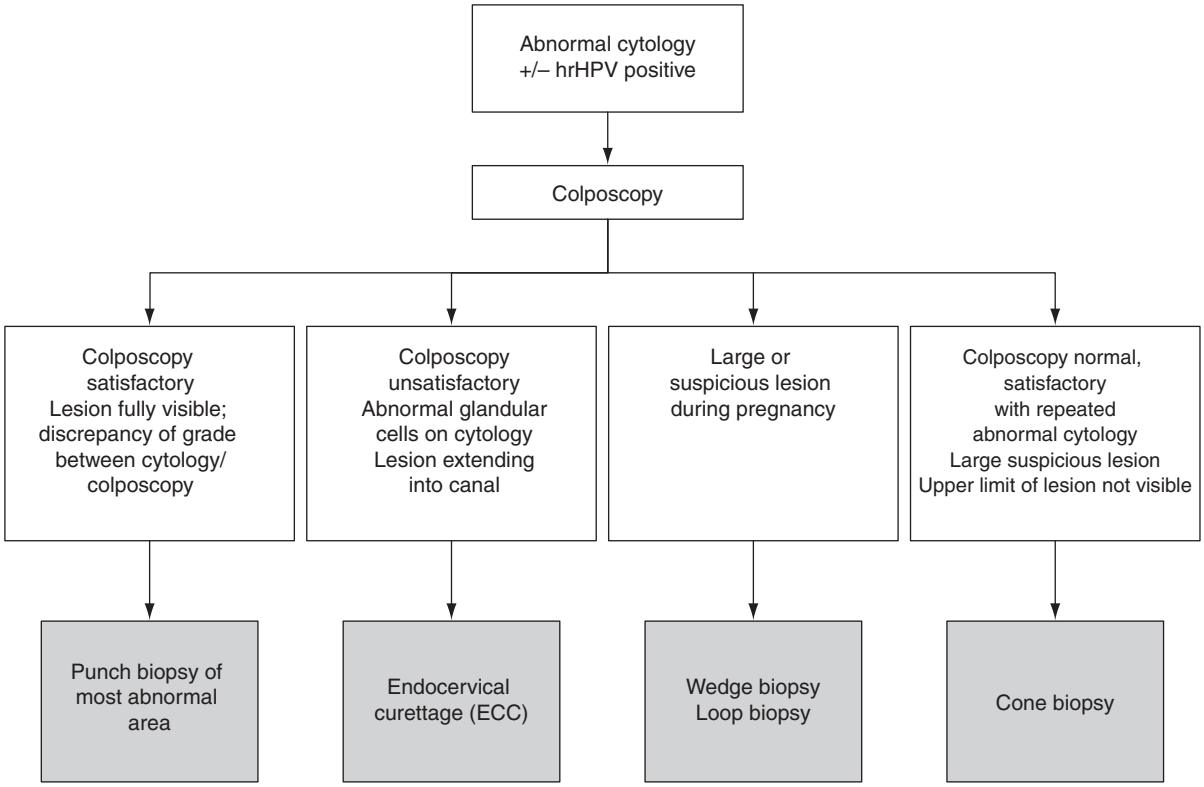


Fig 5.9 Flowchart showing indications for different colposcopically directed biopsies.

Learning points

- Cytology, colposcopic findings, and the histology should combine to give a diagnosis in any given individual.
- The biopsy taken should be adequate to make the diagnosis as well as exclude invasive disease if this is suspected.
- Certain biopsy procedures may provide a cure for the disorder.
- Histology reports should have a minimum dataset and agreed proforma can be useful in this respect.
- There is considerable inter- and intra-observer variation in histological assessment, particularly at the lower end of the disease spectrum.

Chapter 6

Invasive cervical disease

The majority of women with cervical cancer will present with symptoms, the most common being vaginal bleeding. Others will present with an abnormal cervical cytology sample of varying degree. The more severe the cytological abnormality, the greater the likelihood of finding invasive disease. Features suggestive of invasion include finding tumor diathesis on the cervical cytology sample.

Colposcopic appearance

At colposcopy, invasive disease is more likely in large lesions rather than small lesions. Colposcopically, abnormal irregular surface pattern, rolled edges, ulcerative or raised lesions, and the presence of atypical blood vessels are suggestive of an invasive process. These, taken in conjunction with the cervical cytology report and patient's age, are important in forming a colposcopic suspicion of invasive disease.

If invasion is suspected cytologically or colposcopically, the diagnosis must be confirmed by performing a suitably large biopsy. A punch biopsy will not reliably exclude an invasive process and therefore has limited value. A wedge, loop, or cone biopsy will provide enough tissue for diagnosis. With early invasive lesions, a good excisional technique will allow assessment of excision margins and tumor volume, which can inform further treatment plans. A suitably performed loop or cone biopsy may be therapeutic in early invasive disease.

Invasive disease may present as an overt exophytic, fragile mass. In such cases cytology is not useful; an excisional biopsy is performed followed by staging of the disease.

Staging

The main objectives of staging are to help the clinician plan appropriate management, giving some indication of prognosis. Staging also facilitates exchange of information amongst different treatment centers. Cervical cancer is staged clinically for assessment of tumor

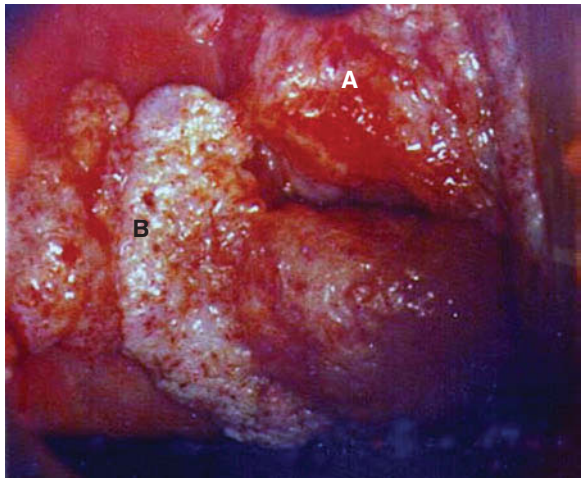


Fig 6.1 Extensive invasive cervical cancer (A) extending to vaginal fornices (B).

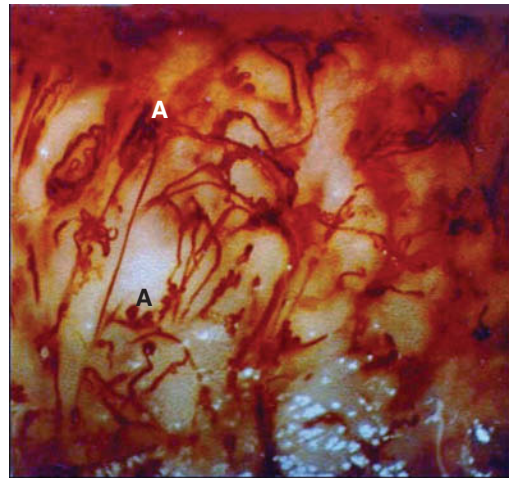


Fig 6.2 Atypical vessels (A) with varying branching.

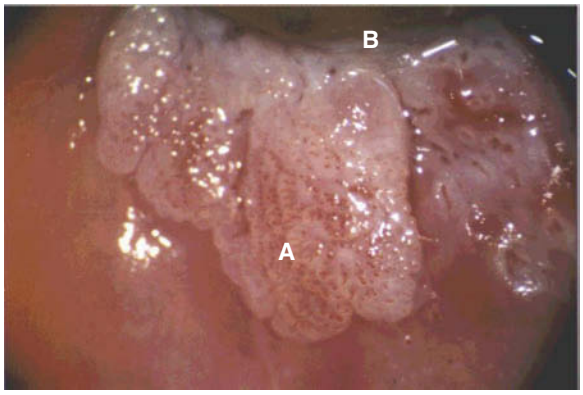


Fig 6.3 Punctation and coarse changes (A) extending into the cervical canal (B).

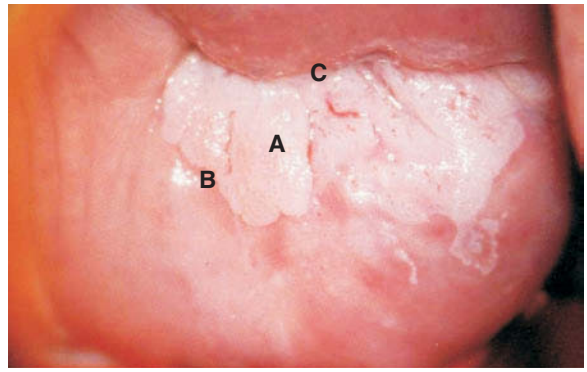


Fig 6.4 Dense acetowhite changes (A) with raised edge (B) and extending into cervical canal (C).

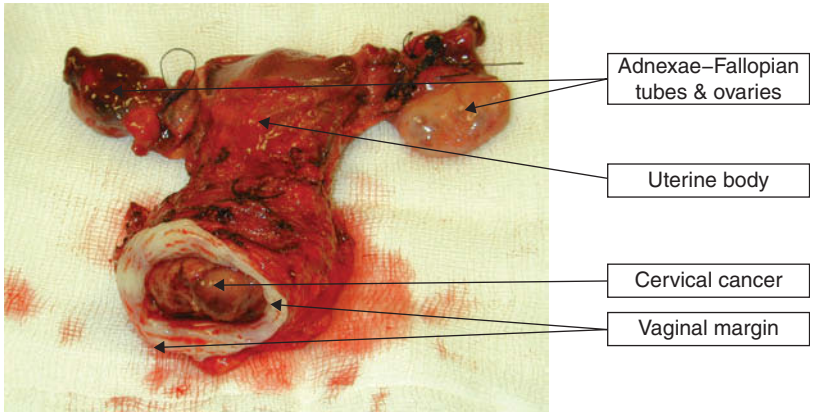


Fig 6.5 Cervical cancer in surgical specimen following radical hysterectomy.

volume and extent of disease spread. In the early invasive phase (stage IA), careful assessment of the histological findings is important for staging. Cervical cancer spreads by direct extension to pelvic organs and tissues, and by the lymphatics, preferentially to the pelvic nodes and thence to the para-aortic nodes. Though clinical staging remains the norm, other diagnostic tests are undertaken according to the clinical situation. Imaging can provide additional information allowing treatment to be tailored to the individual.

Procedures permitted for clinical staging

- Inspection, palpation, colposcopy, endocervical curettage, hysteroscopy.
- An adequate biopsy to confirm histological diagnosis.
- Examination under anesthesia (EUA), including a combined rectovaginal examination.
- Cystoscopy.
- Proctoscopy.
- X-ray of the lungs and skeleton.
- Intravenous urogram (IVU).

Findings of optional examinations, like computed tomographic scan (CT scan), magnetic resonance imaging (MRI), positron emission tomography (PET), lymphangiography, laparoscopy, and ultrasound can provide additional information for planning therapy, but does not alter FIGO staging. Fine-needle aspiration (FNA) of scan-detected suspicious lymph nodes may be helpful in treatment planning.

Five-year survival by stage for cervical cancer

Stage	Five-year survival (%)
I	80–99
II	60–90
III	30–50
IV	20
Overall	*68*

FIGO staging and tumor, node, metastasis (TNM) categories for carcinoma of the cervix uteri

Stage 0 TIS	Carcinoma in situ, intraepithelial carcinoma
Stage I	The carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded).
Stage IA	Invasive carcinoma, which can be identified only by microscopy, with deepest invasion ≤5mm and largest extension ≤ 7mm.
Stage IA1 T1a1 N0 M0	Measured stromal invasion of ≤3.0 mm in depth and extension of ≤7.0 mm.
Stage IA2 T1a2 N0 M0	Measured stromal invasion of >3.0 mm and not >5.0 mm with an extension of not >7.0 mm.
Stage IB	Clinically visible lesions limited to the cervix uteri or preclinical cancers greater than IA.
Stage IB1 T1b1 N0 M0	Clinically visible lesion ≤4.0 cm in greatest dimension.
Stage IB2 T1b2 N0 M0	Clinically visible lesion >4.0 cm in greatest dimension.
Stage II	Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina.
Stage IIA	Without parametrial invasion.
Stage IIA1 T2a1 N0 M0	Clinically visible lesion ≤4.0 cm in greatest dimension.
Stage IIA2 T2a2 N0 M0	Clinically visible lesion >4.0 cm in greatest dimension.
Stage IIB T2b N0 M0	With obvious parametrial invasion.
Stage III	The tumor extends to the pelvic wall and/or involves the lower third of the vagina and/or causes hydronephrosis or non-functioning kidney.
Stage IIIA T3a N0 M0	Tumor involves lower third of the vagina, with no extension to the pelvic wall.
Stage IIIB T1 N1 M0 T2 N1 M0 T3a N1 M0 T3b Any N M0	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney.
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous oedema, as such, does not permit a case to be allotted to Stage IV.
Stage IVA T4 Any N M0	Spread of the growth to adjacent organs.
Stage IVB Any T Any N M1	Spread to distant organs.

T= primary tumor; N= lymph node involvement; M=metastasis

Regional lymph nodes (N)

Regional lymph nodes include paracervical, parametrial, hypogastric, common internal and external iliac, presacral and sacral nodes.

- Nx: regional lymph nodes cannot be assessed
- N0: no regional lymph node metastases
- N1: regional lymph node metastases

Distant metastases (M)

- Mx: presence of distant metastases cannot be assessed
- M0: no distant metastases
- M1: distant metastases (including peri–aortic lymph nodes)

Notes about the staging for cervical carcinoma

- All macroscopically visible lesions – even with superficial invasion – are allotted to stage IB carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.0 mm and a horizontal extension of not >7.0 mm. Depth of invasion should not be >5.0 mm and a horizontal extension of not >7.0 mm. Depth of invasion should not be >5.0 mm taken from the base of the epithelium of the original tissue – superficial or glandular. The depth of invasion should always be reported in millimeters, even in those cases with 'early (minimal) stromal invasion' (~1 mm).
- The involvement of vascular/lymphatic spaces should not change the stage allotment.
- On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. All cases with hydronephrosis or non-functioning kidney are included, unless they are known to be due to another cause.
- When in doubt as to which stage a given tumor should be classified, the lower/earlier stage should be chosen.

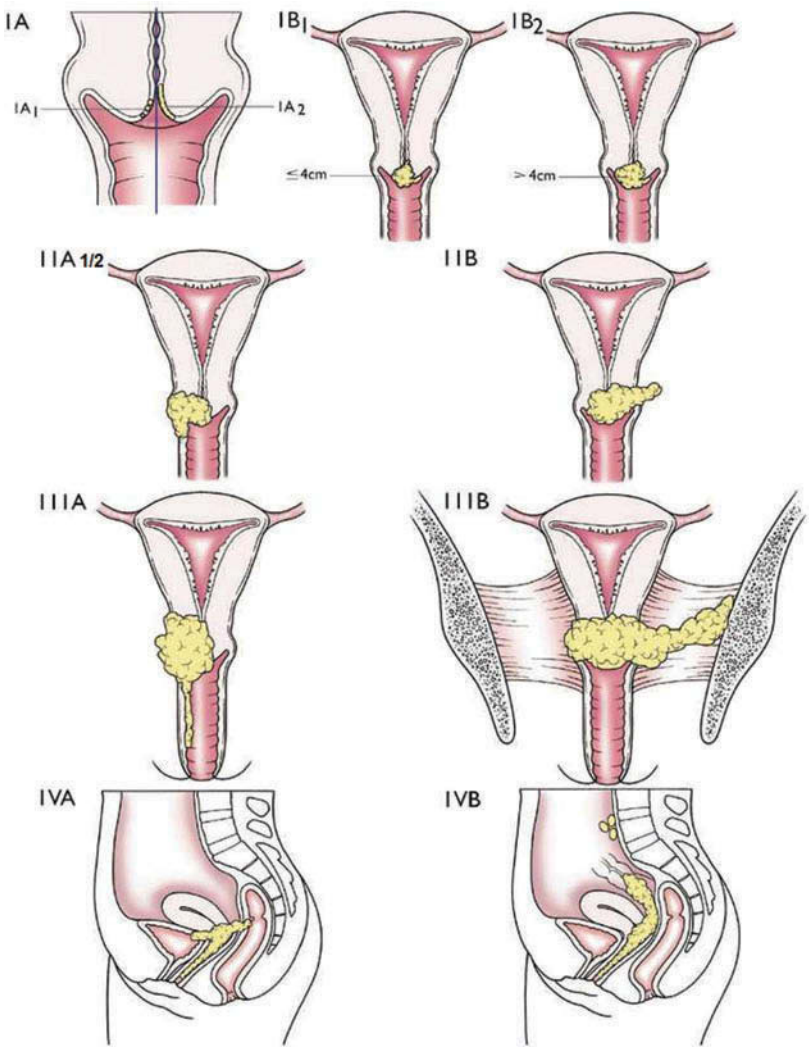


Fig 6.6 Diagrammatic representation of cervical cancer stage.

Learning points

- Cervical cancer is staged clinically.
- Histological assessment is especially important in early stage disease.
- Imaging (e.g. MRI) may provide further useful information but does not alter the clinical stage.
- Those women diagnosed with invasive disease in the absence of symptoms appear to have better prognosis than those diagnosed secondary to symptomatology.
- Volume of tumor and stage are related to prognosis.
- Cervical cancer spreads by direct extension.
- Locoregional lymph nodes may be involved but blood-borne metastases are rare.

Chapter 7

Glandular disease

The cervical cytology screening program is primarily concerned with detection and treatment of squamous abnormalities. The incidence of cervical glandular neoplasia continues to increase, both preinvasive and invasive disease. In many series, adenocarcinoma of the cervix represents 20–30% of all primary cervical cancers. The majority of the invasive adenocarcinomas are purely glandular but a significant percentage (40%) has a mixed adeno–squamous pattern. Adenocarcinoma is more likely to be diagnosed in younger women. Specific types of HPV are associated with glandular neoplasia, in particular HPV 18. Outcome in comparison with squamous lesions is poorer and this is partly reflective of a delay in diagnosis due to its endocervical distribution.

The premalignant form may be suspected from atypical glandular cytology, colposcopic abnormalities or a chance finding on biopsy or excisional method of treatment for women thought to have CIN.

Normal endocervical columnar epithelium is characterized by a regular single layer of tall columnar cells with basal nuclei and abundant mucin-rich cytoplasm.

Cytological classification

TBS 2001 classifies glandular cytological abnormalities into four subcategories:

- Atypical glandular cells (AGC); endocervical, endometrial, or glandular cells not otherwise specified (NOS).
- AGC, favor neoplastic, endocervical, endometrial, or NOS.
- Endocervical adenocarcinoma in situ (AIS).
- Adenocarcinoma.

The latter three categories are more likely to have associated pathology in comparison with the first category.

Classification of precancerous lesions

Just like its squamous counterpart, the glandular lesions are graded I, II, and III. Many names are used but the current one preferred is cervical glandular intraepithelial neoplasia (CGIN). In CGIN, the normal columnar epithelium is replaced by an epithelium that shows loss of polarity, stratification, and an increased nuclear size, which can vary in size and shape. The columnar epithelium appears atypical involving surface epithelium or gland crypts. There is often a sharp line of demarcation between normal and abnormal epithelium. It is the degree of nuclear change that distinguishes low-grade from high-grade CGIN. The point at which invasion occurs can be difficult to recognize and experienced gynecological histopathological review is vital.

Differential diagnosis

Diagnosis of CGIN by colposcopy is difficult as the lesions are often small and may occur away from the SCJ. Potentially the whole endocervix is at risk during the development of CGIN. The majority will be found in association with CIN and occur within 1 cm of the SCJ. There is also the possibility of 'skip lesions' further up the endocervical canal in a minority (13%) of those with CGIN.

Colposcopic appearance

The findings are often non-specific and uncharacteristic. In the absence of overt invasive disease, colposcopy does not reliably assess the presence of CGIN or even early invasive adenocarcinoma. Some suggest that presence of stark acetowhiteness either of individual or fused columnar villi may be seen. This may be particularly relevant if seen in association with colposcopically evident CIN where the two lesions may co-exist. The findings of such colposcopic features are non-specific and often other conditions such as metaplasia will produce similar changes.

As the lesions are small, may be multifocal and occur or extend high into the endocervical canal, punch biopsies will not reliably exclude glandular disease or invasive cancer, therefore a larger excisional method of diagnosis and treatment is required.

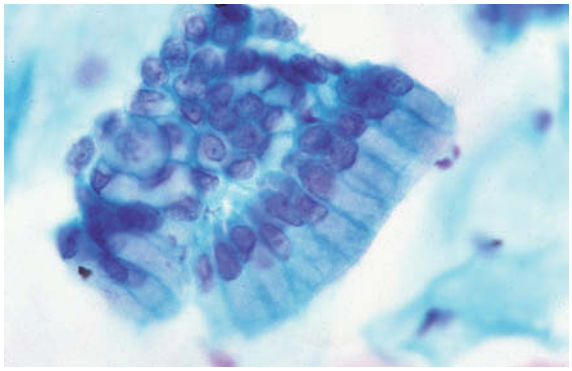


Fig 7.1 Cytology – normal endocervical cells.

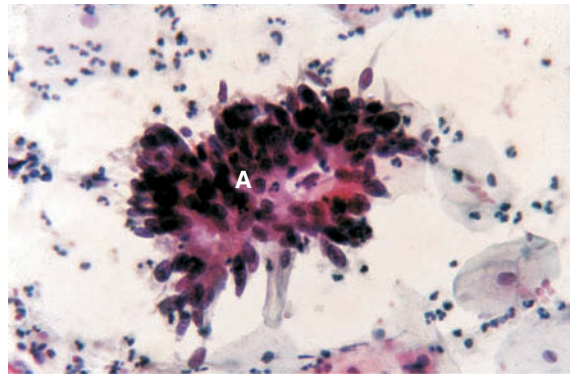


Fig 7.2 Cytology – atypical glandular cells consistent with glandular abnormalities (A).

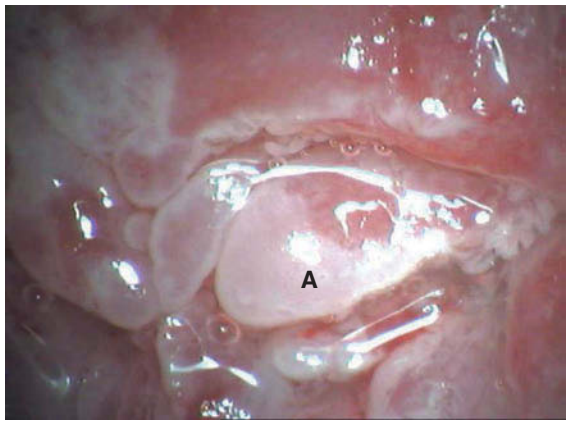


Fig 7.3 Colposcopy – changes minor and difficult to detect. Stark acetowhiteness of villi (A).

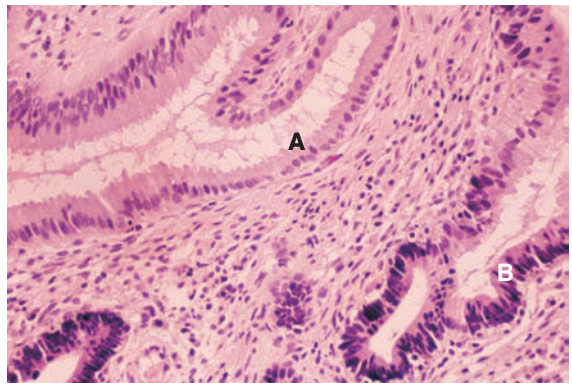


Fig 7.4 Histology – abrupt changes to columnar epithelium. Normal columnar epithelium (A). Atypical columnar epithelium (B).

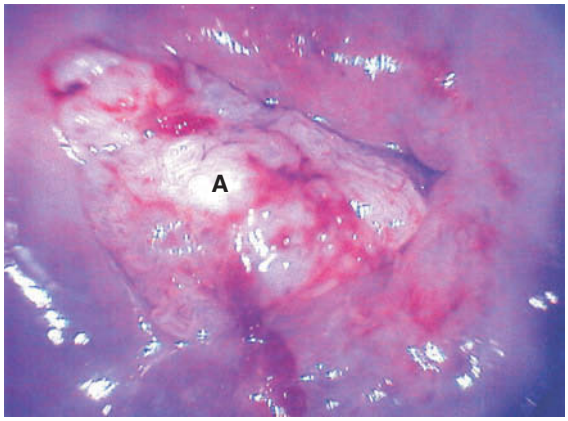


Fig 7.5 Invasive disease. Lesion seen arising from endocervix (A).

Management

The management of CGIN is far more contentious than treatment of CIN. Studies are small and usually retrospective due to the relative rarity of the condition.

Traditionally when CGIN is diagnosed, treatment has either been in the form of hysterectomy or a very large conisation of the cervix. A large prospective study of conisation has shown that it is a safe therapeutic procedure when the margins are not involved with disease. More recently large loop excision of the cervical TZ has been deemed as adequate treatment for CGIN as long as adequate follow-ups can be undertaken. In these circumstances, endocervical cytology is essential and presence of endocervical cells are required for meaningful assessment of cytology in patients treated for CGIN. If necessary, endocervical as well as cervex brush can be used to take paired samples, which are supplied in the same pot for cytological assessment.

In younger women and/or women who wish to retain fertility with a colposcopically visible SCJ, a cylindrical-shaped cervical excision of the TZ and at least 1 cm of the endocervix above the SCJ is recommended. In older women, or those where the SCJ is not visible at colposcopy, the cylindrical excision should include all the visible TZ and 2–2.5 cm of the endocervical canal. If clear margins are obtained, then the CGIN may be managed expectantly. Hysterectomy may need to be considered if clear margins are not attainable or the woman does not wish to retain fertility. It should also be considered in those with ongoing high-grade cytological abnormality after treatment or in those with cervical stenosis, making cytological assessment difficult. Following local treatment, it is recommended that cervical cytology should be performed every six months for five years and then annually for a further five years. Colposcopy is of no value and any residual/recurrent lesion may be more difficult to detect cytologically as compared with squamous lesions. HPV testing as 'test of cure' is not useful as virtually all cases of CGIN are HPV positive. The lesions can be present high in the cervical canal leading to under sampling. Reliance is placed on good quality cervical cytology.

Issues

As the disease is uncommon, careful assessment of the cervical cytology and colposcopy is warranted. An adequate excisional form of treatment is appropriate and expert histological diagnosis required. Differentiation of preinvasive disease from the invasive lesions is of paramount importance as treatment options are significantly different.

Learning points

- Adenocarcinoma of the cervix is becoming relatively more important as cervical screening impacts primarily on squamous cancers.
- The natural history of cervical adenocarcinoma and CGIN is less well understood.
- A significant percentage of women will want conservative management of their CGIN in view of their age and fertility considerations.
- Excisional treatments are appropriate for those with suspected or confirmed CGIN.
- Close follow-up after treatment is required with cytology indicating sampling from the TZ including endocervical cells.

Chapter 8

Inflammatory and infective conditions of the cervix and anogenital tract

Changes other than preinvasive or invasive disease of the cervix and the anogenital tract can also be seen at colposcopic examination. It is important to understand how colposcopic examination can be beneficial beyond its traditional role of detecting preinvasive lesions. Certain inflammatory and/or infective conditions of the genital region, in particular of the cervix, can mask or make diagnosis of neoplastic changes difficult. On the other hand, colposcopy can help recognize important changes, especially in asymptomatic women, so that appropriate investigations and treatment can be undertaken; however, in asymptomatic woman attending for colposcopy, there is no need to routinely test for chlamydia and other infections. This chapter looks at the inflammatory and infective conditions for which colposcopic examination can be particularly useful.

Human papilloma virus

Human papilloma virus (HPV) infection is largely transmitted sexually, although evidence of autoinoculation has been documented. All HPV types are epitheliotropic, completing their growth cycle only in differentiating keratinocytes of the skin and the anogenital/oropharyngeal mucosa. There are more than 40 HPV types that are known to infect the human genitalia. HPV can affect the cervix in a subclinical (flat warts) and/or clinical (exophytic) manner causing condylomas. The cervical changes associated with subclinical infections can be similar to those seen in low-grade CIN. These lesions are not visible to the naked eye and become apparent only with the application of acetic acid. Satellite lesions may be present outside the TZ.

In clinical infections, exophytic warts are visible on naked eye inspection. They may mimic a variety of clinical lesions and histological confirmation is important. The viral type is usually non-oncogenic (often types 6 or 11) and other lesions may be present within the lower genital tract. Lesions may take on some of the characteristics of invasive lesions and excisional biopsy would be recommended in this scenario.

In approximately 70–80% of immunocompetent individuals the infection disappears spontaneously within two years. Treatment of the wart will however, reduce viral load and diminish its ability to transmit the virus to sexual partners. Other indications for treatment are symptomatic cases (itching, dyspareunia) or concomitant epithelial dysplasia proven on biopsy. Various treatment options exist for lesions caused by HPV infection. No single modality is universally successful in eradicating the infection or preventing its recurrence. Most infections respond well after repeated treatments.

HPV and CIN differential diagnosis

- Precancerous lesions tend to be confined to the TZ, whereas benign HPV lesions may also exist in the native squamous epithelium, sometimes also extending onto the vagina.
- HPV lesions can also present as map-like areas of acetowhitening within the original squamous epithelium.
- HPV lesions can be apparent even prior to acetic acid application.
- CIN lesions in the atypical TZ show some characteristic features – punctations and mosaicism.
- CIN lesions are sharply delineated from the normal epithelium and their distal border is cranial to the SCJ.
- CIN lesions almost always do not stain with iodine.

Treatment options for HPV infections

Surgical		Medical
Excision	**Ablation**	
Laser	Laser	Trichloracetic acid (85%TCA in 70% alcohol)
LEEP/ LLETZ	Electrodiathermy	Podophylline crude extract (25% podophylin in benzoin)
Cold-knife	Cryotherapy	Podophyllotoxin 5-Fluorouracil (5FU) Interferons-α and δ Imiquimod

Fig 8.1 Cervical cytology showing koilocytosis (A) associated with HPV.

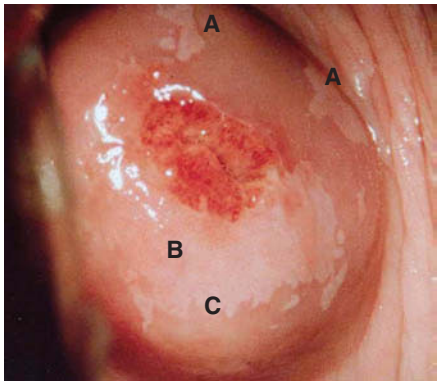


Fig 8.2 Subclinical HPV infection on cervix – becomes visible following application of acetic acid. Satellite acetowhite lesions (A) outside TZ and minor acetowhite changes (B) with indistinct border (C) consistent with low-grade CIN.

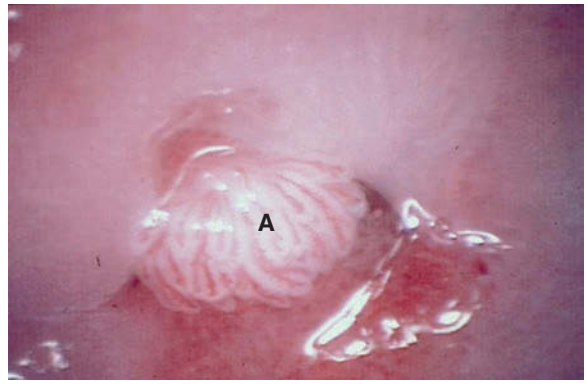


Fig 8.3 Clinical HPV infection causing cervical wart (A) with typical fronds/micropapillary without acetic acid.

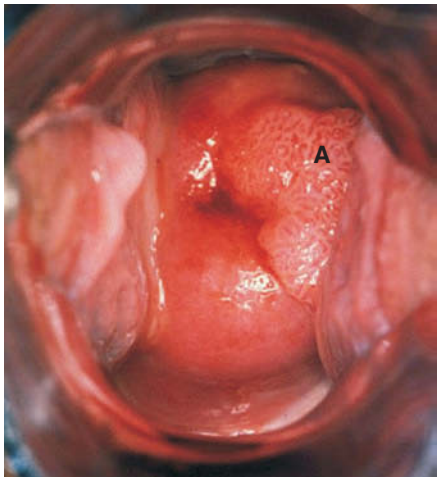


Fig 8.4 Warty lesion (A) on cervix. These can have variable appearance and are visible in the absence of acetic acid.

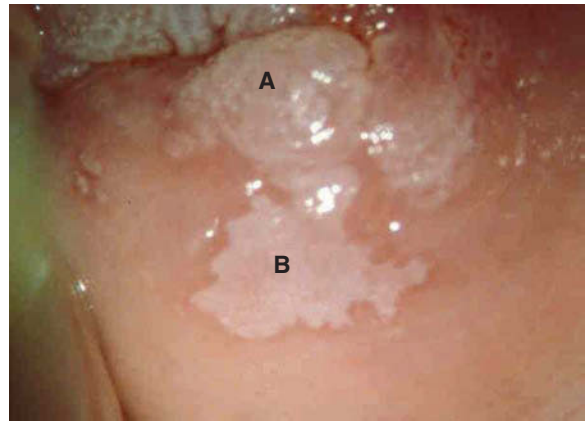


Fig 8.5 Wart on cervix (A) following application of acetic acid and subclinical HPV or low-grade CIN changes (B).

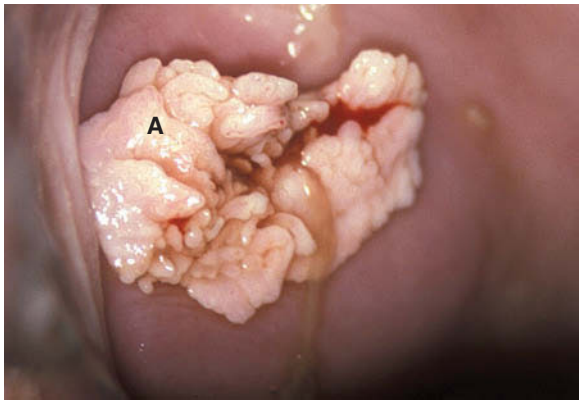


Fig 8.6 Warty lesion (A) encircling cervical canal following the application of acetic acid.

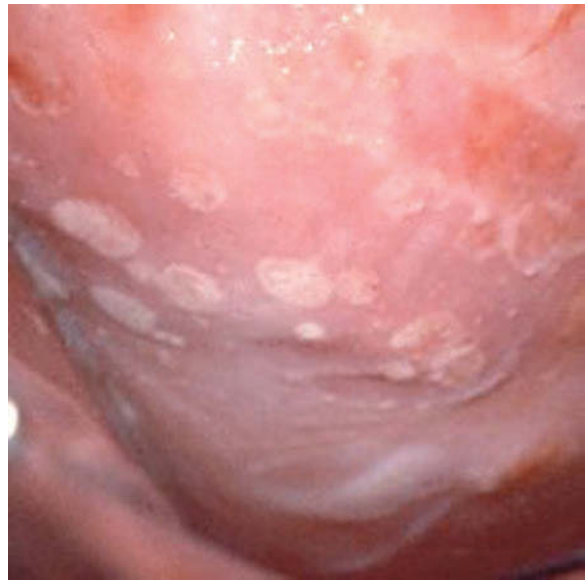


Fig 8.7 Herpetic lesions seen on the cervix in the vesicular phase.

Herpes simplex virus

Genital herpes is a highly contagious sexually transmitted disease caused by either herpes simplex virus (HSV) type 1 or 2. The former usually infects the oral area often causing 'cold sores'. HSV type 2 is the common infection within the genital area.

Initial infection is characterized by a prodrome of malaise, chills, fever, and enlargement of inguinal lymph nodes. The lesions can occur on any part of the vulva, perineum, or anus. Burning and itching may precede the skin eruption. Typically they appear as one or more blisters/vesicles. The blisters rapidly break, leaving painful, tender ulcerated areas (sores), 1–2 mm in size. The vesicles may coalesce to form large ulcers with irregular borders and pale yellow centre. Dysuria is often present either due to periurethral lesions or herpetic urethritis/cystitis. The lesions reach their maximum size in 7–10 days, thereafter a crust forms with gradual resolution. Complete healing is within 14–21 days.

Further outbreaks can occur but are almost always less severe and shorter than the first episode. Although the infection can stay in the body indefinitely, the number of outbreaks tends to decrease over a period of years.

In 70–90% women with vulvar herpes infection with HSV1 or 2 there is a concomitant herpetic infection of the cervix. This virus causes characteristic lesions on the cervix. The infection can be asymptomatic or can cause ulceration, which may be painful or give vaginal discharge. Biopsy is rarely warranted given the history and clinical findings. The infection is self-limiting but its resolution can be hastened with antiviral therapy such as aciclovir, especially if given within first 2–3 days of infection. This is for use on external genitalia only.

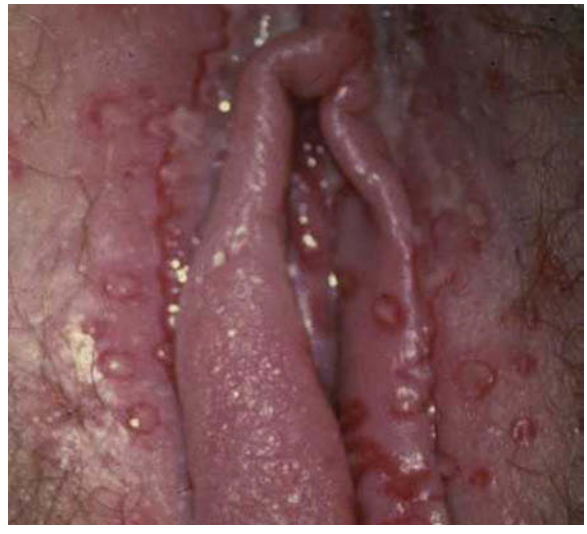


Fig 8.8 Multiple herpetic vesicles on the vulva. This patient had severe discomfort and problems with micturition.

Actinomyces-like organisms

Actinomyces-like organisms (ALOs) detected on cervical cytology do not require any specific intervention in the vast majority of women and are usually associated with intrauterine contraceptive devices (including the levonorgestrel intrauterine system). If the woman is asymptomatic, then an abdominal and pelvic examination is undertaken. She should be advised in relation to a small risk of developing pelvic actinomyces and advised to seek medical help if symptoms develop.

If there are specific symptoms, then the device may need to be removed, after ensuring that sexual intercourse has not occurred in the preceding five days. Relevant symptoms include pelvic pain, deep dyspareunia, persistent intermenstrual bleeding, vaginal discharge, dysuria or significant pelvic tenderness. Recommended medical treatment comprises a two-week course of antibiotics (e.g. amoxicillin or erythromycin).

Trichomoniasis

Infection with the protozoa *Trichomonas vaginalis* is highly prevalent in sexually active populations. Although it is considered as a sexually transmitted infection, it is not always the case. It is site-specific for genitourinary tract and can cause vaginitis, cervicitis, urethritis, and pelvic inflammatory disease especially in HIV-infected women. Asymptomatic infection is common both in men and women. Clinically the infection is characterized by profuse, greenish, offensive discharge with erythema, itching, burning, and dyspareunia.

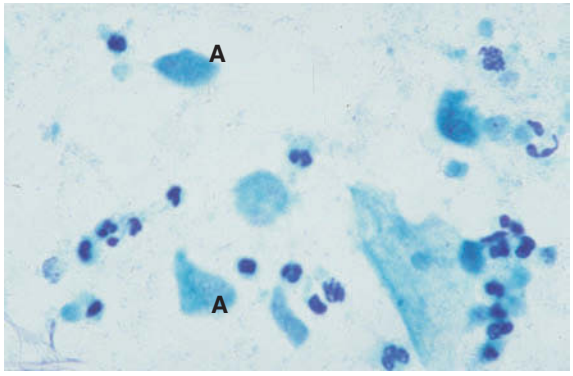


Fig 8.9 Cervical cytology sample showing infection with TV. Pear-shaped organism (A) with indistinct nuclei.

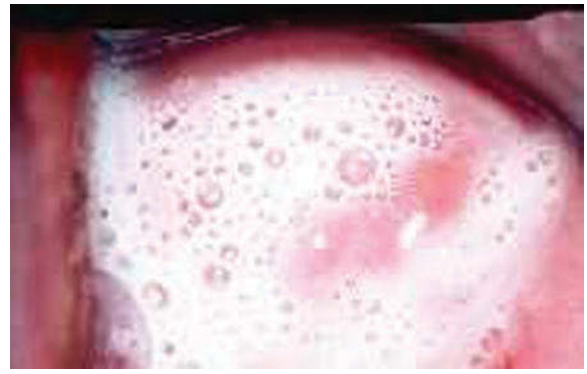


Fig 8.10 Discharge associated with TV.

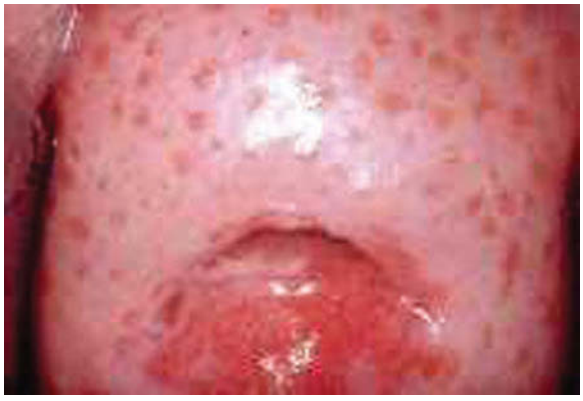


Fig 8.11 Colposcopic appearance of chronic TV infection showing 'strawberry cervix' pattern.

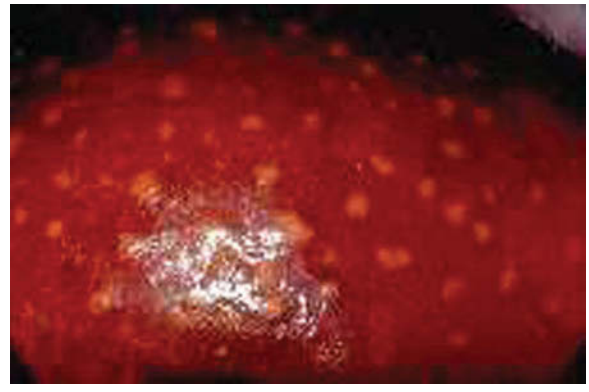


Fig 8.12 Chronic TV infection on cervix following application of Lugol's iodine to display 'leopard skin' type changes.

The colposcopic changes are those of generalized cervico–vaginal inflammation with associated red spots due to cytolytic foci of squamous epithelium with dilated epithelial capillaries surrounded by leucocytes – the changes have been likened to a 'strawberry cervix' or 'colpitis macularis'. After acetic acid the red spots may become prominent. Application of Lugol's iodine gives a characteristic appearance likened to 'leopard skin' with dark background staining of squamous epithelium and failure of staining of the epithelial spots.

Generally, the clinical picture is characteristic. Diagnosis is usually made from wet mount microscopy, directly visualizing the motile *Trichomonas* organisms. The organism may be visualized on the cervical cytology sample with Pap stain or special stain called Diff-Quick. Cultures can be taken from the cervix and vagina.

The treatment consists of nitroimidazole drugs (metronidazole) either in a single dose (2 g) or classical regimen of 250 mg three times daily for seven days. Topical metronidazole is not an effective therapy for Trichomoniasis. The sexual partner should be treated concomitantly.

Candidiasis

The *Candida albicans* organism is a common vaginal commensal along with the large intestine and oral cavity. Predisposing factors for the development of a clinical infection include: antibiotics, corticosteroids, chemotherapy, oral contraceptives, high carbohydrate diet, diabetes, immunosuppression, and pregnancy. The facilitation into vagina can occur from the rectum, cutaneous foci, or sexual transmission.

Patients with *Candida* infection will often present with vulvar pruritus and thick creamy, cheesy or curd-like, non-offensive vaginal discharge. Examination shows erythema and edema of the vulva and introitus and in severe forms a white pseudo-membrane adherent to the mucosa of vulva, vagina, and cervix. After acetic acid application, fine diffuse whitish patches appear on the vagina and cervix. These patches do not stain with Lugol's iodine.

Clinical picture is pathognomonic for *Candida* infection. Diagnosis can be confirmed on wet mount microscopy with spores and hyphae being apparent in active infection. *Candida* is easily identifiable on cervical cytology especially with gram staining. Culture gives the most accurate diagnosis.

Treatment consists of either imidazole antifungals (clotrimazole) vulvo–vaginal therapy with vaginal pessaries and cream, or triazole antifungals (fluconazole) oral therapy (tablets and cream). Either treatment can be effective both in a single or multiple doses. The sexual partner should also be treated to avoid cross-infection.

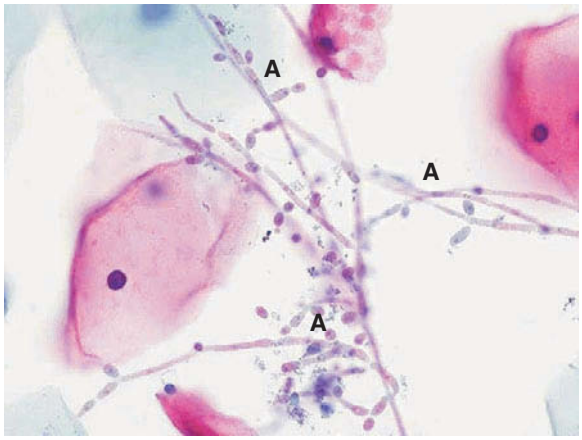


Fig 8.13 Candida organisms (A) visible on cervical cytology.

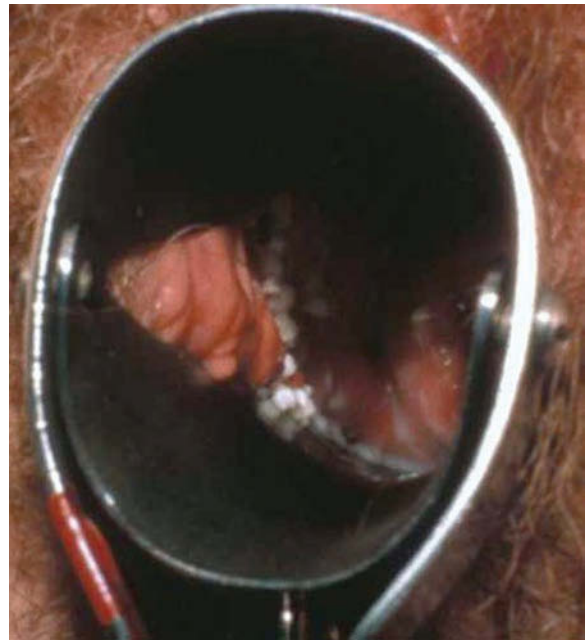


Fig 8.14 Candida infection can be seen on speculum inspection. Thick, creamy white discharge visible.

Chlamydia trachomatis

Chlamydia trachomatis is the commonest sexually transmitted infection in the UK and perhaps the rest of the world. Up to 1 in 10 women under the age of 25 may be infected in the UK. Women over the age of 25 are also at risk if they have a new sexual partner or have had two or more sexual partners in the previous 12 months.

Chlamydia trachomatis is a gram-negative intracellular parasite with some bacterial properties. Its different immunotypes are responsible for ocular trachoma (A,B,Ba,C); lymphogranuloma venerium (L1, L2,L3); genitourinary infections, and pelvic inflammatory disease (PID) (B-K).

Most cases of *Chlamydia* infection are either mild or asymptomatic; however, it can lead to an ascending infection causing PID and tubal damage. This in turn can lead to chronic pelvic pain, subfertility and/or tubal-factor infertility, or a high-risk of ectopic pregnancy. Chlamydial infection has also been linked to various obstetric complications such as preterm rupture of membranes and labor. If the baby is exposed to *Chlamydia* during childbirth, then it can develop eye infection or pneumonia.

Diagnostic tests for *Chlamydia* are expensive and technically complicated. Swabs from the cervix or male urethra can be cultured; however, tests based on DNA amplification (polymerase chain reaction, PCR or ligase chain reaction, LCR) are more sensitive and specific and can be performed on cervical and urethral swabs and also first-catch urine from both males and females.

Given the high incidence rates the following categories should be screened:

- All those attending genitourinary clinics and their partners.
- All women seeking or have had a termination of pregnancy and their partners.
- Asymptomatic sexually active women under the age of 25, especially teenagers.
- Asymptomatic women over the age of 25 who have a new sexual partner or have had two or more partners in a year.

Treatment is with doxycycline 100 mg twice daily for seven days. If compliance is a problem, treatment can be with 1 gm azithromycin taken immediately. Partner notification should be routinely performed and every effort made to treat the partner also. Advise 'no sex' until both sexual partners have been treated. Consider screening for other sexually transmitted infections if there is a history of multiple sexual partners.

Bacterial vaginosis

Bacterial vaginosis (BV) involves an alteration of the vaginal microecological environment and is associated with organisms *Gardnerella vaginalis*, *Mobiluncus* and other anaerobes. These organisms are believed to be essentially sexually transmitted. BV is not caused by poor hygiene – in fact, excessive washing of the vagina may alter the normal balance of bacteria in the vagina, which may make BV more likely to develop. About 1 in 10 women will have BV at some time in their life. Whilst any woman can be affected, it is more common in those with an intrauterine contraceptive device.

In 50% of cases it produces no symptoms. On examination, the vagina is not inflamed, hence the term vaginosis, and there is a thin greyish discharge with fishy odor. When a drop of this discharge is added to a drop of saline on a glass slide with a drop of 10% potassium hydroxide, a characteristic 'fishy amine' odor is released.

Diagnosis can be confirmed by gram stain microscopy showing typical 'clue cells' and absence of *lactobacilli* or by culture. Clue cells are vaginal epithelial cells surrounded by microorganisms.

Treatment is with 250 mg metronidazole three times a day for seven days or a single dose of 2 gm.

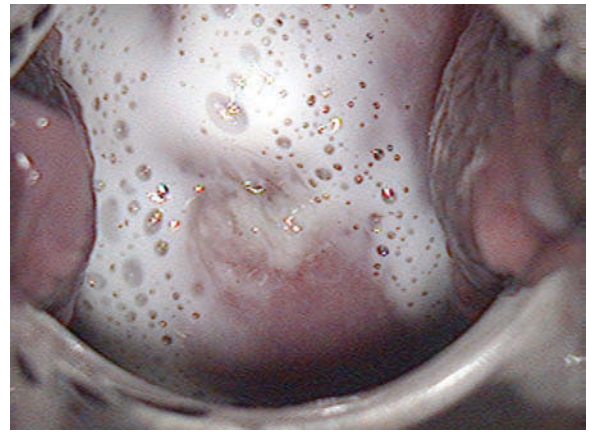


Fig 8.15 Discharge associated with BV seen on speculum examination.

Chronic cervicitis

Inflammatory conditions have a varying affect on the appearance of the cervix. The vascular pattern needs careful assessment and the cervix may be tender to touch. Dyspareunia, postcoital bleeding, or vaginal discharge may be the presenting symptom. Possibility of an infective organism should be ruled out by appropriate microbiology. In some of these women, the appearance can suggest an invasive process and recourse to cervical biopsy may be necessary to diagnose the inflammatory process and exclude any invasive component.

In the absence of any specific infection and invasive changes, symptomatic treatment can be given by increasing vaginal acidity and flora (Aci-gel; Gynoflor etc.) or anti-inflammatory agents. Cryocautery or diathermy can be considered in cases of persistent intractable symptoms.

Nabothian cysts

Whilst these are normal, they can cause concern to the untrained clinician. The cysts occur due to the cervical gland openings becoming covered and mucus collection forming within. Any vessels seen are regular branching (tree-like pattern) and do not justify biopsy. They do not require any treatment and the woman should be reassured.

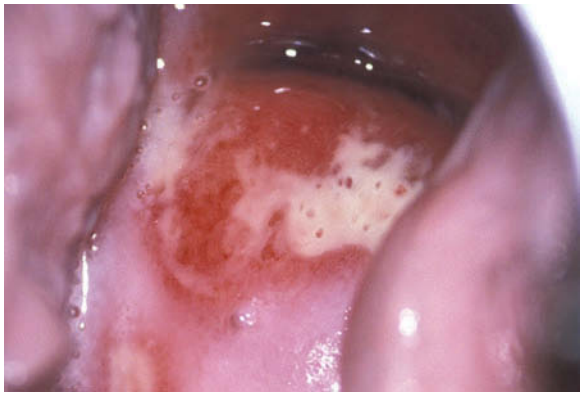


Fig 8.16 Chronic cervicitis can be difficult to assess with colposcopy and recourse to cervical biopsy may be required to conclusively exclude invasive disease.

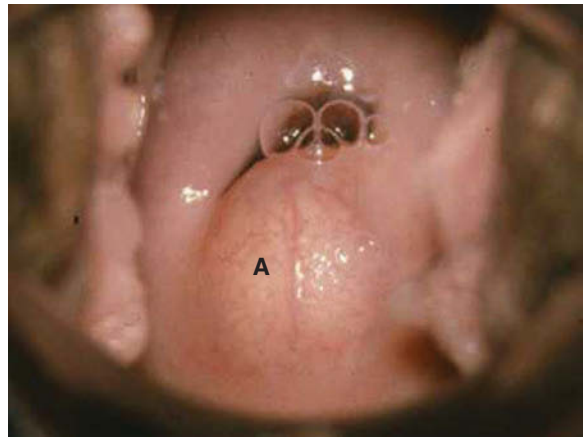


Fig 8.17 Nabothian cyst (A). Collection of fluid within cervical gland.

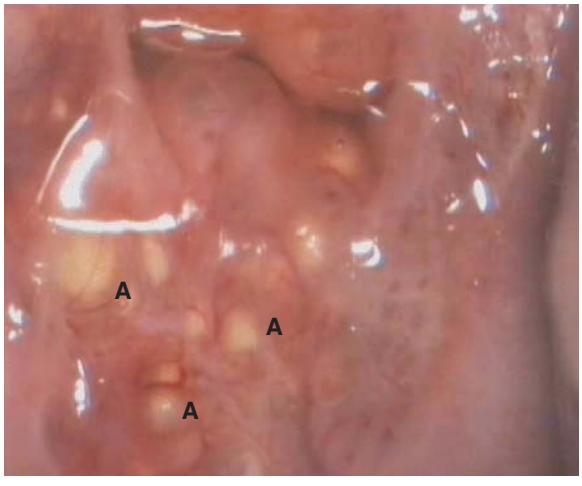


Fig 8.18 Multiple Nabothian cysts (A), which may appear suspicious for significant pathology.

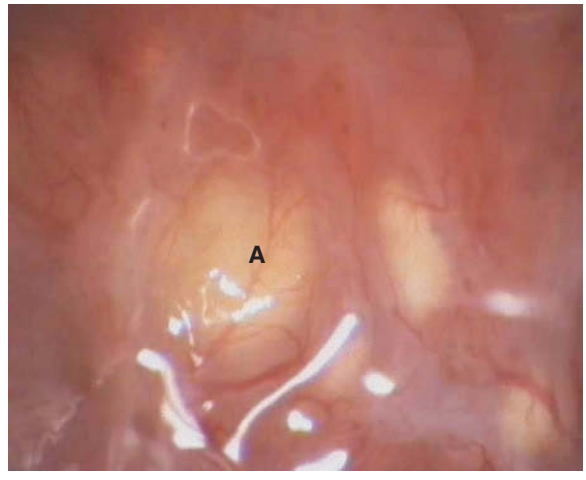


Fig 8.19 Vessels (A) coursing over the Nabothian cyst seen to be regular with no atypical features.

Learning points

- Colposcopy is a useful adjunct in those with infections of the lower genital tract.
- Cytology should not be relied upon to diagnose infection.
- Appropriate bacteriological/virological samples should be performed.
- Routine cervical cytology is inappropriate in those presenting with lower genital infections.
- The inflamed-looking cervix or that with warty lesions should be considered as suspicious and invasive disease should be excluded.
- Ablative treatment for warts should only be performed in the context of the woman having a reported normal cervical cytology.
- Young women may present with postcoital bleeding who have an inflammatory condition.

Chapter 9

Management techniques

Treatment is designed with the aim of preventing cervical cancer development by eradicating the preinvasive process with minimal morbidity. An ideal treatment procedure would be:

- Office based
- Cheap
- Quick
- With minimal or no discomfort
- Curative
- With little or no adverse effects (bleeding, discharge, stenosis)
- Followed by good healing
- Allow for adequate cytology follow-up

Two main treatment principles are used, ablation (destruction) or excision (cutting out) of the atypical TZ. Regardless of treatment modality used, the aim should be to remove the entire TZ.

Ablative techniques include:

- Cryotherapy
- Electrocoagulation diathermy
- Cold coagulation
- CO_2 laser ablation

All these rely on heat or cold treatment being applied to the cervix in order to destroy the abnormal skin on the cervix. They can all be performed as office procedures under local anesthesia. Laser treatment is relatively expensive compared to the other modalities.

Requirements for ablative treatment

- Satisfactory colposcopy – TZ fully visualized.
- Possibility of invasive or microinvasive disease ruled out by adequate biopsy.

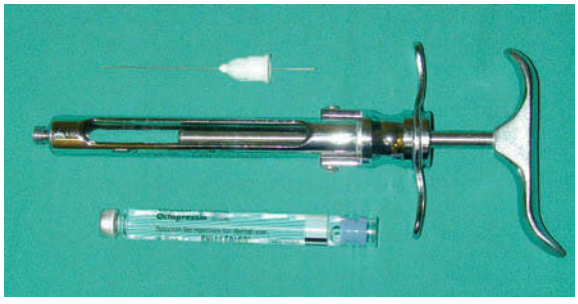


Fig 9.1 Fine needle (27 gauge size), dental syringe and cartridge of local anesthetic with vasoconstrictor (e.g. citanest containing prilocaine hydrochloride 3% with octapressin).

Fig 9.2 Dental syringe with cartridge loaded and needle attached.

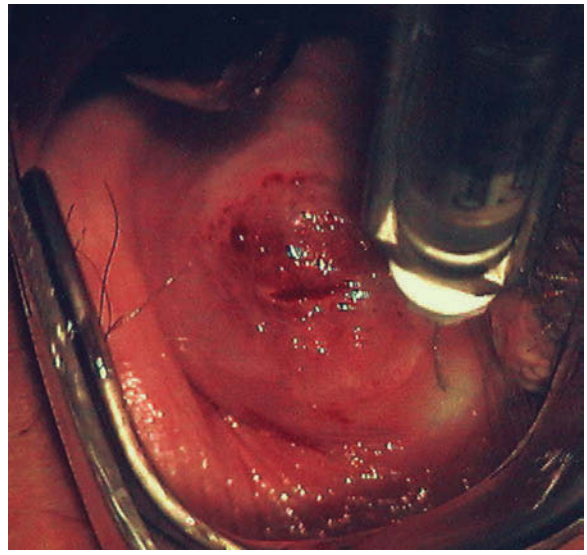


Fig 9.3 Injection around cervical TZ allowing enough time for the local anesthetic and vasoconstrictor to take effect.

- The lesion is confined to the ectocervix and is visible in its entirety.
- Concordance between cytology/colposcopy/histology.
- No evidence of a glandular lesion – CGIN or invasive adenocarcinoma.
- There is no evidence of endocervical involvement as determined by colposcopy/endocervical curettage.
- No previous treatment of the cervix.

Cryotherapy

Cryotherapy refers to the application of a super-cooled probe using refrigerant gases (nitrous oxide or CO_2) directly to the cervical lesion. Cryonecrosis occurs as a result of formation of an iceball. Freezing point of nitrous oxide is –90°C and that of CO_2 is –60°C. Cell death occurs at –20°C and the margin of the iceball is equivalent to 0°C. Crystallization of the intracellular water destroys the cells. The margin of the iceball should be at least 3–5 mm in excess of the area to be destroyed. A variety of probes are available of differing size and shape.

Cryocautery is ideally reserved for small, low-grade lesions. Whilst size of lesion is important for most treatment modalities, it is especially so for cryotherapy. Duration of treatment should be 2 minutes from the time of appearance of the ice ball. When the probe has been allowed to defrost, ascertainment that the entire lesion has been destroyed by the iceball extending beyond the lesion should take place. A freeze–thaw–freeze (double-freeze) technique is associated with improved efficacy. If the lesion is large, then multiple applications should be employed. The size, grade, and anatomical position of the cervical lesion are significant variables for success of the cryotherapy. CIN III lesions or lesions at 3 or 9 o'clock positions give lower success rates perhaps because of profuse vascular supply at these sites. Other important factors to ensure high success rates are the type of probe, freezing time, temperature, and adequate gas pressure. Nitrous oxide gas is recommended and a constant pressure of 750–830 mmHg.

Mild cramping sensations usually accompany the procedure. Copious vaginal discharge can occur for several weeks. Complications are rare with post-treatment infections being the most common and significant problem. The advantage of cryoprobes is that they are cheap and treatment is easily conducted in an office setting without recourse to analgesia.

Cold coagulation

This technique of ablation employs heat applied to tissue using a Teflon-coated thermosound. Treatment is conducted usually at 100–120°C for 30 seconds. These temperatures are much lower as compared to earlier electrocautery, hence the term 'cold'. Superficial epithelium blisters off and underlying stroma and glandular crypts are destroyed by desication. Treatment areas are overlapped to ensure uniform coagulation. There is a choice of thermosounds available with which to convey the heat to the tissues. The thermosounds can be easily cleaned and sterilized at 140°C by simply pressing a button on the machine.

Following treatment there is no need to place any restriction on sexual intercourse or the use of menstrual tampons. The procedure does not usually require analgesia. Some women may experience pelvic cramp during treatment.

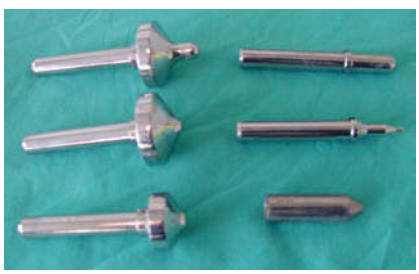


Fig 9.4 Cryotips available in a variety of shapes and sizes. These are attached to the source to produce the low temperatures for treatment.

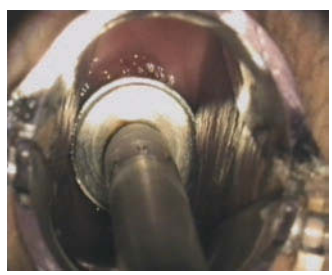


Fig 9.5 Cryocautery being performed on cervix – notice iceball effect around probe and on cervix.

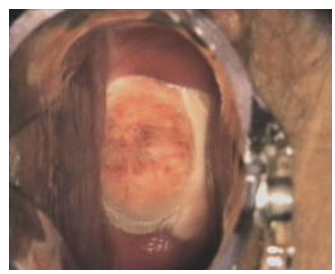


Fig 9.6 Cryocautery completed and cervix appearance immediately afterwards. The cervix should be allowed to thaw and if necessary further treatment conducted.

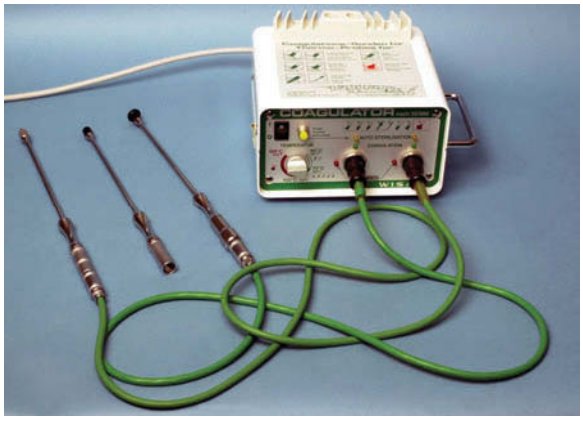


Fig 9.7 Cold coagulation apparatus with probes attached.

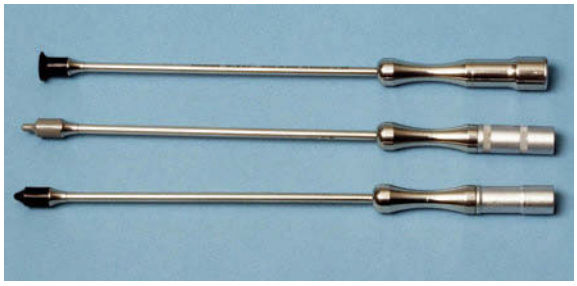


Fig 9.8 Variety of probes are available and these need to be appropriately selected depending on the shape of the cervix and colposcopic assessment.

Electrodiathermy

This destroys tissue by burning using high-frequency alternating current. It requires general, regional, or local anesthesia. A vaginal speculum with a smoke extractor is necessary. The current can be applied continuously or periodically for 2–3 seconds at a time. Under colposcopic control, it is possible to destroy up to 1 cm depth using a combination of needle and ball electrodes. The ball achieves destruction of surface epithelium by a process of fulguration and coagulation. To destroy the deeper gland crypts, a needle is inserted repeatedly at 1–2 mm intervals until the whole transformation zone has been covered. The end point of diathermy is recognized as when the area is desiccated and no more mucus exudes. There may be considerably more thermal necrosis than anticipated, leading to discharge and slough following therapy. Post-treatment complications are rare and include secondary haemorrhage, pelvic infection, and cervical stenosis. Whilst fibrosis is more common than with other forms of ablation, this does not appear to affect subsequent fertility and obstetric outcome. The electrosurgical unit is available in most operating theatres, and is cheap and easy to maintain.

Laser

This is an acronym for light amplification by stimulated emission of radiation. In gynecological surgery, the carbon dioxide laser is the most widely used. Laser

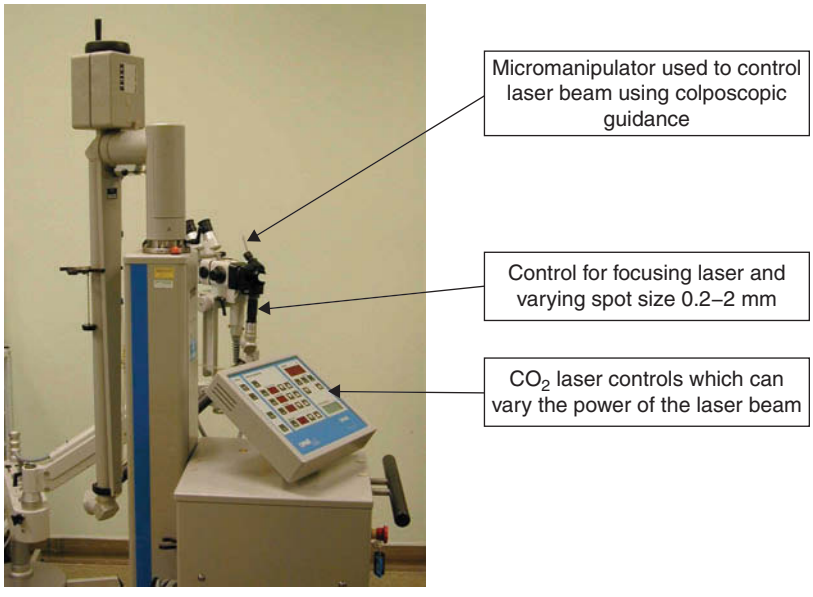


Fig 9.9 Laser apparatus.

is a precise tool that can be used for either ablative or excisional techniques. Using mirrors and lenses, the laser energy can be focused to a specific spot 0.2–2 mm diameter. The biologic effect is thermal as laser beam energy is absorbed by water-containing material, such as cervical tissue. The tissue at the focal point of the laser is vaporized at the speed of light. A speculum connected to a smoke evacuator is required. Local anesthetic helps reduce the per-operative pain. A micromanipulator attached to the colposcope is used to manipulate the laser and treatment is conducted under direct vision.

As the technique is precise, it allows good control of the depth of destruction, good haemostasis, and excellent healing because there is minimal thermal damage to the adjacent tissue. A major advantage is that laser may be used for disease that extends onto the vagina. As there are no gland crypts in the vaginal epithelium, destruction to 2–3 mm depth is adequate. The major disadvantage is the initial cost of equipment and maintenance of these machines.

Note: For most effective results with any ablative technique, destruction of the entire TZ and the deepest crypts is necessary. Depth of treatment should be to 7 mm because studies have shown that gland crypts involved with CIN may extend to 5 mm into the cervical stroma.

Excisional techniques

In recent years there has been a tendency towards use of excisional methods because of the added value afforded by the modern excisional methods. They allow use of a 'select and treat' protocol. Histopathological analysis of the excised specimen provides additional information on diagnosis, perhaps missed on punch biopsy. Excision techniques help recognize incomplete treatment, or the presence of adjacent microinvasive or glandular disease. Excisional methods are appropriate for any type of TZ and size or grade of the lesion. Excisional histology can be used in quality assurance (QA) of the colposcopist.

Indications for excision of the TZ

- Unsatisfactory colposcopy in presence of persistent cytological abnormality
- Cervical lesion extending into endocervical canal
- Disparity between cytology/biopsy and colposcopy
- Suspicion of microinvasive or invasive disease
- Suspicion of glandular lesion
- Residual or recurrent dysplasia after treatment of TZ

Excisional methods

- Diathermy loop excision
- Laser cone biopsy
- Cold knife cone biopsy
- Hysterectomy

The main objective of cone biopsy is to remove the entire TZ and any abnormal glandular epithelium in order to perform a comprehensive histopathological examination.

Diathermy loop excision and cone biopsy

Diathermy loop excision involves the use of low-voltage diathermy apparatus available in most surgical units. The technique is referred to as large loop excision of transformation zone (LLETZ) in Europe and as loop electrosurgical excision procedure (LEEP) in North America.

Because of ease of performance and very low associated morbidity, this has become the leading mode of treatment in many countries. A recent modification has been the introduction of needle excision of the transformation zone (NETZ) using a straight wire to fashion the excision rather than a loop. This has been developed to allow individualization of the excision and to try and minimize tissue removed without sacrificing cure. Three basic principles apply to LLETZ:

- A competent colposcopic examination is a prelude to LLETZ.
- The intention of LLETZ should be to remove the entire TZ. An adequate margin of normal epithelium should surround the dysplastic process and the squamocolumnar epithelium should be identifiable on histopathology.
- LLETZ should inflict the minimal amount of artifactual damage to the specimen and to the remaining cervix.

Treatment is ideally conducted with the whole of the TZ visible within one field of view with low magnification colposcopy. The TZ has a variable anatomy and the loop chosen should take this into account so that adequate excision may take place. When undertaking LLETZ procedures it is important to understand the

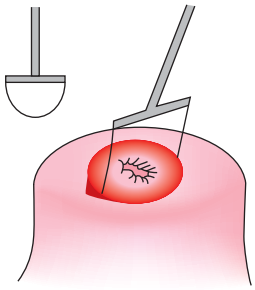


Fig 9.10 Diagrammatic representation of LLETZ being performed.

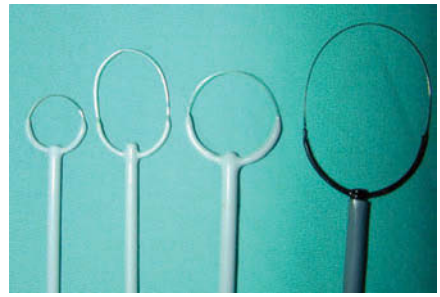
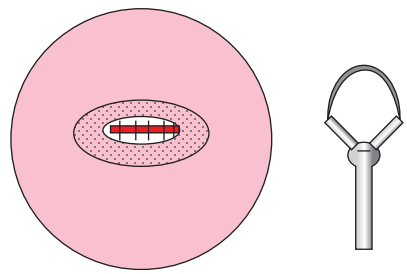
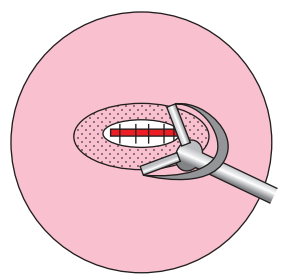
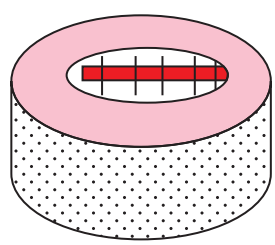
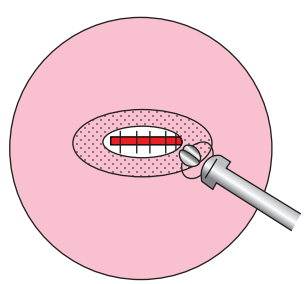


Fig 9.11 Selection of loops used to perform LLETZ.

Fig 9.12a Choose a diathermy loop appropriate to cervix and TZ.	
Fig 9.12b Traverse loop across cervix removing TZ to depth of approximately 7 mm. Traverse can be side-to-side or back-to-front of the cervix.	
Fig 9.12c Excised cervical specimen removed and sent for histological assessment.	
Fig 9.12d Diathermy ball (3–5 mm diameter) used to fulgurate the base of the cervix.	

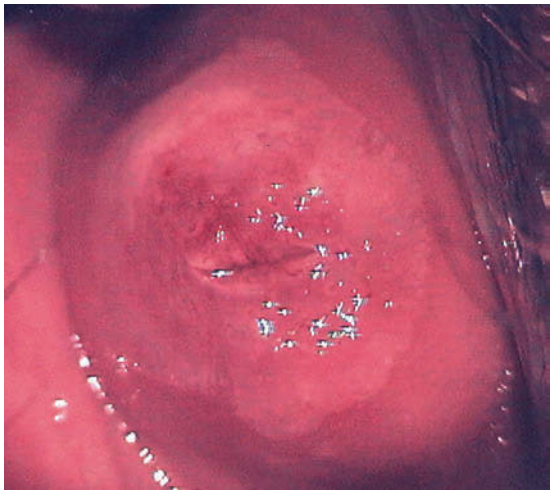


Fig 9.13 High-grade lesion identified after application of acetic acid involving all four quadrants of the cervix. Local anesthetic injection delivered.

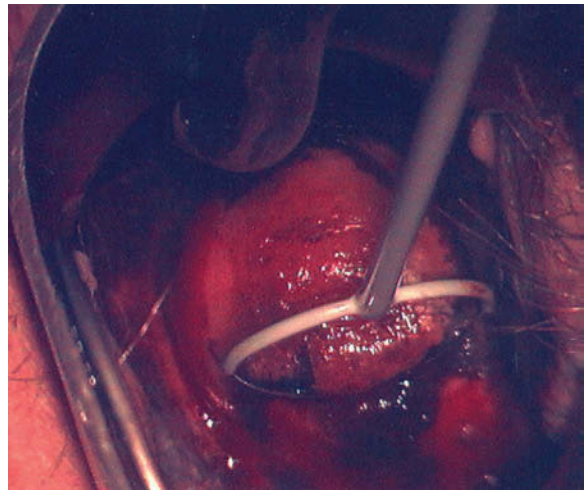


Fig 9.14 Appropriate loop chosen and excision conducted to a few millimeters outside lesion to ensure complete removal of abnormality.

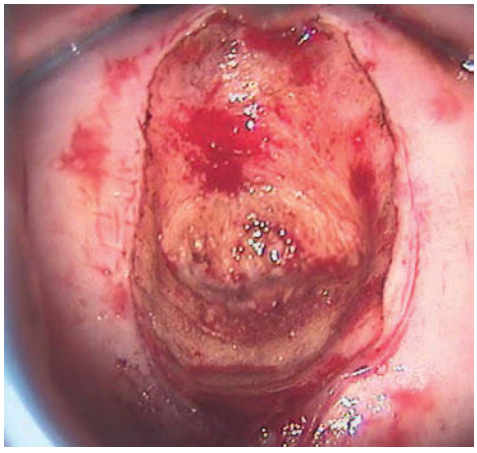


Fig 9.15 Appearance of the cervical crater following loop excision with some minor bleeding points.

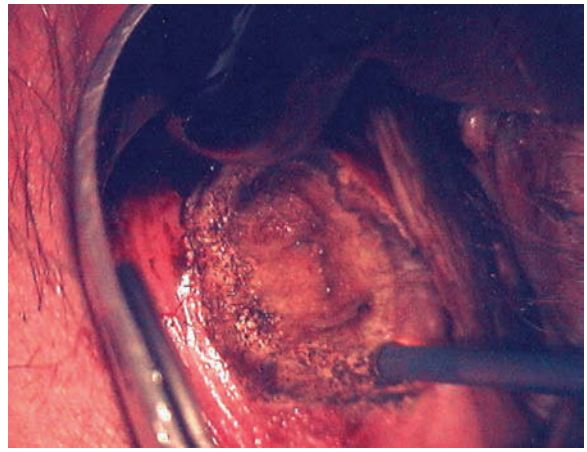


Fig 9.16 Diathermy ball fulguration or desiccation conducted to achieve haemostasis.

principles of desiccation or fulguration electrosurgery. Desiccation occurs when the electrode or wire is physically touching the tissue and causes more thermal damage. With fulguration the electrode is placed a millimeter or so from the tissue to be treated. This can occur either with the loop when excising or with the ball when gaining haemostasis. Using a blend of cutting and coagulation for the excision, the loop is traversed slowly so that a fulgurative cutting and coagulative effect ensues. If the loop is pushed or a hurried procedure conducted, then desiccation occurs and thermal damage occurs to the excised specimen.

The straight-wire excision of the transformation zone (SWETZ) or NETZ is used when the excision required is asymmetrical or when a large cone biopsy type procedure needs to be performed. It allows the operator to fashion the excision to the individual patient's requirements. The technique is similar to that when CO_2, laser, or knife cone excision is performed.

Following excisional treatment, the cervical base is treated to gain haemostasis. A variety of techniques are acceptable. Using a diathermy ball in coagulative mode, the cervix can be treated quickly using either desiccation or fulguration. The rollerball makes this easier to perform as the ball rotates over the surface

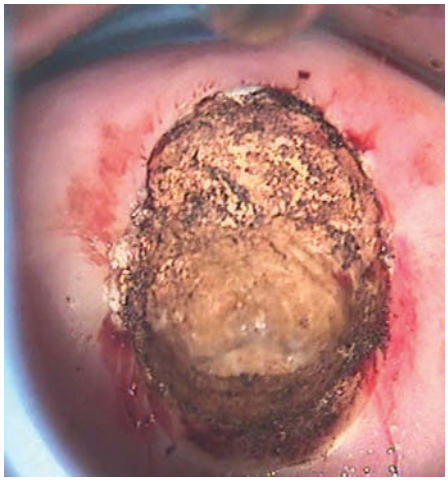


Fig 9.17 Appearance after cervical crater has been fulgurated. Notice minimal amount of charring.

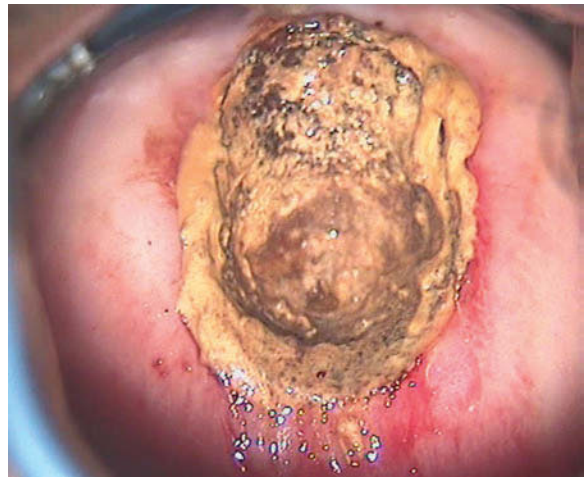


Fig 9.18 Monsels (ferric subsulphate) solution can be applied for haemostatic purposes. Ideally used in paste format.

and fulgurates the base. With troublesome bleeding, suction, cotton-tips, or jumbo swabs are used to remove/wipe any excess blood and display bleeding points that may require coagulation. Other haemostatic techniques include:

- Oxycel/surgicel or other haemostatic preparations.
- Application of ferric subsulphate (solution or paste). The paste is prepared by aerating the solution over 48 hours, which allows a degree of evaporation to occur. The consistency of the paste can be changed by further additions of ferric subsulphate solution.
- Pack the wound with gauze soaked in ferric subsulphate.
- Silver nitrate.

Following treatment, advice is given to avoid sexual intercourse and insertion of vaginal tampons for four weeks or until the discharge settles. Swimming should be avoided for two weeks. Secondary haemorrhage is usually infective in origin and settles with the use of broad-spectrum antibiotics. Fertility does not appear to be affected following treatment with LLETZ. Obstetric function may be compromised with a propensity to preterm labor and preterm prelabor rupture of membranes, especially in those with deeper excisions (>1 cm depth) or those with repeated excisions. Long-term sequelae are related to the size of the loop, particularly the depth and may be a function of the percentage cervix removed at excision. Stenosis may occur if depth of excision is excessive or repeat loops have been performed.

The histology report should assess the excision margins as this is related to the likelihood of finding residual/recurrent disease. Both the lesion size and excision margins are correlates of follow-up cytology. In those with involved margins, particularly if endocervical, careful follow-up cytology is warranted, including endocervical and ectocervical cytology. In women with involved endocervical or lateral margin who are ≥50 years age, consideration should be given to re-excision where satisfactory cytology and colposcopy cannot be guaranteed. In those with two-margin involvement, there is a much higher risk of residual/recurrent disease and consideration should be given to further excision. Similar consideration to further excision should be given if there is endocervical or ectocervical margin involvement in the presence of stromal-involved margin (i.e. two of the three margins are involved).

Laser excision

This gives a similar effect as diathermy loop excision; however, it requires greater skill and increased treatment time. High-energy laser beam is used with a small spot size to fashion the excision of the cervical tissue. The treatment may require to be performed under general anesthesia depending on the size of excision required.

Cold-knife cone biopsy

This technique is still used but mainly reserved for cases where the TZ is not fully visualized, or there is suspected

invasive disease or glandular abnormality that requires histopathological ascertainment of the excision margins. The size and shape of the cone biopsy is governed by the colposcopic findings (Chapter 5). The internal os and as much as possible of the endocervical canal are left intact within the confines of disease eradication. This limits haemorrhagic morbidity and fertility will only be slightly compromised, both of these are affected by the length of the cone biopsy.

Hysterectomy

Some women may need hysterectomy to be contemplated if CIN is present with other gynecological conditions such as fibroids, menorrhagia, or prolapse. Prior to operation, colposcopy will identify the extent of the lesion and avoid incomplete excision, which may result in vaginal intraepithelial neoplasia (VaIN). If the lesion is seen to extend on to the vagina, this may be excised as part of the hysterectomy procedure. A vaginal approach may be ideal to locate the abnormality and excise it in its entirety. If this is not possible, then abdominal approach is utilized taking into consideration the colposcopic findings.

Learning points

- Ablative and excisional treatments are equally successful in eradicating disease if conducted carefully and with appropriate patient selection.
- Best practice is for a histology report to be available prior to undertaking ablative treatment.
- Depth of treatment should be to a depth of 7 mm to ensure adequate eradication of CIN that may involve gland crypts.
- Cold-knife cone biopsy and hysterectomy retain a place in the management of women with abnormal cytology under certain conditions.
- Audit should be conducted of treatment outcomes to maintain QA.

Chapter

10 Follow-up after treatment

Following treatment, all women require regular follow-up for a certain period of time. Women who have undergone treatment for CIN remain at a significantly increased risk of developing cervical cancer (odds ratio (OR) 3–5). In those women that develop abnormal cervical cytology following treatment, the OR for development of invasive disease is 25–30. Close surveillance is required for a number of years and any abnormality during this time warrants a further colposcopic reassessment. If all cytology samples during surveillance remain negative, the normal recall may be resumed.

Objectives of follow-up

- To ascertain any complications associated with the treatment.
- To detect residual disease.
- To detect any recurrent disease as early as possible.

Method of follow-up

Ideally, follow-up surveillance should be with cytology and colposcopy. The role of colposcopy in post-treatment patients is still debated by some on the grounds that it can be technically difficult because of scarring, TZ may not be visible in its entirety and the regenerating epithelium is often misjudged as CIN. Cytology has also been reported to give false negative results because the residual disease may be very small or covered by regenerated normal epithelium. Both modalities used in conjunction provide a safety net for early detection of disease.

Post-treatment complications

Generally, morbidity is very low with all forms of treatment methods. These can be:

- **Early** – excessive bleeding, which may require further corrective management. Most will settle with diathermy or application of Monsel's solution. The Cold coagulator is another useful method of gaining haemostasis. In a small number, suture of the bleeding area may be required. Infection may occur as a secondary event and patients may complain of prolonged vaginal loss, which may be offensive. This generally settles with a course of broad-spectrum antibiotics. No intervention around the time of treatment has been shown to significantly reduce the risk for secondary infection.
- **Late** – Cervical stenosis may occur and is more common after cryotherapy and cold-knife conization. This is particularly the case where sutures have been used as part of the conization procedure. Stenosis is primarily a function of the depth of excision/ablation undertaken, especially if more than 50% of the endocervical canal has been removed. This can be relevant in patients undergoing their second or third treatment. Depending on the degree of stenosis, menstrual problems may occur (amenorrhea, dysmenorrhea) and there will be difficulties in gaining adequate sample for cytology. Fertility problems may also occur. Failure of the cervix to dilate in labor is an unusual complication.

Where cytological sampling is not possible due to cervical stenosis, the options are hysterectomy, cervical dilatation, or withdrawal from further cervical cytology recall with the agreement of the woman. Cervical dilatation should be considered in all cases. In those with a history of high-grade CIN, CGIN, or unexplained high-grade cytology, cervical dilatation or hysterectomy is recommended.

Residual or persistent disease

Disease that is identified within 12 months of treatment is classified as residual/persistent disease. Abnormalities picked up after this time are usually referred to as recurrent. Most of the persistent/recurrent lesions will be picked up within 24 months of treatment.

Risk factors for treatment failure

- Large lesions extending to occupy more than three or four quadrants of the cervix. Measurement of lesion surface area suggests that lesions larger than 1 cm^2 are more likely to be associated with high-grade disease and failure to eradicate with treatment.
- High-grade lesions, especially CIN3.
- Older women – the TZ is not always fully visualized and the lesion is more likely to extend into the endocervix. Fifty years is often the age used to identify women at increased risk of residual/recurrent disease, especially if there is margin involvement with CIN.
- Incomplete excision margins. This is particularly so if the endocervical margin is involved with disease where an excisional treatment modality has been used.
- Inability to recognize severity of disease at the hand of an inexperienced colposcopist.
- Inappropriate choice of treatment method.
- Operative difficulties during treatment. This may either be due to poor access or excessive bleeding giving rise to technical problems with concluding the treatment effectively.

Positive excision margins seen on histology do not always result in residual disease, as evidenced by negative cytology and colposcopy on follow-up. This is due to complementary ablative effect of diathermy and the inflammatory reaction of healing. Equally true is the fact that residual disease may be present even after an apparent complete excision evidenced by histology. This could be due to multicentric foci of the disease.

Recurrent disease

Women treated for CIN are at increased risk of developing neoplastic disease. Disease identified two years after treatment with normal cytology in the interim period following treatment is referred to as true recurrence. These are supposed to be lesions developed de novo in the regenerated TZ. To distinguish between a true recurrence and residual disease is a diagnostic dilemma. It is believed that most second lesions are due to progressive enlargement of small foci of residual disease previously not detectable by cytology. With the increasing use of excisional methods for treatment, the histological assessment could help identify women who need close surveillance and plan timely intervention if indicated.

Duration of follow-up

Following treatment for CIN, cervical cytology is undertaken at six months. In those with abnormal cervical cytology, they are further assessed with colposcopy and further cytology according to national guidelines. Following on from the 'test-of-cure' studies, the national screening program in England plans to roll this out in 2012. In those with normal cervical cytology at six months following treatment, co-testing for hrHPV is undertaken. If both cervical cytology and hrHPV test is normal, these women can safely be returned to routine three-year recall as they have a very low risk (<1%) of developing high-grade CIN over this timeframe. If the hrHPV test is positive, despite a normal cervical cytology, referral is made for further colposcopic assessment. If colposcopy is satisfactory and normal, then these women can be recalled in three years.

Women smokers who have undergone treatment for CIN have a much higher failure rate (three-fold) compared to non-smokers. Also other high-risk patients such as those immunocompromised or with micro-invasive disease may require more intensive follow-up after treatment.

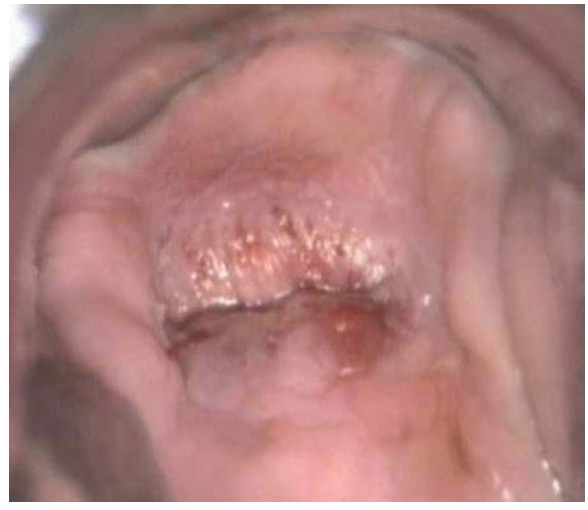


Fig 10.1 Post-LLETZ appearance of cervix. The appearance can be varied depending on the degree of scarring.

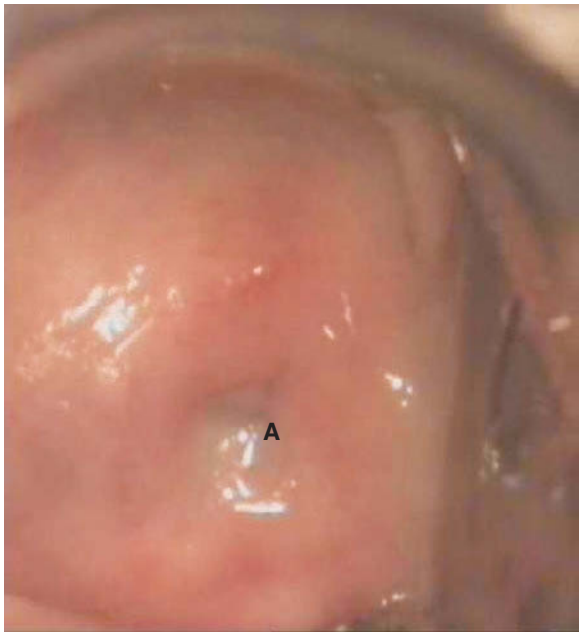


Fig 10.2 Cervical stenosis. Pinhole cervical os (A). This patient complained of severe dysmenorrhea and adequate cervical cytology sampling is difficult.

Learning points

- Women remain at increased risk for preinvasive and invasive disease following treatment of CIN.
- Residual disease is usually detected within 12 months of treatment.
- Recurrent disease can occur a considerable time period following treatment.
- The addition of hrHPV testing as a test-of-cure is valuable, and women who are cytology and hrHPV negative at the six-month follow-up visit, can revert back to routine recall.
- Women diagnosed with CGIN or those having hysterectomy for CIN can have follow-up treatment as per protocol without recourse to testing for hrHPV.
- Women with large lesions, high-grade disease, incomplete excision of CIN, older age, and those with difficulties at the time of treatment are at highest risk of residual/recurrent disease.
- Women undergoing treatment should be made aware of potential complications and risks associated with the treatment method.

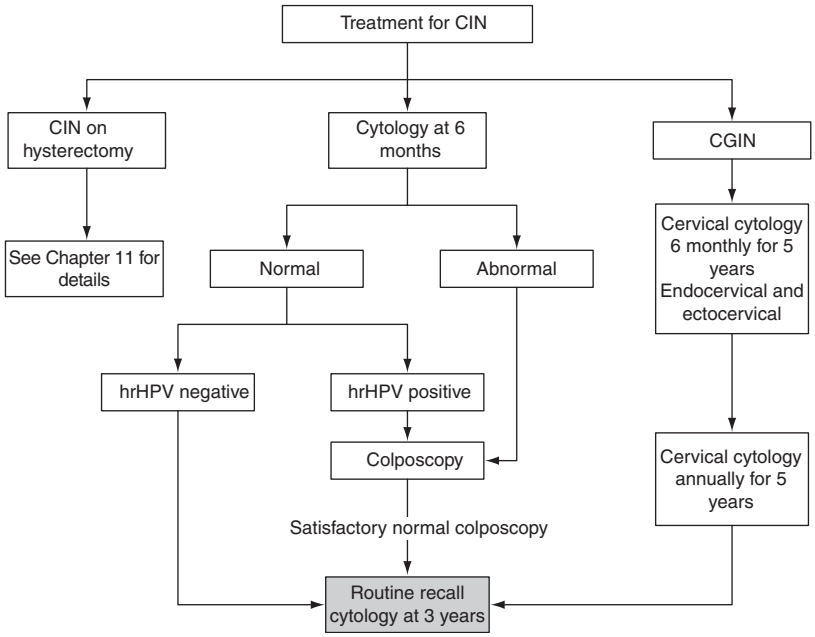


Fig 10.3 Follow-up flow chart following treatment for CIN.

Chapter 11

Vaginal abnormalities

Colposcopic examination of the vagina forms an integral part of lower genital tract diseases. Its most important role however, is in the assessment of vaginal dyskaryosis/VaIN and vaginal carcinoma.

The true incidence of VaIN is not known. VaIN is relatively uncommon in comparison with the corresponding cervical and vulvar lesions. The extremely low incidence does not warrant routine screening for the disease. Women with VaIN are asymptomatic and most lesions are discovered during investigation of abnormal cervical cytology. This lower incidence is proposed to be due to the fact that vaginal epithelium lacks an active TZ.

The specific cause of VaIN is not clear. It is highly likely that it shares the same predisposing factors as CIN. Infection by certain types of HPV perhaps is the most plausible cause. The knowledge concerning the preinvasive changes is not precise. Most likely it is a multistep process involving other co-factors such as immune status, smoking, exposure to diethylstilboestrol (DES) and radiation treatment. Occurrence of primary or de novo VaIN without concomitant or previous history of CIN is rare. Approximately 1–2.5% of women with CIN have an extension of the disease process onto the vagina.

Classification

There is no universally agreed terminology for classification of VaIN. Histologically a similar classification to CIN has been proposed. The degree of epithelial involvement with abnormality confers a grade.

VaIN I – inner third of epithelium involved with atypia.
VaIN II – inner two-thirds of epithelium involved with atypia.
VaIN III – whole of the epithelium involved with atypia.

Another suggested classification based on clinico–pathological description recognizes four situations:

- De novo or found alone.
- Associated with CIN or invasive cervical cancer.
- Associated with VIN or invasive vulvar cancer.
- Associated with both CIN or VIN, or their invasive counterparts.

Colposcopic appearance

The technique of colposcopy is the same as for the cervix; however, assessment of the vagina is more difficult to perform and more uncomfortable for the woman. There is no TZ, the vagina has a much larger surface area and there are rugose folds, which make the vaginoscopy more challenging. The speculum blades can obscure even large lesions on the vagina. The examination is laborious requiring greater patience as the speculum needs to be rotated and gradually withdrawn for complete assessment of all the vaginal walls. The disposable transparent bivalve speculum may be useful to aid visualization. In the postmenopausal woman and in those receiving post-irradiation, local estrogen therapy for a couple of weeks can facilitate the colposcopic examination. This helps thicken the epithelium and ensures more accurate differential staining with Lugol's iodine. It is also important to perform a bimanual examination to exclude an obvious tumor.

The lesions are mostly confined to the upper third of the vagina and are usually multifocal. The commonest sites are the apex or the lateral vaginal fornices. Lesions can occur in the middle and lower third part of the vagina. Involvement of the whole vaginal length is rare and is usually due to HPV infection. The lesions may appear somewhat raised without suspicion of malignancy. After acetic acid they appear white with granular surface and distinct borders. Punctation is a more common feature than mosaicism. Abnormal epithelium appears yellow due to non-uptake of Lugol's iodine.

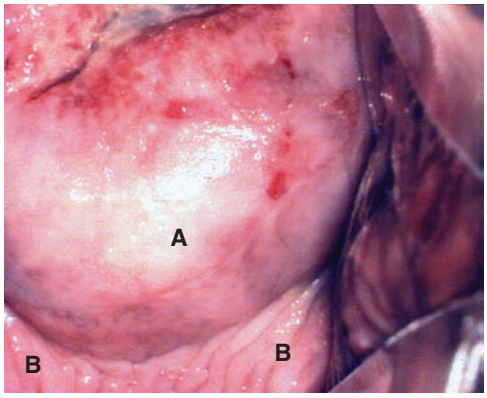


Fig 11.1 High-grade CIN (A) with extension to vaginal epithelium posteriorly (B) – VaIN III.

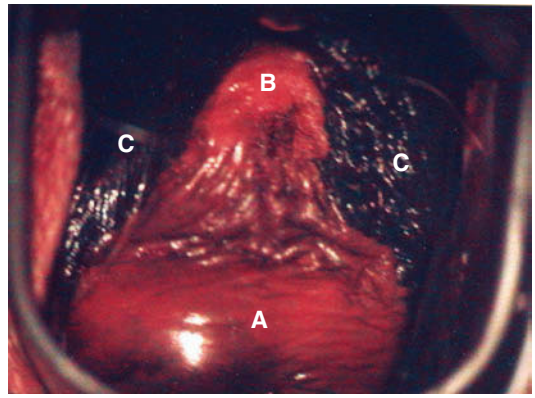


Fig 11.2 CIN (A), VaIN (B) and normal vagina (C) after application of Lugol's iodine. Note patchy uptake of Lugol's over the vaginal portion with VaIN.

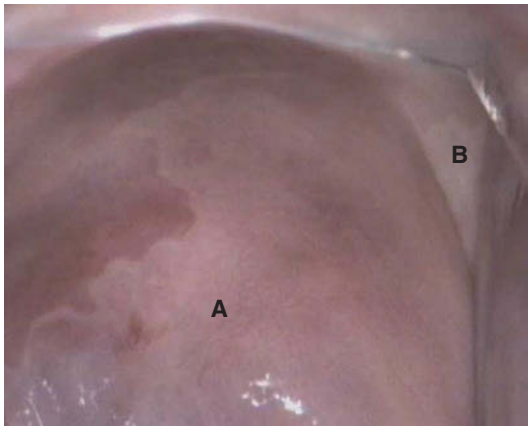


Fig 11.3 Acetowhite lesion on cervix (A) extending to vaginal vault consistent with VaIN (B).

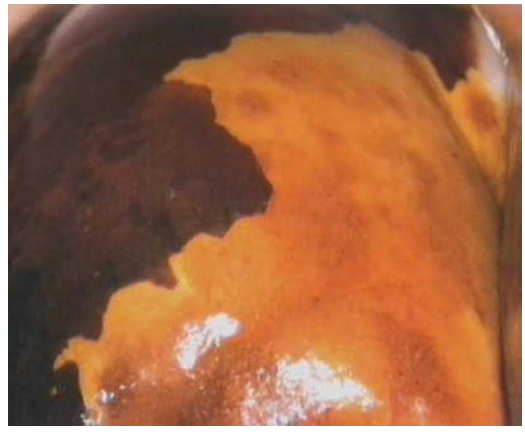


Fig 11.4 Same lesion as Fig 11.3 after application of Lugol's iodine showing patchy uptake within CIN and VaIN lesions.

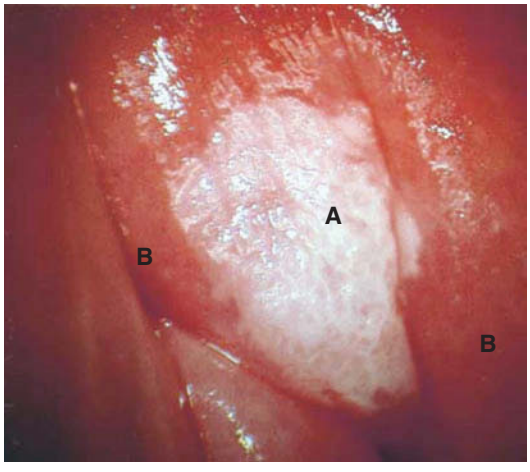


Fig 11.5 Acetowhite change at vaginal angle with VaIN III (A) following total hysterectomy surrounded by normal vaginal epithelium (B).

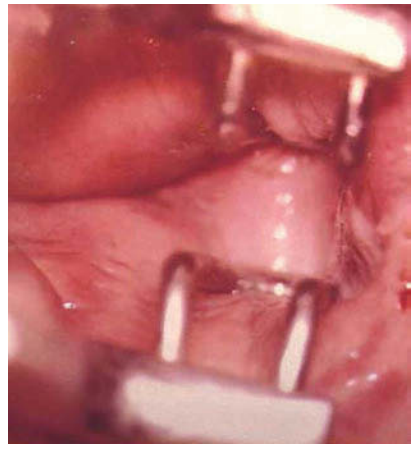


Fig 11.6 Looking for VaIN at vaginal angles using endocervical speculum.

Features of possible invasion include:

- Elongated, irregular atypical vessels.
- Raised, nodular lesions.
- Papillary excrescences, especially at the vaginal vault.
- Ulceration and erosion.

Nomenclature

The International Federation for Cervical Pathology and Colposcopy (IFCPC) agreed an international revised nomenclature in 2011. This is reproduced in table format.

2011 IFCPC clinical/colposcopic terminology of the vagina		
General assessment		Adequate/inadequate for a reason (i.e. inflammation, bleeding, scar) Transformation zone
Normal colposcopic findings		Squamous epithelium: • Mature • Atrophic
Abnormal colposcopic findings	**General principles**	Upper third/lower two-thirds, Anterior/posterior/lateral (right or left)
	Grade 1 (Minor)	Thin acetowhite epithelium Fine punctation Fine mosaic
	Grade 2 (Major)	Dense acetowhite epithelium Coarse punctation Coarse mosaic
	Suspicious for invasion	Atypical vessels **Additional signs**: fragile vessels, irregular surface, exophytic lesion, necrosis, ulceration (necrotic), tumor/gross neoplasm
	Non-specific	Columnar epithelium (adenosis) Lesion staining by Lugol's solution (Schiller's test): stained/non-stained Leukoplakia
Miscellaneous finding		Erosion (traumatic), condyloma, polyp, cyst, endometriosis, inflammation, vaginal stenosis, congenital transformation zone (CTZ)

Colposcopy of the vaginal vault after hysterectomy

Women in whom CIN is confirmed in hysterectomy specimens should be followed up by vault cytology as they are at risk of developing VaIN and invasive vaginal disease. There is no clear evidence that colposcopy increases the detection of disease on follow-up. Consensus recommendations are:

- For women on routine recall and with no CIN in their hysterectomy specimen, no further vaginal vault cytology is required.
- Women not on routine recall, and with no CIN in their hysterectomy specimen, should have vaginal vault cytology at six months following their hysterectomy.
- Women who undergo hysterectomy and have completely excised CIN should have vaginal cytology at six and 18 months following their hysterectomy.
- Women who undergo hysterectomy and have incompletely excised CIN (or uncertain excision), should have follow-up as if their cervix remained in situ.

Colposcopy of the vaginal vault after total hysterectomy is more difficult than with an intact cervix. Distortion of the vault because of scarring can hamper full visualization especially at the angles. Certain surgical techniques can leave deep lateral angles with inaccessible recesses. Sometimes the abnormal epithelium is sequestered beneath the suture line. If the cytological abnormality persists in the face of inadequate visualization, examination under anesthesia should be conducted to assess the difficult areas.

Punch biopsy in these cases is also difficult especially if the lesion is along the suture line due to lack of subepithelial stroma and proximity of the peritoneum. Cold knife, diathermy needle excision, or CO_2 laser excisional biopsy are the preferred techniques.

Vaginal biopsy

Biopsy of any atypical vaginal epithelium is essential as a prelude to treatment. These can be undertaken using punch biopsy forceps or small LLETZ/LEEP apparatus. Multiple biopsies are required to exclude invasive disease. The biopsy can be difficult especially with atrophic epithelium e.g. after menopause or irradiation. In such cases a skin hook can be used to stabilize the epithelium or the speculum retracted to create a mucosal fold. Biopsy is usually well tolerated with little discomfort. Haemostasis is achieved as usual, using silver nitrate or Monsel's or by tampon pressure. CO_2 laser biopsy/excision of atypical epithelium can also be undertaken.

Management of VaIN

The natural history of VaIN is not clearly defined and the true potential of these lesions is not precisely understood. Observational studies have shown that the majority of low-grade VaIN lesions probably regress spontaneously. Regression is less frequent when VaIN occurs in association with CIN or VIN. VaIN III lesions have a higher malignant potential than low-grade VaIN.

Treatment options range from observation to total vaginectomy. Based on current knowledge of the disease, the following regimen is recommended:

- Low-grade disease (VaIN I) – observation with cytologic and colposcopic assessment at 4–6 month intervals. If there is evidence of disease progression then appropriate biopsy and more aggressive management should be considered.
- High-grade disease (VaIN II or III) – should be treated. The treatment options consist of medical, surgical, or radiotherapy. The choice of treatment should be based on the site and size of the lesion, histological grade of the abnormality, age and medical condition of the patient, and equally importantly is the available resources and expertise of the treating physician.

Treatment options for VaIN

	Surgical		
Medical	**Ablation**	**Excision**	**Other**
Topical 5-Fluorouracil	CO_2 laser	CO_2 laser	Radiotherapy
Estrogen	Electrodiathermy	LLETZ/LEEP	
Intralesional interferon	Cryotherapy	Cold-knife Partial or total vaginectomy	

Ideally in those without a cervix, the lesion should be excised and this can be performed using a knife, CO_2 laser, or LLETZ/LEEP. Depth of excision/destruction needs to be only 2–3 mm because the vagina does not contain glands that may harbor the preinvasive disease. Radiotherapy has been used to treat VaIN, especially multifocal disease which is resistant to other modalities, but the long-term results are varied with considerable associated morbidity. With appropriate patient selection, cure rates of 80% may be achieved by the judicious use of laser ablation and partial vaginectomy. Failure is more often seen in those with multifocal lesions and in those with associated CIN or VIN.

If ablation is planned, then the lesion should be accurately mapped with the use of vaginoscopy and biopsies. In those submitted to surgery, the approach may be vaginal, abdominal, or a combined abdomino–vaginal procedure. The more radical surgical procedures are associated with a risk for urinary dysfunction/injury and bowel complications. There are psychosexual sequelae associated with surgery and shortening of the vagina. Appropriate counseling is important as well as the use of vaginal dilators to maintain function.

Whatever treatment is undertaken, the patients require long-term colposcopic and cytologic follow-up to ensure early diagnosis of any recurrent or progressive disease.

Other vaginal lesions

Occasionally other vaginal lesions may be noted. These are usually benign. Common lesions are mucus retention cysts or warts. Vaginal adenosis is an uncommon condition where columnar epithelium is found in the vagina. This is mainly seen in women exposed to DES but can also occur without exposure. This can give rise to profuse mucus discharge or present as post coital bleeding.

In women who have had pelvic radiation therapy, the lower genital tract, particularly vaginal epithelium,

appears hyperemic, atrophic, and thin. Colposcopy becomes difficult because of patient discomfort and the epithelium is prone to injury. Appearance of irregular vessels may raise suspicion of malignancy. When in doubt, biopsy should be performed. The risk of haemorrhage is high and healing may be delayed. Examination of such cases should always be performed by an experienced colposcopist.

Learning points

- VaIN colposcopically and histologically has similar features to CIN.
- Presence or absence of the cervix is important for assessment as well as treatment.
- The majority of VaIN lesions will affect the upper one-third of the vagina.
- VaIN after hysterectomy commonly occurs at the vaginal suture line and the vaginal angles.
- Treatment needs individualization according to patient details, disease extent, and previous therapeutic procedures.

Chapter

12 Vulvar disease

Examination of the vulva is an important part of any gynecological exam especially when colposcopy is being performed for cervical or vaginal disease. The greatest role of colposcopy of the vulva is in evaluating lesions considered precursor to malignancy and to rule out invasive disease. Vulvar colposcopy is less informative in relation to the grade of the lesions compared with cervix colposcopy. It helps identify multifocality and extent of the lesion and in performing adequate biopsies and treatment.

Classification of the International Society for Study of Vulvovaginal Disease (ISSVD)

Non-neoplastic epithelial disorders of vulvar skin and mucosa	Vulvar intraepithelial neoplasia (VIN)	Vulvar carcinoma
Lichen sclerosus (LS)	Squamous intraepithelial neoplasia • VIN 1 – mild dysplasia • VIN 2 – Moderate dysplasia • VIN 3 – Severe dysplasia/carcinoma in situ	
Squamous cell hyperplasia	Non-squamous intraepithelial neoplasia • Paget's disease • Melanoma in situ	
Other dermatoses		

Colposcopy of vulva – vulvoscopy

The examination of the vulva should include mons pubis, labia majora and minora, clitoris, urethral opening, vestibule, introitus, perineum, perianal area, and perhaps the anal canal. The varied structures within the vulva present different epithelial types because of differing embryological origin. This complex nature of epithelial mix makes vulvoscopy much more difficult and challenging. Vulvar lesions usually do not have a typical appearance and histologically identical lesions can have varied appearances.

Vulvoscopy is performed by gently cleaning the vulva with normal saline and then applying 3–5% acetic acid. The thick hair-bearing epithelium e.g. external surface of labia majora, does not exhibit features of vascular aberration (mosaicism, punctation). In the non-hair bearing parts, e.g. labia minora and the vestibule, the skin is thinner and acetowhiteness with punctation and mosaicism can be identified. The acetic acid should be applied for longer and the apparition of lesions is also later (2–5 minutes) than the cervix.

Toluidine blue, a nuclear stain, can also be used to mark vulvar lesions (Collin's Test). Aqueous toluidine solution (1%) is applied after cleaning the vulva. Two minutes later, the area is rinsed with 1% acetic acid. Abnormal cells with high nuclear content retain the blue stain. Whilst the test lacks specificity, it can be helpful in identifying areas for appropriate biopsy.

Indications for referral for vulvoscopy:

- Color change e.g. whitening, pigmentation, redness.
- Ulceration.
- Swelling.
- Fungating mass.
- Wart non-responsive to standard treatment.
- Enlarged inguinal lymph nodes.

Biopsy of vulva

All vulvar lesions should be biopsied for confirmation of diagnosis. This helps exclude the possibility of invasive disease masked by an apparent benign superficial condition. Large or multicentric lesions require multiple biopsies. The biopsy specimen should include the area of transition from normal to abnormal tissue.

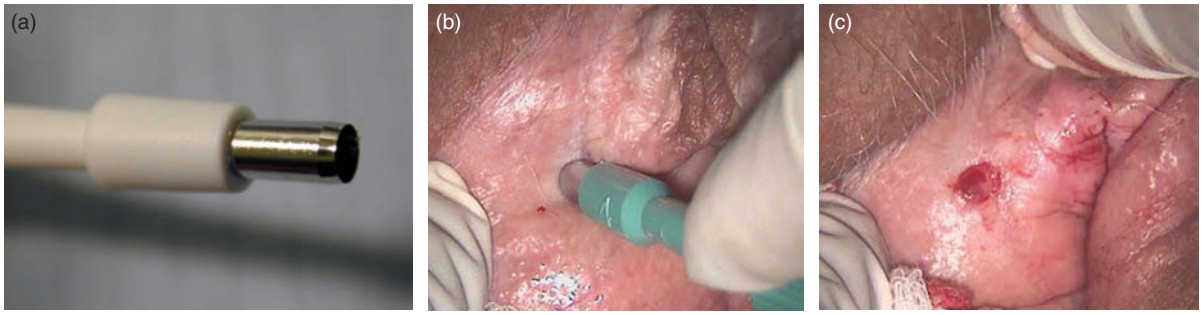


Fig 12.1 Keyes punch biopsy of vulva being performed. Circular biopsy then can be taken in a variety of sizes, usually 3–6 mm.

Different instruments can be used for vulvar biopsy, which is relatively easy to perform. Biopsy can be taken in an office setting using local anesthetic.

Keyes punch forceps are a suitable method. It removes a round skin area 3–6 mm in diameter. The depth depends on the pressure applied and the thickness of the epithelium. The biopsy site can be left to heal (two weeks). Any bleeding can be stopped by either application of Monsel's solution, silver nitrate, diathermy, or by sutures.

Biopsy is mandatory in the following situations:

- Fast-growing lesions.
- Ulcerations.
- Areas of bleeding.
- Each suspicious area of any color.

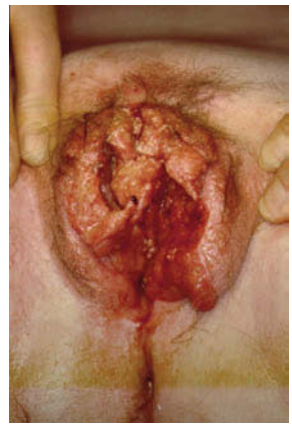


Fig 12.2 Extensive vulvar carcinoma affecting both labia and invading into the vagina.

Vulvar carcinoma

Carcinoma of the vulva is uncommon compared to other genital tract malignancies. The exact etiology is unknown but there is evidence suggestive of risk factors that include vulvar warts, which lead to VIN, and inflammatory conditions such as lichen sclerosus and atypical epithelial hyperplasia. The other risk factors include age, immuno-suppression, and smoking. The malignancy risks associated with VIN is 5–10% and 3–5% for lichen sclerosus. The clinical features that may suggest malignant transformation are change or aggravation of symptoms, rapid expansion, or irregular change in the surface contour. Adjacent to vulvar cancers, lichen sclerosus is found in about 60% of cases and VIN (HPV-related) in about 30%.

The most common presenting symptom is pruritus. Other symptoms could be pain, burning, ulceration, or swelling. The lesions are mostly multifocal and commonly occur on the labia or clitoris. The clinical appearance may be straightforward comprising of a mass or a suspicious looking ulcer with rolled edges. Small microinvasive lesions in an area of VIN maybe difficult to recognize and in these cases a colposcope can help identify the area, with highest probability of severity, to be biopsied.

If the lesion is small (<2 cm) and unifocal, an excisional biopsy with 1.5 cm of healthy tissue margin can be therapeutic. These women may benefit from sentinel lymph node biopsy rather than formal groin lymphadenectomy. For large or multifocal disease, treatment options are surgical excision, with or without lymphadenectomy of inguinal nodes. Radiotherapy is another option in an adjuvant or neo-adjuvant setting to surgery. Chemoradiotherapy may also be considered for advanced disease.

Vulvar intraepithelial neoplasia

The exact incidence of different grades of VIN is not known but for VIN 3 it has been estimated to be 2.1/100,000. Substantial increase has been noted over the last few decades especially amongst young women. The risk factors for VIN include multiple sexual partners, recurrent genital infections, immunosuppression, smoking, and HPV. Most cases of VIN 3 are associated with HPV, mainly type 16. Vulvar condylomas are associated with 20–30 % of VIN lesions.

Spontaneous regression of VIN is well documented, especially for the milder forms. Even VIN 3 lesions can regress in the absence of treatment. Regression is most likely in younger women (under 30 years age) with multifocal disease. VIN has malignant potential and the risk of progression is much lower than for CIN (5–10%). These quoted risks are in treated individuals, whereas progression risk may be significantly higher in untreated women. The risk seems to be higher in the postmenopausal age group with unifocal lesions. The true potential of progression, however, is not known. Grading of VIN as 1, 2, and 3 is done along the same lines as for CIN and VaIN.

Unlike CIN, vulvar dysplasia usually presents with symptoms, commonest being pruritus, pain, burning, or dyspareunia. A small percentage will present with a lump/lesion. VIN can affect both hair and non-hair bearing skin. The lesions are usually present on the posterior fourchette, perineum, around clitoris, or lower parts of labia majora and minora. Older women often have a single lesion while young women, under the age of 50, tend to have multifocal or multicentric disease.

The clinical appearance of VIN is variable, presenting in a variety of colors and surface patterns. Typically, they are papular with sharp borders and keratotic rough surfaces. They may sometimes resemble condyloma acuminata. The color varies between white, red, and brown. The diagnosis is always based on histological assessment of an appropriate biopsy. Microinvasive changes may be noted in a significant number of women (16–22%). It is mandatory to do a thorough assessment of the whole lower genital tract including cervical cytology and colposcopy.

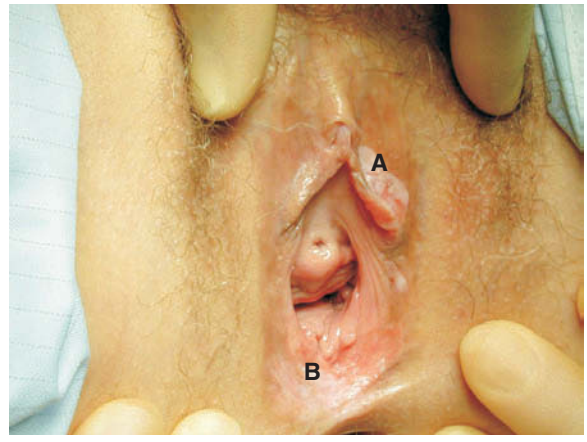


Fig 12.4 VIN 3 affecting the left labia (A) and fourchette (B).

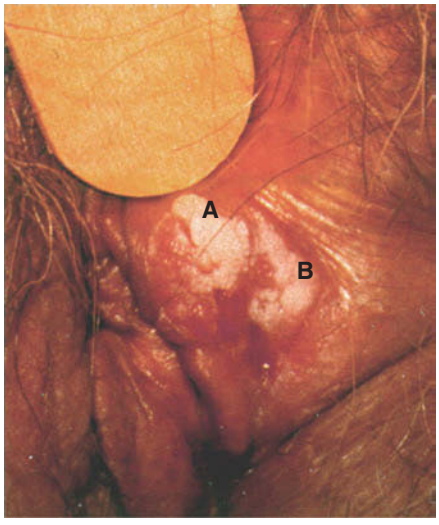


Fig 12.3 Discrete area of VIN affecting labia (A and B).

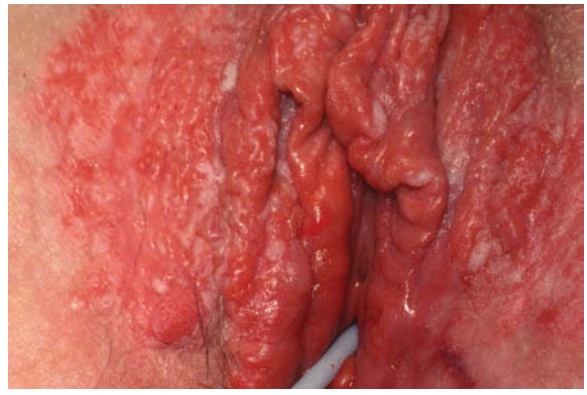


Fig 12.5 Extensive VIN presenting as erythematous and raised areas.

Treatment is primarily aimed at eradicating symptoms and prevention of potential malignant transformation. A variety of treatment modalities are available. The choice depends on the site, size, focality, and grade of the disease. The age and general condition of the patient are taken into account, as should the preservation, appearance, function of the vulva, and the psychosocial issues.

Treatment modalities for VIN

- Conservative: surveillance with vulvoscopy and biopsy.
- Medical: 5-FU, imiquimod, α-interferon.
- Laser ablation.
- Surgical:
  - Laser excision;
  - Local excision with knife;
  - Simple vulvectomy; and
  - Skinning vulvectomy and skin grafting.

VIN 1 and 2, because of their apparent low risk of progression, can be managed conservatively. Intervention can be reserved for persistent, recurrent or progressive disease.

Whilst medical treatment may help alleviate symptoms, surgical intervention is important in long-term management. Recurrence rates after laser ablation are high, especially in hair-bearing skin. Local excision is appropriate in the majority of cases and vulvectomy needs be performed in a minority of selected cases. An excision margin of 5 mm of healthy tissue is recommended to reduce risk of recurrence. Post-surgical complications are increased with the radicality of the excision.

CO_2 laser still has a place as an adjunct to surgery, especially in young women, to limit surgical damage. It is particularly useful for small areas of peri-urethral and peri-clitoral disease. Laser excision, a more difficult technique, has been described that provides the advantage of laser ablation and offers the possibility of a surgical specimen for histological examination.

Lichen sclerosus

This is an inflammatory skin disorder whose exact underlying cause is not known. It probably has an autoimmune origin with seemingly genetic predisposition. It is usually seen in the elderly but can occur at young ages. Amongst affected patients, about 15% are children, mostly girls. There is not much known about the pathogenesis of the disease. The affected tissues retain their maturation potential and the associated atrophic changes are reversible. An association with invasive disease has been reported, with a life-time risk of developing vulvar carcinoma quoted to be 3–5% in women with lichen sclerosus.

Lichen sclerosus mainly affects the vulva but not exclusively. The commonest presenting symptom is pruritus, usually intractable. Other complaints may include vulvodynia, dyspareunia and dysuria. The common sites of affection are the labia minora, inner surfaces of labia majora, clitoris, and the perineum. Lesions may extend posteriorly to the perianal area forming a 'figure-of-eight' pattern. The classical clinical appearance of lichen sclerosus is ivory pallor of the vulva with epidermal atrophy giving a parchment-like wrinkled surface. There is a loss of elasticity and fissuring. As the disease progresses, the architecture of the vulva is distorted, with resorption and fusion of labia minora and loss of clitoral hood. The epithelial surface is waxy, shiny, and speckled. The commonest complications are adhesions and narrowing of the introitus, which may make intercourse impossible.

The clinical features are often straightforward but diagnosis should always be confirmed with an appropriate biopsy. This also helps rule out underlying significant dysplasia or microinvasive disease.

The treatment aims at relief of symptoms and arrest of the atrophic process to prevent complications.

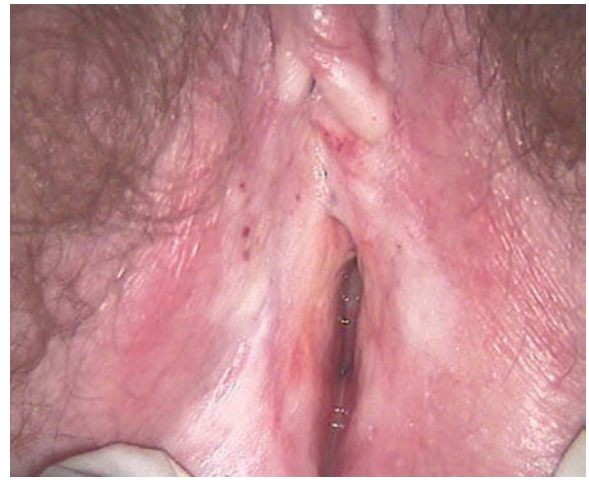


Fig 12.6 Clitoral fusion associated with lichen sclerosus.

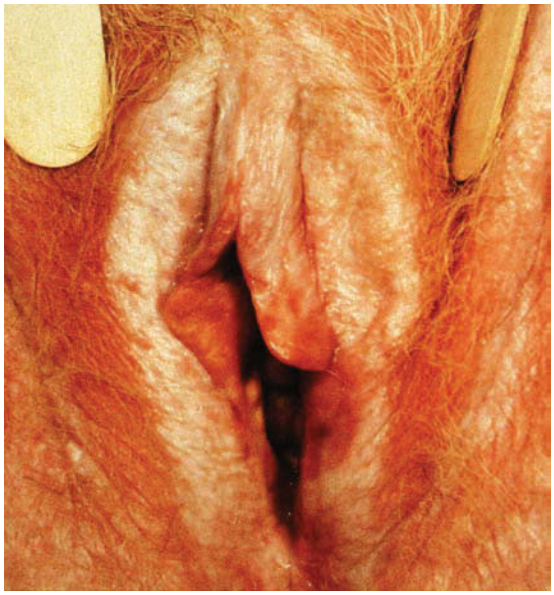


Fig 12.7 Ivory pallor type appearance over labia majora and to a lesser extent the labia minora.

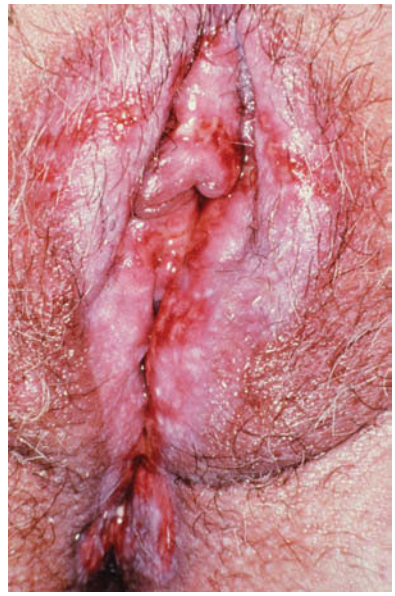


Fig 12.8 Severe changes associated with lichen sclerosus. There is distortion of the vulvar architecture and changes can be seen to extend towards the perineum.

Several treatments have been used but the most effective is the use of potent topical corticosteroids with maintenance therapy at the lowest possible dose. The patient should be advised to use treatment only on the affected areas and could use a mirror to aid application of corticosteroid cream if necessary. Treatment is recommended if there are clinical signs of lichen sclerosus, even if asymptomatic or with mild symptoms, in order to prevent progression. Surgery should be avoided in these cases as it is not more effective than conservative treatments and local recurrences are common. Long-term follow-up is required in view of possible malignant potential.

Squamocellular hyperplasia

This is a type of vulvar epithelial dystrophy without atypia. Squamous cell hyperplasia is not a distinct entity and is merely a description of the morphologic alteration of vulvar skin. The proposed predisposing factor is chronic pruritus due either to chemical irritation, eczema, or recurrent mycotic infection. Since the causes of squamous hyperplasia are many, they should be properly identified, diagnosed, and treated accordingly. Squamous cell hyperplasia on it own is rarely observed in association with invasive cancer. When it is associated with VIN or lichen sclerosus, then these women are at higher risk of developing invasive cancer.

These lesions usually present with itching accompanied by red swollen skin. It mostly affects the labia majora, clitoris, and perianal areas. Clinically they appear as thick, dry, keratinised, elevated epithelial patches with diffuse edges. Diagnosis is confirmed on biopsy.

Treatment is symptomatic with withdrawal of the possible irritant, treatment of mycotic infection, topical steroids, and emollients.

Paget's disease

The vulva is the commonest site affected by extramammary Paget's disease (EMPD), and can either arise as a primary epithelial disorder or a secondary spread from another adenocarcinoma. The invasive potential of Paget's disease has been established but the incidence of progression is unclear.

Typical clinical presentation is erythematous, eczematous eruption with areas of hyperkeratosis. The commonest occurrence is after the age of 60. Common symptoms are pruritus and burning. Paget's disease may exhibit minimally invasive foci but this is not common. It is more notable for its

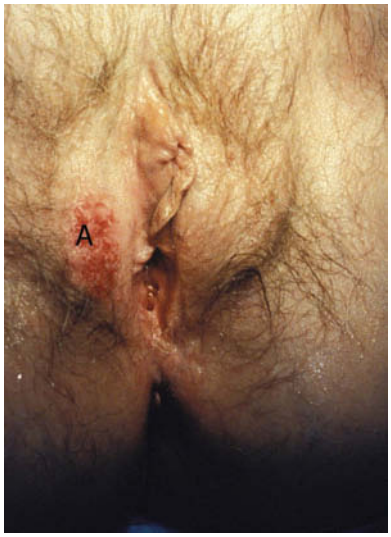


Fig 12.9 Paget's disease affecting right labia (A).

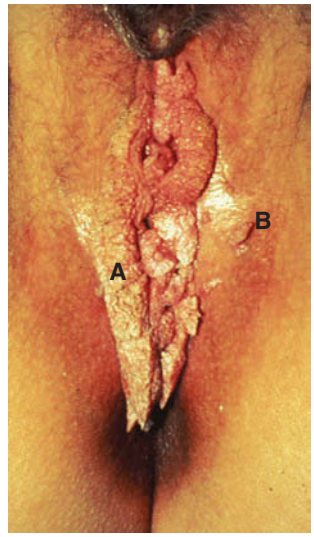


Fig 12.10 Extensive vulvar warts (A) with some satellite lesions (B).

association (20–40%) with adenocarcinoma of contiguous (anogenital) and non-contiguous (e.g. breast) structures.

Treatment is essentially surgical with wide local excision. Pathological changes tend to extend beyond the clinical borders. Recurrence is common and can be treated with re-excision.

HPV lesions (vulvar warts/condylomas)

The typical HPV-related lesions on the vulva are warts or condylomas. The incriminating HPV types are 6 and 11.

The mode of transmission is mainly sexual, though autoinoculation has also been reported. The incubation period from the sexual contact to the appearance of lesions can be from one month to three years. Most lesions regress spontaneously but risk factors for persistence or progression are multiple sexual partners, immunosuppression, smoking, and recurrent genital infections.

The quadrivalent HPV vaccine includes protection against HPV 6 and 11 and vaccination has been shown to prevent the majority (90%) of vulvar warts. HPV vaccination against HPV 16 and 18 is effective in the prevention of VIN, which will reduce the risk for vulvar cancer.

Learning points

- Vulvar conditions usually present as a result of symptoms.
- Vulvar skin is more difficult to assess as there are a wide variety of features associated with vulvar disorders and the vulva is less likely to stain with acetic acid and toluidine blue.
- Neoplastic disease of the lower genital tract is mostly multicentric, therefore evidence of a lesion in one part necessitates thorough assessment of all the other parts.
- Histological confirmation of the disease process is important and can be undertaken in the majority as an outpatient procedure under local anesthetic.
- Treatment of symptoms is necessary as well as the actual disorder.
- Counseling skills are vital in the long-term care of patients with vulvar symptomatology.
- Several vulvar skin disorders can co-exist and some definitely have malignant potential.
- Vaccination is protective against vulvar warts (using the quadrivalent vaccine) and VIN.

Chapter

13

Pregnancy and puerperium

The incidence of abnormal cervical cytology is the same as amongst non-pregnant women. The prognosis of dysplasia, irrespective of grade, also remains unchanged. Women should not have routine cervical samples taken during pregnancy if they have had regular screening under a national screening program; however, if a pregnant woman has not availed herself of a screening cervical sample, then this would be an opportunity to perform one. If a previous cervical sample was abnormal and the woman became pregnant before investigation or treatment, then further investigations should not be delayed. The principle aim of colposcopy during pregnancy is to rule out invasive disease and help pursue conservative management until after delivery.

Normal cervix in pregnancy and puerperium

During the first trimester, the cervix does not appear much different than in non-pregnant state. Under the influence of increased hormones, the cervix is enlarged and softer due to increased vascularity and interstitial edema. This also leads to marked eversion of the endocervical canal. The hypertrophy of the villi and the decidual changes give a polypoid appearance of the columnar epithelium. The TZ is enlarged with marked active metaplasia. There is also thick, tenacious mucus production. All these changes become increasingly prominent as the pregnancy advances. Similar changes are also seen in the vaginal mucus causing edematous hypertrophy of vaginal walls and increased laxity.

Cytohistological changes

Cervical cytology samples taken during pregnancy and the early puerperium (six weeks post-partum) maybe of suboptimal quality and the risk of false negative cytology is higher. The reason is due to the epithelial changes and the enlarged TZ during pregnancy. In those where there is excessive progestogenic effect, there maybe clumping of cells, making analysis difficult. Decidual change may give rise to the appearance of large cells on the cytology sample which could be confused with dyskaryosis or glandular abnormality.

CIN in pregnancy

The referral criteria for colposcopy are the same as in the non-pregnant state. Colposcopy is more difficult during pregnancy and certainly more uncomfortable for the woman. They should be advised that colposcopy has no risks to the pregnancy. As the changes in the cervix can be marked, an experienced colposcopist should undertake the examination. The cervix will appear larger and access is more difficult due to positioning and patient discomfort. The area for assessment (TZ) is greater and extensive metaplasia will be apparent. If a cervical cytology sample is performed, there is a greater tendency for contact bleeding and the woman will need reassurance.

Colposcopy becomes progressively difficult as pregnancy advances and is rarely performed in the third trimester, unless there is suspicion of invasive disease. A careful, systematic assessment of all the quadrants of the cervix should be undertaken. The TZ is much enlarged and there is marked metaplastic process. A small area of CIN maybe present in this large area. The acetowhite reactions of CIN (density, mosaicism, and punctation) are more pronounced in pregnancy because of increased vascularity. This can lead to over-diagnosis.

Treatment of CIN is almost never indicated during pregnancy, therefore biopsies should only be undertaken during pregnancy if there is suspicion of malignancy. Punch biopsies are not recommended because the samples are usually unsatisfactory in pregnancy and insufficient to rule out invasive process. The biopsy should be either wedge or cone-shaped and performed in a theatre setting. The intent is diagnostic not

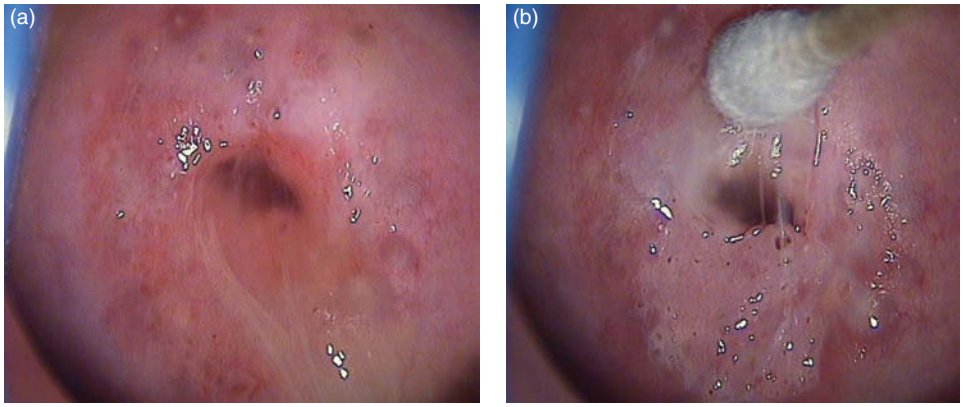


Fig 13.1 Deciduosis changes affecting cervix during pregnancy (before and after application of acetic acid).

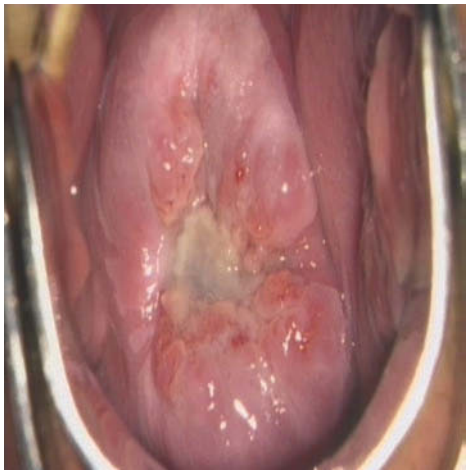


Fig 13.2 Pregnant at 16 weeks gestation. Large cervix with high-grade changes and difficulty in assessing lesion extent and vascularity.

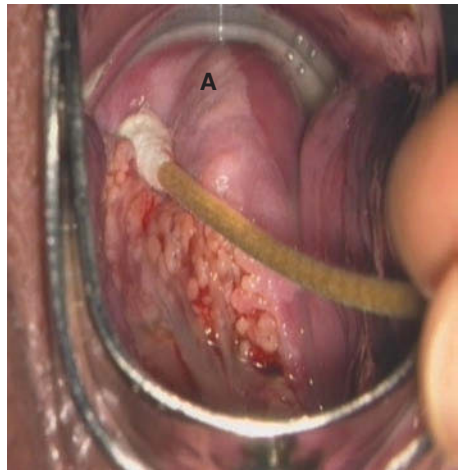


Fig 13.3 Gentle manipulation of cervix to assess lesion extent (A) and rule out any area suspicious for malignancy that may warrant immediate histological confirmation.

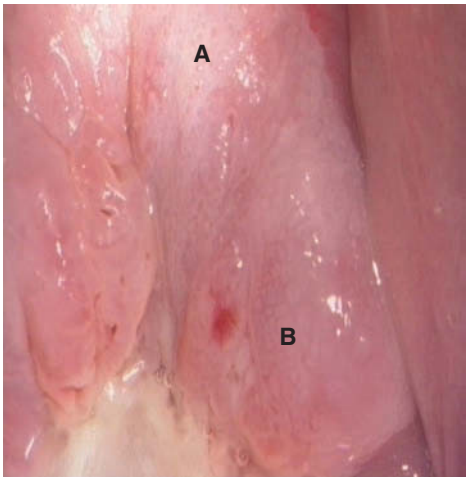


Fig 13.4 Lesion displaying both punctation (A) and mosaic (B) patterns consistent with CIN III.

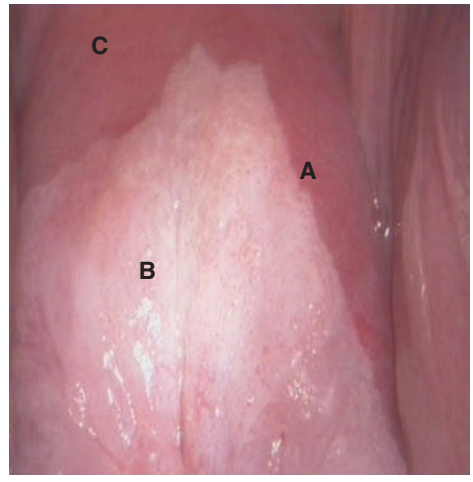


Fig 13.5 Lesion with distinct border (A) between acetowhite changes (B) and native squamous epithelium (C). Coarse punctation present throughout lesion.

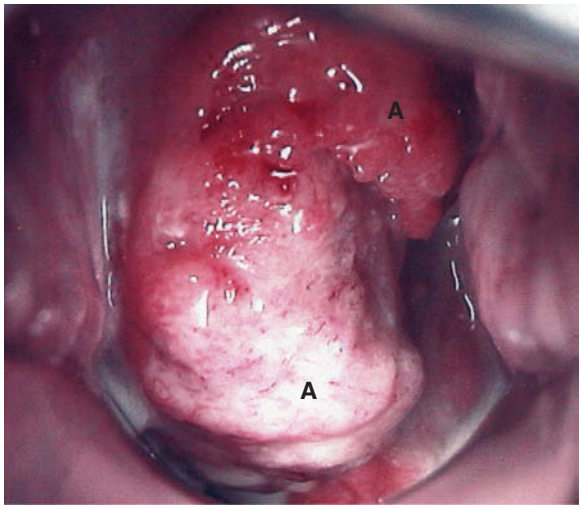


Fig 13.6 Pregnant woman at 20 weeks gestation with large tumor (A) replacing cervix. Difficult to assess due to tumor size and changes associated with pregnancy.

therapeutic. There is risk of significant haemorrhage and/or miscarriage. If invasive disease is confirmed, the subsequent management depends on the stage of the disease and the gestational age. The decision is made in collaboration with the parents and the obstetrician.

If invasive disease is ruled out, then the management is conservative with cytology and colposcopy, and the decision of treatment deferred till re-evaluation after the delivery, usually 8–12 weeks.

Puerperium

Women managed conservatively during pregnancy should be re-assessed after delivery within 8–12 weeks. During this time gestational changes on the cervix would have reverted back to normal and any tissue damage resolved. Occasionally, hypo-estrogenic state, especially in those breastfeeding, can make cytological or colposcopic assessment difficult. In such

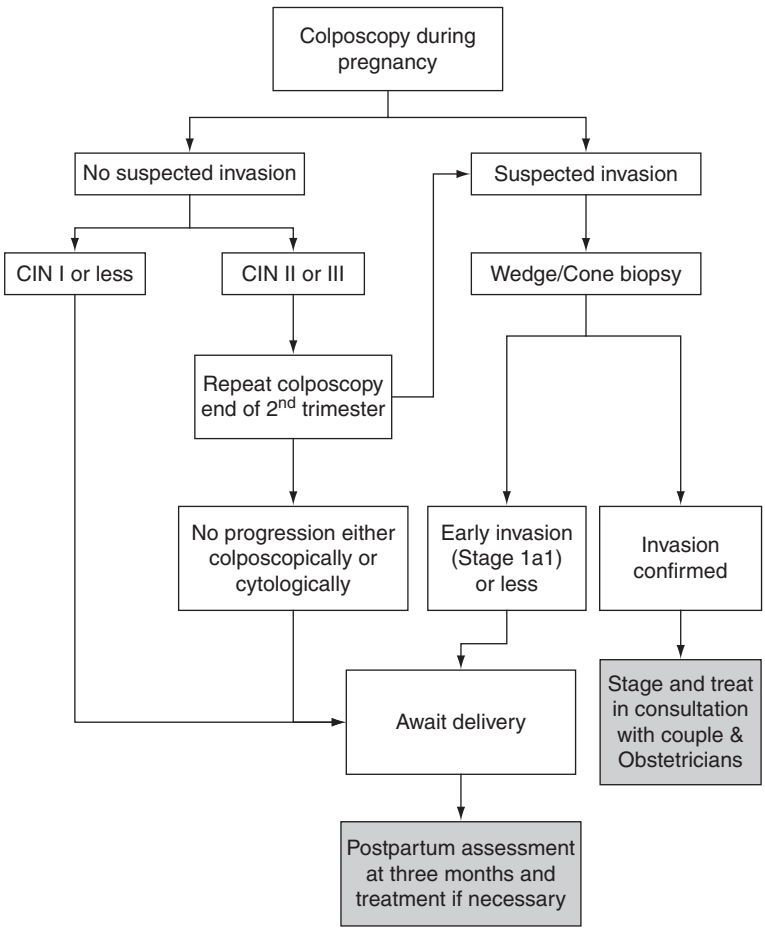


Fig 13.7 Flowchart for colposcopy during pregnancy.

cases, a course of local estrogens (2–6 weeks) may be helpful.

Learning points

- The principle aim of colposcopy in pregnancy is to rule out invasive disease.
- Pregnancy and the puerperium affects cytology and colposcopic appearances, making assessment more difficult.
- The cervix is larger and colposcopy more uncomfortable during pregnancy.
- The vascular changes can cause overcall of any abnormality present.
- If invasion is suspected, then a suitable biopsy should be performed.
- If changes are consistent with preinvasion, then biopsy and treatment can safely be deferred to the postnatal period.

Chapter

14 Menopause, contraception, immunosuppression, HIV, and smoking

Menopause

Postmenopausal women remain at risk of cervical cancer. This particularly applies if the woman has not availed herself of the screening program. Those who have had a normal screening history are at very low risk for invasive disease. In the UK, as in many other countries, routine screening for cervical cancer ceases at 64 years. Women therefore continue to have cervical cytology samples for almost 15 years following menopause. However, in the absence of antecedent screening, or if a woman presents with postmenopausal bleeding, a complete cervical assessment along with endometrial evaluation should be undertaken even after age 64.

The estrogen deficiency produces significant changes in the lower genital tract and cervix. There is decreased vasculature and interstitial fluid with flattening of the endocervical epithelium. The TZ appears to recede within the cervical canal. Thinning of the squamous epithelium and reduced mucus production leads to atrophy. The tissue is susceptible to even minor trauma. The epithelium is poorly glycogenated. Taking cervical cytology samples and colposcopic examination are made difficult due to these changes. The inadequate rate for cervical cytology is higher in postmenopausal women as the sampling device has difficulty in reaching the TZ.

Colposcopic appearance

The indications for colposcopy are the same as in premenopausal women. Colposcopy is made more difficult as the cervix appears atrophic and examination may be more uncomfortable. Examination is more likely to be deemed unsatisfactory as the SCJ recedes and the TZ may not be visualized in its entirety.

The cervix appears small, sometimes flush with the vaginal vault. The squamous epithelium is atrophic and may be traumatized, revealing subepithelial petechiae. Acetic acid may not give significant effect because of lack of vasculature and thinning of the epithelium. On the other hand if the surface is denuded because of physical trauma (speculum, swabbing, cervical cytology sample taking), it may give false appearance of acetowhitening. Application of Lugol's iodine can give a patchy yellow appearance because of lack of glycogen. In older women it may be uniformly yellow because of complete absence of glycogen. TZ is retracted into the endocervical canal because of shrinkage of the cervical stroma.

In those with unsatisfactory colposcopy, the use of local vaginal estrogen (ovules or cream) for a couple of weeks may help to reverse some of the atrophic changes and improve appearance of the TZ, hence allowing a more accurate assessment.

The use of estrogen locally or parenterally in those women with minor cervical cytological abnormalities (borderline or ASC-US), due to atrophic changes, may help improve colposcopic diagnosis in those that are hrHPV positive or those with unsatisfactory colposcopy.

Women with persistent cytological abnormality in the face of unsatisfactory colposcopy (despite estrogen use), or with significant cytological abnormality should have invasive disease ruled out by an excisional

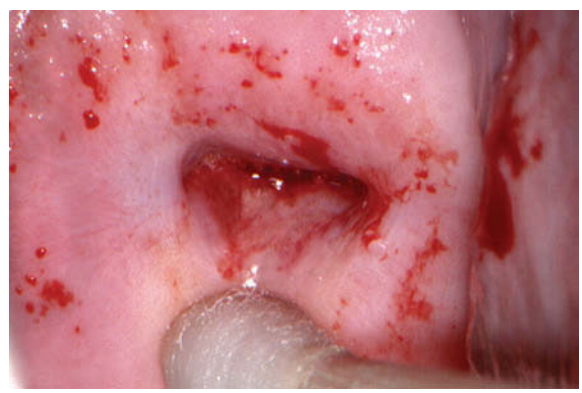


Fig 14.1 Atrophic cervix showing multiple petechiae. These changes can be reversed with a course of local or systemic estrogen.

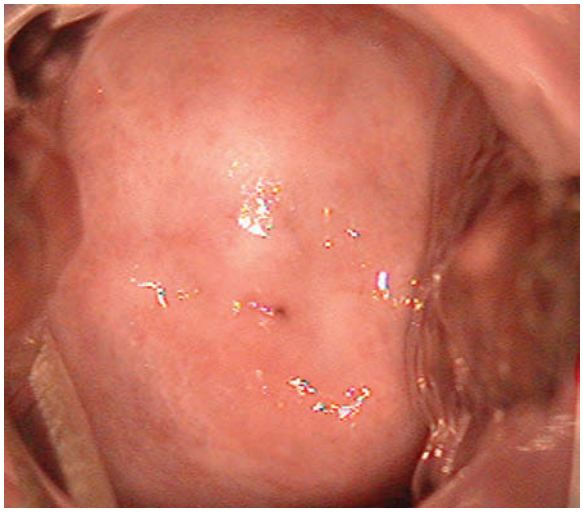


Fig 14.2 Stenotic cervix in postmenopausal woman.

cone biopsy. In cases of glandular abnormality, the endometrium should also be assessed by ultrasound and endometrial biopsy.

Contraception

Many women attending for colposcopy will be taking oral contraception. The woman should be advised not to stop taking this, as any abnormality present will not be affected by oral contraception. The changes commonly seen due to hormonal contraception is cervical ectopy, hypertrophy, and a viscid mucus, especially with progestogen-only pills. Sometimes the ectopy can appear quite hyperemic and florid, giving rise to a suspicious-looking cervix, often a cause of referral for colposcopy. In women where the assessment is likely to occur at the time of withdrawal bleeding, women can safely be advised to continue with their oral contraceptives without taking a break.

An intrauterine contraceptive device (IUCD) in situ should not affect the cervical cytology sample or colposcopic examination and treatment can usually be performed without removal of the IUCD. This is especially so for ablative treatments but is also appropriate for excisional treatments such as LLETZ. In a minority, the IUCD will be removed and one should aim to do this in the first half of the menstrual cycle. Alternative methods of contraception will need to be discussed. The IUCD can then be re-inserted 4–6 weeks later at the time of her menstruation. Reinsertion at the time of treatment is associated with a higher infection rate and is generally avoided.

Barrier methods of contraception (condoms, diaphragm, and cervical cap) have some protective effect against HPV and other sexually transmitted diseases (STD). These should be used in conjunction with a spermicidal that is also virucidal. There is no evidence suggesting benefit with use of barrier contraception in patients with CIN or after its treatment.

Immunosuppression

This includes women who are on immunosuppressing medication, transplant recipients, and all other forms of immunosuppression. Close cooperation is necessary with other physicians to ensure that the women get the appropriate care they deserve. These women are at increased risk of CIN but this needs to be balanced against morbidity of treatment and the comorbidity of the underlying disease process.

All women aged 25–64 years with renal failure needing renal dialysis must have cervical cytology performed at or shortly after diagnosis. Colposcopy should be performed if resource permits. All women about to undergo renal transplantation should have had cervical cytology performed within a year. Coexisting CIN should be managed according to national guidelines. In women taking immunosuppresants postransplatation, cervical screening should be in accordance with national guidelines for the non-immunosuppressed.

Human immunodeficiency virus

All women newly diagnosed with HIV should have cervical surveillance performed. Annual cytology should be undertaken with an initial colposcopy if resources permit. Subsequent management should be according to national guidelines. Use of highly active antiretroviral therapy (HAART) reduces HIV viral load and may also reduce HPV viral load. This may reduce the prevalence and incidence of cervical abnormality in such women, but the evidence is inconsistent.

Smoking

There is evidence to suggest that tobacco can induce carcinogenic effects at sites not directly exposed to cigarette smoke e.g. bladder, kidney, and pancreas. Smoking has also been shown to be associated with

increased risk of developing squamous cell cervical cancer. Evidence regarding association with cervical adenocarcinoma is still lacking. There are various proposed mechanisms for this association. Nicotine derivatives and tobacco-specific nitrosamines have been detected in cervical cells. Detectable genotoxic damage in cervical exfoliated cells has also been found. Reductions of local immune mechanisms in the cervix have been shown with decrease in Langerhans cells and other immune markers. Significantly higher rates of regression of CIN have been reported in women who stopped smoking compared to those who continued. In women who undergo treatment, recurrence rates are higher in those that smoke.

Women need to be made aware of these facts and every opportunity should be taken to reinforce the message of prevention. With increasing trends of smoking amongst younger women in some countries, this could have an important impact on their incidence of cervical cancer.

Learning points

- Cytology and colposcopy is more difficult in the postmenopausal woman.
- Local or systemic estrogen therapy is useful to obtain good cytology and allow satisfactory colposcopy to be conducted.
- Women can continue with contraception throughout the period of assessment with cervical cytology and colposcopy.
- Women on immunosuppressants or those with HIV are at increased risk for cervical disease.
- Women should be made aware of the risks associated with smoking, not only to their general health but also in relation to cervical disease.

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Index