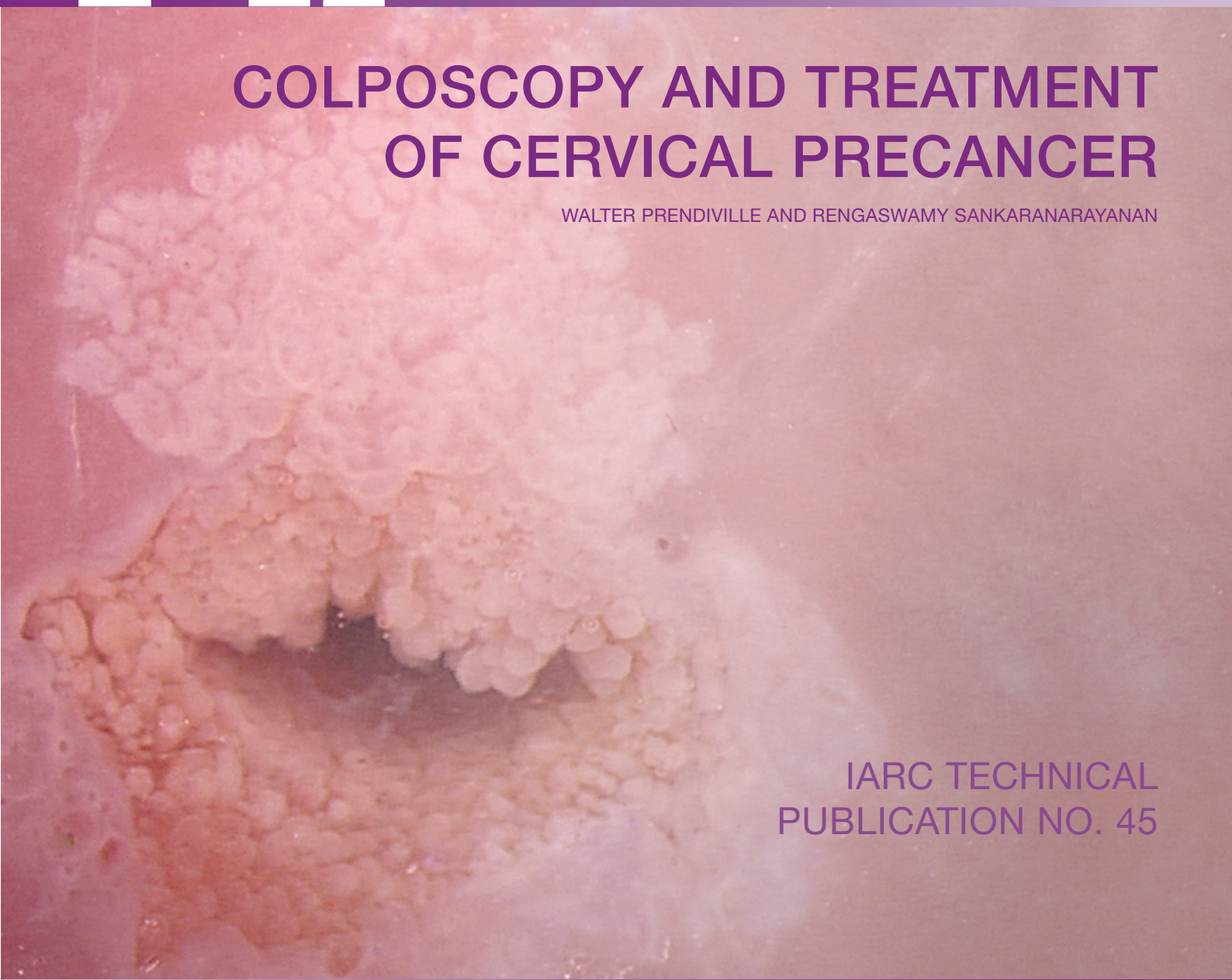
IARC TECHNICAL PUBLICATIONS

COLPOSCOPY AND TREATMENT OF CERVICAL PRECANCER

WALTER PRENDIVILLE AND RENGASWAMY SANKARANARAYANAN



IARC TECHNICAL PUBLICATION NO. 45

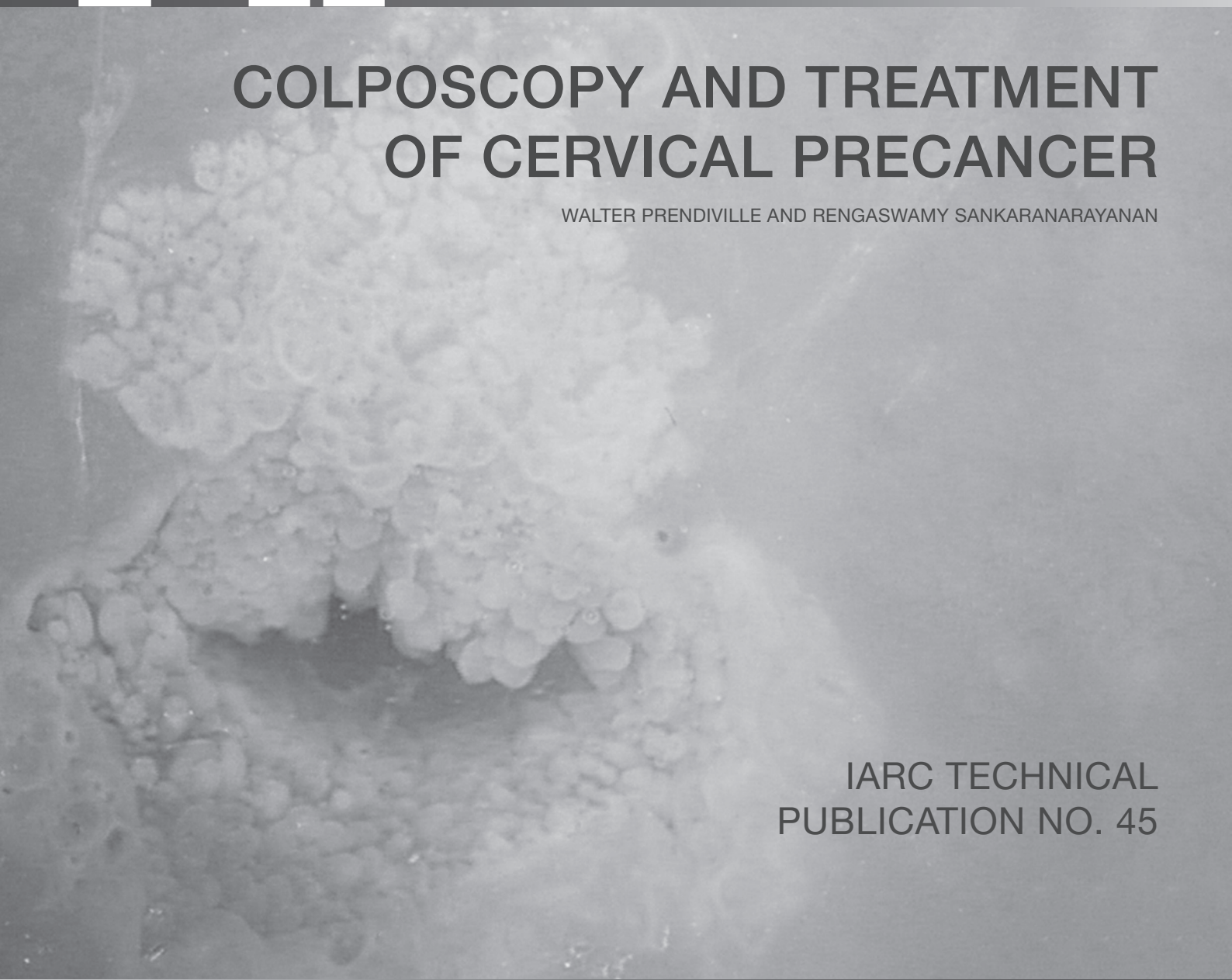
International Agency for Research on Cancer

World Health Organization

IARC TECHNICAL PUBLICATIONS

COLPOSCOPY AND TREATMENT OF CERVICAL PRECANCER

WALTER PRENDIVILLE AND RENGASWAMY SANKARANARAYANAN



IARC TECHNICAL PUBLICATION NO. 45

International Agency for Research on Cancer

World Health Organization

Published by the International Agency for Research on Cancer,
150 cours Albert Thomas, 69372 Lyon Cedex 08, France

Distributed by
WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland
(tel: +41 22 791 3264; fax: +41 22 791 4857; email: bookorders@who.int).

Cover image: The photo shows a mosaic blood vessel pattern and mild acetic acid uptake in a small type 1 transformation zone surrounding copious clear mucus, through which normal columnar epithelium is clearly seen. Photo reproduced with kind permission from Dr Montserrat Cararach and the Spanish Colposcopy Society.

This book is also available in electronic format from
http://publications.iarc.fr.

IARC Library Cataloguing in Publication Data

Colposcopy and treatment of cervical precancer / Walter Prendiville, Rengaswamy Sankaranarayanan

(IARC Technical Publications; 45)

1. Cervical Intraepithelial Neoplasia – Diagnosis 2. Cervical Intraepithelial Neoplasia – Pathology 3. Uterine Cervical Neoplasms – Therapy 4. Uterine Cervical Dysplasia 5. Colposcopy 6. Human papillomavirus 7. Manuals as Topic
I. Prendiville, W. II. Title III. Series

ISBN 978-92-832-2459-4 (NLM Classification: W1)
ISSN 1012-7348

This book is dedicated to the memory of the late Dr John W. Sellors, in recognition of his valuable contributions to *Colposcopy and Treatment of Cervical Intraepithelial Neoplasia: A Beginners' Manual* and to cervical cancer prevention and control and improving the health of women in low- and middle-income countries.

Table of contents

Contributors vii
Acknowledgements viii
Foreword ix
Abbreviations xi

Chapter 1 1
The role of colposcopy in cervical precancer

Chapter 2 13
Anatomy of the uterine cervix and the transformation zone

Chapter 3 23
Squamous intraepithelial lesions: cytology–histology correlation

Chapter 4 29
The effect of oncogenic HPV on transformation zone epithelium

Chapter 5 37
Equipment for a colposcopic examination

Chapter 6 45
A systematic approach to colposcopic examination

Chapter 7 51
Colposcopic terminology: the 2011 IFCPC nomenclature

Chapter 8 59
Colposcopic appearance of the normal cervix

Chapter 9 67
Inflammatory lesions of the cervix

Chapter 10 77
Colposcopic examination of the abnormal cervix

Chapter 11 85
Treatment of cervical intraepithelial neoplasia (CIN)

Chapter 12 101
Glandular abnormalities, adenocarcinoma in situ, and glandular intraepithelial neoplasia

Chapter 13 107
Microinvasive squamous cervical cancer

Chapter 14 115
Surgical management of early invasive cervical cancer

Chapter 15 123
Non-surgical management of cervical cancer

Chapter 16 131
Follow-up after treatment of cervical intraepithelial neoplasia (CIN)

Chapter 17 135
Pregnancy, contraception, menopause, and hysterectomy

Chapter 18 139
Quality assurance: fail-safe protocols and clean equipment

References 147

Annex 1 157
Transformation zone types

Annex 2 158
Standard form for documenting the examination findings

Annex 3 159
2011 IFCPC colposcopic terminology of the cervix

Annex 4 160
The Swede score

Annex 5 161
Preparation of 5% acetic acid, Lugol's iodine solution, and Monsel's paste

Disclosures of interests 163

Sources 164

Index 170

Contributors

Authors

Professor Walter Prendiville
Screening Group
Section of Early Detection and Prevention
International Agency for Research on Cancer (IARC)
150 cours Albert Thomas
69372 Lyon Cedex 08
France
walter123prendiville@gmail.com

Dr Rengaswamy Sankaranarayanan
Special Advisor on Cancer Control
Head, Screening Group
Section of Early Detection and Prevention
International Agency for Research on Cancer (IARC)
150 cours Albert Thomas
69372 Lyon Cedex 08
France
sankarr@iarc.fr

Other Contributor

Dr Partha Basu
Screening Group
Section of Early Detection and Prevention
International Agency for Research on Cancer (IARC)
150 cours Albert Thomas
69372 Lyon Cedex 08
France
basup@iarc.fr

Reviewers

Professor Margaret Cruickshank
Department of Obstetrics and Gynaecology
University of Aberdeen
Aberdeen, Scotland
United Kingdom
m.e.cruickshank@abdn.ac.uk

Ms Mary Martin
Suite 8
Tallaght Hospital
Tallaght
Dublin 24
Ireland
mary.martin@amnch.ie

Professor Pierre Martin-Hirsch
Royal Preston Hospital
Sharoe Green Lane North
Fulwood, Preston
Lancashire PR2 9HT
United Kingdom
martin.hirsch@mac.com

Professor Groesbeck Parham
University of North Carolina
Department of Obstetrics and Gynecology
Campus Box 7570
Chapel Hill, NC 27599-7570
USA
professorparham@gmail.com

Professor John Tidy
G18, Royal Hallamshire Hospital
Glossop Road
Sheffield S10 2JF
United Kingdom
john.tidy@sth.nhs.uk

Production Team

Karen Müller
English Editor

Sylvia Lesage
Publishing Assistant

Nicholas O'Connor
Publishing Assistant

Krittika Pitaksaringkarn
Publications Technician

Acknowledgements

This book, IARC Technical Publication No. 45, attempts to guide practising or trainee clinicians caring for women with, or at risk of, precancer and early cancer of the cervix. Partha Basu kindly contributed Chapters 14 and 15.

Profound thanks go to the reviewers of individual chapters or the entire book: Margaret Cruickshank, Mary Martin, Pierre Martin-Hirsch, Groesbeck Parham, and John Tidy. Thank you also to those who generously allowed their photographs to be used in this manual: Mihaela Badea, Partha Basu, Christine Bergeron, Montserrat Cararach, Xavier Carcopino, René and Isabelle Cartier, Quek Swee Chong, John Doorbar, Goran Grubišić, David Hicks, Michael Jeffers, Peter J. Pronovost, Ramani Rajendran, Catherine Sauvaget, and Mark H. Stoler (a full list of sources is provided at the end of this book). All of these people were immensely helpful in preparing and editing the manual.

Krittika Pitaksaringkarn was indispensable in keeping the project on track and managing the timely publication, as well as performing the layout. We are grateful to our in-house publishing team of Karen Müller and Sylvia Lesage, for ensuring the typographical, grammatical, and labelling accuracy of the text. We thank Lakshmi Sankaranarayanan, who helped with the drawings of illustrations.

Foreword

Cervical cancer is preventable. A combination of vaccination against human papillomavirus (HPV) and early detection and treatment after screening should lead to this cancer becoming a rarity among women in all parts of the world in the decades to come, if these life-saving preventive interventions are implemented.

Colposcopy is an important triaging investigation of screen-positive women and thus represents an important component of cervical cancer screening. Colposcopy permits careful inspection of the cervical and vaginal mucosa to detect cervical intraepithelial neoplasia (CIN) and subclinical cervical cancer, and facilitates the treatment of cervical precancerous lesions under colposcopic control. Well-trained and informed providers are critical for performing accurate and safe colposcopy. This colposcopy manual was developed in the context of the cervical cancer screening research studies of the International Agency for Research on Cancer (IARC) and the related technical support provided to national programmes. It is thus a highly comprehensive manual, both for the training of new colposcopists and for the continuing education and reorientation of those who are more experienced.

In the past few years, there has been enormous progress in the understanding of the etiology and pathogenesis of cervical cancer, with important implications for early detection and prevention and for the practice of colposcopy. Currently, a number of women around the world are screened using visual inspection with acetic acid (VIA) or HPV testing. Performing colposcopy in VIA or HPV screen-positive women could be challenging because there are no prior morphological details linked to the screen positivity with which to guide and interpret the examination, in contrast to the situation with cytology screening. However, irrespective of the type of screening test used, colposcopy, if it is available in health services, remains the best method to direct biopsies to confirm the severity of clinical disease and to inform subsequent management of detected lesions.

Another evolution that will pose substantial challenges for colposcopy practice is the increasing implementation of HPV vaccination in many countries. Over time this will lead to a significant decline in the prevalence of HPV infection and of cervical abnormalities among vaccinated cohorts of women. On average, colposcopists will see fewer abnormalities on the cervix, and the lesions caused by the HPV types other than 16 and 18 are likely to have less florid abnormal features. Therefore, highly skilled providers will be required for accurate and safe colposcopy practice, and thus the continuing education and reorientation of colposcopy practitioners with respect to the new developments is essential. This manual offers a valuable learning resource in this context, incorporating recent developments in the understanding of the etiology and pathogenesis of CIN, as well as in colposcopy and cervical pathology.

Expertise in performing adequate, safe, and accurate colposcopic examinations requires high competence in the technical, interpretive, and cognitive aspects, and the capability to develop pragmatic and effective management plans and treatment. The competencies needed are manifold and include: basic theoretical knowledge of the instrumentation, the anatomy and pathophysiology of the cervix, the natural history and manifestations of transient and persistent HPV infections, the natural history of cervical neoplasia, the cytological and histopathological aspects of metaplasia, dysplasia, and cancer,

and colposcopic indications and procedures; the ability to recognize and interpret the colposcopic appearances of normal, inflammatory, and neoplastic conditions; acquisition of skills in directing biopsies and managing colposcopic abnormalities; treatment of cervical cancer precursor lesions under colposcopic control; skills in avoiding and controlling bleeding and other complications; and acquisition of communication skills. This comprehensive and concise manual covers all these aspects and will serve as a useful handbook for acquiring the necessary skills for the visual recognition and interpretation of colposcopic findings and for developing the personal and professional attributes required for competence in colposcopy. Thus, I believe that this IARC Technical Publication will be a valuable contribution to cancer control and research in the years ahead.

Dr Christopher P. Wild
Director, International Agency for Research on Cancer

Abbreviations

AGUS	atypical glandular cells of undetermined significance
ASCCP	American Society for Colposcopy and Cervical Pathology
ASCUS	atypical squamous cells of undetermined significance
ASCUS-H	ASCUS, cannot exclude HSIL
CCRT	concurrent chemoradiotherapy
CGIN	cervical glandular intraepithelial neoplasia
CIN	cervical intraepithelial neoplasia
CO_2	carbon dioxide
CT	computed tomography
EBRT	external beam radiotherapy
ESU	electrosurgical unit
FIGO	International Federation of Gynecology and Obstetrics
HLD	high-level disinfection
HPV	human papillomavirus
HSIL	high-grade squamous intraepithelial lesion
IARC	International Agency for Research on Cancer
ICR	intracavitary radiotherapy
IFCPC	International Federation of Cervical Pathology and Colposcopy
IUCD	intrauterine contraceptive device
LAST	Lower Anogenital Squamous Terminology
LEEP	loop electrosurgical excision procedure
LLETZ	large loop excision of the transformation zone
LMICs	low- and middle-income countries
LSIL	low-grade squamous intraepithelial lesion
LVSI	lymphovascular space involvement

MRI	magnetic resonance imaging
N_2O	nitrous oxide
NETZ	needle excision of the transformation zone
NHS	United Kingdom National Health Service
OSCE	Objective Structured Clinical Examination
PET	positron emission tomography
RCTs	randomized controlled trials
SCJ	squamocolumnar junction
SIL	squamous intraepithelial lesion
SOPs	standard operating procedures
SWETZ	straight wire excision of the transformation zone
TZ	transformation zone
VIA	visual inspection with acetic acid
VILI	visual inspection with Lugol's iodine
WHO	World Health Organization

CHAPTER 1.

The role of colposcopy in cervical precancer

A positive *diagnostic* test result reveals an abnormality or disease. Advice about management is usually accepted willingly. When a woman receives an abnormal cervical screening test result, the expectations and fears that she carries are quite different. Cervical *screening* tests – whether visual inspection, cervical cytology, or human papillomavirus (HPV) tests – do not give a diagnosis; rather, they modify the risk for an individual of developing cervical cancer. The progression to precancer and cancer is slow and is a very uncommon outcome for screen-positive women (Fig. 1.1).

The threshold of abnormality at which the risk of cancer outweighs any disadvantage of treatment varies according to patient characteristics and local service considerations. The World Health Organization (WHO) advises treatment at the high-grade squamous intraepithelial lesion (HSIL) level (cervical intraepithelial neoplasia grade 2 [CIN2] or greater). However, in many countries with established screening programmes and where low rates of default from follow-up exist, the threshold for treatment may be higher, especially in young women. The management of screen-positive women would

Fig. 1.1. Relative rates of human papillomavirus (HPV) infection, low-grade squamous intraepithelial lesion (LSIL), and cervical cancer (high-grade squamous intraepithelial lesion [HSIL]).

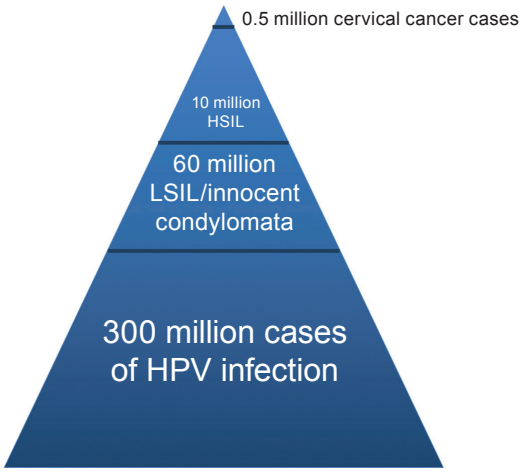
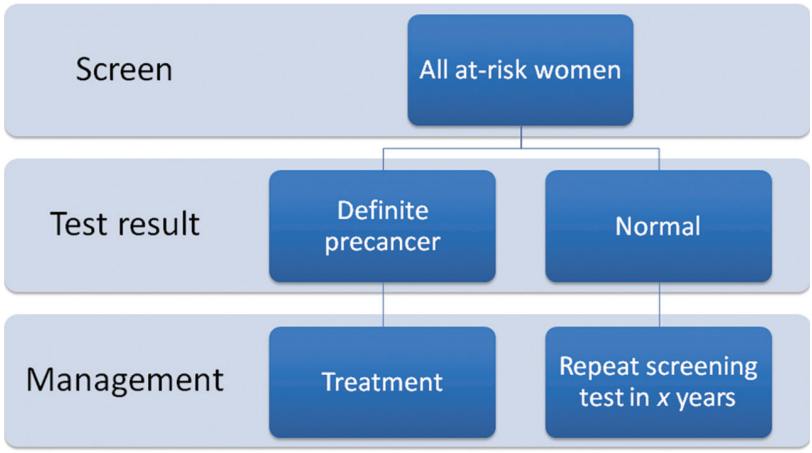


Fig. 1.2. The ideal, dichotomous screening test.



be much easier if the results of screening tests were diagnostic and dichotomous. An ideal screening test would provide two possible answers, and management advice would be simple (Fig. 1.2).

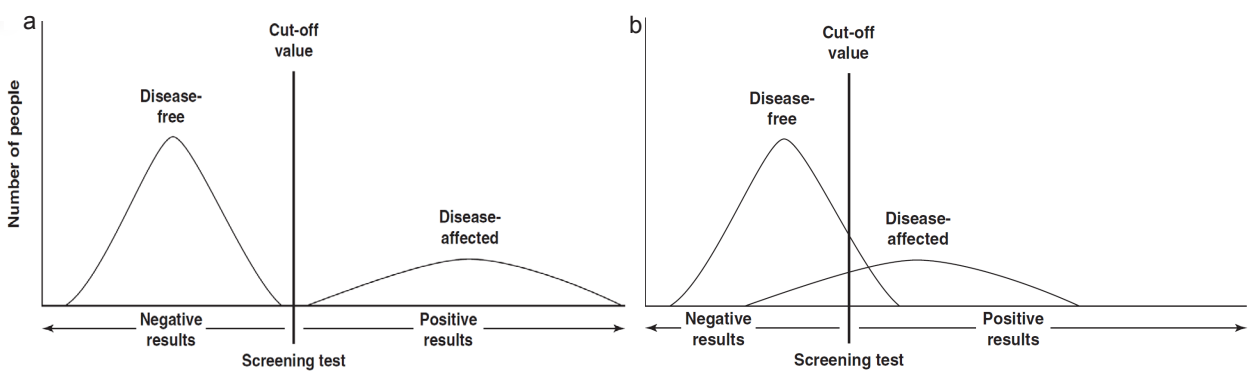
But current screening tests for cervical precancer are neither completely sensitive nor absolutely specific. For example, testing for oncogenic (or high-risk) HPV will pick up almost all cervical precancerous lesions but will also test positive in women who have innocent and transient high-risk HPV infection. In a recent study, 73% of women with a positive oncogenic HPV test also had a negative or normal smear (Katki et al., 2011). Cytology, in contrast, is far more specific than HPV testing but will miss a number of women in whom there is a risk of precancer. Because of this, cytology testing has to be performed relatively frequently (3–5-yearly). The long natural history of cervical cancer is forgiving of the relatively poor sensitivity of cytology.

Also, cytology will sometimes recognize cells that are very mildly abnormal, or even of a "borderline" nature: borderline nuclear abnormality, and atypical squamous cells of undetermined significance (ASCUS). These categories of abnormality create headaches and frustration for both clinician and patient. They include mostly women who are not at a high risk of progression, as well as a minority of women who are. Clearly, the ideal test – not yet available – would identify only the women who are at a high risk of progression to cancer. The problem of imperfect sensitivity and specificity is illustrated in Fig. 1.3.

Visual inspection with acetic acid (VIA) is fast becoming the de facto screening method of choice in many regions where cytology and HPV testing are out of reach. A "screen-and-treat" approach is gaining popularity as an efficient method of reaching large numbers of women in difficult circumstances. However, the specificity of VIA is poor, and the difficulty of missing endocervical lesions (whether they are squamous or glandular) is a real problem. Overtreatment of women with false-positive VIA test results is perceived as a necessary trade-off to reduce the overall incidence of cervical cancer.

Thus, screening tests (VIA, cytology, and HPV testing) are imperfect, and women with an abnormal primary screening test need further consideration before reflex referral to colposcopy and/or management. For those women in whom a suspicion of CIN2 has been reported, referral to colposcopy is still the appropriate advice. (When considering treatment, lesser grades of abnormality, or CIN2 with negative p16, the cost–benefit equation is less certain.) The concept of triage is to use other tests for women who have an imprecise primary screening test report, so that those women who have a genuine risk of progression to cancer

Fig. 1.3. (a) The ideal screening test. (b) The real screening test.



may be identified and referred for colposcopy and management. Also, just as importantly, women who are at a very low risk of progression may be spared the interventions of biopsy and/or treatment. Colposcopy is also important in avoiding overtreatment that may occur with "screen-and-treat" programmes where false-positive rates may be very high (Basu et al., 2015). Finally, colposcopy may recognize invasive cancer not heralded by a screening test.

1.1 Traditional screening: rationale and practice

Systematic high-coverage and quality-assured population screening and treatment for precursors to cervical cancer are highly effective. The conditions for an ideal screening test as enunciated by Wilson and Jungner (1968) apply very precisely to cervical cancer. The disease has a long precancerous phase, effective screening tests are available and are easily performed, and the disease is common enough to justify the expense of population screening, even in low- and middle-income countries (LMICs) (Denny and Prendiville, 2015). Finally, there are effective and low-morbidity preventive treatments of proven value for screen-positive women. In those countries and regions that have implemented quality-assured, high-coverage call-and-recall screening programmes for cervical precancer, large reductions have been demonstrated in the rates of both incidence of and mortality from cervical cancer (Figs. 1.4 and 1.5).

1.2 Management of screen-positive women

In the traditional system, a cervical smear test is the usual screening tool (Fig. 1.6). The microscopic examination of cellular material to recognize morphological changes allows cytologists to report different degrees of abnormality, classified as borderline, low-grade, or high-grade in squamous or glandular cells. High-grade smear abnormalities are associated with a higher risk of cervical cancer development over the subsequent decade, and low-grade and borderline smears are associated with a dramatically lower risk.

Of course, it is not the screening itself that prevents cervical cancer, but rather the subsequent management of screen-positive women. Screen-positive women may be stratified according to risk and either referred to a colposcopist or retested some time later. Classically, colposcopic examination facilitates the recognition and localization of genuinely high-grade abnormality within the "at-risk" epithelium – i.e. the transformation zone (TZ) – and facilitates either confirmatory biopsy or excision/ablation of the TZ, or both.

Fig. 1.4. Age-standardized incidence of invasive cervical cancer and coverage of screening in England, showing a decrease in incidence after the introduction of a national call-and-recall screening programme.

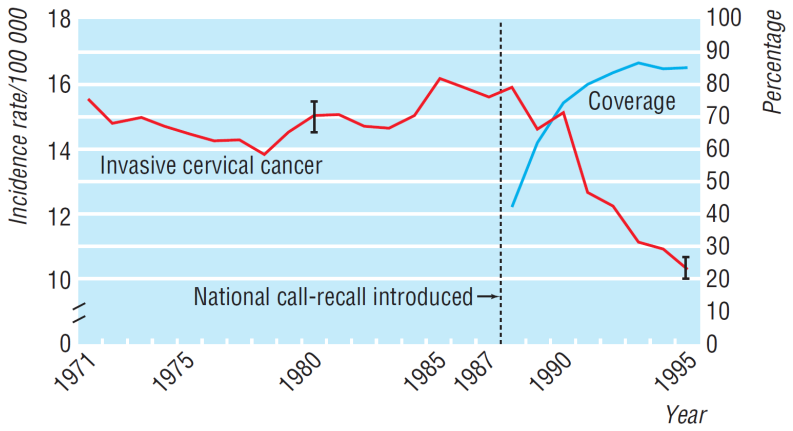


Fig. 1.5. Projected cervical cancer deaths without any screening (England and Wales). Dashed line represents cervical cancer deaths that would have happened after 1987 without screening. Solid line shows annual deaths from 1953 to 2002. Arrow indicates start of national screening in 1988.

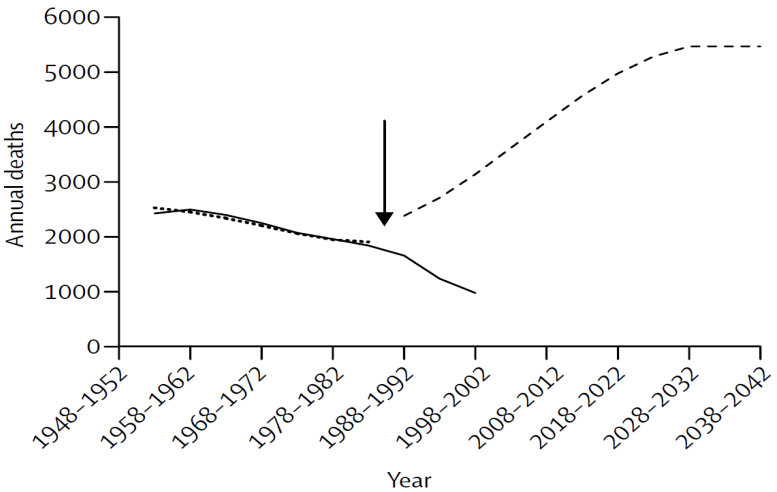
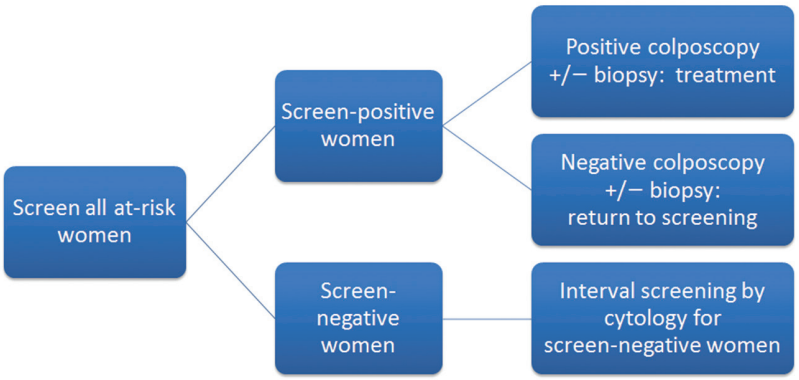


Fig. 1.6. Traditional algorithm for screen-positive cases.



Established treatment modalities are effective. Through well-organized screening programmes and the management of screen-positive women, incidence and mortality rates have been reduced significantly (Arbyn et al., 2009; IARC, 2005; Miller, 1993; Peto et al., 2004; Sasieni et al., 2003). For many years, this system or model of *screen, colposcope, and treat selected patients* has been standard and highly successful.

But the protocol is not perfect. It was a practical and workable system 30 years ago. For example, in the United Kingdom, women were not, at that time, referred for colposcopic examination unless the cytologist considered there to be a significant risk of progression to cancer – in other words, when there was a smear report describing changes suggesting severe dysplasia (i.e. a smear report of severe dyskaryosis). At that time, women with minor abnormalities were followed up with repeat cytology. The threshold for referral to colposcopy was relatively high, and most women who were referred had a high-grade smear report that was usually confirmed and managed at colposcopy. The decision to proceed to treatment was uncomplicated and had consensus support. Also in the 1980s, large loop excision of the transformation zone (LLETZ), which later became known as loop electrosurgical excision procedure (LEEP) in the USA, was introduced as a simple excisional outpatient treatment (Prendiville et al., 1989). This technique largely replaced laser treatment and other destructive methods because of its simplicity, cost–effectiveness, and facility for comprehensive histological assessment of the removed TZ. In selected cases it obviated the need for a preliminary colposcopically directed biopsy.

Although it has been known for some time that low-grade abnormalities have a low risk of progression (Moscicki et al., 2010), it became clear that some cytological low-grade or borderline smears harbour higher-grade lesions. As a result, women with minor-grade abnormalities were increasingly referred for immediate colposcopic evaluation, and in time the majority of women with an abnormal smear of almost any grade were, in some regions, referred for colposcopic examination. In some parts of Europe and the USA, where screening was routinely offered annually and often to very young women, the risk of unnecessary treatment became commonplace.

During the 1980s and 1990s, the number of women referred for colposcopic examination increased exponentially. To add fuel to the fire of overtreatment, the ease with which routine office or outpatient LLETZ could be learned and performed, compared with laser treatment or cold-knife cone biopsy, meant that the threshold for treatment fell. At about the same time, reporting rates for low-grade and borderline abnormalities varied enormously. In Ireland's National Cancer Screening Service, for example, at the beginning of its cervical screening programme all smears were sent to a laboratory in the USA. Of these specimens, 14.9% were reported as "not normal", rates similar to those for VIA. Finally, as the very high sensitivity of oncogenic HPV testing became apparent, the test became used widely, either on its own or in combination with cytology. The management of screen-positive women became more complex. The optimal "next step" for most women with any "not normal" smear is no longer automatic referral for colposcopy and treatment.

1.3 Clinical guidelines

Against this background, some national societies of colposcopy and cervical pathology have taken on the responsibility of generating clinical guidelines for physicians and colposcopists as an aid to management.

For example, in the United Kingdom, the National Health Service (NHS) Cervical Screening Programme produced a clinical guidelines document entitled *Colposcopy and Programme Management: Guidelines for the NHS Cervical Screening Programme* (NHS, 2004), which encompassed screening, management, and follow-up guidelines for clinicians involved in the United Kingdom screening programme. It was updated in 2010 and 2016 (NHS, 2010, 2016) and is a valuable reference document for anyone involved in cervical precancer screening and/or management.

In 2001, a new reporting system for cytology smears was published in the USA, and at about the same time the results were published of a large study in the USA reporting different strategies for managing minor cytological abnormalities (ASCUS-LSIL Triage Study (ALTS) Group, 2003a, 2003b). To guide physicians in the USA, the American Society for Colposcopy and Cervical Pathology (ASCCP) implemented a process that developed broad consensus guidelines to aid clinicians in managing women with abnormal cervical cytology. These guidelines became a defensible and practical aid for a busy gynaecologist to use in everyday practice in the USA (Massad et al., 2013; Nayar and Wilbur, 2015; Wright et al., 2003), and they apply to the context of screening principle and practice in the USA. This is not meant to be a criticism of the process but should make the reader wary about using management algorithms outside of the context in which they were generated.

1.4 Risk assessment in patient management

When to advise the asymptomatic screen-positive woman to have further intervention requires an assessment of risk. Does the risk of intervention outweigh the risk of cancer evolving? Many of the triage recommendations contained in management algorithms depend exclusively on the result of the screening test. For example, it may advise an oncogenic HPV test for a woman with a smear report of ASCUS. But there are other factors that modify the relative risk of progression (Mergui et al., 2010). A smear reporting *HSIL-moderate dyskaryosis* carries a very different risk of progression to cancer in a woman younger than 30 years compared with a woman older than 40 years. Age, smoking, and other influences modify the risk equation. Finally, the likelihood of default from follow-up monitoring of untreated patients needs to be taken into consideration. This thinking was developed in a clinical opinion paper in 2007 (Castle et al., 2007). The paper put forward cogent arguments for using a quantifiable risk assessment rather than an individual test result as the arbiter of management. It extended the principle beyond cytology to colposcopy and histology (Fig. 1.7).

When assessing the threshold for referral to colposcopy or for treatment, some researchers have defined thresholds of risk. The 2012 ASCCP clinical guidelines document (Massad et al., 2013) includes a risk of progression (Table 1.1) that reflects this approach.

1.5 Screening and triage options in current practice

There are several different scenarios where triage might be useful in the management of cervical precancer. Local circumstances, cost, availability of test facilities, and expertise will all play a role in determining which primary screening tool is used and which secondary or triage test is used. Examples are illustrated in Figs. 1.8–1.11.

Primary screening tests may also be used as triage tools (cytology, HPV testing, or VIA), and some are used in conjunction with others to improve the test characteristics of the primary screening test (co-testing with cytology and HPV; dual testing, i.e. p16/Ki-67, with HPV). Finally,

Fig. 1.7. Graphical representation of the risk of cervical precancer at different stages and results of screening and clinical management for cervical cancer prevention. The risks for each stage and result are approximate risks for cervical intraepithelial neoplasia grade 3 (CIN3) within a screening interval. The axis to the right of the figure represents increasing risk, from nearly 0% (blue) to 100% (red), of cervical precancer on a logarithmic scale. Each stage of screening and clinical management is represented by a different pattern, and the arrows at the bottom indicate the sequence of the stages. # Less than half of the cases of CIN2 on biopsy are subsequently diagnosed as CIN3 on excisional tissue (precancer). † Within a screening interval. * Test results at the next follow-up visit (≥ 6 months).

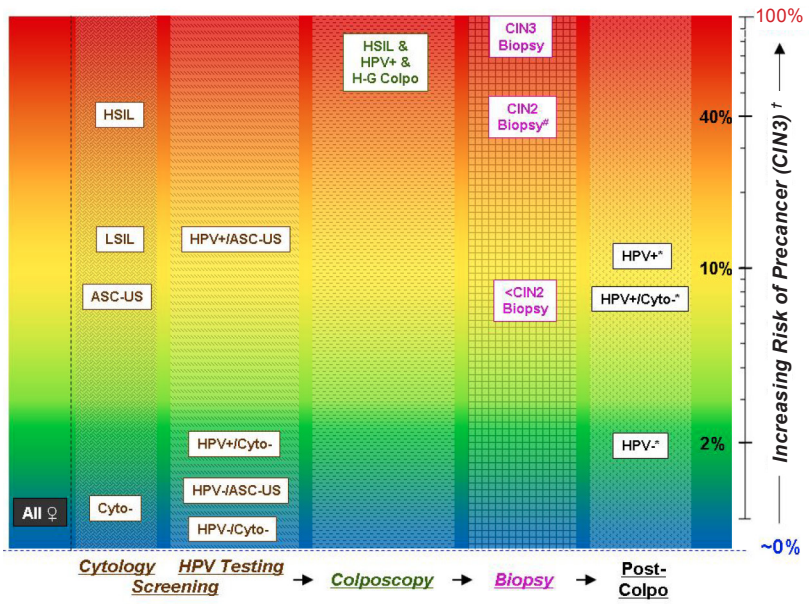


Table 1.1. Referral or follow-up according to risk of CIN3

Risk of CIN3	Recommended action
> 5%	Immediate referral for colposcopy
2–5%	6–12-month follow-up
0.1–2%	3-year follow-up
< 0.1%	5-year follow-up

CIN3, cervical intraepithelial neoplasia grade 3.

Fig. 1.8. Generic use of triage after primary screening.

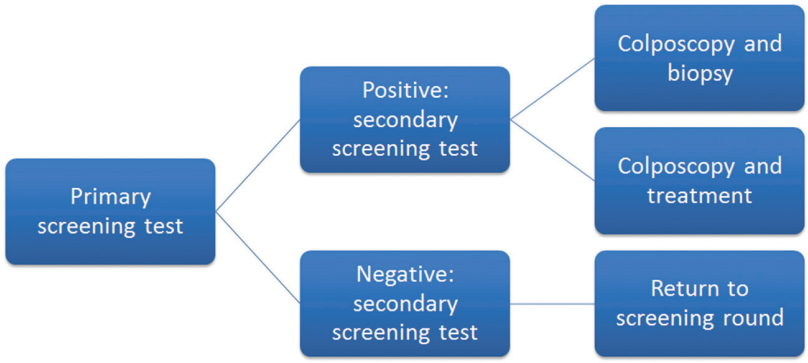
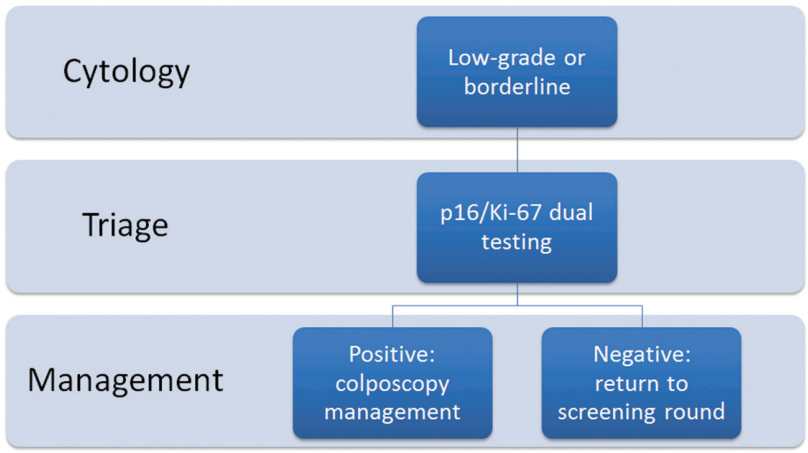


Fig. 1.9. Possible triage of low-grade and borderline smears using p16/Ki-67 dual testing.



repeat cytology has also been used as a triage tool for minor-grade cytology reports.

1.5.1 VIA and VILI

Two naked-eye inspection methods are in widespread use in LMICs: VIA and visual inspection with Lugol's iodine (VILI). They may be performed by nurses or other primary health-care workers. They use light-illuminated speculum examination of the cervix after the application of 5% acetic acid (VIA) or Lugol's iodine (VILI).

VIA and VILI are inexpensive and simple, and can be carried out by primary care staff trained in a relatively short time. Visual inspection provides an immediate result that can be determined on-site in hospitals, in clinics, or in the field and allows the health-care worker the opportunity to immediate treat those TZs that are possibly abnormal. The sensitivity and the specificity of visual inspection techniques are highly variable and are very reliant on quality-assured training and retraining (Sankaranarayanan et al., 2007; Sauvaget et al., 2011). Of course, these methods only assess the ectocervix and will miss endocervical lesions, with consequent poorer performance in older women. Finally, visual inspection is very unlikely to detect glandular intraepithelial lesions or squamous lesions in the canal (some type 2 TZs and most type 3 TZs).

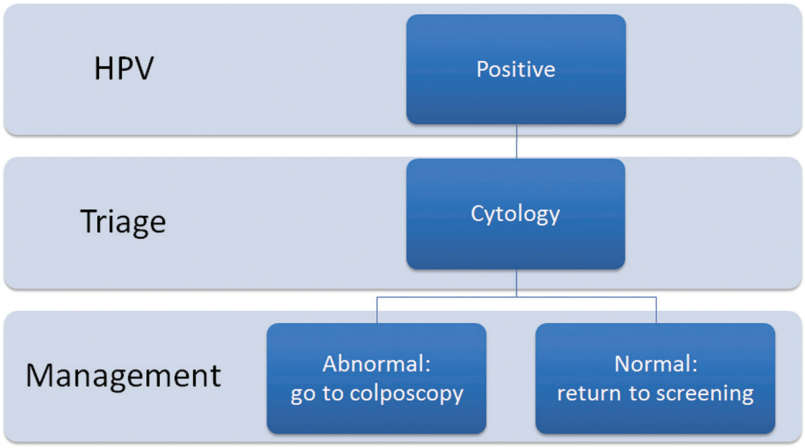
1.5.1.1 Digital VIA

Given the concerns about suboptimal sensitivity and lack of an efficient quality assurance mechanism for VIA-based screening, modifications of the method have been used in some regions. For example, Parham et al. (2015) have used enhanced magnification of cervical lesions, peer review, quality assurance, continuing medical education, objective recording of screening test results, and access to expert opinion in their screen-and-treat programme in Zambia. Treatment decisions are made primarily on the basis of VIA. However, if there are disagreements between VIA and enhanced magnified images, then the images are used to make the final decision.

1.5.2 Cytology

Cervical cytology smears need to be examined by properly trained and quality-assured cytologists. The subsequent treatment of women

Fig. 1.10. Possible triage of positive HPV test using cytology.



with high-grade CIN prevents the development of cancer (Miller, 1993). However, in LMICs, cytology has not been as successful, for several reasons. Unless strict and continuing quality control programmes are in place, cytology may perform poorly in terms of recognizing abnormal lesions. It has good specificity but lacks sensitivity, and in some series may be associated with sensitivity rates of only 50% (Arbyn et al., 2009; Nanda et al., 2000). Also, the test requirements are expensive, and the screening interval needs to be relatively frequent (3–5 years). Finally, in many regions the facilities necessary to collect, process, and report cytology are simply not available. It is highly unlikely that health systems in LMICs will wish to establish cytology as the primary screening tool for cervical cancer prevention.

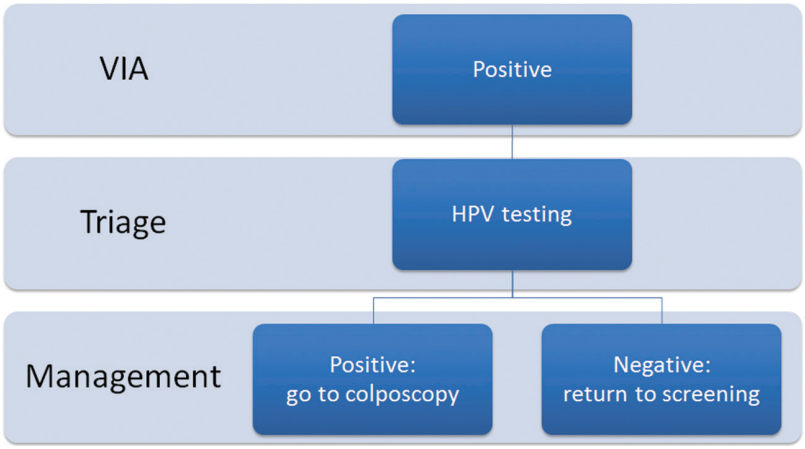
1.5.3 HPV testing

HPV DNA testing will probably replace or complement cytology as the primary screening tool in many developed countries for women older than 30 years (Arbyn et al., 2013). Because of the absolute relationship between oncogenic HPV infection and cervical cancer, the negative predictive value of HPV testing is very high. A large number of studies have investigated how best to use this information. HPV testing for all known oncogenic types has been available and approved for many years.

There are essentially three realms where oncogenic HPV testing is of proven clinical utility:

- as a screening tool in women older than 30 years;
- as a triage tool for women with low-grade cytological abnormalities; and
- as a follow-up tool for women who have been treated for squamous or glandular cervical precancer.

Fig. 1.11. Possible use of HPV testing for triage of positive visual inspection with acetic acid (VIA) test.



1.5.3.1 Oncogenic HPV testing as the primary screening tool

Sankaranarayanan et al. (2009) first demonstrated in a large cluster randomized controlled trial (RCT) that a single round of HPV testing was superior to cytology or VIA or no screening in reducing the incidence of advanced cervical cancer and in reducing mortality from cervical cancer.

Four RCTs of HPV screening versus routine cytological screening have been undertaken in Europe. In these studies together, 176 464 women aged 20–64 years were randomly assigned to HPV-based (experimental arm) or cytology-based (control arm) screening in England, Italy, the Netherlands, and Sweden.

In all four studies, the incidence of CIN3 was lower in those women who had initially been screened by HPV than in those initially screened by cytology, and similar rates of reduction were recorded in each study. This reduced rate was true across all studies despite differences in screening protocols between the studies. Because none of the individual studies was sufficiently large to show a reduction in cancer

incidence, a recent overview of the pooled data has been undertaken by Ronco et al. (2014).

The 176 464 women were followed up for at least two rounds of cervical screening, equating to a median of 6.5 years. A total of 107 invasive cervical carcinomas were found. The authors concluded in their summary: "HPV-based screening provides 60–70% greater protection against invasive cervical carcinomas compared with cytology. Data of large-scale randomised trials support initiation of HPV-based screening from age 30 years and extension of screening intervals to at least 5 years." The results of this overview are very convincing.

1.5.3.2 Oncogenic HPV testing as a triage tool for women with low-grade cytological abnormalities

As the threshold for referral for investigation of smear abnormalities fell over the past two decades, the number of women attending colposcopy increased. As a general principle, women with any degree of cytological abnormality require either follow-up or treatment, depending on the risk of progression to cancer. There is consensus that most women with high-grade lesions should be referred for colposcopy and managed according to colposcopic assessment and/or biopsy results. However, for low-grade abnormalities, no such consensus exists (Cox, 2005; Sawaya, 2005; Soutter, 1994). The reason is that it is not possible to predict the natural history of minor-grade lesions on the basis of cytology alone. Low-grade abnormalities often regress (Melnikow et al., 1998; Ostör, 1993), and the potential for overtreatment is obvious. However, some studies reported relatively high rates of high-grade or moderate-grade abnormalities in women with low-grade cytology reports, even as high as 30% (Kinney et al., 1998). The search has continued for a triage tool to discriminate women at genuine risk of having or developing CIN3.

However, the management of women with minor-grade lesions remains controversial, and follow-up recommendations for women with ASCUS and low-grade squamous intraepithelial lesion (LSIL) have varied from conservative management (i.e. repeat cytology) to immediate referral for colposcopy and biopsy (Soutter et al., 2004). Because of the crucial role that HPV infection plays in the genesis of cervical cancer, HPV testing has been investigated as an alternative to repeat cytological testing, in a large number of disparate studies. Several formal reviews of these studies have been performed. The most recent Cochrane review (Arbyn et al., 2013) advised that for triage of women with LSIL, the Hybrid Capture 2 (HC2) oncogenic HPV test yields a significantly higher sensitivity, but a significantly lower specificity, compared with repeat cytology.

1.5.3.3 Oncogenic HPV testing as a follow-up tool for women who have been treated for squamous or glandular cervical precancer

Because residual disease and recurrent disease can occur up to 20 years after treatment, it is important to implement a follow-up protocol wherever possible (Soutter et al., 2006). A number of RCTs and several meta-analyses have demonstrated that HPV testing is the best *test of cure* (Arbyn et al., 2005). It has replaced cytology and colposcopy in several national clinical guidelines documents, although many still advise co-testing with cytology. Finally, several reviews have concluded that HPV testing is more cost-effective than cytology in the context of a European national screening programme (Coupé et al., 2007; Legood et al., 2012).

1.6 Colposcopy

1.6.1 What is colposcopy?

Colposcopy is low-powered microscopic and light-illuminated examination of the lower genital tract epithelium. The first reported use of a colposcope was in Hamburg, Germany, in the early 1920s as a result of a collaboration between the University of Hamburg and the German microscope manufacturer Leitz.

The early work published in the 1930s from Hamburg described the origins of cervical cancer being in a sheet of epithelium, i.e. intraepithelial, as opposed to arising from a single focal lesion. During the 1930s and 1940s, colposcopy practice spread and evolved throughout Europe. It was not until the 1960s and 1970s that colposcopy became more widely established, through individual experts.

1.6.2 What can colposcopy be used for?

Colposcopy may be used to examine any epithelial surface of the lower genital tract. Some of the indications for colposcopy are given in Table 1.2. It may be used as a primary screening tool and as a way of facilitating different treatment modalities. Colposcopy does not perform well as a primary screening tool (Leeson et al., 2014). It is also used to examine the vulva, the anus, the vagina, and more recently the oropharynx as well as the penile epithelium, because each of these sites is prone to developing colposcopically recognizable precancerous lesions. Colposcopy has also been used in

Table 1.2. Common indications for colposcopy

What is colposcopy best used for?
• A suspicious-looking cervix
• Symptoms suggestive of cervical cancer, e.g. persistent postcoital bleeding, persistent intermenstrual bleeding
• Cervical leukoplakia
• A cytological abnormality
• A positive VIA or VILI screening test
• A positive high-risk HPV test in the presence of a low-grade or borderline smear abnormality or other screening test abnormality

HPV, human papillomavirus; VIA, visual inspection with acetic acid; VILI, visual inspection with Lugol's iodine.

clinics investigating lower genital tract infection. However, the great majority of colposcopic examinations are of the cervix with suspected precancer.

The performance of colposcopy as a purely diagnostic tool is known to be influenced by the result of the screening test, and there are several studies where colposcopy has not performed well (Jeronimo and Schiffman, 2006; Pretorius et al., 2011). However, in those countries where colposcopy is part of a properly constructed, quality-assured programme, it is associated with a very high negative predictive value (Cruickshank et al., 2015; Kelly et al., 2012; Ricci et al., 2015). Also, colposcopy is not just a diagnostic tool; indeed, that is not even its most valuable role.

The colposcopic examination should undertake and document the following:

1. Assess the state of the cervix at the time of examination, and determine whether it is possible to undertake an adequate examination (see Chapter 6).
    a. Assess the hormonal status.
        i. Is the epithelium well-estrogenized?
        ii. Are pregnancy changes present?
        iii. In postmenopausal women, is the degree of atrophic epithelial change sufficient to consider prescribing topical estrogen before colposcopic assessment?
    b. Determine whether there is inflammation.
        i. Is infection (viral, fungal, bacterial) present, and is investigation and treatment prudent before colposcopic assessment?
    c. Confirm full visibility of the entire cervix and upper vagina under colposcopic view.
    d. Determine whether there is evidence of previous treatment, or any degree of epithelial fibrosis.

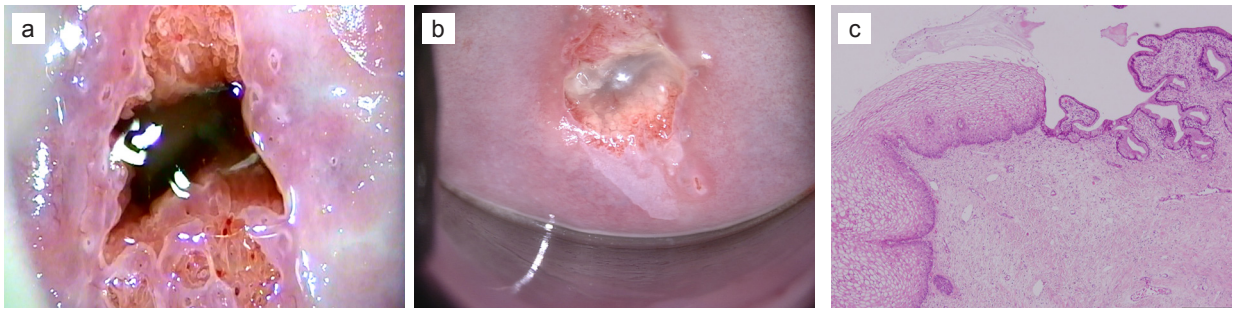
Once these assessments have been made, it will be possible to determine whether a complete colposcopic examination can be undertaken. If so, the following steps should be performed.

2. Determine the type and size of the TZ:
    a. TZ type (see nomenclature in Chapter 7, and Annex 1)
    b. TZ size (small or large).
3. Recognize epithelial abnormality (i.e. is disease present?).
    a. Cervical precancer non-invasive or intraepithelial abnormality classified as:
        i. CIN1 or LSIL
        ii. CIN2 or HSIL-CIN2
        iii. CIN3 or HSIL-CIN3.
4. Document the above examination findings in a standard and auditable format (see Annex 2) using the most recent International Federation of Cervical Pathology and Colposcopy (IFCPC) nomenclature or terminology (see Annex 3).
5. Compile a Swede score (see Annex 4).
6. Where possible, take a video or a number of pictures of the examination findings so as to record:
    a. the TZ type and size
    b. the site(s) of greatest abnormality
    c. the site of any biopsy
    d. the treatment, if performed.

Misunderstanding the role of the colposcopic examination is common, to the extent that some authors consider the major role of colposcopy to be guiding the diagnostic biopsy (Jeronimo and Schiffman, 2006; Wentzensen et al., 2015). Some aspects of colposcopic evaluation are contextual, and some are not. Diagnostic acumen and recognition of high-grade abnormality will vary according to the prevalence of high-grade abnormality in the clinic referral population. Other aspects of colposcopic evaluation are independent of case characteristics – for example, TZ type, adequacy of examination, hormonal status, and infection state.

Every colposcopy should assess the degree of abnormality as reflected in a simple scoring system, for example the Swede score (Strander et al., 2005) (see Annex 4). Sometimes it will be appropriate to take a biopsy, and sometimes not. Sometimes it will be appropriate to treat at the first/assessment visit, and sometimes not. Sometimes it will be appropriate to take a sample for cytology, for HPV testing, for endocervical brush cytology, or for other biomarkers of cervical cancer progression. If the TZ is not fully visible, the examination will be incomplete. In that case, the decision about management will depend on other case characteristics and whether to excise the TZ by way of a type 2 or type 3 excision. These

Fig. 1.12. (a) Colposcopic image of a normal transformation zone (TZ). (b) Colposcopic image of a TZ exhibiting low-grade changes. (c) Histological section of a normal squamocolumnar junction (40× magnification).



characteristics include:

- the patient's age and fertility aspirations;
- the reliability of the referral smear or other screening test;
- the risk of default from follow-up;
- the grade of suspected abnormality; and
- the availability of ancillary investigations (e.g. endocervical brush cytology, HPV testing, other biomarker tests).

Discovering high-grade abnormality when the smear reports a low-grade or borderline abnormality is more difficult, and it will often be prudent to take one or even two biopsies, but in a quality-assured colposcopy service the negative predictive value of a negative/normal colposcopic examination is very high, even without a colposcopically directed biopsy.

1.6.3 Diagnostic performance of colposcopy

The diagnostic accuracy of colposcopic examination, like that of any subjective test, will vary according to the training and expertise of the colposcopist as well as the prevalence of the disease. Also, it is influenced by knowledge of the referral screening test report. Finally, it performs better at the extremes of abnormality: normal/low-grade (Fig. 1.12) and definite high-grade (Fig. 1.13). The weakest diagnostic performance is with the middle or equivocal grade of abnormality. This is also true for cytology and pathology. The subjective error inherent in colposcopic assessment is very similar to the range of disparity that exists among cytologists and pathologists when assessing middle-grade or equivocal abnormalities. There is no gold standard. A systematic and adequate colposcopic examination by a properly trained colposcopist will nearly always recognize HSIL when cytology has heralded it and the report is known (Fig. 1.13). It will sometimes recognize microinvasive disease (Fig. 1.14), but not always (Howe and Vincenti, 1991). This is not an issue if the TZ has been excised in its entirety.

When the cytology report suggests a low-grade or borderline abnormality and an adequate colposcopic examination by a trained colposcopist reveals low-grade or normal appearance (Fig. 1.12), the risk of HSIL occurring in the next 4 years or more is very low. In this situation, the negative predictive value of a quality-assured colposcopic examination, even with a positive

Fig. 1.13. (a) Colposcopic image of high-grade cervical intraepithelial neoplasia (CIN); coarse punctation. (b) Low-power colposcopic image of high-grade CIN; coarse mosaic pattern. (c) Low-power colposcopic image of high-grade CIN; note the atypical vessels and sharp margin at the 5 o'clock position.

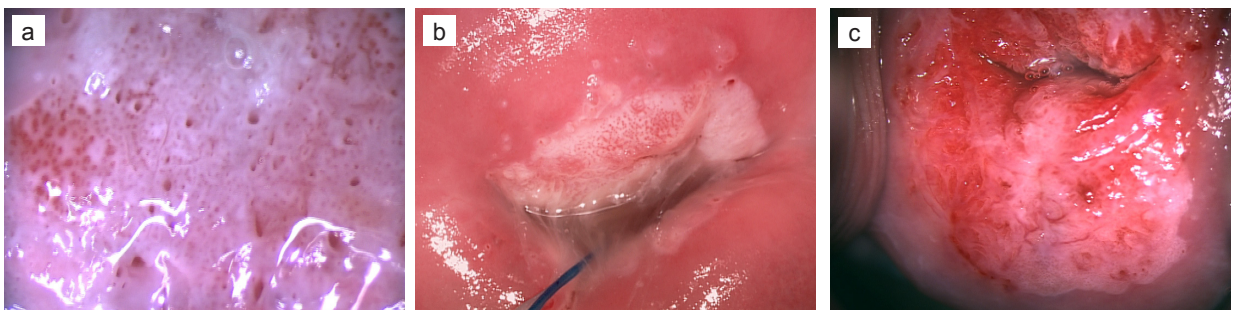
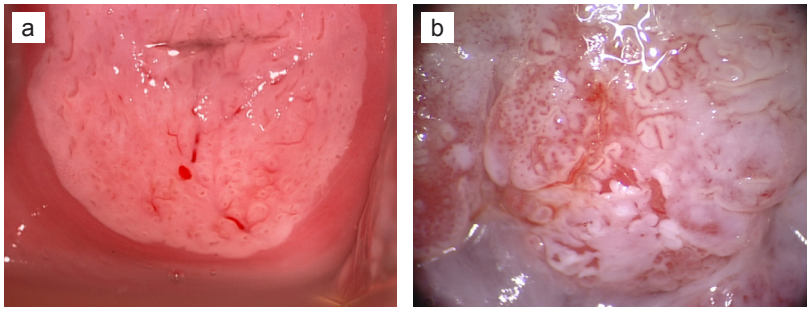


Fig. 1.14. (a) Microinvasive squamous carcinoma. (b) Colposcopic image of microinvasive disease.



HPV test, is very high (Cruickshank et al., 2015; Kelly et al., 2012; Ricci et al., 2015). Completely normal cervical epithelium in a fully visible TZ is, again, usually very clear. Lesser grades of CIN are more difficult to discriminate from normal epithelium, but low-grade disease carries an exceedingly low risk of progressing to cancer.

Colposcopically directed biopsies are sometimes necessary and sometimes not. For most women, a colposcopic impression of CIN3 in the presence of a high-grade smear warrants excision of the TZ rather than a directed biopsy. Indeed, when a quality-assured laboratory reports a smear as CIN3, colposcopy will reveal a high-grade lesion in the great majority of cases. In this situation, when colposcopy does not find evidence of CIN3 the colposcopist should consider a colposcopically directed biopsy and, even more importantly, consultation with the referring laboratory and review of the referral smear, before deciding management. It is far better to competently perform a colposcopy than to rely on random biopsies. When an adequate colposcopic examination is normal, a random biopsy will very rarely find high-grade CIN (Song et al., 2015; Wentzensen et al., 2015). These comments, of course, pertain to the colposcopic examination that is adequate and is not compromised by infection, previous treatment, or atrophy.

It is possible to miss a high-grade lesion when performing colposcopy, particularly if the lesion is small and possibly transient or when the colposcopic examination is compromised by inflammation, bleeding, or hormonal changes (atrophy or pregnancy) such that the examination should be recognized as being inadequate. Other reasons why colposcopy might underperform at a diagnostic level are that the colposcopist is inadequately trained or that the women being examined are an unscreened population or women referred because of a screening test with low specificity.

In deciding whether to take a biopsy, the colposcopist should consider whether the biopsy will alter management. At each end of the spectrum of suspected abnormality, a biopsy will not usually affect management. It is where uncertainty prevails that a colposcopically directed biopsy is valuable. Figs. 1.15 and 1.16 illustrate simplified approaches to managing suspected low-grade and high-grade lesions, respectively, in the context of a cytologically screened population.

Attempts to improve colposcopic diagnostic accuracy vary in their approach. One way is to improve colposcopic quality control. The Italian region of Emilia-Romagna has introduced a voluntary quality assurance system. The programme recently reported an Internet-based quality assurance programme. Of 65 colposcopists in the region, 59 participated in a review of 50 selected colpo-photographs and classified them according to colposcopic visibility of

Fig. 1.15. Algorithm of management where smear report is low-grade squamous intraepithelial lesion (LSIL)/atypical squamous cells of undetermined significance (ASCUS), given an adequate colposcopic examination in a type 1 transformation zone (TZ) by a properly trained colposcopist and with a cytology report from a quality-assured laboratory.

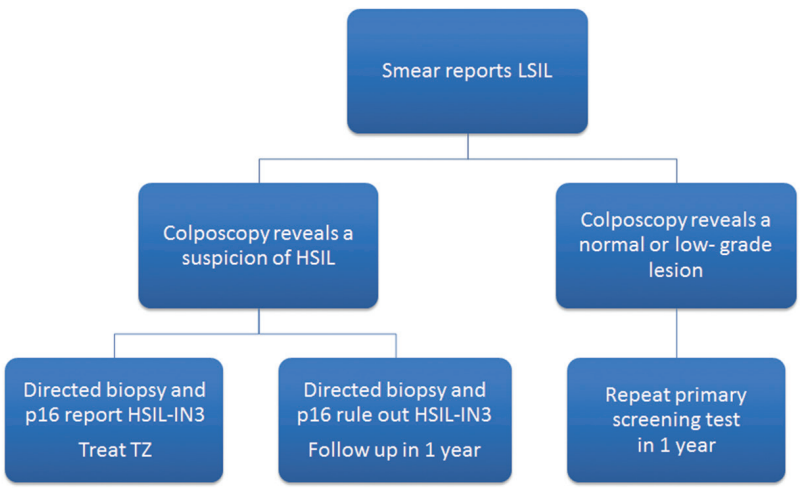
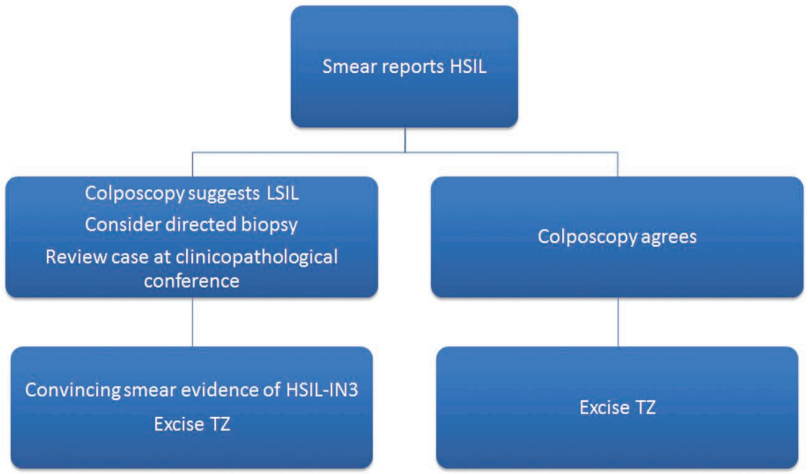


Fig. 1.16. Algorithm of management where smear report is high-grade squamous intraepithelial lesion (HSIL), given an adequate colposcopic examination in a type 1 transformation zone (TZ) by a properly trained colposcopist and with a cytology report from a quality-assured laboratory.



the squamocolumnar junction (i.e. TZ type), degree of abnormality, and need for biopsy. In that study, a biopsy was advised in 99% of women who ultimately had histologically proven CIN3. The authors (Bucchi et al., 2013) acknowledged that assessment of still images is not as good as video or in vivo assessment, but the colposcopists in that programme performed exceptionally well.

Another approach has been to advocate multiple random biopsies (Pretorius et al., 2004). The Chinese group that originally reported the advantage of random biopsy at colposcopy has recently reviewed its database (Song et al., 2015) and concluded that "random biopsy is not effective in the negative quadrant in women with positive colposcopy". Wentzensen and colleagues (Wentzensen et al., 2015) have come to a similar conclusion.

Key points

- Colposcopy is an assessment and diagnostic tool and offers the best way to manage women with suspected cervical precancer.
- A colposcopic examination should be systematic and structured and should always record the adequacy of the examination, the transformation zone type and size, and the degree of abnormality as reflected in an objective diagnostic scoring system, for example the Swede score.
- When quality-assured, colposcopic examination has a high negative predictive value.
- Excisional therapy for cervical precancer should always be performed under colposcopic vision.

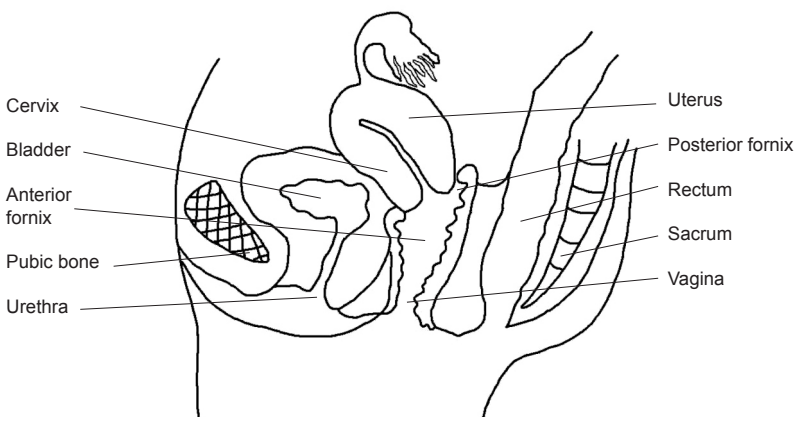
CHAPTER 2.

Anatomy of the uterine cervix and the transformation zone

The cervix is a fibromuscular organ that links the uterine cavity to the vagina. Although it is described as being cylindrical in shape, the anterior and posterior walls are more often ordinarily apposed. The cervix is approximately 4 cm in length and 3 cm in diameter. The cervix of a parous woman is considerably larger than that of a nulliparous woman, and the cervix of a woman of reproductive age is considerably larger than that of a postmenopausal woman. The cervix occupies both an internal and an external position. Its lower half, or intravaginal part, lies at the upper end of the vagina, and its upper half lies above the vagina, in the pelvic/abdominal cavity (Fig. 2.1). The two parts are approximately equal in size. The cervix lies between the bladder anteriorly and the bowel posteriorly. Laterally, the ureters are in close proximity, as are the uterine arteries superiorly and laterally.

The cervix has several different linings. The endocervical canal is lined with glandular epithelium, and the ectocervix is lined with squamous epithelium. The squamous epithelium meets the glandular epithelium at the squamocolumnar junction (SCJ). The SCJ is dynamic and moves during early adolescence and during a first pregnancy. The *original* SCJ originates in the endocervical canal, but as the cervix everts during these

Fig. 2.1. Line drawing of normal female genital tract anatomy: sagittal section. In this drawing, the uterus is anteverted.



times, the SCJ comes to lie on the ectocervix and becomes the new SCJ. In colposcopy terminology, the SCJ is this *new* SCJ. The epithelium between these two SCJs is the TZ or transition zone, and its position is also variable. It may be small or large and usually becomes more ectocervical during a woman's reproductive years, returning to an endocervical position after menopause.

When the uterus is anteverted, the cervix enters the vaginal vault through a slightly posterior approach, whereby at speculum examination the cervical os is directed towards the posterior vaginal wall (Fig. 2.1). When the speculum is opened, the cervix tends to be brought more centrally into view and into line with the longitudinal axis of the vagina. Most women have an anteverted uterus. When the uterus is retroverted, the cervix tends to enter the vagina slightly more anteriorly, and in this case the cervix may be more difficult to locate at first speculum exposure. When the speculum is positioned properly and opened, the cervix tends to become positioned centrally and in a plane perpendicular to the longitudinal axis of the vagina.

The external os of the cervix will nearly always be visible to the naked eye at speculum examination. The visible external lining of the cervix derives from the vaginal (squamous) epithelium. The endocervical or glandular epithelium is not usually visible to the naked eye at speculum examination. At the upper end of the endocervical canal, the endocervical epithelium becomes the endometrial lining of the uterine cavity. The lower half, or intravaginal part, of the cervix lies at the top of the vagina, surrounded by the vaginal fornices. These are the lateral, anterior, and posterior fornices and are where the vaginal epithelium sweeps into the cervix circumferentially. Squamous cervical cancer accounts for the majority of cervical cancer and originates in the TZ. Glandular cervical cancer originates in either the TZ or the glandular epithelium above the TZ.

2.1 Tissue constituents of the cervix

2.1.1 Stroma

The stroma of the cervix is composed of dense, fibromuscular tissue through which vascular, lymphatic, and nerve supplies to the cervix pass and form a complex plexus.

The arterial supply of the cervix is derived from the internal iliac arteries through the cervical and vaginal branches of the uterine arteries. The cervical branches of the uterine arteries descend in the lateral aspects of the cervix at the 3 o'clock and 9 o'clock positions. The veins of the cervix run parallel to the arteries and drain into the hypogastric venous plexus. The lymphatic vessels from the cervix drain into the common iliac, external iliac, internal iliac, obturator, and parametrial nodes.

The nerve supply to the cervix is derived from the hypogastric plexus. The endocervix has extensive sensory nerve endings, whereas there are very few in the ectocervix. Hence, procedures such as biopsy, thermal coagulation, and cryotherapy are relatively well tolerated in most women, although there is good evidence that local anaesthesia effectively prevents the discomfort of these procedures. Also, the cervix of a parous woman tends to have slightly less sensory appreciation, which may be due to damage to nerve endings during childbirth. Because sympathetic and parasympathetic fibres are also abundant in the endocervix, dilatation and/or curettage of the endocervix may occasionally lead to a vasovagal reaction.

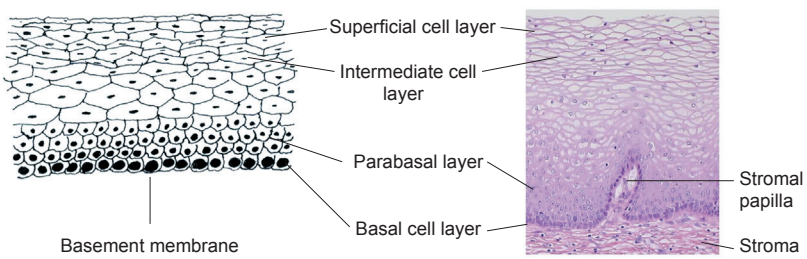
The cervix is covered by both stratified, non-keratinizing squamous epithelium and columnar epithelium. As mentioned above, these two types of epithelium meet at the SCJ.

2.1.2 Squamous epithelium

Usually, most of the ectocervix and the entire length of the vagina is lined with squamous epithelium, which is uniform, stratified, and non-keratinizing. Because mature squamous epithelium contains glycogen, it readily takes up Lugol's iodine (and is therefore Schiller test-negative). When epithelium does not take up Lugol's iodine, it is Schiller test-positive. Cervical squamous epithelium is smooth and looks slightly pink to the naked eye in its non-pregnant state. During pregnancy it becomes progressively more vascular and develops a bluish hue.

The lowest level of cells in the squamous epithelium (Fig. 2.2) is a single layer of round basal cells with large dark-staining nuclei and little cytoplasm, attached to the basement membrane. The basement

Fig. 2.2. Squamous epithelium of the vagina and ectocervix.



membrane separates the epithelium from the underlying stroma. The epithelial–stromal junction is usually straight. Sometimes it is slightly undulating, with short projections of stroma, which occur at regular intervals. These stromal projections are called papillae, and the parts of the epithelium between the papillae are called rete pegs.

The basal cells divide and mature to form the next few layers of cells, called parabasal cells, which also have relatively large dark-staining nuclei and greenish-blue basophilic cytoplasm. Further differentiation and maturation of these cells leads to the intermediate layers of polygonal cells with abundant cytoplasm and small, round nuclei. These cells form a basket-weave pattern. With further maturation, the superficial layers of large and markedly flattened cells with small, dense, pyknotic nuclei and transparent cytoplasm are formed. Overall, from the basal layer to the superficial layer, these cells undergo an increase in size and a reduction in nuclear size.

The cells in the intermediate and superficial layers contain abundant glycogen in their cytoplasm, which stains mahogany brown or black after the application of Lugol's iodine and magenta with periodic acid–Schiff stain in histological sections. Glycogenation of the intermediate and superficial layers is a sign of normal maturation and development of the squamous epithelium. Abnormal or altered maturation is characterized by a lack of glycogen production.

The maturation of the squamous epithelium of the cervix is dependent on estrogen, and if estrogen is lacking, full maturation and glycogenation do not take place. Hence, after menopause, the cells do not mature beyond the parabasal layer and do not accumulate as multiple layers of flat cells. Consequently, the epithelium becomes thin and atrophic. On visual examination, it appears pale, sometimes with subepithelial petechial haemorrhagic spots, because it is easily prone to trauma.

2.1.3 Columnar epithelium

The endocervical canal is lined with columnar epithelium (often referred to as glandular epithelium). It is composed of a single layer of tall cells with dark-staining nuclei close to the basement membrane (Fig. 2.3). Because of its single layer of cells, it is much shorter in height than the stratified squamous epithelium of the cervix. On visual examination, it appears reddish, because the thin single-cell layer allows penetration of the stromal vascularity. At its distal or upper limit, it merges with the endometrial epithelium in the lowest part of the body of the uterus. At its proximal or lower limit, it meets with the squamous epithelium at the SCJ. It covers a variable extent of the ectocervix, depending on the woman's age and reproductive, hormonal, and menopausal status.

The columnar epithelium does not form a flattened surface in the endocervical canal but is thrown into multiple longitudinal folds protruding into the lumen of the canal, giving rise to papillary projections. It forms several invaginations into the substance of the cervical stroma, resulting in the formation of endocervical crypts (sometimes referred to as endocervical glands) (Fig. 2.4). The crypts may traverse as far as 5–6 mm from the surface of the cervix. This complex architecture, consisting of mucosal folds and crypts, gives the columnar epithelium a grainy or grape-like appearance on visual inspection.

A localized overgrowth of the endocervical columnar epithelium may occasionally be visible as a reddish mass protruding through the external os on visual examination of the cervix. This is called a cervical polyp (Figs. 2.5 and 2.6). It usually begins as a localized enlargement of a single columnar papilla and appears as a mass as it enlarges. It is composed of a core of endocervical stroma

Fig. 2.3. Columnar epithelium of the endocervical canal.

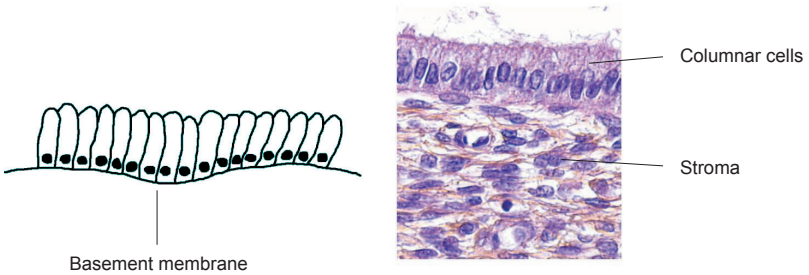


Fig. 2.4. Endocervical crypts lined with columnar epithelium.

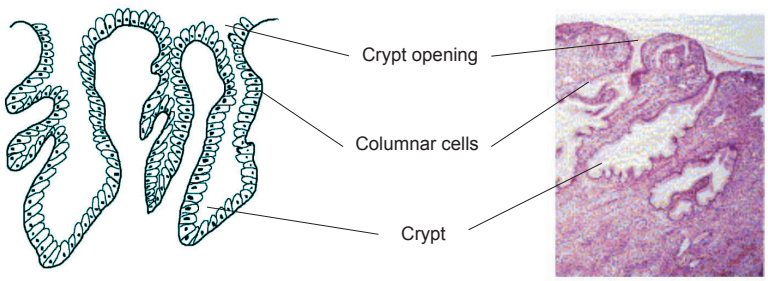


Fig. 2.5. A cervical polyp in the endocervical canal. It is protected from the vaginal environment by abundant mucus in the canal. It is lined with columnar epithelium.

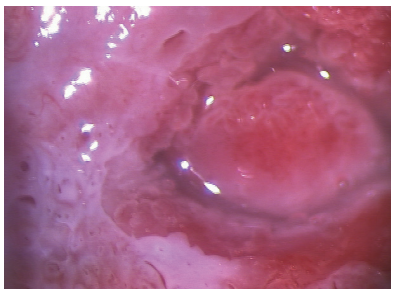


Fig. 2.6. A cervical polyp that has undergone a degree of metaplasia so that it is partially covered by squamous epithelium.

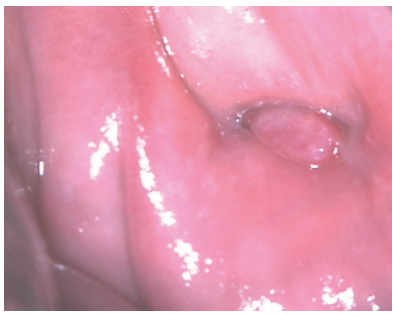
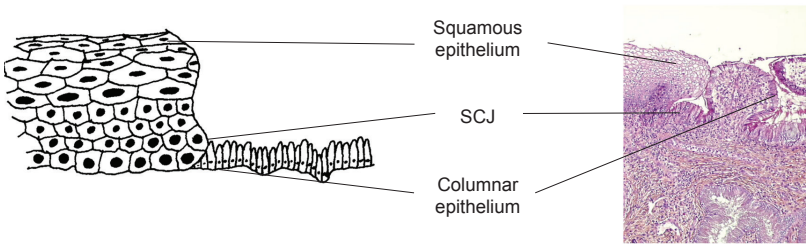


Fig. 2.7. The squamocolumnar junction (SCJ).



lined with columnar epithelium with underlying crypts. Occasionally, multiple polyps may arise from the columnar epithelium. The polyp shown in Fig. 2.5 is lined with columnar epithelium, and it is protected from the metaplastic influence of the vaginal environment by endocervical mucus. The polyp shown in Fig. 2.6 has undergone a degree of metaplasia so that it is partially covered by squamous epithelium.

Glycogenation and mitoses are absent in the columnar epithelium. Because of the lack of intracellular cytoplasmic glycogen, the columnar epithelium does not change colour after the application of Lugol's iodine or remains slightly discoloured with a thin film of iodine solution.

2.1.4 Squamocolumnar junction (SCJ)

The SCJ (Fig. 2.7) sometimes appears as a sharp line with a step, because of the difference in the height of the squamous and columnar epithelium. The location of the SCJ in relation to the external os is variable over a woman's lifetime and depends on factors such as age, hormonal status, birth trauma, use of oral contraceptives, and pregnancy.

The SCJ that is visible during childhood, during perimenarche, after puberty, and in early reproductive life is referred to as the ***original*** SCJ, because this represents the junction between the columnar epithelium and the ***original*** squamous epithelium laid down during embryogenesis in intrauterine life. During childhood and around the menarche, the original SCJ is located at, or very close to, the external os (Fig. 2.8).

After puberty and during the reproductive period, the female genital organs develop under the influence of estrogen. Thus, the cervix swells and enlarges and the endocervical canal elongates. This leads to eversion of the columnar epithelium in the lower part of the endocervical canal out onto the ectocervix (Fig. 2.9). This condition is called ectropion or ectopy, which is visible as a strikingly reddish-looking ectocervix on visual inspection (Fig. 2.10). It is sometimes called an erosion or ulcer, which are misnomers. Thus, the original SCJ is located on the ectocervix, far away from the external os (Fig. 2.9). An ectropion may begin or become much more pronounced during pregnancy.

The buffer action of the mucus covering the columnar cells is interfered with when the everted columnar epithelium of an ectropion is exposed to the acidic vaginal environment. This leads to the destruction and eventual replacement of the columnar epithelium by the

Fig. 2.8. Before puberty, the squamocolumnar junction is positioned above and very close to the external os.

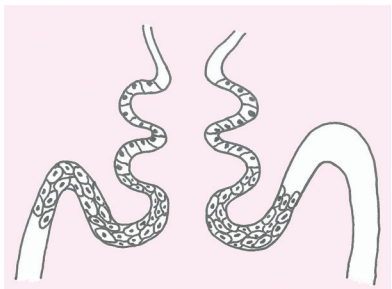


Fig. 2.9. The squamocolumnar junction after eversion of the columnar epithelium out onto the ectocervix, which occurs most commonly during adolescence and early pregnancy.

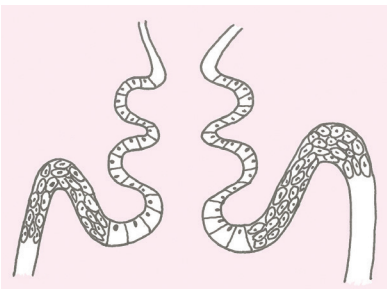
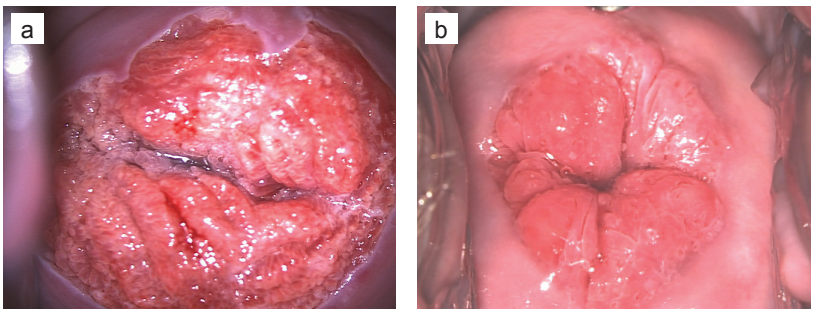


Fig. 2.10. (a) Ectropion with the original squamocolumnar junction (SCJ) situated on the ectocervix. Inside or proximal to this is an area of columnar epithelium. (b) Ectropion with the original SCJ situated on the ectocervix. Inside or proximal to this is an area of columnar epithelium. In this image, the ectropion is beginning to metaplase to squamous epithelium.



newly formed metaplastic squamous epithelium (metaplasia refers to the change or replacement of one type of epithelium by another).

The metaplastic process starts at the original SCJ and proceeds centripetally towards the external os throughout the reproductive period and finally to the menopause. It is also thought that some metaplasia may occur by ingrowth of the squamous epithelium from the squamous epithelium of the ectocervix. Thus, a new SCJ is formed between the newly formed metaplastic squamous epithelium and the columnar epithelium (Fig. 2.11).

As the woman passes from reproductive to perimenopausal life, the new SCJ moves towards the external os (Fig. 2.12). Hence, it is located at a variable distance from the external os, as a result of the progressive formation of new metaplastic squamous epithelium on the exposed areas of the columnar epithelium in the ectocervix. From the perimenopausal period and afterwards, the atrophic cervix shrinks, and consequently, the movement of the new SCJ towards the external os and into the endocervical canal is accelerated. In postmenopausal women, the new SCJ is often invisible on visual examination, because it has become entirely endocervical. The new SCJ is usually simply referred to as the SCJ.

2.2 Ectropion or ectopy

Ectropion or ectopy is defined as the presence of everted endocervical columnar epithelium on the ectocervix. It appears as a large reddish area on the ectocervix surrounding the external os (Fig. 2.10). The eversion of the columnar epithelium is usually more pronounced on the anterior and posterior lips of the ectocervix, and less so laterally. This is a normal, physiological occurrence. Occasionally, the columnar epithelium extends to the vaginal fornix. The whole mucosa, including the crypts and the supporting stroma, is displaced in ectropion. It is the region in which physiological transformation to squamous metaplasia occurs, and it is the area that is susceptible to cervical squamous disease.

2.3 Squamous metaplasia

The physiological replacement of the everted columnar epithelium by squamous epithelium is called squamous metaplasia. The vaginal environment is relatively acidic during reproductive life and during pregnancy. The acidity is thought to play a role in squamous metaplasia.

The columnar cells exposed are eventually replaced by metaplastic squamous epithelium. Initially, the irritation of exposed columnar epithelium by the acidic vaginal environment results in the appearance of subcolumnar reserve cells, and these cells proliferate, producing reserve cell hyperplasia, and eventually become metaplastic squamous epithelium.

The reserve cells multiply, differentiate, and eventually lift off the columnar epithelium (Fig. 2.13b and c). The exact origin of the reserve cells is not known.

Fig. 2.11. (a) The incomplete metaplasia that has occurred in the ectocervical columnar epithelium produces a mixed squamous/columnar epithelium in the physiological transformation zone (TZ), lying between the labels a and b in the drawing. (b) The TZ in this image is the area of epithelium (which in this case is normal) between the original squamocolumnar junction (SCJ) and the new SCJ, lying close to the endocervical canal. Gland openings can be clearly seen in a sea of normal mature squamous epithelium in this normal TZ.

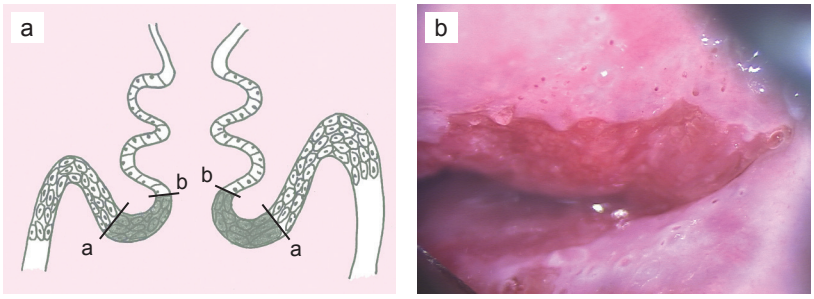
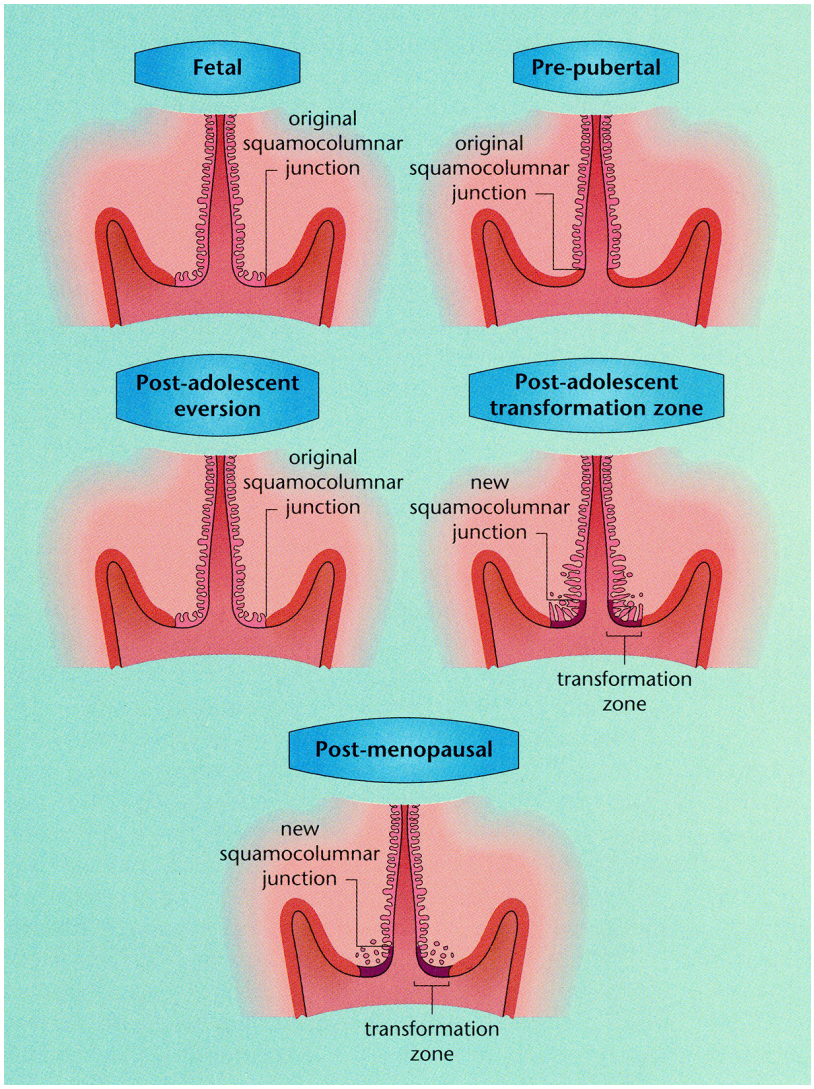


Fig. 2.12. Development of the transformation zone from fetal life to postmenopausal life.



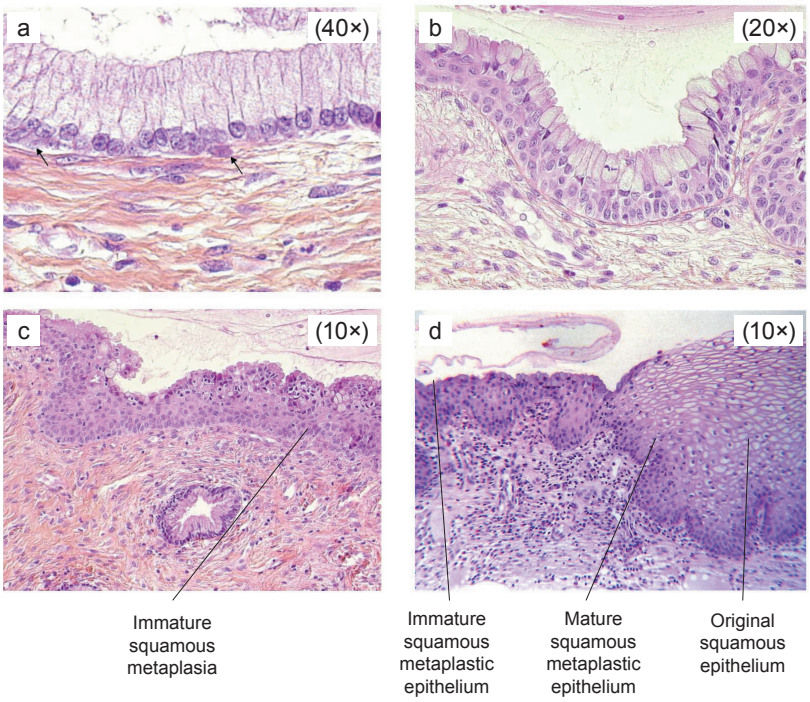
The first sign of squamous metaplasia is the appearance and proliferation of reserve cells (Fig. 2.13a and b). This is initially seen as a single layer of small, round cells with dark-staining nuclei, situated very close to the nuclei of columnar cells, which further proliferate to produce reserve cell hyperplasia (Fig. 2.13b). Morphologically, the reserve cells have a similar appearance to the basal cells of the original squamous epithelium, with round nuclei and little cytoplasm. As the metaplastic process progresses, the reserve cells proliferate and differentiate to form a thin, multicellular epithelium of immature squamous cells with no evidence of stratification (Fig. 2.13c). The term "immature squamous metaplastic epithelium" is used when there is little or no stratification in this thin, newly formed metaplastic epithelium. Immature squamous metaplastic epithelium does not produce glycogen and, hence, does not stain brown or black with Lugol's iodine. Groups of mucin-containing columnar cells may be seen embedded in the immature squamous metaplastic epithelium at this stage.

Numerous continuous and/or isolated fields or foci of immature squamous metaplasia may arise at the same time. It has been proposed that the basement membrane of the original columnar epithelium dissolves and is reformed between the proliferating and differentiating reserve cells and the cervical stroma. Squamous metaplasia usually begins at the original SCJ at the distal limit of the ectopy, but it may also occur in the columnar epithelium close to this junction or as islands scattered in the exposed columnar epithelium.

As the process continues, the immature metaplastic squamous cells differentiate into mature stratified metaplastic epithelium (Fig. 2.13d). For all practical purposes, this resembles original stratified squamous epithelium. Some residual columnar cells or vacuoles of mucus are seen in the mature squamous metaplastic epithelium, which contains glycogen from the intermediate cell layer onward. Thus, the more mature the metaplasia is, the more it will stain brown or black after the application of Lugol's iodine (Fig. 2.14).

Inclusion cysts, also called nabothian follicles or nabothian cysts, may be observed in the TZ in mature metaplastic squamous epithelium (Fig. 2.15). Nabothian cysts are retention cysts that develop as a result of the occlusion of an endocervical crypt opening or outlet by the overlying metaplastic squamous epithelium. The buried columnar epithelium continues to secrete mucus, which eventually fills and distends the cyst. The columnar epithelium in the wall of the cyst is flattened and ultimately destroyed by the pressure of the mucus in it. The outlets of the crypts of columnar epithelium, not yet covered by the metaplastic epithelium,

Fig. 2.13. Development of squamous metaplastic epithelium. (a) The arrows indicate the subcolumnar reserve cells. (b) The reserve cells proliferate. (c) The reserve cells further proliferate and differentiate. (d) Mature squamous epithelium, indistinguishable from native squamous epithelium.

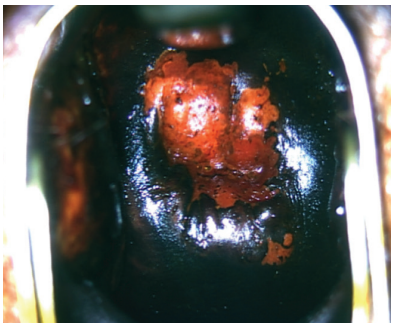


remain as persistent crypt openings (Fig. 2.11b). The farthest extent of the metaplastic epithelium onto the ectocervix can be best judged by the location of the crypt opening farthest away from the SCJ. Fig. 2.16 is a diagrammatic representation of normal TZ tissue components.

Squamous metaplasia is an irreversible process; the transformed epithelium (now squamous in character) cannot revert to columnar epithelium. The metaplastic process in the cervix is sometimes referred to as indirect metaplasia, because the columnar cells do not transform into squamous cells but are replaced by the proliferating subcolumnar cuboidal reserve cells. Squamous metaplasia may progress at varying rates in different areas of the same cervix, and hence many areas of widely differing maturity may be seen in the metaplastic squamous epithelium with or without islands of columnar epithelium. The metaplastic epithelium adjacent to the SCJ is composed of immature metaplasia, and the mature metaplastic epithelium is found near the original SCJ.

Further development of the newly formed immature metaplastic epithelium may take two directions. In the vast majority of women, it develops into mature squamous metaplastic epithelium, which is similar to the normal glycogen-containing original squamous epithelium for all practical purposes. In a very small minority of women, an atypical, dysplastic epithelium may develop. Certain oncogenic HPV types may infect the immature basal squamous metaplastic cells and, rarely, turn them into precancerous cells. The uncontrolled proliferation and expansion of these atypical cells may lead to the formation of an abnormal dysplastic epithelium, which may regress to normal, persist as dysplasia, or progress to invasive cancer after several years, depending on whether the HPV infection is allowed to become a transforming infection (see Chapter 4).

Fig. 2.14. Uptake of Lugol's iodine in the cervix of a premenopausal woman.



2.4 Transformation zone (TZ)

The TZ is that area of epithelium that lies between the native and unaffected columnar epithelium of the endocervical canal and the native squamous epithelium deriving from the vaginal and ectocervical squamous epithelium (Fig. 2.17).

The eversion of endocervical epithelium from inside the endocervical canal onto the outside of the cervix, i.e. the ectocervix, takes place at variable times and rates, but

Fig. 2.15. A nabothian follicle is seen at the 7 o'clock position in this image of a normal transformation zone. There is a little light reflection seen at its tip.

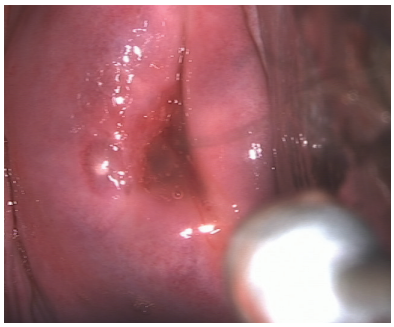


Fig. 2.16. Epithelial components of the transformation zone.

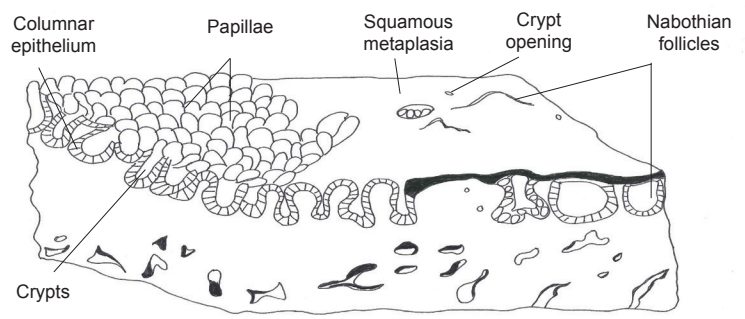
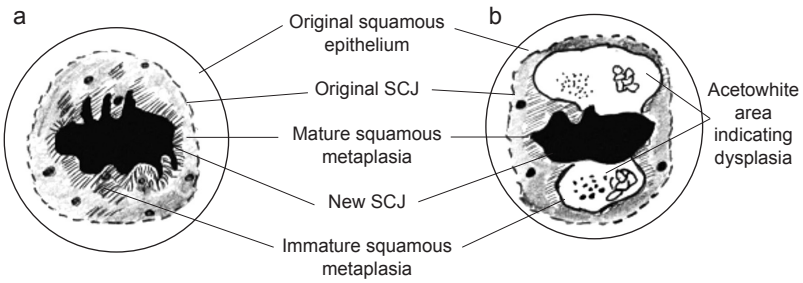


Fig. 2.17. (a) Schematic diagram of the normal transformation zone. (b) Schematic diagram of the abnormal or atypical transformation zone harbouring dysplasia. SCJ, squamocolumnar junction.



generally speaking it occurs during adolescence and during a first pregnancy (Fig. 2.12). As a result, the columnar epithelium on the ectocervix is exposed to the relatively acidic vaginal environment and undergoes squamous metaplasia, producing the physiological TZ, as described above. This process, when complete, probably results in protection from HPV infection, but during this process the dynamic TZ is susceptible to HPV infection, whereby it may infect the basal layers of the epithelium in the TZ and, in a small proportion of cases, initiate the development of CIN (Fig. 2.18). Why this dysplastic epithelium develops in some women and not in others is currently uncertain, but it is associated with oncogenic HPV types in 99% of cases. Most people will be infected with oncogenic HPV types early on in their normal sexual life, but the great majority will clear the infection without consequence (see Chapter 4). When the TZ becomes abnormal or atypical, it is called the atypical TZ. The components of the TZ are also depicted in Fig. 2.16.

The TZ varies in its size and its precise position on the cervix, and it may lie partially or completely in the endocervical canal. Where it is and how visible it is determine its type (see Annex 1). In most women of reproductive age, the TZ is of type 1, and the magnified and light-illuminated view afforded by colposcopy will usually present the colposcopist with a clear view of all the components of the TZ as well as the native squamous epithelium and the native and untransformed columnar epithelium of the endocervical canal (Fig. 2.16). Occasionally (in about 4% of cases), the examination will reveal a so-called original or congenital TZ, as depicted in Fig. 2.19.

2.4.1 Congenital transformation zone

During early embryonic life, the cuboidal epithelium of the vaginal tube is replaced by the squamous epithelium, which begins at the caudal end of the dorsal urogenital sinus. This process is completed well before birth, and the entire length of the vagina and the ectocervix is normally covered by squamous epithelium. This process proceeds very rapidly along the lateral walls, and later in the anterior and posterior vaginal walls. If the epithelialization proceeds normally, the original SCJ will be located at the external os at birth. If this process is arrested for some reason, or incomplete, the original

Fig. 2.18. Effect of infection with oncogenic HPV on immature squamous epithelium.

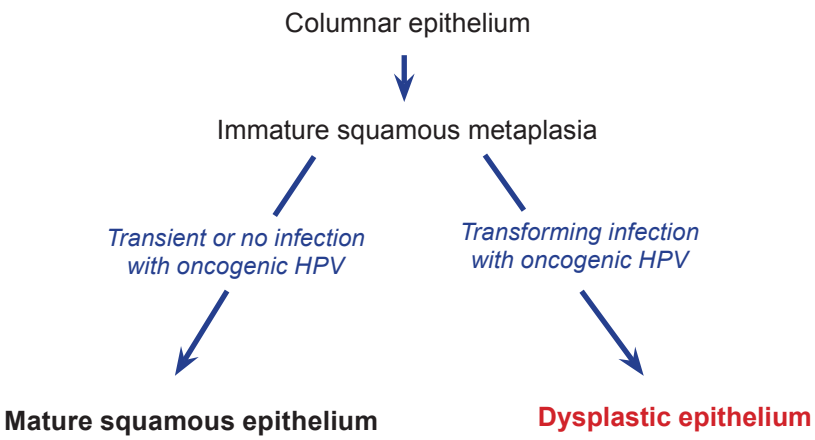
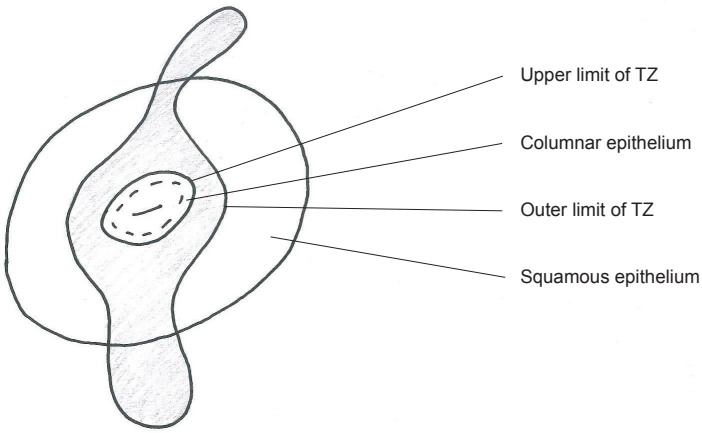


Fig. 2.19. The typical congenital or original transformation zone (TZ).



SCJ will be located distal to the external os or may rarely be located on the vaginal walls, particularly involving the anterior and posterior fornices. The cuboidal epithelium remaining here will undergo squamous metaplasia. This late conversion to squamous epithelium in the anterior and posterior vaginal walls, as well as the ectocervix, results in the formation of the congenital TZ. Thus, it is a variant of intrauterine squamous metaplasia in which differentiation of the squamous epithelium is not fully completed because of an interference with normal maturation. Excessive maturation is seen on the surface (as evidenced by keratinization), with delayed, incomplete maturation in deeper layers. Clinically, it may be seen as an extensive whitish-grey, hyperkeratotic area extending from the anterior and posterior lips of the cervix to the vaginal fornices. Gradual maturation of the epithelium may occur over several years. This type of TZ is seen in fewer than 5% of women and is a variant of the normal TZ.

Key points

- The cervix enters the vagina anteriorly or posteriorly depending on its version.
- The position of the original squamocolumnar junction moves during periods of relatively high circulating estrogen levels.
- The exposed everted columnar epithelium will metaplase over time to become mature glycogen-laden squamous epithelium, which stains iodine-positive (Schiller test-negative).
- The transformation zone is where squamous cervical cancer originates.
- The transformation zone is an area of partially squamous, partially columnar, and partially metaplastic epithelium, which lies between the original and new squamocolumnar junctions.

CHAPTER 3.

Squamous intraepithelial lesions: cytology–histology correlation

This chapter discusses the natural history of cervical precancer, HPV and oncogenesis, cytology nomenclature, and the cytological and histological recognition of cervical precancer.

3.1 Current understanding of the natural history of cervical precancer

Cervical cancer has a long precursor stage. The cervix is accessible and sheds exfoliated cells easily, and cytological examination of these cells reveals precancerous changes that are easily eradicated. The essential causative agent of cervical cancer is the presence of high-risk HPV, which is easily detectable. Cervical cancer is a completely preventable disease. This is quite apart from the availability of an effective vaccination. The disease should not exist.

3.2 Historical context

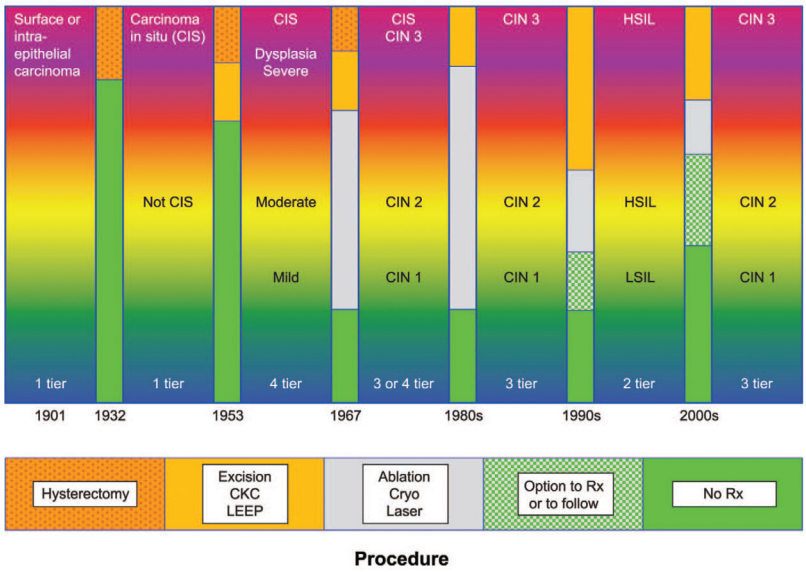
The precursor phase of the natural history of cervical cancer is characterized by cellular changes within the epithelial lining of the cervix; in other words, the abnormality is entirely intraepithelial. John Williams first described intraepithelial cellular changes in tissue adjacent to invasive cancer more than 125 years ago (Williams, 1888). During the early decades of the 20th century, the concept of intraepithelial dysplasia gained acceptance (Cullen, 1900; Rubin, 1910). It implied cancerous-looking cells confined to the epithelium above the basement membrane and led to the term “carcinoma in situ” (Broders, 1932), which was defined as full-thickness cellular changes that looked morphologically similar to undifferentiated invasive carcinomatous cells but were confined to the epithelium. The term “dysplasia” was coined about 20 years later by Reagan and Hicks (1953), and dysplasia was categorized as being mild, moderate, or severe depending on the proportion of the epithelial layers involved in the dysplastic process. Carcinoma in situ was considered to have a greater degree of abnormality and to be the final precancerous state. The term “koilocyte” (halo or vacuolated cytoplasm or empty space cytoplasm) was coined by Koss and Durfee (1956). Meisels and Fortin (1976) first recognized these cells as being infected with HPV.

Richart (1968) introduced the concept of a continuum and subdivided the spectrum of abnormality into three categories, called CIN grades 1 (mild dysplasia), 2 (moderate dysplasia), and 3 (severe dysplasia). In this classification, carcinoma

in situ was combined with severe dysplasia. The cytological classification was similar in that mild, moderate, and severe dyskaryosis were suggestive (but not diagnostic) of CIN1, 2, and 3, respectively. The relative ease of treatment afforded by outpatient therapy, which had begun to replace hysterectomy and cold-knife conization in the 1970s and 1980s, lowered the threshold for treatment of cervical lesions. In an attempt to simplify the classification and because it had become clear that minor-grade lesions did not often progress to cancer, Richart (1990) proposed a two-tier classification system. High-grade lesions were thought to be much more likely to be genuinely precancerous. Low-grade lesions were considered to be transient and rarely precancerous. Many low-grade lesions were associated with koilocytosis and recognized as being HPV-related. However, this classification system was not universally used. Also, moderate abnormalities, some of which were undoubtedly low-grade in nature, were included in the high-grade category and perhaps treated too readily. The different classifications are represented in the diagram in Fig. 3.1, with treatment patterns included below. The traditional "screen, diagnose, and treat" pathway (Fig. 3.2) worked reasonably well when the threshold for referral to colposcopy was set high.

The concept of a continuum persisted until relatively recently. A greater understanding of the biology of oncogenic HPV and its different effects in squamous epithelium of the lower genital tract has led to a different concept. It now seems clear that there are two different types of HPV infection. The first type is an innocent and transient infection, which may produce mild or low-grade lesions that are recognizable cytologically, colposcopically, or histologically.

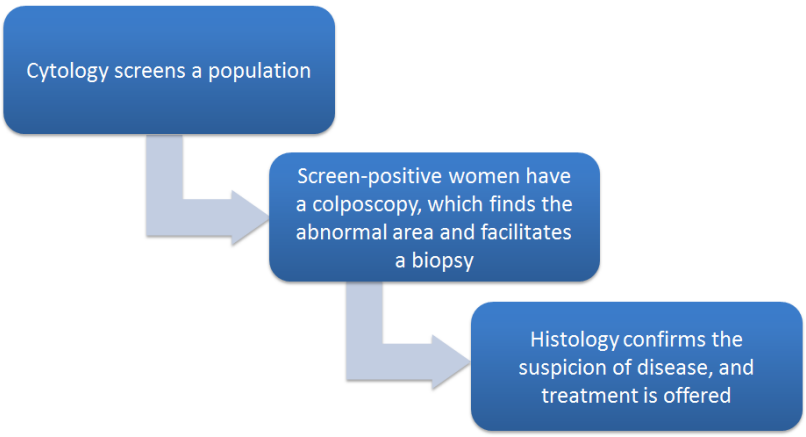
Fig. 3.1. Changing terminology and treatment trends for cervical precancer over the past century. CKC, cold-knife conization; Cryo, cryotherapy; LEEP, loop electrosurgical excision procedure; Rx, treatment.



These lesions have limited, if any, precancerous potential for progression to cancer. This type of infection is called a productive infection. The key step in the pathogenesis of HPV-linked cancers is the activation of the viral oncogenes E6 and E7 in the basal and parabasal cells of the infected epithelium (Bergeron et al., 2015; Doorbar et al., 2012; Duensing and Münger, 2004). If these viral genes are expressed in basal or parabasal cells, they trigger chromosomal instability and major numerical and structural alterations of the host cell chromosomes. This leads to uneven distribution of the overall DNA content (aneuploidy) and is reflected by shifts of the nuclear staining pattern (the staining intensity). This type of infection is more readily recognized cytologically, colposcopically, and histologically and is called a transforming infection (see Chapter 4).

Sometimes moderate dyskaryosis (at cytology) or moderate

Fig. 3.2. Traditional process of screening test, colposcopic assessment, histological diagnosis, and treatment.



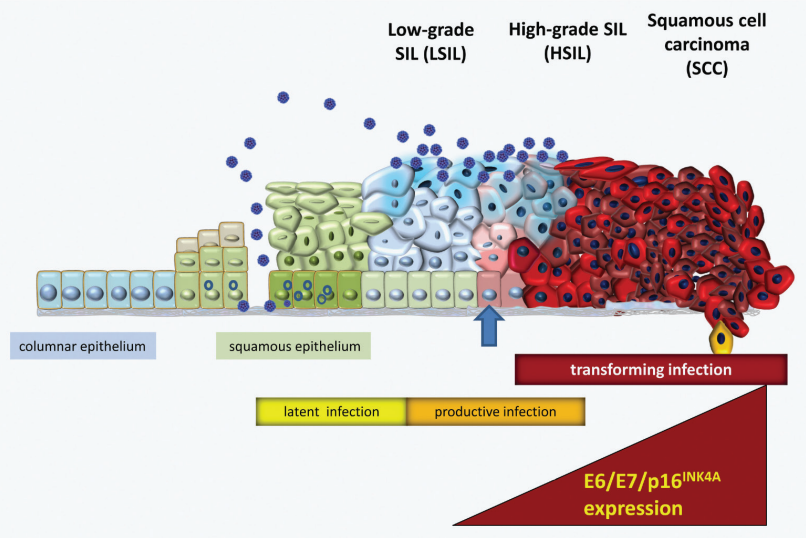
dysplasia (at histology) may contain both types of infection, and these are difficult to distinguish using cytology or histology. Fortunately, developments in molecular biology have led to specific biomarkers of cell biology that can discriminate between these types where doubt exists (see Chapter 4).

3.3 HPV and the genesis of cervical cancer

Several different risk factors have been implicated for cervical cancer and precancer. These include smoking, early age at first intercourse, nutritional deficiency, chlamydial infection, multiple sexual partners, multiple pregnancies, and long-term use of oral contraceptives (Bosch et al., 1995; Franco et al., 1999; IARC, 2007, Schiffman et al., 1996; Walboomers et al., 1999). However, the fundamental and essential causative agent is the persistence of oncogenic HPV in the epithelium of the TZ and/or adjacent glandular epithelium. The relationship between oncogenic HPV and cervical precancer appears, at first, paradoxical. Cervical cancer is always associated with oncogenic HPV, but oncogenic HPV is a normal and usually transient infection that most healthy sexually active women will encounter in early reproductive life. The current thinking is that the oncogenic HPV gains entry to the cervical epithelium at the new SCJ, possibly associated with minor abrasions, and that this allows the virus to access reserve cells underneath the single layer of columnar epithelium (Fig. 3.3).

Most women will be infected with oncogenic HPV, and the great majority will clear the infection without any residual harm or increased risk of cervical cancer. In a small percentage of women, the infection persists, and in a small proportion of those, it becomes integrated into the epithelial cell nuclei and changes from a latent to a transforming infection. It is in those cases that the risk of progression is high. It is not known what distinguishes those cases in which the virus becomes integrated and transforming from those in which the infection is transient and harmless. The relationship between oncogenic HPV infection and the risk of progression or clearance is discussed in Chapter 4. The crucial step is that of the HPV infection becoming a transforming infection.

Fig. 3.3. Different HPV infection stages.



3.4 Cytology nomenclature

To this day, there are several different cytological classifications for cervical precancer. The German classification is used in Germany, Austria, and some countries in eastern Europe. The United Kingdom has its own classification, as do Australia and New Zealand. Perhaps the most widely used classification is the Bethesda terminology system, first introduced in 1988 by the United States National Cancer Institute (Solomon, 1989). It embraced the concept of a two-tier gradation and has undergone several revisions over the past 25 years. These revisions reflect the changing understanding of risk associated with different cytological and histological reporting and a greater understanding of the role of oncogenic HPV. The United Kingdom classification now reflects the Bethesda two-tier classification. To help clinicians manage their patients with different grades of abnormality, the ASCCP developed a series of clinical guidelines linked to the Bethesda classification (Wright et al., 2003). In the United Kingdom, the NHS Cervical Screening Programme (NHS, 2010) produced an evidence-based guidelines document, which linked management to the degree of cytological abnormality and other relevant case characteristics (e.g. HPV test result, age, and smoking history). It has recently been updated (NHS, 2016). Fig. 3.1 attempts to relate some of the previous cytology nomenclatures to the current Bethesda classification, which is probably the most widely used system today.

There has always been an interdisciplinary dependency in management of cervical precancer. Traditionally, this has been using

cytology to screen, using colposcopy to assess and direct biopsy, and using histology to confirm the diagnosis (Fig. 3.2). In this idealized scenario, the cytology screening test identified cases that may or may not have genuine precancer, colposcopy was able to recognize or rule out the lesion, and a colposcopically directed biopsy facilitated definitive histological proof of disease before treatment was advised. But all three of these disciplines are subjective in nature. Until recently, histology was considered the gold standard and HSIL was considered the threshold at which treatment was necessary. It is now clear that morphological assessment at histology is also less than perfect, in particular the determination of disease severity when morphological or histopathological examination reports HSIL-CIN2. A paper from the Lower Anogenital Squamous Terminology (LAST) Project (Darragh et al., 2012) finally confirmed the relative subjectivity of histopathology, especially in the middle grade of CIN2. The WHO 2014 histology terminology (Kurman et al., 2014) proposed a two-tier classification, HSIL and LSIL, with the help of biomarkers to differentiate the difficult or equivocal cases.

3.5 Cytological and histological recognition of cervical precancer

3.5.1 Normal cervical epithelium

Cytological examination of exfoliated cells from the normal ectocervical squamous epithelium will reveal mostly superficial cells; the nuclei are small, are not hyperchromatic, and have normal density and shape with normal chromatin patterns. Crucially, the nuclear–cytoplasmic ratio is low, and mitotic figures are only occasionally seen in the basal layers (Fig. 3.4a).

Histological examination of a tissue biopsy of normal squamous epithelium will reveal normally stratified epithelium with regular maturation and few mitotic figures in the basal layers. As with cytology, there will be normal nuclear–cytoplasmic ratios and the nuclei will be morphologically normal (Fig. 3.4b and Fig. 2.2).

3.5.2 LSIL (HPV infection; CIN1; mild dyskaryosis)

3.5.2.1 Cytology

The cytological recognition of abnormality is based on the finding of nuclear enlargement and variation in the size and shape of abnormal cells. An increased intensity of staining with irregular chromatin patterns is another common feature of abnormality. These abnormalities in the superficial and intermediate cells are koilocytosis, typical of a productive infection (LSIL). Abnormal nuclei and other cell changes in parabasal and basal cells are typical of a transforming infection (HSIL). In the case of an LSIL, as in Fig. 3.5a, there is a productive viral infection, and cytology will reveal enlarged nuclei with vacuolated cytoplasm in superficial and intermediate cells.

3.5.2.2 Histology

Histological determination of abnormality is essentially recognition of abnormal cellular proliferation. It is based on the morphological assessment of cells in the epithelium, the architecture of the cellular layers, and the degree of maturation and cellular differentiation. The relative proportion of the epithelium that is involved with abnormality, the degree of maturation, and the persistence of mitotic figures throughout the epithelium are the usual parameters used to grade the abnormality. Histological examination of LSIL will reveal

Fig. 3.4. (a) Normal cytology preparation; intermediate cells are indicated with arrows. (b) Normal histological section of squamous epithelium.

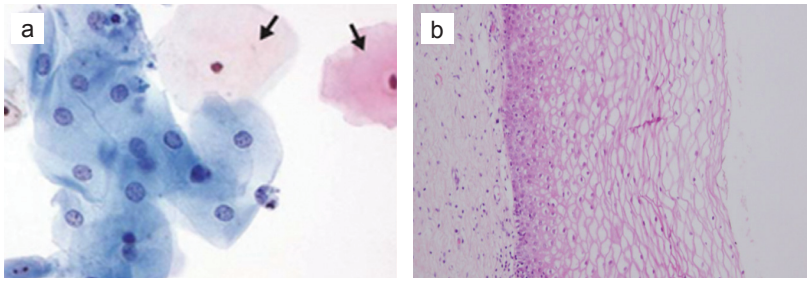
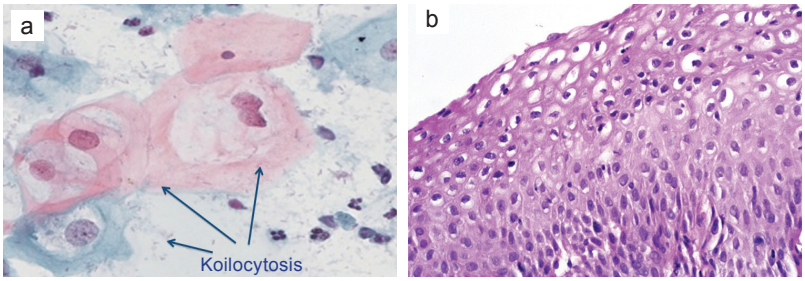


Fig. 3.5. (a) Cytology slide of LSIL. (b) Histological section of LSIL.



koilocytosis in the superficial layers and even part of the intermediate layer, but the undifferentiated cells will be limited to the lower third of the epithelium (Fig. 3.5b).

3.5.3 HSIL (CIN2, CIN3; moderate dyskaryosis, severe dyskaryosis)

3.5.3.1 Cytology

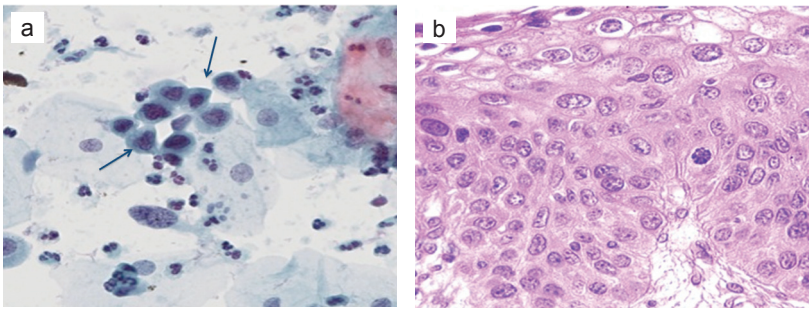
With a severely abnormal CIN3 lesion, cytology will report the diagnosis of HSIL. Cytology, by itself, cannot distinguish between CIN2 and CIN3. The changes seen at cytology will usually include a definite increase in the nuclear–cytoplasmic ratio as well as abnormal nuclear size and density and altered chromatin patterns of basal or parabasal cells (Fig. 3.6a).

3.5.3.2 Histology

At histological examination of a clear case of CIN3, the great majority of pathologists will agree, because the morphological cellular and architecture changes in the epithelium are relatively unequivocal and are disordered throughout all cellular layers (Fig. 3.6b). Cytological examination of an HSIL cannot be as precise, and a cytologist reporting HSIL will probably describe basal cells that have risen to the intermediate or superficial layers, which are abnormal with enlarged nuclei and reduced cytoplasm, as in Fig. 3.6b.

However, the histological diagnosis is not robust in the middle grade, and the category of CIN2 or HSIL-IN2 contains some cases where the virus is transforming and the risk of progression is real and some cases where the virus is proliferative and not transforming and the risk of progression to cancer is very small. Morphological examination of tissue biopsies from CIN2 cases is not reliable, and pathologists will often not agree. Some will call the case CIN3, and some will call it CIN1. In this situation, molecular biology tests can resolve the disparity. To appreciate how molecular biology tests can help, it is necessary to understand a little about the biology of oncogenic HPV and its effect on squamous epithelium (see Chapter 4).

Fig. 3.6. (a) Cytology slide of HSIL. The arrows indicate abnormal squamous basal cells. (b) Histological section of HSIL-CIN3. Cellular abnormality prevails throughout the full thickness of the epithelium. There is an increased nuclear–cytoplasmic ratio, anisocytosis, and a loss of nuclear polarity. Several mitoses are present throughout the upper two thirds of the epithelium.



Key points

- Oncogenic (or high-risk) HPV is an extremely common infection in healthy sexually active women of reproductive age.
- Cervical cancer is a very rare outcome of oncogenic HPV infection but does not occur in its absence. Up to 80% of women will harbour oncogenic HPV during their reproductive life, but only 1 in 10 000 or fewer will develop cervical cancer.
- A positive high-risk HPV test does not imply cancer, precancer, or even an active infection.
- Cytological, colposcopic, and histological recognition of cervical cancer precursor states are all imperfect, because of their innate subjectivity.

CHAPTER 4.

The effect of oncogenic HPV on transformation zone epithelium

All squamous cervical cancer (and probably all cervical adenocarcinoma) is associated with oncogenic HPV, and the absence of oncogenic HPV means that there is virtually zero risk of developing cervical cancer or genuine precancer during the next 5 years or more Oncogenic HPV tests will reveal the presence or absence of viral DNA in a sample taken from the cervical epithelium or adjacent epithelial surfaces. But the presence of oncogenic HPV does not always mean that an active infection is present. The virus may be latent or may even be present at the epithelial surface but not active or productive. Even when an infection is present, this does not, by itself, mean that disease or pre-disease is likely. An infection may be transient and therefore harmless, and this is the usual outcome in young women. An infection may also be highly productive and yet confer no increased risk of cervical precancer. Many LSILs are highly productive and have very high viral load counts but confer minimal risk of progression to high-grade lesions and, thereafter, cancer. Fig. 3.3 illustrates the difference between latent, productive, and transforming infections. A positive oncogenic HPV test does not indicate whether the infection is latent or productive or whether it is the much rarer transforming infection.

Fortunately, an increasing number of molecular biological markers have enabled a better understanding of the pathway that progressive lesions take (Bergeron et al., 2010; Doorbar, 2006; Doorbar et al., 2012). Different measurable viral or cellular products are produced at different stages of oncogenic HPV infection, depending on whether it is a productive infection or a transforming infection.

The secondary biomarkers produced at different biological stages of viral activity are proteins that are viral or cellular gene products, and these proteins are measurable in cervical samples cytologically and/or histologically. In summary, oncogenic HPV tests determine the presence or absence of virus particles, but protein biomarkers determine the virus activity, and it is this activity that reflects the risk of progression to cervical cancer. These markers include HPV proteins, surrogate markers (e.g. p16), and methylation patterns. Perhaps the best way to understand the relative value of cytology, histology, and these biomarkers in the recognition and management of cervical precancer is by looking at cytological, histological, and biomarker images of normality, LSIL, and HSIL.

4.1 Biomarker assessment

4.1.1 Normal viral cellular pathway

In a normal but HPV-infected cell, the viral infection expresses proteins in a defined order and in different layers at different stages of the normal cell life-cycle (Fig. 4.1).

The E6 and E7 viral proteins are expressed in the lower layers of the epithelium, and they reflect an initiation of the cell cycle. The basal cells proliferate, and viral copy numbers increase. The E6 and E7 proteins are expressed at very low levels, but fortunately surrogate markers, such as MCM and Ki-67, are identifiable, and they faithfully reflect the presence of E6 and E7. Also, some true viral proteins are measurable, for example E4. This protein is not part of the virus particle but is present in very high quantities during the normal cell cycle. It is a marker for cell-cycle completion.

4.1.2 LSIL

With an LSIL, there is early deregulation of the cell cycle. There are increased levels of E6 and E7 in the basal and parabasal layers, and therefore MCM is present (Fig. 4.2).

Also, the biomarker p16 begins to appear in the lower epithelial layers, for two reasons: because of E6 and E7 deregulation, but also because p16 is a marker for oncogenic HPV activity, especially activity of HPV type 16. It is not necessary to use the biomarker p16 when there is clear cytological and histological evidence of LSIL, because the morphological criteria for diagnosis are clear and most cytologists and pathologists will agree.

Fig. 4.1. Productive HPV infection; normal viral life-cycle. Expression of E6 and E7 is recognized by the presence of surrogate markers, such as MCM. E4 is present and detectable mostly in the upper layers of the epithelium.

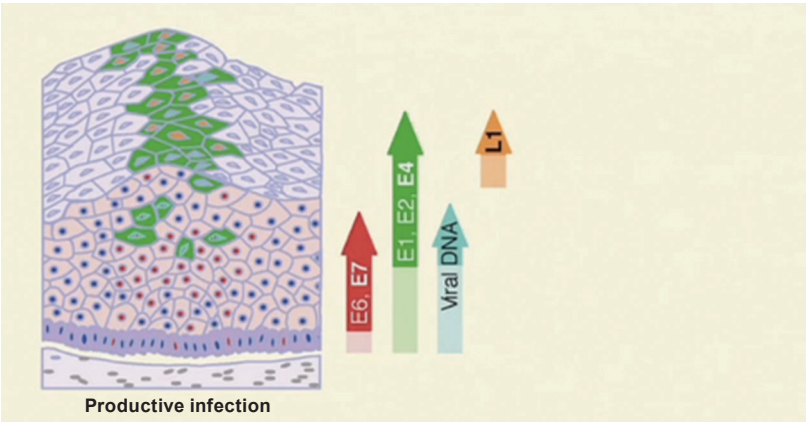
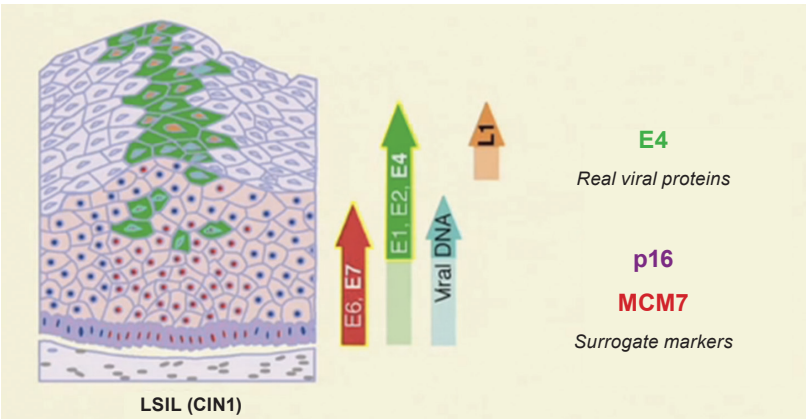


Fig. 4.2. Biomarker expression in a low-grade lesion.



4.1.3 HSIL-CIN3

In a case of HSIL-CIN3, cellular activity is completely disordered and the abnormal basal and parabasal cells get pushed up through the cellular layers. At the same time, E4 (which reflects cell-cycle completion) appears higher and higher up the cellular layers and eventually disappears. p16 will be present and detectable in the histological section (Fig. 4.3). This is because p16 is overexpressed in high-grade lesions, because the normal regulatory inhibition of p16 is diminished. With CIN3, the morphological patterns are again relatively clear and interobserver variation is uncommon, so it is not necessary to use p16 because the morphological changes are clear and almost all pathologists will agree on the grade.

4.1.4 HSIL-CIN2

Biomarkers are particularly helpful in the evaluation of a case reported as being HSIL that histologically appears to be a moderate abnormality of CIN2. The pattern of MCM, p16, and E4 can discriminate between whether the CIN2 is actually just a proliferative infection and is destined to behave like a CIN1 lesion or whether it is associated with a transforming infection and will behave like a CIN3 lesion (Fig. 4.4). Here, both E4 and p16 will discriminate between those lesions that have a transforming infection and are CIN3 and those that do not and may be classified

Fig. 4.3. Biomarker expression in CIN3.

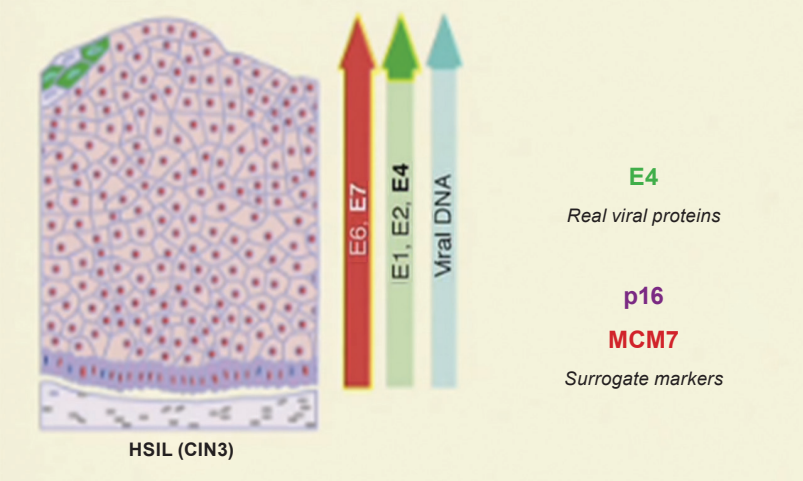
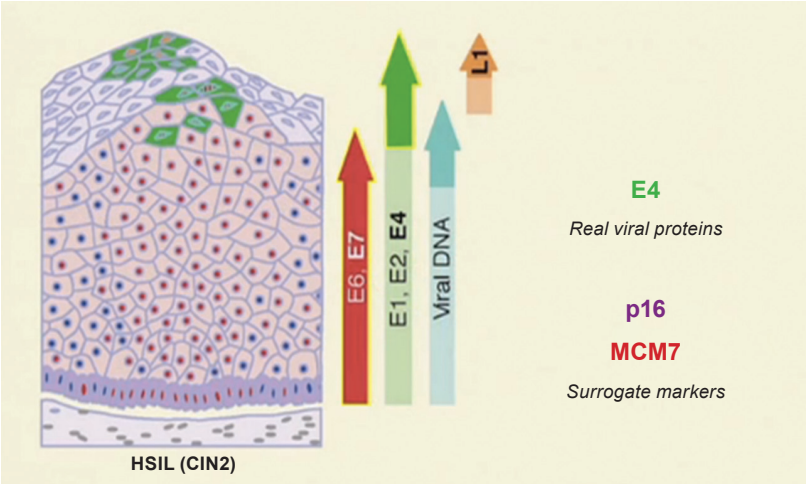


Fig. 4.4. Biomarker expression in an HSIL case that is CIN2.



as CIN1. E4 will be absent and p16 will be strongly present throughout the full thickness of the epithelium in those HSILs that are actually CIN3 but that morphologically may be considered to be CIN2. Fig. 4.5 illustrates the markers of different oncogenic HPV infection states.

4.2 Clinical utility of biomarkers

4.2.1 Biomarkers in histology

In the recent consensus report of the LAST Project (Darragh et al., 2012), the authors read more than 2000 articles dealing with molecular markers and culled this to 72 publications that satisfied pre-specified quality criteria. Of these, there were 53 that dealt with p16, and from these 53 studies consensus recommendations were derived. p16 is the only biomarker that the consensus document considered had sufficient evidence to recommend its routine use in histological specimens in defined cases. These recommendations are summarized in Table 4.1.

Fig. 4.6 shows an example of how p16 can aid in the evaluation of a lesion perhaps considered to be CIN2, which is best interpreted as HSIL. Fig. 4.7 shows an example of a histological section where p16 influenced the diagnosis as LSIL, which might otherwise have been considered HSIL.

4.2.2 Biomarkers in cytology

p16 on its own is not currently considered to be a useful discriminator in cytology. As described above, its value is in histological examination of specific equivocal diagnoses where the degree of staining and where the stain can be seen throughout the cell layers of the epithelium. p16 is expressed in about 40% of low-grade lesion smears in the lower epithelial levels. In cytology, the cellular architecture and site of staining cannot be recognized, and p16 is therefore less valuable.

Ki-67 is a proliferative marker and is expressed in proliferating cells within the nucleus of parabasal cells of normal epithelium. When Ki-67 is overexpressed, it indicates a proliferative cellular state.

The combination of p16 and Ki-67 (known as dual testing) is useful in cytology (Fig. 4.8). The recent international multicentre study of the utility of p16 and Ki-67 in cytology has produced good evidence that this combination will confirm that

Table 4.1. Recommendations for biomarkers in HPV-associated lower anogenital squamous lesions

Recommendation	Comment
1. p16 IHC is *recommended* when the H&E morphological differential diagnosis is between precancer (CIN2 or CIN3) and a mimic of precancer (e.g. processes known to be not related to neoplastic risk, such as immature squamous metaplasia, atrophy, reparative epithelial changes, tangential cutting).	Strong and diffuse block-positive p16 results support a categorization of precancerous disease.
2. If the pathologist is entertaining an H&E morphological interpretation of CIN2 (under the old terminology, which is a biologically equivocal lesion falling between the morphological changes of HPV infection [low-grade lesion] and precancer), p16 IHC is *recommended* to help clarify the situation. Strong and diffuse block-positive p16 results support a categorization of precancer. Negative or non-block-positive staining strongly favours an interpretation of low-grade disease or a non-HPV-associated pathology.	
3. p16 is *recommended* for use as an adjudication tool for cases in which there is a professional disagreement in histological specimen interpretation, with the caveat that the differential diagnosis includes a precancerous lesion (CIN2 or CIN3).	
4. WG4 *recommends against* the use of p16 IHC as a routine adjunct to histological assessment of biopsy specimens with morphological interpretations of negative, CIN1, and CIN3.	
a. SPECIAL CIRCUMSTANCE: p16 IHC is recommended as an adjunct to morphological assessment for biopsy specimens interpreted as ≤ CIN1 that are at high risk for missed high-grade disease, which is defined as a prior cytological interpretation of HSIL, ASC-H, ASCUS/HPV-16+, or AGC (NOS).	Any identified p16-positive area must meet H&E morphological criteria for a high-grade lesion to be reinterpreted as such.

AGC (NOS), atypical glandular cells – not otherwise specified; ASC-H, atypical squamous cells, cannot exclude HSIL; ASCUS, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; H&E, haematoxylin and eosin; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; IHC, immunohistochemistry; WG4, Working Group 4.

Fig. 4.5. High-risk HPV infection and its possible consequences. (a) The detection of HPV DNA in a tissue biopsy may indicate productive (LSIL) or abortive (HSIL) infection, the presence of virus particles at the epithelial surface without infection (e.g. from recent transmission), or a latent or silent infection. Infection requires the entry of HPV virions into the mitotically active epithelial cells of the basal layer, which in stratified epithelium is thought to require a microwound. In the columnar cell layers, infection is thought to be facilitated by the proximity of the target cell to the epithelial surface, which may allow the virus to access a cell type that is unable to support the full productive life-cycle (right). The significance of infection of different cell types remains to be properly assessed. (b) After infection, shown in (a), expression from the viral genome can sometimes be suppressed (e.g. by genome methylation), leading to a "silent" infection in which the viral genomes are retained in the basal layer without apparent disease. Infection may alternatively lead to an ordered pattern of viral gene expression, leading to virus synthesis and release from the upper epithelial layers (productive infection or LSIL [CIN1]) or to deregulated viral gene expression and high-grade neoplasia (HSIL [CIN2/CIN3]). Persistent high-grade disease is associated with an increasing risk of genome integration into the host cell chromosome and progression to cancer. Cells in cycle are indicated by the presence of red nuclei. Cells expressing E4 are shown in green, and those expressing L1 are shown in yellow. The brown shading identifies all the cells (differentiated and undifferentiated) that contain viral genomes. (c) In most cases, HPV infections are resolved as a result of a cell-mediated immune response (left). This may lead to viral clearance or to viral latency and the persistence of viral episomes in the epithelial basal layer without life-cycle completion. Viral gene expression patterns during latency are not well characterized. Persistent deregulated gene expression, as occurs in CIN3 and after viral genome integration, can lead to the accumulation of secondary genetic changes in the infected host cell and development of cancer. This is facilitated by overexpression of the high-risk E6 and E7 proteins. Cells in cycle are shown by red nuclei. Brown shading in the immune latency state indicates cells harbouring viral episomes. In cervical cancer, the viral genome is often integrated, with loss of expression of full-length E1, E2, E4, and E5 and the L1 and L2 capsid proteins, and with deregulated expression of E6 and E7.

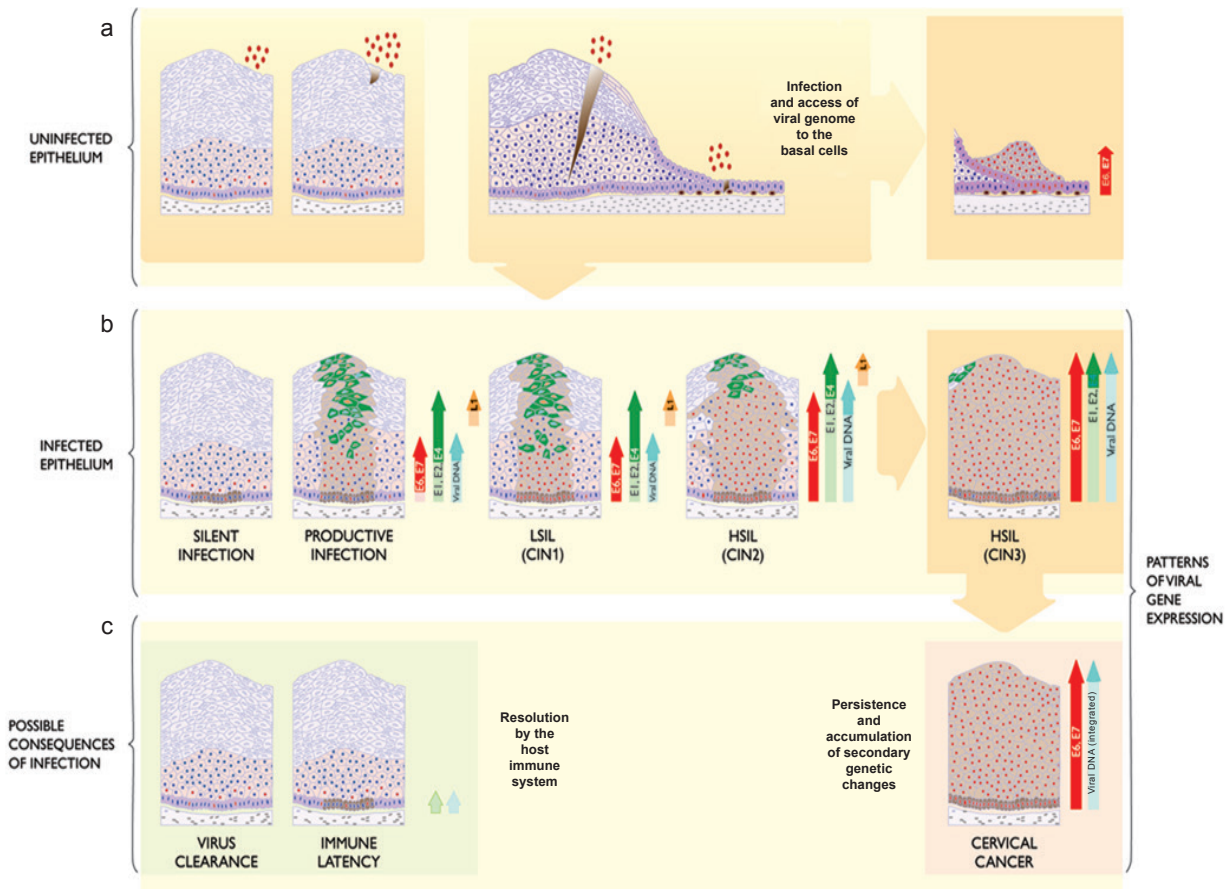


Table 4.2. Utility of biomarkers to qualify cytological and histological interpretation

Test	Performance	Biomarker	How biomarker helps
Cytology	75% sensitivity and 95% specificity	HPV	98% sensitivity but low specificity
		p16/Ki-67	90% sensitivity but better specificity than HPV and similar specificity to cytology
Histology	High kappa for HSIL (CIN3) Poor discrimination of CIN2 lesions	p16	Pushes CIN2 to either true low-grade or true high-grade lesion

CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion.

Fig. 4.6. Cervical biopsy with SIL showing partial maturation; some might question the lesion grade (CIN2?). (a, c) Haematoxylin and eosin morphology at low and medium power with atypical parabasal-like cells extending into the middle third of the epithelium (c). (b, d) Corresponding p16 immunohistochemical stains with diffuse strong staining meeting the definition of strong and diffuse block-positive p16. Therefore, this case is best interpreted as HSIL.

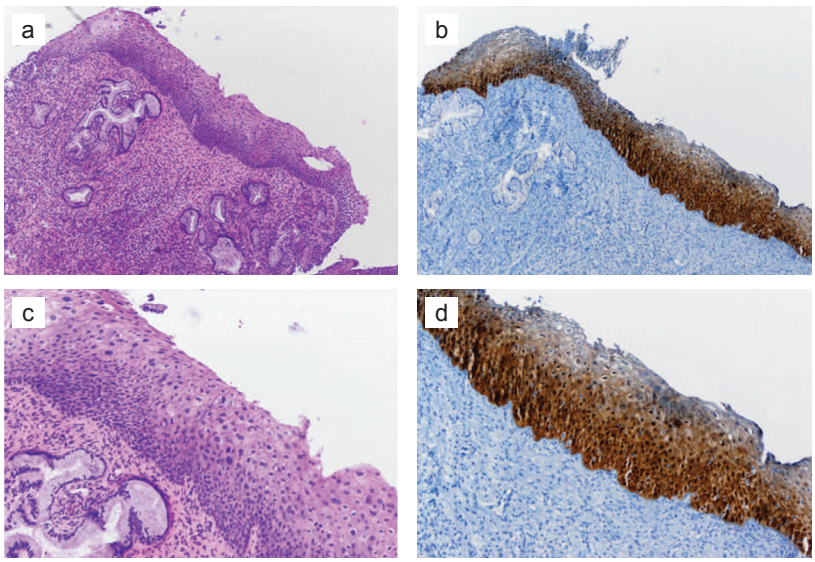
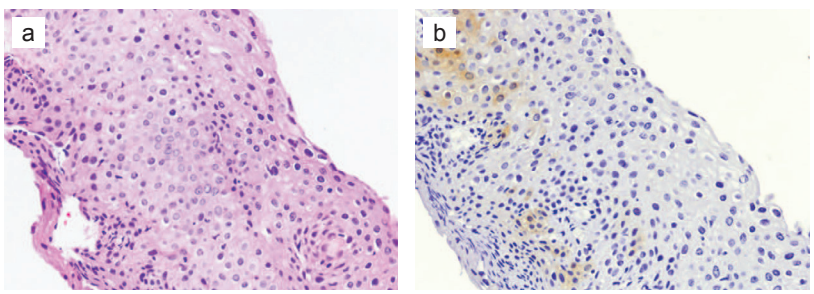


Fig. 4.7. (a) Cervical biopsy (high power, haematoxylin and eosin) with unequivocal SIL that is tangentially cut, raising the differential diagnosis of LSIL versus HSIL. (b) High-power p16 immunohistochemical stain, demonstrating weak, patchy p16 reactivity that starts above the basal layer, a pattern that should be interpreted as negative, which, in this case, supports the final combined interpretation as LSIL.



there is a proliferative cellular state and a transforming infection, thereby indicating the likelihood of genuine cervical precancer, i.e. a high-grade lesion (Ikenberg et al., 2013). Indeed, as Ikenberg and colleagues concluded in their large pan-European multicentre study of dual testing, "The p16/Ki-67 dual-stained cytology combines superior sensitivity and non-inferior [similar] specificity over Pap cytology for detecting CIN2+. It suggests a potential role of dual-stained cytology in screening, especially in younger women where HPV testing has its limitations."

4.3 Summary

The understanding of the biology of HPV and precancerous lesions has improved, and there are now objective biomarkers to identify specific and clinically important stages in the natural history of oncogenic HPV and the host cervical epithelium. As a result, the discipline of molecular biology has entered the arena of management and has improved the functional test characteristics of both cytology and histology (Table 4.2). As well as the information resulting from cytology, histology, colposcopy, and biomarker tests, the individual case characteristics of each patient will be weighed up by the colposcopist in deciding management (Fig. 4.9). There is no doubt that the newer objective biomarker tests are likely to make this decision analysis easier.

Fig. 4.8. p16/Ki-67-positive abnormal basal cells.

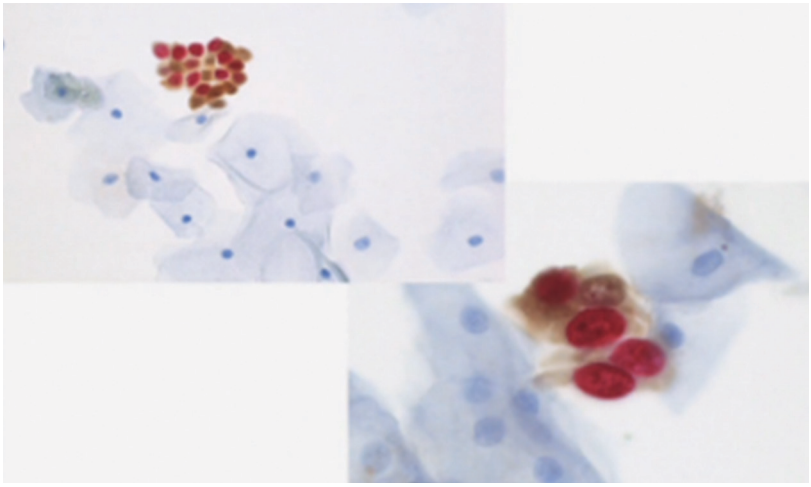
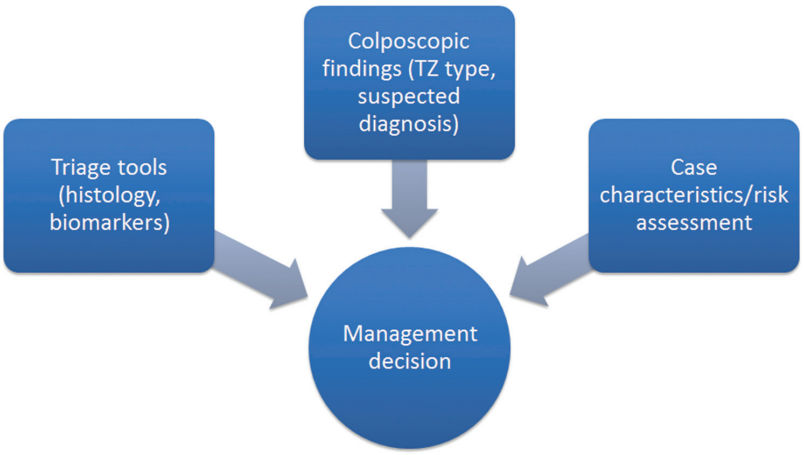


Fig. 4.9. Influences on the colposcopist's management advice. TZ, transformation zone.



Key points

- HPV affects the genital tract of most women early on in their reproductive life and only very seldom causes cervical precancer.
- The negative predictive value of a negative oncogenic HPV test approaches 100% over the subsequent 5 years.
- Secondary biomarkers produced at different biological stages of viral activity are measurable in cervical samples. Some protein biomarkers reflect viral activity rather than viral presence and are helpful in selecting those HPV states that are likely to progress to cancer.

CHAPTER 5.

Equipment for a colposcopic examination

This chapter describes the equipment needed to perform a colposcopic examination and its more common uses in clinical practice. A step-by-step description of the colposcopy technique and how to optimize the examination follows in Chapter 6.

5.1 Colposcope

The colposcope is a relatively simple instrument that allows examination of the cervix under light illumination at various low-power magnifications. It consists of a binocular microscope and light source, often incorporating a beam splitter to allow attachment of a still or video camera. It may either be attached to a central upright rigid bar, as in the original colposcope introduced in Germany in the 1920s, or be connected to a weighted stand with an adjustable arm, which allows the colposcope head to be placed more precisely and without interfering with the operator's comfort. There are a large number of colposcopes on the market. Fig. 5.1 shows a typical colposcope mounted on a floor stand.

Certain instrument characteristics should be considered before buying a colposcope. ***It must be binocular***, so that depth of field may be appreciated. This is particularly important when performing excisional treatment and when trying to assess surface contour and perform examination of endocervical epithelium (Carcopino et al., 2014). The lens should have a focal length of 30 cm, which is short enough to allow the examiner to reach the cervix with instruments, swabs, and spatulas and yet long enough to allow the colposcopist's hands to move between the colposcope and the cervix without interference. Any shorter and it is difficult to use handheld instruments under direct colposcopic view; any longer and it is too far to comfortably

Fig. 5.1. A typical colposcope with a movable base.

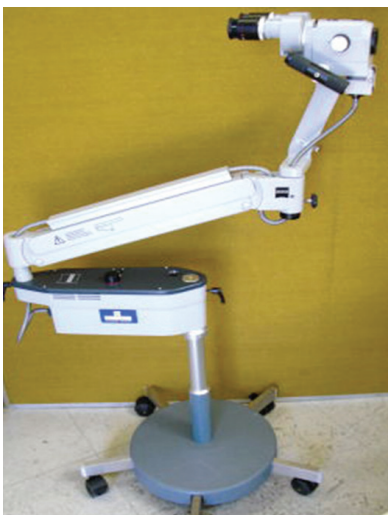
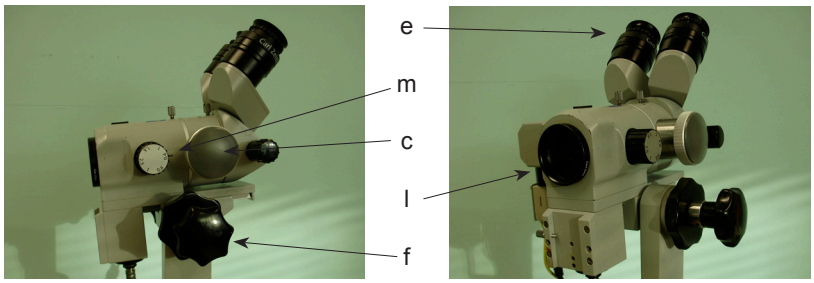


Fig. 5.2. Two views of the colposcope head, showing the two eyepieces (e), the magnification changer (m), the camera access port (c), and the 30 cm lens (l). Coarse focus is attained by moving the entire colposcope head. Fine focus is achieved using the fine focus handle (f).



reach the cervix. The colposcope head must be universally movable and should be easily fixed once in position, so as to allow the colposcopist freedom of hand movement. A camera attachment (and therefore a beam splitter) is very useful for both training and documentation.

The colposcope head (Fig. 5.2) comprises an objective lens; two eyepieces, which may be adjusted to each person's eye position and may be focused independently; and a light source, which in the instrument shown comes from a light cable attached to a light source. Halogen lights are very powerful, are easily replaced, and are relatively inexpensive. Light-emitting diode (LED) lamps last longer. Most colposcopes have a green filter, which takes away the background redness so that the vessels appear black and fine vessel changes may be more easily appreciated.

Also, most colposcopes have a magnification changer, although some are variable and allow a zoom capacity. In practice, it is rarely necessary to examine at a greater magnification than 15×. There is a trade-off. At greater magnification, the field of view diminishes, the depth of focus decreases, and the light required increases. At higher magnifications, it is sometimes easier to appreciate fine vessel changes. However, it is important to be able to visualize the entire cervix in one field, especially during treatment. A good colposcope will have a low enough magnification setting to allow this (i.e. 4×). Three or four different magnifications between 4× and 15× are ideal. Rapid change from one magnification to another is effected with a simple knob (the magnification changer). For coarse focus, the colposcope head can be moved manually, and for fine focus, there is a separate knob.

Before starting a colposcopic examination, one should first confirm personal visual acuity settings, in other words that the colposcope is set up properly for the examiner's eyes (see Chapter 6). It is prudent to do this while looking at an inanimate object at the beginning of a clinic session, before a patient undresses.

Colposcope manufacturers nearly all supply a camera, monitor, and computerized image storage and database package. Fig. 5.3 illustrates an integrated colposcopy system.

5.2 Gynaecological couch and operator's stool

For most women, any gynaecological examination couch (Fig. 5.4) that allows the patient to adopt the

Fig. 5.3. A colposcope with integrated video camera, monitor, and data collection system attached to the colposcope's movable stand.

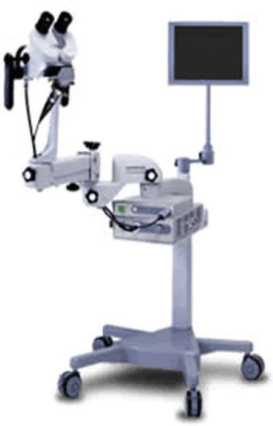


Fig. 5.4. A colposcopy/hysteroscopy gynaecological examination couch. It may be elevated and flattened independently. A waste receptacle is fitted just below the patient's perineum.

lithotomy or semi-lithotomy position may be used to perform colposcopy. However, it is important that the base of the couch may be tilted so that the TZ on the cervix will become almost perpendicular to the colposcopic line of vision. The back of the couch should also be adjustable, and it should be possible to easily elevate or lower the whole couch. A comfortable couch is hugely important for the patient, who will need to be in position for several minutes in relative undress and who is very likely to be anxious. It is important to be able to elevate or lower and tilt the couch to allow optimal positioning of the patient. Also, an examiner's stool that can be elevated or lowered is very helpful. Being able to quickly flatten the couch so as to deal with the rare vasovagal attack is important. Finally, the same couch may be used for most outpatient gynaecological procedures (e.g. hysteroscopy, intrauterine contraceptive device [IUCD] insertion, and transvaginal ultrasonography).

If a decision is made to perform excisional treatment, it should usually be performed as an outpatient procedure using electrosurgery to resect the TZ epithelium, i.e. LLETZ/LEEP. A loop electrode is attached to an electrosurgical unit (ESU) (Fig. 5.5). The loop electrode is housed in a so-called pencil. Suction tubing will connect the ESU to the suction speculum, and a ground plate will connect the patient to the ESU. Some ESUs have a suction unit incorporated into the unit; others do not, in which case it will be necessary to have a separate suction machine. The equipment for LLETZ/LEEP, thermal coagulation, and cryosurgery is described in Chapter 11.

5.3 Camera system

Almost all of the major camera companies will supply a camera and attachment for a colposcope. Unfortunately, the colposcopes usually need a C-mount for the camera to attach to the colposcope, and C-mounts are expensive. Many modern colposcopes have a camera system incorporated into the instrument, without the need for a C-mount. Nowadays, the cost of a reasonable video camera is almost the same as that of a still image camera, and very high quality video images can be obtained and stored for future reference. This is immensely valuable as a clinical aid in following up screen-positive patients, whether or not treatment has been performed, and also as an educational tool for attending colposcopy trainees.

5.4 Computerized data management system

Many companies provide a software package that allows sociodemographic, clinical, colposcopic, and laboratory data and image capture as well as automatic audit of colposcopic diagnostic performance. In this way, it is relatively easy to create a full audit of performance for an individual colposcopist and to maintain a clinical database for the clinic service. However, the programs are expensive.

5.5 Instrument trolley

An instrument trolley may seem an unnecessary luxury in colposcopy clinics where budgets are tight. However, the reusable and disposable equipment and the fluids needed to perform a proper colposcopic examination have to be housed somewhere, and to have them all to hand in one compartmentalized trolley is both efficient and ergonomically sensible. The last thing a colposcopist or the patient needs is to have to wait for an assistant to find a particular instrument when it is needed. Finally, if instruments are not housed in a compartmentalized trolley they are not within arm's length of the colposcopist, and they should be. Figs. 5.6–5.8 illustrate how some reusable instruments and some disposable equipment may be conveniently housed in a trolley. The contents of the top, middle, and bottom drawers are shown in Figs. 5.6, 5.7, and 5.8, respectively. In Fig. 5.9, the top surface of the trolley shows some instruments laid out for a colposcopic examination. A needle disposal box and a fluid tray are attached on the side (Fig. 5.10).

Fig. 5.5. A portable, battery-driven electrosurgical unit incorporating a suction unit. Ports for the electrosurgical pencil and the ground plate are displayed. A simple electrical battery charger access point and the on/off switch complete the display at the front. The suction port site is at the rear of the unit.

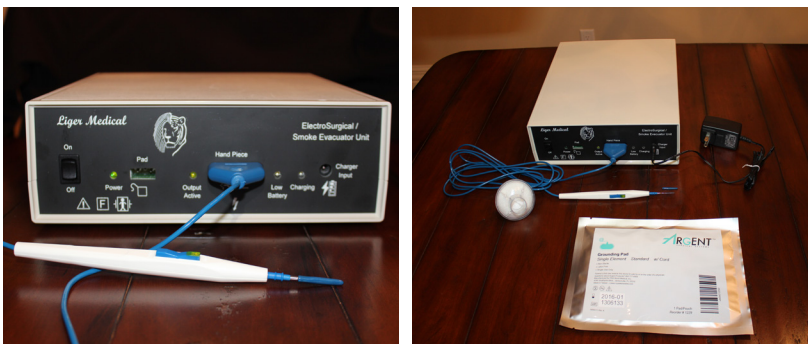
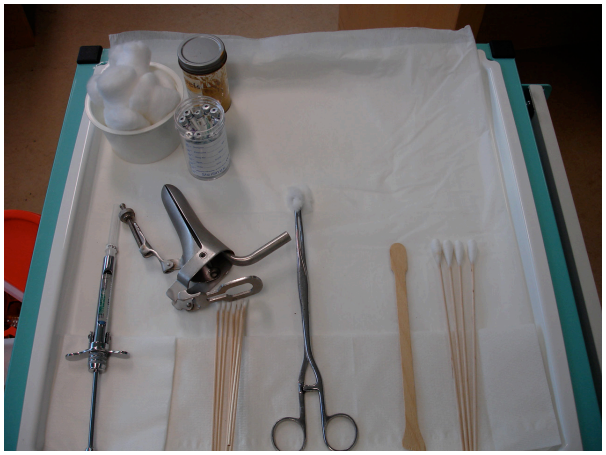


Fig. 5.6. Open top drawer of a colposcopy clinic trolley, which conveniently stores in adjustable compartments a variety of disposable equipment: lubricating jelly, chlorhexidine gluconate sachets, cork boards for biopsy specimen pinning, dental syringe needles, culture swabs, cotton swabs and jumbo swabs, endocervical smear brushes, and cytology fluid bottles.

Fig. 5.7. Open middle drawer of a colposcopy clinic trolley, which stores a variety of disposable examination gloves, gauze swabs, and cotton balls.

Fig. 5.8. Open bottom drawer of a colposcopy clinic trolley, which stores colposcopy suction specula of three different sizes.

Fig. 5.9. Top surface of the equipment trolley used in many colposcopy clinics. Some of the equipment used during a colposcopic examination and treatment are laid out on an incontinence pad. These include cotton swabs and jumbo swabs, a sponge forceps and cotton balls, a suction speculum of medium size, some dental vials containing local analgesic fluid for injection using the dental syringe system, and a loaded dental syringe.

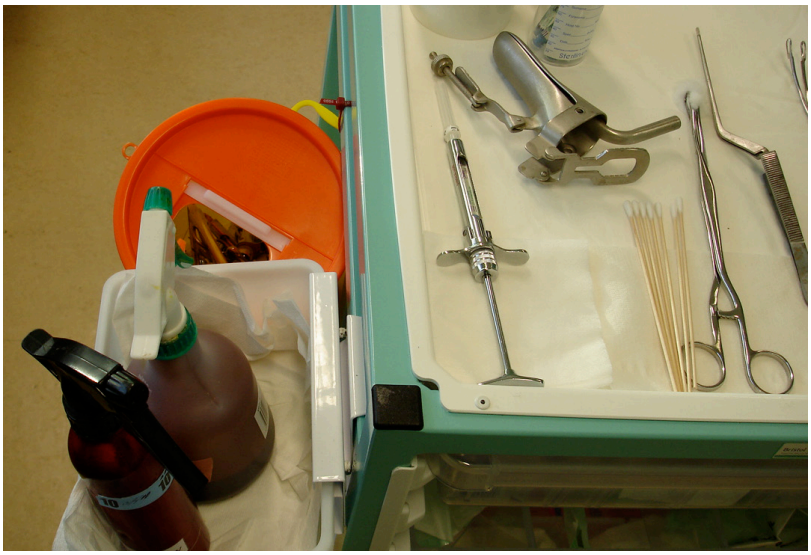


5.6 Reusable instruments

5.6.1 Specula

It is fundamentally important to have a full set of different sized specula available when performing colposcopy. A speculum that is too small will not comfortably expose the cervix in the perpendicular plane, and a speculum that is too large will hurt the patient. Parity and bimanual examination will reveal the appropriate speculum to be used for colposcopy. Specula may be metal or plastic. If LLETZ/LEEP or a “small loop” diagnostic biopsy is to be performed, the speculum should have a suction tube on the underside of the anterior blade (Fig. 5.11a). ***Insulated specula are to be avoided,*** *even* ***if using diathermy.*** After several sterilization cycles, the insulated speculum can lose some of its covering, and this may not be noticeable to the naked eye. If this happens, an electrical contact could indeed burn the

Fig. 5.10. On the side of the equipment trolley are attached a needle disposal box and a receptacle for the acetic acid and Lugol's iodine spray bottles.



patient's vagina. With the uninsulated speculum, no such risk arises. The area of contact with the vaginal skin is so large that burns are extremely unlikely even if contact with the loop or ball electrode happens accidentally. Also, if one ensures that LLETZ/LEEP is performed at low-power magnification, the entire loop should be visible before and during the procedure, so that contact with the vagina or speculum is extremely unlikely. Occasionally, the patulous parous vagina is so lax that it is not possible to completely visualize the cervix with the colposcope. Although lateral vaginal wall retractors are available to attach to some specula, they are relatively uncomfortable; a condom (Fig. 5.11b) or the finger of a large glove (with its end cut off) is a simpler and often more effective alternative.

5.6.2 Sponge forceps

Colposcopists vary in their choice of method for applying acetic acid or Lugol's iodine. Some use cotton balls soaked in the fluid and applied using a sponge forceps (Fig. 5.9). Others prefer spray bottles, which may be less cumbersome (Fig. 5.10). If the spray bottles are used, it is important to be aware that splashback can occur and to protect one's eyes from exposure either with glasses or with the colposcope.

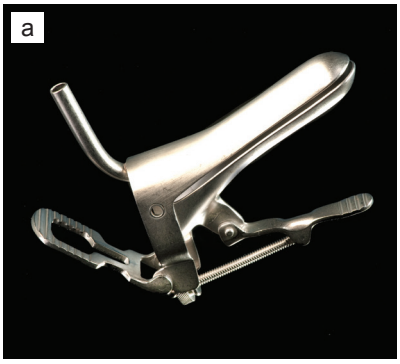
5.6.3 Endocervical forceps

The epithelium that is at risk of developing squamous cervical cancer is usually on the ectocervix in young women, and this is defined in the IFCPC nomenclature (Bornstein et al., 2012b) as a type 1 TZ. The type 2 TZ, by definition, has an endocervical component but is fully visible to the examining colposcopist. To accurately determine the TZ type, it is necessary to carefully examine the SCJ as fully as possible. Also, when investigating a suspicion of adenocarcinoma or glandular precancer, it is necessary to examine the endocervix. This will usually require the use of an endocervical forceps. There are several good ones on the market. User-friendly ones are the Kurihara and the Desjardins forceps, which are shown in Fig. 5.12.

5.6.4 Local analgesia (dental) syringes

Metal dental syringes house 2.2 mL vials of either prilocaine with felypressin or lignocaine with adrenaline. They allow attachment of 27-gauge needles, which automatically puncture the vials when they are loaded into the dental syringes, ready for use. They allow exchange of empty vials for new, full ones in a matter of seconds, so that complete local analgesia may be achieved in less than a minute (see Chapter 2). A loaded dental syringe is shown in Fig. 5.13. The loaded syringe is long enough to

Fig. 5.11. (a) A Cusco speculum with a suction tube on the underside of the anterior blade for smoke evacuation. (b) A condom (with its end cut off) placed around a Cusco speculum to facilitate examination when the vaginal walls are exceptionally patulous.



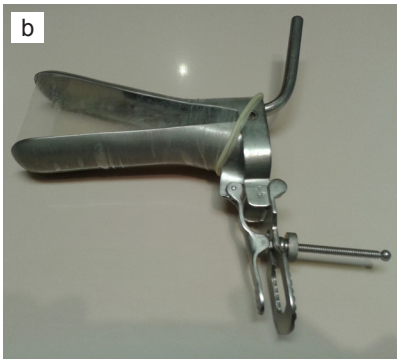


Fig. 5.12. (a) Kurihara forceps. (b) Higher-magnification view of Desjardins forceps.

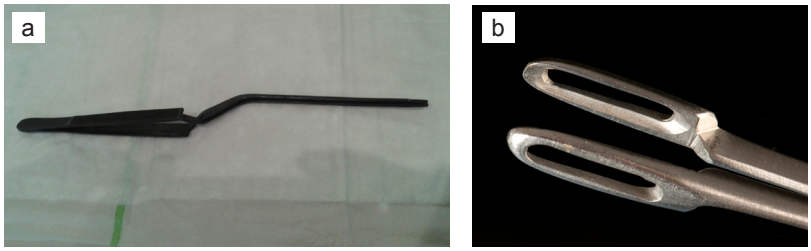


Fig. 5.13. Loaded dental syringe.

Fig. 5.14. Punch biopsy forceps.

easily reach the cervix, and because the needle itself is relatively short, it will not bend sufficiently to cause a problem with infiltration. Finally, it is narrow enough not to obscure colposcopic vision during infiltration.

5.6.5 Tissue sampling instruments

The threshold for taking a biopsy varies from one setting to another. In some colposcopy clinics a biopsy is considered mandatory for every examination, whereas in others a "see-and-treat" policy prevails for women with convincing evidence of high-grade dysplasia (see Chapter 1). Endocervical curettes are routinely used in many practices in the USA but are not often used in the United Kingdom. Many patients find an endocervical curette to be uncomfortable; it often produces inadequate material and usually precipitates bleeding. It rarely influences practice, and a good endocervical brush smear sample is considered a superior method by many. Biopsy forceps (Fig. 5.14) need to be sharp if they are to procure adequate biopsies, and some manufacturers make disposable forceps or disposable cutting parts for the reusable biopsy forceps handles. The common ones available are the Kevorkian and Tischler-Morgan forceps. When performing biopsies, some colposcopists use infiltration of local analgesic, and some do not. A small, long hook may be used to fix the cervix before taking a biopsy, but it is not usually necessary if the biopsy forceps instrument is sharp. Fig. 5.15 shows a small loop, which is a convenient way of taking a diagnostic biopsy. Fig. 5.16 shows a range of loops that are used for taking biopsies as well as for excising the TZ. Fig. 5.17 shows a ball diathermy electrode, used to achieve haemostasis after excision of the TZ or to seal a biopsy site. Other haemostatic agents include Monsel's paste (see Annex 5) and silver nitrate sticks.

Fig. 5.15. A small loop used to take colposcopically directed biopsies using an electrosurgical unit.

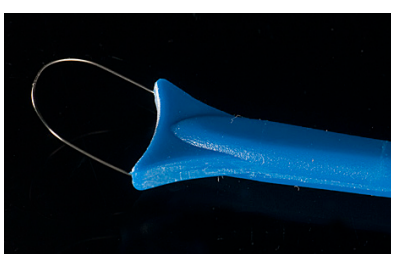
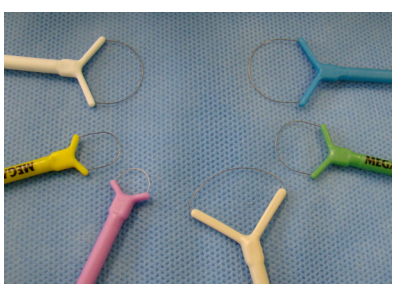


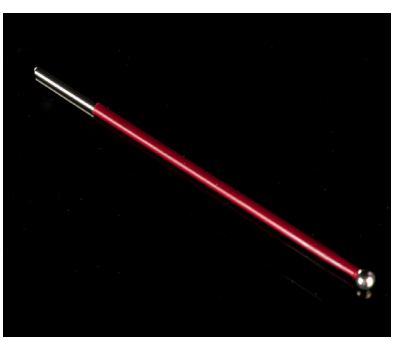
Fig. 5.16. An array of loops used for LLETZ/LEEP of different sizes and types of transformation zone, and cervical biopsy loops (pink and green) used for taking diagnostic biopsies.



5.7 Disposable equipment

Either a 3% or a 5% concentration of acetic acid may be used to highlight colposcopically recognized epithelial lesions. There is no evidence to suggest that one strength is superior to the other, although some authorities say that the 3% concentration takes a little longer to effect whiteness. What is important is that the same concentration is used for all patients. Care is needed in preparing the solution; disasters have occurred with *glacial* acetic acid, which will de-epithelialize cervical and vaginal epithelium.

Fig. 5.17. A ball diathermy electrode, used to achieve haemostasis after excision of the transformation zone or to seal a biopsy site.

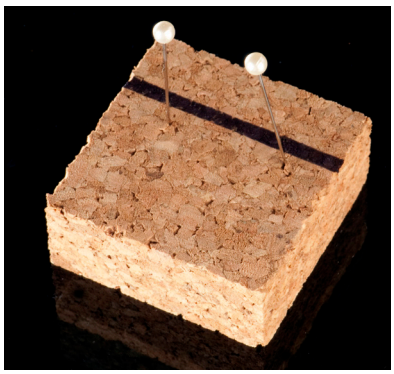


Lugol's iodine stains mature squamous epithelium dark mahogany brown and affects immature and dysplastic epithelium variably (see Chapter 8). Saline is advocated by several authorities as a cleaning agent before the application of acetic acid or Lugol's iodine. Cotton swabs are useful to manipulate the cervical epithelium, and jumbo swabs or cotton balls are alternatives (to spray bottles) for the application of acetic acid or Lugol's iodine. If treatment is contemplated, 27-gauge dental syringe needles and vials of prilocaine with felypressin or lignocaine with adrenaline are needed, and various biopsy forceps or small loops are used to take colposcopically directed biopsies. When one is trying to recognize or rule out the presence of intraepithelial neoplasia, punch biopsy forceps are adequate, but if one is concerned about invasive disease, a small loop electrode (Figs. 5.15 and 5.16) should be considered, because it allows a greater depth and confidence in revealing the basement membrane at histological examination.

5.8 Cork boards and pins to mount LLETZ/LEEP specimens

Liaison with one's local laboratory will determine in which way excised LLETZ/LEEP specimens will be received. One option is to open the specimen and then pin it onto a cork board (Fig. 5.18) before immersion in formalin, so that it may be sectioned longitudinally and an accurate assessment of the SCJ may be reported.

Fig. 5.18. Cork board and pins to mount LLETZ/LEEP specimens.



Key points

- Certain instrument characteristics should be considered before buying a colposcope.
- The gynaecological examination couch should be adjustable, so that it can be elevated or lowered and tilted to allow optimal positioning of the patient.
- Video and/or still images are very valuable as a clinical aid and as an educational tool.
- Reusable instruments and disposable equipment may be conveniently housed in a compartmentalized trolley.

CHAPTER 6.

A systematic approach to colposcopic examination

A colposcopic examination may be easy or difficult. It will be easy for the colposcopist who is properly trained, is well equipped, and has a comfortable, relaxed patient. Without these ingredients, the examination will be difficult.

Colposcopy performs less well as a screening procedure than when it is used to manage women who are screen-positive, are symptomatic, or have signs suggestive of disease. Recognizing high-grade CIN or HSIL is usually straightforward and unchallenging in the presence of a high-grade smear. Recognizing a high-grade abnormality when the screening test suggests a mild abnormality is more difficult but is reliable if the colposcopic examination is performed systematically as part of a quality-assured service (see Chapter 1).

Also, optimal cervical conditions will make the examination easier and less likely to be inadequate. An uninfected, non-pregnant, and well-estrogenized cervix is ideal, but, of course, this is not always the case. However, colposcopy is rarely urgent, and treating infection or achieving estrogenization of the cervical epithelium will sometimes tip the balance between an inadequate and an adequate examination.

Finally, it is so easy to have a "quick look" at the cervix with a colposcope. This is a mistake. A structured examination and the documentation of specific findings, particularly the TZ type (see Annex 1) and the Swede score (see Annex 4), will result in the best care.

This chapter describes the preparation required and the steps involved in performing colposcopy competently.

6.1 Colposcopy training needs

Colposcopy expertise is attained by proper training and continuing case experience. This manual is a reference manual and an introduction to colposcopy rather than a comprehensive training course. Training in colposcopy involves several components:

1. Theoretical knowledge
   a. This may be acquired at home, online, or by reading and attending a theoretical course or courses.
2. Image recognition skills
   a. These may be acquired at home, online, or by attending a busy colposcopy clinic.
3. Case management skills
   a. These may be acquired online using video case material or by attending a busy colposcopy clinic.

4. Clinic and colposcopic in vivo experience
   a. Requires the trainee to attend a colposcopy trainer in a clinic
   b. Seeing and managing ≥ 50 cases under supervision
   c. Seeing and managing ≥ 100 cases unsupervised but submitted to a preceptor for assessment.
5. Taking an Objective Structured Clinical Examination (OSCE)
6. Accreditation
7. Case experience and audit
8. Reaccreditation every few years.

IFCPC, in collaboration with the Screening Group of the International Agency for Research on Cancer (IARC), runs a distance learning course that offers training in colposcopy without the need to attend a colposcopy clinic for a long period of time.

Components 1 to 3 listed above may be acquired online. The clinic and colposcopic in vivo teaching may take place ad hoc during the 1-year course at a regional or local colposcopy clinic (http://www.ifcpc.org/en/). Once a colposcopist is trained, it is important to continue to see a sufficient number of cases to maintain expertise.

Expert colposcopy is not compatible with occasional practice.

6.2 Equipment check

The time to check the availability and functionality of equipment is just before each clinic session and not while examining a patient.

6.2.1 Setting up the colposcope to achieve binocular focus

If other colleagues also use the colposcope, it is prudent to set up the colposcope eyepieces before the first patient arrives. A few simple steps will achieve this.

1. Use a small coin or pencil placed on the examination couch as the object of focus.
2. Adjust the eyepieces to your own interpupillary distance. Start by placing the two eyepieces far apart. Then, while looking down both eyepieces simultaneously at the coin on the couch, move the eyepieces closer together until the two images become one (Fig. 6.1).
3. If a (still or video) camera is attached, adjust the coarse focus and then the fine focus so that the image on the monitor is exactly focused. Fix the colposcope in position so that it becomes immobile, by using the tension knobs on the supporting arms (Fig. 5.2).
4. Determine which eyepiece is in line with the camera (the primary eyepiece).
5. Adjust the primary eyepiece so that the image on the monitor and that seen through the primary eyepiece are equally and correctly focused.
6. Adjust the secondary eyepiece so that it is also finely focused.

This will mean that each eye and the monitor are in harmonious focus when examining the coin. The colposcope is now ready for use with a patient.

6.2.2 Colposcope ergonomics

After learning how to set up the colposcope eyepieces, the next step is to familiarize yourself with its ergonomics. Take time to sit down with the colposcope and examine an orange, a grape, or an almond as well as a host of other inanimate objects. Loosen the tension knobs, and move the colposcope head into and out of position. The mechanism varies from one colposcope to another. Examine your friend's fingernails, and remove splinters under colposcopic guidance. Learn how to change the colposcope's light bulb, and become thoroughly familiar with the light connections, the green filter switch, the magnification mechanism, the camera head orientation, and the coarse and fine focusing. In this way, the colposcope will become an extension of your eyes, and you will become comfortable with the instrument.

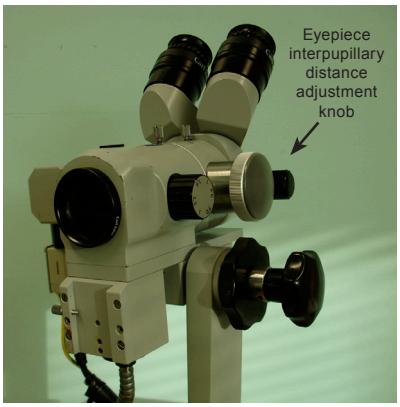
6.3 Biopsy and electrosurgical excision

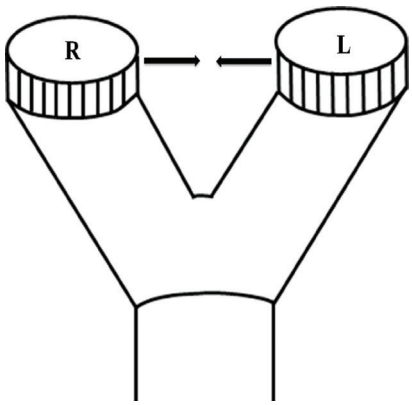
For biopsy and electrosurgical excision, as with most surgical procedures, learning the technique in a simulated manner is preferable to learning on a patient. The consistency of meat is relatively similar to that of the cervix, and meat has a similar feel to the cervix when taking a biopsy. The trainee should become expert at using the biopsy forceps with a piece of meat (typically ox tongue or chicken breast) at the end of a speculum on the gynaecology couch before approaching a patient. Also, there are several plastic pelvic anatomical models available that allow the trainee to simulate a small loop diagnostic biopsy or a LLETZ/LEEP procedure.

6.4 Counselling

The need for counselling of patients before medical or surgical intervention is, of course, obvious. In repetitive low-risk situations, it is sometimes overlooked or considered unnecessary. This is a mistake. A woman who has been properly counselled is informed, relaxed, and confident in her colposcopist. A woman who has not been properly counselled and is uninformed is more likely to be anxious, scared, and ultimately dissatisfied. Complications from any intervention do occur, albeit infrequently at colposcopy and treatment of CIN. A complication that occurs as a result of an intervention

Fig. 6.1. Adjusting the colposcope eyepieces to your own interpupillary distance. Start by placing the two eyepieces far apart. Then, while looking down both eyepieces simultaneously, move the eyepieces closer together until the two images become one. The colposcope shown has a control knob that adjusts the interpupillary distance.





for cancer or a serious medical condition is one thing; a complication in a healthy and asymptomatic woman is quite another. Counselling takes only a few minutes but rewards both the colposcopist and the patient. Most colposcopy services have written information covering screening, investigation, and treatment. Written information is important but does not replace the need for face-to-face, open, and reactive counselling by the colposcopist who is about to perform the examination. Delegating this task to someone else is improper.

6.5 Consent

Many centres rely on verbal consent for the colposcopic examination and biopsy, as well as for treatment, where necessary. Other centres insist on written consent after providing extensive printed information. Different medicolegal and sociocultural settings require different levels of medicolegal protection.

6.6 Privacy and support

It is difficult for those who have not undergone a gynaecological or colposcopic examination to fully appreciate the relative indignity of the experience and the potential for distress. The very least that colposcopists can do is to try to mitigate the circumstances by setting in place those arrangements that they would expect for themselves if they were patients. This includes privacy while recording personal information and a private place to undress. Most patients prefer to have the fewest people necessary present during the examination. This usually means the colposcopist, an attendant, and, often, a trainee. The colposcopist should introduce both the attendant and the trainee. Few patients will object to the presence of a trainee if the trainee is appropriately introduced. Finally, the examination room should be locked and the patient made aware of this.

The stress of having an abnormal screening test and a colposcopic examination is significant and has been reported as being equivalent to that of major surgery. A professional, sympathetic attendant is hugely reassuring to most patients, and the attendant can usually fulfil this task better than a friend or relative. Occasionally, a patient requests the presence of a friend or relative, and this does not usually present a problem.

6.7 The colposcopy nurse attendant

A professional attendant who can both assist the colposcopist and provide support to the patient is worth their weight in gold. The role of the attendant is sometimes underappreciated. The position should be highly valued, remunerated, and protected. The attendant will support the patient during the examination, ensure easy access to and availability of equipment during the examination, and aid with camera adjustment and recordings, filling in forms, and processing specimens. Without a dedicated attendant, the colposcopic examination will not be complete, easy, or rewarding. A properly trained attendant may wish to become a colposcopist later in their career and is likely to make an excellent colposcopist.

6.8 The colposcopic examination

Being prepared is key to a smooth and rewarding colposcopic examination. Have the relevant equipment ready, including treatment equipment, if necessary and appropriate at the time. The woman should be relaxed and fully informed. The steps involved in performing colposcopy competently are the following.

6.8.1 Passing a speculum

First, have the woman adopt the lithotomy position on a gynaecological couch. If the couch has a cut-out just under the buttocks, this is ideal. If not, the woman can move down the couch so that her buttocks are just over the end of the couch. It is almost impossible to describe how best to pass a speculum without doing an in vivo demonstration or using a pelvic

model. The examiner has to be able to pass the speculum comfortably and position it so that the cervix is fully visible in a plane perpendicular to the colposcopic line of vision. Most practitioners use a metal bivalve speculum (Cusco speculum, Graves speculum, or equivalent). A little gel lubricant or warm water should allow smooth passage through the introitus. The speculum should have a suction tube on the underside of its anterior blade (Fig. 5.11a) so that the smoke plume may be evacuated immediately during electrosurgical biopsy or LLETZ/LEEP. If the woman has a particularly patulous vagina, it may be necessary to surround the speculum with a condom (Fig. 5.11b) or the finger of a large glove (with its end cut off) so that the lateral walls are held out of the line of vision. Lateral vaginal wall retractors are rarely necessary.

6.8.2 Initial assessment

Assess the state of the cervix at the time of examination.

1. Assess the hormonal status.
   a. Is the epithelium well-estrogenized?
   b. Are pregnancy changes present?
   c. In postmenopausal women, is the degree of atrophic epithelial change sufficient to consider prescribing topical estrogen before colposcopic assessment?
2. Determine whether there is inflammation.
   a. Are signs of infection (viral, fungal, or bacterial) apparent, and are investigation and treatment prudent before colposcopic assessment?
3. Confirm full visibility of the entire cervix and upper vagina under colposcopic view.
4. Determine whether there is evidence of previous treatment, or any degree of epithelial fibrosis.

6.8.3 Low-power view

Having satisfied yourself that it is possible to adequately examine the cervix, apply saline and wash away as much mucus as possible without causing epithelial bleeding, in other words gently but thoroughly. It is not always necessary to use the green filter, but it does offer the best way of examining fine vessel patterns. Using the green filter takes away the background redness, and the vessels stand out as black lines. Examining the TZ with the green filter will often help the novice and is to be recommended for the first few hundred cases. Examination with saline and the green filter needs to take place before the application of acetic acid or iodine.

The entire cervix should be examined at low-power magnification. The type of TZ is usually apparent at this stage (see Annex 1). If the TZ is type 1, then the SCJ will be visible on the ectocervix. If not, it will be necessary to use an endocervical forceps to establish whether the TZ is of type 2 or type 3. The application of acetic acid (applied later) sometimes helps to exaggerate the SCJ.

6.8.4 Epithelial examination

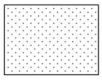
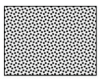
The major part of a colposcopic examination of the cervix will be low- and high-power examination of the TZ epithelium after the application of acetic acid (3% or 5%). It may be applied with a spray bottle or with a soaked cotton swab. Either way, it should be applied as gently as possible, so that all the mucus has been wiped away and the acetic acid can affect the epithelium. If the mucus has not all been wiped away, the acetic acid will not reach the epithelium, thereby giving a false impression of non-uptake. Also, if a spray bottle is used, be aware of possible splashback to the examiner's eyes, which may be a risk with HIV-infected patients.

1. Apply acetic acid.
   a. Wait 1 minute.
   b. Examine the entire cervix and upper vaginal epithelium at low-power magnification.
   c. Again, confirm visibility of the entire SCJ (the upper limit of the TZ) and therefore determine the TZ type.
   d. Examine the entire TZ at high power.
   e. Determine the worst area(s) of abnormality and assess the need for biopsy.
   f. Calculate the Swede score.
   g. Take a biopsy (or biopsies), if appropriate.
2. Apply iodine.
   a. Attempt to determine the outer limit of the TZ and document the size of the TZ.
   b. Examine the extent of the iodine-negative area. Is the TZ congenital or original in distribution?
3. Perform treatment where appropriate (see Chapter 11).

Immediately after the examination, document the findings using a standard records form (see Annex 2). It should include the adequacy of the examination (initial assessment above), the TZ type and size, the Swede score, and a management plan. A variety of icons for image characteristics are used (e.g. Fig. 6.2). Video and/or still images are very valuable as an educational tool and as a means of explaining the findings to the patient, and also to compare the findings over time, whether or not treatment has been performed.

Finally, after the patient has changed into her clothes, the findings should be explained and a management plan outlined.

Fig. 6.2. Diagrammatic representation of some image characteristics seen at colposcopy.

	Columnar epithelium		Mosaic – fine
	Dense acetowhite epithelium – mild		Mosaic – coarse
	Dense acetowhite epithelium – dense		Atypical vessels
	Punctation – fine		"Character writing" atypical vessels
	Punctation – coarse		Pollarded vessels

Key points

- It is relatively easy to perform a comfortable and competent colposcopic examination, providing that circumstances are optimized.
- Performing the ideal colposcopy requires a relaxed and informed patient, a trained colposcopist, a nurse assistant, and a set of appropriate equipment.
- Colposcopic examination should be performed in a systematic and structured way, which documents the adequacy of the examination, the type and size of the transformation zone, and the degree of abnormality as reflected in an objective diagnostic scoring system, for example the Swede score.

CHAPTER 7.

Colposcopic terminology: the 2011 IFCPC nomenclature

In any branch of science, progress evolves from a clear understanding of previous research and experience. Clarity of terminology and practice is fundamental to understanding both published research and reports of experience in similar and in different clinical circumstances. Otherwise, it is very difficult to accurately compare existing practice or to evaluate new evidence. The latest IFCPC nomenclature (Bornstein et al., 2012a) attempts to bring greater clarity to terminology in diagnostic and therapeutic colposcopy practice. Individual terms are listed in Annex 3.

Screening programmes for cervical precancer have reduced the incidence of cervical cancer, especially in those countries with properly organized, quality-assured call-and-recall systems. Of course, it is not the screening itself that reduces the risk of cervical cancer, but rather the subsequent treatment of screen-positive women who are found to be at significant risk of developing cancer.

Most screen-positive women are at very low risk of progression to cancer. These women may be reassured and followed up appropriately. Colposcopic assessment of the grade of abnormality, and therefore the risk of progression, is crucial to the process of managing screen-positive women. So also is assessment of other TZ characteristics, for example the TZ site and size, and the visibility of the entire TZ. Most importantly, when properly undertaken, colposcopy will reduce the risk of both overtreatment and undertreatment.

For those women who are at a relatively high risk of progression to cancer and who do need to be treated, precise excision of the TZ is associated with the lowest risk of pregnancy-related morbidity (Khalid et al., 2011; Carcopino et al., 2013) and the highest chance of achieving successful eradication of all precancerous epithelium (Ghaem-Maghami et al., 2007; Manchanda et al., 2008).

7.1 Terms that have been omitted from the 2011 IFCPC nomenclature

To most colposcopists in the United Kingdom, “cone biopsy” means excision of a significant portion of the endocervical canal, and the term would be reserved for those cervices where the lesion is thought to be out of colposcopic view in the endocervical canal, either wholly or in part. However, to many colposcopists in the USA and Europe, “cone biopsy”

or “conization” means excision of any type of TZ, no matter how much of the endocervical canal has been excised. Also, dimensional terms like “height” and “depth” are used almost interchangeably in different publications, and this can lead to invalid comparison of treatment methods. For these reasons, the 2011 IFCPC nomenclature omits the terms “cone biopsy” and “conization” (see TZ excision types 1, 2, and 3 in Table 7.1) as well as “depth” and “height”.

7.2 General assessment

A general and initial assessment of the cervix will allow the colposcopist to determine whether examination of the cervical epithelium is adequate or whether it is compromised by inflammation, bleeding, atrophy, scar tissue, or subepithelial fibrotic change.

Making an assessment of whether the TZ is fully visible and where it is situated will allow determination of the TZ type.

7.3 Transformation zone type

After it is established that the examination is adequate, the TZ type and size should be determined (Figs. 7.1–7.3).

A fully visible and ectocervical TZ is a type 1 TZ. A TZ that is partially or completely endocervical but is fully visible is a type 2 TZ. A TZ that is partially or completely endocervical but is not fully visible is a type 3 TZ.

Fig. 7.1. Type 1 transformation zone (TZ). (a) Illustration. (b–d) Examples of type 1 TZs. In each, the entire TZ is visible on the ectocervix.

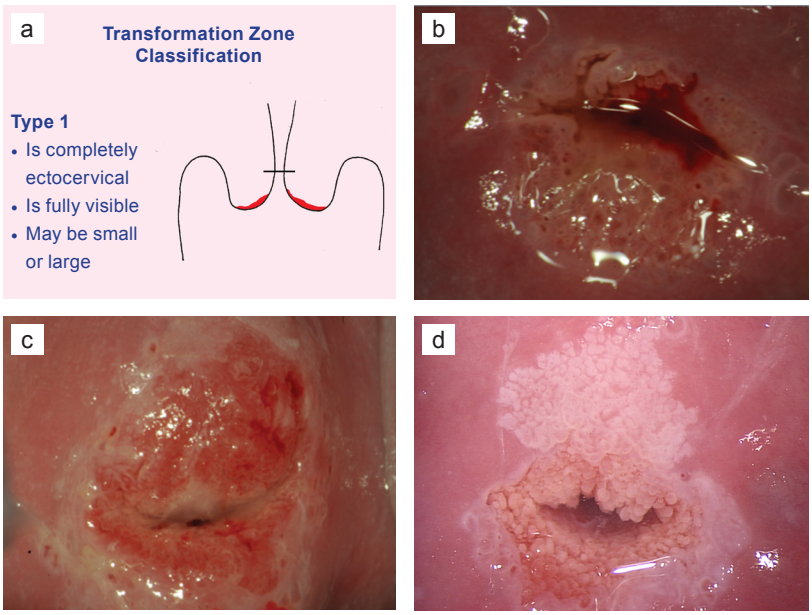


Fig. 7.2. Type 2 transformation zone (TZ). (a) Illustration; the upper limit of the TZ is in the endocervical canal but is visible below the upper limit of visibility, here represented by the horizontal line. (b, c) A large type 2 TZ; two images of the same cervix. The upper limit of the TZ is easily seen on the posterior lip but is visible in the canal only with the aid of a cotton swab. In this young woman, the abundant and clear mucus of an uninfected and well-estrogenized cervix allows easy manipulation and visualization of the lower endocervical canal and the upper limit of the TZ.

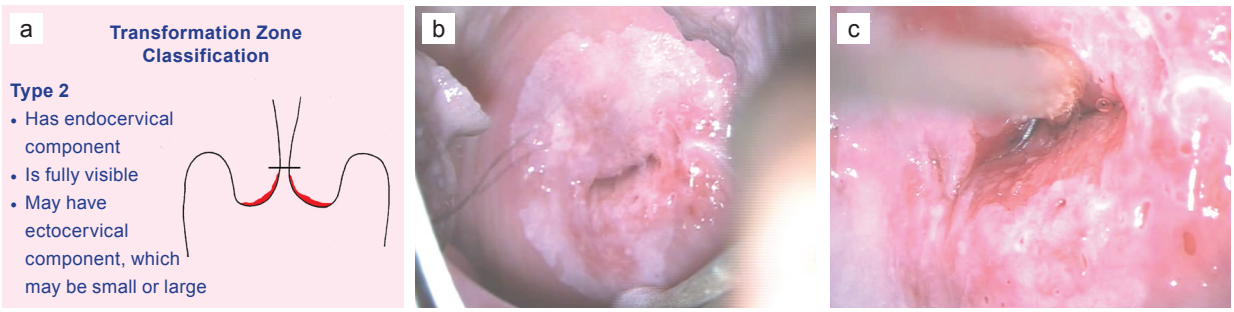
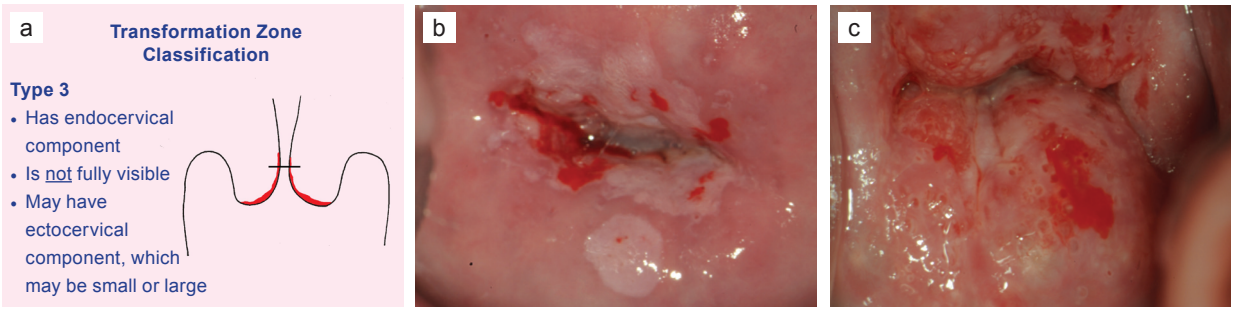


Fig. 7.3. Type 3 transformation zone (TZ). (a) Illustration; the upper limit of the TZ extends beyond the upper limit of visibility, here represented by the horizontal line. (b, c) Examples of type 3 TZs. In each, the upper limit of the TZ cannot be seen, because it extends into the canal above the field of view.



The visibility and precise location of the TZ influence both whether colposcopy is adequate and the method of treatment.

7.4 Excision type

A fully visible ectocervical and small TZ is both easy to assess and simple to treat, either by destruction or by simple excision. In contrast, a large type 3 TZ will not be possible to assess completely, and treatment will be associated with greater difficulty, a higher risk of morbidity (Khalid et al., 2011), and an increased risk of failure to eradicate the disease (Ghaem-Maghami et al., 2007). The TZ excision types are illustrated in Fig. 7.4. Table 7.1 lists the excisional treatments and when they are indicated.

The first two excision types, types 1 and 2, are illustrated in Figs. 7.5 and 7.6. They relate exactly to the TZ types 1 and 2. A type 3 excision, in contrast, may be used in several circumstances not dictated purely by TZ type. For example, excision of a glandular lesion will usually warrant a type 3 excision. Also, some clinicians may wish to perform a type 3 excision in the presence of microinvasive disease in a woman who has completed her family or in a patient who has previously been treated.

Fig. 7.4. Excision types. (a) Type 1 excision. The dotted green line resects a completely ectocervical or type 1 transformation zone (TZ). In this case, which is the most common in women of reproductive age, the LLETZ/LEEP procedure need not encroach on the endocervical canal and need not be greater than 8 mm thick throughout the resection. A small type 1 TZ may also be treated by destruction of the TZ. (b) Type 2 excision. The dotted green line resects a type 2 TZ, which, although it has an endocervical component, is still completely visible with the colposcope. In this case, the amount of excised endocervical epithelium may be tailored according to how far up the canal the TZ extends. (c) Type 3 excision. The dotted green line resects a longer and larger amount of tissue. In this case, the upper limit of visibility does not reach the upper limit of the TZ, and the excision has to resect a significant proportion of *endocervical* epithelium.

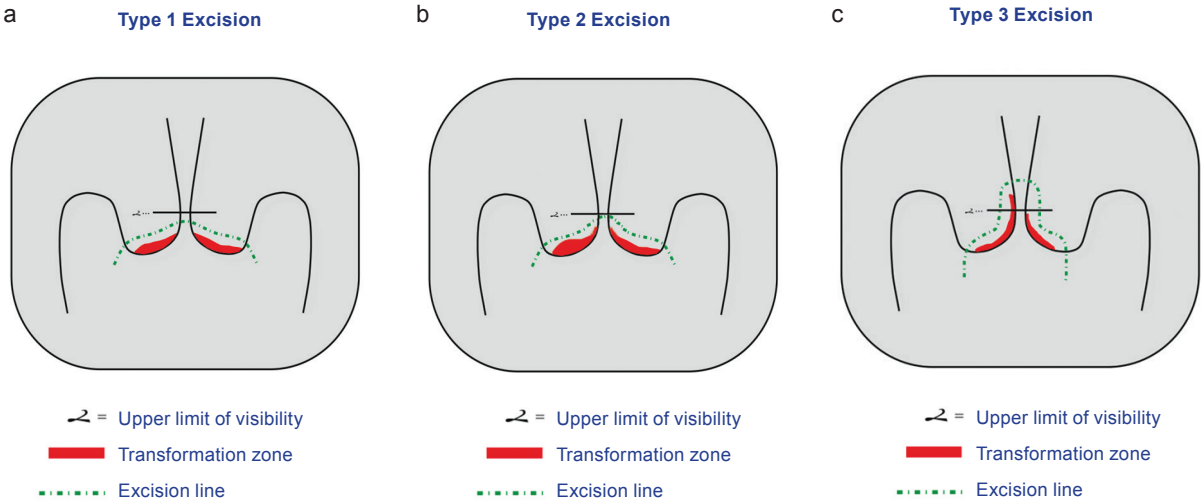


Table 7.1. Classification of excisional treatment

Characteristic	Excision type		
	Type 1 excision	**Type 2 excision**	**Type 3 excision**
Transformation zone type	Type 1	Type 2	Type 3
Condition	Any grade of squamous CIN Serious consideration should be given to excising CIN3 disease	Any grade of squamous CIN Glandular disease in women younger than 36 years Suspected microinvasion	Any grade of squamous CIN Glandular disease in women older than 36 years Suspected microinvasion
Other circumstances		Previous treatment	Previous treatment
Techniques included in this category of excision	LLETZ/LEEP Laser excision	LLETZ/LEEP SWETZ Laser excision Cold-knife cone biopsy/cylindrical excision	LLETZ/LEEP SWETZ Cold-knife cone biopsy/cylindrical excision
Alternative treatment choices	Transformation zone ablation or destruction		

CIN, cervical intraepithelial neoplasia; LEEP, loop electrosurgical excision procedure; LLETZ, large loop excision of the transformation zone; SWETZ, straight wire excision of the transformation zone.

Fig. 7.5. Type 1 excision with LLETZ/LEEP.

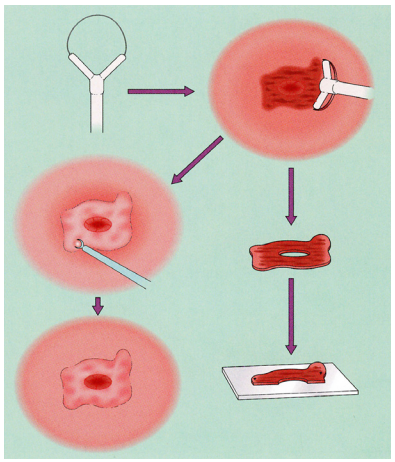


Fig. 7.6. Type 2 excision with LLETZ/LEEP.

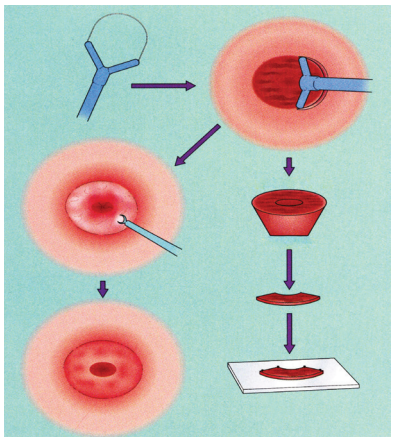
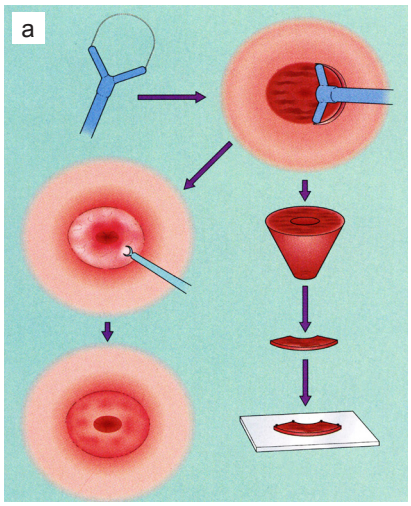
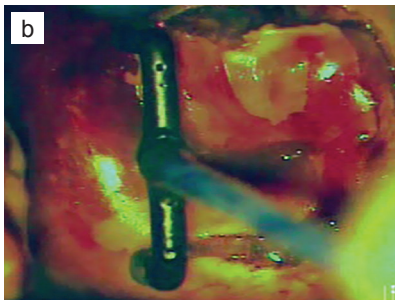
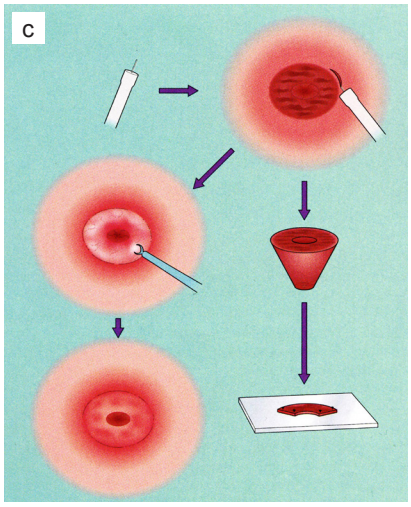


Fig. 7.7. (a, b) Type 3 excision using a large loop (LLETZ/LEEP). (c, d) Type 3 excision using a straight wire (SWETZ).







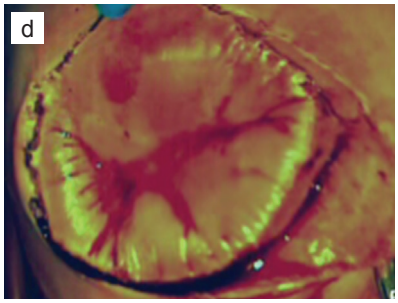


Fig. 7.8. The "top-hat" resection. (a) A first pass of the loop resects the ectocervical TZ and a part of the endocervical TZ. (b) A second pass with a smaller loop resects a further part of the endocervical TZ.

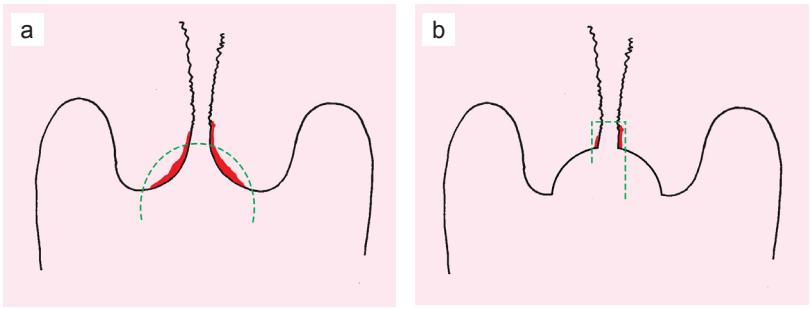


Fig. 7.7 depicts two different ways of performing a type 3 excision: the first with LLETZ/LEEP using a longer loop, and the second using a straight wire excision of the TZ (SWETZ), as described by Camargo et al. (2015). Finally, Fig. 7.8 illustrates the "top-hat" technique for removing a type 2 or type 3 TZ. The top-hat excisional technique has little to recommend it, because it compromises histological interpretation.

7.5 The excised specimen

The size of the excised TZ specimen is proportional to the risk of subsequent pregnancy-related complications, so accurate dimensional terms are important. Some terms have consensus agreement, and others, like "depth", do not. In the 2011 IFCPC nomenclature, the terms "depth" and "height" have been abandoned. "Length" and "thickness" of an opened specimen are universally understood and are included in the 2011 IFCPC nomenclature. When multiple excision specimens are obtained, as is the case with the top-hat technique, each specimen should be measured separately. Fig. 7.9 depicts the dimensions of the opened specimen (thickness, length, and circumference) just before pinning onto a cork board and immersion in formalin.

7.6 Colposcopic terminology of cervical epithelium

7.6.1 Normal colposcopic findings

Normal epithelial variations that may be recognized at colposcopic examination of the cervix include original squamous epithelium, nabothian follicles (also known as nabothian cysts), metaplastic squamous epithelium, crypt or gland openings, and decidual changes associated with pregnancy.

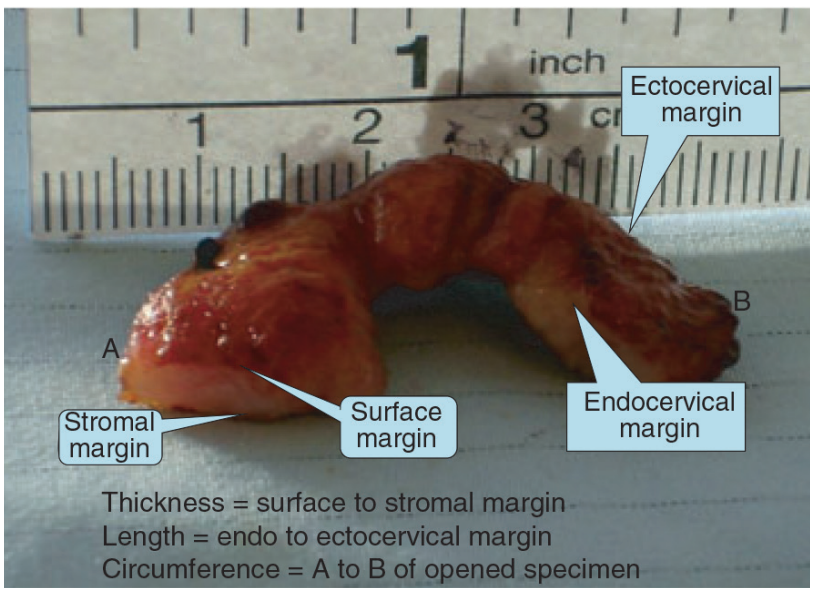
7.6.2 Abnormal colposcopic findings

Where a squamous lesion is present, it will be either proximal or distal to the original SCJ. In other words, it may be inside or outside the TZ. The lesion may be small or large and cover from one to four quadrants of the TZ. The size of the lesion and the proportion of the TZ that it covers appear to be important predictors of lesion grade, and this is included as one of the indices of severity in the Swede score (see Annex 4).

Minor-grade changes include fine vascular patterns (i.e. mosaicism or punctation), faint white epithelial uptake after the application of 3% or 5% acetic acid, irregular or geographical borders, and satellite lesions. Major-grade changes include sharp lesion borders, inner borders (within the TZ), the ridge sign, dense and/or rapid uptake of acetic acid, coarse vascular patterns (mosaic or punctate), and "cuffed" crypt or gland openings.

Non-specific abnormal findings include leukoplakia (keratosis or

Fig. 7.9. An opened LLETZ/LEEP specimen after removal, with the dimensions used to determine thickness, length, and circumference.



hyperkeratosis) and erosion. Features that might raise the suspicion of invasive disease include atypical vessels, fragile vessels, an irregular epithelial surface, exophytic lesions, necrosis, ulceration, tumour formation, or gross neoplasm. Miscellaneous findings included in this classification are the congenital or original TZ, condyloma, polyps, inflammation, stenosis, congenital anomaly, post-treatment epithelial changes, and endometriosis.

Some of these terms are open to subjective interpretation. For example, it is difficult to define in words the difference between irregular or geographical margins and straight ones. However, margin status has been found to be important in predicting high-grade abnormality (Hammes et al., 2007; Reid and Scalzi, 1985).

7.7 Individual terms in the IFCPC nomenclature

Colposcopic examination begins with a general assessment of the cervix, and most colposcopists will aim to determine the level of reliability of the examination at this stage. The popular terms "satisfactory colposcopy" and "unsatisfactory colposcopy" have been discarded, because they have the connotation of an examination that needs to be repeated. The colposcopic examination is now assessed by three variables: adequacy, visibility of the SCJ, and TZ type (Annex 3).

The first variable is whether the examination is adequate, and if not why not. The reason should be documented; for example, the cervix may be obscured by inflammation, bleeding, or scarring. The second variable is visibility of the SCJ, which can be described as "completely visible", "partially visible", or "not visible". The reason that the visibility and site of the SCJ are so important is that this influences both the ability to perform a complete examination and, when treatment is indicated, the extent and type of excision. The terms "adequacy" and "SCJ visibility" are not mutually exclusive; the SCJ may be partially visible because a portion of its inner margin is located high in the endocervical canal, whereas the examination is still adequate because the cervix is not obscured by blood or inflammation. The third parameter is the TZ type. It overlaps to some degree, but not completely, with the visibility of the SCJ. The TZ and the SCJ are not the same thing; the SCJ is the inner margin of the TZ. Both type 1 and type 2 TZs are completely visible, and the difference between the two is important, mainly for planning treatment. The TZ type defines both the site and the visibility of the SCJ.

Localization of the lesion inside or outside the TZ is important. This is because a lesion inside the TZ, as opposed to one outside (Fig. 7.10), has been shown to be an independent predictor of a high-grade lesion or carcinoma (Hammes et al., 2007). Lesion size (Figs. 7.11 and 7.12) has also been shown to be an independent predictor of high-grade disease (Kierkegaard et al., 1995; Shaw et al., 2003). The size may be quantified as (i) the number of cervical quadrants the lesion covers or (ii) the size of the lesion as a percentage of the cervix.

Two relatively new colposcopic image terms are included in the grade 2 (major) lesions of the 2011 IFCPC nomenclature: the "inner border sign" and the "ridge sign". Published work has validated their worth as markers of high-grade CIN (Scheungraber et al., 2009a, 2009b). A sharp border around a lesion has also been reported as being associated with a more severe lesion. The term "leukoplakia" is included in the category of non-specific abnormal findings. This is because it has been reported to have a 25% independent predictive value of

Fig. 7.10. Satellite lesions. In this normal cervix, there are two small satellite lesions outside the transformation zone.

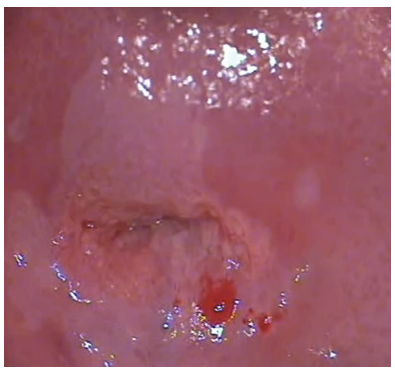


Fig. 7.11. A small lesion occupying only one quadrant of the transformation zone, with several satellite lesions at the 12 o'clock position.

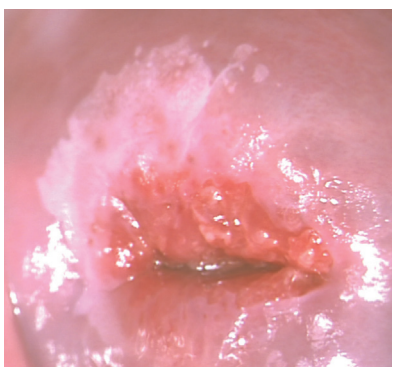
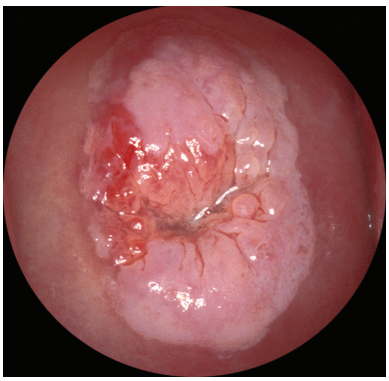


Fig. 7.12. A large lesion occupying more than three quadrants of a large transformation zone.



containing high-grade or invasive neoplasia (Hammes et al., 2007). In truth, leukoplakia may cover innocent or pathological epithelium, and colposcopic examination cannot reliably determine which. The uptake of Lugol's iodine is part of the non-specific findings because several publications have suggested relatively poor reliability of the test (Rubio and Thomassen, 1976). Cervical polyps are placed in the category of miscellaneous findings. They may, of course, be ectocervical or endocervical in origin.

Key points

- The 2011 IFCPC nomenclature is the global reference standard for cervical colposcopic examination findings.
- Transformation zone type and size as well as transformation zone excision type have been included in the latest nomenclature.
- Using the IFCPC classification allows valid comparison between researchers publishing research or reports of experience.

CHAPTER 8.

Colposcopic appearance of the normal cervix

The anatomy of the cervix has been outlined in Chapter 2. The colposcopic appearances of normal squamous epithelium, columnar epithelium, the SCJ, immature and mature metaplasia, and the congenital TZ are described in this chapter. An awareness of and the ability to identify the colposcopic features of the normal cervix provide the basis for recognizing abnormal cervical epithelium.

The most important anatomical entity in colposcopy is the TZ. This anatomical zone is where CIN and invasive cervical carcinoma arise.

An examination is *adequate* if it is possible to examine the entire TZ without it being obscured by inflammation, atrophy, bleeding, scarring, or other problems.

The TZ is categorized according to the site, size, and visibility of the TZ (Annex 1).

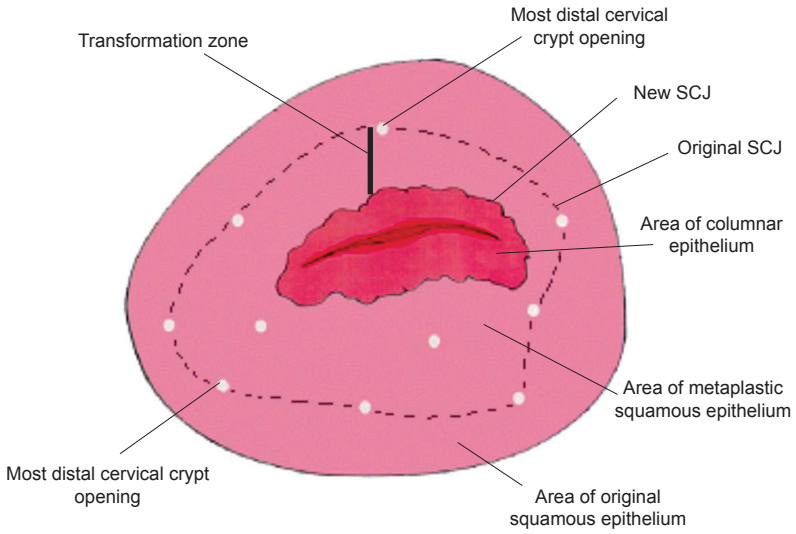
Because CIN and squamous cervical cancer always derive from the TZ, it is essential that the entire TZ can be visualized for the colposcopist to be able to recognize or rule out disease. The ectocervical part of the TZ is very rarely inaccessible, but the upper limit of the TZ may be partially or wholly endocervical, and it may be partially or fully visible to the examining colposcopist. Even though no abnormal findings may be evident in the visible, ectocervical part of the TZ, the presence of cervical neoplasia in the hidden, endocervical component cannot be ruled out.

8.1 After application of normal saline solution

8.1.1 Squamous epithelium

Squamous epithelium is pink, partially translucent, and smooth. The original squamous epithelium may appear slightly darker pink compared with the lighter shade of the metaplastic squamous epithelium of the TZ. If one looks closely, it is apparent in some women that a few crypt openings, which look like tiny circular holes, are scattered over the surface of the squamous epithelium of the TZ (Figs. 8.1 and 8.2). When these are occluded, they become nabothian follicles. Looking distally, away from the os towards the outer part of the ectocervix, one comes to a point where no more crypt openings and/or nabothian follicles are apparent. An imaginary line drawn connecting the most distal of these defines the original SCJ (the junction between the original or native squamous epithelium and the metaplastic squamous epithelium). The original SCJ forms the outer, distal, or caudal border of the TZ through its entire

Fig. 8.1. Illustration of the outer limit of the transformation zone. SCJ, squamocolumnar junction.



360° circumference. Sometimes, it is the subtle colour variation between the native and metaplastic or dysplastic squamous epithelium that defines the original SCJ. Unfortunately, this method is not foolproof. Lugol's iodine is also an unreliable test of the outer limit of the TZ, because the metaplastic epithelium covering the TZ may be more or less mature and therefore strongly or weakly positive. Finally, glands underneath the apparent outer reaches of the TZ may travel distally underneath the surface epithelium, and these glands are, of course, part of the TZ epithelium.

The next task is to identify the proximal or inner border of the TZ, which defines the new SCJ, which is the line of demarcation between the metaplastic squamous epithelium of the TZ and the native and untransformed columnar epithelium above the TZ (Figs. 8.2 and 8.3a). Where the new SCJ is situated and whether it is fully visible will determine the TZ type. The new SCJ tends to recede towards, and eventually into, the endocervical canal as a woman ages, most particularly after menopause (Fig. 8.3b). It is often possible to visualize the new SCJ, by the gentle use of an endocervical forceps such as the Desjardins or the Kurihara forceps (Fig. 5.12). If the SCJ is situated in the endocervical canal more than 10 mm from the external os, it may not be visible even with the aid of endocervical forceps. Also, when the speculum is properly and comfortably positioned, the cervico-uterine axis straightens and the cervix tends to come in line with the colposcopic view. Manipulation with endocervical forceps is then much easier. The vast majority of CIN lesions occur in the TZ, and the most severe changes tend to be closer to or abutting the new SCJ.

8.1.2 Columnar epithelium

In most young women, the new SCJ will be located at or close to the cervical os (Figs. 8.2 and 8.3a). The columnar epithelium, surrounded by the new SCJ, may appear at first glance to be "an erosion", which of course it is not. An erosion implies denuded epithelium, and erosions do often

Fig. 8.2. A series of images of a normal cervix at increasing magnifications. The patient was in early reproductive life and mid-cycle. The cervix is well estrogenized, and normal columnar epithelium is clearly seen through abundant clear mucus. The last image is after the application of Lugol's iodine. The outer limit of the transformation zone does not coincide with iodine positivity, because much of the transformation zone is often covered by relatively mature squamous epithelium, as in this case.

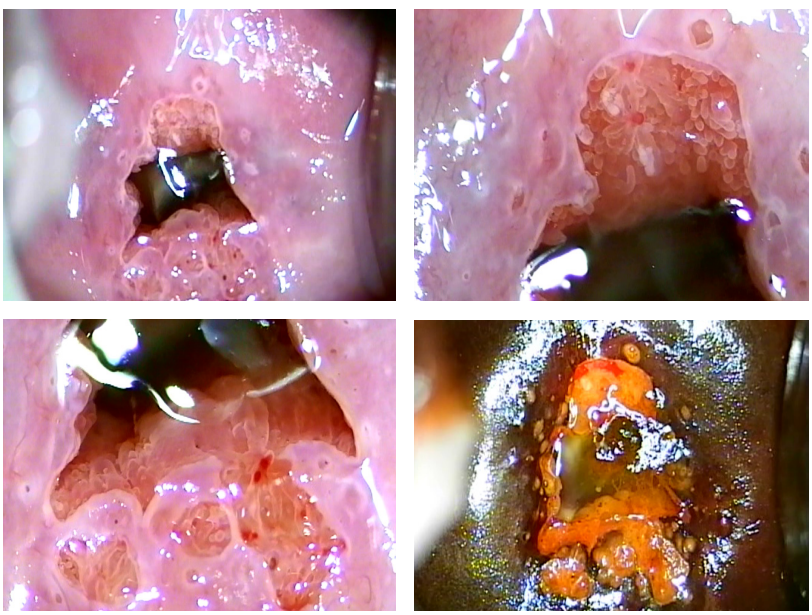
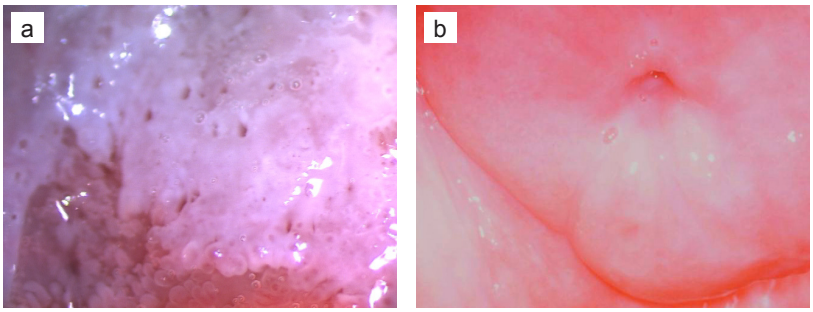


Fig. 8.3. (a) Squamocolumnar junction; clear demarcation between normal columnar epithelium and transformation zone epithelium. (b) The squamocolumnar junction is not visible here, in a postmenopausal woman. It is in the endocervical canal.



look red. Normal columnar epithelium is single-layered and therefore looks redder than the surrounding pinkish squamous epithelium. The columnar epithelium is thrown into crypts or folds, which often produce a grape-like or villous appearance, in contrast to the smooth, light pink squamous epithelium, which is multilayered and does not allow the stromal redness to penetrate as easily. Each columnar villous structure contains a fine capillary (Fig. 8.4), and the blood in the capillary and the vascularity of the underlying connective tissue give the columnar epithelium its strikingly dark reddish appearance. Small polyps may be detected during examination of the endocervical canal.

8.1.3 Vasculature

If a green or blue filter is used after cleaning away mucus with saline, the vasculature will be easier to see. These filters remove the background redness, thereby enhancing the image of the vessels, which will appear to be black. Using higher-power magnification (about 10×) is also helpful. Depending on the thickness or opacity of the overlying squamous epithelium, smaller vessels may or may not be visible. The smaller vessels that may be visible are capillaries that are in the stroma below the epithelium.

Two types of capillaries are apparent in or underneath the native or original squamous epithelium: reticular (network) or hairpin-shaped capillaries (Fig. 8.5). The reticular pattern is especially visible because the epithelium is thinner, for example in women using oral contraceptives and in postmenopausal women. The hairpin capillaries actually ascend vertically, loop over, and then descend back into the stroma where they came from. Because these loops are seen end-on, the colposcopic view usually is of dots with only a slight, if any, appearance of a loop at each. Inflammation of the cervix (e.g. trichomoniasis) often causes hairpin vessels to form staghorn-like shapes, so that the vessels become more prominent and the loop appearance is more apparent. Often, no vascular pattern is seen in or through the original squamous epithelium.

The appearances of ectocervical vessels described above are more prominent towards the outer TZ, closer to the original SCJ. In the more recently formed immature metaplastic squamous epithelium closer to the new SCJ, other vascular patterns become more prominent. These are large (compared with capillaries) branching surface vessels with three recognizable basic patterns (Fig. 8.5). The first pattern is much like a tree branching, and the second is commonly seen overlying nabothian cysts (Figs. 8.5 and 8.6). The regular structure and branching of the blood vessels suggest a benign (normal) nature. A third pattern sometimes occurs when healing has taken place after therapy for CIN, when the vessels are long and run parallel to one another.

The vessels in the columnar epithelium are actually terminal capillary networks. One capillary network is confined to the stromal core of each grape-like villus (Fig. 8.4), which projects up to the epithelial surface. With the colposcope, the rounded tips of the individual villi are the main features seen, and the top of the vessel network in each villus appears as a dot. Large, deep branching vessels may be seen in some cases.

Fig. 8.4. Diagrammatic representation of the capillary network projecting up into a columnar villus.

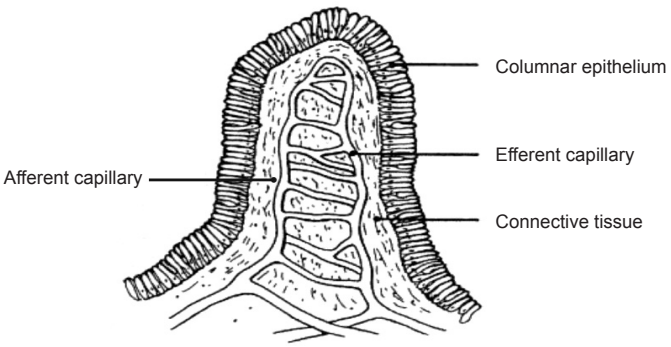
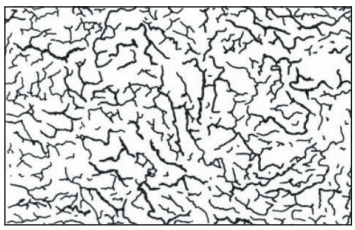
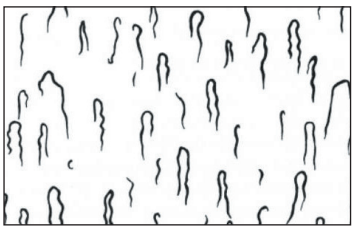


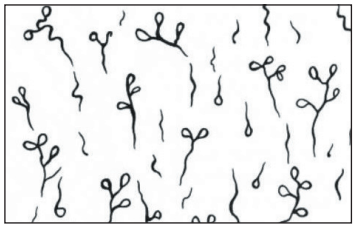
Fig. 8.5. Normal blood vessel patterns seen with a colposcope, usually best seen at 10× to 15× magnification.



Network capillaries



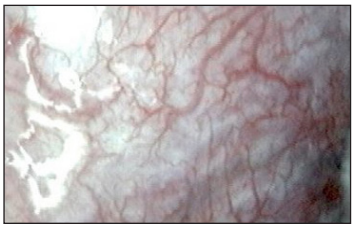
Hairpin capillaries

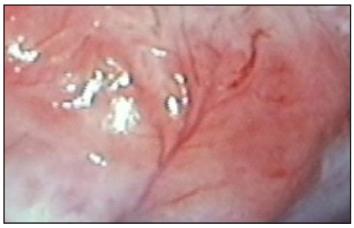


Staghorn-like vessels

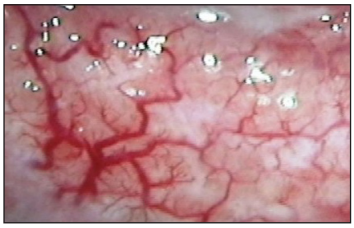
Long, parallel blood vessels

Regular vascular network





Long, regular branching vascular tree with gradual decrease in calibre



Blood vessels showing regular branching

8.2 After application of 5% acetic acid

8.2.1 Squamous epithelium

A minute or so after acetic acid has been applied and has taken effect, well-estrogenized squamous epithelium will appear to be a little duller and paler. Sometimes the SCJ will be prominently visible as a sharp, step-like white line, because of the presence of actively dividing immature squamous metaplasia around the edge, medial (proximal) to the junction (Fig. 8.3a).

Postmenopausal squamous epithelium is variably atrophic and looks paler, brittle, without lustre, and sometimes with subepithelial petechiae due to subepithelial capillaries from the slightest trauma to the epithelium, even the insertion of the vaginal speculum. The new SCJ may not be visible in postmenopausal women, because it has usually receded into the endocervical canal (Fig. 8.3b).

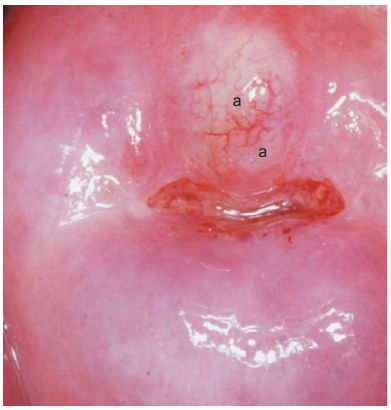
8.2.2 Columnar epithelium

Columnar epithelium is usually noticeably less dark red after acetic acid has been applied than it was with saline application, and the pale aceto-whitening of the villi may resemble a grape-like appearance (Figs. 8.2 and 8.3a). After the endocervical mucus among the villi has been coagulated by the acetic acid and wiped away, the topography may be seen more easily. In pregnant women, the villi are hypertrophied and the grape-like appearance is easier to observe.

8.2.3 Squamous metaplasia

During the different stages of the development of metaplasia, a range of colposcopic appearances may be seen. This can present a challenge to an inexperienced colposcopist,

Fig. 8.6. Normal branching vessels (labelled a) stretched over a nabothian follicle.



but in truth it does not usually affect management. The differences between normal, metaplastic, and low-grade squamous lesions are not reliably recognizable colposcopically and are not important clinically. Women should be treated if they have evidence of HSILs that are truly precancerous (HSIL-IN3) – this is when a transforming infection has taken place – and not when there is a LSIL or squamous metaplasia (see Chapters 4 and 11).

The development of squamous metaplasia may be recognized colposcopically (Jordan and Singer, 2006). In the earliest stage, the translucence of the columnar epithelial villi is lost and the villi become opaque at their tips; the villi widen and flatten, and successive villi fuse into clusters and sheets with a pale pink colour. Consequently, the metaplastic epithelium looks like a patchily distributed pale cluster, or sheet-like area, in the ectopic columnar epithelium (Fig. 8.7a).

As the metaplasia progresses, the grape-like configuration of the columnar epithelium disappears (Fig. 8.7b) and the spaces between the villi are fused with glassy, pinkish-white finger- or tongue-like membranes pointing towards the external os (Fig. 8.7c). There may be numerous crypt openings and islands of columnar epithelium scattered throughout the metaplastic epithelium. The rims of the crypt openings may not turn white with acetic acid early in the process of metaplasia, but may turn mildly white as the metaplastic process progresses. Gradually, the tongue-like metaplastic areas fuse together to form a continuously advancing glassy, shining, pinkish-white, or mildly pale epithelial area.

8.3 Nabothian follicles

Immature metaplastic epithelium eventually becomes fully developed mature metaplastic squamous epithelium resembling the original native squamous epithelium, except for the presence of some crypts (Fig. 8.3a) or nabothian follicles in the metaplastic epithelium (Fig. 8.6). Nabothian follicles may appear as white, dot-like areas in the beginning, before they enlarge with progressive accumulation of mucus within the follicle, presenting as pimple- or button-like ivory-white or mildly yellowish areas. The typical vessel formations in the metaplastic epithelium include long regular branching vessels with gradually decreasing calibre and a network of regular branching vessels. These vascular patterns may be seen more prominently over the nabothian follicles simply because they have been stretched over the distending surface of the follicle.

8.4 Cervical polyps

Cervical polyps are common and are usually benign. When they are protected in the endocervical canal by endocervical mucus, their

Fig. 8.7. (a) Early immature squamous metaplasia seen after acetic acid application. The tips of the villi are becoming white (labelled a), and some are fusing together (labelled b). (b) Immature squamous metaplasia seen after acetic acid application. Some of the villi have coalesced to form a thin squamous layer (labelled a). In other areas, some villi are beginning to fuse together (labelled b). (c) Immature metaplasia seen after acetic acid application. Peninsulas or tongues of metaplastic epithelium can be seen (labelled a), and some crypt openings are apparent (labels b and c, also arrow).

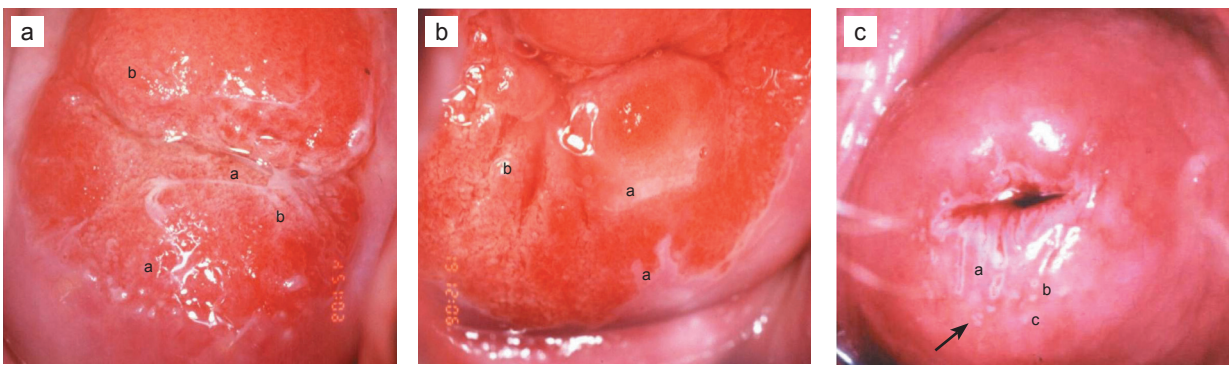
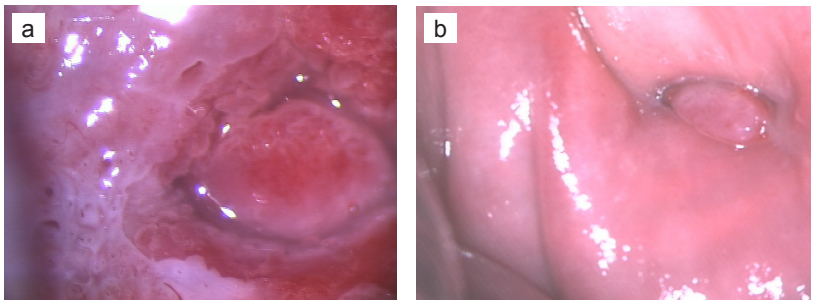


Fig. 8.8. (a) An endocervical polyp protected in the endocervical canal by the canal mucus has not yet undergone metaplasia. (b) A cervical polyp whose tip is permanently exposed to the vaginal environment. The exposed epithelium has undergone metaplasia.



surface epithelium does not metaplase (Fig. 8.8a). When metaplasia occurs in the epithelium covering a protruding cervical polyp, it is covered by pale white epithelium (Fig. 8.8b).

8.5 After application of Lugol's iodine

As described in Chapter 2, glycogenated cells take up iodine; the more mature they are, the more they take up iodine. Fully mature squamous epithelium has a uniform dark mahogany brown colour when stained with Lugol's iodine. Therefore, well-estrogenized squamous epithelium, whether original or mature squamous, will become dark or mahogany brown (Fig. 8.9a). This is sometimes helpful in distinguishing normal areas from abnormal areas in the TZ that were faintly acetowhite, and is one of the indices of normality/abnormality in the Swede score. Columnar epithelium does not stain with iodine. Immature squamous metaplastic epithelium usually does not stain with iodine or may partially stain if it is partially glycogenated (Fig. 8.9b and c). The vascular features, so easily seen with saline, may be difficult to observe after application of iodine.

Cervical polyps do not stain with iodine, because they are usually covered with columnar or immature metaplastic epithelium. If the maturation of the metaplastic epithelium varies, one may observe various fields of no uptake or partial to full iodine uptake on the polyp.

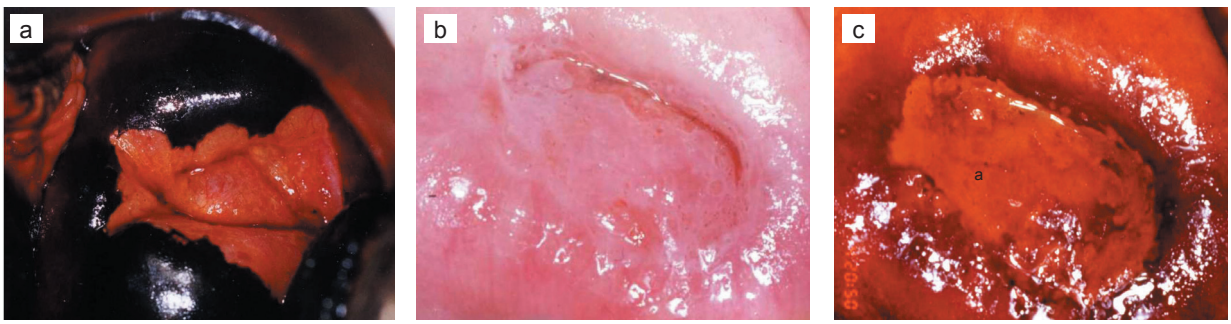
In postmenopausal women, the atrophic ectocervix will not stain fully with iodine.

8.6 Congenital transformation zone

The congenital or original TZ stains faint white after the application of acetic acid. In this condition, the metaplastic epithelium formed during the latter portion of fetal life, lying distal to the TZ formed after birth, is located far out on the ectocervix, some distance from the cervical os, and in some cases may even extend onto the vagina. It is important to recognize this as a normal condition, for which no treatment is necessary. It commonly extends onto the vaginal walls anteriorly and posteriorly, and less so laterally.

With acetic acid, the congenital TZ will usually take on a mild acetowhite stain and the capillary vasculature may have a fine mosaic or punctate pattern. It does not take up iodine after the application of iodine. If a biopsy is taken of the tissue to confirm the diagnosis, it is best to alert the pathologist of the colposcopic impression.

Fig. 8.9. (a) Clear distinction between full uptake of Lugol's iodine in the native squamous epithelium (Schiller test-negative) outside a transformation zone and no uptake in the immature squamous metaplastic epithelium (Schiller test-positive). (b) Immature squamous metaplasia in this normal transformation zone before the application of Lugol's iodine. (c) Minimal patchy uptake of Lugol's iodine in this normal transformation zone with immature squamous metaplasia (labelled a) (same cervix as in part b).



Key points

- Squamous epithelium appears smooth and translucent, with a pinkish tinge.
- The original squamous epithelium, i.e. outside the transformation zone, appears slightly darker pink than the metaplastic epithelium within the transformation zone.
- Columnar epithelium appears darker red, with a grape-like or villous appearance.
- Often no vascular patterns are seen in or through the original squamous epithelium.
- After the application of acetic acid, the transformation zone squamous epithelium appears dull and pale in contrast to the usual pink hue.
- Squamous metaplasia has a range of colposcopic appearances, which cannot be reliably distinguished from low-grade squamous intraepithelial lesion.
- Both the original squamous and the mature squamous metaplastic epithelium of the transformation zone stain mahogany brown with Lugol's iodine (Schiller test-negative).
- Immature squamous metaplastic epithelium will usually partially take up Lugol's iodine.
- Postmenopausal squamous epithelium will not take up Lugol's iodine (Schiller test-positive).

CHAPTER 9.

Inflammatory lesions of the cervix

This chapter describes the colposcopic appearances of a variety of common inflammatory conditions but is not a substitute for a full description of lower genital tract infection.

The interested reader is referred to Hicks (2002) for a fuller description of the investigation and management of gynaecological infections.

Inflammatory conditions are extremely common in many parts of the Southern Hemisphere and in particular for socioeconomically disadvantaged women. They are usually, but not always, caused by infection, which may be viral, bacterial, or protozoal.

Non-infective causes of inflammation include a foreign body (tampon, IUCD), trauma, or chemical irritation in the form of gels, creams, and other non-proprietary formulations that have been prescribed for symptomatic reasons. Table 9.1 lists the common infections responsible for cervicovaginitis. Lower genital tract infections are usually symptomatic and should always be treated.

Pruritus and vaginal discharge, which is often offensive, and dysuria and introital dyspareunia are additional burdens for affected women. They should always be treated.

The more common infections are trichomoniasis (caused by *Trichomonas vaginalis*), candidiasis, bacterial vaginosis, chlamydia, gonorrhoea, and herpes simplex.

Less common infections that occur in the cervicovaginal epithelium are tuberculosis, amoebiasis, schistosomiasis, *Haemophilus ducreyi, Mycoplasma hominis,* and *Escherichia coli.*

9.1 Wet preparation, cytological, and histological appearances of infection

The infective organism responsible for cervicovaginitis is most accurately identified in the laboratory. At a tissue level, inflammatory changes in the epithelium are characterized by vascular hypertrophy and intraepithelial cellular damage and denudation. Cellular layers may be denuded through the full spectrum of desquamation, from fewer epithelial layers to frank ulceration. In the deeper layers, the cells may be enlarged and swollen with a neutrophilic infiltration. There is an associated collection of cellular debris and fluid as discharge on the epithelial surface.

Gram staining or even cytological examination of infection is diagnostically specific.

Table 9.1. Treatment of reproductive tract infections

Reproductive tract infection	Treatment guidelines	
	Non-pregnant women	**Pregnant women**
Trichomonas vaginalis (trichomoniasis)	Metronidazole 400–500 mg orally, 2 times daily for 7 days or a single dose of metronidazole 2 g orally or a single dose of tinidazole 2 g orally.	Metronidazole 400–500 mg orally, 2 times daily for 7 days. High-dose treatment not recommended. Safety of tinidazole not well evaluated.
Candidiasis	Clotrimazole pessary 500 mg immediately or clotrimazole pessary 200 mg for 3 nights or a single dose of fluconazole 150 mg orally. All topical and oral azoles are effective.	Clotrimazole pessary 200 mg for 3 nights or clotrimazole pessary 100 mg for 6 nights. Oral treatment contraindicated.
Bacterial vaginosis	Metronidazole 400 mg orally, 2 times daily for 5–7 days or metronidazole 2 g immediately or intravaginal metronidazole gel (0.75%) once daily for 5 days or intravaginal clindamycin cream (2%) once daily for 7 days.	Metronidazole 400 mg orally, 2 times daily for 5–7 days or intravaginal metronidazole gel (0.75%) once daily for 5 days or intravaginal clindamycin cream (2%) once daily for 7 days.
Chlamydial infection	Doxycycline 100 mg orally, 2 times daily for 7 days or a single dose of azithromycin 1 g orally.	A single dose of azithromycin 1 g orally or erythromycin 500 mg orally, 4 times daily for 7 days or amoxicillin 500 mg orally, 3 times daily for 7 days. Pregnant women require a test of cure.
Gonococcal infection	**Refer to local sensitivity data.** A single dose of intramuscular ceftriaxone 500 mg plus a single dose of oral azithromycin 2 g. Alternatives include a single dose of intramuscular ceftriaxone 500 mg or a single dose of intramuscular spectinomycin 2 g plus a single dose of oral azithromycin 2 g or other regimens as guided by sensitivities.	**Refer to local sensitivity data.** A single dose of intramuscular ceftriaxone 500 mg plus a single dose of oral azithromycin 1 g. Alternatives include a single dose of intramuscular ceftriaxone 500 mg or a single dose of intramuscular spectinomycin 2 g plus a single dose of oral azithromycin 1 g or other regimens as guided by sensitivities.
Syphilis	Early syphilis: A single dose of intramuscular benzathine penicillin 2.4 MU or doxycycline 100 mg, 2 times daily for 14 days. Late syphilis: Intramuscular benzathine penicillin 2.4 MU weekly for 3 doses or doxycycline 100 mg, 2 times daily for 28 days. Neurosyphilis: Seek specialist advice.	Early syphilis: A single dose of intramuscular benzathine penicillin 2.4 MU or intramuscular ceftriaxone 500 mg, once daily for 10 days. Late syphilis: Intramuscular benzathine penicillin 2.4 MU weekly for 3 doses. Neurosyphilis: Seek specialist advice.
Lymphogranuloma venereum	Doxycycline 100 mg orally, 2 times daily for 21 days or erythromycin 500 mg orally, 4 times daily for 21 days.	Erythromycin 500 mg orally, 4 times daily for 21 days.
Chancroid	Ciprofloxacin 500 mg orally, 2 times daily for 3 days or a single dose of azithromycin 1 g orally or erythromycin 500 mg orally, 4 times daily for 7 days.	A single dose of azithromycin 1 g orally or erythromycin 500 mg orally, 4 times daily for 7 days.
Granuloma inguinale	Azithromycin 1 g orally, weekly or ciprofloxacin 500 mg, 2 times daily or doxycycline 100 mg, 2 times daily. All treatment should be for a minimum of 3 weeks or until lesions have healed.	Erythromycin 500 mg, 4 times daily for 3 weeks or until ulcers have healed.
Genital herpes	Acyclovir 400 mg orally, 3 times daily for 5 days or famciclovir 250 mg, 3 times daily for 5 days.	Acyclovir 400 mg orally, 3 times daily. Seek specialist advice.
Pelvic inflammatory disease	A single dose of intramuscular ceftriaxone 500 mg plus a single dose of azithromycin 1 g orally plus doxycycline 100 mg, 2 times daily and metronidazole 400 mg, 2 times daily for 14 days.	A single dose of intramuscular ceftriaxone 500 mg plus a single dose of azithromycin 1 g orally plus erythromycin 500 mg orally, 4 times daily for 14 days. Poor evidence available.

Figs. 9.1–9.9 show examples of specific infections recognized at either Gram staining or cytological examination. Cytology is not the best method of detecting cervicovaginal infections but will sometimes incidentally recognize them and can alert the clinician to an unsuspected infection.

9.2 Colposcopic appearance of cervicovaginitis

The epithelium of a mild infection may be minimally altered, but by the time it presents to a gynaecologist the appearances are usually very abnormal. Typically, there is a vascular response as well as evidence of epithelial damage. The inflammatory response does not usually reflect the infecting organism. The vascular response includes redness, punctation (often grouped in a distribution commonly known as “strawberry appearance”), and a diffuse, fluffy acetowhiteness not dissimilar to LSIL but distributed non-specifically and

Fig. 9.1. (a) A Gram stain view of a trichomonad. (b) A cytology preparation revealing trichomoniasis.

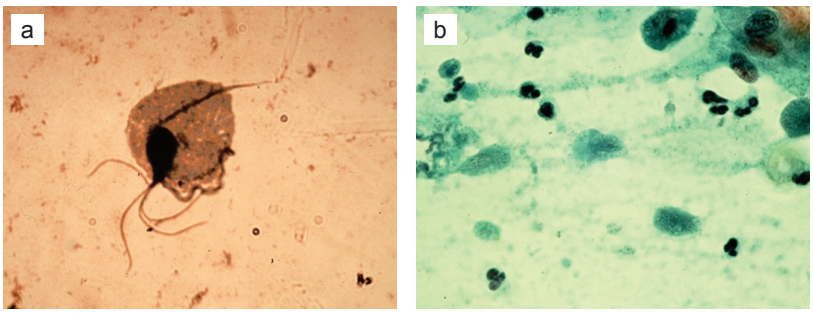


Fig. 9.2. A cytology preparation showing a typical cytoplasmic halo, characteristic of HPV infection.

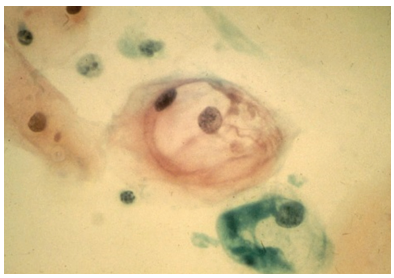


Fig. 9.3. (a) A Gram stain preparation of candidiasis. (b) A cytology slide showing candidiasis.

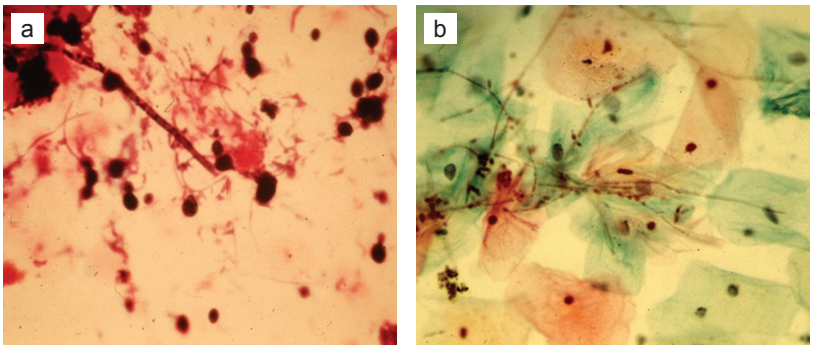


Fig. 9.4. A cytology preparation showing a case of herpes simplex.

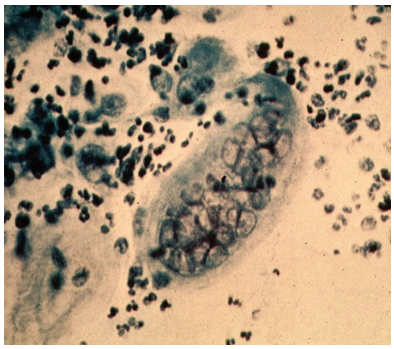


Fig. 9.5. A cytology preparation showing a case of actinomycosis.

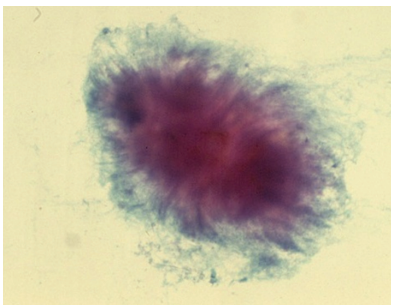


Fig. 9.6. (a) A Gram stain revealing bacterial vaginosis. (b) A cytology slide showing a case of bacterial vaginosis.

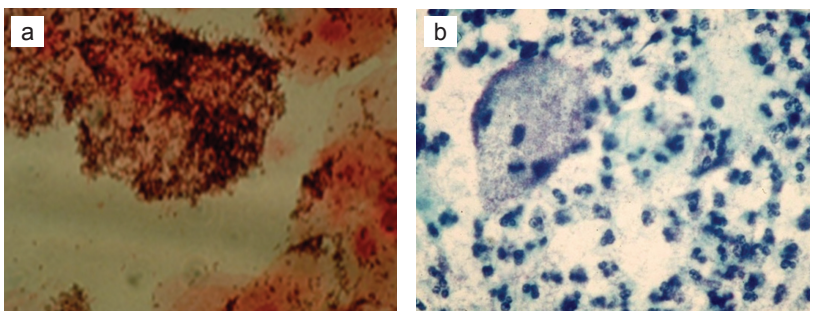


Fig. 9.7. A tissue culture slide showing a case of chlamydia.

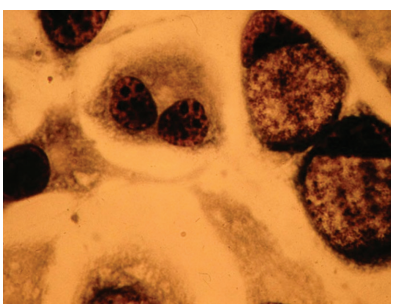


Fig. 9.8. (a) A Gram stain showing an (intracellular) gonococcus infection. (b) A cytology preparation showing an (intracellular) gonococcus infection.

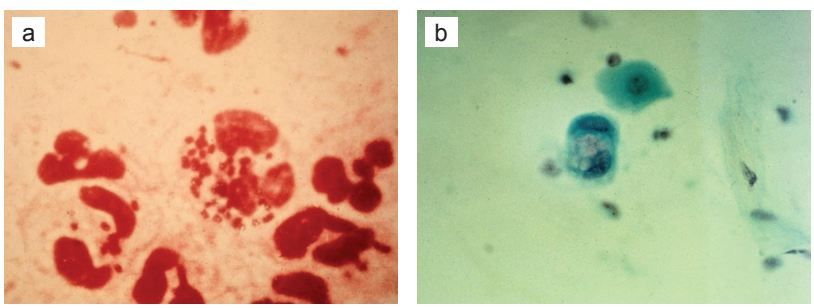
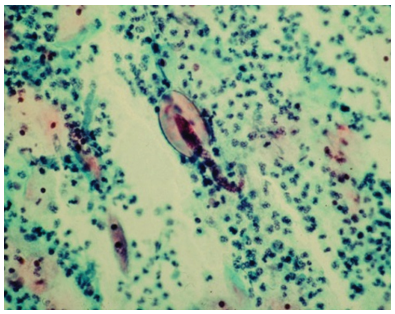


Fig. 9.9. A cytology preparation showing threadworm (*Enterobius vermicularis*), which is actually hatching in this image.



very widely, both inside and outside the TZ. Terminal capillaries may become hypertrophied, i.e. they may appear coiled, duplicated, or simply dilated. Vertical capillary loops in the epithelium may become hyperaemic and, again a little like mild squamous intraepithelial lesion (SIL) changes, may have a punctate appearance, sometimes in specific clumps, creating the strawberry appearance referred to above. When the infection has produced these appearances, there will almost always be an associated vaginal discharge and it is usually pruritic.

9.3 Colposcopic examination

9.3.1 Before application of acetic acid

An examination in the presence of infection is usually more uncomfortable for the patient. Swabs for culture should be taken before any fluids have been applied. Examination, before the application of acetic acid, may reveal moderate to severe cervical and vaginal secretions, and these may sometimes suggest the nature of underlying infection. Bacterial infections are associated with thin, liquid, seropurulent discharge. The secretion may be foul-smelling in the case of anaerobic bacterial overgrowth, bacterial vaginosis, and *Trichomonas* infection. Gonorrhoea results in a purulent vaginal discharge and cervical tenderness. Excoriation marks may be present with trichomoniasis, moniliasis, and mixed bacterial infections. Foul-smelling, dark-coloured mucopurulent discharges are associated with inflammatory states due to foreign bodies, for example a retained tampon.

A large coalesced ulcer due to herpes, or other inflammatory conditions, may mimic the appearance of invasive cancer. Chronic inflammation may cause recurrent ulceration and healing of the cervix, resulting in distortion of the cervix due to healing by fibrosis. There may be associated necrotic areas as well. When there is any doubt, a biopsy should be taken. Rare and uncommon cervical infections, due to protozoal infections (schistosomiasis and amoebiasis) or tuberculosis, cause extensive ulceration and necrosis of the cervix with symptoms and signs that mimic invasive cancer; again, a biopsy will discriminate.

If the infectious process is accompanied by marked ulceration (with or without necrosis), the ulcerated area may be covered with purulent exudate, with marked differences in the surface level of the cervix. There may be exudation of serous droplets.

Long-standing bacterial, fungal, or protozoal infection and inflammation may lead to fibrosis, which appears white or pink, depending on the degree of fibrosis. The epithelium covering the connective tissue is fragile, leading to ulceration and bleeding. Appearances after the application of acetic acid and iodine are variable, depending on the integrity of the surface epithelium.

In the case of cervicitis, the columnar epithelium is intensely red and bleeds on contact, and an opaque purulent discharge may be present. The columnar villous or grape-like appearance may be lost because of flattening of the villi, because of repeated inflammation, and because there are no clearly defined papillae (Fig. 9.10). Extensive areas of the cervix and infected vaginal mucosa appear red because of congestion of the underlying connective tissue.

9.3.2 After application of acetic acid

The liberal application of acetic acid clears the cervix and vagina of secretions but may cause pain or discomfort. Cervicovaginitis is associated with oedema, capillary dilatation, enlargement of the stromal papillae (which contain the vascular bundles), and infiltration of the stroma with inflammatory cells. The chronically inflamed cervix may appear reddish, with ill-defined, patchy acetowhite areas scattered in the cervix, not restricted to the TZ, and it may bleed on contact. The enlarged stromal papillae appear as red spots (red punctation) on a pinkish-white background, usually in the case of *T. vaginalis* infection, after the application of acetic acid.

An inexperienced colposcopist may confuse the inflammatory punctations with those seen in CIN. However, one can differentiate using the

Fig. 9.10. An inflamed cervix; non-specific infection.

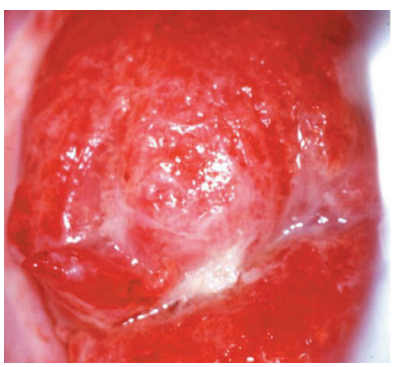
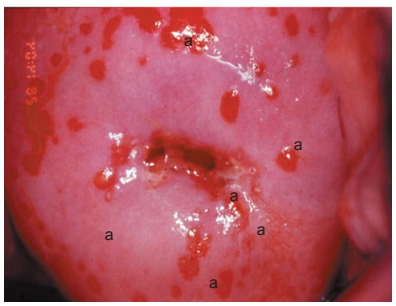


Fig. 9.11. Strawberry appearance in an inflamed cervix, with multiple red spots (labelled a).

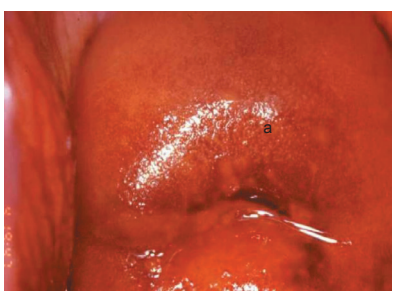


following criteria. Inflammatory punctations are fine, with extremely minimal intercapillary distances, and are diffusely distributed (not restricted to the TZ), and they involve the original squamous epithelium and vagina. As the inflammation persists and becomes chronic, it results in large, focal red punctations due to large collections of capillaries grouped together, which appear as several red spots of different sizes visible on a pinkish-white background, producing the so-called strawberry spots (Fig. 9.11). Colposcopically, a chronically inflamed cervix may sometimes resemble invasive cervical cancer.

9.3.3 After application of Lugol's iodine

The test outcome after the application of Lugol's iodine depends on the desquamation and loss of cell layers containing glycogen. If desquamation is limited to the summit of the stromal papillae, where the squamous epithelium is thinnest, a series of thin yellow spots are seen on a mahogany-brown background, giving a stippled appearance (Fig. 9.12). When the inflammation persists and the infection becomes chronic, the small desquamated areas become confluent to form large desquamated areas, leading to the so-called leopard-skin appearance (Fig. 9.13). These features are often found with *Trichomonas* infection but also may be seen with fungal and bacterial infections. If there is marked desquamation, the cervix appears yellowish-red, with involvement of the vagina. Again, the application of Lugol's iodine can be intensely uncomfortable in the presence of infection.

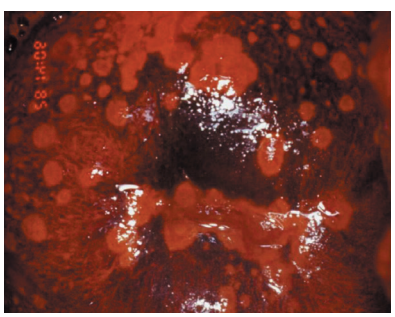
Fig. 9.12. Stippled appearance (labelled a) after the application of Lugol's iodine in a case of trichomoniasis.



9.3.4 Summary

Inflammatory conditions of the cervix are associated with excessive, usually malodorous, mucopurulent, seropurulent, or whitish discharge, red punctations, ulceration, and healing by fibrosis. The secretion is frothy with bubbles in the case of trichomoniasis, and sticky and cheese-white in candidiasis. Inflammatory lesions of the cervix may be differentiated from CIN by their large, diffuse involvement of the cervix, extension to the vagina, red colour tone, and associated symptoms such as discharge and pruritus.

Fig. 9.13. Leopard-skin appearance of vaginitis associated with a trichomoniasis infection.



9.4 Specific infections

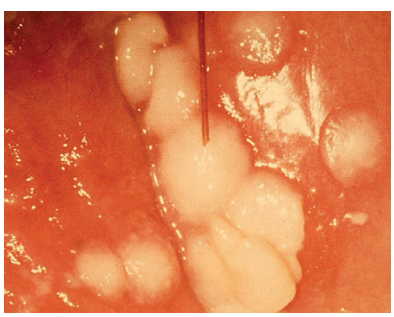
9.4.1 Candidiasis

Infection with *Candida albicans* is extremely common and, with low-grade chronic infection, may be entirely asymptomatic. It is sometimes called a thrush infection, because the breast of the common thrush bird has the speckled grey-white appearance once thought typical of candidal pharyngitis. When it flourishes, it nearly always becomes symptomatic, producing a thick cheese-like discharge and pruritus of the vulva and vagina. There may be a concurrent vulvitis. The appearances are more specific than for most cervicovaginal infections and do not usually require laboratory confirmation, but where simple treatment does not work, the usual workup for candidal vulvovaginitis should be implemented. Fig. 9.14 depicts candidal cervicitis and vaginitis seen through the colposcope.

9.4.2 Trichomoniasis

This extremely common infection causes serious discomfort by way of an intensely pruritic and offensive discharge often described as fishy

Fig. 9.14. Typical candidiasis seen at high-power examination of the cervix.



in odour. The discharge is frothy, sometimes almost green, and quite profuse, sometimes even requiring a sanitary towel to prevent staining of underclothes. It produces the classic strawberry appearance more commonly than other infections, but not exclusively, and may be present in association with other pathology (cancer, polyps, a foreign body, and/or surgical intervention). Colposcopically, the epithelial inflammatory response is non-specific. The colposcopic appearance of trichomoniasis is shown in Figs. 9.12, 9.13, and 9.15.

9.4.3 Herpes simplex

Small vesicles filled with serous fluid may be observed in the cervix and vaginal epithelia in the early vesicular phase of herpes simplex viral infection. Herpetic infections are associated with episodes of painful vulvar, vaginal, and cervical ulceration lasting for up to 2 weeks. The ulceration that accompanies some herpetic infection can be so pronounced and the associated epithelial inflammatory response so severe as to render the colposcopic appearances very similar to those of cancer. A biopsy will sometimes be necessary to discriminate between them. Fig. 9.16 shows typical appearances of a herpetic infection on the cervix and vulva.

9.4.4 Bacterial vaginosis

The classic sign of bacterial vaginosis is the relative lack of inflammatory response in the epithelium despite the presence of significant symptoms and a profuse grey-white fluid discharge (Fig. 9.17). When mixed with potassium hydroxide, the discharge also has a fishy smell (Fig. 9.18).

9.4.5 Syphilis

Syphilis is not often symptomatic. Also, a primary cervical ulcer is not usually the sole site of a syphilitic lesion. Any ulcer can and does mimic invasive cancer, and it is often necessary to take a biopsy to rule out cancer. Table 9.2 lists the differential diagnosis of a cervical ulcer.

9.4.6 Chlamydia and gonorrhoea

The clinical presentation of chlamydia and gonorrhoea, both sexually transmitted infections, is not disease-specific. In other words,

Table 9.2. Differential diagnosis of a suspicious cervical ulcer

Condition
Cervical cancer
Syphilis
Herpes simplex
Chancroid
Tuberculosis (or protozoal infection)
Lymphogranuloma venereum
Behçet disease

Fig. 9.15. Three examples of colposcopic appearance of typical trichomoniasis.

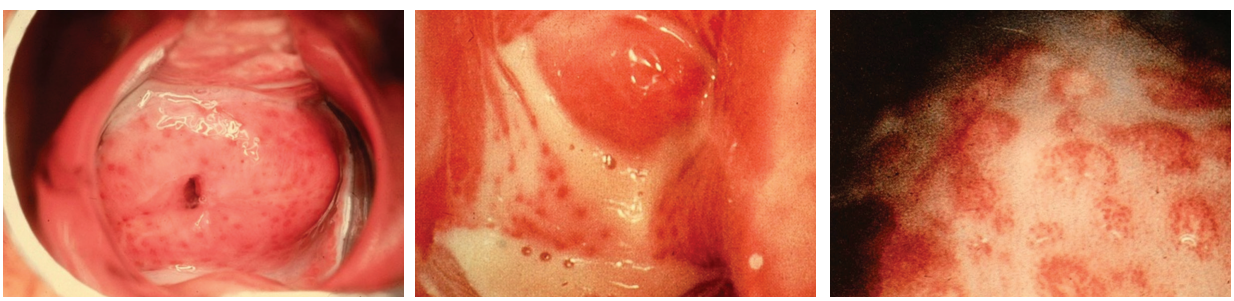


Fig. 9.16. Colposcopic appearance of cervical and vulvar herpes simplex, representing the (a) blistering, (b) ulcerating, (c) healing (arrow indicates healing vulvar ulcer), and (d) scabbing phases of the condition.

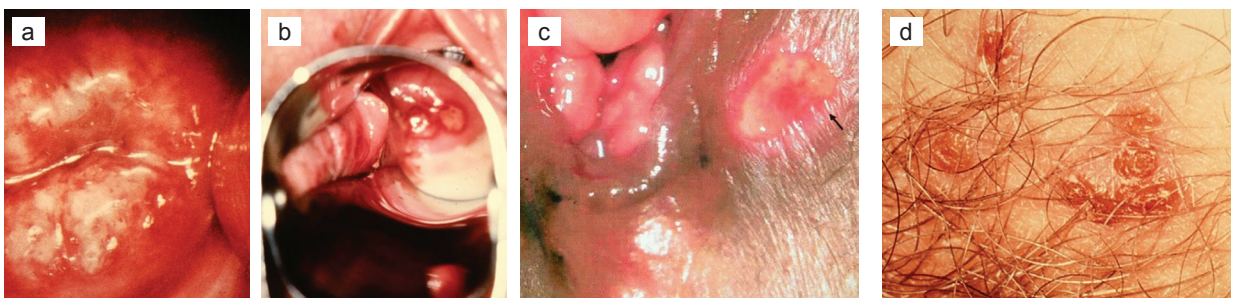


Fig. 9.17. Greyish discharge suggestive of bacterial vaginosis.

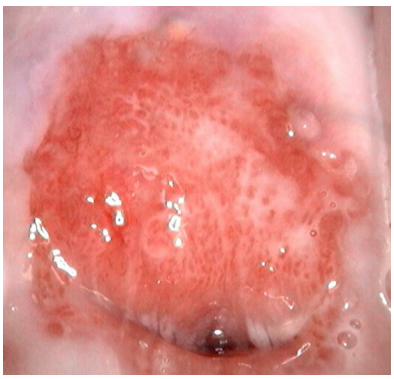
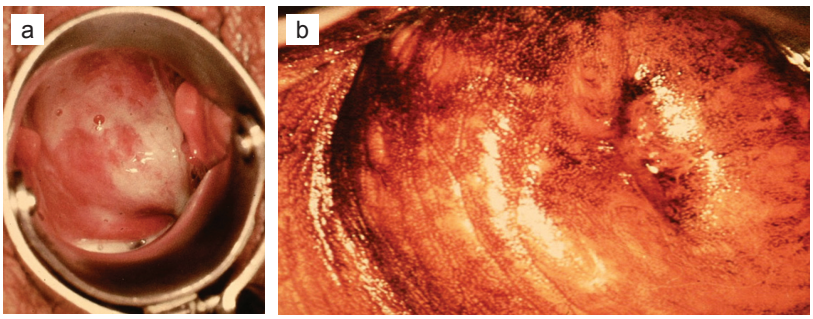
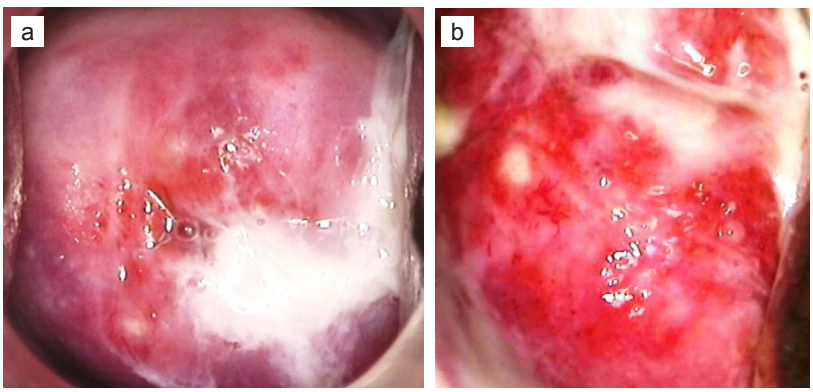


Fig. 9.18. Bacterial vaginosis (BV) before (a) and after (b) the application of Lugol's iodine. Note the nondescript discharge in (a). The BV infection has produced relatively little inflammatory response and shows the thick, adherent nature of the discharge associated with BV.



chlamydia and gonorrhoea may present in completely asymptomatic women or they may present with cervicitis of a varying degree. To confirm or rule out the suspicion of either requires a laboratory diagnosis from swabs taken from the endocervical canal. This will often cause contact bleeding. These infections are both intracellular infections. Gonorrhoea is an obligate human pathogen. It is a gram-negative diplococcus. The bacterial parasite chlamydia is also an intracellular organism. When symptomatic, chlamydia does produce a relatively specific cervical folliculitis, but this is not in all cases, and it may infect the upper genital tract with significant organ function damage without any lower genital tract symptoms or signs. The interested reader is referred to Faro (2006) for a fuller description of both gonorrhoeal and chlamydial cervicitis (Fig. 9.19).

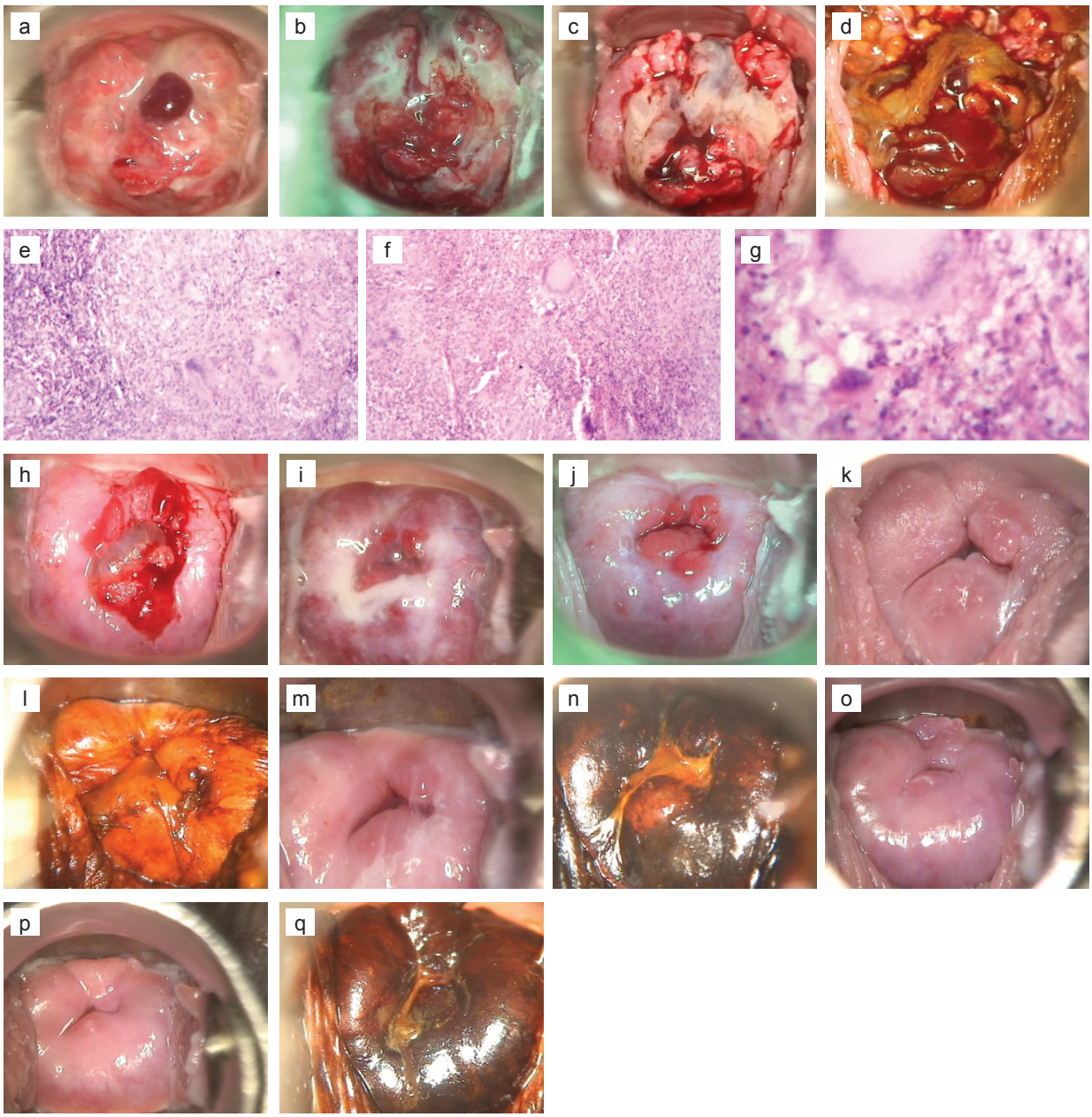
Fig. 9.19. (a) Cervical discharge suggestive of cervicitis. (b) Beefy-red cervix with discharge suggestive of cervicitis.



9.4.7 Other infections

Tuberculosis, schistosomiasis, and amoebiasis may all produce such a profound inflammatory response that they are indistinguishable from cancer and a biopsy is required for diagnosis. Fig. 9.20a–q follows the chronology of a case of cervical tuberculosis. The case is typical in that it was difficult to recognize and responded completely to appropriate therapy. The patient, a 26-year-old nulliparous and married woman, presented after many years of postcoital bleeding, serosanguinous vaginal discharge, and, eventually, almost continuous per vaginal bleeding. She was seen for colposcopic evaluation 7 years after symptoms began, and at examination, contact bleeding was immediate. The series of images reveals the cervical appearance over 6 years from before diagnosis to post-treatment follow-up. The diagnosis was made at histological examination of a colposcopically directed biopsy. A cytology smear was persistently reported as normal over 6 years after treatment with antituberculous therapy.

Fig. 9.20. (a) First colposcopic assessment before acetic acid application. (b) Green-filter low-power view. Pap smear contact produced immediate brisk bleeding. (c) Appearance after acetic acid application. (d) Appearance after iodine application. (e) A granuloma seen at histological examination of a biopsy taken at the first colposcopic assessment visit. (f) Langhans giant cell reaction seen at low-power magnification. (g) Langhans giant cell reaction seen at high-power magnification. (h) Colposcopic appearance 4 weeks after beginning antituberculous therapy. (i) Colposcopic appearance before saline application, 8 weeks after treatment. (j) Colposcopic appearance after saline washing of the epithelium, 8 weeks after treatment. (k) Colposcopic appearance after saline washing of the epithelium, 6 months after treatment. (l) Colposcopic appearance after Lugol's iodine application, 6 months after treatment. (m) Colposcopic appearance at low-power magnification after saline application, 2 years after antituberculous therapy. (n) Colposcopic appearance after Lugol's iodine application, 2 years after antituberculous therapy. (o) Colposcopic appearance after saline washing, 3 years after antituberculous therapy. (p) Colposcopic appearance after saline washing, 4 years after antituberculous therapy. (q) Colposcopic appearance after Lugol's iodine application, 4 years after antituberculous therapy.



Key points

- Inflammatory lesions of the cervix are most commonly caused by specific infections and will produce a non-specific inflammatory response, which typically includes redness, discharge, vascular abnormalities, and varying degrees of epithelial desquamation.
- Inflammatory lesions are not confined to the transformation zone.
- Cervical infections may mimic intraepithelial lesions or cancer. A biopsy will sometimes be necessary to discriminate between infection and squamous intraepithelial lesion or cancer.
- Colposcopy and cytology are not methods to be relied upon in diagnosing sexually transmitted infection.
- A delay in treating a significant sexually transmitted infection can be the cause of more morbidity than delay in treating squamous intraepithelial lesion, particularly low-grade (e.g. gonorrhoea or chlamydia).

CHAPTER 10.

Colposcopic examination of the abnormal cervix

To perform a useful colposcopic examination of the abnormal cervix, one should first be thoroughly familiar with the appearances of the normal cervix and with the current international standard nomenclature (see Annex 3).

Also, to maximize the examination, the colposcopist should use a standard reporting method so that self-audit and comparison with normal parameters of quality may be performed. The examination should always record the core findings listed in Table 10.1.

A large drawing or a video recording should always be made for future reference (see Annex 2). Fig. 6.2 shows some commonly used icons to document individual colposcopic features. Fig. 10.1a shows an example of a drawing with some of the patterns seen at a colposcopic examination.

Colposcopy is a dynamic process, not a single-image examination, and so documentation needs to describe findings at different times during the examination (before and after saline application, after acetic acid application, at low and high power, after Lugol's iodine application). A video recording is ideal but is not always available. Clear drawings on standard diagram templates are good substitutes.

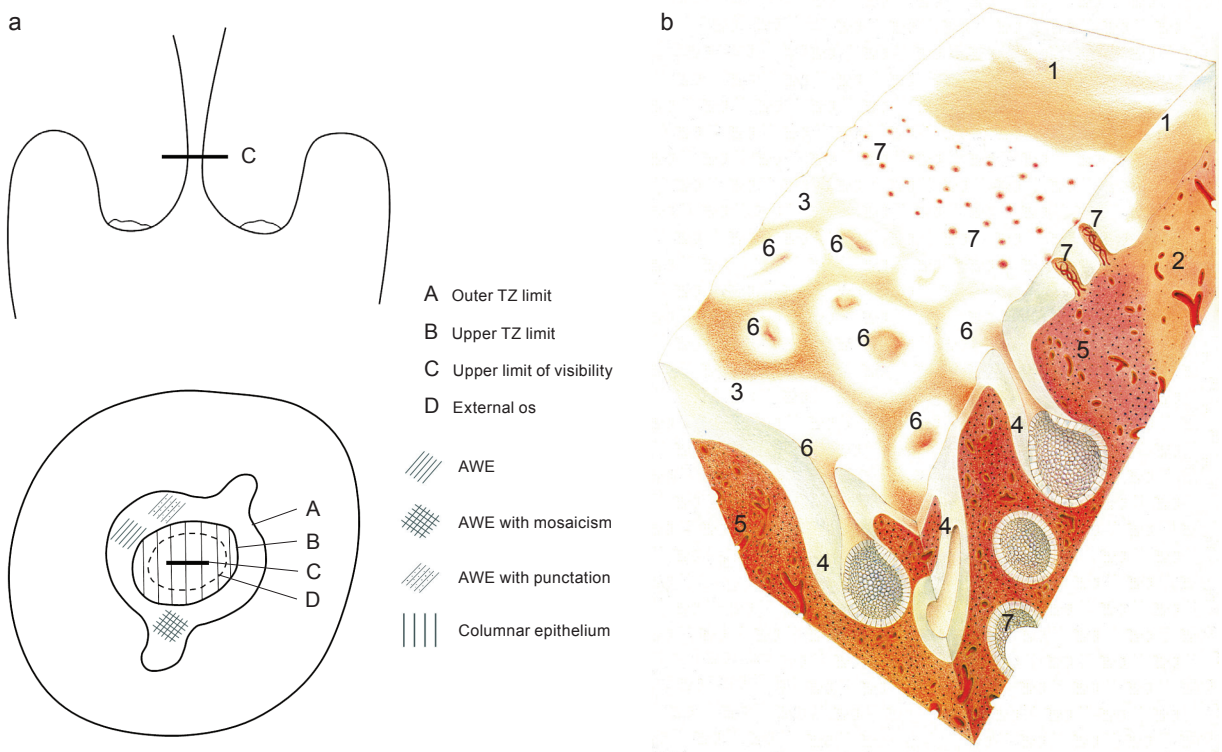
After it is established that the examination is adequate (i.e. it is not compromised by any circumstances such as infection, bleeding, or scarring), the TZ type and size should be determined. In some colposcopy clinics, it is routine to examine the entire lower genital tract; in many others, the examination is confined to the cervix and upper vagina.

The diagnostic accuracy of colposcopy (see Section 1.6.3) relies on image recognition skills to discriminate between different lesional characteristics. These characteristics are best assessed formally using a scoring system (Bowring et al., 2010; Reid and Scalzi, 1985; Strander et al., 2005). The Swede score (see

Table 10.1. Core findings of every colposcopic examination

Finding
Adequacy of examination
Transformation zone type
Transformation zone size
Swede score
Drawing of transformation zone and lesion(s)
Biopsy (if required) taken and from where
Management options
Details of treatment, if performed

Fig. 10.1. (a) Drawing of colposcopic findings; acetowhiteness and vessel patterns indicated in a type 1 transformation zone (TZ). Note that the upper margin of the TZ is outside the external os. The denseness of acetowhiteness and the coarseness of vessel patterns are recorded in the Swede score. AWE, acetowhite epithelium. (b) Illustration of some of the characteristics of dysplasia seen at colposcopy. Normal squamous epithelium (1) remains translucent after the application of acetic acid. It covers normally vascularized connective tissue (2). This part of the cervix is pink. Dysplasia, coagulated by acetic acid, has whitened (3). It occupies the neck of the glands (4). The connective tissue is congested (5), with numerous dilated vessels and dense leukocytic infiltration (black spots). Around the opening of the glands (6), very thick dysplastic epithelium completely masks the congestion and forms a white ring. In areas where the epithelium is thinner, congestion is visible and the cervix is red. At the summit of the vascular bundles, the vessels appear in the form of red dots (7).



Annex 4) is a simple, user-friendly, and reliable scoring system and is to be recommended. It incorporates five different characteristics: acetowhiteness, margin status, vascular patterns, lesion size, and iodine uptake. Each is scored as 0, 1, or 2. It is a simpler and more user-friendly system than the Reid Colposcopic Index (also known as the Reid score), which did not include lesion size, and it appears to have good positive and negative predictive values.

This manual is not a comprehensive atlas of colposcopic images, but several are available. The IARC digital atlas of colposcopy (available from http://screening.iarc.fr/atlascolpo.php) is perhaps the most practical from a trainee's perspective and may be considered a sister publication to this manual.

Also, IARC and IFCPC have collaborated on a training course in colposcopy and cervical cancer prevention, which uses the atlas as one of its teaching modules (www.ifcpc.org). Finally, the interested reader is referred to one of several colposcopy atlases in book form (Cartier and Cartier, 1993; Mayeaux and Cox, 2011). Some of Cartier's classic illustrations of vascular abnormality are reproduced here.

The colposcopic determination of abnormality and its severity depends on the recognition and qualitative assessment of five, or perhaps six, characteristics, which are listed in Table 10.2. Five of the six are included in the Swede score.

10.1 Acetowhiteness

After the application of 3% or 5% acetic acid, the TZ epithelium will appear white to a differing degree across a range of conditions, many of which are normal. It will appear faintly white with most immature metaplastic change, with almost all

grades of CIN, with some inflammatory conditions, and with any kind of condylomatous change. In severe dysplastic lesions, the whiteness is often denser and is sometimes called oyster white. But acetowhiteness, by itself, is not a reliable discriminator between normal and abnormal or between a transient and a transforming HPV infection (HSIL-IN3). Also, the speed with which the epithelium becomes white and how quickly the whiteness fades may vary according to the degree of abnormality. Still images, of course, miss this feature, which is why they are not a thoroughly reliable means of assessing the cervix or of comparing colposcopists' performance. Finally, the SCJ will often appear white, as Cartier's illustration (Fig. 10.2a) depicts. Fig. 10.2b–h reflects some of the different effects of acetic acid application that will present in colposcopic practice.

10.2 Vascular patterns

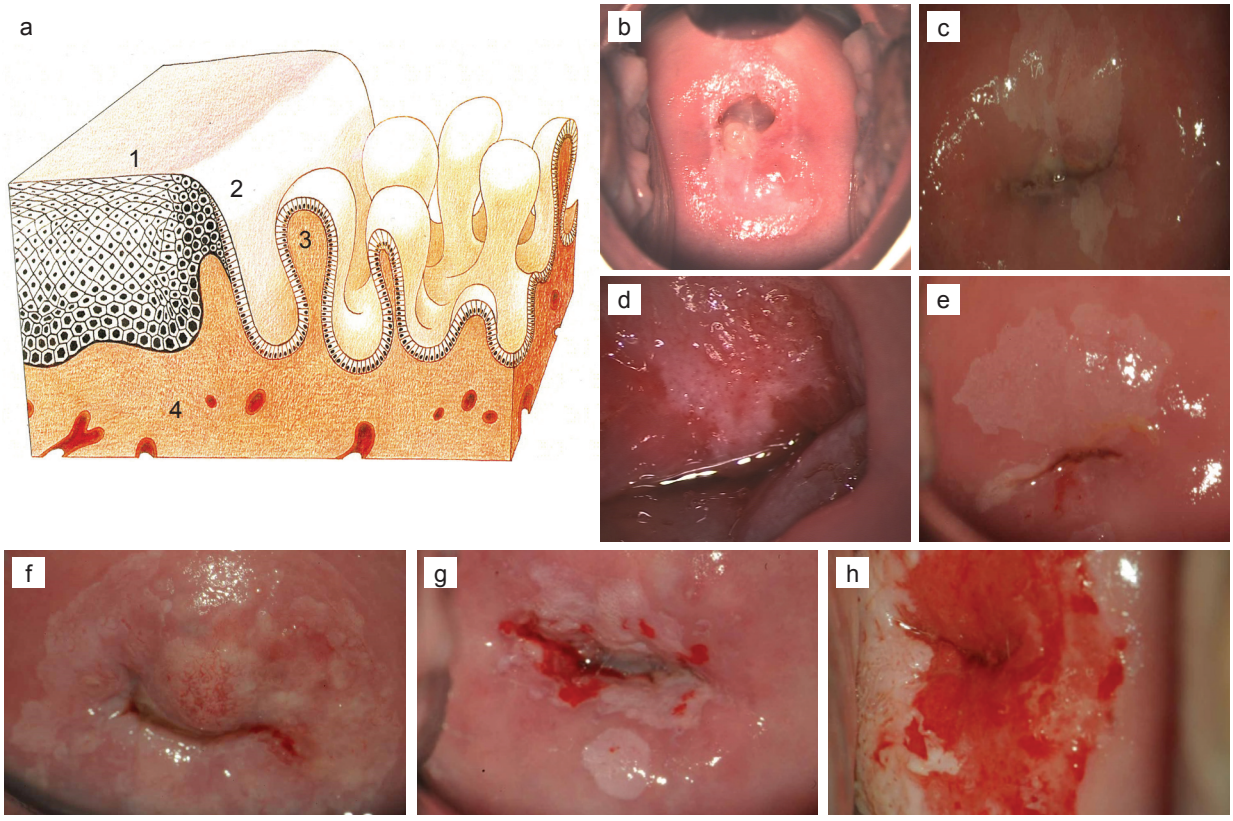
10.2.1 Classic patterns

The classic vascular patterns associated with dysplasia are mosaicism, punctation, and atypical vessels. The degree of coarseness of these

Table 10.2. Characteristics to be recognized for colposcopic determination of abnormality

Characteristic
Acetowhiteness
Vascular pattern
Margin status
Lesion size
Iodine uptake
Surface contour/tissue friability

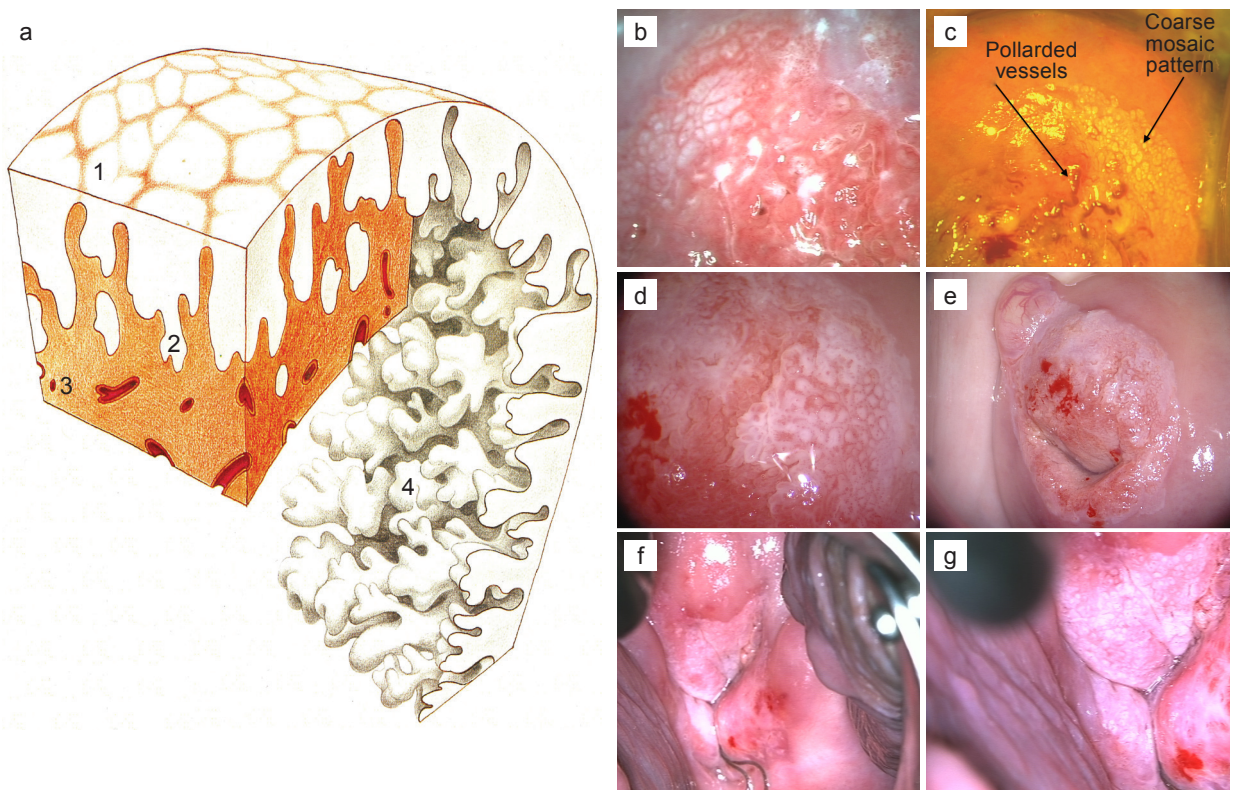
Fig. 10.2. (a) Illustration of acetowhiteness at the squamocolumnar junction: (1) normal squamous epithelium laden with glycogen; (2) small area of squamous epithelium lacking glycogen and corresponding to the white margin; (3) papillae of glandular mucosa; (4) connective tissue. (b) Mild or faint acetowhiteness on the posterior lip of a low-grade/normal lesion. (c) Faint acetowhiteness in LSIL. (d) Acetowhite epithelium in the endocervical part of an abnormal transformation zone (TZ). (e) Faint acetowhiteness throughout the anterior lip of the cervix but denser whiteness at the 9 o'clock position. (f) Large TZ with HSIL. The acetowhiteness in this case varies throughout the TZ from faint to dense. (g) Dense acetowhiteness is evident in much of this HSIL. (h) Blood obscures assessment of much of this cervix, but between the 7 o'clock and 10 o'clock positions there is very dense acetowhiteness.



patterns relates to the likelihood of there being high-grade intraepithelial disease, i.e. the finer the pattern, the less likely, and the coarser the pattern, the more likely. With the green (or blue) filter before the application of acetic acid and with a high-power magnification view, even subtle vessel changes may be identified.

The afferent and efferent capillaries within the villi (Fig. 8.4) of columnar epithelium become compressed during the normal metaplastic process and are not incorporated within the newly formed squamous epithelium. Instead, they form a fine network below the basement membrane. When CIN develops as a result of HPV infection and atypical metaplasia, the afferent and efferent capillary system may be trapped (incorporated) into the diseased dysplastic epithelium through several elongated stromal papillae (Figs. 10.3a and 10.4a), and a thin layer of epithelium may remain on top of these vessels. This forms the basis of the punctate and mosaic blood vessel patterns (Figs. 10.3 and 10.4). The terminating vessels in the stromal papillae underlying the thin epithelium may appear as black points in a stippling pattern in an end-on view under the colposcope, making what are called punctate areas (Fig. 10.4b and d). The interconnecting blood vessels in the stromal papillae surrounding the rete pegs of the epithelium, running parallel to the surface, may be observed colposcopically as cobbled areas similar to a mosaic pattern (Fig. 10.3). In mosaic areas,

Fig. 10.3. (a) Illustration of mosaicism: (1) cobbles of mosaic, unequal and separated by a red interval, which corresponds to the areas where the epithelium is very thin; (2) epithelial buds dip in and become ramified in the connective tissue; (3) connective tissue: (4) deep surface of the epithelium without connective tissue (note the shape of the digital processes of the squamous epithelium and their ramification). (b) Coarse mosaic pattern seen centrally in a case of HSIL. (c) Coarse mosaic pattern between the 1 o'clock and 3 o'clock positions. Proximal to this are some pollarded vessels. Suspicion of CIN3 or microinvasion. (d) High-power view of both mosaic and punctate vessel pattern. (e) Higher-power view of coarse mosaic and punctate pattern. Also, an innocent normally branching blood vessel is seen stretched over a nabothian follicle at about the 11 o'clock position. (f) Low-power view of HSIL. Coarse mosaicism is seen developing quickly after the application of acetic acid. The upper limit of the transformation zone is not seen in this image, and it is not possible to say whether it is a type 2 or type 3 transformation zone. (g) Higher-power view of the same case of HSIL as in (f). The acetowhiteness has intensified, and the mosaic pattern is more evident. The lesion has a relatively sharp margin anteriorly.



the epithelium appears as individual blocks: small or large, round or polygonal, and regular or irregular. Punctation and mosaic areas may be classified as either fine or coarse. Coarse vascular changes tend to be associated with more severe degrees of abnormality (CIN2 or greater including microinvasion). When both punctation and mosaic patterns are found to coexist, the same evaluation criteria for colposcopic prediction of disease are used as when they exist separately.

Vessels exhibiting punctation and mosaics are usually more strikingly obvious than the normal stromal vessels because these vessels penetrate into the epithelium and are thus closer to the surface. When acetic acid is applied, these abnormal vascular patterns are usually confined to the acetowhite areas.

"Fine punctation" refers to looped capillaries – viewed end-on – that appear to be of fine calibre and located close to one another, producing a delicate stippling effect (Fig. 10.4b). Fine mosaics are a network of fine-calibre blood vessels that appear in close proximity to one another, as a mosaic pattern, when viewed with the colposcope. These two vascular appearances may occur together and may be found in low-grade (CIN1) lesions. The patterns do not necessarily appear throughout the whole lesion.

Coarse punctation (Fig. 10.4d) and coarse mosaics (Fig. 10.3b–d, g, and h) are formed by vessels of larger calibre and with larger intercapillary distances, in contrast to the corresponding fine changes. Coarse punctation and mosaicism tend to occur in more severe neoplastic lesions, such as CIN2 and CIN3 lesions and early preclinical invasive cancer. Sometimes, the two patterns are superimposed in an area so that the capillary loops occur in the centre of each mosaic "tile". This appearance is called umbilication (Fig. 10.3e).

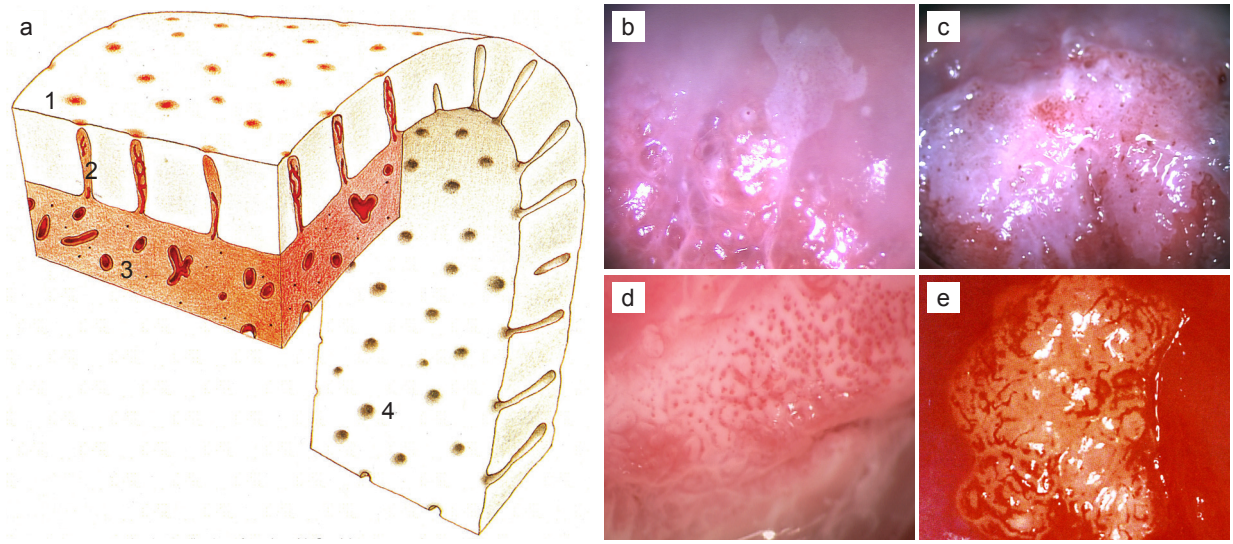
Coarse mosaicism or coarse punctation scores 2 in the Swede score.

10.2.2 Atypical patterns

Abnormal vessel patterns that do not appear mosaic or punctate include corkscrew vessels, comma-like vessels, and character-writing-type vessels. These are associated with high-grade lesions or microinvasive and invasive disease. Character-writing-type vessels are particularly associated with adenocarcinoma in situ or invasive adenocarcinoma (Fig. 10.4e).

A pollarded branch refers to one that is cut off at the trunk (see Fig. 13.5b), and in colposcopic vessel terminology this refers to a vessel that does not appear to branch but seems cut off. A pollarded vessel is seen in Fig. 10.5c and d.

Fig. 10.4. (a) Illustration of punctation: (1) red dots visible on colposcopy; (2) vascular bundles – at the summit of each papilla, the squamous epithelium is very thin, allowing the vessels to show through; (3) connective tissue; (4) the deep surface of the epithelium is flat, and the points of depression corresponding to each vascular bundle are visible. (b) Faint and fine punctation seen in a case of LSIL. (c) Low-power magnification image of the anterior lip of a dysplastic transformation zone with acetowhite epithelium in which there are many gland openings. (d) Coarse punctation in a high-grade lesion. (e) Atypical "character writing" vessel patterns, sometimes seen with severe glandular dysplasia or early adenocarcinoma.



Bizarre vessels are a sign that a high-grade or microinvasive lesion may be present. Bizarre vessels are completely irregular, with no discernible decrease or branching pattern.

10.3 Other markers of abnormality

No single colposcopic characteristic is uniquely diagnostic of a high-grade lesion or of early invasive cancer. Also, some patterns may be found in both low-grade and high-grade lesions (mosaic and punctate vascular patterns) and vary in coarseness with the grade, but they are not reliable parameters of HSIL. Intercapillary distance has been reported as increasing with the degree of abnormality. Acetowhiteness is even less discriminatory. A less common marker of intraepithelial neoplasia is gland cuffing, which is an exaggerated whiteness around the meatus of gland openings and is thought to reflect dysplasia continuing into the gland epithelial lining (Fig. 10.5a).

10.4 Margin status

The sharpness of a lesion's margin is also an indicator of severity. In Fig. 10.5a, the low-grade lesion margin is irregular, whereas in Fig. 10.5b and c, there is a sharp margin associated with a high-grade lesion.

10.5 Leukoplakia (hyperkeratosis)

Leukoplakia or hyperkeratosis (Fig. 10.5j) is a white, well-demarcated area on the cervix that may be apparent to the unaided eye before the application of acetic acid. The white colour is due to the presence of keratin and is an important observation. Usually leukoplakia is idiopathic, but it may also be caused by chronic foreign-body irritation, HPV infection, or squamous neoplasia.

No matter where the area of leukoplakia is located on the cervix, it should be biopsied to rule out high-grade CIN or malignancy. It is not usually possible to colposcopically evaluate the vasculature beneath such an area.

10.6 Condylomata

Condylomata (Fig. 10.5k–m) are multiple, exophytic lesions, which are more frequently found in the vagina or on the vulva. Depending on their size, they may be obvious to the naked eye. They present as soft pink or white vascular growths with multiple, fine, finger-like projections on the surface, before the application of acetic acid. Under the colposcope, condylomata have a typical appearance, with a vascular papilliferous or frond-like surface, each element of which contains a central capillary. Occasionally, the surface of a condyloma may have a whorled, heaped-up appearance with a brain-like texture, known as an encephaloid pattern. Often, the surface of the lesion may be densely hyperplastic. These lesions may be located inside the TZ but are more often found outside the TZ. After the application of acetic acid, there is blanching of the surface, with acetowhite change persisting for some time. A condyloma at the SCJ can sometimes be confused with a prominent area of columnar epithelial villi. Both tend to be acetowhite, but a condyloma is whiter. It is sometimes prudent to obtain a biopsy to confirm the diagnosis of a condylomatous lesion and to rule out malignancy or CIN underneath the condyloma. Condylomatous lesions may not take up iodine stain or may stain only partially brown.

10.7 Lesion size and site

The size of a lesion is also related to severity (Ferris and Litaker, 2006; Kierkegaard et al., 1995; Shafi et al., 1991). In Fig. 10.5e, a small geographical lesion with some mosaic pattern is seen in a case of LSIL, which regressed over time to normality. In Fig. 10.5f, a relatively large lesion is seen in a small TZ, i.e. the lesion is relatively large, occupying all four quadrants of the TZ, whereas in Fig. 10.2f a large lesion is seen, which is large relative to the size of the cervix.

The site of a lesion is also important; one that is inside the TZ is more likely to be HSIL than one outside the TZ (Hammes et al., 2007).

10.8 Iodine uptake

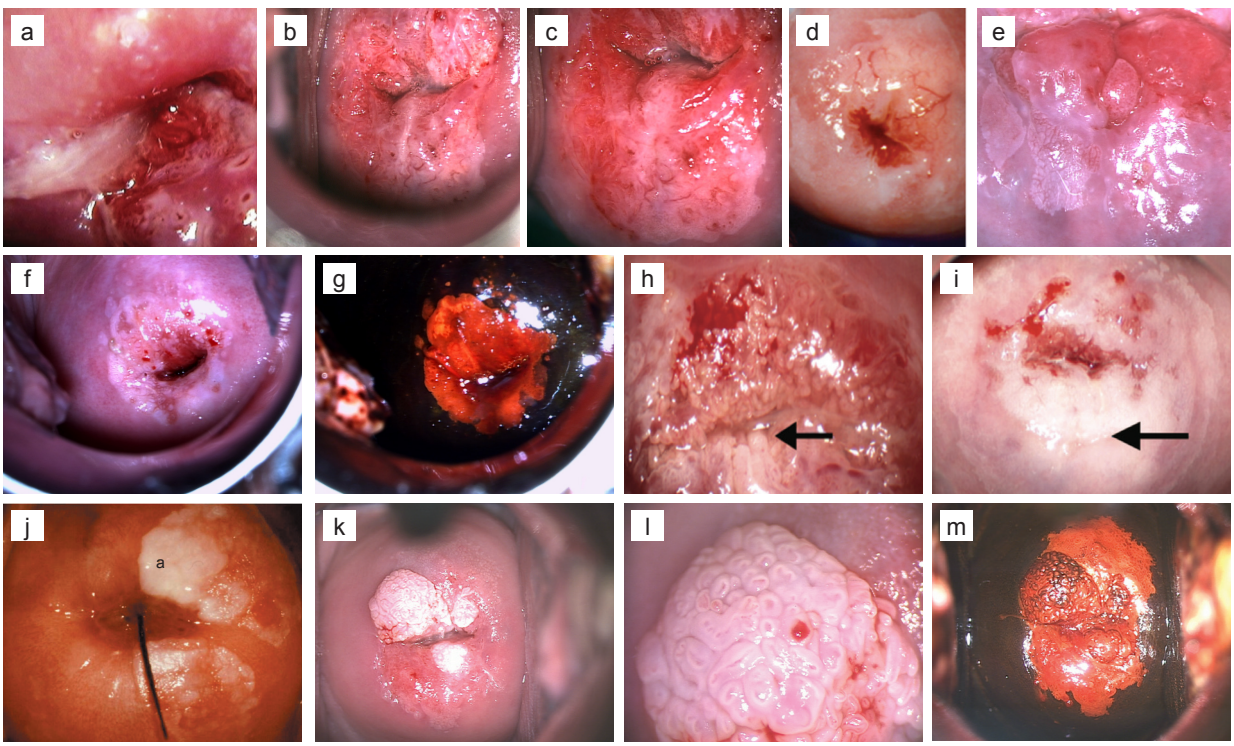
Iodine uptake is related to glycogen content in the cytoplasm of squamous cells. Where this is reduced or where the nuclear content is relatively increased, there will be less iodine uptake, for example in immature metaplasia, atrophic states, CIN (Fig. 10.5g), or even HPV infection. relatively increased, there will be less iodine uptake, for example in immature metaplasia, atrophic states, CIN (Fig. 10.5g), or even HPV infection.

10.9 Summary

Acetowhite staining is not specific for CIN; it may also occur, and usually does to a lesser degree, in immature squamous metaplasia, the congenital TZ, and inflammation, as well as in healing and regenerative epithelium. However, acetowhite changes associated with CIN are most often found localized in the TZ, abutting the SCJ and well demarcated from the surrounding epithelium. Low-grade lesions tend to be thin, less dense, and less extensive, with irregular, feathery, geographical, or angular margins and with fine punctation and/or mosaic. Sometimes, low-grade lesions may be detached from the SCJ. Atypical vessels are

seldom observed in low-grade lesions. In contrast, high-grade lesions are associated with dense, opaque, grey-white, acetowhite areas with coarse punctation and/or mosaic and with regular and well-demarcated borders. These lesions often involve both lips and may occasionally harbour atypical vessels. CIN3 lesions tend to be complex, involving the os.

Fig. 10.5. (a) Occasional cuffed gland openings are seen on the posterior lip of this case of HSIL. (b) Sharp margin of an HSIL seen at the 5 o'clock position on the posterior lip of the cervix at low-power magnification. (c) Higher-power view of the same case as in (b), which again reveals a sharp lesion margin and a pollarded vessel. (d) A pollarded vessel is seen at the 11 o'clock position in this case of HSIL. (e) A small lesion in an otherwise normal transformation zone (TZ) in the presence of a mild smear which regressed to normal without intervention. (f) A large lesion relative to the size of the TZ, i.e. the lesion occupies all four quadrants of the small TZ. (g) Low-power view of the same case of HSIL as in (a) after the application of Lugol's iodine. (h) The ridge sign. The arrow points to an opaque protuberance within a white lesion within the TZ. (i) The inner border sign. The arrow points to a sharp demarcation between thin and dense acetowhite areas in a large TZ. (j) Leukoplakia (labelled a). This white lesion is apparent before acetic acid is applied. Leukoplakia prevents adequate examination of the underlying epithelium and frequently warrants biopsy. (k) Colposcopic view of cervical condyloma at low-power magnification. (l) Colposcopic view of the same cervical condyloma at high-power magnification. (m) Colposcopic view of the same cervical condyloma after the application of Lugol's iodine, showing partial uptake of iodine.



Key points

- Colposcopic examination is a dynamic process, which should be performed systematically.
- Recognition of abnormality will be improved if specific image characteristics are documented at each examination. Scoring the individual components of the Swede score is more likely to provide an accurate diagnosis. These are acetowhiteness, margin status, vascular patterns, lesion size, and iodine uptake.
- Beware the leukoplakic epithelium, because it is not possible to see the underlying epithelium, which may or may not be innocent.
- Microinvasive lesions usually exhibit more pronounced characteristics of high-grade disease.

CHAPTER 11.

Treatment of cervical intraepithelial neoplasia (CIN)

Because current screening tests (cytology, oncogenic HPV testing, and visual inspection methods) are not specific for cervical precancer, treatment methods need to be effective but also minimally damaging and uncomplicated.

Treatment methods of actual or suspected CIN should be both effective and safe. *Effective* treatment of CIN implies eradicating the TZ and reducing risk of cancer to nearly zero. *Safe* treatment implies reducing the risk of complications to an absolute minimum.

At the outset, the patient should be counselled about the need for treatment, the risks of the procedure, and the risk of not treating the lesion, as well as the need for follow-up and how this should be performed. The decision to treat should not be automatic and should not depend exclusively on the results of an individual screening or diagnostic test but should take into account the individual case characteristics, which may modify the risk of progression to cancer and the need to treat as well as the relative risks of treatment. Relevant case characteristics include age, parity, previous treatment, fertility aspirations, likelihood of default from follow-up, HPV status, and any other available biomarker triage test results.

Safe treatment will mean a preliminary colposcopic examination by a properly trained colposcopist with adequate documentation of findings in a structured format (see Annex 2). It should record the TZ type, the adequacy of the examination, and an objective diagnostic score, for example the Swede score (Strander et al., 2005) (see Annex 4). Ideally, if the treatment advised is a destructive method, there should be sufficient biopsy material for an accurate diagnosis. If the treatment is excisional, then it should be performed under binocular colposcopic guidance, to minimize excising excessive or insufficient normal tissue (Carcopino et al., 2013) and inflicting minimal artefactual damage, so that an adequate histology report may be generated and so that the cervical wound is not excessively damaged.

Treatment should accomplish complete eradication of the TZ and not only the lesion. It should ablate the TZ, the whole TZ, and, ideally, nothing but the TZ.

Whether the TZ is being excised or destroyed, ablation to a depth of 7 mm is considered optimal (Shafi et al., 2006). This is because the deepest gland crypt can contain CIN as low as 4 mm (Anderson and Hartley, 1980), and destroying to 7 mm gives a sufficient degree of safety.

11.1 Excision or destruction of the transformation zone

The eradication of CIN may be achieved by excision or destruction. There are advantages to each, and either may be achieved using different techniques. Table 11.1 lists the different techniques currently in use and the circumstances where they may be appropriate choices of treatment. The advantages and disadvantages of destructive therapy are listed in Table 11.2. Where facilities allow, treatment should probably be excisional using electrosurgery. Most authorities consider excision to be superior to destruction, because it is possible to perform histological examination of the excised TZ, whereby the grade of abnormality can be determined more accurately, cancer may be ruled out, the completeness of excision can be confirmed, and the dimensions of the excised tissue can be calculated. Also, histological examination will sometimes recognize glandular disease, where present. The excision margin status (i.e. involved with CIN or not) and the size of the TZ will also be revealed, and these are important prognostic indicators for the risk of future pregnancy-related complications. Finally, histological examination allows the colposcopist to audit their own diagnostic acumen in terms of both the diagnosis and the geographical limits of the TZ.

LLETZ/LEEP should usually be performed in a clinic with access to resuscitation facilities. Also, if excision is to be used as a method of treatment, it implies histological examination of the extirpated tissue by a pathologist. Whether or not a pathologist is available, when the lesion is partially endocervical, these lesions need to be treated by way of an excisional technique. For high-grade lesions, excision may often be performed at the first visit, providing that the patient is fully informed, that there is no disparity between the referral cytology and the colposcopic assessment, and that the TZ is sufficiently small and accessible (i.e. type 1 or shallow type 2 TZ). For every other circumstance, there is no urgency about management, providing that the risk of default from follow-up attendance is low.

11.2 Pre-treatment conditions

Ideally, every treatment should be preceded by an adequate, comprehensive colposcopic examination, whereby the examination may determine the type and size of the TZ and recognize or rule out cancer, microinvasive disease, or precancer as well as assessing the grade of abnormality suspected by the screening test. Once the decision to treat has been made, it is necessary to choose an appropriate method of treatment. The conditions that should be met before performing destructive therapy are detailed in Table 11.3. These conditions apply where facilities allow.

11.3 Destructive methods

A variety of energy sources have been used to destroy the TZ in women with suspected CIN. These

Table 11.1. Treatment choices for CIN

Technique	Recommendation
Excision	
LLETZ/LEEP	Universal application
Laser excision	Universal application
SWETZ or NETZ	Some type 2 or type 3 transformation zones Glandular disease Suspicion of microinvasion
Hysterectomy	Rarely appropriate
Cold-knife conization	Suspicion of glandular disease or microinvasion
Destruction	
Thermal coagulation	CIN1 and CIN2 All type 1 transformation zones Some type 2 transformation zones No suspicion of cancer, glandular disease, previous treatment, or uncertainty about the grade of abnormality
Laser ablation	As above
Cryocautery	As above

CIN, cervical intraepithelial neoplasia; LEEP, loop electrosurgical excision procedure; LLETZ, large loop excision of the transformation zone; NETZ, needle excision of the transformation zone; SWETZ, straight wire excision of the transformation zone.

Table 11.2. Advantages and disadvantages of destructive treatment

Advantages	Disadvantages
• Simple and cheap	• The destroyed transformation zone cannot be examined histologically
• Widely available equipment	• True diagnosis uncertain
• Effective, when used expertly	• Not possible to rule out cancer or glandular disease
• No expense of histological examination of the transformation zone	• Concern about depth of excision
	• Margin status not known

Table 11.3. Conditions for destructive treatment

Condition
• The TZ must be fully visible (i.e. type 1 or type 2 TZ) and accessible (i.e. type 1 TZ or shallow type 2 TZ).
• The TZ must be small enough to be covered by the destructive method probe.
• Invasive disease must be ruled out.
• There should be no suspicion of glandular disease.
• There should be no disparity between cytology and colposcopy.
• There should not have been a previous treatment of the cervix.
• There should not be upper or lower genital tract infection (relative contraindication).
• The patient should not be pregnant.
• If the patient has recently delivered, she should be at least 3 months postpartum.

TZ, transformation zone.

include laser treatment (Monaghan, 1995), radical diathermy (Chanen and Rome, 1983), and cryosurgery (Hatch et al., 1981). The temperature applied in radical diathermy reached 300 °C; it is no longer used and is of historical interest only. As a destructive technique, laser treatment has few advantages over cryosurgery or thermal coagulation in resource-limited regions and will not be discussed in depth here. The interested reader is referred to excellent descriptive publications (Monaghan, 1995).

This chapter is devoted to two methods of destructive therapy and several excisional methods. The destructive techniques are cryosurgery (also known as cryocautery, cryotherapy, or cryo) and thermal coagulation (also called cold coagulation). The excisional techniques are LLETZ/LEEP and other modifications of electrosurgical excision. Cold-knife conization is also used in some regions and may have a role in excising a type 3 TZ or where there is a suspicion of glandular disease, but otherwise cold-knife excision has little to recommend it. Although hysterectomy is also used as a method of excising CIN, this is nearly always inadvisable. For women with precancerous lesions, hysterectomy offers no advantage over local excision of the lesion, and for those women in whom unsuspected invasive disease is revealed at hysterectomy, the patient will have been poorly served. After a simple hysterectomy, it is not possible to offer the appropriate radiotherapy regime, and radical hysterectomy is also not possible. Hysterectomy should not be used as a treatment of CIN.

11.3.1 Cryotherapy

Cryotherapy, which was popular in the USA during the 1970s and 1980s, was introduced into clinical practice by Crisp et al. (1967) and has been used in many countries for several decades. Cryotherapy is also known as cryocautery, cryosurgery, or cryo. Where the equipment is available and the gas supply is assured and when the preconditions for destructive therapy have been met, it is a reasonable choice of therapy. It has few serious complications, and although it is described as causing relative discomfort, it is usually well tolerated without the need for local infiltration, so that it may be performed as an outpatient procedure or in a rural clinic. The capital equipment necessary is inexpensive, although the price of gas and the cost of transporting the gas cylinders are quite variable. Cryotherapy gas tanks are large and are heavy (10–15 kg) and thus difficult to transport. They require refilling relatively frequently. At a clinical level, the major disadvantage of cryotherapy, and of all destructive techniques, is the lack of tissue to allow histological examination. Finally, cryotherapy treatment takes considerably longer (approximately 15 minutes from start to finish) than thermal coagulation or LLETZ/LEEP, each of which may be completed in a minute or two, although infiltration of local anaesthetic may add a minute to LLETZ/LEEP. Cryotherapy had become very popular as part of a see-and-treat approach to screening and management in many LMICs in the past decade, but difficulties with maintaining a cheap and reliable supply of carbon dioxide (CO_2) have limited its popularity.

Cryotherapy achieves a destructive effect by freezing tissue down to less than −20 °C. A metal probe is held in close contact with the TZ epithelium (Figs. 11.1–11.3). Gaseous CO_2 is allowed to escape and circulate *in* the probe head, thereby cooling the cryocautery probe surface that is in contact with the epithelium. The cellular necrosis of the affected epithelial cells occurs as a result of intracellular fluid crystallization and consequent cell membrane rupture. The probe tip must be the appropriate size and shape for the relevant TZ. When the TZ involves the endocervical canal for more than 5 mm (i.e. beyond a shallow type 2

Fig. 11.1. Cryoprobe tips.

TZ), it is probably wise not to use a destructive technique. If the method is used for only type 1 TZs and these are small enough to be completely covered by the probe, then success rates are likely to be high. Failure rates are high for lesions that extend to four quadrants of the TZ.

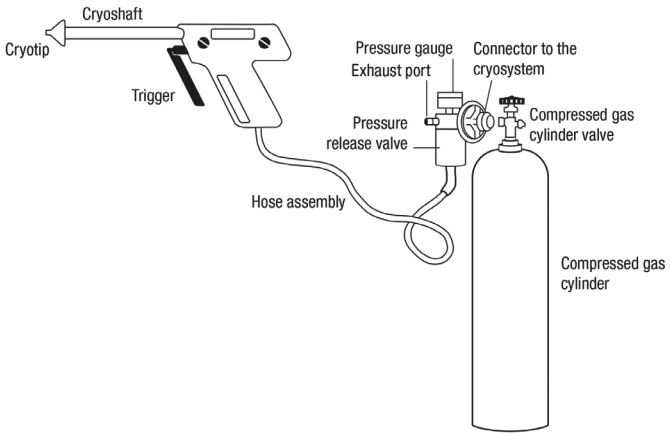
11.3.1.1 Equipment for cryotherapy

With the exception of the particular difficulty of gas supply in LMICs, the equipment for cryosurgery is widely available, relatively cheap, and easy to use. A flexible plastic tube connects the handheld cryosurgery device to the liquid gas cylinder. It is important that this tubing is checked for leaks periodically to ensure an adequate and effective supply of gas to the probe. At the cylinder head, the tubing is connected to the cylinder by a tightening knob around a connecting bracket (Fig. 11.2).

After passing through the connecting aperture, the gas travels through a silencer and pressure gauge. In most machines, the gauge will display when pressure is sufficient to provide the necessary temperature drop *throughout* the procedure. Small gas cylinders, although more easily transported, do not contain enough gas for more than a few procedures, and so larger cylinders are better for busy clinic sessions. CO_2 and nitrous oxide (N_2O) are equally effective cryogenic gases.

When the gas reaches the device, its release is controlled by a trigger. This releases the gas through a small aperture in the cryoprobe; it then circulates within the probe and freezes the probe tip. When applied to the TZ epithelium, the probe tip then effects tissue necrosis. Whether CO_2 or N_2O is used, the temperature of the tissue for ablation should reach −20 °C throughout. Providing that the gas cylinder maintains sufficient pressure (> 40 kg/cm^2), the tissue in contact with the probe will necrose if the probe is held in contact with it. Table 11.4 details the temperature achieved at cryotherapy. When the pressure drops below 40 kg/cm^2, the gas cylinder should be replaced with a full one.

Fig. 11.2. A typical cryosurgical unit attached to a cylinder of either CO_2 or N_2O.



Details of standards in cryocautery equipment and how to perform the procedure, as well as details of sterilization procedures, are contained in the WHO technical specifications document "Cryosurgical equipment for the treatment of precancerous cervical lesions and prevention of cervical cancer" (WHO, 2012).

11.3.1.2 Treatment with cryotherapy

Providing that the conditions for using a destructive method (Table 11.3) have been satisfied, cryosurgery may be performed at the first assessment visit or after a diagnostic biopsy. The purpose of this manual is not to proscribe patient management, and local circumstances will modify management strategies, but a comprehensive colposcopic examination with or without a directed biopsy (or biopsies) is the gold standard pre-treatment investigation for women who are screen-positive. Financial, equipment, and training constraints may preclude the possibility of providing colposcopy. Successful screen-and-treat protocols have been implemented in many LMICs.

After an adequate colposcopic examination and informed consent, with the patient in the lithotomy position and a speculum in place, the cervix should be perpendicular to the colposcopic line of vision so that the probe may be applied evenly across the TZ. The speculum should be comfortable and large enough to expose the entire cervix and to separate the cervix from adjacent vaginal

Table 11.4. Cryocautery equipment temperature, when contact between probe and epithelium is uniformly good and gas pressure is maintained at > 40 kg/cm^2

Gas used	Temperature at probe tip	Temperature at probe edge	Temperature of central tissue	Temperature at edge of tissue
CO_2	< −68 °C	−20 °C	−68 °C	About −20 °C
N_2O	< −89 °C	−20 °C	−89 °C	About −20 °C

walls. A support person, usually a nurse attendant, is invaluable in comforting and reassuring the patient before and during the procedure. The clean, non-pregnant and uninflamed cervix should be free of mucus, and the TZ should be completely accessible to contact with the cryoprobe. This will usually mean a small type 1 TZ or a small and shallow type 2 TZ.

After cleaning, the cryosurgery probe should be firmly applied to the TZ on the cervix and the cryosurgical effect begun by activating the trigger (Fig. 11.3a and b). A stopwatch is useful to time the procedure. The operator should observe the procedure, to ensure adequate contact and to ensure that the vaginal walls are not in contact with the probe during the freeze. The procedure is uncomfortable but is not usually described as painful. A slight hissing noise is emitted from the cryosurgery probe during active freezing. Treatment should be performed in two phases – a 3-minute freeze, followed by a 5-minute thaw, followed by a 3-minute freeze – so as to ensure adequate depth of tissue necrosis (≥ 5 mm). Ideally, a stopwatch should be used; otherwise, a busy clinician may overestimate the passage of time. Technically, it is a simple procedure. Maintaining even but firm contact with the tissue is important at the outset, but once a freeze has occurred, the probe does not detach from the tissue. It is important to be careful that the vaginal walls do not fall against the frozen tissue or probe, so as not to cause inadvertent damage. Finally, after each freeze a minute or so should be allowed before detaching the probe, to allow it to easily separate from the tissue. The probe and cryosurgery device should then be thoroughly cleaned (see Chapter 18).

After cryosurgery, the vagina should not be packed. Providing that the cervix was not inflamed, there is no need for antibiotic or other treatment. The patient should be advised not to use internal tampons, not to douche, and not to have penetrative intercourse for at least a month or until all discharge has stopped. A take-home information sheet is valuable. It should detail the follow-up arrangements and briefly describe the usual effects and complications associated with cryosurgery. Healing is usually complete after 6 weeks, and during this time it is common to experience a light watery and slightly bloodstained discharge. Excessive and/or offensive discharge, bleeding, pain, fever, or any suspicion of cervicitis or pelvic inflammatory disease warrants a clinic visit. A checklist for cryosurgery is given in Table 11.5. Finally, the risk of HIV acquisition by HIV-negative women (or transmission between patients) after cryosurgery is unknown; very limited data are available.

To perform as effectively as possible, the machine needs to be working properly and needs to have a constant supply of CO_2, and the operator should use the double-freeze technique. Results in the literature are somewhat variable. In the early non-controlled studies, the success of cryocautery for CIN3 varied between 77% and 93% (Benedet et al., 1981; Hatch et al., 1981; Popkin et al., 1978). The Cochrane meta-analysis review of 29 trials covering 4509 cases, 1843 of whom had CIN3, found a lower rate of treatment success for CIN3 for cryotherapy compared with thermal coagulation (Martin-Hirsch et al., 2013). The single-freeze cryotherapy technique was associated with a non-significant increase (relative risk, 2.66; 95% confidence interval, 0.96–7.37) in the risk of residual disease compared with the double-freeze technique (Schantz and Thormann, 1984). The authors of the Cochrane review concluded that there was no overwhelmingly superior surgical technique for eradicating CIN and that cryotherapy appeared to be an effective treatment of low-grade disease ***but not of high-grade disease.*** This conclusion concurs with recent results of non-comparative

Fig. 11.3. (a) The cryoprobe in place during treatment. (b) The activated cryoprobe on the cervical transformation zone. Note that the frozen epithelium extends a few millimetres beyond the edge of the cryoprobe. (c) The cervical wound immediately after cryosurgery.

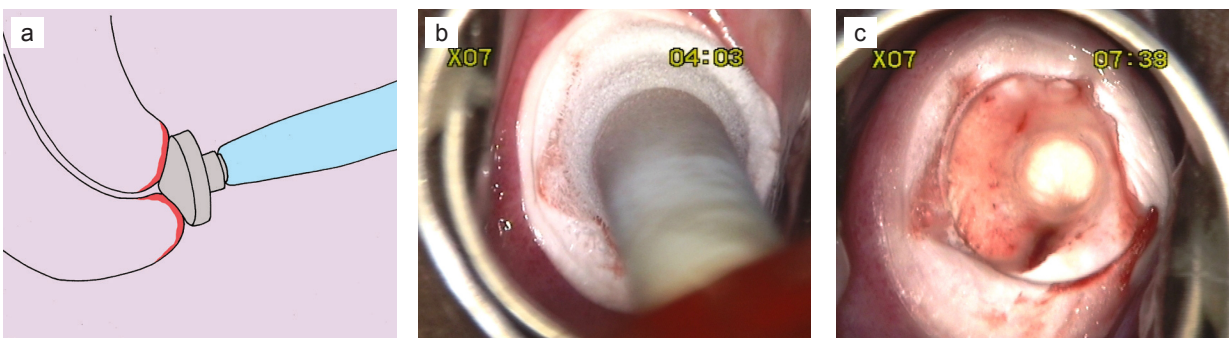


Table 11.5. Cryosurgery procedure

Steps/checklist
• Colposcopic examination with or without a biopsy (or biopsies)
• Confirmation of suitability (see Table 11.3)
• Counselling and informed consent
• Check equipment status (probe clean, pressure > 40 kg/cm^2, no leaks)
• Speculum insertion, lithotomy position
• Procedure room door locked, nurse attendant present, patient relaxed
• Probe applied to transformation zone on the cervix
• Contact with epithelium good
• Gas release trigger activated, stopwatch started
• Freeze observed, vaginal walls not in contact with probe or any frozen tissue
• Freeze maintained for 3 minutes
• Thaw allowed for 5 minutes
• Second freeze maintained for 3 minutes
• Remove probe after thawing

observational studies. For example, in the study of Nene et al. (2008) of cryotherapy performed by midwives in India, the cure rate of CIN3 was 82.1% (95% confidence interval, 74.7–89.4%) for CIN2 and CIN3 lesions combined. These relatively low rates of cure may be unacceptable in some regions. However, WHO has stated that where resources are limited, cryosurgery, as part of a screen-and-treat programme, is an acceptable option to treat high-grade lesions also.

11.3.2 Thermal coagulation

The term "cold coagulation" is a misnomer, and the method should properly be called thermal coagulation. The probe is heated electrically and reaches temperatures of 100–120 °C (Duncan, 1983). The technique was named cold coagulation to discriminate it from radical diathermy, which reaches temperatures of 300 °C. The method was introduced to clinical practice by Kurt Semm (Semm, 1966) in Kiel, Germany, and was used widely throughout Europe in the 1970s and 1980s. Much of the published work on cold coagulation came from the United Kingdom, in particular from Ian Duncan's unit in Dundee (Duncan, 1983, 1984; Gordon and Duncan, 1991). The method was not widely used in North America, where cryocautery and then laser ablation were the destructive method of choice. With thermal coagulation, the intracellular water reaches boiling point and the cells necrose. It achieves tissue destruction to a depth of 4–7 mm (Haddad et al., 1988). The method fell out of popularity (Semple et al., 1999) when LLETZ/LEEP was introduced but is now being reconsidered, because of its apparent advantages over cryocautery and because excisional techniques are not considered feasible in remote regions by relatively untrained staff in poorly equipped facilities without the necessary additional resources (e.g. histopathology services and the very occasional need for general anaesthesia). Thermal coagulation has equivalent success rates to cryosurgery, is quicker to perform with similarly low complication rates, and does not require refrigerated gas. The procedure takes less than 2 minutes to complete and is usually performed without either general or local anaesthesia; it appears to be well tolerated. Finally, although the energy is produced electrically, newer thermal coagulation units are battery-operated and can provide sufficient battery power for 30 procedures before recharging is necessary.

11.3.2.1 Equipment for thermal coagulation

In the early papers reporting the use of thermal coagulation, Gordon and Duncan wrote that the Semm coagulator was very user-friendly, because it was quick and silent and did not require local or other analgesia. In their original series, 95% of patients required no anaesthesia. The capital equipment is relatively inexpensive (equivalent to costs for cryosurgery) and easily portable. The therapeutic temperature is 100 °C, which is not high enough to produce charring or smoke, thereby avoiding any unpleasant odour for the patient and doctor. Neither a suction machine nor a filter is required, because there is no smoke plume. All the equipment is reusable. There are enough probes of different dimensions to accommodate almost all type 1 TZs, and postoperative discharge and bleeding were not reported to be a problem for most women.

Subsequent pregnancy and fertility rates do not appear to be affected by thermal coagulation. Also, it may be applied as one or several applications for large or irregular ectocervical TZs. Finally, at the time (in the 1970s and 1980s), it was rightly seen as an inexpensive alternative to the then-popular laser ablation technique. Its singular disadvantage is that the TZ epithelium is destroyed rather than preserved, thereby negating the opportunity for histopathological examination.

11.3.2.2 Treatment with thermal coagulation

Treating the TZ using the thermal coagulator could not be simpler. Several manufacturers produce thermal coagulators (Figs. 11.4 and 11.5). Each produces clear instructions about when the temperature of 100 °C has been reached and when it has returned to normal body temperature. Applying the probe is exactly the same as applying a cryoprobe, except that there is no visible ice ridge just outside the probe during activation and, unlike electrosurgical techniques (LLETZ/LEEP, etc.), there is no smoke plume to evacuate. As with any destructive or excisional technique, it is entirely possible to damage the epithelium and other adjacent structures if the probe is applied to anywhere other than the cervix, but it is difficult to do this, providing that the vaginal walls are clearly seen to be distant to the cervix and the thermal coagulation probe head. A checklist for thermal coagulation is given in Table 11.6.

Fig. 11.4. The Liger thermal coagulator.

Fig. 11.5. The WISAP "cold" coagulator.

Table 11.6. Thermal coagulation procedure

Steps/checklist
• Colposcopic examination with or without a biopsy (or biopsies)
• Confirmation of suitability (see Table 11.3)
• Counselling and informed consent
• Check equipment status (probe clean, temperature gauge functional)
• Speculum insertion, lithotomy position
• Procedure room door locked, nurse attendant present, patient relaxed
• Probe applied to transformation zone on the cervix
• Contact with epithelium good
• Vaginal walls not in contact with probe or any frozen tissue
• Thermal coagulation probe activated, stopwatch started
• Temperature > 100 °C maintained for 45 seconds
• If transformation zone larger than thermal coagulation probe head, apply probe for further 45 seconds to untreated area, overlapping with the previous treatment
• Remove probe

11.4 Excisional methods

There are several ways of removing the TZ. These include hysterectomy, cold-knife excision (also known as cold-knife cone biopsy or cold-knife conization), laser cone biopsy, LLETZ/LEEP, and other variations of electrosurgical excision, for example SWETZ, which is an alternative to LLETZ/LEEP, laser excision, or cold-knife excision when performing a type 3 excision (Camargo et al., 2015).

11.4.1 Hysterectomy

Hysterectomy has been very widely used to treat suspected or proven cervical precancer. The advantage of ridding a woman of fertility and menstruation and any associated symptoms as well as treating separate benign pathology (e.g. fibroids or adenomyosis) may seem attractive in the presence of CIN. However, the risk of undertreatment of unsuspected invasive disease means that an adequate and satisfactory colposcopic examination should be performed before hysterectomy for CIN. If invasive disease is discovered at hysterectomy, the woman will have been undertreated and it will no longer be possible to offer the optimal radical hysterectomy or radiotherapy regime. In the great majority of cases, it is far more sensible to resect the TZ first and deal with associated pathology subsequently.

11.4.2 Cold-knife cone biopsy

Cold-knife cone biopsy, the oldest method of local excision, is still widely used, especially where colposcopy facilities and/or expertise are not available. It has similar success rates to other excisional techniques (Larsson, 1983). The technique leaves a relatively large cervical defect and will often remove more tissue than is necessary. The procedure is usually performed under general anaesthesia. A suture or sutures are often used to achieve post-excision haemostasis. Cold-knife cone biopsy is associated with well-recognized short- and long-term complications, including primary and secondary haemorrhage, cervical stenosis, and cervical incompetence. It may be worth considering with a type 3

excision for glandular or microinvasive disease, but otherwise cold-knife excision has no advantage over LLETZ/LEEP or laser excision and is associated with greater morbidity and long-term pregnancy-related complications than the other excisional techniques (Arbyn et al., 2008; Jones et al., 1979; Kristensen et al., 1993).

11.4.3 Large loop excision of the transformation zone (LLETZ/LEEP)

LLETZ is the term coined in the early 1980s to describe excision of the TZ using a low-voltage diathermy loop of thin wire usually with blended diathermy under local anaesthesia. The term was coined to discriminate it from the small loops that René Cartier used for taking biopsies in his practice in Paris, and it is from his technique that LLETZ (and LEEP) was developed. It was developed in Bristol, United Kingdom, in the early 1980s (Prendiville et al., 1986, 1989). LEEP is a term that was introduced after the introduction of LLETZ to the USA and was purportedly coined to describe loop electrosurgical excisions of the TZ and for other lower genital tract lesions. In truth, LEEP is identical to LLETZ.

11.5 Electrosurgery for CIN

A simple glossary of terms is given in Table 11.7.

Table 11.7. Glossary of terms related to electrosurgery for CIN

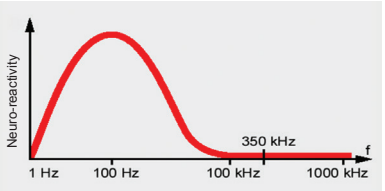
Term	Explanation
Ampere	The unit of measurement of electric current; the amount of electricity passing along a circuit (the number of electrons per second passing through a circuit).
Cautery	Heating tissue to produce coagulation.
Coagulation diathermy	Electrosurgical effect achieved by interrupted passage of high-frequency electricity, whereby cells are exploded at temperatures < 100 °C, typically about 70 °C.
Cutting diathermy	Electrosurgical effect achieved by constant passage of high-frequency electricity, whereby cells are exploded at temperatures > 100 °C.
Diathermy	Stimulation of tissue with electrically induced heat. The diathermy effect may be coagulative or cutting and occurs at the point of contact.
Electrosurgery	Electrical stimulation of tissue. The effect may be coagulative or cutting and occurs at the point of contact.
Ohm	The unit of measurement of electrical resistance of tissue.
Volt	The unit of measurement of electromotive force, which is required to send electrons through a circuit.

11.5.1 Principles of electrosurgery

Electrosurgery has been used for more than a century to both cut and coagulate tissue. Heat has been used for centuries to coagulate bleeding wounds and vessels. The heat was originally transmitted using a metal implement heated in a fire. For the past century, electrical generation has been used as a controlled way of providing localized heat to coagulate tissue and blood vessels. The passage of electricity to and through tissue produces heat. The discovery by Faraday that muscle does not contract when contacted by alternating current of very high frequency (> 100 000 Hz, i.e. > 100 kHz) means that it is possible to perform safe passage of electricity through controlled circuits in the human body and to use the localized point-of-contact effect to achieve cutting or coagulation, or a combination (blend) of the two. Electrosurgical energy operates at frequencies of more than 300 kHz, when contraction of muscle is overcome (Fig. 11.6).

Monopolar diathermy or electrosurgery is used during LLETZ, whereby electrical current passes from the ESU through the electrode (here, a loop) to the tissue and thence through the body to the return electrode (ground plate) and ultimately back to the ESU. Since the electrical energy is concentrated into a very small area (here, the loop wire), the electrosurgical effect will be achieved at the point of contact, i.e. as the wire approaches and passes through the tissue. For most electrosurgical machines, a blend of cutting and coagulation achieves the desired effect of cutting through tissue and achieving relative haemostasis of the stromal vessels, without inflicting significant diathermy artefactual damage on either the biopsy specimen being removed or the cervical stromal wound left behind. Output and waveforms vary between ESUs, but a blend of about 20% coagulation and 80% cutting is usually optimal. The loops themselves (i.e. the active electrode) are usually made of stainless steel or tungsten wire (Fig. 5.16). The technique is simple and easy to learn, but it is best learned using ox tongue or

Fig. 11.6. Electrosurgical energy operates at frequencies of more than 300 kHz, when contraction of muscle is overcome (the Faraday effect).



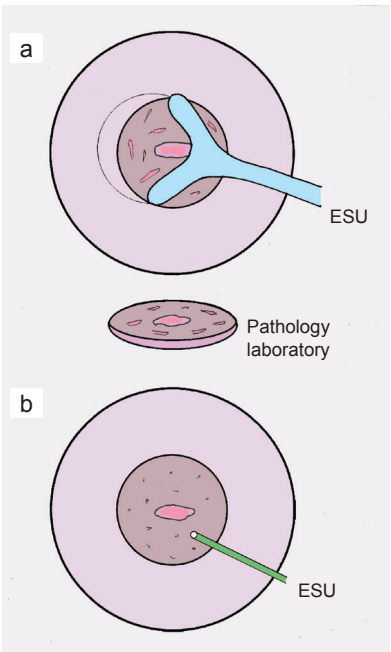
some other meat or simulated tissue (e.g. playdough). The method is illustrated diagrammatically in Figs. 11.7 and 11.8.

11.5.2 Electrosurgical effects: fulguration versus desiccation

When passing the activated electrode through the tissue or when achieving coagulative diathermy to effect haemostasis of the LLETZ wound, it is important to try to produce a fulgurative rather than a desiccative electrosurgical effect. With fulguration, the electricity passes across a very small air gap to the tissue at relatively high temperatures. This will usually achieve very superficial tissue damage and a sufficient cutting or coagulative effect for LLETZ. With desiccation, there is full contact between the electrode and the tissue, and the electrosurgery produces a lower temperature but a deeper diathermy effect. It is less coagulative and more damaging in its effect. Desiccation is appropriate in diathermy ablation of the endometrium, for example, but undesirable when cutting through or coagulating the post-LLETZ wound. In practice, one can achieve a fulgurative rather than a desiccative effect by:

- activating the electrode (i.e. the loop) before contacting the tissue;
- passing the loop slowly through the tissue, whereby a small steam window will occur between the loop and the tissue; in this way, the loop will not bend as it passes through the tissue underneath and around the TZ (Fig. 11.8); and
- holding the ball diathermy electrode just off the tissue when attempting haemostasis, and producing a visible spray of electricity between the ball and the tissue (Fig. 11.7b).

Fig. 11.7. Diagrammatic representation of (a) the LLETZ technique and (b) post-LLETZ ball diathermy management of the wound (ground plate not shown). ESU, electrosurgical unit.



11.6 Safety issues with LLETZ

11.6.1 Ground-plate contact

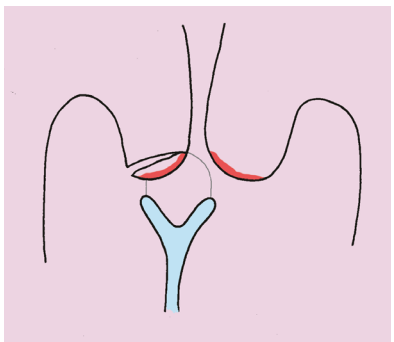
LLETZ uses monopolar electrosurgery and therefore needs a ground plate for the electricity to return to the ESU after achieving its effect at the point of contact between the loop and the tissue (or the ball electrode and the post-LLETZ wound). If there is poor ground-plate contact, an injury can occur when the current finds an easier pathway to return to ground. Examples of sites are the metal stirrups of some gynaecological couches, jewellery, or other metal body adornments. Metal jewellery and adornments should, of course, be removed before any electrosurgery, but they are unlikely to cause injury if the ground plate is large and in good contact with the skin, especially if the ESU has a resistance recognition system and uses a split ground plate.

To prevent passage of electricity to somewhere other than the ground plate, it should be positioned relatively close to the point of contact. For LLETZ, a convenient and appropriate position is under the patient's buttocks. Having the patient's buttocks on the ground plate will help ensure complete contact, which reduces the risk of burn injury. The ground plate (return electrode or dispersive pad) is wide, and this together with good contact of skin to the entire plate will prevent focal contact and a burn. Many recently manufactured ESUs incorporate a resistance recognition system in the ground-plate circuitry such that electricity will be cut off if there is not good contact. Typically, these ground plates are split, and an even flow through both is necessary to allow electricity to pass around the circuit. Often, an alarm warns the operator if there is not good ground-plate contact.

11.6.2 Prevention of electrosurgical injuries

It is possible to injure the vaginal wall and the structures immediately adjacent to it. Electrosurgical injuries to

Fig. 11.8. The loop should be passed slowly through the cervix underneath the transformation zone, so slowly that the loop wire does not bend. If it does, the operator is pushing it too quickly through the tissue, and the electrosurgical effect changes from fulgurative to desiccative.



the bladder, urethra, and bowel have been reported. The loop electrode has no respect for tissue planes. Care while introducing the electrode through the vagina and while removing it is fundamental to all vaginal surgery. Complete visualization of the electrode during activation is mandatory. Finally, the cervix and the entire loop should be seen under colposcopic visualization before, during, and after the LLETZ procedure. To ensure complete visualization, the operator has to switch the magnification control to the *lowest* magnification setting (about 4×) before starting the LLETZ procedure. Activating the electrode without being able to see all of it and the entire cervix is dangerous.

If the vagina is touched by the loop or ball electrode, it may cause a superficial or deep injury, and injury to deeper organs may not become apparent until some days after the procedure. It is very difficult to defend a direct electrosurgical injury to the vaginal wall or an adjacent organ.

It is nearly always possible to keep the vaginal walls distant from the cervical TZ by using an appropriately sized speculum. If the walls are particularly patulous, a condom (with its end cut off) placed around the speculum (Fig. 5.11b) is usually effective; if this does not work, ancillary speculum blades or lateral wall retractors will do, but they are rarely necessary.

11.6.3 Speculum insulation

Some authorities have advocated the use of insulated specula when using electrosurgery, in the belief that this will reduce the risk of accidental electrosurgical injury due to contact of the loop or ball electrode with the speculum. This is unwise. Insulated specula lose their insulation over time, particularly if autoclaved. Tiny holes will occur, which are not often visible to the naked eye; if any insulation-free area of the speculum has contact with the electrode, these holes are so small as to create a high current density on the return to the ESU, whereby an injury is *more* likely to occur. If an uninsulated speculum is accidentally contacted by a loop or ball electrode, the surface area of the speculum is so large that a burn is unlikely. In other words, hitting an uninsulated speculum with the activated electrode is less likely to cause injury than touching a poorly insulated speculum with the electrode.

11.6.4 Other avoidable injuries

To avoid injuries due to alcohol-containing fluids, it is fundamental that no explosive or inflammable fluids are used in the vicinity of electrosurgical procedures.

Accidents may occur during the learning curve of LLETZ. A woman expects, rightly, that the colposcopist will be skilled in LLETZ before approaching a patient. It is relatively easy to become competent at LLETZ before one's first procedure on a patient, by learning and performing the technique using ox tongue or other meat samples or on a simulator, under supervision and repeatedly. Common sense means that this should be routinely practised as part of any training scheme.

11.7 A practical approach to the LLETZ procedure

After clear, adequate counselling and informed consent, ask the patient to lie on a gynaecological couch in the lithotomy position (see Chapter 5). With all the necessary equipment to hand and with an attendant present, introduce an appropriately sized suction speculum and expose the cervix. Adjust the speculum so that the cervix is perpendicular to the colposcopic line of vision. Examine the cervix and TZ as described, and after confirming the indication for treatment, begin the procedure.

It should start with adequate infiltration of local anaesthetic. A variety of methods for local infiltration have been described. A popular technique is to use a dental syringe to infiltrate either prilocaine with felypressin or lignocaine with adrenaline subepithelially. The dental syringe has the advantage of having fewer side-effects and a much reduced risk of vasovagal attack. Local anaesthesia in this procedure is not attempting a regional block, and the aim is to infiltrate everywhere that the loop will pass. If using prilocaine with felypressin, infiltrate 2–4 vials (2.2 mL in each) for a medium-sized TZ. It is possible to use less, but side-effects with this preparation are exceedingly rare and using this much will ensure adequate anaesthesia; indeed, this is usually a totally pain-free procedure. Using sufficient infiltration also reduces the amount of peri- and post-LLETZ bleeding, so that haemostasis is more easily achieved. Some bleeding does occur from the infiltration needle puncture sites but is rarely problematic.

After infiltration of local anaesthetic, attach the diathermy ground plate from the ESU port to the patient, and attach the suction tubing to the suction tube on the underside of the anterior blade of the speculum and activate the suction. At this stage, the colposcope should be set to low magnification so that the entire loop, cervix, and vaginal walls may be seen. Set the appropriate power setting on the ESU. Next, the *unactivated* loop should be introduced and held only a millimetre or so off the entry point for resection under direct binocular colposcopic view. The loop electrode should be activated just before making cutting contact with the epithelium. A blend of

coagulation and cutting may be used (i.e. blend 1, or 20% coagulation and 80% cutting) so as to minimize the coagulating diathermy effect on the extirpated TZ and the LLETZ wound. The entry point should usually be only a millimetre or two outside the outer limit of the TZ.

It is preferable to resect the TZ, usually in one piece from the 9 o'clock position, thereby passing from the patient's right to left. In this way, the resected TZ does not fall onto the loop, as can happen when resecting antero-posteriorly. While performing the procedure, the colposcopist should be conscious of the depth of the loop in the stroma underneath the TZ epithelium. Fig. 11.9 presents a simple LLETZ in a type 1 TZ, i.e. a type 1 TZ excision.

After the TZ is removed, it should be transferred to the attendant, who may transect it and pin it onto a cork board before immersion in formalin (Fig. 11.10). It is also worth immersing the extirpated TZ in a graduated cylinder of fluid to assess volume. Volume of excision appears to be a reliable prognosticator for future pregnancy-related complications (Castanon et al., 2014; Khalid et al., 2012; Kyrgiou et al., 2014).

The aim of treatment by LLETZ is to excise the entire TZ and only the TZ to a depth of about 5–7 mm. This is sufficient to resect virtually all epithelial crypts, and the diathermy artefactual damage of the loop will inflict artefactual diathermy necrosis for a further 2–3 mm. Although it might seem sufficient to resect only the lesion within the TZ, the published treatment success rates relate to treatment by excising or destroying the entire TZ and not only the lesion.

11.8 Post-LLETZ wound management

There are few RCTs of post-LLETZ management, but the evidence suggests that Monsel's paste (see Annex 5), on its own or after initial ball electrode *point diathermy* of any bleeding points, is highly effective and minimally damaging to the LLETZ wound bed. If using diathermy to achieve coagulative haemostasis, use a small ball and a fulgurative technique. Try to ensure that the upper limit of resection (the new SCJ) is *not* diathermized, to reduce the risk of functional stenosis (Paraskevaidis et al., 2001a). Finally, any blood or iodine may be evacuated from the posterior vaginal fornix with a large cotton swab, and the speculum then removed. While the patient is dressing, the procedure should be documented. Thereafter, the patient may be counselled about the procedure and the follow-up arrangements.

11.9 Management of the specimen

The extirpated TZ will be processed according to the preferences of the pathologist. Some prefer to section

Fig. 11.9. A simple type 1 excision in a patient with HSIL in a type 1 transformation zone. (a) The cervix after the application of Lugol's iodine. (b) Local infiltration of prilocaine with felypressin. (c) The loop just before the procedure. (d) The cervix immediately after the procedure, with the resected transformation zone still in situ. (e) The cervical wound before fulgurative diathermy coagulation. (f) The cervical wound after fulgurative diathermy coagulation.

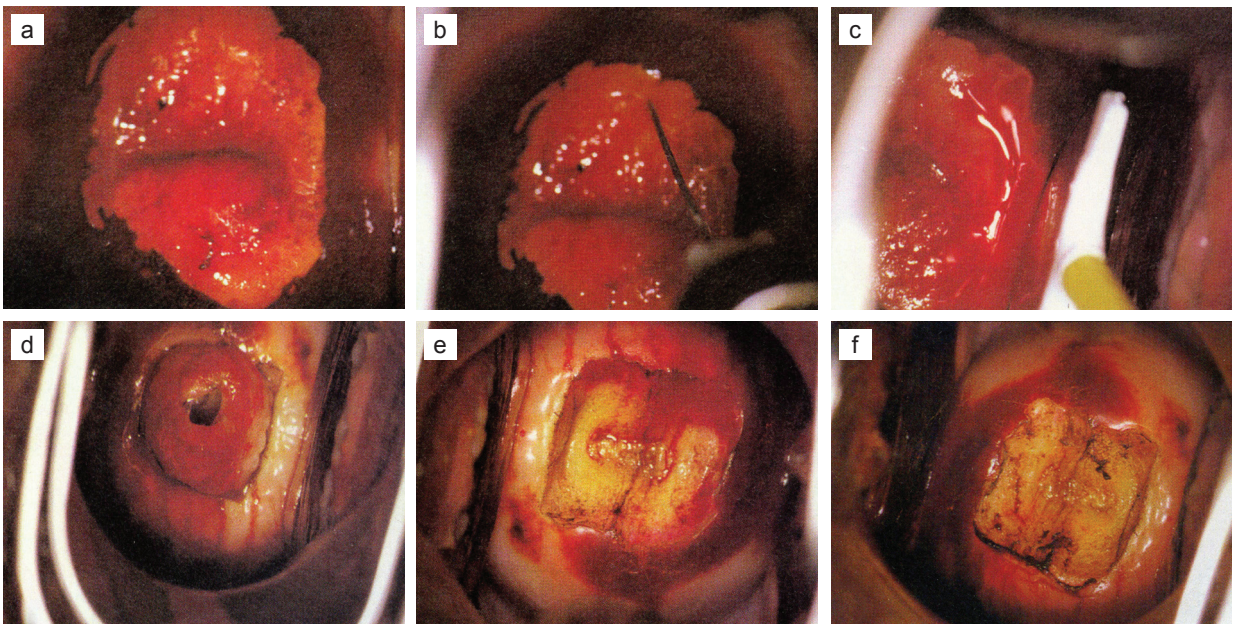
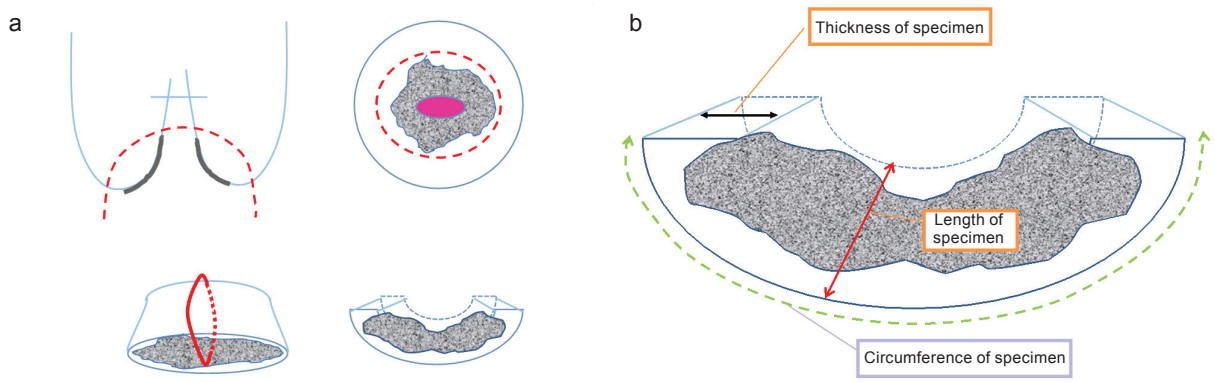


Fig. 11.10. A type 1 transformation zone that has been removed at LLETZ and opened. (a) A simple LLETZ; after resection, the removed transformation zone is opened and pinned onto a cork board before immersion in formalin. (b) The dimensions of the opened specimen.



the unopened disc of tissue, and others to open it before fixing in formaldehyde. The latter technique has the advantage that it allows for longitudinal sections through the entire length of the excised TZ and allows assessment of margin status at either end of the specimen (i.e. endocervical and ectocervical margins). Because of the confusion in the literature between terms like "depth" and "height", these terms have been abandoned in the latest IFCPC nomenclature, and instead the more universally understood terms "length" and "thickness" (of the open specimen) have been included. These dimensions are illustrated in Fig. 11.10 (see also Fig. 7.9).

11.10 Post-treatment advice to patients

Every patient should be given a clearly written handout of post-LLETZ instructions, and these should be explained verbally before the patient leaves the clinic. The handout should state what has been performed, describe the likely short-term course (mild bleeding for a few weeks), provide advice to abstain from penetrative intercourse for a month, and state what follow-up arrangements have been made. The patient should be advised to return to the clinic if there are symptoms suggestive of either a severe infection or, more seriously, an electrosurgical injury.

11.11 Complications after LLETZ

In the short term, complications after LLETZ are mild but are to be expected. These include light per vaginal bleeding, mild discomfort, and a little discharge. The bleeding during the first 2 or 3 weeks is not usually more than that which occurs during normal menstruation, providing that the cervix was not inflamed at the time of LLETZ. Severe bleeding or symptoms suggestive of a secondary infection (bleeding greater than during normal menses, discharge, and/or pain) are uncommon and should precipitate immediate return to the clinic service.

It is entirely biologically plausible that excision of part of a reproductive organ is likely to compromise its function. Since the review of Kyrgiou et al. (2006), there have been a plethora of publications reporting conflicting evidence about the risk of premature labour after excisional treatment for cervical precancer. The most recent review of the evidence suggests that removing a small type 1 TZ is associated with an insignificant increase in subsequent pregnancy-related complications, whereas removing a large amount of tissue by cold-knife excision, laser excision, or electrosurgery is likely to cause a definite increase in subsequent pregnancy-related complications (Arbyn et al., 2008; Castanon et al., 2014; Khalid et al., 2012; Kyrgiou et al., 2006, 2014; Strander and Adolfsson, 2014).

11.12 See-and-treat

"See-and-treat" has several interpretations. It may mean that:

- every patient with an abnormal smear report who has been referred for colposcopy is treated at their first visit in the colposcopy clinic (non-selective see-and-treat); or
- every woman who has a positive screening test (e.g. VIA) is treated at the time of the screening test (non-selective screen-and-treat); or
- only those women in whom both the primary screening test and the colposcopic impression are in agreement and suspect a high-grade abnormality are treated (selective see-and-treat).

Non-selective see-and-treat (i.e. screen-and-treat) protocols will treat a large proportion of patients who

would not have developed cancer. This is not to say that this policy is wrong; it may be the most efficient and effective way of reducing cancer rates in a particular region. But where competently performed colposcopic examination is available, it is better to select for treatment only those who have a high risk of progression and to monitor those who have a low risk of progression. There is now good evidence that the risk of progression to cancer for histologically proven CIN1 is similar to the risk for normal epithelium.

The logic supporting a selective see-and-treat protocol is that for women with a clinically significant risk of progression to cancer (i.e. HSIL suspected cytologically and also at colposcopic examination) or when there is an obvious need to treat, there is little advantage to taking a biopsy and asking the patient to return when the result is available. During one calendar year at the Coombe Women & Infants University Hospital in Dublin, Ireland, where a selective see-and-treat protocol prevailed, histological audit revealed a very low rate of negative histology in the extirpated TZs (< 1%). There were, however, a relatively large number of low-grade lesions (13.0%, or 30 of 230 cases) revealed at histology. On closer examination of the case records of these patients, the majority (19 of 30) were older than 40 years and had completed their family. The remainder had a referral smear that suspected ASCUS-H (ASCUS, cannot exclude HSIL) or CIN2 (6 cases), ASCUS (4 cases), or atypical glandular cells of undetermined significance (AGUS) (1 case). The United Kingdom clinical guidelines document expects that a see-and-treat protocol should not produce negative or low-grade histological reports in more than 10% of cases (NHS, 2016). However, in women older than 40 years who have completed their family, it is reasonable to treat at a lower threshold than HSIL. A selective see-and-treat protocol is very patient-friendly and is a very efficient use of limited resources.

11.13 Modifications of LLETZ technique: SWETZ; type 2 and type 3 excisions

The LLETZ (or LEEP) technique described above is for a type 1 excision and is appropriate for the great majority of women with CIN, i.e. for a small or medium-sized type 1 TZ, which will be resectable as an outpatient procedure using local anaesthesia with a small or medium-sized loop (Fig. 11.8). However, for some cases the technique needs to be modified, and some cases require general anaesthesia, most commonly for a type 3 TZ excision. Two examples of different excisional methods follow.

11.13.1 Excision of a large and/or irregular TZ

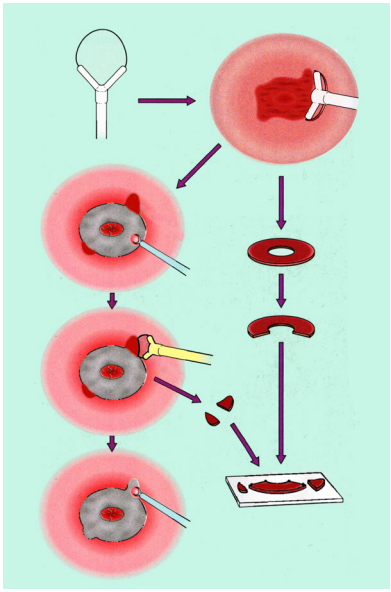
Optimal excisional treatment is a balance between removing the entire TZ and not removing unnecessary amounts of normal tissue. When the ectocervical component of the TZ (of any type, 1, 2, or 3) is very large or very irregular, it is possible that trying to remove it in one piece may remove a lot of normal tissue. In this case, it is worth considering removing the central part (always including the SCJ). It is then easy to remove or destroy the remaining peripheral TZ parts separately, as depicted in Fig. 11.11.

11.13.2 Type 3 excision

Excision types are illustrated in Fig. 7.4. Although type 3 excisions, especially large ones, are known to be associated with an increase in the risk of subsequent pregnancy-related complications (primarily premature labour) (Khalid et al., 2012), it is sometimes necessary to perform a type 3 excision. Examples include a type 3 TZ with suspected HSIL, glandular disease, or even suspected microinvasion. Performing a type 3 excision is not as simple as performing a type 1 excision and may require general anaesthesia, depending on how large and how long the excision needs to be, access to the cervix, and patient compliance.

Sometimes a large, long loop will be perfectly adequate (Fig. 11.12). However, some colposcopists feel that the risk of inadequate excision margin status at the upper limit is greater with a loop and that a straight wire, laser excision, or even cold-knife excision under general anaesthesia is better. Camargo et al. (2015) have recently published

Fig. 11.11. LLETZ removal of the central portion of a large transformation zone (TZ) with the medium loop (20 × 15 mm) in one sweep including the squamocolumnar junction, followed by removal of the peripheral parts of the TZ separately as one or more pieces with one or more passes of the medium or small loop.



a comparison of SWETZ versus LLETZ for the type 3 excision, and they found that SWETZ and LLETZ were equally effective for the treatment of endocervical disease, with no difference in margin involvement. Higher, but not severe, blood loss and longer surgical time were recorded for SWETZ procedures. Fig. 11.13 illustrates the SWETZ technique. Finally, some colposcopists prefer to remove the type 3 TZ by way of the top-hat technique, whereby the TZ is removed in two pieces. After the initial pass removes the ectocervical component, a second, smaller loop removes the upper part of the endocervical TZ (Fig. 11.14; see also Fig. 7.8). However, this technique inevitably inflicts more diathermy damage on the specimen margins.

11.14 Comparison of treatment success rates between LLETZ, thermal coagulation, and cryocautery

Theoretically, one would not expect there to be a large difference between the methods of treating type 1 TZs. It does not matter whether the TZ is boiled, frozen, or removed; so long as it has been ablated, the precancerous tissue will no longer be present. It is clear that an excisional technique will have certain advantages because of the ability to examine the resected tissue histologically, but providing that cancer and glandular disease were not present and that the TZ was indeed a type 1 TZ, residual disease rates should be similar. Any difference in success rates might reasonably be attributed to the operator rather than the technique.

In fact, the published success rates are very similar, with the possible exception of cryosurgery for CIN3. Among excisional methods, cure rates of CIN confirmed by biopsy reached 90–94% with cold-knife cone biopsy, 91–98% with LLETZ, and 93–96% with laser conization. Among ablative techniques, cure rates reached 85–94% with cryotherapy and 95–96% with laser ablation. In terms of side-effects, thermal coagulation appears to be superior to cryocautery; watery discharge persists for the majority of patients (93%) after cryocautery and for relatively few (17%) after thermal coagulation (Fergusson and Craft, 1974). The interested reader is referred to the meta-analytical reviews of cryosurgery (Sauvaget et al., 2013), of cold coagulation (Dolman et al., 2014), and of all treatments for CIN (Martin-Hirsch et al., 2013). In the Cochrane meta-analysis by Martin-Hirsch et al. (2013), the authors concluded: “The evidence from the 29 RCTs identified [in this meta-analysis] suggests that there is no overwhelmingly superior surgical technique for eradicating CIN. Cryotherapy appears to be an effective treatment of low-grade disease but not of high-grade disease. Choice of treatment of ectocervical situated lesions [type 1 TZs] must therefore be based on cost, morbidity, and whether excisional treatments provide more reliable biopsy specimens for assessment of disease compared to colposcopic directed specimens taken before ablative therapy. Colposcopic directed biopsies have been shown to underdiagnose microinvasive disease

Fig. 11.12. LLETZ excision of an entirely endocervical, but fully visible, transformation zone as one piece with one sweep of a large (blue) loop (20 × 20 mm).

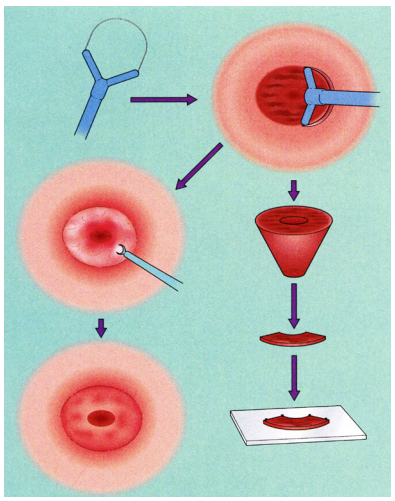


Fig. 11.13. SWETZ excision of a fully visible and endocervical transformation zone as a cone biopsy using a 1 cm long straight wire as a knife.

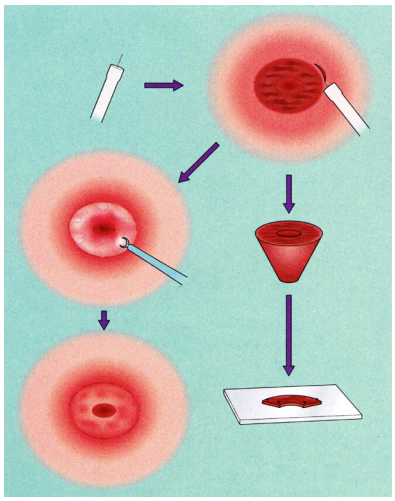
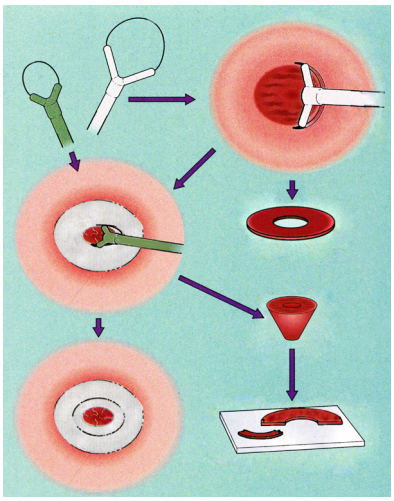


Fig. 11.14. LLETZ excision of an entirely endocervical, but fully visible, transformation zone using first the medium (white) loop (20 × 12 mm), with subsequent excision of the remaining endocervical part using a small or medium (green) loop (15 × 12 mm).



compared with excisional biopsies performed by knife or loop excision, particularly if high-grade disease is present (Anderson, 1986; Chappatte et al., 1991)."

The available data are not definitive, and often the early observational trials of a treatment are published from centres of excellence. Their experience may not equate to success rates in normal practice. But in summary, from the available data and the practicality issues mentioned above, thermal coagulation would appear to be the treatment of choice where colposcopy and histopathology services are sparse or unavailable. Where they are available, colposcopy and LLETZ are still the gold standard for investigation and management of women with suspected CIN.

11.15 Follow-up after treatment of CIN

Because treatment methods are not associated with a 100% success rate, it is important to establish a follow-up protocol to identify the small percentage (< 10%) of those treated who will have residual CIN. The rates of residual disease vary considerably in the published literature, but some things are well established. First, women who have been treated for cervical precancer are much more likely to develop cervical cancer. This increased risk has been quantified as being 2–5 times the background risk, and much of it is a result of poor long-term follow-up (Soutter et al., 1997; Strander et al., 2007). Several case series of cancer demonstrated that more than 50% of cancers are in women who are lost to follow-up (Ghaem-Maghami et al., 2007) and that this increase in risk lasts for 20 years or more. Excisional treatments permit histological assessment of a biopsy and can determine specific risk factors for residual disease. The NHS Cervical Screening Programme clinical guidelines document details several retrospective studies (Dobbs et al., 2000; Flannelly et al., 2001; NHS, 2010; Schantz and Thormann, 1984) that report residual disease rates after excision and have demonstrated that negative excision margins are associated with lower risk of residual disease and positive excision margins are associated with higher risk of residual disease. Also, those studies that compared endocervical with ectocervical margin status have demonstrated that disease at the endocervical resection margin is associated with increased risk of residual disease compared with involved ectocervical margins. Women aged 50 years or older are particularly at risk of persistent/recurrent disease (Flannelly et al., 2001; Ghaem-Maghami et al., 2007).

As a result of these studies, it is clear that women need follow-up after treatment. Regional facilities and the cost of colposcopy, cytology, and HPV testing will dictate the appropriate follow-up strategies, but in terms of test characteristics, there is no doubt that HPV testing is the most sensitive test and that it has the best negative predictive values. Several meta-analytical reviews have attested to this (Arbyn et al., 2005). In the context of an organized, systematic call-and-recall screening programme, HPV testing has also been shown to be cost-effective (Coupé et al., 2007), but the cost of HPV testing varies and may not be perceived as being affordable in some LMICs. No matter which method of follow-up is arranged, it should continue for at least 20 years.

Key points

- Where possible, every patient requiring treatment should have a colposcopic examination to determine the transformation zone type and the presence or absence of precancerous or cancerous change.
- Excisional treatment is superior to destructive therapy because it facilitates histological examination of the transformation zone, whereby the diagnosis may be verified and margin status confirmed.
- Where excisional therapy is not available, destructive therapy is an entirely reasonable alternative to excision. When destructive therapy is used, the transformation zone should be of type 1 and small, and there should be no suspicion of invasive or glandular abnormality.
- Excisional therapy should always be performed under colposcopic vision, so as to achieve complete excision and minimize removal and damage of normal tissue. Some workers would advocate the same for ablative therapy, particularly where the transformation zone is larger than the probe tip and warrants overlapping application (e.g. using cold or thermal coagulation).

CHAPTER 12.

Glandular abnormalities, adenocarcinoma in situ, and glandular intraepithelial neoplasia

The implementation of a high-coverage and quality-assured cytology-based screening programme will reduce the incidence of and mortality from cervical cancer, largely because of the effect on squamous disease. This is to be expected, given that cervical cancer preventive screening programmes are designed to detect squamous cell abnormalities and not glandular disease. Even in well-screened populations, adenocarcinoma rates have been largely unaffected. Glandular abnormalities are rare (reported in 0.5–0.8 cases per 1000), but a smear report of glandular abnormality is more predictive of disease than an equivalent squamous abnormality, and not only of purely glandular abnormalities (Krane et al., 2001). The study of Pisal et al. (2003) of 50 smears reporting glandular dyskaryosis found that 13 cases were cervical glandular disease and only one of those was pure glandular dysplasia. There were 4 cases of microinvasive adenocarcinoma, 2 undifferentiated cancers, 1 squamous cell cancer, and 21 cases of HSIL. Thirteen women had endometrial pathology (8 endometrial cancers), and one woman even had colon cancer. In all, 16 of the 50 women had a malignancy (Pisal et al., 2003).

As many programmes move to HPV-based screening, this may change. Because most glandular disease exists in the endocervical site, glandular precancer will often be missed by visual inspection methods. However, many glandular lesions coexist in the TZ. Furthermore, many glandular lesions are associated with concurrent ectocervical squamous disease. A good illustration of the failure of screening to prevent glandular cancer is the ratio of abnormal glandular smear reports to glandular cancer rates. Although glandular precancer smear reports are 0.02 times as common as squamous lesions, glandular cancer accounts for 20% or all cervical cancer cases.

12.1 Glandular disease

The natural history of glandular precancer (adenocarcinoma in situ) or high-grade glandular abnormality (cervical glandular intraepithelial neoplasia [CGIN]) is not as well mapped out as that of squamous disease. It is highly likely that glandular dysplasia will progress to invasive cancer in a significant proportion of cases, for several reasons.

- Glandular intraepithelial lesions are often found adjacent to invasive lesions.

Fig. 12.1. High-grade glandular dysplasia in a gland crypt.

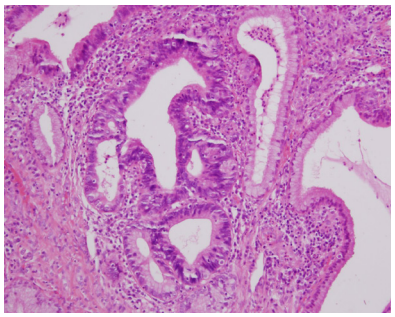
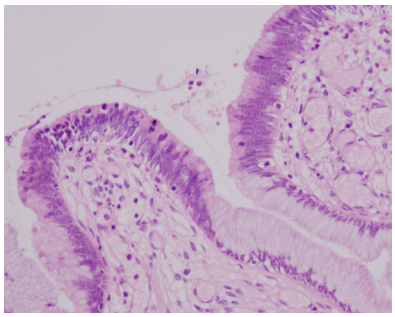


Fig. 12.2. Higher-power magnification view of glandular dysplasia.



- The cellularity of CGIN and glandular cancer are very similar morphologically; indeed, differentiating the very earliest stages of invasive adenocarcinoma from intraepithelial disease can be challenging and is often highly subjective (Cullimore et al., 1992).
- The mean age of women who develop adenocarcinoma in situ is about 15 years less than that for invasive glandular cancer.
- Similar HPV types are found in CGIN and glandular cancer cases (Zaino, 2000).

As with squamous disease, low-grade abnormalities are not easily defined or uniformly agreed upon between pathologists, whereas high-grade CGIN (Figs. 12.1 and 12.2) or adenocarcinoma is a relatively robust diagnosis. Also, because high-grade glandular disease is much less common than high-grade squamous cancer (at a ratio of about 1:50), it is not as easily discovered, either cytologically or colposcopically. Finally, the colposcopic signs of high-grade CGIN are less recognizable than those of HSIL.

Several lessons derive from the above-mentioned situation. First, a histological diagnosis is mandatory in making a diagnosis of high-grade CGIN, and the diagnosis needs to be made with a sufficiently large biopsy, whereby it is possible to recognize or rule out disease. There is no place for punch biopsies in the investigation of CGIN. At the very least, a small loop biopsy (or biopsies) is necessary. CGIN and adenocarcinoma (Fig. 12.3) is a challenging diagnosis. Colposcopic examination does not usually discover covert glandular disease, and this is not surprising: the disease is largely endocervical; the concept of an adequate or satisfactory colposcopic examination does not usually apply to glandular lesions, because of their endocervical site; and the colposcopic signs of glandular disease are more difficult to recognize. Also, because glandular disease is so much less common, it is more difficult to acquire image recognition skills for glandular disease. Colposcopy is important in the investigation and management of suspected glandular disease but on its own has a poor negative or positive predictive value for glandular disease (Ullal et al., 2009), and abnormal cytology is more likely to predict histologically proven glandular disease than is colposcopy. This is one of the reasons why excisional treatment of suspected high-grade glandular disease is fundamentally important. Although colposcopy may recognize signs of glandular disease (Fig. 12.4), it will also often miss the unheralded case (i.e. not suspected cytologically).

The interested reader is referred to an excellent atlas of colposcopic images of glandular disease (Wright, 2010); however, not many colposcopists feel able to reliably recognize glandular disease using colposcopy alone. Typical signs that have been reported include white lesions adjacent to the SCJ, character writing (Fig. 12.5), large gland openings, fused clumped villi, variegated red and white lesions after acetic acid

Fig. 12.3. Cross-section of an adenocarcinoma.

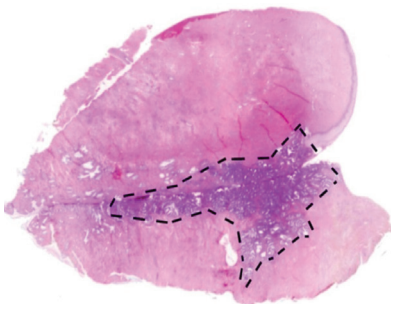


Fig. 12.4. Colposcopic image of a high-grade glandular lesion.

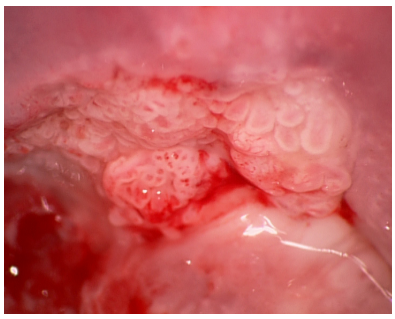
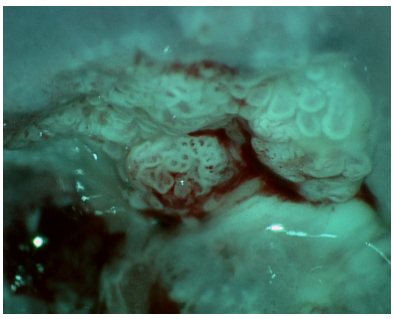


Fig. 12.5. Colposcopic image of a high-grade glandular lesion using the green filter to highlight blood vessel patterns.



application, and exophytic white lesions.

12.2 Management of suspected glandular dysplasia

The definitive management of glandular dysplasia is excision of the TZ and a proportion of full-thickness endocervical canal epithelium. When a borderline glandular smear has been reported, it may be sufficient to perform colposcopy and biopsy, but where there is any suspicion of genuine CGIN, excisional treatment is mandatory. This is for several reasons.

- Most glandular disease has an endocervical component, and therefore destructive techniques are contraindicated.
- It is often not possible to determine the extent of endocervical involvement of dysplastic epithelium in the canal. Colposcopic assessment of glandular dysplasia is less reliable than with squamous disease.
- Multicentric disease (skip lesions) occurs with glandular disease in about 15% of cases.
- About 50% of cases of glandular disease will have concomitant squamous disease.

12.3 Excisional treatment with CGIN: what type and how big?

A cylindrical type 3 excision should be performed using a straight wire, a cold knife, or a laser to perform the excision. LLETZ may also be used if the operator is experienced and audit reveals clear undamaged margins in excised tissue. It is crucial that the pathologist has sufficient and undamaged tissue with which to make a diagnosis and assess margin involvement. The diagrams in Figs. 12.6 and 12.7 illustrate this point. The traditional cone biopsy has a cone shape and is likely to miss disease at the base of deep cervical clefts, which can extend up to 5 mm from the margin of the canal (Bertrand et al., 1987). Cylindrical type 3 excisions avoid this potential problem.

12.4 Anatomical distribution of CGIN

The interested reader is referred to John Cullimore's excellent chapter on glandular disease (Cullimore, 2003), and his illustrations of the distribution of CGIN are reproduced in Fig. 12.8. Bertrand et al. (1987), Nicklin et al. (1991), and Teshima et al. (1985) have also examined the subject in detail. The disease is unicentric in more than 85% of cases and arises just above the SCJ. It

Fig. 12.6. A traditional cone biopsy, which risks inadequate excision at the upper margin and excessive removal of stromal tissue.

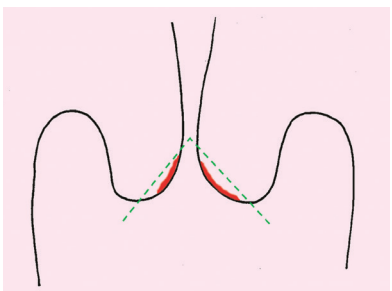


Fig. 12.7. A cylindrical type 3 excision, which is less likely to produce incomplete excision and removes less normal stromal tissue.

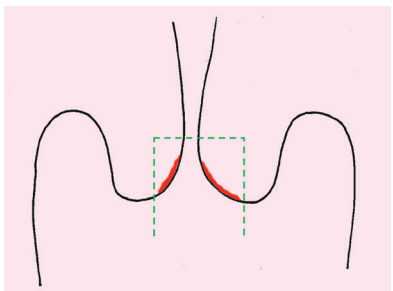
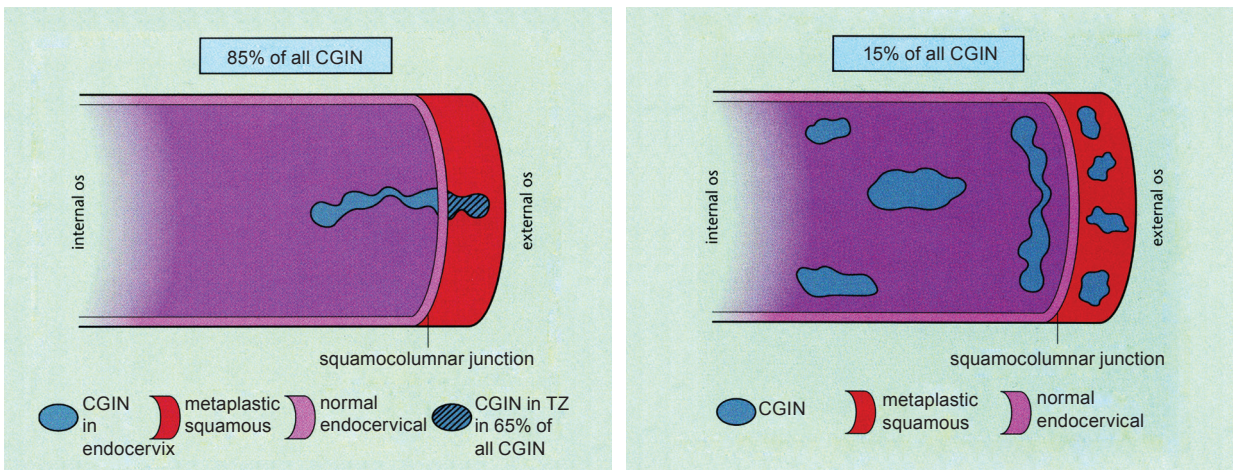


Fig. 12.8. Distribution of cervical glandular intraepithelial neoplasia (CGIN). TZ, transformation zone.

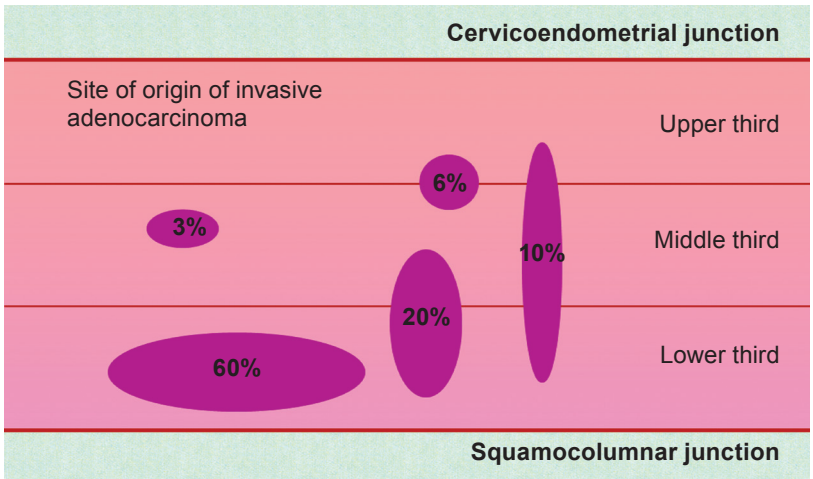


usually extends in a contiguous fashion up the endocervical canal. Skip lesions are uncommon but not rare (Zaino, 2002), but the distribution is multicentric in approximately 15% of cases. Fortunately, in more than 95% of cases in women younger than 36 years, the disease appears to be confined to within 10 mm of the SCJ, whereas in women older than 35 years it can extend to 20 mm or 25 mm above the SCJ.

As for invasive disease, the distribution is equally important (Fig. 12.9). Teshima et al. (1985), reporting the histological findings of 30 cases of early adenocarcinoma of the endocervical glandular epithelium, reported that 27 of 30 originated in the lower third of the canal, and of these 18 were exclusively in the lower third. Lee and Flynn (2000) reported that invasive disease was found originating in or immediately adjacent to the TZ in 78% of their case series. Also, 85% of the cases in their series had associated CGIN or adenocarcinoma in situ. When managing women with abnormal glandular disease, one is as likely to discover covert cancer as covert adenocarcinoma in situ. This is another reason that complete excision and histopathologically clear margins are crucial when treating glandular dysplasia.

These findings have important clinical implications. How much of the endocervical canal should be excised is influenced by the position of the SCJ (the upper limit of the TZ) as well as the woman's age, her fertility aspirations, and the likelihood of default from follow-up. Glandular disease typically presents in women of reproductive age, and many women will not have completed their family, so that taking the minimum amount of tissue necessary would seem sensible. However, there is good evidence that histologically involved margins are a risk factor for residual disease,

Fig. 12.9. Distribution of the site of origin of adenocarcinoma in the endocervical canal.



and clear margins are powerful as negative predictors of residual/recurrent disease. Salani et al. (2009) undertook a meta-analysis of observational studies including a total of 1278 patients and found positive margins to be associated with a clinically important increase in the risk of both residual precancerous glandular disease and the development of invasive disease (Table 12.1).

12.5 Individualizing treatment with CGIN

Taking the above-mentioned data into account, a reasonable approach to the management of CGIN is to individualize it. For young women who still wish to have children, it is reasonable to limit the excision to 12–15 mm above the TZ and, also, to include the entire TZ in the specimen. Coincident squamous disease is common (NHS, 2010). If the woman has completed her family, then the initial excision should include a further 5 mm of endocervical canal. For women older than 35 years in whom future fertility is not desired, the initial excision should be 20–25 mm of endocervical canal epithelium and, of course, should also include the TZ. For whichever excisional length is chosen, the excision should be cylindrical and should excise a one-piece specimen. Invasive disease (squamous or glandular) should not be excised in pieces. After the precise diagnosis has been made and invasive cancer has been ruled out, the patient may be followed up until she has completed her family. It is important to recognize that clear margins do not give the same degree of negative prediction against recurrence as with squamous disease. The risk of recurrence after treatment for glandular disease is 3 times that for squamous disease. Once the patient has

Table 12.1. Risk associated with incomplete excision

Risk	Positive margins	Negative margins
Risk of residual CGIN	19.4%	2.6%
Risk of subsequent invasive cancer	6%	0.35%

CGIN, cervical glandular intraepithelial neoplasia.

completed her family, a hysterectomy is probably wise. Until then, follow-up with endocervical brush cytology, HPV testing, and colposcopic examination at least annually is prudent; recent NHS Cervical Screening Programme guidelines imply that this can be further rationalized since the addition of HPV testing (NHS, 2016), although the evidence base for this recommendation is unclear. Women who decide not to have a hysterectomy in the presence of true glandular disease need to know that there is a risk of residual disease and of the development of invasive cancer, which is more difficult to monitor than ectocervical squamous precancer. Finally, when HPV vaccination programmes become universal, CGIN rates will begin to fall. CGIN is universally associated with high-risk HPV (types 16 and 18).

Key points

- The diagnosis of cervical glandular intraepithelial neoplasia (CGIN) can only be made at histology.
- Cytology and colposcopy are unreliable methods of detecting CGIN.
- Punch biopsies are an unreliable means of detecting CGIN.
- Excision of the transformation zone and part of the endocervical canal is the diagnostic and treatment method of choice for CGIN.
- Negative margins are good but not absolutely reliable markers of complete treatment.
- With precancerous glandular disease, the definitive treatment is hysterectomy, which may usually be deferred until the patient has completed her family.
- Conservative management of CGIN is justified in young women, assured of adequate follow-up, until the patient has completed her family, when hysterectomy should be considered.
- Follow-up should continue for 10 years or more, or until hysterectomy and for 1 year after hysterectomy.

CHAPTER 13.

Microinvasive squamous cervical cancer

This chapter deals with microinvasive squamous cervical cancer (Fig. 13.1). It is an introduction to the disease and not a reference text. A gynaecologist caring for women with cervical cancer should, ideally, undertake a subspecialist training course.

13.1 Early preclinical microinvasive disease of the cervix (stages IA1 and IA2)

The management of cancer depends crucially on the stage of the disease. Microinvasive disease, or International Federation of Gynecology and Obstetrics (FIGO) stages IA1 and IA2, constitutes invasive cancer at its earliest stage. It has broken through the basement membrane but does not extend beyond a depth of 3 mm (stage IA1) or 5 mm (stage IA2) or a width of 7 mm.

The risk of lymph node involvement in stage IA1 disease is very low. Ostör (1993), in a study of several thousand cases, estimated the probability of lymph node involvement to be 0.1% if the depth of invasion was less than 1 mm (3 out of 2274 cases) and 0.5% if the depth was between 1 mm and 3 mm (7 out of 1324 cases).

Microinvasive disease is not often symptomatic but may present with abnormal per vaginal bleeding. The referral smear, if there is one, will usually report features of an HSIL but may occasionally describe specific cytological markers for invasion.

13.2 Clinical features of microinvasive disease

"Microinvasive disease" is a widely used term, which refers to very early disease that has breached the basement membrane but has not spread beyond the superficial stroma. Currently, the term is reserved for lesions with a depth of less than 3 mm (stage IA1) or 5 mm (stage IA2) and a width of less than 7 mm. Table 13.1 details the FIGO staging of early invasive squamous cervical cancer.

As noted above, these very early lesions are usually asymptomatic

Fig. 13.1. Low-power view of invasive squamous cervical cancer.

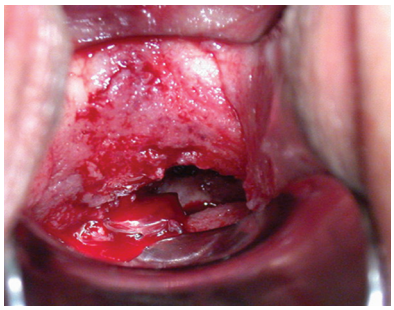


Table 13.1. FIGO staging of early invasive squamous cervical carcinoma

Stage of disease	Description
Stage 0	Precancer or squamous intraepithelial lesion (previously known as CIN)
Stage IA1	Microinvasive lesion Depth < 3 mm, width < 7 mm
Stage IA2	Microinvasive lesion Depth 3–5 mm, width < 7 mm
Stage IB1	Clinical lesion < 4 cm
Stage IB2	Clinical lesion > 4 cm

CIN, cervical intraepithelial neoplasia; FIGO, International Federation of Gynecology and Obstetrics.

and are recognized either colposcopically or, more usually, at histological examination of colposcopically directed biopsies.

A screening test may have been positive. Symptoms, when present, would usually be confined to intermenstrual or postcoital bleeding. There may be a history of previous treatment for cervical precancer or untreated HSIL. Default from follow-up of treated precancer is a common cause of subsequent development of cancer.

Fig. 13.2 shows histological sections of microinvasive disease. In Fig. 13.2a, malignant cells can be seen breaching the basement membrane and spilling into the underlying stroma.

13.3 Colposcopic recognition of microinvasive disease

The colposcopic features of microinvasive disease are not clearly distinguishable from those of HSIL. From a management perspective, it is preferable to know the diagnosis before treatment, because complete excision is so important. When the diagnosis of microinvasion is known, or suspected, it is perhaps worth excising a slightly larger margin of normal tissue around the TZ to allow the pathologist the best possible chance of determining the precise depth of invasion, the lesion margin status, the width and/or volume of the lesion, and, if present, lymphovascular space involvement (LVSI).

The colposcopic features of microinvasion are largely the exaggerated signs associated with HSIL, i.e. a high Swede score (see Annex 4). The lesions are often larger. The acetic acid uptake is faster, and the whiteness is denser and is sometimes described as oyster white. The vascular patterns of punctation and mosaicism are coarser. Also, particular vessel patterns are sometimes present (Fig. 13.3). These include vessel loops, corkscrew patterns, and pollarded vessels (Figs. 13.4–13.7). Completely bizarre and abnormally branching vessels may be present. Also, sometimes the ridge sign or inner border sign may be evident (Figs. 13.8 and 10.5h). Finally, the epithelium may be more friable than normal, and the edges of the lesion may easily peel off or strip away from the underlying stroma during colposcopic application of fluids or contact with cotton swabs

Fig. 13.2. Histological sections of (a, b) a very early stage of invasion: microinvasive disease; (c) stage IA1 disease at low-power magnification; (d) stage IA2 disease at low-power magnification.

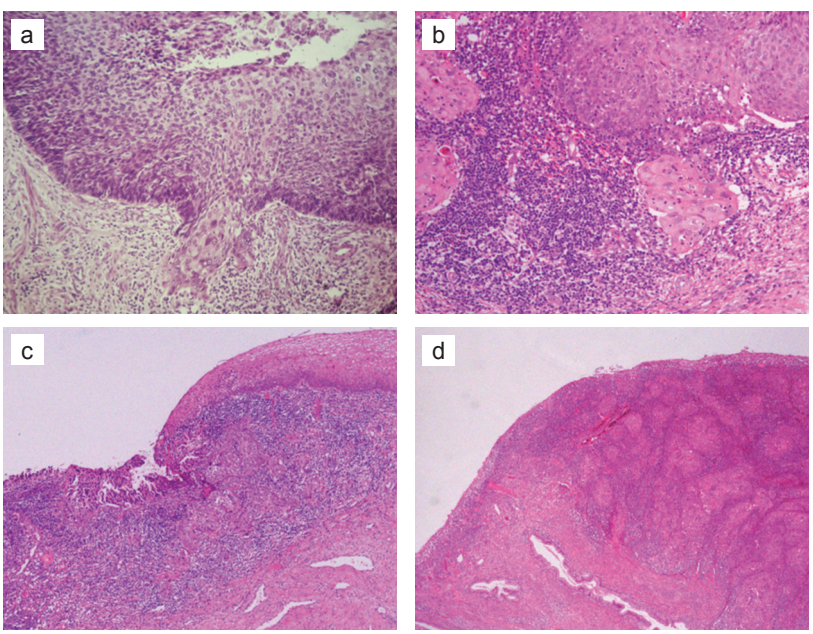


Fig. 13.3. Exaggerated colposcopic signs of HSIL in a case of microinvasion.

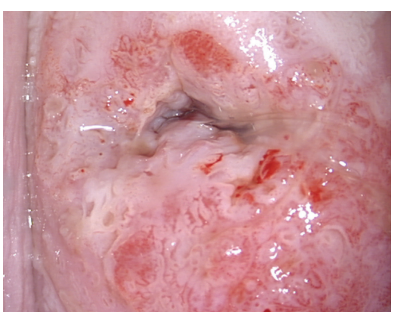


Fig. 13.4. Vascular patterns. (a–f) Abnormal blood vessel patterns (apart from mosaic and punctate patterns) are irregular in a variety of ways. Their common feature is lack of branching and any form of symmetry. (a) Wide hairpin-like vessel. (b) Waste thread vessel. (c) Tendril-like vessel. (d) Bizarre branching waste thread vessel. (e) Pollarded vessel. (f) Comma-shaped or tadpole vessel. Normal blood vessel patterns branch like a tree does. (g) Normal branching vascular patterns, often best seen stretched over a nabothian follicle.

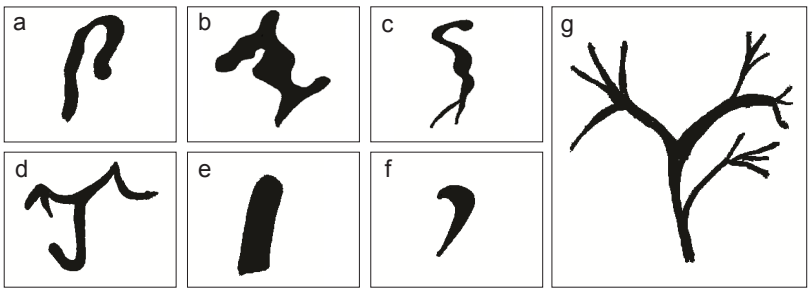


Fig. 13.5. (a) A normally branching tree. (b) A pollarded tree.

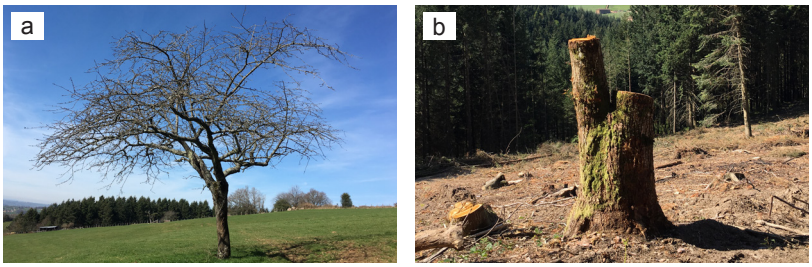


Fig. 13.6. An example of a pollarded vessel, at the centre of the image.

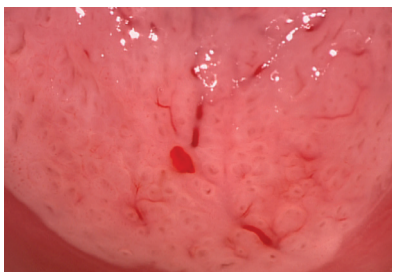


Fig. 13.7. Bizarre branching vessels, seen here using the green filter.

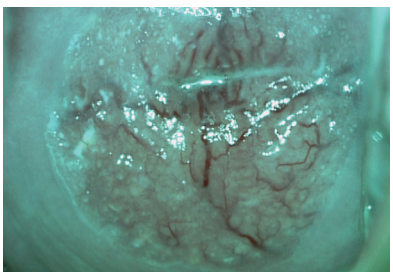


Fig. 13.8. The ridge sign, seen here in an island of acetowhite epithelium.

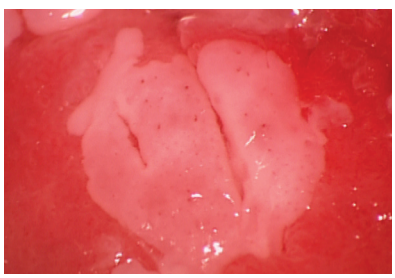
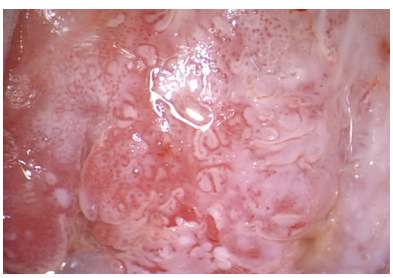


Fig. 13.9. Epithelial stripping, seen here at the 6 o'clock position in this case of microinvasion.



(Fig. 13.9). The colposcopist needs to be especially gentle in performing application of fluid and manipulation of the cervix when the diagnosis of microinvasion is suspected.

13.4 Management of suspected microinvasive disease

The diagnosis of microinvasion can only be made at histology. Furthermore, the stage of invasion can only be accurately assessed if the entire lesion is presented to the pathologist, preferably as one excised specimen.

Unfortunately, punch biopsies are unreliable when assessing possible microinvasion as they are sometimes not deep or wide enough for the pathologist to confidently recognize the disease or its extent. A small loop biopsy or removal of a wedge-shaped piece of tissue using a cold knife (a wedge biopsy) will usually provide an adequate specimen, but once the diagnosis of microinvasion is made or seriously suspected, the entire TZ with a clear margin of normal tissue should be excised as one piece. How this specimen is removed will vary; depending on the experience and expertise of the colposcopist, it is entirely reasonable to use LLETZ, SWETZ, laser excision, or cold-knife excision, providing that the colposcopist can ensure a sufficient margin of normal tissue surrounding the lesion. When there is any extent of endocervical involvement (type 2 or type 3 TZ), the procedure should excise a cylindrical specimen such that the upper extent of the specimen does not cut across or damage lesional tissue with diathermy (Figs. 12.6 and 12.7). For the inexperienced operator, it is probably wiser to perform the excision under general anaesthesia in an operating theatre.

Once the diagnosis has been made, the histology slides should be reviewed by the pathologist to assess as accurately as possible the

lesion's margin status and the depth and width of the invasive disease. LVSI should be actively sought. The case should then be discussed at a multidisciplinary team meeting or, at the very least, at a consultation between the colposcopist and the pathologist.

At the multidisciplinary team meeting, the depth and volume of invasive tissue should be discussed, as well as the degree, if any, of LVSI and the margin status. If there is any question of incomplete excision, which may occur when the diagnosis is first recognized at histology, a repeat excision should be performed. Once the stage of disease is confirmed, treatment may be decided. With microinvasive disease, the excisional treatment already performed may be adequate (Table 13.2).

Table 13.2. Treatment options for cervical cancer

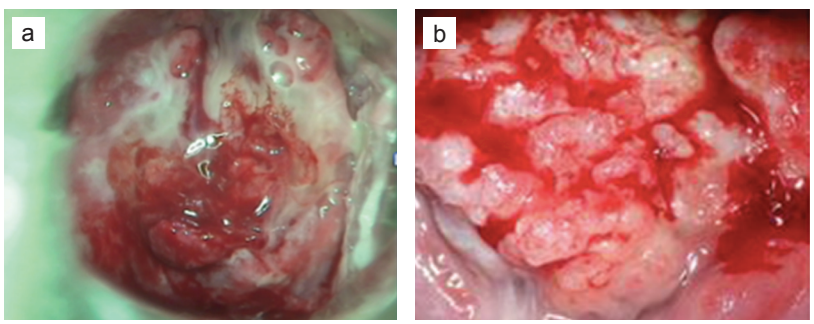
Stage of disease	Minimum treatment	Alternative treatments
Stage IA1	Complete excision of the transformation zone, usually as a type 3 excision	Simple hysterectomy
Stage IA2	Complete excision of the transformation zone, either as a type 3 excision or as a radical trachelectomy and Pelvic lymph node dissection	Radical hysterectomy and pelvic lymph node dissection
Stage IB	Radiotherapy	—
Stages II–IV	Radiotherapy	—

Cervical cancer staging is primarily a clinical assessment (Kurman et al., 2014). The stage is determined according to the size of the tumour and the degree of local and distant spread. The accurate staging of cervical cancer is the most important prognostic indicator for both patient and clinician, and its early and accurate assessment is crucial in determining appropriate therapy. It is detailed precisely in Table 13.1. Initial staging is a clinical assessment using speculum visualization and bimanual digital vaginal and rectal examination. Further assessment after initial suspicion will, of course, include colposcopy and biopsy as well as cystoscopy, endocervical sampling, hysteroscopy, urinary tract imaging, and local and general X-ray and computed tomography (CT) imaging, magnetic resonance imaging (MRI), and even laparoscopic nodal assessment. Unfortunately, imaging techniques will not be available in every unit, and a careful clinical examination will then be even more crucial. The investigations in common use are listed in Table 13.4. The clinical features of invasive cervical cancer are very variable, because the disease in its earliest stage is not visible to the naked eye and in its late stages will have involved several systems.

The early clinical features of cervical cancer are, in many respects, similar to those of cervical infection and include an offensive vaginal discharge and abnormal per vaginal bleeding as well as a friable-looking cervix on naked-eye inspection. Chlamydial infection, protozoal infection (tuberculosis, schistosomiasis, or amoebiasis), and other cervical infections may mimic cervical cancer. Investigation for these infections should include a microbiology and virology screen as well as a colposcopy and biopsy. In later-stage disease, a colposcopy will be of limited value.

The diagnosis of invasive cervical cancer can only be made on the basis of a histological report. Clinical assessment is simply unreliable. Fig. 13.10 shows two cases of cervical disease with exactly similar symptoms (abnormal per vaginal bleeding and an offensive vaginal discharge). Fig. 13.10a shows a case of cervical tuberculosis, and Fig. 13.10b shows a case of invasive cervical cancer. In the case of tuberculosis, the cervix returned to normal after a full course of antituberculous therapy.

Fig. 13.10. (a) A case of tuberculous cervicitis, presenting with postcoital bleeding, intermenstrual bleeding, and offensive vaginal discharge. (b) A case of cervical cancer, presenting with postcoital bleeding, intermenstrual bleeding, and offensive vaginal discharge.



13.5 Stage 1B and greater

Clinical features that may herald cervical cancer include abnormal per vaginal bleeding, particularly contact bleeding. Vaginal discharge and pelvic pain are often present in late-stage disease. Symptoms usually reflect local disease. For example, with lateral spread into the parametrium, ureteric obstruction may occur. Spread to the lateral pelvic sidewall may cause sciatic pain or even

Table 13.3. FIGO classification of malignant tumours of the cervix

Stage	Description
Stage I	Stage I is carcinoma strictly confined to the cervix; extension to the uterine corpus should be disregarded. The diagnosis of both stages IA1 and IA2 should be based on microscopic examination of removed tissue, preferably a cone, which must include the entire lesion.
Stage IA	Invasive cancer identified only microscopically. Invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7 mm in diameter.
Stage IA1	Measured invasion of the stroma no greater than 3 mm in depth and no wider than 7 mm in diameter.
Stage IA2	Measured invasion of the stroma greater than 3 mm but no greater than 5 mm in depth and no wider than 7 mm in diameter.
Stage IB	Clinical lesions confined to the cervix or preclinical lesions greater than stage IA. All gross lesions even with superficial invasion are stage IB cancers.
Stage IB1	Clinical lesions no greater than 4 cm in size.
Stage IB2	Clinical lesions greater than 4 cm in size.
Stage II	Stage II is carcinoma that extends beyond the cervix but does not extend into the pelvic wall. The carcinoma involves the vagina, but not as far as the lower third.
Stage IIA	No obvious parametrial involvement. Involvement of up to the upper two thirds of the vagina.
Stage IIB	Obvious parametrial involvement, but not into the pelvic sidewall.
Stage III	Stage III is carcinoma that has extended into the pelvic sidewall. On rectal examination, there is no cancer-free space between the tumour and the pelvic sidewall. The tumour involves the lower third of the vagina. All cases with hydronephrosis or a non-functioning kidney are stage III cancers.
Stage IIIA	No extension into the pelvic sidewall but involvement of the lower third of the vagina.
Stage IIIB	Extension into the pelvic sidewall or hydronephrosis or a non-functioning kidney.
Stage IV	Stage IV is carcinoma that has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum.
Stage IVA	Spread of the tumour into adjacent pelvic organs.
Stage IVB	Spread to distant organs.

FIGO, International Federation of Gynecology and Obstetrics.

lymphoedema. When the tumour spreads anteriorly, it may cause any urinary symptom, including haematuria, bladder pain, and urinary retention, or even symptoms associated with a vesicovaginal fistula. Posterior involvement will often cause back pain, tenesmus, and symptoms associated with a rectovaginal fistula. With late-stage disease, the symptoms of severe anaemia are common.

On examination of the cervix, early-stage disease (microinvasion) may not be evident to the naked eye, but as the disease progresses, it becomes grossly apparent. Invasive cervical cancer will typically present as an ulcerative or proliferative tumour, which bleeds readily on contact and will often be infected. When tumours are exophytic and grow out into the vaginal space, they tend to become polypoid or papillary and appear as a cauliflower-like growth. When tumours are endophytic, they may infiltrate extensively, with very little epithelial revelation. Endophytic growths may expand the cervix for several centimetres before breaching the epithelial surface. Endophytic cancers often produce a hard, barrel-shaped cervix. Some cancers may be both endophytic and exophytic. Infection is commonly associated with exophytic cancers. With advanced cervical cancer, the cervix usually bleeds on contact. Regional

Table 13.4. Available investigations for staging cervical cancer

Type of investigation	Available investigations
Clinical assessment	• Bimanual vaginal examination • Digital rectal examination • Speculum examination
Endoscopic	• Colposcopy • Cystoscopy • Hysteroscopy
Ultrasonography	
Radiological	• Intravenous urography imaging • Chest and body X-ray examination • Lymphangiography • Computed tomography (CT) scan • Magnetic resonance imaging (MRI) • Positron emission tomography (PET) scan
Histopathological	• Colposcopically directed biopsy • Endocervical curettage • Lymph node sampling

lymph node involvement occurs relatively early.

Later-stage disease will have spread to bladder, rectum, bone (particularly the spine), and the psoas muscle. Ultimately, distant metastases will involve para-aortic lymph nodes, lungs, liver, bone, and other organs.

13.6 Histopathology

In the absence of systematic, high-coverage cervical precancer screening, approximately 90–95% of cases of invasive cervical disease are squamous cell carcinomas (Fig. 13.11a and b), and less than 10% are adenocarcinomas (Fig. 13.11c).

Microscopically, most squamous cell carcinomas appear as infiltrating networks of bands of neoplastic cells with intervening stroma, with a great deal of variation in growth pattern, cell type, and degree of differentiation. The cervical stroma separating the bands of malignant cells is infiltrated by lymphocytes and plasma cells. These malignant cells may be subdivided into keratinizing and non-keratinizing types. The tumours may be well, moderately, or poorly differentiated carcinomas. Approximately 50–60% are moderately differentiated cancers, and the remainder are evenly distributed between the categories of well-differentiated and poorly differentiated cancers.

Keratinizing squamous cell carcinoma is composed of characteristic whorls of epidermoid cells containing central nests of keratin (keratin pearls) (Fig. 13.11a). The nuclei are large and hyperchromatic with coarse chromatin. Intercellular bridges are visible, along with keratohyalin granules and cytoplasmic keratinization. Only few mitotic figures are visible.

Non-keratinizing squamous cell carcinoma (Fig. 13.11b) appears as irregular, jagged nests of plump polygonal cells invading the cervical stroma. There may be dyskeratosis and intercellular bridges. Cellular and nuclear polymorphism is more obvious, and mitotic figures are quite numerous. Keratin pearls are usually absent.

Other, uncommon types of squamous cell carcinoma include condylomatous squamous cell carcinoma (also called verrucous carcinoma), papillary squamous cell carcinoma, lymphoepithelioma-like carcinoma, and squamotransitional cell carcinoma.

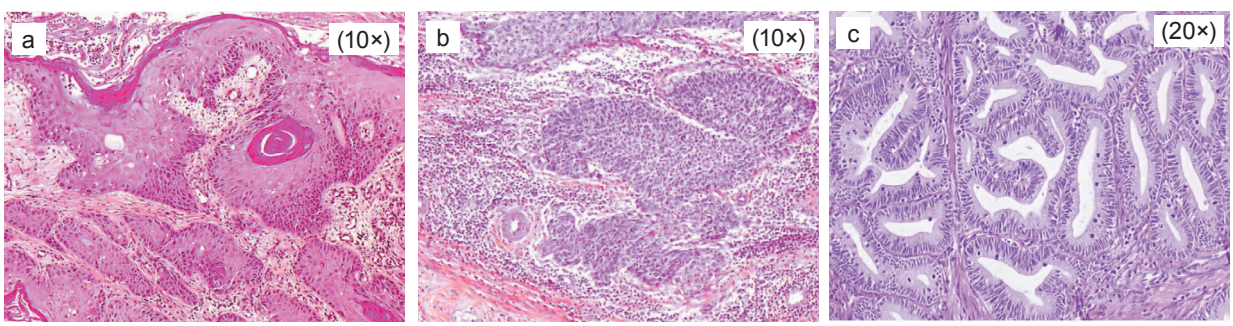
In the absence of screening, adenocarcinoma constitutes approximately 5% of all cervical cancers. Usually, it arises in the endocervical canal from the glandular epithelium.

The most common form of adenocarcinoma is the endocervical cell type, where the abnormal glands are of various shapes and sizes with budding and branching. Most of these tumours are well to moderately differentiated. The glandular elements are arranged in a complex pattern. Papillae may project into the gland lumen and from the surface. Some of the cells may contain a moderate to large amount of mucin.

The other types of adenocarcinoma include intestinal-type, signet ring cell adenocarcinoma, adenoma malignum, villoglandular papillary adenocarcinoma, endometrioid adenocarcinoma, and papillary serous adenocarcinoma. Adenosquamous carcinoma includes tumours with glandular and squamous growth patterns.

The presence of tumour cells within the lumen of a capillary space is evidence of aggressive growth potential in both squamous cell carcinoma and adenocarcinoma of the cervix, and has been correlated with increased risk of regional lymph node metastasis. Invasion of blood vessels occasionally occurs and is a particularly poor prognostic sign, correlating with distant, bloodborne metastasis. Although the cytological features associated with invasive squamous cell carcinoma of the cervix have been well described, cytology is not a reliable method of diagnosing invasive lesions. The definitive diagnosis of an invasive cancer is always based on histopathology. A tissue specimen taken from the periphery of the

Fig. 13.11. (a) Keratinizing well-differentiated squamous cell carcinoma of the cervix. (b) Non-keratinizing well-differentiated squamous cell carcinoma of the cervix. (c) Adenocarcinoma of the cervix.

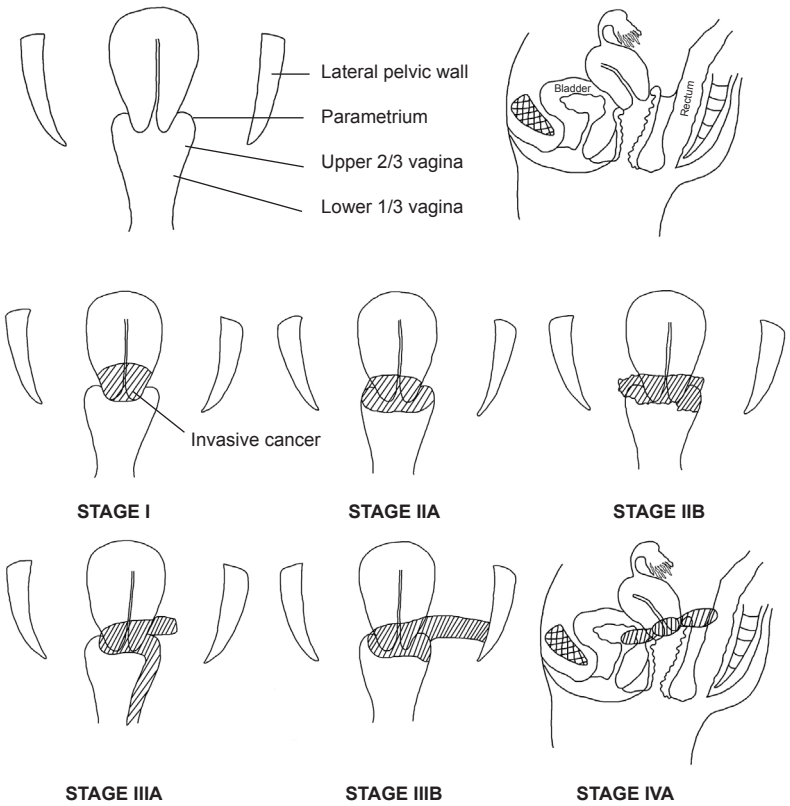


growth is preferred for diagnosis, because this is more likely to contain morphologically intact tumour tissue, whereas a biopsy specimen taken from the centre of a growth may contain necrotic material, which will compromise the accuracy of histological diagnosis. Also, punch biopsies may not procure enough tissue to allow for a confident histological diagnosis. A large punch biopsy, a small loop biopsy, or a wedge biopsy (or a TZ excision biopsy) will allow for a definitive diagnosis.

The best management for a patient with cervical cancer depends crucially on the accurate staging of the disease as well as a comprehensive evaluation of the patient's general physical condition and her individual circumstances. Currently, optimal care cannot be offered to all women in LMICs because of the lack of equipment, lack of trained staff, competing health-care needs, and other factors. Case mortality differences between LMICs and developed countries reflect the lack of resources in LMICs as well as the relative deficiency in health for many low-income women in LMICs.

The global standard staging system is that provided by FIGO. Fig. 13.12 is a diagram of this cervical cancer staging system. It is primarily a clinical staging system, based on the tumour size and the extent of spread from the original epithelium source. As well as clinical assessment of tumour size and spread, an array of methods, if available, will allow more precise staging of disease (Table 13.4). Usually, as well as clinical assessment, X-ray assessment, intravenous pyelogram, skeletal X-ray, and cystoscopy will be available in dedicated cancer centres in LMICs. After as full an assessment as possible has been undertaken, the findings should be documented precisely and the stage determined. Then a management plan may be outlined to the patient and treatment may be begun.

Fig. 13.12. Diagrammatic representation of cervical cancer staging.



13.7 Treatment of squamous microinvasive cervical cancer

The treatment of squamous cervical cancer may be surgical and/or radiotherapeutic. Radiotherapy may be used for all stages of squamous cervical cancer, although in practice few centres would treat stage IA1 disease other than by surgical excision. Surgery is usually reserved for disease confined to the cervix. Radiotherapy regimes vary and may be used exclusively or to shrink the tumour in preparation for surgical excision.

There have been more than 20 different definitions of microinvasion in the literature (Marsden et al., 2006). In summary, the most recent and widely used is the FIGO classification (Kurman et al., 2014), which limits microinvasive disease to a depth of 5 mm and a width of 7 mm (stage IA1 limits the depth to 3 mm and stage IA2 to 5 mm). The likelihood of there being positive lymph nodes in stage IA1 disease is remote. For stage IA1 disease, a simple but complete and intact (i.e. one-piece) excision is the treatment of choice. Chapters 14 and 15 deal, respectively, with the surgical and non-surgical treatment of later-stage disease.

Key points

- The stage of disease is the most crucial factor in managing invasive disease.
- The colposcopic appearances of microinvasion are similar to but often more exaggerated than those associated with high-grade but pre-invasive or intraepithelial change.
- Excisional therapy is the mainstay of treatment for microinvasion.

CHAPTER 14.

Surgical management of early invasive cervical cancer

Wertheim described the principles of surgical management of invasive cervical cancer more than 100 years ago in his treatise on 500 cervical cancers operated by radical hysterectomy (Wertheim, 1912). Wertheim's radical hysterectomy included removal of the uterus, upper vagina, and adjacent supporting tissues medial to the ureters, along with the metastatic lymph nodes. In the 1940s, Meigs introduced the concept of routine systematic pelvic lymphadenectomy along with extended parametrial dissection up to the lateral pelvic wall. With his improved technique, he demonstrated a high survival rate (Meigs, 1951). By that time, the surgical practice had become much safer with the use of antibiotics, thromboprophylaxis, and administration of blood products. As a result, Meigs could also demonstrate significantly lower morbidity, including intra-operative deaths, in his case series. Radical vaginal hysterectomy was initially described by Schauta (1908) and was subsequently combined with extraperitoneal lymphadenectomy by Mitra (1959). Over the past decades, two major developments have taken place in the surgical management of early cervical cancer: the increasing use of minimal access techniques for radical surgery, and tailoring the radicality of surgery to the extent of the disease. With the increasing popularity of minimal access surgeries, there has been a renewed interest in radical vaginal hysterectomy.

Because of the effective screening programmes, early-stage cervical cancers are increasingly being detected in younger women. These women have a long life expectancy after treatment, and the management strategies are increasingly focusing on improvement in quality of life, free of long-term treatment sequelae. Like for any other malignancies, involvement of a multidisciplinary team comprising gynaecological oncologists, radiation and medical oncologists, pathologists, and radiologists can optimize the patient care.

The management of microinvasive cancer (stage IA1) has been described in Chapter 13. In this chapter, the discussion is restricted to principles of surgical management of more advanced cervical cancers. Detailed descriptions of the steps of radical surgeries are beyond the scope of this manual.

14.1 Diagnosis and staging

Diagnosis of cervical cancer should be confirmed by histology before treatment is planned. Like for cancers of other sites, the management of

cervical cancer is essentially based on the extent of the disease. Cervical cancer spreads through direct extension to the paracervical tissues, the vagina, and the parametrium, and can invade the urinary bladder and rectum in more advanced stages. Although spread to the endometrium/body of the uterus is uncommon, such involvement has been shown to increase the risk of distant metastasis. However, involvement of the endometrium/body of the uterus is not taken into account in staging and does not alter stage. For instance, in a patient with stage I cancer, stromal involvement of the endometrium/body of the uterus does not alter the stage.

The disease spreads to the pelvic lymph nodes, which comprise the paracervical, obturator, internal iliac, external iliac, presacral, and common iliac nodes. The extension of the disease to the para-aortic nodes is considered distant metastasis. Other common sites of distant metastasis are bone (particularly the spine), lungs, and liver.

The staging of cervical cancer by FIGO was last updated in 2009 and is described in Table 14.1 (Wiebe et al., 2012). The FIGO staging is essentially clinical, backed by a limited number of investigations, like chest X-ray, ultrasonography, and cystoscopy and proctosigmoidoscopy if indicated. For cervical cancer, the pre-treatment staging is the most clinically relevant staging, on which therapeutic decisions are based. Although CT scans and MRI – and even positron emission tomography (PET) scans, in advanced healthcare settings – are increasingly used to define pre-treatment staging in many settings, these are not mandatory investigations for clinical staging of cervical cancer.

Ideally, the clinical examination required for staging should be performed under anaesthesia, although this is not mandatory. In LMICs, the majority of cervical cancers present at advanced stages and can be staged clinically in the outpatients department with reasonable accuracy. Every patient should have a thorough pelvic examination that includes inspection and palpation to note the position and size of the cervical growth, as well as extension to the vagina and the parametrial tissues. Colposcopy is useful to note the extent of the tumour in the vagina and the presence of vaginal

Table 14.1. FIGO staging for cervical cancer (last updated in 2009)

FIGO stage (2009)	Description
I	Cervical carcinoma confined to uterus (extension to body of uterus should be disregarded)
IA	Only microscopically visible lesion with stromal invasion not exceeding 5.0 mm and horizontal extension not exceeding 7.0 mm
IA1	Stromal invasion no greater than 3 mm in depth and no wider than 7 mm in diameter
IA2	Stromal invasion greater than 3 mm but does not exceed 5 mm in depth and no wider than 7 mm in diameter
IB	Microscopic lesion exceeding stage IA2 or clinically visible lesion confined to the cervix
IB1	Size of lesion 4.0 cm or less in the greatest dimension
IB2	Size of lesion exceeds 4.0 cm in the greatest dimension
II	Tumour extends beyond the cervix but not to the pelvic wall or to the lower third of the vagina (extension to corpus should be disregarded)
IIA	No parametrial invasion
IIA1	Size of lesion 4.0 cm or less in the greatest dimension
IIA2	Size of lesion exceeds 4.0 cm in the greatest dimension
IIB	Parametrial invasion present
III	Tumour extends to the pelvic wall and/or involves the lower third of the vagina and/or causes hydronephrosis or non-functioning kidney
IIIA	Extends to the lower third of the vagina without any spread to the lateral pelvic wall
IIIB	Extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney
IV	Tumour involves the bladder or rectal mucosa and/or extends beyond the true pelvis
IVA	Tumour involves the bladder or rectal mucosa
IVB	Distant metastases

FIGO, International Federation of Gynecology and Obstetrics.

intraepithelial neoplasia. Vesical involvement should be suspected if there is extensive involvement of the anterior vaginal wall by a large growth with induration of the bladder base. Rectal examination is very valuable to diagnose the nature and extent of parametrial involvement and infiltration of the disease to the rectal mucosa. Pelvic and abdominal ultrasonography has replaced routine intravenous urography to exclude hydroureter and hydronephrosis. Ultrasonography provides additional information, such as the size of the growth, possible invasion of the bladder and rectum, metastasis to the liver, and so forth. Cystoscopy and proctosigmoidoscopy should be performed if there are clinical and/or radiological suspicions of bladder and rectal involvement, respectively. Bladder or rectal mucosal involvement has to be proven by histology. Bullous oedema of the bladder epithelium does not, by itself, confirm malignant infiltration of the bladder wall. Additional information may be obtained from CT scans, MRI, and PET scans. MRI (thin-section T2-weighted images perpendicular to the cervix) is more accurate than other imaging modalities in assessing the tumour volume and the extent of spread to the vagina or parametrium and is useful in selecting cases for more conservative surgery. Involvement of pelvic and para-aortic nodes can be best assessed by PET-CT scan. However, the results of these specialized diagnostic procedures should not alter the initial clinical FIGO staging.

14.2 Principles of surgical treatment of early cervical cancer

The management of cervical cancer depends on the age of the patient, the stage of the disease, whether fertility preservation is required, co-morbidities, and availability of and access to different treatment options. Radical surgery for early cervical cancer requires good surgical skills and operative facilities. Definitive surgical management is feasible only in early stages of the disease, such as stages IA, IB1, and IIA1, when the vaginal involvement does not extend beyond 2 cm. Radiotherapy can be equally effective at the early stages, although surgical treatment is preferred. The major advantages of surgery are preservation of ovarian function, better preservation of sexual function (by avoiding radiation-induced stenosis and shortening of the vagina), accurate assessment of the lymph node status, and avoidance of long-term radiation sequelae, such as vaginal atrophy, stenosis, and bladder and rectal morbidity. Fertility can also be preserved by specialized surgical procedures. Radiation-induced long-term complications, especially cystitis and proctitis, can be very distressing to the patient and difficult to treat. Radiotherapy may be the treatment of choice for early cervical cancer in women with co-morbid conditions that may make surgical interventions more risky. For small-volume early disease, survival outcomes are similar for surgery and radiotherapy. As a general principle, surgery should be avoided if there is a need for adjuvant radiotherapy or chemoradiotherapy.

From stages IB2, IIA1 with vaginal involvement of more than 2 cm, and IIA2 onward, radiotherapy (with or without concomitant cisplatin-based chemotherapy) is the treatment of choice, because the incidence of lymph node metastasis increases significantly (> 35%) if the size of the lesion exceeds 4 cm (stage IB2 or stage IIA2). It is important to understand that the combination of surgery and radiotherapy increases the risk of post-treatment morbidities several-fold and should be avoided as much as possible. Surgery should not be attempted or may be abandoned if there is any suspicion that the patient would require radiotherapy in spite of surgery. Patients with bulky tumour volume and radiological evidence of lymph node involvement should not be scheduled for surgery and should be referred directly for radiotherapy.

14.3 Radical hysterectomy for cervical cancer

The most common surgery for early invasive cervical cancer is a combination of radical hysterectomy and bilateral pelvic lymphadenectomy. Radical hysterectomy involves en bloc removal of the uterus with the cervix, the upper vagina, and the parametrium. Ovaries can be preserved in younger women with squamous cell cancers, because the risk of the tumour spreading to the ovaries is very low in these patients. During surgery, the ovaries are trans-positioned retroperitoneally above the pelvic brim so that they escape radiation-induced damage in case the patient requires postoperative radiotherapy.

The extent of radicality of the surgery depends on the size and the nature of the tumour. Piver et al. (1974) classified radical hysterectomy into five types, ranging from extrafascial hysterectomy (type I) to partial resection of the ureter and bladder along with the uterus and vagina (type V). Each class requires progressively more radical resection than the previous one and is associated with increased morbidity (Fig. 14.1). Querleu and Morrow (2008) modified Piver's classification and included paracervical lymph node dissection and nerve-sparing radical hysterectomy. The comparison between the two classifications is shown in Table 14.2. Piver type V has become obsolete, because the

majority of the patients requiring this grade of radical surgery are treated by radiotherapy with or without chemotherapy.

As described in Chapter 13, all cases of microinvasive cancer (stage IA1) should have a large type 3 excision of the TZ, preferably with a scalpel (cold-knife conization). Patients who have LVSI and/or positive cone margin and who do not desire future fertility should have an extrafascial (type A) hysterectomy after cone biopsy. The rest of the patients need careful monitoring through annual screening. For a stage IA1 tumour, the risk of lymph node metastasis is less than 1% unless there is LVSI. Bilateral pelvic lymphadenectomy is indicated along with hysterectomy only in the presence of LVSI, because the likelihood of lymph node involvement is higher.

For patients with stage IA2 and small (< 2 cm) stage IB1 disease, parametrial dissection up to the lateral pelvic wall (as originally proposed by Meigs) is not required. The spread of disease through the pelvic lymphatics is an embolic phenomenon. In these early cancers, disease is found in the lateral parametria very rarely, especially when the lymph nodes are also negative for any metastasis. For these stages, the surgery is less radical, including only medial parametrectomy, and is called modified radical hysterectomy (type B1). Type C1 or C2 radical hysterectomy is appropriate for more advanced (> 2 cm) stage IB1 or stage IIA1 disease.

Some recent publications suggest that even less radical surgery for small (< 2 cm) stage IB1 disease has a similar oncological outcome with significant reduction in immediate and late morbidities and improved quality of life (Reade et al., 2013). The risk of parametrial infiltration is less than 1% if the cancer is less than 2 cm in diameter, does not have LVSI or lymph node metastasis, and has a maximum depth of infiltration less than 10 mm (Gemer et al., 2013). In carefully selected cases of stage IA2 or stage IB1 disease with a cancer that is smaller than 2 cm, non-radical surgeries may be performed. A Gynaecologic Oncology Group trial is currently evaluating this. Several case series and case–control studies evaluating simple hysterectomy or simple trachelectomy in such cases observed no increase in recurrence or mortality. A randomized case–control study by Landoni et al. (2012) found the same results in tumours smaller than 3 cm. However, this approach should be practised in centres with high-quality pathology services after adequately counselling the women about the need for regular follow-ups.

Many oncologists are hesitant to recommend conservative treatment of adenocarcinomas, because pathological interpretation of adenocarcinoma is more complicated due to lack of concordance in assessing the tumour volume, depth of infiltration, and LVSI. This is in spite of the fact that the majority of the studies showed no difference in outcome (Al-Kalbani et al., 2012).

Protection of the autonomic pelvic nerve plexus from injury during surgery results in faster recovery of bladder function and reduced incidence of bladder dysfunction after surgery (Ceccaroni et al., 2012; Fujii et al., 2007). This technique, originally described by Okabayashi, is known as nerve-sparing radical hysterectomy (Fujii et al., 2007). The hypogastric nerves originating from the superior hypogastric plexus and the upper part of the inferior hypogastric plexus are exposed along the lateral border of the mesorectum. The inferior hypogastric plexus, which comprises the hypogastric nerve and the pelvic splanchnic nerve, is mobilized and protected before transection of the uterosacral ligaments. The vesical branch of the plexus is also preserved. Studies have also reported better preservation of sexual function after nerve-sparing surgery (Jarruwale et al., 2013).

Fig. 14.1. Sagittal section of female pelvis showing the different pelvic spaces and extent of dissection in different classes of radical hysterectomy.

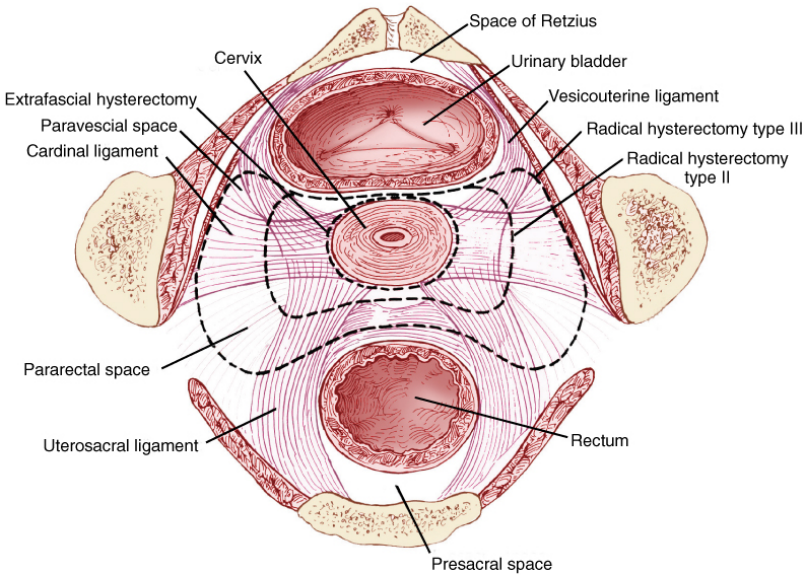


Table 14.2. Comparison between the classifications of radical hysterectomy by Piver et al. (1974) and Querleu and Morrow (2008)

Piver–Rutledge classification		Querleu–Morrow classification		Indications
Class I	Extrafascial hysterectomy Ureter not dissected Cardinal and uterosacral ligaments resected as close as possible to uterus Vagina not excised	Type A	Extrafascial hysterectomy Cardinal and uterosacral ligaments resected as close as possible to uterus Removal of < 1 cm of vagina	Stage IA1 with LVSI
Class II	Modified radical hysterectomy Uterine artery ligated medial to the ureters Ureter freed from paracervical tissues but not mobilized from pubovesical ligament Cardinal ligament resected up to medial half Uterosacral ligament resected midway from sacral insertion	Type B1	Ureters mobilized laterally Partial resection of vesico-uterine and uterosacral ligaments Resection of paracervical tissue at ureteric tunnel At least 1 cm of vagina from cervix or tumour excised Lateral paracervical lymph nodes not removed	Stage IA2
		Type B2	All resections as per type B1 Removal of lateral paracervical lymph nodes	Stage IB1 (≤ 2 cm)
Class III	Radical hysterectomy Complete mobilization of ureter including from pubovesical ligament Uterine artery ligated at origin Cardinal ligament resected close to pelvic wall Uterosacral ligament excised near sacral insertion Upper half of vagina removed	Type C1	Complete mobilization of ureter Complete resection of paracervical tissue Sectioning of uterosacral ligaments at the level of the rectum 1.5–2 cm of vagina from cervix or tumour resected with paracolpos Autonomic nerve supply preserved	Stage IB1 (> 2 cm); stage IIA1
		Type C2	All resections as per type C1 Autonomic nerve supply not preserved	
Class IV	Complete dissection of ureter Umbilical-vesical artery sacrificed Three quarters of upper vagina excised	Type D1	Ureter fully mobilized Complete resection of paracervical tissues up to lateral pelvic wall Internal iliac vessels tied Sciatic nerve roots exposed	Recurrent (central, < 4 cm) cervical cancer
		Type D2	All resections as per type D1 Resection of muscles and adjacent fascia	
Class V	Class IV along with partial excision of ureter and/or bladder	—	—	—

LVSI, lymphovascular space involvement.

14.4 Pelvic lymphadenectomy for cervical cancer

Pelvic lymphadenectomy includes removal of all the lymph nodes along with the fibro-fatty tissues from the external iliac, internal iliac, and common iliac vessels and also from the obturator fossa. The distal extent of nodal dissection is the crossing of the deep circumflex iliac vein over the external iliac artery, and the proximal extent is the aortic bifurcation or at least the middle of the length of the common iliac artery. The obturator nodes should be collected from below the obturator nerve up to the level of the pelvic diaphragm.

Identification of the sentinel node and tailoring of the subsequent management based on the histology of the node is widely practised in breast cancer, vulvar cancer, and so forth. The sentinel lymph node is the first node involved in case of lymphatic spread, and if the sentinel node is negative, the remainder of the nodes in the nodal basin are considered to be free of disease. In early cervical cancer, the sentinel node can be detected either by injecting 1% isosulfan blue dye around the tumour or by injecting ^{99m}Tc-nanocolloid into the tumour after anaesthesia (van de Lande et al., 2007). Sometimes both are used, for more accurate detection. The sentinel node is detected mostly in the internal iliac, obturator, or external iliac group of nodes, in that order of frequency, and has a high negative predictive value. If the frozen-section histopathology of the sentinel node is negative, further systematic lymphadenectomy and the consequential risk of

lymphocysts and lymphoedema can be avoided (Gortzak-Uzan et al., 2010). Sentinel node biopsy does not have any value in more advanced disease (tumour size > 2 cm or stage IIA) or if there are already grossly enlarged lymph nodes. Systematic lymphadenectomy is always recommended in those cases, along with radical hysterectomy. Sentinel node detection is not yet recommended for routine practice, because long-term follow-up data are still awaited.

Para-aortic lymphadenectomy is not recommended for the management of early cervical cancer. If suspicious nodes are seen in the para-aortic region during surgery, they should be removed and sent for frozen-section histopathology. A positive para-aortic lymph node is an indication for abandoning the radical hysterectomy and referring the patient for radiotherapy.

14.5 Fertility preservation in cervical cancer

Hysterectomy can be avoided in stage IA1 cervical cancer by performing cold-knife conization if the woman desires preservation of fertility. In more advanced cases (stage IA2 or stage IB1), the surgical technique of choice for fertility preservation is radical trachelectomy, which can be performed by both vaginal and abdominal routes. Radical vaginal trachelectomy is practised more commonly and was first described by Dargent more than 20 years ago (Dargent, 1994). In this surgery, the cervix along with the contiguous upper 1–2 cm of the vagina and the medial parts of the Mackenrodt's and uterosacral ligaments are resected through the vaginal approach. A prophylactic cerclage suture is applied after transection of the cervix near the isthmus. Radical trachelectomy must be preceded by bilateral pelvic lymphadenectomy (usually by laparoscopic approach) and frozen-section histopathology of all the nodes.

The criteria for selection of cases for radical trachelectomy are:

- stage IA1 (with LVSI), IA2, or IB1;
- tumour size less than 2 cm;
- limited endocervical extension;
- histology other than clear cell carcinoma, neuroendocrine tumour, or sarcoma;
- no deep stromal infiltration (greater than 10 mm);
- pelvic lymph nodes free of metastasis;
- patient desires preservation of fertility; and
- no known infertility problem.

The excised specimen after radical trachelectomy should be sent for frozen-section histopathology to assess the proximity of the tumour to the resected margin. If the gap is less than 5 mm, the surgery has to be converted into radical hysterectomy. A preoperative MRI is very useful to assess the tumour volume and the extent of the cervical growth to the parametrium or inside the endocervical canal. Studies that compared radical hysterectomy with radical trachelectomy and controlled for age, tumour size, histology, grade, depth of invasion, LVSI, pelvic node metastasis, and adjuvant therapy observed similar 5-year recurrence-free or overall survival. A meta-analysis of 346 patients treated with radical trachelectomy reported a recurrence rate of 4.1% after a median follow-up of 44 months (Plante et al., 2004). Fertility rates after radical trachelectomy vary between 40% and 70%, with a live birth rate of about 70%. The delivery has to be by Caesarean section (Pareja et al., 2013).

14.6 Minimal access surgery in cervical cancer

The laparoscopic pelvic lymphadenectomy for cervical cancer was first performed by Querleu et al. (1991). Soon after that, Nezhat et al. (1992) performed the radical hysterectomy and pelvic lymphadenectomy laparoscopically. Minimal access surgery by laparoscopy has been proven to have similar surgical and oncological outcomes to those of open surgery. The major benefits of minimally invasive surgery are better visualization, less blood loss, fewer wound-related problems, increased patient comfort, decreased analgesic requirements, a shorter hospital stay, and earlier recovery. Laparoscopic lymphadenectomy combined with radical vaginal hysterectomy or laparoscopic lymphadenectomy combined with laparoscopic radical hysterectomy have become acceptable alternatives to open surgery.

Robotic technology, an advanced innovation aimed at overcoming the shortcomings of conventional laparoscopy, offers stable, three-dimensional, high-resolution vision, surgical dexterity, and precision. It is now being increasingly used for minimally invasive surgery in cervical cancer.

14.7 Adjuvant therapy after surgery

The excised specimen should be carefully assessed for the size of the primary tumour, the depth of stromal invasion, the presence or absence of LVSI, the proximity of the tumour to the vaginal and parametrial margins, and the presence of intraepithelial neoplasia at the vaginal margin. The lymph nodes should be counted, and all of them should be examined microscopically. A total pelvic lymph node count of less than 10 indicates a suboptimal lymphadenectomy.

Patients with the following high-risk features should undergo postoperative radiotherapy (with or without concomitant chemotherapy):

- tumour size > 4 cm;
- lymph node metastasis;

- deep stromal invasion (greater than 10 mm);
- LVSI;
- parametrial infiltration;
- positive or close vaginal or parametrial margin.

For these high-risk cases, postoperative pelvic irradiation substantially reduces the local recurrence rate, at the cost of a high incidence of some of the distressing side-effects, like lymphoedema, increased urinary frequency, bladder dysfunctions, diarrhoea, radiation cystitis, and radiation proctitis. Radiotherapy involves a combination of external beam radiotherapy and brachytherapy.

14.8 Survival after treatment of early-stage cervical cancer

The survival rate after radical hysterectomy and pelvic lymphadenectomy in appropriately selected cases is high. Rates of 5-year disease-free survival have been reported to be between 80% and 95% (Ware and van Nagell, 2010). The survival rate decreases significantly with the involvement of lymph nodes and the parametrium, in spite of the adjuvant radiotherapy. Although there is concern about the prognostic significance of adenocarcinoma, large prospective and retrospective studies have not found any difference in survival between early-stage patients with squamous cell carcinoma and those with adenocarcinoma.

14.9 Surgical management of early cervical cancer during pregnancy

The treatment of cervical cancer during pregnancy is determined by the clinical extent of disease and the gestational age. A biopsy is mandatory to confirm diagnosis, and it may be necessary to resort to MRI to establish the stage of disease. In patients with stage IA2 or stage IB disease, waiting for viability of the fetus may be an option if there is no evidence of lymphatic spread. Patients with stage IA2 or stage IB disease and with lymph node spread should undergo immediate treatment.

Patients with stage II and greater disease should undergo radiotherapy or chemoradiotherapy. If possible, fetal evacuation should be performed before radiotherapy is initiated. If evacuation is not feasible, radiation will result in spontaneous abortion 4–5 weeks after initiation of radiotherapy.

Key points

- Radical hysterectomy with lymph node dissection is the classic surgical option for the treatment of early cervical cancer, up to stage IIA1.
- Radiation may be used for every treatable stage of cervical cancer.
- Radical trachelectomy is increasingly popular as fertility-preserving surgery for stage IA2 or stage IB1 disease.
- Laparoscopic access is the preferred access method for treatment, where adequate training and equipment are in place.

CHAPTER 15.

Non-surgical management of cervical cancer

This chapter deals with the treatment modalities used in the non-surgical management of cervical cancer. These include radiotherapy, chemotherapy, and various combinations of radiotherapy and chemotherapy.

15.1 Radiotherapy

Radiotherapy for cervical cancer usually involves a combination of external beam radiotherapy (EBRT) and brachytherapy using intracavitary radiotherapy (ICR). The goal of the treatment is to balance EBRT and ICR in a way that maximizes the likelihood of loco-regional tumour control while minimizing the risk of treatment complications.

The total radiation dose that can be delivered to the pelvis by EBRT is limited by the tolerance of normal tissues in the pelvis, such as the urinary bladder and the small and large bowels, and thus ICR is needed to deliver cancerocidal doses to the gross tumour in the cervix and parametrium.

For many patients with advanced loco-regional disease, radiotherapy may be integrated with concomitant chemotherapy to augment the prospects of a cure. The primary goals of EBRT are to sterilize regional disease and to shrink the central tumour, to facilitate subsequent ICR. Ideally, the entire course of treatment should be completed in less than 8 weeks; excessive prolongation of the overall treatment time may compromise disease control.

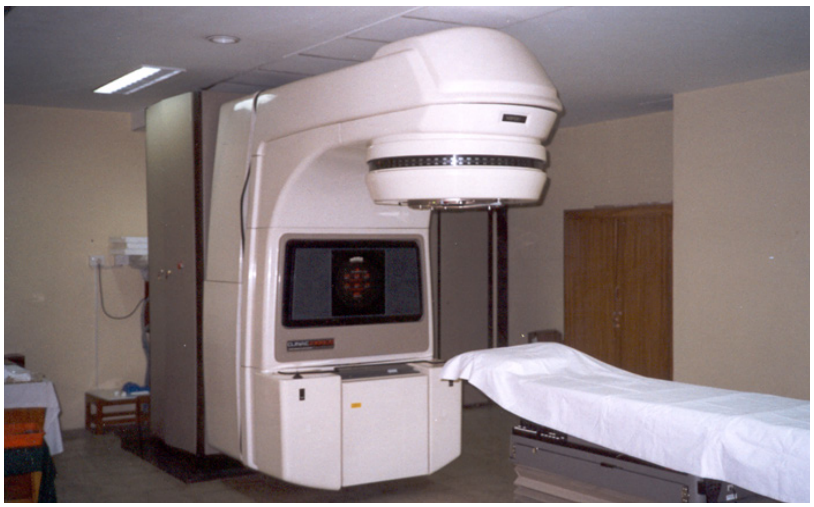
With image-based technical advances such as three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, and image-guided radiotherapy, it is possible to provide more precise and accurate radiation delivery, with the potential for dose escalation, improved tumour control, and reduced toxicity by minimizing the dose to the surrounding normal tissues. However, these techniques require sophisticated equipment infrastructure and adequately trained personnel and are not feasible in low-income countries with weak health systems.

15.1.1 Radiotherapy equipment

Radiotherapy for cervical cancer involves both EBRT and ICR.

In EBRT, the radiation is delivered as a beam from a radioactive source kept at a source-to-axis distance of 100 cm or 80 cm in a teletherapy machine such as a linear accelerator (linac) (Fig. 15.1) or a telecobalt machine (Fig. 15.2). Modern teletherapy machines are

Fig. 15.1. Linear accelerator (linac).



isocentrically mounted, allowing the beam to rotate around the patient at a fixed source-to-axis distance of 100 cm (linacs) or 80 cm (telecobalt machines). Linacs use electricity to generate high-energy X-rays (15–25 MeV) and permit homogeneous delivery of radiation to deep tissues with relative sparing of superficial tissues, whereas telecobalt machines emit gamma rays from a radioactive cobalt (cobalt-60) source kept in the head of the machine.

From the 1950s onward, telecobalt machines were at the forefront of delivering EBRT for many years. However, linacs have largely replaced telecobalt machines in many high- and middle-income countries as the most widely used radiation source in modern radiotherapy. For instance, in France, there are no more functional telecobalt machines, and in Morocco, all 32 of the teletherapy machines are linacs. In India, in 2000 there were 245 telecobalt machines and 34 linacs, and in 2014 there were 238 telecobalt machines and 308 linacs.

Over the course of five increasingly sophisticated generations, linacs have become compact, versatile, efficient, and affordable, with a wide range of energies. Linacs require more sophisticated maintenance in terms of medical physics and dosimetry support; they require continuous electricity and consume large amounts of electricity. In contrast, in telecobalt machines, the cobalt-60 source is replaced after two or three half-lives (approximately 10.6 years or 15.9 years). The telecobalt machine has been the preferred teletherapy machine in low-income developing countries, because of its affordability and sturdy reliability. Finally, in many countries manual treatment planning has largely been replaced by computerized treatment planning systems.

ICR is a necessary component of radiotherapy for cervical cancer. In ICR, radioactive sources are placed into the uterine cavity and vagina to deliver a very high radiation dose to the cervix and uterus with relative sparing of surrounding tissues, such as the bladder, rectum, small bowel, and superficial soft tissues. Early ICR techniques involved the placement of sealed radioactive sources such as radium-226 or caesium-137, which is not optimal from a radiation protection perspective; automatic afterloading devices using empty applicators are now used to deliver ICR.

For ICR, the radiation source is encapsulated within a non-radioactive metallic capsule. After accurate positioning of the delivery devices (applicators) in the vagina (ovoids) and uterine cavity (tandem) with the help of X-ray, ultrasonography, or CT imaging, the radiation sources are afterloaded; after the delivery of the radiation dose, the sources are removed manually by a radiation oncologist. Alternatively, the sources may be inserted using a computer-aided remote afterloading machine (Fig. 15.3), which automatically removes them when the treatment has been completed. Precise placement of the applicator is essential for improved local control and reduced morbidity.

For treatment planning, a computer is used to calculate the amount of time required to deliver the prescribed dose of radiation to the tumour. Although low-dose-rate brachytherapy with caesium-137 has been the traditional approach, the use of high-dose-rate brachytherapy with iridium-192 is increasing. High-dose-rate brachytherapy eliminates radiation exposure to medical personnel and allows a shorter treatment time and greater patient convenience. The outcome of high-dose-rate

Fig. 15.2. Telecobalt machine.

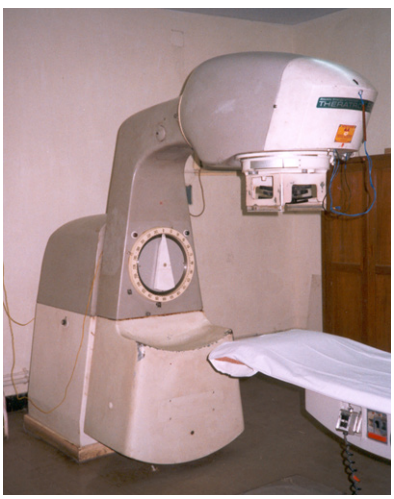
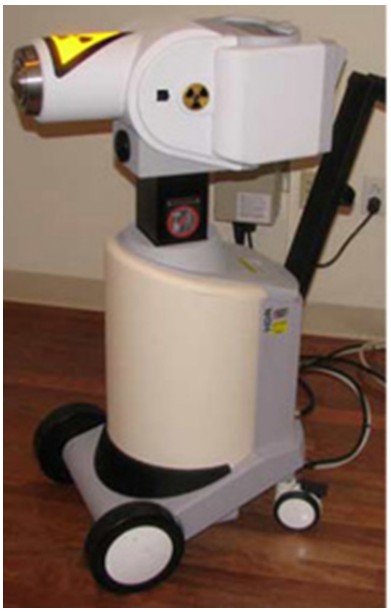


Fig. 15.3. High-dose-rate remote afterloading brachytherapy machine.



brachytherapy is similar to that of low-dose-rate brachytherapy in terms of loco-regional control and complication rates.

15.1.2 Radiotherapy dose

It is important to prescribe the optimal dose for both radical and palliative radiotherapy and to measure the dose correctly to avoid unintended damage to normal tissues. Radical treatment refers to prescription of a high dose of radiation with curative intent, while accepting a certain amount of side-effects, complications, and late sequelae and anticipating an eventual cure or long-term disease-free survival. Palliative treatment refers to the delivery of smaller doses of radiation (which by itself does not cause any toxicity or complications) to relieve symptoms, accepting that long-term survival or a cure is unlikely because of the very advanced clinical extent of disease, as in disease with distant metastases.

The choice of radiotherapy dose and delivery techniques takes into account the normal tissue/organ tolerance in the radiotherapy portals or fields and the cancerocidal dose required to destroy the cancer cells and the lesion in radical treatments. The normal tissue tolerance dose varies between tissues/organs and depends on the proportion of tissues/organs treated.

Radiotherapy dose is described in terms of grays (Gy) or centigrays (cGy = 0.01 Gy). The total radiation dose is usually divided into several small fractions of radiation (about 180 cGy or 200 cGy per fraction), which, as daily treatment progresses, gradually accumulate to the total dose prescribed. Radiation is usually delivered as one fraction per day, 5 days per week for a total period of 4–8 weeks. Fractionation of the total radiation dose over a period of 4–8 weeks leads to maximum cancer cell kill while allowing maximal recovery of and minimal damage to normal cells. During the interval between the fractions, normal cells recover much faster than tumour cells, ideally resulting in maximum tumour cell kill and minimal damage to normal tissues.

Radical radiotherapy doses are typically 35–40 Gy in 15–20 fractions over 3–4 weeks for highly radiosensitive lymphomas and germ-cell tumours, whereas the doses range from 50 Gy in 15 fractions over 3 weeks to 65–70 Gy in 30–35 fractions over 6–7 weeks for most squamous cell carcinomas. Palliative radiotherapy doses are on the order of 30 Gy in 10 fractions over 2 weeks or 20 Gy in 5 fractions over 1 week, or even a single dose of 8–10 Gy.

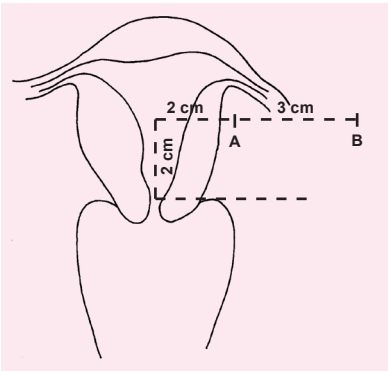
The skin may be marked to indicate the radiotherapy portal where treatment should be delivered. The patient should be immobilized so that the target region receives the intended dose. The daily treatment setup is reproduced by in-room laser alignment to either skin marks or fixation aids such as thermoplastic devices.

ICR can be given using a high dose rate over a few minutes (5–15 minutes) per session or a low dose rate over 20–60 hours. Low-dose-rate brachytherapy is delivered at a dose rate to point A (see below) of less than 0.5 Gy/hour, typically using caesium-137. Since the early 2000s, the traditional low-dose-rate brachytherapy with caesium-137 has largely been replaced by high-dose-rate brachytherapy with iridium-192. With high-dose-rate brachytherapy, a remote afterloading technology allows the iridium source attached to the end of a cable to be robotically driven through multiple channels, stopping at predetermined dwell positions for varied lengths of time. The most common fractionation schedules for high-dose-rate brachytherapy are 5–6 Gy in 5 fractions or 7 Gy in 4 fractions. High-dose-rate fractions are typically delivered 1 or 2 times per week.

15.1.3 Radiotherapy reference points and EBRT portals

The target volume for treatment of cervical cancer involves the gross tumour as defined by clinical and radiological investigations as well as the suspected subclinical disease and the parametrial, pararectal, internal iliac, external iliac, common iliac, obturator, and presacral lymph node regions. Radiotherapy protocols for patients with cervical cancer have traditionally used dosing at two anatomical points, called point A and point B (Fig. 15.4), to standardize the doses delivered. Point A is defined as a point 2 cm from the external os and 2 cm lateral to the endocervical canal. Point B is defined as a point 2 cm from the external os and 5 cm lateral to the patient's midline, relative to the bony pelvis. In general, for smaller cervical cancers, such as stage IA2 and IB1 disease, the radical (with curative intent) dose to

Fig. 15.4. Diagram showing point A and point B.



point A is about 70–75 Gy, whereas for larger cervical cancers, such as stage IB2 disease and beyond up to stage IVA, the dose to point A may be 80–90 Gy. The dose indicated is the sum of both EBRT and ICR.

The basic standardized treatment planning for EBRT is based on two-dimensional treatment planning. This process makes use of a radiotherapy X-ray simulator, a two-dimensional computerized treatment planning system used for calculation of dose distributions in a single plane or a few planes of the treatment volume, and treatment verification. The radiotherapy simulator mimics the functions and motions of a radiotherapy treatment unit. It allows the beam direction and treatment fields to be determined to encompass the target volume and spare normal structures from excessive radiation.

The EBRT portals to deliver radiation doses include the pelvis from the L5–S1 junction (so as to include the common iliac nodes) to the lower border of the obturator foramen; the lower border may be extended further to 2–3 cm down to the introitus if there is vaginal involvement. The lateral border extends to 1.5–2 cm lateral to the pelvic brim (bony pelvis). The portals usually measure 15 × 12 cm or 15 × 15 cm. A four-field box technique with an anterior portal, a posterior portal, and two lateral portals (12 × 8 cm or 15 × 8 cm) is used when the separation at mid-pelvis (or the inter-field distance between the anterior and posterior portals) is more than 20 cm. Lateral portals allow a decrease in the dose to the small bowel and the lower rectum. The anterior margin of the lateral portals is at the cortex of the symphysis pubis, and the posterior margin extends to the sacral hollow.

A 4 cm-wide divergent, wedge-shaped alloy midline block may be used (after the initial dose of 30 Gy in 15 fractions) to shield the rectum and bladder for part of the pelvic irradiation (20 Gy in 10 fractions), to allow a higher dose to be given by brachytherapy and to reduce late rectal and bladder sequelae. EBRT with midline block is followed by ICR of 30–35 Gy to point A, taking the total dose to point A to 80–90 Gy.

The use of CT and MRI has made it easier to obtain more accurate tumour localization, which has led to three-dimensional treatment planning.

In the 1990s, the treatment planning for EBRT involved three-dimensional treatment planning and conformal radiotherapy, in which the target volumes and organs at risk are delineated using CT scans or MRI. In the 2000s, modern treatment planning systems permitted the development of intensity-modulated radiotherapy. However, facilities in public health services in many low-income countries lack the equipment and human resources to deliver these advanced radiotherapy techniques.

15.1.4 Survival outcomes after radiotherapy

The 5-year survival rates after radiotherapy for cervical cancer are as follows: stage IA, 95%; stage IB1, 85%; stages IB2 and IIA, 60–65%; stage IIB, 50%; stage III, 30–40%; stage IVA, 10–15%; and stage IVB, 5%.

15.1.5 Sequelae of radiotherapy for cervical cancer

Acute side-effects during radiotherapy may include abdominal cramps, rectal discomfort, diarrhoea, occasional rectal bleeding, dysuria, increased urinary frequency, nocturia, haematuria, erythema, dry/moist desquamation of the perineum or intergluteal fold, radiation vaginitis, and superficial ulceration of the vagina. Late sequelae include proctitis/cystitis (3–10%), vaginal stenosis, vaginal atrophy, dyspareunia, anal incontinence, vesicovaginal or rectovaginal fistula, lumbosacral neuropathy, and femoral neck fracture.

15.2 Chemotherapy

Commonly used chemotherapeutic agents for treating cervical cancer include cisplatin, carboplatin, 5-fluorouracil, ifosfamide, irinotecan, and taxanes. Of these, the mostly widely used agent is cisplatin, alone or in combination with 5-fluorouracil. Administration of cancer chemotherapy is associated with considerable systemic toxicity, particularly haematological, gastrointestinal, renal, and skin toxicity, and alopecia. Chemotherapy requires careful monitoring of general health, blood counts, and liver and kidney function during and after treatment.

15.3 Concurrent chemo-radiotherapy

In 1999, after RCTs demonstrated that concurrent chemoradiotherapy (CCRT) improved survival over radiotherapy alone, the United States National Cancer Institute issued an alert recommending that cisplatin-based CCRT should be considered instead of radiotherapy alone when there is an indication of radiotherapy in cervical cancer. Since that alert, CCRT has been widely practised and has

largely replaced radiotherapy alone for locally advanced cervical cancer.

In a Cochrane review of RCTs comparing CCRT with radiotherapy for locally advanced cervical cancer, adding chemotherapy to radiotherapy seemed to offer a modest but significant additional benefit on all outcomes and for all stages of disease. However, the interpretation of the benefits was complicated by the use of different treatments in the control arms of the included studies, heterogeneity in trial results, and inconsistency in the definition of outcomes between trials (Green et al., 2005). In a meta-analysis based on 13 trials comparing chemoradiotherapy versus the same radiotherapy, there was a 6% improvement in 5-year survival with chemoradiotherapy (hazard ratio, 0.81; $P < 0.001$) (Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration, 2008; Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC), 2010). A meta-analysis of seven RCTs found insufficient evidence that hysterectomy with radiotherapy, with or without chemotherapy, improves the survival of women with locally advanced cervical cancer who are treated with radiotherapy alone or CCRT (Kokka et al., 2015).

However, acute haematological, renal, and gastrointestinal toxicities are increased with chemoradiotherapy. Serious haematological toxicity increased by approximately 2–10-fold in several individual trials. There was also a significant increase in serious gastrointestinal toxicity associated with platinum-based chemoradiotherapy (Green et al., 2005).

15.4 Neoadjuvant chemotherapy

The use of chemotherapy before the application of definitive treatments, such as surgery or radiotherapy, with the aim of decreasing tumour size and extent and improving curability, is called neoadjuvant chemotherapy. Despite significant response rates to chemotherapeutic agents such as cisplatin and paclitaxel, the role of neoadjuvant chemotherapy in the treatment of cervical cancer remains controversial. Neoadjuvant chemotherapy followed by radiotherapy is not superior to radiotherapy alone or CCRT. To date, there is no evidence that overall survival improves after neoadjuvant chemotherapy and definitive treatment, and the toxicity of chemotherapy and the delay of definitive radiotherapy could reduce overall survival.

15.5 Non-surgical options by stage

The various options for treatment of cervical cancer using radiotherapy and chemotherapy are listed in Table 15.1 and outlined below.

15.5.1 Stage IA2

Patients with stage IA2 cervical cancer who are poor surgical risk may be treated with EBRT plus brachytherapy or with brachytherapy alone. If the depth of invasion is less than 3 mm and there is no lymphovascular invasion, EBRT is not needed and these patients may be treated with ICR alone to a total dose of 65–75 Gy to point A in one or two sessions. Alternatively, patients with stage IA2 disease may be treated with EBRT

Table 15.1. Non-surgical options for treatment of cervical cancer

Stage	Treatment option
IA2	• External beam radiotherapy with intracavitary brachytherapy • Intracavitary brachytherapy alone
IB and IIA	• External beam radiotherapy with intracavitary brachytherapy • Concurrent chemoradiotherapy with external beam radiotherapy, intracavitary brachytherapy, and concurrent chemotherapy with cisplatin or cisplatin plus 5-fluorouracil • External beam radiotherapy with intracavitary brachytherapy with surgery for any residual disease • Radical hysterectomy followed by postoperative radiotherapy for cases with a high risk of recurrence
IIB and III	• Concurrent chemoradiotherapy with external beam radiotherapy, intracavitary brachytherapy, and concurrent chemotherapy with cisplatin or cisplatin plus 5-fluorouracil is the standard treatment of choice • External beam radiotherapy with intracavitary brachytherapy
IVA	• Radical or palliative treatment, based on extent of rectal/bladder involvement, renal function, parametrial involvement, general health, and performance status • If patient is in good general health, concurrent chemoradiotherapy with external beam radiotherapy, intracavitary brachytherapy, and concurrent chemotherapy with cisplatin or cisplatin plus 5-fluorouracil • If extensive rectal/bladder involvement, renal failure, bilateral, hard, fixed parametrial involvement, palliative short-course radiotherapy or palliative chemotherapy
IVB	• Palliative short-course radiotherapy • Palliative single-agent chemotherapy with cisplatin or carboplatin or ifosfamide • Palliative combination chemotherapy with cisplatin plus 5-fluorouracil or cisplatin plus ifosfamide or carboplatin plus paclitaxel or carboplatin plus gemcitabine

of 40–45 Gy in 20–25 fractions over 4–5 weeks and ICR of 30–35 Gy.

15.5.2 Stages IB and IIA

Patients with stage IB1 and stage IIA (with the length of vaginal involvement < 2 cm) cervical cancer who are poor surgical risk may be treated with a combination of EBRT and ICR, to a dose of up to 80–85 Gy to point A. Primary therapy for these stages should avoid routine use of both radical surgery and radiotherapy, in order to minimize morbidity associated with multimodality treatment.

One RCT found that there was no significant difference in the overall survival of patients treated with surgery and those treated with radiotherapy for stage IB and stage IIA cervical cancers (Landoni et al., 1997). That study also documented significantly poorer outcomes for patients with bulky cancers (> 4 cm in diameter) who underwent either surgery or radiotherapy compared with those with smaller tumours (< 4 cm in diameter).

Patients with stage IB2 and bulky stage IIA (> 4 cm) cancers and stage IIA cancers with the length of vaginal involvement exceeding 2 cm should be treated with EBRT and ICR to a total dose of 85–90 Gy to point A and concurrent chemotherapy with cisplatin or cisplatin plus 5-fluorouracil. For these patients, adjuvant pelvic irradiation may also be warranted, providing one of the following pertains:

- more than two thirds stromal invasion;
- lymphovascular invasion;
- tumour size > 4 cm.

Pelvic irradiation with concurrent cisplatin-based chemotherapy should be considered in women with positive pelvic nodes, positive surgical margin, or positive parametrium. Finally, vaginal brachytherapy may be considered where the surgical specimen reveals a positive vaginal margin.

15.5.3 Stages IIB and III

The treatment of choice for patients with stage IIB and stage III cervical cancer is CCRT with EBRT, ICR, and concurrent chemotherapy. The chemotherapy may be either

- cisplatin (e.g. 40 mg/m^2 weekly for 4–6 weeks), or
- cisplatin plus 5-fluorouracil (e.g. cisplatin 50–75 mg/m^2 intravenously on day 1 plus 5-fluorouracil 1000 mg/m^2 as a 24-hour continuous intravenous infusion on days 1–4 every 3 weeks for 2–4 cycles).

Patients with stage IIB and stage III disease who are in poor general health may still be treated with EBRT and ICR, but concurrent chemotherapy should be avoided because of the associated increased toxicity. The dose should be at most 85–90 Gy to point A. In low-income countries, many clinicians still consider radical radiotherapy alone to be an acceptable approach in view of poor socioeconomic and nutritional status, doubtful tolerance of chemotherapy due to already low haemoglobin and impaired renal function, and poor patient compliance. A large RCT comparing CCRT with radiotherapy alone at the Tata Memorial Centre, in Mumbai, India, has completed patient recruitment, and the results are awaited. The results are likely to clarify the role and utility of CCRT in developing countries.

15.5.4 Stage IVA

For patients with stage IVA cervical cancer who are in good general health with good performance status, minimal rectal and bladder involvement, and normal renal function, CCRT may be considered. However, extensive rectal or bladder involvement with fistula, impaired renal function, hard, fixed, extensive parametrial involvement on both sides, and poor performance status preclude any scope for radical CCRT, and these patients are candidates for either

- palliative short-course radiotherapy (30 Gy in 10 fractions over 2 weeks, or 20 Gy in 5 fractions over 1 week), or
- palliative chemotherapy (e.g. paclitaxel 175 mg/m^2 intravenously over 3 hours on day 1 every 3 weeks to a total of 2–4 cycles, or paclitaxel 135 mg/m^2 intravenously over 24 hours on day 1 and cisplatin 50 mg/m^2 every 3 weeks to a total of 2–4 cycles).

The management of rectovaginal or vesicovaginal fistulas requires substantial supportive care.

15.5.5 Stage IVB

Patients with stage IVB disease are candidates for palliative radiotherapy to the pelvis (30 Gy in 10 fractions or 20 Gy in 5 fractions or 8–10 Gy in 1 fraction) and to metastatic sites, such as bone and para-aortic nodes, or for management with palliative chemotherapy.

15.6 The need for cancer diagnosis and treatment infrastructure in LMICs

The wider implementation of national HPV vaccination programmes and HPV-based screening programmes has the potential to substantially decrease the burden of cervical cancer in LMICs. However, the financial and organizational difficulties faced in these countries and the lack of government policy initiatives to support resources for comprehensive and quality-assured cervical cancer prevention programmes mean that a substantial number of women will continue to be affected by cervical

cancer. Unfortunately, many LMICs have extremely limited cancer health-care services, and access to and availability of radiotherapy and chemotherapy continue to be barriers to effective treatment in many developing countries. For instance, there are no radiotherapy services available in 22 countries in sub-Saharan Africa, and access to cancer medication is meagre.

The main objective of including the chapters on management of invasive cervical cancer in this manual is to convince the reader how easy it is to prevent cervical cancer by screening and vaccination, while emphasizing the need to care for those women affected by cervical cancer now and in the future in LMICs by developing basic health infrastructure to offer much-needed and affordable cancer diagnosis and treatment services. These services will also provide care for patients with a wide range of other common cancers.

It is illustrative to read about the experience at the Tata Memorial Centre, in Mumbai, India. There, the phased development of infrastructure and skills and the adoption of new developments in management and cervical cancer care have, over time, led to substantial improvements in outcomes (Shrivastava et al., 2013). This retrospective analysis based on 6234 patients with cervical cancer treated over a 15-year period illustrates how much patient treatment and outcomes can be improved with the acquisition of new equipment, the improvement of clinical skills, the introduction of multidisciplinary tumour clinics, and the introduction of evidence-based management policies.

Cervical cancer prevention is easy and affordable, by introducing population-based screening and vaccination programmes, but there is still a need to care for the women affected by cervical cancer now and in the future in those LMICs where these proven programmes have not yet been introduced. The best way to do this is by developing basic health infrastructure to offer much-needed and affordable cancer diagnosis and treatment services. These will serve not only patients with cervical cancer but also those with a wide range of other common cancers.

Key points

- The treatment modalities used in the non-surgical management of cervical cancer include radiotherapy, chemotherapy, and various combinations of radiotherapy and chemotherapy, particularly concomitant or concurrent chemoradiotherapy.
- Adding chemotherapy to radiotherapy seems to offer a modest but significant additional benefit on all outcomes and for all stages of disease, but the combination has significant side-effects.
- The best way to care for women with cervical cancer is by developing basic health infrastructure, whereby affordable cancer diagnosis and treatment services will serve not only patients with cervical cancer but also those with a wide range of other common cancers.

CHAPTER 16.

Follow-up after treatment of cervical intraepithelial neoplasia (CIN)

International practice varies for almost every clinical circumstance, and follow-up after treatment of CIN is no exception. The availability of clinical, laboratory, and nursing staff as well as the cost to the patient of attendance for follow-up will influence the follow-up arrangements. The advice that follows is based on the available evidence and does not take into account which tests or facilities are available locally.

Traditionally, women have been invited to attend for a follow-up colposcopic examination and cervical smear at relatively frequent intervals for 1–2 years before being returned to routine screening in the community. Table 16.1 details advice in the United Kingdom in 2016 (NHS, 2016). Practice in most European countries is similar, although in office practice, more frequent attendance for colposcopy is often advised.

16.1 Risk of development of invasive disease in treated women

Treatment confers a profoundly reduced risk of developing cancer for women who have had SIL (Kalliala et al., 2005; McCredie et al., 2008). However, treated women remain at risk. Indeed, treated women have a 2–5-fold increased risk of developing cervical cancer compared with the general population (Soutter et al., 1997). Much of this increased risk may be attributed to poor compliance with long-term follow-up (Khalid et al., 2011; Soutter et al., 2006; Strander et al., 2007). It does not appear that the grade of abnormality or the type of treatment affects the long-term risk (Kalliala et al., 2005, 2007). The nightmare scenario for every colposcopist is to see a patient with cancer some years after treatment for cervical precancer. Such a case is shown in Fig. 16.1.

Some women are more at risk than others. Women who have positive margins at histology, i.e. incomplete excision, have a 6-fold increased risk of residual disease (Ghaem-Maghami et al., 2007). Women who are older than 50 years at the time of treatment (Flannelly et al., 2001) or who have a persistently positive oncogenic HPV test are also more likely to have residual disease. Women who have a large type 2 or type 3 TZ have a 3-fold increased risk of having incomplete excision reported at histology. For women with a large, endocervical TZ, particular attention should be paid to the SCJ during initial treatment, to avoid a second excision. In most women who have a positive margin, there is no need to do an automatic second excision, because the great majority

Table 16.1. Clinical guidelines of the NHS Cervical Screening Programme

Duration and frequency of follow-up after treatment for CIN under the HPV "test of cure" protocol
• Women who have been treated for CIN1, CIN2, or CIN3 should be invited 6 months after treatment for "test of cure" repeat cytology in the community. Patient compliance with follow-up protocols should be encouraged.
• Women with a sample that has been reported as negative, or as showing borderline changes or low-grade dyskaryosis, and whose HR-HPV test is negative should be recalled in 3 years, whatever their age. Where the 3-year test is negative, women older than 50 years can return to 5-yearly routine recall.
• Women with a sample that has been reported as negative, or as showing borderline changes or low-grade dyskaryosis, and whose HR-HPV report is positive should be referred for colposcopy.
• Women with a sample that has been reported as showing high-grade dyskaryosis should be referred for colposcopy. No HR-HPV test is required.
• Women with a sample that has been reported as negative, or as showing borderline changes or low-grade dyskaryosis, and whose HR-HPV test result is unavailable should undergo repeat cytology at 3 months.
• Women who reach 65 years must still complete the protocol and otherwise comply with national guidance.
• Women in annual follow-up after treatment for CIN are eligible for the HPV test of cure at their next screening test unless that test is carried out at colposcopy.

CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; HR-HPV, high-risk HPV; NHS, United Kingdom National Health Service.

of these women (86%) will have normal epithelium (Ghaem-Maghami et al., 2011). However, they do require more considered and perhaps longer follow-up in the clinic than those who have complete excision reported at histology. Finally, women who are older than 50 years *and also* have involved margins should have elective retreatment by way of excision (Flannelly et al., 2001).

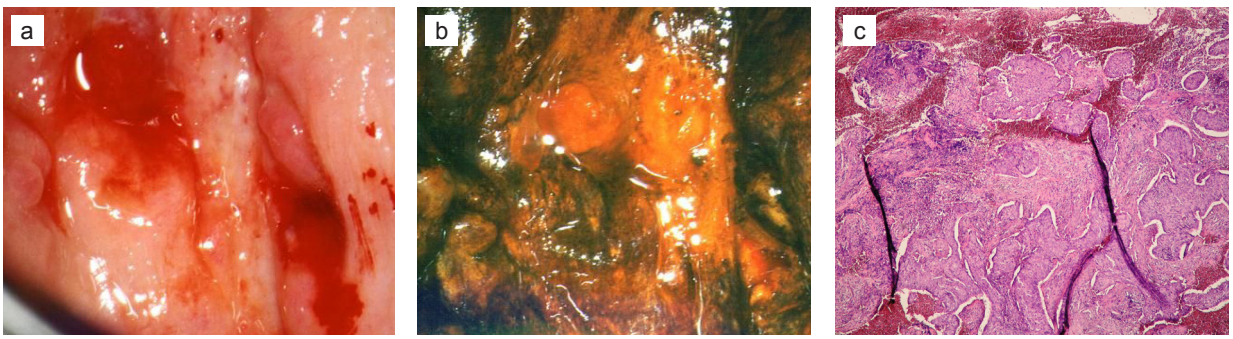
16.2 Current guidelines

Because most residual disease will be recognized in the first 1–2 years (Chew et al., 1999), follow-up testing should be comprehensive in these first 2 years. Until recently, the standard follow-up regime in most colposcopy centres has involved two or more cytology smears and two or more colposcopic examinations during the first 1–2 years, followed by regular cytology for 10 years or more. There is conflicting evidence about the effectiveness of colposcopy over cytology in detecting treatment failures, with some reporting that colposcopy enhances detection (Baldauf et al., 1998) and others reporting no advantage (Gardeil et al., 1997).

A visit to a colposcopy clinic offers other advantages, for example the opportunity to review the case history and counsel the patient about the need for longer-term follow-up, as well as the colposcopic recognition of cervical stenosis or possible functional incompetence. However, colposcopy is relatively expensive. In developing countries it is sometimes simply too difficult and too expensive for women to attend for colposcopic examination, and self-testing for high-risk HPV is a very reasonable alternative.

Self-testing for HPV has been shown to be superior to cytology collection by a physician in terms of sensitivity for CIN2 or greater (Lazcano-Ponce et al., 2011). A physician-taken HPV sample is even more

Fig. 16.1. This case reveals invasive cancer at the vaginal vault some 10 years after treatment for cervical precancer as HSIL-CIN3. (a, b) Low-power colposcopy images of the vaginal vault (a) before and (b) after the application of iodine. (c) Histopathology image; invasive disease is evident.



sensitive and is the gold standard test for post-treatment monitoring. There is very good evidence that HPV testing is more sensitive than cytology for detecting HSIL (Ronco et al., 2014). In the screening context, this means more sensitive detection of HSIL, less frequent testing, and lower surveillance costs (Uijterwaal et al., 2014).

16.3 Oncogenic HPV testing after treatment

The advantages of HPV testing make it the test of choice after treatment, when its high sensitivity and negative predictive value are so important (Arbyn et al., 2005).

Figs. 16.2 and 16.3 show meta-analyses of studies that compared high-risk HPV testing with cytology and with positive margin status for the detection of residual disease after treatment of CIN; HPV testing was superior in both comparisons. Several subsequent comparisons have confirmed the superiority of HPV testing as the best test of cure (Uijterwaal et al., 2014). Where cost is not a factor and facilities are available, there is also evidence that the recognition of HPV type 16 confers a particular risk of residual disease (Gök et al., 2007), but this test is still relatively expensive and is not yet universally available.

Perhaps not surprisingly, co-testing with cytology and oncogenic HPV is the most reassuring of all, and a negative co-test at both 6 months and 24 months carries a risk of finding HSIL during the subsequent 5 years of less than 1%, which is as low as that associated with a normal smear in a screened population (Kocken et al., 2011). The positivity rate for HPV testing after treatment falls steeply from 3 months to 12 months, and therefore it is prudent to perform the HPV test 12–18 months after treatment (Coupé et al., 2007).

16.4 Specific circumstances

16.4.1 Microinvasive disease and incomplete excision

Incomplete excision of microinvasive cancer should be managed, a priori, by a repeat excision without waiting for follow-up tests.

16.4.2 Adenocarcinoma in situ

The natural history of glandular precancer is less well documented than with squamous disease, and follow-up protocols should be even more rigorous. Because skip lesions occur in about 15% of cases

Fig. 16.2. Meta-analysis of studies comparing high-risk HPV testing with cytology for the detection of residual disease after treatment of CIN.

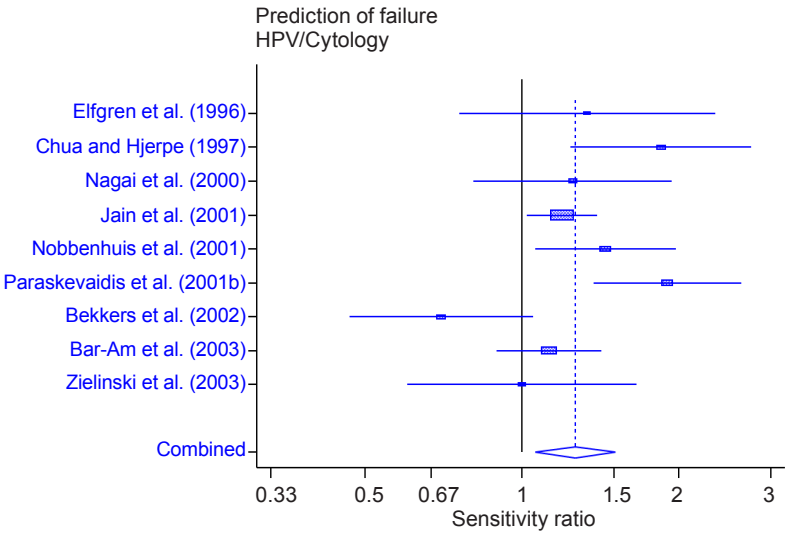
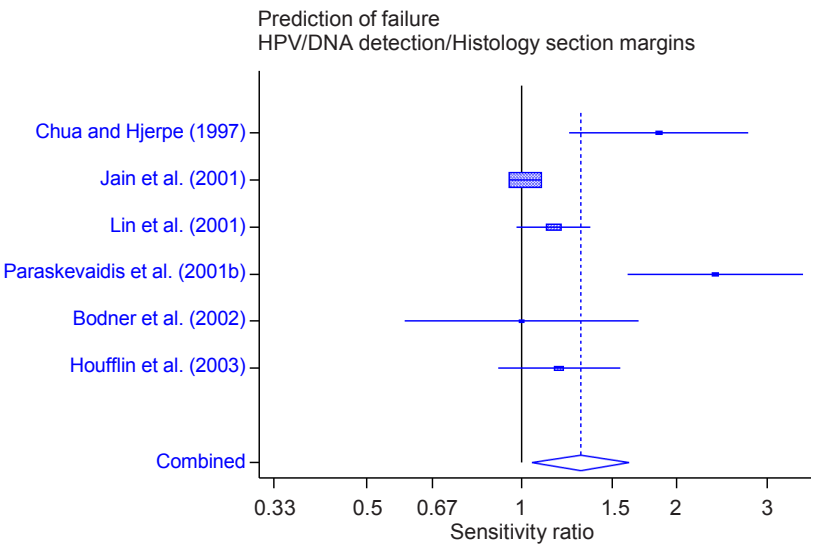


Fig. 16.3. Meta-analysis of studies comparing high-risk HPV testing with positive margin status for the detection of residual disease after treatment of CIN.



of glandular disease, margin status is less reassuring. Where there is any doubt about margin status, a repeat excision of endocervical epithelium should be performed. Also, residual/recurrent glandular disease occurs more frequently (15%) than with squamous disease. Follow-up of women treated for adenocarcinoma in situ should include cytology specimens taken from the endocervical canal separately to the ectocervical smear, and HPV testing should be performed on all follow-up cervical samples. When the patient has completed her family, a simple hysterectomy should be performed (NHS, 2010).

16.4.3 Duration of follow-up

Long-term studies have found a 5-fold increased risk of developing cervical cancer in women who have been treated for CIN, and this increased risk lasts for at least 20 years (Soutter et al., 2006). Therefore, most authorities advise follow-up for at least this long, although not necessarily in a clinic setting. Also, the profound protection afforded by a negative co-test (negative cytology and HPV testing) means that women may usually be followed up in the community.

16.4.4 Follow-up after hysterectomy

For women in whom previous frequent screening tests have been normal, there is no need for continued screening. Where a hysterectomy was done in part because of CIN and where the margins of excision were complete, it would seem prudent to perform co-testing at least annually for the first 2 years, and if these are both negative, then no further follow-up is necessary.

For women with incomplete or uncertain excision of CIN, follow-up should be conducted as if the cervix were still in situ (vault smear and HPV test at 6 months and 18 months, and annual combined tests for 20 years, regardless of the grade of the original disease).

16.5 Summary

Women being offered treatment for SIL or microinvasive disease should be advised that follow-up treatment is essential to reduce the risk of cancer to almost zero. Default from follow-up is probably the single most important reason for cancer development in women who have been treated for SIL. HPV testing is the most sensitive test of cure currently available. Self-testing is a reasonable alternative to attendance at a colposcopy clinic or doctor's office.

Key points

- Follow-up monitoring is crucial.
- Women who have been treated for suspected cervical precancer have a 5-fold increased risk of developing cervical cancer compared with women who have not had an abnormal smear.
- No method of treatment of CIN is 100% successful.
- The increased risk of residual or recurrent disease lasts for at least 20 years.
- Risk factors for residual disease include:
  - positive margins at histology;
  - older than 50 years at the time of treatment; and
  - positive oncogenic HPV test at follow-up after treatment.
- The main reason for the development of cancer after treatment is default from follow-up.
- Default rates may be improved by considering self-testing for oncogenic HPV.
- Co-testing with cytology and oncogenic HPV is superior to all other methods of monitoring women after treatment.

CHAPTER 17.

Pregnancy, contraception, menopause, and hysterectomy

This chapter discusses with the management of CIN during pregnancy, use of contraception and hormone replacement therapy, and hysterectomy.

17.1 Management of CIN during pregnancy

The management of CIN during pregnancy is dealt with comprehensively elsewhere (Freeman-Wang and Walker, 2006).

Inevitably, CIN will sometimes be first recognized during pregnancy, particularly if the population has not been systematically screened. CIN is also the most common gynaecological cancer of pregnancy (Yoonessi et al., 1982). Opinions vary as to whether it is wise to perform a smear during pregnancy. If a comprehensive screening programme is in place, it is not necessary, but if not, it may be the only opportunity to do so.

The pregnant cervix is both easier and more difficult to examine than the non-pregnant one. It is usually easier to see the entire TZ because of eversion of the cervical epithelium, whereby there is a relatively large ectropion, which inverts postpartum. However, the extra mucus, increased vascularity, stromal hypertrophy, and decidual changes induced by pregnancy are more difficult to interpret in the presence of an abnormal screening test, and this is one of the few times that cancer may be mistakenly suspected when the tissue is actually normal. As pregnancy progresses, the vaginal walls may become highly patulous and the cervix more difficult to visualize. The use of lateral vaginal wall specula or, more comfortably, a condom (with its end cut off) placed around a speculum will often be necessary to hold back the vaginal walls (Fig. 5.11b). Engorged vulvovaginal varices may add to the difficulty.

However, there are times when colposcopy will be necessary during pregnancy. If so, it is wise to refer the woman to a colleague who is experienced with colposcopy during pregnancy. If a woman meets the criteria for colposcopy, pregnancy should not defer it, but biopsy and treatment thresholds will be different. The primary ambition of a colposcopic examination during pregnancy is to recognize or rule out malignancy. Precancerous lesions are usually left untreated until about 3 months postpartum (NHS, 2010). However, it is often prudent to monitor suspected HSIL colposcopically and cytologically as pregnancy progresses.

Although the evidence is not conclusive, several observational

studies have reported the safety of delaying treatment during pregnancy (Coppola et al., 1997; Palle et al., 2000; Paraskevaidis et al., 2002; Woodrow et al., 1998). In the report of Paraskevaidis et al. of 98 pregnant women with CIN followed up until postnatal treatment by LLETZ, regression occurred in 36% of women with the antenatal suspicion of CIN1 and in 48% of women with suspected CIN2/CIN3. Of seven women with suspected microinvasion, only one had histological evidence (early stromal invasion < 1 mm), but there was one case of microinvasion (< 1.5 mm) not suspected antenatally. The opposite view was taken by Siegler et al. (2014), who reported safe treatment of precancer during pregnancy and suggested high rates of HSIL progression to cancer in women not treated during pregnancy. In their observational study of 31 pregnant women with HSIL, 18 were conservatively followed up and 13 underwent LLETZ during the first 14 weeks of pregnancy. Four women (12.9%) in the study group were diagnosed with invasive cervical cancer. Of the women who underwent LLETZ, nine continued their pregnancies, of which seven had full-term normal deliveries and two had late preterm deliveries. No complications of severe bleeding or miscarriage were reported in any of the treated patients. Siegler et al. advocate treatment of HSIL during pregnancy. However, most authorities recommend a conservative approach to the management of CIN during pregnancy, for two reasons: because of the risks of treatment during pregnancy, and because progression to cancer is thought to be uncommon (Massad et al., 2013; NHS, 2010).

The optimal management of CIN during pregnancy is uncertain at this time. What is universally agreed is that where a suspicion of microinvasive disease is present, a large biopsy needs to be taken. ***Punch biopsies are inadequate in this situation.*** Several alternative means of taking a biopsy are available. An adequate biopsy sufficient to allow the pathologist to rule out or recognize cancer will be achieved using a small loop biopsy or a wedge biopsy. Occasionally, it may be necessary to take larger pieces of tissue or even to perform an excision of the TZ. If so, these procedures are better performed in hospital, usually under general anaesthesia with a suture set to hand and sometimes with a prophylactic cerclage in place. Haemorrhage is a real risk (Robinson et al., 1997).

Either way, it is crucial that women in whom CIN is first recognized during pregnancy are at least followed up and managed at 3 months postpartum, because the untreated disease usually persists (LaPolla et al., 1988).

In summary, colposcopy should be performed at the same threshold during pregnancy as for women who are not pregnant. For women with suspected LSIL, management may be deferred until 3 months postpartum. A large biopsy must be performed for women with suspected microinvasive or invasive disease. Endocervical curettage is contraindicated during pregnancy. Women with suspected HSIL should have a follow-up examination in the second half of pregnancy and again 3 months postpartum.

17.2 Contraception and CIN

17.2.1 Combined oral contraceptive pill

Women should not be advised to change their method of contraception because of the recognition of CIN at screening. Some studies have shown a slight increase in CIN among women using the combined oral contraceptive pill, but no study has shown an advantage to discontinuing use. Also, in a large meta-analytical review, Smith et al. (2003) found no association between use of the combined oral contraceptive pill and CIN in women who had used the combined oral contraceptive pill for up to a decade (Ylitalo et al., 1999).

17.2.2 Intrauterine contraceptive device

There is no need to remove an IUCD in women who are being investigated for suspected CIN. It does not appear to have any effect on CIN progression or regression. Colposcopy is unaffected by the presence of an IUCD. However, there are implications for women who are undergoing excisional treatment. It is quite easy to resect the threads of an IUCD during excision of any kind. To prevent this, it is often possible to push the threads up above the field of resection under colposcopic guidance. It is thus possible to resect the TZ without disturbing the IUCD, and the threads (and not the IUCD) may then be gently pulled back down into their correct position.

However, sometimes it is not possible to ensure that the threads stay out of the field of resection. If the threads are resected, the woman should be informed about this, because she may need to attend a gynaecologist to achieve removal of the IUCD when it is due for removal or replacement. This is usually not difficult using a Nelson-Roberts forceps, particularly if the examination is performed in the follicular phase and with exogenous estrogen taken for a few days up to and including the day of the examination. With exogenous estrogen and in the follicular phase, the cervix is more likely to be relaxed, open, and amenable to forceps exploration of the endocervical canal and lower uterine cavity, whereby

the IUCD may be grasped and gently removed. It is rarely necessary to resort to general anaesthesia.

17.3 Hormone replacement therapy and CIN

Use of hormone replacement therapy does not increase or decrease the risk of CIN development or progression. There is no reason to advise cessation of hormone replacement therapy use because of a suspicion of CIN (Sawaya et al., 2000). In women who are not using hormone replacement therapy, it is sometimes useful to prescribe it for several weeks, when estrogen-related atrophic change confuses the colposcopic appearances or to increase the chance of successfully examining the endocervical canal.

17.4 Hysterectomy and treatment of CIN

It is prudent to take a smear or perform another screening test for any woman who is having a hysterectomy for benign pathology. Every woman who is due to have a hysterectomy and who has an abnormal screening test should have a preliminary colposcopic examination (NHS, 2010). The inadvertent undertreatment or overtreatment of CIN at hysterectomy is a preventable error. Where HSIL is present, if the TZ is not completely excised at hysterectomy, the risk of subsequent cancer developing will be increased and monitoring the vaginal vault is difficult. Some dysplastic epithelium may be buried in the scar of a hysterectomy, and this vaginal intraepithelial neoplasia is difficult to evaluate or treat (see Chapter 16).

For women who have no other pathology, hysterectomy is gross overtreatment of CIN, which is better treated locally (by excision or ablation). Hysterectomy is associated with far greater morbidity than local treatment. Finally, simple hysterectomy is an inadequate treatment for invasive cancer (Roman et al., 1992). Where coexisting benign pathology exists or where unexplained endocervical pathology persists, it may be justifiable to perform hysterectomy, providing that all reasonable efforts have been made to rule out cancer and providing that iodine is applied just before hysterectomy to ensure excision of any vaginal intraepithelial neoplasia (Mohamed-Noor et al., 1997).

Key points

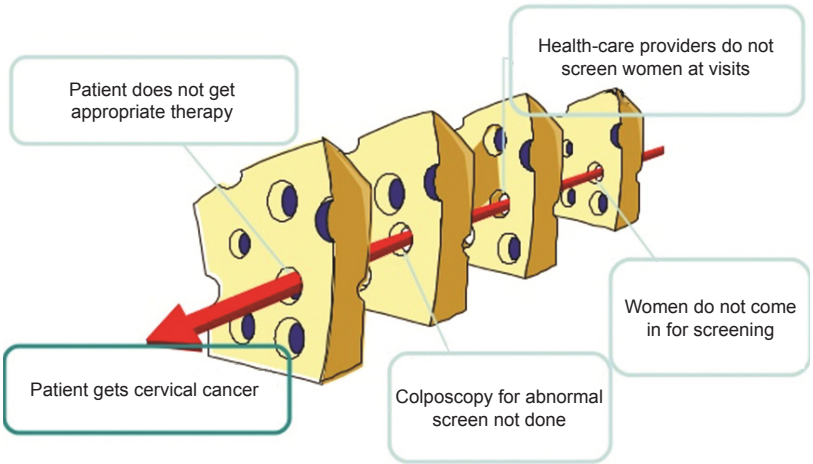
- Colposcopy should be performed at the same threshold during pregnancy as for women who are not pregnant, but for women with suspected LSIL, management may usually be deferred until 3 months postpartum.
- A large biopsy must be performed for women with suspected microinvasive or invasive disease, and endocervical curettage is contraindicated during pregnancy.
- Women with suspected HSIL should have a follow-up examination in the second half of pregnancy and again 3 months postpartum.
- The investigation of abnormal bleeding after menopause must include direct visual inspection of the cervix.
- All patients in the cervical screening age range undergoing a hysterectomy for other gynaecological reasons should have a negative test result within the screening interval or as part of their preoperative investigations.
- All patients being considered for hysterectomy who have an undiagnosed abnormal sample or symptoms attributable to cervical cancer should have diagnostic colposcopy and an appropriate biopsy.

CHAPTER 18.

Quality assurance: fail-safe protocols and clean equipment

In tandem with a national HPV vaccination programme, a systematic, quality-assured call-and-recall system of cervical screening is the best way to reduce rates of cervical cancer and associated mortality. In an opportunistic programme, opportunities may be lost, leading to a diagnosis of cervical cancer (Fig. 18.1). For a screen-positive patient attending a colposcopy service, there is still potential for error. After proper training, a colposcopist will be able to competently perform colposcopic examination and undertake treatment for women with suspected cervical precancer. To deliver this service, the colposcopist needs a facility in which to provide the service as well as appropriate nursing and administrative resources and equipment. Once a service has been established, it is important that it be *quality-assured*. Every aspect of a cervical precancer screening programme needs to be included in a quality assurance programme, but the screening, organizational, and laboratory components of the programme are outside the scope of this manual. The interested reader is referred to the NHS Cervical Screening Programme website (https://www.gov.uk/guidance/cervical-screening-programme-overview) for a fuller description of

Fig. 18.1. In an opportunistic screening programme, lost opportunities may ultimately lead to cancer.



every aspect of the quality assurance system of the United Kingdom screening programme.

18.1 Standard operating procedures

It is possible to reduce the risk of mistakes in any clinical case by conscientious attention to detail. However, when a colposcopy service is managing large numbers of similar clinical presentations (i.e. screen-positive women) and dealing with large numbers of similar laboratory reports, it is easy for mistakes to happen.

The organizational aspects of a colposcopy service are as important as the diagnostic skill of the colposcopist. If a *system* of routine patient care and management of laboratory reports is established at the outset, failures and oversights will be much less likely to occur (Fig. 18.2). A manual of standard operating procedures (SOPs) of how to routinely manage every presentation will reduce the chance of mistakes happening. SOPs will contain the expected protocol for: how to deal with patient appointment default; how to arrange supply of disposable equipment; how to clean, disinfect, and sterilize reusable equipment; how laboratory reports should be filed and acted upon; and how samples should be routinely processed, labelled, and delivered on time. SOPs should be available and known to everyone in the clinic.

Auditing of how these SOPs are being adhered to and how effective they are will allow a centre of excellence to evolve (Fig. 18.3). Constant updating of the manual on the basis of changing evidence in the literature and review of the audit cycle will maintain excellence. Table 18.1 lists some of the issues that a quality assurance programme will attempt to maintain at a level of excellence, or at least competence.

Fig. 18.2. Some clinic management mistakes that may occur in a patient pathway through a colposcopy clinic service.

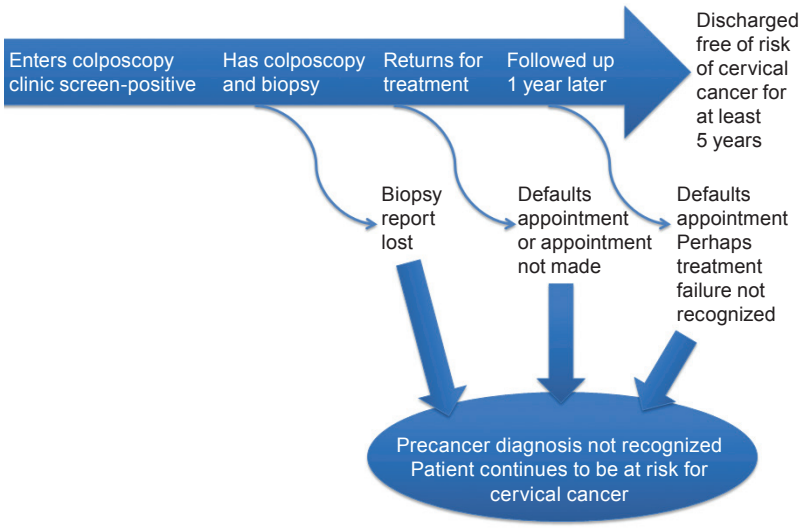
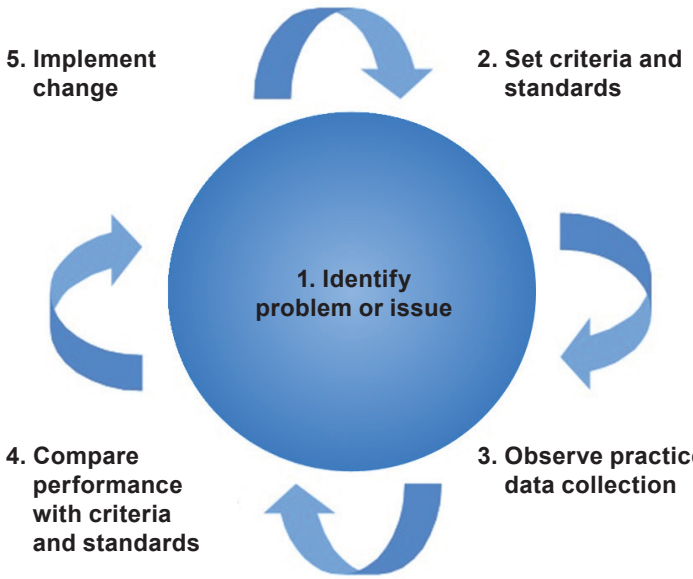


Fig. 18.3. The audit cycle: trying to achieve excellence.



18.2 Protection against infection

First, if a patient has a genital tract infection, it is almost always necessary to treat it before proceeding to colposcopic examination. Any degree of cervicitis will usually preclude an adequate examination. The treatment policies for pregnant and non-pregnant women diagnosed with reproductive tract infection are outlined in Table 9.1. Use of oral metronidazole is contraindicated during the first trimester of pregnancy, but it can be safely used during the second and third trimesters. Patients taking oral metronidazole should be cautioned not to consume alcohol while they are taking the drug or up to 24 hours after taking the last dose. Patients with advanced syphilis may

Table 18.1. Quality assurance issues

Issue	Explanation	Examples
Clinical guidelines	Details best practice according to best evidence and available local circumstances	NHS Cervical Screening Programme clinical guidelines (NHS, 2016) WHO comprehensive cervical cancer control guide (WHO, 2014)
Manual of standard operating procedures (SOPs)	Lists agreed clinic and service management protocols	Locally produced; includes how to process samples, ensure that laboratory reports are acted upon, ensure that appointment system is effective, etc.
Fail-safe protocols	Details strategies to prevent mistakes in patient and report management, particularly oversights in report management	Establish a tracking system for cytology and biopsy specimens and reports
Audit logs of colposcopic performance	Measures agreed parameters of clinical performance	• Cytology–histology correlation • Percentage treatment under local anaesthesia • Rate of false-negative histology at excisional histological examination
Waiting time for appointments Time to treatment when cancer diagnosed	Maximum time allowed for implementing management (e.g. for a cancer diagnosis)	Time from when cancer report is made until management is implemented should be < 2 weeks
Equipment log	Equipment maintenance and replacement arrangements	List all functional equipment failures and act to correct them
Information leaflets	Patient information Waiting-time lists Follow-up arrangements	Ensure that all information leaflets and other routine paperwork are up to date and available
Documentation	How records are collected	Standardized forms for colposcopic examinations (new visits, follow-up visits, treatment visits, etc.) Ideally, computerized
Cleaning, disinfection, sterilization	How patients and staff are protected from infection in the clinic	Equipment management before, during, and after an examination

require prolonged treatment with antibiotics. There is no known cure for genital herpes infections, but the course of symptoms can be modified if systemic therapy with acyclovir or its analogues is initiated.

Establishing a system of equipment management is fundamental to good practice. This is true for managing the equipment before, during, and after the colposcopic examination. Ideally, a clean room should house the clean equipment and a separate cleaning room (sometimes called a sluice room) should receive equipment after use in the clinic room, where it can be cleaned before disinfection and/or sterilization. SOPs for the care of equipment and disposable supplies are a crucial part of preventing systematic errors in the flow and use of safe equipment. For a new clinic or for new staff in an existing service, SOPs are particularly useful. There are three different infection risks to consider in the colposcopy clinic: (i) managing equipment before it enters the clinic room area; (ii) managing equipment in the colposcopy room and during colposcopy; and (iii) managing equipment after it has been used.

18.2.1 Managing equipment before it enters the clinic room area

Clean, disinfected, or sterile instruments and all disposable equipment should be stored in a clean, simple environment, preferably a dedicated room, which should be kept free of any used or clinically unclean equipment. The equipment should be accessible and organized, and the room should preferably be kept locked.

18.2.2 Managing equipment in the colposcopy room and during colposcopy

Establishing a system of equipment flow in the clinic room will reduce the risk of accidental infection. Such a system is both easy to arrange and ergonomically efficient. Given the repetitive nature of colposcopy, it is prudent to procure and stock a compartmentalized trolley to accommodate the reusable and disposable equipment needed for the clinic (see Chapter 5). Dirty or used equipment should never be placed on or in this trolley. Care should be taken to arrange the hardware used

in colposcopy so that the equipment and cables are not in the line of potential infection and will not trip anyone up. If possible, the monitor, computer, camera system, ESU, and ablative treatment equipment should be stacked on fixed wall-mounted shelving. The cables and tubes from this equipment should come from only one side of the colposcopist.

A simple layout illustrating the different parts that come together in the working interface is shown in Fig. 18.4. This interface is where the risk of contamination is greatest. The colposcopist should take care not to place used or dirty instruments back onto the clean supplies trolley. The flow of equipment should be in one direction: from the instrument trolley to the working interface area and then to the receptacle for used equipment. It is often useful to have a temporary storage bowl or dish just underneath the patient's perineum where instruments and swabs may be kept during the procedure until finished with (Fig. 18.5). Equipment may then be transferred to the receptacle for used equipment. There should be a hand wash basin for the patient to wash her hands and, ideally, a separate one for the colposcopist to do so after each procedure.

18.2.3 Managing equipment after it has been used

Before equipment may be used or reused, it needs to be decontaminated, cleaned, and then either sterilized or disinfected using high-level disinfection (HLD).

18.3 Decontamination

Decontamination comprises a series of steps to make a medical instrument or device safe for handling by reducing its contamination with microorganisms or other harmful substances. Usually, these procedures are performed by the nursing, technical, or cleaning staff, and decontamination protects these workers from inadvertent infection. If these procedures are carried out properly, decontamination of the instruments will be ensured before they are handled for cleaning. This step results in the inactivation of most organisms, such as hepatitis B virus and HIV. Further processing is needed to ensure that the object is cleaned and then sterilized.

18.3.1 Method of decontamination

Immediately after use, place instruments and other items, such as gloves, in a large clean plastic bucket containing a 0.5% chlorine solution for 10 minutes. The 0.5% chlorine solution can be prepared by adding 1 part of concentrated household bleach (sodium hypochlorite solution, 5% available chlorine) to 9 parts of water.

The general formula for making a dilute solution from a commercial preparation of any given concentration is as follows: total parts of water = [% concentrate/% dilute] − 1. For example, to make a 0.5% dilute solution of chlorine from 5% concentrated liquid household bleach, total parts of water = [5.0%/0.5%] − 1 = 10 – 1 = 9; hence, add 1 part of concentrated bleach to 9 parts of water.

If commercially available dry powder chlorine is used to make the solution, use the following formula to calculate the amount (in grams) of dry powder required to make a 0.5% chlorine solution: grams/litre = [% dilute/% concentrate] × 1000. For example, to make a 0.5% dilute solution of chlorine from a dry powder of 35% calcium hypochlorite, grams/litre = [0.5%/35%] × 1000 = 14.2 g. Hence, add 14.2 g of dry powder to

Fig. 18.4. Layout of equipment and cables relative to the working interface. The colposcopist should ensure that used equipment does not contaminate the permanently stacked hardware or the relevant cables, or the clean supply trolley.

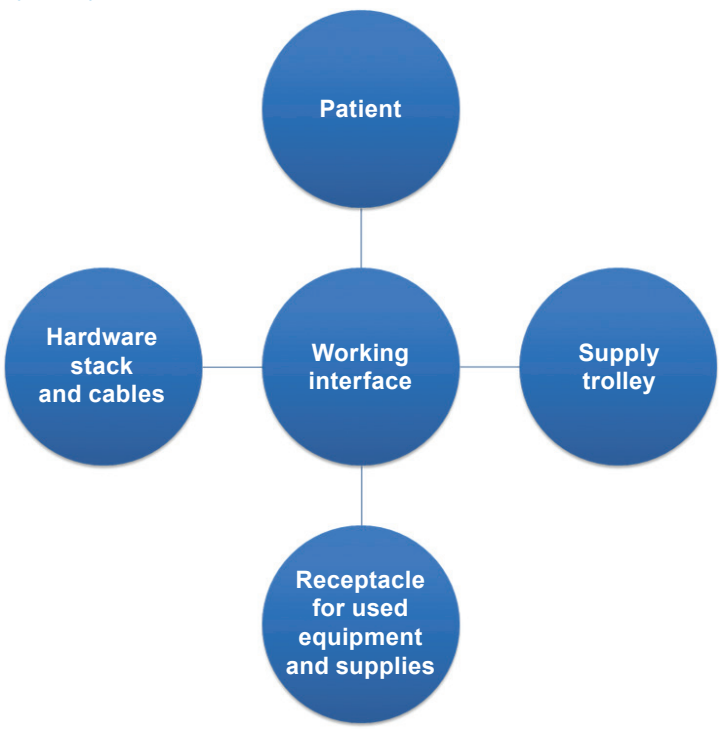
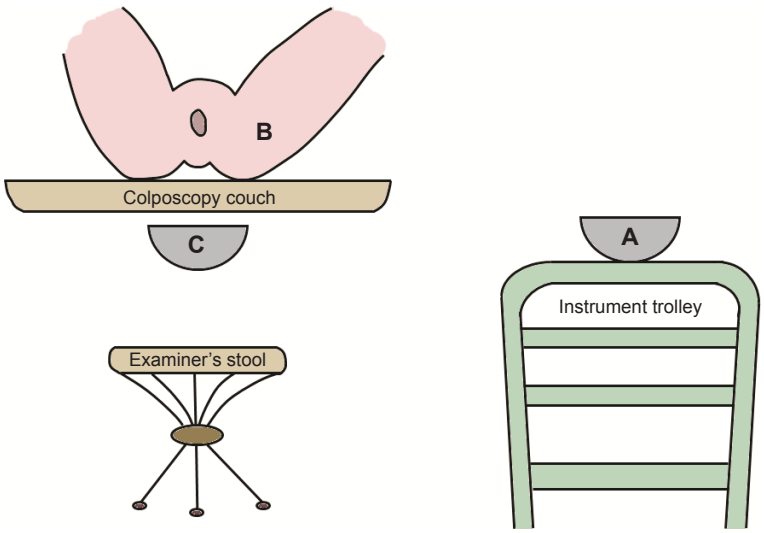


Fig. 18.5. The flow of instruments and equipment (reusable and disposable) should be in one direction: from the instrument trolley (A) to the working interface area (B) and then to the receptacle for used equipment (C) and never back to A.



1 litre of water or 142 g of dry powder to 10 litres of water.

The instruments should not be left in dilute bleach for more than 10 minutes and should be cleaned in boiled water immediately after decontamination to prevent discoloration and corrosion of metal.

18.4 Cleaning

Cleaning is a crucial step in providing safe, infection-free instruments. Vigorous manual cleaning with running water and liquid soap or detergent removes biological material such as blood, body fluids, and tissue remnants. Instruments should be cleaned as soon as possible after use.

If biological material is left behind, it can act as a sanctuary for residual microorganisms, protecting them from the effects of disinfection and sterilization.

18.4.1 Method of cleaning

Thorough manual cleaning of instruments with water and detergent to remove all organic material, after decontamination in 0.5% chlorine solution for 10 minutes, is of the utmost importance before sterilization or HLD. A brush should be used to scrub the instruments free of biological matter. Instruments should be cleaned as soon as possible after use, so that no organic material will dry and stick to the instruments, providing a sanctuary for microbes. The person cleaning should use utility gloves while washing the instruments.

Protective glasses or goggles should be worn by the cleaners to protect their eyes from contaminated water. Special attention should be given to instruments with teeth (e.g. biopsy punches) or joints and screws (e.g. vaginal specula), to which biological material can become stuck. After cleaning, rinse the instruments thoroughly with boiled water to remove detergent residue.

18.5 Sterilization or high-level disinfection

Sterilization is defined as the process of destroying all microorganisms on an instrument by exposure to physical or chemical agents. This process kills all forms of microbial life, including bacterial spores. In practice, sterility is considered to be achieved if the probability of a surviving microorganism is less than 1 in 1 million. The sterilization process is fundamental to the safe reuse of instruments in clinical care.

When sterilization equipment is not available or the instrument cannot be sterilized, HLD is used. Disinfection implies that the microbial burden of an instrument is reduced but is not entirely eliminated. The extent of this reduction depends on the disinfection process used and the resistance of the microbial forms present. In practice, however, HLD results in all forms of microbial life being destroyed except bacterial spores.

18.5.1 Methods of sterilization

Instruments that are considered critical (instruments that enter sterile body tissues or the vascular system, such as biopsy punches, surgical instruments, electrocautery tips, and vaginal specula; see Table 18.3) require sterilization before reuse. Two methods of sterilization are described here: steam sterilization and chemical sterilization.

High-pressure saturated steam sterilization using autoclaves is recommended for sterilization. Unwrapped instruments should be exposed for 20 minutes to temperatures of 121–132 °C at a pressure of 106 kPa (15 lb/inch^2). The manufacturer's recommendations should be followed, because pressure settings may vary slightly depending on the make of the autoclave. Small wrapped packs of instruments should be exposed for 30 minutes. The material used for wrapping should be porous enough to let steam through. Wrapped sterile instruments have a shelf life of up to 7 days, if kept dry

and intact. Unwrapped instruments should be placed in a sterile container. Small autoclaves are ideal for use in clinics.

Chemical sterilization by soaking in 2–4% glutaraldehyde for 8–10 hours or in 8% formaldehyde for 24 hours is an alternative to steam sterilization. This requires special handling with gloves, and the instruments thus sterilized should be rinsed with sterile water before use, because these chemicals form a residue on the instruments. Glutaraldehyde is very expensive, whereas formaldehyde is more irritating to skin, lungs, and eyes. Steam sterilization is preferred to chemical sterilization.

18.5.2 Methods of high-level disinfection

Two methods of HLD are described here.

Boiling plain tap water in a clean vessel offers a cheap and readily accessible form of HLD. The contact time for instruments should be at least 20 minutes after boiling has started. Water in the vessel should be changed daily. The vessel should be washed and kept dry every day.

Alternatively, HLD may be obtained by soaking instruments in one of the following solutions for 20–30 minutes.

- *0.1% Chlorine solution:* If boiled water is used to make the solution, 0.1% chlorine may be used for HLD. If not, 0.5% chlorine solution should be used. The contact time required is 20 minutes. The solution is very corrosive to stainless steel. After disinfection, instruments should be rinsed thoroughly with boiled water and then air-dried or dried with a sterile cloth before use. The shelf life of prepared solution is 1 week.
- *6% Hydrogen peroxide solution:* It can be prepared by adding 1 part of a 30% solution to 4 parts of boiled water. The contact time required is 30 minutes. After disinfection, instruments should be rinsed thoroughly with boiled water and then air-dried or dried with a sterile cloth before use. However, this solution will damage the external surfaces of rubbers and plastics and will corrode copper, zinc, and brass instruments after prolonged use.
- *2% Glutaraldehyde:* It must be prepared according to the manufacturer's instructions. Activated 2% solution in a covered container has a shelf life of 2 weeks. The contact time required is 20 minutes. Because glutaraldehyde forms a residue on instruments, which is toxic to tissues, the instruments must be rinsed thoroughly with sterile water and dried with a sterile cloth before use.

18.6 Quality assurance of equipment safety and sterility

Strict implementation of decontamination, cleaning, and sterilization or HLD of instruments according to a written manual is helpful in quality assurance of the procedures. The manual must be prominently displayed in the clinic for ready reference. The quality assurance process includes regular audits, analysis, system adjustments, and education. The audits should include: review of the methods of sterilization used, the items being sterilized, and the duration and temperature of exposure; identification of the person performing the sterilization; and periodic review and inspection of the equipment being used for sterilization. The frequency of pelvic infection after clinical procedures in this context (i.e. screening, early detection, and treatment of cervical precancer) is a good indicator of the quality of the sterilization process in place.

18.7 Spaulding's classification of medical instruments (modified)

Spaulding (1968) categorized medical instruments as critical, semi-critical, or non-critical, according to how they are used (Table 18.2). This classification is useful in guiding the processing of instruments for reuse.

Intermediate-level disinfection results in destruction of *Mycobacterium tuberculosis*, vegetative bacteria, most viruses (HIV, hepatitis B virus, and herpes simplex viruses), and most fungi (*Candida*, *Aspergillus*), but it does not kill bacterial spores. Low-level disinfection destroys most bacteria, some viruses, and some fungi, but not *Mycobacterium tuberculosis* or bacterial spores. Antiseptics such as 60–90% ethyl or isopropyl alcohol or iodophors such as 10% povidone iodine act as intermediate-level or low-level disinfectants. Alcohol does not leave a residue on instruments, but iodophors do.

A guide to the processing of instruments and materials used for screening of cervical neoplasia, colposcopy, and treatment of CIN is given in Table 18.3.

Table 18.2. Spaulding's categorization of medical instruments

Class	Use	Processing
Critical (C)	Enters sterile body site or vascular system	Decontamination and cleaning followed by sterilization
Semi-critical (SC)	Comes into contact with intact mucous membrane or non-intact skin	Decontamination and cleaning followed by high-level disinfection
Non-critical (NC)	Comes into contact with intact skin	Decontamination and cleaning followed by intermediate-level or low-level disinfection

18.8 Decontamination of surfaces in the screening clinic

Procedure tables, trolleys, and equipment (colposcope, cryosurgical equipment, ESU, smoke evacuator, halogen lamp, etc.) in the screening clinic may be contaminated with body fluids such as vaginal secretions, purulent discharge, and blood. The surface of the procedure table should be decontaminated after each patient procedure, and the other surfaces should be decontaminated daily by wiping with 0.5% chlorine solution, 60–90% ethyl or isopropyl alcohol, or other chemical disinfectants such as iodophors. The floor of the screening clinic should also be decontaminated daily.

Table 18.3. Guide to the processing of instruments and materials used for early detection and treatment of cervical neoplasia

Instrument/material	Category	Processing	Suggested procedure
Vaginal speculum, vaginal retractor, biopsy forceps, endocervical curette, endocervical speculum, needle holder, toothed forceps, vulsellum forceps, mosquito forceps, insulated speculum, vaginal sidewall retractor	C	Decontamination and cleaning followed by sterilization or HLD	Autoclaving or disinfection with boiling water
Gloves	C	Decontamination and cleaning followed by sterilization	Autoclaving as wrapped packs
Cryoprobes	SC	Decontamination and cleaning followed by HLD	Disinfection with 0.1% chlorine or 2% glutaraldehyde or 6% hydrogen peroxide
Colposcope head, stand LLETZ/LEEP equipment, cryogun and regulator, cryo gas cylinder, examination table, hand lens, handheld magnification device, torch lights, halogen lamp, instrument trolley, trays	SC	Intermediate-level or low-level disinfection	Wiping with 60–90% ethyl or isopropyl alcohol

C, critical; HLD, high-level disinfection; LEEP, loop electrosurgical excision procedure; LLETZ, large loop excision of the transformation zone; SC, semi-critical.

Key points

- The organizational aspects of a colposcopy service are as important as the diagnostic skill of the colposcopist.
- Contamination and cross-infection are risks for both patients and staff in a colposcopy clinic.
- Decontamination, cleaning, sterilization, and high-level disinfection are different terms with precise meanings.

References

Al-Kalbani M, McVeigh G, Nagar H, McCluggage WG (2012). Do FIGO stage IA and small (≤2 cm) IB1 cervical adenocarcinomas have a good prognosis and warrant less radical surgery? Int J Gynecol Cancer. 22(2):291–5. http://dx.doi.org/10.1097/IGC.0b013e3182339fff PMID:22080884

Anderson M (1986). Are we vaporizing microinvasive lesions? In: Sharp F, Jordan JA, editors. Gynaecological laser surgery: proceedings of the Fifteenth Study Group of the Royal College of Obstetricians and Gynaecologists. Ithaca (NY), USA: Perinatology Press; pp. 127–31.

Anderson MC, Hartley RB (1980). Cervical crypt involvement by intraepithelial neoplasia. Obstet Gynecol. 55(5):546–50. PMID:7366912

Arbyn M, Kyrgiou M, Simoens C, Raifu AO, Koliopoulos G, Martin-Hirsch P, et al. (2008). Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis. BMJ. 337:a1284. http://dx.doi.org/10.1136/bmj.a1284 PMID:18801868

Arbyn M, Paraskevaidis E, Martin-Hirsch P, Prendiville W, Dillner J (2005). Clinical utility of HPV-DNA detection: triage of minor cervical lesions, follow-up of women treated for high-grade CIN: an update of pooled evidence. Gynecol Oncol. 99(3 Suppl 1):S7–11. http://dx.doi.org/10.1016/j.ygyno.2005.07.033 PMID:16154623

Arbyn M, Rebolj M, De Kok IM, Fender M, Becker N, O'Reilly M, et al. (2009). The challenges of organising cervical screening programmes in the 15 old member states of the European Union. Eur J Cancer. 45(15):2671–8. http://dx.doi.org/10.1016/j.ejca.2009.07.016 PMID:19695867

Arbyn M, Roelens J, Simoens C, Buntinx F, Paraskevaidis E, Martin-Hirsch PP, et al. (2013). Human papillomavirus testing versus repeat cytology for triage of minor cytological cervical lesions. Cochrane Database Syst Rev. 3:CD008054. PMID:23543559

ASCUS-LSIL Triage Study (ALTS) Group (2003a). A randomized trial on the management of low-grade squamous intraepithelial lesion cytology interpretations. Am J Obstet Gynecol. 188(6):1393–400. http://dx.doi.org/10.1016/S0002-9378(03)00413-7 PMID:12824968

ASCUS-LSIL Triage Study (ALTS) Group (2003b). Results of a randomized trial on the management of cytology interpretations of atypical squamous cells of undetermined significance. Am J Obstet Gynecol. 188(6):1383–92. http://dx.doi.org/10.1016/S0002-9378(03)00418-6 PMID:12824967

Baldauf JJ, Dreyfus M, Ritter J, Cuenin C, Tissier I, Meyer P (1998). Cytology and colposcopy after loop electrosurgical excision: implications for follow-up. Obstet Gynecol. 92(1):124–30. http://dx.doi.org/10.1016/S0029-7844(98)00144-6 PMID:9649107

Bar-Am A, Gamzu R, Levin I, Fainaru O, Niv J, Almog B (2003). Follow-up by combined cytology and human papillomavirus testing for patients post-cone biopsy: results of a long-term follow-up. Gynecol Oncol. 91(1):149–53. http://dx.doi.org/10.1016/S0090-8258(03)00435-9 PMID:14529675

Basu P, Mittal S, Banerjee D, Singh P, Panda C, Dutta S, et al. (2015). Diagnostic accuracy of VIA and HPV detection as primary and sequential screening tests in a cervical cancer screening demonstration project in India. Int J Cancer. 137(4):859–67. http://dx.doi.org/10.1002/ijc.29458 PMID:25631198

Bekkers RL, Melchers WJ, Bakkers JM, Hanselaar AG, Quint WG, Boonstra H, et al. (2002). The role of genotype-specific human papillomavirus detection in diagnosing residual cervical intraepithelial neoplasia. Int J Cancer. 102(2):148–51. http://dx.doi.org/10.1002/ijc.10691 PMID:12385010

Benedet JL, Nickerson KG, White GW (1981). Laser therapy for cervical intraepithelial neoplasia. Obstet Gynecol. 58(2):188–91. PMID:7254731

Bergeron C, Ordi J, Schmidt D, Trunk MJ, Keller T, Ridder R; European CINtec Histology Study Group (2010). Conjunctive p16^{INK4a} testing significantly increases accuracy in diagnosing high-grade cervical intraepithelial neoplasia. Am J Clin Pathol. 133(3):395–406. http://dx.doi.org/10.1309/AJCPXSVCDZ3D5MZM PMID:20154278

Bergeron C, Ronco G, Reuschenbach M, Wentzensen N, Arbyn M, Stoler M, et al. (2015). The clinical impact of using p16^{INK4a} immunochemistry in cervical histopathology and cytology: an update of recent developments. Int J Cancer. 136(12):2741–51. http://dx.doi.org/10.1002/ijc.28900 PMID:24740700

Bertrand M, Lickrish GM, Colgan TJ (1987). The anatomic distribution of cervical adenocarcinoma in situ: implications for treatment. Am J Obstet Gynecol. 157(1):21–5. http://dx.doi.org/10.1016/S0002-9378(87)80338-1 PMID:3605256

Bodner K, Bodner-Adler B, Wierrani F, Kimberger O, Denk C, Grünberger W (2002). Is therapeutic conization sufficient to eliminate a high-risk HPV infection of the uterine cervix? A clinicopathological analysis. Anticancer Res. 22(6B):3733–6. PMID:12552985

Bornstein J, Bentley J, Bösze P, Girardi F, Haefner H, Menton M, et al. (2012a). 2011 Colposcopic terminology of the International Federation for Cervical Pathology and Colposcopy. Obstet Gynecol. 120(1):166–72. http://dx.doi.org/10.1097/AOG.0b013e318254f90c PMID:22914406

Bornstein J, Sideri M, Tatti S, Walker P, Prendiville W, Haefner HK; Nomenclature Committee of International Federation for Cervical Pathology and Colposcopy (2012b). 2011 Terminology of the vulva of the International Federation for Cervical Pathology and Colposcopy. J Low Genit Tract Dis. 16(3):290–5. http://dx.doi.org/10.1097/LGT.0b013e31825934c7 PMID:22659778

Bosch FX, Manos MM, Muñoz N, Sherman M, Jansen AM, Peto J, et al.; International Biological Study on Cervical Cancer (IBSCC) Study Group (1995). Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. J Natl Cancer Inst. 87(11):796–802. http://dx.doi.org/10.1093/jnci/87.11.796 PMID:7791229

Bowring J, Strander B, Young M, Evans H, Walker P (2010). The Swede score: evaluation of a scoring system designed to improve the predictive value of colposcopy. J Low Genit Tract Dis. 14(4):301–5. http://dx.doi.org/10.1097/LGT.0b013e3181d77756 PMID:20885156

Broders AC (1932). Carcinoma in situ contrasted with benign penetrating epithelium. J Am Med Assoc. 99(20):1670. http://dx.doi.org/10.1001/jama.1932.02740720024007

Bucchi L, Cristiani P, Costa S, Schincaglia P, Garutti P, Sassoli de Bianchi P, et al. (2013). Rationale and development of an on-line quality assurance programme for colposcopy in a population-based cervical screening setting in Italy. BMC Health Serv Res. 13(1):237. http://dx.doi.org/10.1186/1472-6963-13-237 PMID:23809615

Camargo MJ, Russomano FB, Tristão MA, Huf G, Prendiville W (2015). Large loop versus straight-wire excision of the transformation zone for treatment of cervical intraepithelial neoplasia: a randomised controlled trial of electrosurgical techniques. BJOG. 122(4):552–7. http://dx.doi.org/10.1111/1471-0528.13200 PMID:25516462

Carcopino X, Barde K, Petrovic M, Beucher G, Capmas P, Huchon C, et al. (2014). Threatened late miscarriage. French guidelines [in French]. J Gynecol Obstet Biol Reprod (Paris). 43(10):842–55. http://dx.doi.org/10.1016/j.jgyn.2014.09.015 PMID:25447364

Carcopino X, Mancini J, Charpin C, Grisot C, Maycock JA, Houvenaeghel G, et al. (2013). Direct colposcopic vision used with the LLETZ procedure for optimal treatment of CIN: results of joint cohort studies. Arch Gynecol Obstet. 288(5):1087–94. http://dx.doi.org/10.1007/s00404-013-2882-0 PMID:23670207

Cartier R, Cartier I (1993). Practical colposcopy. Paris, France: Laboratoire Cartier.

Castanon A, Landy R, Brocklehurst P, Evans H, Peebles D, Singh N, et al.; PaCT Study Group (2014). Risk of preterm delivery with increasing depth of excision for cervical intraepithelial neoplasia in England: nested case-control study. BMJ. 349:g6223. http://dx.doi.org/10.1136/bmj.g6223 PMID:25378384

Castle PE, Sideri M, Jeronimo J, Solomon D, Schiffman M (2007). Risk assessment to guide the prevention of cervical cancer. Am J Obstet Gynecol. 197(4):356.e1–6. http://dx.doi.org/10.1016/j.ajog.2007.07.049 PMID:17904958

Ceccaroni M, Roviglione G, Spagnolo E, Casadio P, Clarizia R, Peiretti M, et al. (2012). Pelvic dysfunctions and quality of life after nerve-sparing radical hysterectomy: a multicenter comparative study. Anticancer Res. 32(2):581–8. PMID:22287748

Chanen W, Rome RM (1983). Electrocoagulation diathermy for cervical dysplasia and carcinoma in situ: a 15-year survey. Obstet Gynecol. 61(6):673–9. PMID:6843923

Chappatte OA, Byrne DL, Raju KS, Nayagam M, Kenney A (1991). Histological differences between colposcopic-directed biopsy and loop excision of the transformation zone (LETZ): a cause for concern. Gynecol Oncol. 43(1):46–50. http://dx.doi.org/10.1016/0090-8258(91)90007-R PMID:1959787

Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration (2008). Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. J Clin Oncol. 26(35):5802–12. http://dx.doi.org/10.1200/JCO.2008.16.4368 PMID:19001332

Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC) (2010). Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis. Cochrane Database Syst Rev. 1:CD008285. PMID:20091664

Chew GK, Jandial L, Paraskevaidis E, Kitchener HC (1999). Pattern of CIN recurrence following laser ablation treatment: long-term follow-up. Int J Gynecol Cancer. 9(6):487–90. http://dx.doi.org/10.1046/j.1525-1438.1999.99066.x PMID:11240816

Chua KL, Hjerpe A (1997). Human papillomavirus analysis as a prognostic marker following conization of the cervix uteri. Gynecol Oncol. 66(1):108–13. http://dx.doi.org/10.1006/gyno.1997.4753 PMID:9234930

Coppola A, Sorosky J, Casper R, Anderson B, Buller RE (1997). The clinical course of cervical carcinoma in situ diagnosed during pregnancy. Gynecol Oncol. 67(2):162–5. http://dx.doi.org/10.1006/gyno.1997.4856 PMID:9367700

Coupé VM, Berkhof J, Verheijen RH, Meijer CJ (2007). Cost-effectiveness of human papillomavirus testing after treatment for cervical intraepithelial neoplasia. BJOG. 114(4):416–24. http://dx.doi.org/10.1111/j.1471-0528.2007.01265.x PMID:17378816

Cox JT (2005). Management of women with cervical cytology interpreted as ASC-US or as ASC-H. Clin Obstet Gynecol. 48(1):160–77. http://dx.doi.org/10.1097/01.grf.0000151571.91814.f3 PMID:15725868

Crisp WE, Asadourian L, Romberger W (1967). Application of cryosurgery to gynecologic malignancy. Obstet Gynecol. 30(5):668–73. PMID:4167866

Cruickshank ME, Cotton SC, Sharp L, Smart L, Walker LG, Little J; TOMBOLA Group (2015). Management of women with low grade cytology: how reassuring is a normal colposcopy examination? BJOG. 122(3):380–6. http://dx.doi.org/10.1111/1471-0528.12932 PMID:24947656

Cullen TS (1900). Cancer of the uterus: its pathology, symptomatology, diagnosis, and treatment. New York, USA: Appleton.

Cullimore J (2003). The management of atypical intraepithelial glandular lesions. In: Prendiville W, Ritter J, Tatti S, Twiggs L, editors. Colposcopy: management options. Saunders; pp. 165–70.

Cullimore JE, Luesley DM, Rollason TP, Byrne P, Buckley CH, Anderson M, et al. (1992). A prospective study of conization of the cervix in the management of cervical intraepithelial glandular neoplasia (CIGN) – a preliminary report. Br J Obstet Gynaecol. 99(4):314–8. http://dx.doi.org/10.1111/j.1471-0528.1992.tb13730.x PMID:1316142

Dargent D, Burn JL, Roy M, Remi I (1994). Pregnancies following radical trachelectomy for invasive cervical cancer. Gynecol Oncol. 52:105.

Darragh TM, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD, et al.; Members of LAST Project Work Groups (2012). The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. Arch Pathol Lab Med. 136(10):1266–97. http://dx.doi.org/10.5858/arpa.LGT200570 PMID:22742517

Denny L, Prendiville W (2015). Cancer of the cervix: early detection and cost-effective solutions. Int J Gynecol Obstet. 131(Suppl 1):S28–32. http://dx.doi.org/10.1016/j.ijgo.2015.02.009 PMID:26433500

Dobbs SP, Asmussen T, Nunns D, Hollingworth J, Brown LJ, Ireland D (2000). Does histological incomplete excision of cervical intraepithelial neoplasia following large loop excision of transformation zone increase recurrence rates? A six year cytological follow up. BJOG. 107(10):1298–301. http://dx.doi.org/10.1111/j.1471-0528.2000.tb11623.x PMID:11028584

Dolman L, Sauvaget C, Muwonge R, Sankaranarayanan R (2014). Meta-analysis of the efficacy of cold coagulation as a treatment method for cervical intraepithelial neoplasia: a systematic review. BJOG. 121(8):929–42. http://dx.doi.org/10.1111/1471-0528.12655 PMID:24597779

Doorbar J (2006). Molecular biology of human papillomavirus infection and cervical cancer. Clin Sci (Lond). 110(5):525–41. http://dx.doi.org/10.1042/CS20050369 PMID:16597322

Doorbar J, Quint W, Banks L, Bravo IG, Stoler M, Broker TR, et al. (2012). The biology and life-cycle of human papillomaviruses. Vaccine. 30(Suppl 5):F55–70. http://dx.doi.org/10.1016/j.vaccine.2012.06.083 PMID:23199966

Duensing S, Münger K (2004). Mechanisms of genomic instability in human cancer: insights from studies with human papillomavirus oncoproteins. Int J Cancer. 109(2):157–62. http://dx.doi.org/10.1002/ijc.11691 PMID:14750163

Duncan ID (1983). The Semm cold coagulator in the management of cervical intraepithelial neoplasia. Clin Obstet Gynecol. 26(4):996–1006. http://dx.doi.org/10.1097/00003081-198312000-00022 PMID:6661847

Duncan I (1984). Destruction of cervical intraepithelial neoplasia at 100°C with the Semm coagulator. In: Heintz APM, Griffiths CT, Trimbos JB, editors. Surgery in gynecological oncology. The Hague, Netherlands: Martinus Nijhoff Publishers; pp. 71–85. http://dx.doi.org/10.1007/978-94-009-6750-2_8

Elfgren K, Bistoletti P, Dillner L, Walboomers JM, Meijer CJ, Dillner J (1996). Conization for cervical intraepithelial neoplasia is followed by disappearance of human papillomavirus deoxyribonucleic acid and a decline in serum and cervical mucus antibodies against human papillomavirus antigens. Am J Obstet Gynecol. 174(3):937–42. http://dx.doi.org/10.1016/S0002-9378(96)70330-7 PMID:8633673

Faro S (2006). Common non-viral infections of the cervix: clinical features and management. In: Jordan JA, Singer A, editors. The cervix. Oxford, UK: Blackwell Publishing; pp. 231–43. http://dx.doi.org/10.1002/9781444312744.ch16

Fergusson IL, Craft IL (1974). A new “cold coagulator” for use in the outpatient treatment of cervical erosion. J Obstet Gynaecol Br Commonw. 81(4):324–7. http://dx.doi.org/10.1111/j.1471-0528.1974.tb00469.x PMID:4824692

Ferris DG, Litaker MS; ALTS Group (2006). Prediction of cervical histologic results using an abbreviated Reid Colposcopic Index during ALTS. Am J Obstet Gynecol. 194(3):704–10. http://dx.doi.org/10.1016/j.ajog.2005.10.204 PMID:16522401

Flannelly G, Bolger B, Fawzi H, De Lopes AB, Monaghan JM (2001). Follow up after LLETZ: could schedules be modified according to risk of recurrence? BJOG. 108(10):1025–30. http://dx.doi.org/10.1111/j.1471-0528.2001.00240.x PMID:11702832

Franco EL, Rohan TE, Villa LL (1999). Epidemiologic evidence and human papillomavirus infection as a necessary cause of cervical cancer. J Natl Cancer Inst. 91(6):506–11. http://dx.doi.org/10.1093/jnci/91.6.506 PMID:10088620

Freeman-Wang T, Walker PG (2006). The management of cervical malignancy and premalignancy in pregnancy. In: Jordan JA, Singer A, editors. The cervix. Oxford, UK: Blackwell Publishing; pp. 491–503. http://dx.doi.org/10.1002/9781444312744.ch34

Fujii S, Takakura K, Matsumura N, Higuchi T, Yura S, Mandai M, et al. (2007). Anatomic identification and functional outcomes of the nerve sparing Okabayashi radical hysterectomy. Gynecol Oncol. 107(1):4–13. http://dx.doi.org/10.1016/j.ygyno.2007.08.076 PMID:17905140

Gardeil F, Barry-Walsh C, Prendiville W, Clinch J, Turner MJ (1997). Persistent intraepithelial neoplasia after excision for cervical intraepithelial neoplasia grade III. Obstet Gynecol. 89(3):419–22. http://dx.doi.org/10.1016/S0029-7844(96)00505-4 PMID:9052597

Gemer O, Eitan R, Gdalevich M, Mamanov A, Piura B, Rabinovich A, et al. (2013). Can parametrectomy be avoided in early cervical cancer? An algorithm for the identification of patients at low risk for parametrial involvement. Eur J Surg Oncol. 39(1):76–80. http://dx.doi.org/10.1016/j.ejso.2012.10.013 PMID:23131429

Ghaem-Maghami S, De-Silva D, Tipples M, Lam S, Perryman K, Soutter W (2011). Determinants of success in treating cervical intraepithelial neoplasia. BJOG. 118(6):679–84. http://dx.doi.org/10.1111/j.1471-0528.2010.02770.x PMID:21083861

Ghaem-Maghami S, Sagi S, Majeed G, Soutter WP (2007). Incomplete excision of cervical intraepithelial neoplasia and risk of treatment failure: a meta-analysis. Lancet Oncol. 8(11):985–93. http://dx.doi.org/10.1016/S1470-2045(07)70283-8 PMID:17928267

Gök M, Coupé VM, Berkhof J, Verheijen RH, Helmerhorst TJ, Hogewoning CJ, et al. (2007). HPV16 and increased risk of recurrence after treatment for CIN. Gynecol Oncol. 104(2):273–5. http://dx.doi.org/10.1016/j.ygyno.2006.10.011 PMID:17157365

Gordon HK, Duncan ID (1991). Effective destruction of cervical intraepithelial neoplasia (CIN) 3 at 100°C using the Semm cold coagulator: 14 years experience. Br J Obstet Gynaecol. 98(1):14–20. http://dx.doi.org/10.1111/j.1471-0528.1991.tb10304.x PMID:1998626

Gortzak-Uzan L, Jimenez W, Nofech-Mozes S, Ismiil N, Khalifa MA, Dubé V, et al. (2010). Sentinel lymph node biopsy vs. pelvic lymphadenectomy in early stage cervical cancer: is it time to change the gold standard? Gynecol Oncol. 116(1):28–32. http://dx.doi.org/10.1016/j.ygyno.2009.10.049 PMID:19875161

Green J, Kirwan J, Tierney J, Vale C, Symonds P, Fresco L, et al. (2005). Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix. Cochrane Database Syst Rev. 3:CD002225. PMID:16034873

Haddad NG, Hussein IY, Blessing K, Kerr-Wilson R, Smart GE (1988). Tissue destruction following cold coagulation of the cervix. Colposcopy Gynecol Laser Surg. 4(1):23–7. http://dx.doi.org/10.1089/gyn.1988.4.23

Hammes LS, Naud P, Passos EP, Matos J, Brouwers K, Rivoire W, et al. (2007). Value of the International Federation for Cervical Pathology and Colposcopy (IFCPC) Terminology in predicting cervical disease. J Low Genit Tract Dis. 11(3):158–65. http://dx.doi.org/10.1097/01.lgt.0000265778.36797.03 PMID:17596761

Hatch KD, Shingleton HM, Austin JM Jr, Soong SJ, Bradley DH (1981). Cryosurgery of cervical intraepithelial neoplasia. Obstet Gynecol. 57(6):692–8. PMID:7231822

Hicks DA (2002). Colposcopy in the setting of a genitourinary clinic. In: Luesley DM, Shafi MI, Jordan JA, editors. Handbook of colposcopy. 2nd ed. London, UK: Hodder Arnold; pp. 138–46.

Houfflin Debarge V, Collinet P, Vinatier D, Ego A, Dewilde A, Boman F, et al. (2003). Value of human papillomavirus testing after conization by loop electrosurgical excision for high-grade squamous intraepithelial lesions. Gynecol Oncol. 90(3):587–92. http://dx.doi.org/10.1016/S0090-8258(03)00372-X PMID:13678729

Howe DT, Vincenti AC (1991). Is large loop excision of the transformation zone (LLETZ) more accurate than colposcopically directed punch biopsy in the diagnosis of cervical intraepithelial neoplasia? Br J Obstet Gynaecol. 98(6):588–91. http://dx.doi.org/10.1111/j.1471-0528.1991.tb10376.x PMID:1651758

IARC (2005). Cervix cancer screening. IARC Handb Cancer Prev. 10:1–302. Available from: http://publications.iarc.fr/380.

IARC (2007). Human papillomaviruses. IARC Monogr Eval Carcinog Risks Hum. 90:1–636. PMID:18354839. Available from: http://publications.iarc.fr/108.

Ikenberg H, Bergeron C, Schmidt D, Griesser H, Alameda F, Angeloni C, et al.; PALMS Study Group (2013). Screening for cervical cancer precursors with p16/Ki-67 dual-stained cytology: results of the PALMS study. J Natl Cancer Inst. 105(20):1550–7. http://dx.doi.org/10.1093/jnci/djt235 PMID:24096620

Jain S, Tseng CJ, Horng SG, Soong YK, Pao CC (2001). Negative predictive value of human papillomavirus test following conization of the cervix uteri. Gynecol Oncol. 82(1):177–80. http://dx.doi.org/10.1006/gyno.2001.6241 PMID:11426982

Jarruwale P, Huang K-G, Benavides DR, Su H, Lee C-L (2013). Nerve-sparing radical hysterectomy in cervical cancer. Gynecol Minim Invasive Ther. 2(2):42–7. http://dx.doi.org/10.1016/j.gmit.2013.02.003

Jeronimo J, Schiffman M (2006). Colposcopy at a crossroads. Am J Obstet Gynecol. 195(2):349–53. http://dx.doi.org/10.1016/j.ajog.2006.01.091 PMID:16677597

Jones JM, Sweetnam P, Hibbard BM (1979). The outcome of pregnancy after cone biopsy of the cervix: a case-control study. Br J Obstet Gynaecol. 86(12):913–6. http://dx.doi.org/10.1111/j.1471-0528.1979.tb11237.x PMID:575050

Jordan JA, Singer A, editors (2006). The cervix. Oxford, UK: Blackwell Publishing. http://dx.doi.org/10.1002/9781444312744

Kalliala I, Anttila A, Pukkala E, Nieminen P (2005). Risk of cervical and other cancers after treatment of cervical intraepithelial neoplasia: retrospective cohort study. BMJ. 331(7526):1183–5. http://dx.doi.org/10.1136/bmj.38663.459039.7C PMID:16293840

Kalliala I, Nieminen P, Dyba T, Pukkala E, Anttila A (2007). Cancer free survival after CIN treatment: comparisons of treatment methods and histology. Gynecol Oncol. 105(1):228–33. http://dx.doi.org/10.1016/j.ygyno.2006.12.028 PMID:17289128

Katki HA, Kinney WK, Fetterman B, Lorey T, Poitras NE, Cheung L, et al. (2011). Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: a population-based study in routine clinical practice. Lancet Oncol. 12(7):663–72. http://dx.doi.org/10.1016/S1470-2045(11)70145-0 PMID:21684207

Kelly RS, Walker P, Kitchener H, Moss SM (2012). Incidence of cervical intraepithelial neoplasia grade 2 or worse in colposcopy-negative/human papillomavirus-positive women with low-grade cytological abnormalities. BJOG. 119(1):20–5. http://dx.doi.org/10.1111/j.1471-0528.2011.02970.x PMID:21624034

Khalid S, Carcopino X, Michail G, Metchette S, Conroy R, Prendiville W (2011). Compliance with follow up cytology after discharge from the colposcopy clinic. Ir Med J. 104(6):167–70. PMID:22111391

Khalid S, Dimitriou E, Conroy R, Paraskevaidis E, Kyrgiou M, Harrity C, et al. (2012). The thickness and volume of LLETZ specimens can predict the relative risk of pregnancy-related morbidity. BJOG. 119(6):685–91. http://dx.doi.org/10.1111/j.1471-0528.2011.03252.x PMID:22329499

Kierkegaard O, Byralsen C, Hansen KC, Frandsen KH, Frydenberg M (1995). Association between colposcopic findings and histology in cervical lesions: the significance of the size of the lesion. Gynecol Oncol. 57(1):66–71. http://dx.doi.org/10.1006/gyno.1995.1100 PMID:7705702

Kinney WK, Manos MM, Hurley LB, Ransley JE (1998). Where's the high-grade cervical neoplasia? The importance of minimally abnormal Papanicolaou diagnoses. Obstet Gynecol. 91(6):973–6. http://dx.doi.org/10.1016/S0029-7844(98)00080-5 PMID:9611007

Kocken M, Helmerhorst TJ, Berkhof J, Louwers JA, Nobbenhuis MA, Bais AG, et al. (2011). Risk of recurrent high-grade cervical intraepithelial neoplasia after successful treatment: a long-term multi-cohort study. Lancet Oncol. 12(5):441–50. http://dx.doi.org/10.1016/S1470-2045(11)70078-X PMID:21530398

Kokka F, Bryant A, Brockbank E, Powell M, Oram D (2015). Hysterectomy with radiotherapy or chemotherapy or both for women with locally advanced cervical cancer. Cochrane Database Syst Rev. 4:CD010260. PMID:25847525

Koss LG, Durfee GR (1956). Unusual patterns of squamous epithelium of the uterine cervix: cytologic and pathologic study of koilocytotic atypia. Ann N Y Acad Sci. 63(6):1245–61. http://dx.doi.org/10.1111/j.1749-6632.1956.tb32134.x PMID:13314471

Krane JF, Granter SR, Trask CE, Hogan CL, Lee KR (2001). Papanicolaou smear sensitivity for the detection of adenocarcinoma of the cervix: a study of 49 cases. Cancer. 93(1):8–15. http://dx.doi.org/10.1002/1097-0142(20010225)93:1<8::AID-CNCR9001>3.0.CO;2-K PMID:11241260

Kristensen J, Langhoff-Roos J, Kristensen FB (1993). Increased risk of preterm birth in women with cervical conization. Obstet Gynecol. 81(6):1005–8. PMID:8497340

Kurman RJ, Carcangiu ML, Herrington CS, Young RH, editors (2014). WHO Classification of Tumours of Female Reproductive Organs. Lyon, France: International Agency for Research on Cancer.

Kyrgiou M, Koliopoulos G, Martin-Hirsch P, Arbyn M, Prendiville W, Paraskevaidis E (2006). Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. Lancet. 367(9509):489–98. http://dx.doi.org/10.1016/S0140-6736(06)68181-6 PMID:16473126

Kyrgiou M, Mitra A, Arbyn M, Stasinou SM, Martin-Hirsch P, Bennett P, et al. (2014). Fertility and early pregnancy outcomes after treatment for cervical intraepithelial neoplasia: systematic review and meta-analysis. BMJ. 349:g6192. http://dx.doi.org/10.1136/bmj.g6192 PMID:25352501

Landoni F, Maneo A, Colombo A, Placa F, Milani R, Perego P, et al. (1997). Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. Lancet. 350(9077):535–40. http://dx.doi.org/10.1016/S0140-6736(97)02250-2 PMID:9284774

Landoni F, Maneo A, Zapardiel I, Zanagnolo V, Mangioni C (2012). Class I versus class III radical hysterectomy in stage IB1-IIA cervical cancer. A prospective randomized study. Eur J Surg Oncol. 38(3):203–9. http://dx.doi.org/10.1016/j.ejso.2011.12.017 PMID:22244909

LaPolla JP, O'Neill C, Wetrich D (1988). Colposcopic management of abnormal cervical cytology in pregnancy. J Reprod Med. 33(3):301–6. PMID:3361522

Larsson G (1983). Conization for preinvasive and early invasive carcinoma of the uterine cervix. Acta Obstet Gynecol Scand Suppl. 114:1–40. PMID:6574684

Lazcano-Ponce E, Lorincz AT, Cruz-Valdez A, Salmerón J, Uribe P, Velasco-Mondragón E, et al. (2011). Self-collection of vaginal specimens for human papillomavirus testing in cervical cancer prevention (MARCH): a community-based randomised controlled trial. Lancet. 378(9806):1868–73. http://dx.doi.org/10.1016/S0140-6736(11)61522-5 PMID:22051739

Lee KR, Flynn CE (2000). Early invasive adenocarcinoma of the cervix. Cancer. 89(5):1048–55. http://dx.doi.org/10.1002/1097-0142(20000901)89:5<1048::AID-CNCR14>3.0.CO;2-S PMID:10964335

Leeson SC, Alibegashvili T, Arbyn M, Bergeron C, Carriero C, Mergui JL, et al. (2014). The future role for colposcopy in Europe. J Low Genit Tract Dis. 18(1):70–8. http://dx.doi.org/10.1097/LGT.0b013e318286b899 PMID:23774077

Legood R, Smith M, Lew JB, Walker R, Moss S, Kitchener H, et al. (2012). Cost effectiveness of human papillomavirus test of cure after treatment for cervical intraepithelial neoplasia in England: economic analysis from NHS Sentinel Sites Study. BMJ. 345:e7086. http://dx.doi.org/10.1136/bmj.e7086 PMID:23117060

Lin CT, Tseng CJ, Lai CH, Hsueh S, Huang KG, Huang HJ, et al. (2001). Value of human papillomavirus deoxyribonucleic acid testing after conization in the prediction of residual disease in the subsequent hysterectomy specimen. Am J Obstet Gynecol. 184(5):940–5. http://dx.doi.org/10.1067/mob.2001.112589 PMID:11303202

Manchanda R, Baldwin P, Crawford R, Vowler SL, Moseley R, Latimer J, et al. (2008). Effect of margin status on cervical intraepithelial neoplasia recurrence following LLETZ in women over 50 years. BJOG. 115(10):1238–42. http://dx.doi.org/10.1111/j.1471-0528.2008.01853.x PMID:18715408

Marsden DE, Hacker NF, Edwards L (2006). The management of microinvasive carcinoma of the cervix. In: Jordan JA, Singer A, editors. The cervix. Oxford, UK: Blackwell Publishing; pp. 531–50. http://dx.doi.org/10.1002/9781444312744.ch37

Martin-Hirsch PP, Paraskevaidis E, Bryant A, Dickinson HO (2013). Surgery for cervical intraepithelial neoplasia. Cochrane Database Syst Rev. 12:CD001318. PMID:24302546

Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, et al.; 2012 ASCCP Consensus Guidelines Conference (2013). 2012 Updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis. 17(5 Suppl 1):S1–27. http://dx.doi.org/10.1097/LGT.0b013e318287d329 PMID:23519301

Mayeaux EJ, Cox JT (2011). Modern colposcopy: textbook and atlas. 3rd ed. Wolters Kluwer.

McCredie MR, Sharples KJ, Paul C, Baranyai J, Medley G, Jones RW, et al. (2008). Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. Lancet Oncol. 9(5):425–34. http://dx.doi.org/10.1016/S1470-2045(08)70103-7 PMID:18407790

Meigs JV (1951). Radical hysterectomy with bilateral pelvic lymph node dissections; a report of 100 patients operated on five or more years ago. Am J Obstet Gynecol. 62(4):854–70. PMID:14885271

Meisels A, Fortin R (1976). Condylomatous lesions of the cervix and vagina. I. Cytologic patterns. Acta Cytol. 20(6):505–9. PMID:1069445

Melnikow J, Nuovo J, Willan AR, Chan BK, Howell LP (1998). Natural history of cervical squamous intraepithelial lesions: a meta-analysis. Obstet Gynecol. 92(4 Pt 2):727–35. http://dx.doi.org/10.1016/S0029-7844(98)00245-2 PMID:9764690

Mergui JL, Carcopino X, Marchetta J, Gondry J, Boubli L (2010). Modern management of cervical intraepithelial neoplasia: a proposal for a risk assessment method in colposcopic decision-making [in French]. J Gynecol Obstet Biol Reprod (Paris). 39(7):520–8. http://dx.doi.org/10.1016/j.jgyn.2010.08.002 PMID:20926205

Miller AB (1993). Cervical cancer screening programmes: managerial guidelines. Geneva, Switzerland: World Health Organization. Available from: http://apps.who.int/iris/handle/10665/39478.

Mitra S (1959). Extraperitoneal lymphadenectomy and radical vaginal hysterectomy for cancer of the cervix (Mitra technique). Am J Obstet Gynecol. 78(1):191–6.

Mohamed-Noor K, Quinn MA, Tan J (1997). Outcomes after cervical cold knife conization with complete and incomplete excision of abnormal epithelium: a review of 699 cases. Gynecol Oncol. 67(1):34–8. http://dx.doi.org/10.1006/gyno.1997.4817 PMID:9345353

Monaghan JM (1995). Laser vaporization and excisional techniques in the treatment of cervical intraepithelial neoplasia. Baillieres Clin Obstet Gynaecol. 9(1):173–87. http://dx.doi.org/10.1016/S0950-3552(05)80365-7 PMID:7600726

Moscicki AB, Ma Y, Wibbelsman C, Darragh TM, Powers A, Farhat S, et al. (2010). Rate of and risks for regression of cervical intraepithelial neoplasia 2 in adolescents and young women. Obstet Gynecol. 116(6):1373–80. http://dx.doi.org/10.1097/AOG.0b013e3181fe777f PMID:21099605

Nagai Y, Maehama T, Asato T, Kanazawa K (2000). Persistence of human papillomavirus infection after therapeutic conization for CIN 3: is it an alarm for disease recurrence? Gynecol Oncol. 79(2):294–9. http://dx.doi.org/10.1006/gyno.2000.5952 PMID:11063660

Nanda K, McCrory DC, Myers ER, Bastian LA, Hasselblad V, Hickey JD, et al. (2000). Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. Ann Intern Med. 132(10):810–9. http://dx.doi.org/10.7326/0003-4819-132-10-200005160-00009 PMID:10819705

Nayar R, Wilbur DC (2015). The Pap test and Bethesda 2014. “The reports of my demise have been greatly exaggerated.” (after a quotation from Mark Twain). Acta Cytol. 59(2):121–32. http://dx.doi.org/10.1159/000381842 PMID:25997404

Nene BM, Hiremath PS, Kane S, Fayette JM, Shastri SS, Sankaranarayanan R (2008). Effectiveness, safety, and acceptability of cryotherapy by midwives for cervical intraepithelial neoplasia in Maharashtra, India. Int J Gynecol Obstet. 103(3):232–6. http://dx.doi.org/10.1016/j.ijgo.2008.07.016 PMID:18817909

Nezhat CR, Burrell MO, Nezhat FR, Benigno BB, Welander CE (1992). Laparoscopic radical hysterectomy with paraaortic and pelvic node dissection. Am J Obstet Gynecol. 166(3):864–5. http://dx.doi.org/10.1016/0002-9378(92)91351-A PMID:1532291

NHS (2004). Colposcopy and programme management: guidelines for the NHS Cervical Screening Programme. NHSCSP Publication No. 20, April 2004. Sheffield, UK: NHS Cancer Screening Programmes.

NHS (2010). Colposcopy and programme management: guidelines for the NHS Cervical Screening Programme. NHSCSP Publication No. 20, Second Edition, May 2010. Sheffield, UK: NHS Cancer Screening Programmes.

NHS (2016). NHS Cervical Screening Programme: colposcopy and programme management. NHSCSP Publication No. 20, Third Edition, March 2016. London, UK: Public Health England. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/515817/NHSCSP_colposcopy_management.pdf.

Nicklin JL, Wright RG, Bell JR, Samaratunga H, Cox NC, Ward BG (1991). A clinicopathological study of adenocarcinoma in situ of the cervix. The influence of cervical HPV infection and other factors, and the role of conservative surgery. Aust N Z J Obstet Gynaecol. 31(2):179–83. http://dx.doi.org/10.1111/j.1479-828X.1991.tb01814.x PMID:1656927

Nobbenhuis MA, Meijer CJ, van den Brule AJ, Rozendaal L, Voorhorst FJ, Risse EK, et al. (2001). Addition of high-risk HPV testing improves the current guidelines on follow-up after treatment for cervical intraepithelial neoplasia. Br J Cancer. 84(6):796–801. http://dx.doi.org/10.1054/bjoc.2000.1689 PMID:11259094

Ostör AG (1993). Natural history of cervical intraepithelial neoplasia: a critical review. Int J Gynecol Pathol. 12(2):186–92. http://dx.doi.org/10.1097/00004347-199304000-00018 PMID:8463044

Palle C, Bangsbøll S, Andreasson B (2000). Cervical intraepithelial neoplasia in pregnancy. Acta Obstet Gynecol Scand. 79(4):306–10. http://dx.doi.org/10.1034/j.1600-0412.2000.079004306.x PMID:10746847

Paraskevaidis E, Koliopoulos G, Alamanos Y, Malamou-Mitsi V, Lolis ED, Kitchener HC (2001b). Human papillomavirus testing and the outcome of treatment for cervical intraepithelial neoplasia. Obstet Gynecol. 98(5 Pt 1):833–6. PMID:11704177

Paraskevaidis E, Koliopoulos G, Kalantaridou S, Pappa L, Navrozoglou I, Zikopoulos K, et al. (2002). Management and evolution of cervical intraepithelial neoplasia during pregnancy and postpartum. Eur J Obstet Gynecol Reprod Biol. 104(1):67–9. PMID:12128266

Paraskevaidis E, Koliopoulos G, Paschopoulos M, Stefanidis K, Navrozoglou I, Lolis D (2001a). Effects of ball cauterization following loop excision and follow-up colposcopy. Obstet Gynecol. 97(4):617–20. http://dx.doi.org/10.1016/S0029-7844(00)01194-7 PMID:11275038

Pareja R, Rendón GJ, Sanz-Lomana CM, Monzón O, Ramirez PT (2013). Surgical, oncological, and obstetrical outcomes after abdominal radical trachelectomy - a systematic literature review. Gynecol Oncol. 131(1):77–82. http://dx.doi.org/10.1016/j.ygyno.2013.06.010 PMID:23769758

Parham GP, Mwanahamuntu MH, Kapambwe S, Muwonge R, Bateman AC, Blevins M, et al. (2015). Population-level scale-up of cervical cancer prevention services in a low-resource setting: development, implementation, and evaluation of the cervical cancer prevention program in Zambia. PLoS One. 10(4):e0122169. http://dx.doi.org/10.1371/journal.pone.0122169 PMID:25885821

Peto J, Gilham C, Fletcher O, Matthews FE (2004). The cervical cancer epidemic that screening has prevented in the UK. Lancet. 364(9430):249–56. http://dx.doi.org/10.1016/S0140-6736(04)16674-9 PMID:15262102

Pisal NV, Sindos M, Desai S, Mansell E, Singer A (2003). How significant is a cervical smear showing glandular dyskaryosis? Eur J Obstet Gynecol Reprod Biol. 108(2):209–12. http://dx.doi.org/10.1016/S0301-2115(02)00466-9 PMID:12781413

Piver MS, Rutledge F, Smith JP (1974). Five classes of extended hysterectomy for women with cervical cancer. Obstet Gynecol. 44(2):265–72. PMID:4417035

Plante M, Renaud MC, François H, Roy M (2004). Vaginal radical trachelectomy: an oncologically safe fertility-preserving surgery. An updated series of 72 cases and review of the literature. Gynecol Oncol. 94(3):614–23. http://dx.doi.org/10.1016/j.ygyno.2004.05.032 PMID:15350349

Popkin DR, Scali V, Ahmed MN (1978). Cryosurgery for the treatment of cervical intraepithelial neoplasia. Am J Obstet Gynecol. 130(5):551–4. PMID:629310

Prendiville W, Cullimore J, Norman S (1989). Large loop excision of the transformation zone (LLETZ). A new method of management for women with cervical intraepithelial neoplasia. Br J Obstet Gynaecol. 96(9):1054–60. http://dx.doi.org/10.1111/j.1471-0528.1989.tb03380.x PMID:2804007

Prendiville W, Davies R, Berry PJ (1986). A low voltage diathermy loop for taking cervical biopsies: a qualitative comparison with punch biopsy forceps. Br J Obstet Gynaecol. 93(7):773–6. http://dx.doi.org/10.1111/j.1471-0528.1986.tb07980.x PMID:3730349

Pretorius RG, Belinson JL, Burchette RJ, Hu S, Zhang X, Qiao YL (2011). Regardless of skill, performing more biopsies increases the sensitivity of colposcopy. J Low Genit Tract Dis. 15(3):180–8. http://dx.doi.org/10.1097/LGT.0b013e3181fb4547 PMID:21436729

Pretorius RG, Zhang WH, Belinson JL, Huang MN, Wu LY, Zhang X, et al. (2004). Colposcopically directed biopsy, random cervical biopsy, and endocervical curettage in the diagnosis of cervical intraepithelial neoplasia II or worse. Am J Obstet Gynecol. 191(2):430–4. http://dx.doi.org/10.1016/j.ajog.2004.02.065 PMID:15343217

Querleu D, Leblanc E, Castelain B (1991). Laparoscopic pelvic lymphadenectomy in the staging of early carcinoma of the cervix. Am J Obstet Gynecol. 164(2):579–81. http://dx.doi.org/10.1016/S0002-9378(11)80025-6 PMID:1825150

Querleu D, Morrow CP (2008). Classification of radical hysterectomy. Lancet Oncol. 9(3):297–303. http://dx.doi.org/10.1016/S1470-2045(08)70074-3 PMID:18308255

Reade CJ, Eiriksson LR, Covens A (2013). Surgery for early stage cervical cancer: how radical should it be? Gynecol Oncol. 131(1):222–30. http://dx.doi.org/10.1016/j.ygyno.2013.07.078 PMID:23863357

Reagan JW, Hicks DJ (1953). A study of in situ and squamous-cell cancer of the uterine cervix. Cancer. 6(6):1200–14. http://dx.doi.org/10.1002/1097-0142(195311)6:6<1200::AID-CNCR2820060614>3.0.CO;2-8 PMID:13106837

Reid R, Scalzi P (1985). Genital warts and cervical cancer. VII. An improved colposcopic index for differentiating benign papillomaviral infections from high-grade cervical intraepithelial neoplasia. Am J Obstet Gynecol. 153(6):611–8. http://dx.doi.org/10.1016/S0002-9378(85)80244-1 PMID:2998190

Ricci C, Martin M, Neenman K, Prendiville W (2015). Management of patients with cytological low grade or borderline abnormalities: how powerful is a negative colposcopy? Oral presentation, EUROGIN, Seville, Spain.

Richart RM (1968). Natural history of cervical intra epithelial neoplasia. Clin Obstet Gynecol. 5:748–84.

Richart RM (1990). A modified terminology for cervical intraepithelial neoplasia. Obstet Gynecol. 75(1):131–3. PMID:2296409

Robinson WR, Webb S, Tirpack J, Degefu S, O'Quinn AG (1997). Management of cervical intraepithelial neoplasia during pregnancy with LOOP excision. Gynecol Oncol. 64(1):153–5. http://dx.doi.org/10.1006/gyno.1996.4546 PMID:8995565

Roman LD, Morris M, Eifel PJ, Burke TW, Gershenson DM, Wharton JT (1992). Reasons for inappropriate simple hysterectomy in the presence of invasive cancer of the cervix. Obstet Gynecol. 79(4):485–9. PMID:1553163

Ronco G, Dillner J, Elfström KM, Tunesi S, Snijders PJ, Arbyn M, et al.; International HPV screening working group (2014). Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet. 383(9916):524–32. http://dx.doi.org/10.1016/S0140-6736(13)62218-7 PMID:24192252

Rubin IC (1910). The pathological diagnosis of incipient carcinoma of the cervix. Am J Obstet Gynecol. 62:668–76.

Rubio CA, Thomassen P (1976). A critical evaluation of the Schiller test in patients before conization. Am J Obstet Gynecol. 125(1):96–9. PMID:775993

Salani R, Puri I, Bristow RE (2009). Adenocarcinoma in situ of the uterine cervix: a metaanalysis of 1278 patients evaluating the predictive value of conization margin status. Am J Obstet Gynecol. 200(2):182.e1–5. http://dx.doi.org/10.1016/j.ajog.2008.09.012 PMID:19019325

Sankaranarayanan R, Esmy PO, Rajkumar R, Muwonge R, Swaminathan R, Shanthakumari S, et al. (2007). Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster-randomised trial. Lancet. 370(9585):398–406. http://dx.doi.org/10.1016/S0140-6736(07)61195-7 PMID:17679017

Sankaranarayanan R, Nene BM, Shastri SS, Jayant K, Muwonge R, Budukh AM, et al. (2009). HPV screening for cervical cancer in rural India. N Engl J Med. 360(14):1385–94. http://dx.doi.org/10.1056/NEJMoa0808516 PMID:19339719

Sasieni P, Adams J, Cuzick J (2003). Benefit of cervical screening at different ages: evidence from the UK audit of screening histories. Br J Cancer. 89(1):88–93. http://dx.doi.org/10.1038/sj.bjc.6600974 PMID:12838306

Sauvaget C, Fayette JM, Muwonge R, Wesley R, Sankaranarayanan R (2011). Accuracy of visual inspection with acetic acid for cervical cancer screening. Int J Gynecol Obstet. 113(1):14–24. http://dx.doi.org/10.1016/j.ijgo.2010.10.012 PMID:21257169

Sauvaget C, Muwonge R, Sankaranarayanan R (2013). Meta-analysis of the effectiveness of cryotherapy in the treatment of cervical intraepithelial neoplasia. Int J Gynecol Obstet. 120(3):218–23. http://dx.doi.org/10.1016/j.ijgo.2012.10.014 PMID:23265830

Sawaya GF (2005). A 21-year-old woman with atypical squamous cells of undetermined significance. JAMA. 294(17):2210–8. http://dx.doi.org/10.1001/jama.294.17.2210 PMID:16264163

Sawaya GF, Grady D, Kerlikowske K, Valleur JL, Barnabei VM, Bass K, et al. (2000). The positive predictive value of cervical smears in previously screened postmenopausal women: the Heart and Estrogen/progestin Replacement Study (HERS). Ann Intern Med. 133(12):942–50. http://dx.doi.org/10.7326/0003-4819-133-12-200012190-00009 PMID:11119395

Schantz A, Thormann L (1984). Cryosurgery for dysplasia of the uterine ectocervix. A randomized study of the efficacy of the single- and double-freeze techniques. Acta Obstet Gynecol Scand. 63(5):417–20. http://dx.doi.org/10.3109/00016348409156695 PMID:6496044

Schauta F (1908). Die erweiterte vaginale Totalexstirpation des Uterus bei Kollumkarzinom. Vienna, Leipzig: Verlag von Josef Šafář.

Scheungraber C, Glutig K, Fechtel B, Kuehne-Heid R, Duerst M, Schneider A (2009a). Inner border – a specific and significant colposcopic sign for moderate or severe dysplasia (cervical intraepithelial neoplasia 2 or 3). J Low Genit Tract Dis. 13(1):1–4. http://dx.doi.org/10.1097/LGT.0b013e31817ff92a PMID:19098598

Scheungraber C, Koenig U, Fechtel B, Kuehne-Heid R, Duerst M, Schneider A (2009b). The colposcopic feature ridge sign is associated with the presence of cervical intraepithelial neoplasia 2/3 and human papillomavirus 16 in young women. J Low Genit Tract Dis. 13(1):13–6. http://dx.doi.org/10.1097/LGT.0b013e318180438a PMID:19098601

Schiffman M, Brinton LA, Devesa SS, Fraumeni JF Jr (1996). Cervical cancer. In: Schottenfeld D, Fraumeni JF Jr, editors. Cancer epidemiology and prevention. New York, USA: Oxford University Press; pp. 1090–116.

Semm K (1966). New apparatus for the "cold-coagulation" of benign cervical lesions. Am J Obstet Gynecol. 95(7):963–6. PMID:5914130

Semple D, Saha A, Maresh M (1999). Colposcopy and treatment of cervical intra-epithelial neoplasia: are national standards achievable? Br J Obstet Gynaecol. 106(4):351–5. http://dx.doi.org/10.1111/j.1471-0528.1999.tb08273.x PMID:10426242

Shafi MI, Finn CB, Luesley DM, Jordan JA, Dunn J (1991). Lesion size and histology of atypical cervical transformation zone. Br J Obstet Gynaecol. 98(5):490–2. http://dx.doi.org/10.1111/j.1471-0528.1991.tb10349.x PMID:2059601

Shafi MI, Jordan JA, Singer A (2006). The management of cervical intraepithelial neoplasia (squamous). In: Jordan JA, Singer A, editors. The cervix. Oxford, UK: Blackwell Publishing; pp. 462–77. http://dx.doi.org/10.1002/9781444312744.ch31

Shaw E, Sellors J, Kaczorowski J (2003). Prospective evaluation of colposcopic features in predicting cervical intraepithelial neoplasia: degree of acetowhite change most important. J Low Genit Tract Dis. 7(1):6–10. http://dx.doi.org/10.1097/00128360-200301000-00003 PMID:17051037

Shrivastava S, Mahantshetty U, Engineer R, Tongaonkar H, Kulkarni J, Dinshaw K (2013). Treatment and outcome in cancer cervix patients treated between 1979 and 1994: a single institutional experience. J Cancer Res Ther. 9(4):672–9. http://dx.doi.org/10.4103/0973-1482.126480 PMID:24518716

Siegler E, Amit A, Lavie O, Auslender R, Mackuli L, Weissman A (2014). Cervical intraepithelial neoplasia 2, 3 in pregnancy: time to consider loop cone excision in the first trimester of pregnancy? J Low Genit Tract Dis. 18(2):162–8. http://dx.doi.org/10.1097/LGT.0b013e318299c0af PMID:23994950

Smith JS, Green J, Berrington de Gonzalez A, Appleby P, Peto J, Plummer M, et al. (2003). Cervical cancer and use of hormonal contraceptives: a systematic review. Lancet. 361(9364):1159–67. http://dx.doi.org/10.1016/S0140-6736(03)12949-2 PMID:12686037

Solomon D (1989). The 1988 Bethesda System for reporting cervical/vaginal cytologic diagnoses: developed and approved at the National Cancer Institute workshop in Bethesda, MD, December 12–13, 1988. Diagn Cytopathol. 5(3):331–4. http://dx.doi.org/10.1002/dc.2840050318 PMID:2791840

Song Y, Zhao YQ, Zhang X, Liu XY, Li L, Pan QJ, et al. (2015). Random biopsy in colposcopy-negative quadrant is not effective in women with positive colposcopy in practice. Cancer Epidemiol. 39(2):237–41. http://dx.doi.org/10.1016/j.canep.2015.01.008 PMID:25684646

Soutter WP (1994). Management of women with mild dyskaryosis. Immediate referral to colposcopy is safer. BMJ. 309(6954):591–2. http://dx.doi.org/10.1136/bmj.309.6954.591 PMID:8086951

Soutter WP, de Barros Lopes A, Fletcher A, Monaghan JM, Duncan ID, Paraskevaidis E, et al. (1997). Invasive cervical cancer after conservative therapy for cervical intraepithelial neoplasia. Lancet. 349(9057):978–80. http://dx.doi.org/10.1016/S0140-6736(96)08295-5 PMID:9100623

Soutter WP, Hanoch J, D'Arcy T, Dina R, McIndoe GA, DeSouza NM (2004). Pretreatment tumour volume measurement on high-resolution magnetic resonance imaging as a predictor of survival in cervical cancer. BJOG. 111(7):741–7. http://dx.doi.org/10.1111/j.1471-0528.2004.00172.x PMID:15198766

Soutter WP, Sasieni P, Panoskaltsis T (2006). Long-term risk of invasive cervical cancer after treatment of squamous cervical intraepithelial neoplasia. Int J Cancer. 118(8):2048–55. http://dx.doi.org/10.1002/ijc.21604 PMID:16284947

Spaulding EH (1968). Chemical disinfection of medical and surgical materials. In: Lawrence C, Block SS, editors. Disinfection, sterilization, and preservation. Philadelphia (PA), USA: Lea & Febiger; pp. 517–31.

Strander B, Adolfsson J (2014). Safety of modern treatment for cervical pre-cancer. BMJ. 349:g6611. http://dx.doi.org/10.1136/bmj.g6611 PMID:25378385

Strander B, Andersson-Ellström A, Milsom I, Sparén P (2007). Long term risk of invasive cancer after treatment for cervical intraepithelial neoplasia grade 3: population based cohort study. BMJ. 335(7629):1077. http://dx.doi.org/10.1136/bmj.39363.471806.BE PMID:17959735

Strander B, Ellström-Andersson A, Franzén S, Milsom I, Rådberg T (2005). The performance of a new scoring system for colposcopy in detecting high-grade dysplasia in the uterine cervix. Acta Obstet Gynecol Scand. 84(10):1013–7. http://dx.doi.org/10.1111/j.0001-6349.2005.00895.x PMID:16167921

Teshima S, Shimosato Y, Kishi K, Kasamatsu T, Ohmi K, Uei Y (1985). Early stage adenocarcinoma of the uterine cervix. Histopathologic analysis with consideration of histogenesis. Cancer. 56(1):167–72. http://dx.doi.org/10.1002/1097-0142(19850701)56:1<167::AID-CNCR2820560126>3.0.CO;2-T PMID:4005786

Uijterwaal MH, Verhoef VM, Snijders PJ, Meijer CJ (2014). Arguments in favor of HPV testing for cervical screening and post-treatment CIN2+ monitoring. Expert Rev Mol Diagn. 14(3):245–8. http://dx.doi.org/10.1586/14737159.2014.893829 PMID:24598044

Ullal A, Roberts M, Bulmer JN, Mathers ME, Wadehra V (2009). The role of cervical cytology and colposcopy in detecting cervical glandular neoplasia. Cytopathology. 20(6):359–66. http://dx.doi.org/10.1111/j.1365-2303.2008.00566.x PMID:18557985

van de Lande J, Torrenga B, Raijmakers PG, Hoekstra OS, van Baal MW, Brölmann HA, et al. (2007). Sentinel lymph node detection in early stage uterine cervix carcinoma: a systematic review. Gynecol Oncol. 106(3):604–13. http://dx.doi.org/10.1016/j.ygyno.2007.05.010 PMID:17628644

Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. (1999). Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 189(1):12–9. http://dx.doi.org/10.1002/(SICI)1096-9896(199909)189:1<12::AID-PATH431>3.0.CO;2-F PMID:10451482

Ware RA, van Nagell JR (2010). Radical hysterectomy with pelvic lymphadenectomy: indications, technique, and complications. Obstet Gynecol Int. 2010:587610. http://dx.doi.org/10.1155/2010/587610 PMID:20871657

Wentzensen N, Walker JL, Gold MA, Smith KM, Zuna RE, Mathews C, et al. (2015). Multiple biopsies and detection of cervical cancer precursors at colposcopy. J Clin Oncol. 33(1):83–9. http://dx.doi.org/10.1200/JCO.2014.55.9948 PMID:25422481

Wertheim E (1912). The extended abdominal operation for carcinoma uteri (based on 500 operative cases). Am J Obstet Dis Women Child. 66:169–232.

WHO (2012). Cryosurgical equipment for the treatment of precancerous cervical lesions and prevention of cervical cancer. WHO technical specifications. Geneva, Switzerland: World Health Organization. Available from: http://www.who.int/reproductivehealth/publications/cancers/9789241504560/en/.

WHO (2014). Comprehensive cervical cancer control: a guide to essential practice. 2nd ed. Geneva, Switzerland: World Health Organization. Available from: http://www.who.int/reproductivehealth/publications/cancers/cervical-cancer-guide/en/.

Wiebe E, Denny L, Thomas G (2012). Cancer of the cervix uteri. Int J Gynecol Obstet. 119(Suppl 2):S100–9. http://dx.doi.org/10.1016/S0020-7292(12)60023-X PMID:22999501

Williams J (1888). Cancer of the uterus. Harvian lectures for 1886. London, UK: HK Lewis.

Wilson JMG, Jungner G (1968). Principles and practice of screening for disease. Geneva, Switzerland: World Health Organization.

Woodrow N, Permezel M, Butterfield L, Rome R, Tan J, Quinn M (1998). Abnormal cervical cytology in pregnancy: experience of 811 cases. Aust N Z J Obstet Gynaecol. 38(2):161–5. http://dx.doi.org/10.1111/j.1479-828X.1998.tb02992.x PMID:9653851

Wright TC Jr, Cox JT, Massad LS, Carlson J, Twiggs LB, Wilkinson EJ; 2001 ASCCP-sponsored Consensus Workshop (2003). 2001 Consensus guidelines for the management of women with cervical intraepithelial neoplasia. J Low Genit Tract Dis. 7(3):154–67. http://dx.doi.org/10.1097/00128360-200307000-00002 PMID:17051063

Wright VC (2010). Color atlas of colposcopy – cervix, vagina, vulva and adjacent sites. Houston (TX), USA: Biomedical Communications.

Ylitalo N, Sørensen P, Josefsson A, Frisch M, Sparén P, Pontén J, et al. (1999). Smoking and oral contraceptives as risk factors for cervical carcinoma in situ. Int J Cancer. 81(3):357–65. http://dx.doi.org/10.1002/(SICI)1097-0215(19990505)81:3<357::AID-IJC8>3.0.CO;2-1 PMID:10209949

Yoonessi M, Wieckowska W, Mariniello D, Antkowiak J (1982). Cervical intra-epithelial neoplasia in pregnancy. Int J Gynecol Obstet. 20(2):111–8. http://dx.doi.org/10.1016/0020-7292(82)90021-2 PMID:6125429

Zaino RJ (2000). Glandular lesions of the uterine cervix. Mod Pathol. 13(3):261–74. http://dx.doi.org/10.1038/modpathol.3880047 PMID:10757337

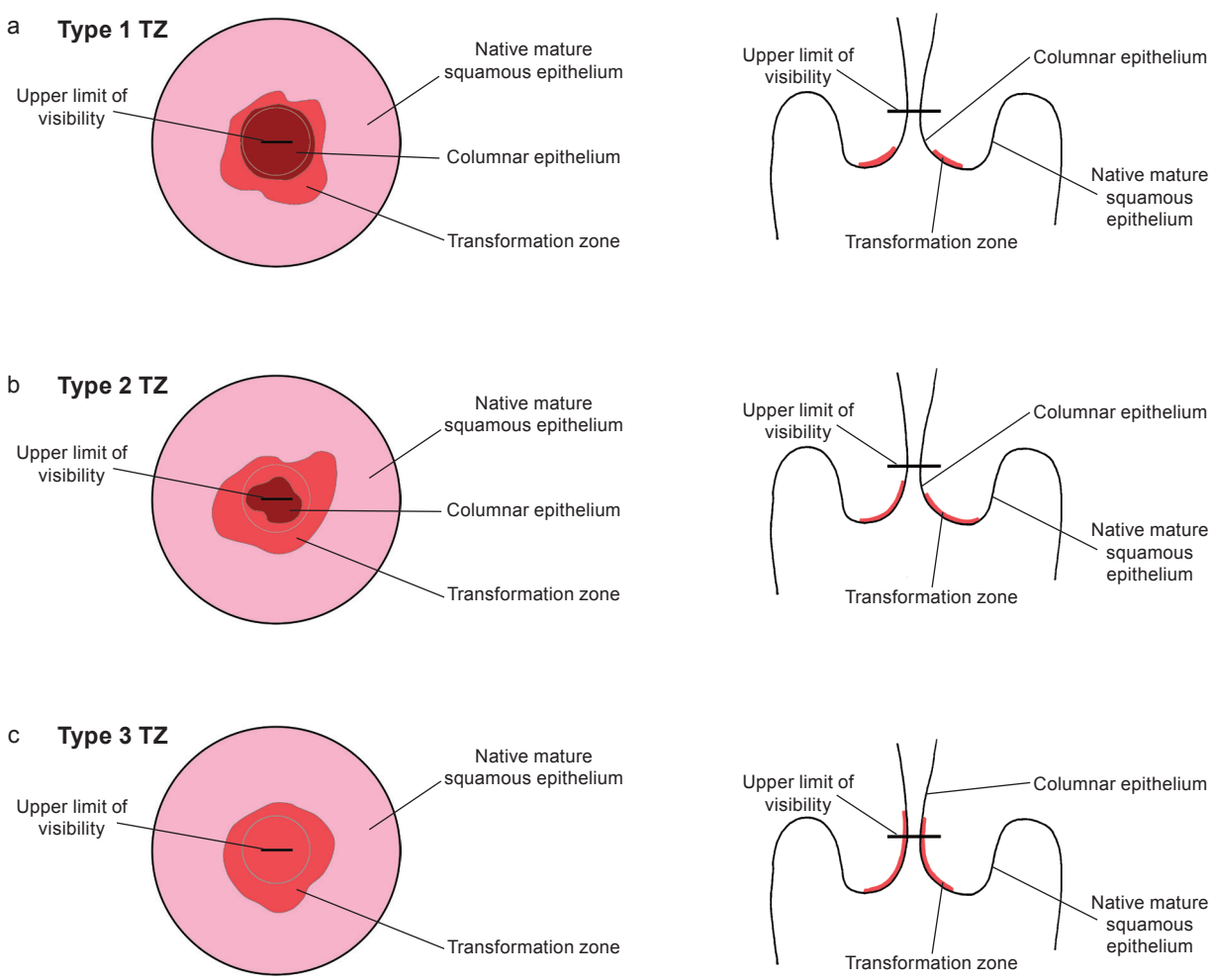
Zaino RJ (2002). Symposium part I: adenocarcinoma in situ, glandular dysplasia, and early invasive adenocarcinoma of the uterine cervix. Int J Gynecol Pathol. 21(4):314–26. http://dx.doi.org/10.1097/00004347-200210000-00002 PMID:12352181

Zielinski GD, Rozendaal L, Voorhorst FJ, Berkhof J, Snijders PJ, Risse EJ, et al. (2003). HPV testing can reduce the number of follow-up visits in women treated for cervical intraepithelial neoplasia grade 3. Gynecol Oncol. 91(1):67–73. http://dx.doi.org/10.1016/S0090-8258(03)00415-3 PMID:14529664

ANNEX 1.

Transformation zone types

Figure A1.1. Diagrammatic representations of types of transformation zone (TZ). (a) Type 1 TZ, which is completely ectocervical, is fully visible, and may be small or large. (b) Type 2 TZ, which has an endocervical component but is still fully visible; the ectocervical component may be small or large. (c) Type 3 TZ, which has an endocervical component, and the upper limit is not fully visible; the ectocervical component, if present, may be small or large.

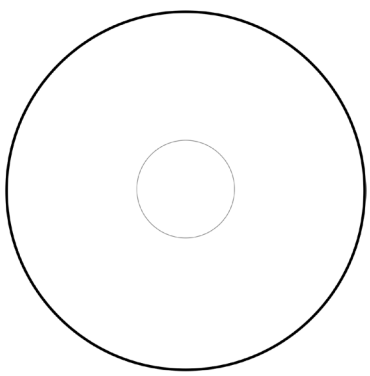


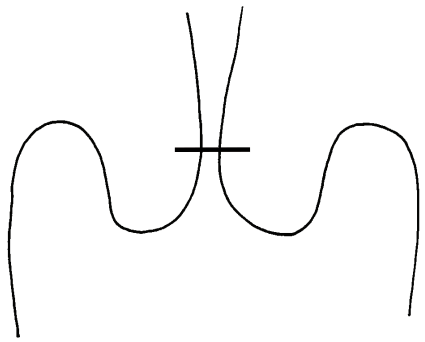
ANNEX 2.

Standard form for documenting the examination findings

Colposcopy	***Any visit***	***Date*** ___/___/___
Patient number:	_____	Screen test result:
Patient last name:	_____	_____
Patient initials:	_____	Symptoms:
Patient date of birth:	____/____/_____	_____
Patient address:	_____ _____ _____	

Colposcopic examination	
TZ classification: (1. Type 1; 2. Type 2; 3. Type 3)	
TZ size: (1. Large; 2. Small)	
Colposcopic opinion: (0. No cervix; 1. Normal; 2. HPV / Inflamm / Benign; 3. CIN/Low grade; 4. CIN/High grade; 5. Invasion; 6. Other; 7. Not performed)	
Swede score	





Management plan
_____ _____ _____ Follow-up appointment ___/___/___ Signature ……

ANNEX 3.

2011 IFCPC colposcopic terminology of the cervix

Table A3.1. 2011 IFCPC colposcopic terminology of the cervix

Section	Pattern	
General assessment	Adequate or inadequate; if inadequate, for what reason (e.g. cervix obscured by inflammation, bleeding, scar) Squamocolumnar junction visibility: completely visible, partially visible, not visible Transformation zone types 1, 2, 3	
Normal colposcopic findings	Original squamous epithelium: mature, atrophic Columnar epithelium; ectopy/ectropion Metaplastic squamous epithelium; nabothian cysts; crypt (gland) openings Deciduosis in pregnancy	
Abnormal colposcopic findings	*General principles* Location of the lesion: • Inside or outside the transformation zone • By the "clock position"	Size of the lesion: • Number of cervical quadrants the lesion covers • Size of the lesion as a percentage of the cervix
	Grade 1 (minor) • Fine mosaic; fine punctation • Thin acetowhite epithelium • Irregular, geographical border	*Grade 2 (major)* • Sharp border; inner border sign; ridge sign • Dense acetowhite epithelium • Coarse mosaic; coarse punctation • Rapid appearance of acetowhitening • Cuffed crypt (gland) openings
	Non-specific • Leukoplakia (keratosis, hyperkeratosis); erosion • Lugol's staining (Schiller test): stained or nonstained	
Suspicious for invasion	Atypical vessels Additional signs: • Fragile vessels • Irregular surface • Exophytic lesion • Necrosis • Ulceration (necrotic) • Tumour or gross neoplasm	
Miscellaneous findings	Congenital transformation zone Condyloma Polyp (ectocervical or endocervical) Inflammation	Stenosis Congenital anomaly Post-treatment consequence Endometriosis
Excision treatment types	Excision types 1, 2, 3	
Excision specimen dimensions	Length: the distance from the distal or external margin to the proximal or internal margin Thickness: the distance from the stromal margin to the surface of the excised specimen Circumference (optional): the perimeter of the excised specimen	

IFCPC, International Federation of Cervical Pathology and Colposcopy.

ANNEX 4.

The Swede score

The Swede score assigns a score of 0, 1, or 2 to each of five different characteristics. The total score ranges from 0 to a maximum of 10.

Table A4.1. The Swede score

Characteristic	Score		
	0	**1**	**2**
Uptake of acetic acid	Zero or transparent	Shady, milky (not transparent, not opaque)	Distinct, opaque white
Margins and surface	Diffuse	Sharp but irregular, jagged, “geographical”. Satellites	Sharp and even; difference in surface level, including “cuffing”
Vessels	Fine, regular	Absent	Coarse or atypical
Lesion size	< 5 mm	5–15 mm or spanning 2 quadrants	> 15 mm or spanning 3–4 quadrants, or endocervically undefined
Iodine staining	Brown	Faint or patchy yellow	Distinct yellow

ANNEX 5.

Preparation of 5% acetic acid, Lugol's iodine solution, and Monsel's paste

5% dilute acetic acid

Ingredients	*Quantity*
1. Glacial acetic acid	5 mL
2. Distilled water	95 mL

Preparation

Carefully add 5 mL of glacial acetic acid into 95 mL of distilled water and mix thoroughly.

Storage

Unused acetic acid should be discarded at the end of the day.

Label

5% dilute acetic acid

Note: It is important to remember to dilute the glacial acetic acid, because the undiluted strength causes a severe chemical burn if applied to the epithelium.

Lugol's iodine solution

Ingredients	*Quantity*
1. Potassium iodide	10 g
2. Distilled water	100 mL
3. Iodine crystals	5 g

Preparation

A. Dissolve 10 g of potassium iodide in 100 mL of distilled water.
B. Slowly add 5 g of iodine crystals, while shaking.
C. Filter and store in a tightly stoppered brown bottle.

Storage

1 month

Label

Lugol's iodine solution
Use by (date)

Monsel's paste

Ingredients	*Quantity*
1. Ferric sulfate base	15 g
2. Ferrous sulfate powder	a few grains
3. Sterile water for mixing	10 mL
4. Glycerol starch	12 g

Preparation

Take care: The reaction is exothermic (emits heat).

A. Add a few grains of ferrous sulfate powder to 10 mL of sterile water in a glass beaker. Shake.
B. Dissolve the ferric sulfate base in the solution by stirring with a glass stick. The solution should become crystal clear.
C. Weigh the glycerol starch in a glass mortar. Mix well.
D. Slowly add ferric sulfate solution to glycerol starch, constantly mixing to get a homogeneous mixture.
E. Place in a 25 mL brown glass bottle.
F. For clinical use, most clinics prefer to allow enough evaporation to give the solution a sticky, paste-like consistency that looks like mustard. This may take 2–3 weeks, depending on the environment. The top of the container can then be secured for storage. If necessary, sterile water can be added to the paste to thin it.

Note: This preparation contains 15% elemental iron.

Storage

6 months

Label

Monsel's paste
Shake well
External use only
Use by (date)

Disclosures of interests

Ms Mary Martin reports receiving personal consultancy fees from Zilico Ltd.

Professor Walter Prendiville reports benefiting from royalties from, and being named in a patent on, an endocervical conization device for excision of a tissue specimen from the uterine cervix, owned by Utah Medical Products, Inc.

Professor John Tidy reports receiving personal consultancy fees from, and holding stocks in his capacity as clinical founder of, Zilico Ltd., and being named in a patent for the electrical impedance spectroscopy (EIS) technology.

Sources

Figures

1.1 & 1.2 Walter Prendiville

1.3 a & b dos Santos Silva I (1999). Cancer epidemiology: principles and methods. Lyon: IARC. Available from: http://publications.iarc.fr/421.

1.4 Reproduced from Quinn M, Babb P, Jones J, Allen E (1999). Effect of screening on incidence of and mortality from cancer of cervix in England: evaluation based on routinely collected statistics. BMJ. 3;318(7188):904–8. https://doi.org/10.1136/bmj.318.7188.904 PMID:10102852, copyright notice 1999, with permission from BMJ Publishing Group Ltd.

1.5 Reprinted from Peto J, Gilham C, Fletcher O, Matthews FE (2004). The cervical cancer epidemic that screening has prevented in the UK. Lancet. 364(9430):249–56. http://dx.doi.org/10.1016/S0140-6736(04)16674-9 PMID:15262102, copyright 2004, with permission from Elsevier.

1.6 Walter Prendiville

1.7 Reprinted from Castle PE, Sideri M, Jeronimo J, Solomon D, Schiffman M (2007). Risk assessment to guide the prevention of cervical cancer. Am J Obstet Gynecol. 197(4):356.e1–6. http://dx.doi.org/10.1016/j.ajog.2007.07.049 PMID:17904958, copyright (2007), with permission from Elsevier.

1.8–1.11 Walter Prendiville

1.12 a–c Walter Prendiville

1.13 a Walter Prendiville **b & c** Courtesy of Quek Swee Chong

1.14 a & b Courtesy of Quek Swee Chong

1.15 & 1.16 Walter Prendiville

2.1 Lakshmi Sankaranarayanan

2.2–2.4 Sellors JW, Sankaranarayanan R (2003). Colposcopy and treatment of cervical intraepithelial neoplasia: a beginners' manual. Lyon: IARC. Available from: http://publications.iarc.fr/402.

2.5 & 2.6 Walter Prendiville

2.7 Sellors JW, Sankaranarayanan R (2003). Colposcopy and treatment of cervical intraepithelial neoplasia: a beginners' manual. Lyon: IARC. Available from: http://publications.iarc.fr/402.

2.8 & 2.9 Walter Prendiville

2.10 a & b Walter Prendiville

2.11 a & b Walter Prendiville

2.12 Prendiville W, Ritter J, Tatti SA, Twiggs LB (2003). Colposcopy: management options. Amsterdam: Elsevier Limited.

2.13 a–d Sellors JW, Sankaranarayanan R (2003). Colposcopy and treatment of cervical intraepithelial neoplasia: a beginners' manual. Lyon: IARC. Available from: http://publications.iarc.fr/402.

2.14–2.16 Walter Prendiville

2.17 a & b Sellors JW, Sankaranarayanan R (2003). Colposcopy and treatment of cervical intraepithelial neoplasia: a beginners' manual. Lyon: IARC. Available from: http://publications.iarc.fr/402.

2.18 & 2.19 Walter Prendiville

3.1 Reproduced from Darragh TM, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD, et al. (2012). The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. Arch Pathol Lab Med. 136(10):1266–97. http://dx.doi.org/10.5858/arpa.LGT200570 PMID:22742517, © 2010 College of American Pathologists.

3.2 Walter Prendiville

3.3 Reproduced, with permission, from Bergeron C, Ronco G, Reuschenbach M, Wentzensen N, Arbyn M, Stoler M, et al. (2015). The clinical impact of using p16(INK4a) immunochemistry in cervical histopathology and cytology: an update of recent developments. Int J Cancer. 136(12):2741–51. http://dx.doi.org/10.1002/ijc.28900 PMID:24740700; and Adapted from von Knebel Doeberitz M, Vinokurova S (2009). Host factors in HPV-related carcinogenesis: cellular mechanisms controlling HPV infections. Arch Med Res. 40(6):435–42. http://dx.doi.org/10.1016/j.arcmed.2009.06.002 PMID:19853183, copyright (2009), with permission from Elsevier.

3.4 a & b Courtesy of Christine Bergeron

3.5 a & b Courtesy of Christine Bergeron

3.6 a & b Courtesy of Christine Bergeron

4.1–4.4 Courtesy of Mark H. Stoler

4.5 a–c Courtesy of Mark H. Stoler

4.6 a–d Reproduced from Darragh TM, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD, et al. (2012). The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. Arch Pathol Lab Med. 136(10):1266–97. http://dx.doi.org/10.5858/arpa.LGT200570 PMID:22742517, © 2010 College of American Pathologists.

4.7 a & b Reproduced from Darragh TM, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD, et al. (2012). The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. Arch Pathol Lab Med. 136(10):1266–97. http://dx.doi.org/10.5858/arpa.LGT200570 PMID:22742517, © 2010 College of American Pathologists.

4.8 Courtesy of Christine Bergeron

4.9 Walter Prendiville

5.1–5.10 Walter Prendiville

5.11 a & b Walter Prendiville

5.12 a & b Walter Prendiville

5.13–5.18 Walter Prendiville

6.1 & 6.2 Walter Prendiville

7.1 a–c Walter Prendiville **d** Courtesy of Montserrat Cararach

7.2 a–c Walter Prendiville

7.3 a–c Walter Prendiville

7.4 a–c Reproduced, with permission, from Khalid S, Dimitriou E, Conroy R, Paraskevaidis E, Kyrgiou M, Harrity C, et al. (2012). The thickness and volume of LLETZ specimens can predict the relative risk of pregnancy-related morbidity. BJOG. 119(6):685–91. http://dx.doi.org/10.1111/j.1471-0528.2011.03252.x PMID:22329499

7.5 & 7.6 Prendiville W, Ritter J, Tatti SA, Twiggs LB (2003). Colposcopy: management options. Amsterdam: Elsevier Limited.

7.7 a–d Prendiville W, Ritter J, Tatti SA, Twiggs LB (2003). Colposcopy: management options. Amsterdam: Elsevier Limited.

7.8 a & b Walter Prendiville

7.9 Reproduced, with permission, from Khalid S, Dimitriou E, Conroy R, Paraskevaidis E, Kyrgiou M, Harrity C, et al. (2012). The thickness and volume of LLETZ specimens can predict the relative risk of pregnancy-related morbidity. BJOG. 119(6):685–91. http://dx.doi.org/10.1111/j.1471-0528.2011.03252.x PMID:22329499

7.10–7.12 Walter Prendiville

8.1 Sellors JW, Sankaranarayanan R (2003). Colposcopy and treatment of cervical intraepithelial neoplasia: a beginners' manual. Lyon: IARC. Available from: http://publications.iarc.fr/402.

8.2 Walter Prendiville

8.3 a Walter Prendiville **b** Sellors JW, Sankaranarayanan R (2003). Colposcopy and treatment of cervical intraepithelial neoplasia: a beginners' manual. Lyon: IARC. Available from: http://publications.iarc.fr/402.

8.4 Sellors JW, Sankaranarayanan R (2003). Colposcopy and treatment of cervical intraepithelial neoplasia: a beginners' manual. Lyon: IARC. Available from: http://publications.iarc.fr/402.

8.5 Line drawings by Lakshmi Sankaranarayanan; images from Atlas of Colposcopy: Principles and Practice (available from: http://screening.iarc.fr/atlascolpo.php).

8.6 Sellors JW, Sankaranarayanan R (2003). Colposcopy and treatment of cervical intraepithelial neoplasia: a beginners' manual. Lyon: IARC. Available from: http://publications.iarc.fr/402.

8.7 a–c Sellors JW, Sankaranarayanan R (2003). Colposcopy and treatment of cervical intraepithelial neoplasia: a beginners' manual. Lyon: IARC. Available from: http://publications.iarc.fr/402.

8.8 a & b Walter Prendiville

8.9 a–c Sellors JW, Sankaranarayanan R (2003). Colposcopy and treatment of cervical intraepithelial neoplasia: a beginners' manual. Lyon: IARC. Available from: http://publications.iarc.fr/402.

9.1 a & b Courtesy of David Hicks

9.2 Courtesy of David Hicks

9.3 a & b Courtesy of David Hicks

9.4 & 9.5 Courtesy of David Hicks

9.6 a & b Courtesy of David Hicks

9.7 Courtesy of David Hicks

9.8 a & b Courtesy of David Hicks

9.9 Courtesy of David Hicks

9.10–9.13 Sellors JW, Sankaranarayanan R (2003). Colposcopy and treatment of cervical intraepithelial neoplasia: a beginners' manual. Lyon: IARC. Available from: http://publications.iarc.fr/402.

9.14 & 9.15 Courtesy of David Hicks

9.16 a–d Courtesy of David Hicks

9.17 Atlas of Colposcopy: Principles and Practice (available from: http://screening.iarc.fr/atlascolpo.php).

9.18 a & b Courtesy of David Hicks

9.19 a & b Atlas of Colposcopy: Principles and Practice (available from: http://screening.iarc.fr/atlascolpo.php).

9.20 a–q Courtesy of Ramani Rajendran

10.1 a Walter Prendiville **b** Cartier R, Cartier I (1993). Practical colposcopy. 3rd ed. Paris: Laboratoire Cartier.

10.2 a Cartier R, Cartier I (1993). Practical colposcopy. 3rd ed. Paris: Laboratoire Cartier. **b–h** Walter Prendiville

10.3 a Cartier R, Cartier I (1993). Practical colposcopy. 3rd ed. Paris: Laboratoire Cartier. **b & c** Walter Prendiville **d & e** Courtesy of Quek Swee Chong **f & g** Walter Prendiville

10.4 a Cartier R, Cartier I (1993). Practical colposcopy. 3rd ed. Paris: Laboratoire Cartier. **b & c** Walter Prendiville **d** Courtesy of Quek Swee Chong **e** Republished, with permission of John Wiley & Sons, Inc., from Jordan JA, Singer A, editors (2006). The cervix. 2nd ed. Oxford: Blackwell Publishing Ltd; permission conveyed through Copyright Clearance Center, Inc.

10.5 a Courtesy of Partha Basu **b & c** Walter Prendiville **d** Reproduced, with kind permission of Goran Grubišić, from Grubišić G (2013). On development of colposcopy in Croatia: on 15th anniversary of the first Croatian colposcopic course (June 20. 1998.–June 20. 2013.). Gynaecologia et Perinatologia. 22(1):16–21. Available from: http://gynaecolperinatol.com/files/pdf/v22n1_16-21.pdf [Croatian]; and Grubišić G, Babić D. "The role of colposcopy in the early diagnosis and prevention of the preinvasive lesions of the uterine cervix and lower genital tract" for attendees of Croatian colposcopic courses from 2001 to 2014. **e–g** Walter Prendiville **h & i** Bornstein J, Bentley J, Bösze P, Girardi F, Haefner H, Menton M, et al. (2012). 2011 colposcopic terminology of the International Federation for Cervical Pathology and Colposcopy. Obstet Gynecol. 120(1):166–72. http://dx.doi.org/10.1097/AOG.0b013e318254f90c PMID:22914406 **j** Sellors JW, Sankaranarayanan R (2003). Colposcopy and treatment of cervical intraepithelial neoplasia: a beginners' manual. Lyon: IARC. Available from: http://publications.iarc.fr/402. **k–m** Walter Prendiville

11.1 Reproduced from WHO (2012). Cryosurgical equipment for the treatment of precancerous cervical lesions and prevention of cervical cancer. WHO technical specifications. Geneva: WHO; p. 7, copyright (2012). Available from: http://www.who.int/reproductivehealth/publications/cancers/9789241504560/en/.

11.2 Reproduced from WHO (2012). Cryosurgical equipment for the treatment of precancerous cervical lesions and prevention of cervical cancer. WHO technical specifications. Geneva: WHO; p. 31, copyright (2012). Available from: http://www.who.int/reproductivehealth/publications/cancers/9789241504560/en/.

11.3 a Reproduced from WHO (2012). Cryosurgical equipment for the treatment of precancerous cervical lesions and prevention of cervical cancer. WHO technical specifications. Geneva: WHO; p. 40, copyright (2012). Available from: http://www.who.int/reproductivehealth/publications/cancers/9789241504560/en/. **b & c** Courtesy of Partha Basu

11.4 Courtesy of Liger Medical

11.5 Courtesy of WISAP Medical Technology

11.6 Walter Prendiville

11.7 a & b Walter Prendiville

11.8 Walter Prendiville

11.9 a–f Prendiville W, Ritter J, Tatti SA, Twiggs LB (2003). Colposcopy: management options. Amsterdam: Elsevier Limited.

11.10 a & b Walter Prendiville

11.11–11.14 Prendiville W, Ritter J, Tatti SA, Twiggs LB (2003). Colposcopy: management options. Amsterdam: Elsevier Limited.

12.1–12.3 Courtesy of Michael Jeffers

12.4 & 12.5 Courtesy of Quek Swee Chong

12.6 & 12.7 Walter Prendiville

12.8 & 12.9 Prendiville W, Ritter J, Tatti SA, Twiggs LB (2003). Colposcopy: management options. Amsterdam: Elsevier Limited.

13.1 Walter Prendiville

13.2 a–d Courtesy of Michael Jeffers

13.3 Courtesy of Quek Swee Chong

13.4 a–g Walter Prendiville

13.5 a & b Krittika Pitaksaringkarn

13.6–13.8 Walter Prendiville

13.9 Courtesy of Quek Swee Chong

13.10 a & b Courtesy of Ramani Rajendran

13.11 a–c Sellors JW, Sankaranarayanan R (2003). Colposcopy and treatment of cervical intraepithelial neoplasia: a beginners' manual. Lyon: IARC. Available from: http://publications.iarc.fr/402.

13.12 Sellors JW, Sankaranarayanan R (2003). Colposcopy and treatment of cervical intraepithelial neoplasia: a beginners' manual. Lyon: IARC. Available from: http://publications.iarc.fr/402.

14.1 DeVita VT, Lawrence TS, Rosenberg SA, editors (2015). Devita, Hellman, and Rosenberg's cancer: principles & practice of oncology. 10th ed. Philadelphia: Wolters Kluwer.

15.1–15.3 Taken at the Cancer Institute, Chennai, India, by Rengaswamy Sankaranarayanan

15.4 Rengaswamy Sankaranarayanan

16.1 a–c Courtesy of Goran Grubišić

16.2 Reprinted from Arbyn M, Paraskevaidis E, Martin-Hirsch P, Prendiville W, Dillner J (2005). Clinical utility of HPV-DNA detection: triage of minor cervical lesions, follow-up of women treated for high-grade CIN: an update of pooled evidence. Gynecol Oncol. 99(3 Suppl 1):S7–11. http://dx.doi.org/10.1016/j.ygyno.2005.07.033 PMID:16154623, copyright (2005), with permission from Elsevier.

16.3 Adapted, with permission, from Arbyn M, Paraskevaidis E, Martin-Hirsch P, Prendiville W, Dillner J (2005). Clinical utility of HPV-DNA detection: triage of minor cervical lesions, follow-up of women treated for high-grade CIN: an update of pooled evidence. Gynecol Oncol. 99(3 Suppl 1):S7–11. http://dx.doi.org/10.1016/j.ygyno.2005.07.033 PMID:16154623, copyright (2005), with permission from Elsevier.

18.1 Courtesy of Peter J. Pronovost

18.2 Walter Prendiville

18.3 Craig Parylo; image accessed at https://commons.wikimedia.org. Licence: GNU Free Documentation License, Version 1.2 and CC-BY-SA-3.0.

18.4 & 18.5 Walter Prendiville

A1.1 a–c Walter Prendiville

Tables

1.1 Compiled from Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, et al. (2013). 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis. 17(5 Suppl 1):S1–27. http://dx.doi.org/10.1097/LGT.0b013e318287d329 PMID:23519301

1.2 Walter Prendiville

4.1 Reproduced from Darragh TM, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD, et al. (2012). The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. Arch Pathol Lab Med. 136(10):1266–97. http://dx.doi.org/10.5858/arpa.LGT200570 PMID:22742517, © 2010 College of American Pathologists.

4.2 Walter Prendiville

7.1 Walter Prendiville

9.1 Compiled from WHO (2003). Guidelines for the management of sexually transmitted infections. Geneva: WHO. Available from: http://www.who.int/hiv/pub/sti/pub6/en/.

9.2 Walter Prendiville

10.1 & 10.2 Walter Prendiville

11.1–11.7 Walter Prendiville

12.1 Compiled from Salani R, Puri I, Bristow RE (2009). Adenocarcinoma in situ of the uterine cervix: a metaanalysis of 1278 patients evaluating the predictive value of conization margin status. Am J Obstet Gynecol. 200(2):182.e1–5. http://dx.doi.org/10.1016/j.ajog.2008.09.012 PMID:19019325

13.1 Adapted with permission from Pecorelli S (2010). Corrigendum to “Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium” [Int J Gynaecol Obstet (2009) 105(2):103–4]. Int J Gynaecol Obstet. 108(2):176. http://dx.doi.org/10.1016/j.ijgo.2009.08.009, copyright (2010), with permission from Elsevier.

13.2 Walter Prendiville

13.3 Reprinted from Mutch DG (2009). The new FIGO staging system for cancers of the vulva, cervix, endometrium and sarcomas [meeting report]. Gynecol Oncol. 115(3):325–8. http://dx.doi.org/10.1016/j.ygyno.2009.10.050, copyright (2009), with permission from Elsevier.

13.4 Walter Prendiville

14.1 Adapted from Wiebe E, Denny L, Thomas G (2012). Cancer of the cervix uteri. Int J Gynaecol Obstet. 119(Suppl 2):S100–9. http://dx.doi.org/10.1016/S0020-7292(12)60023-X PMID:22999501, copyright (2012), with permission from Elsevier; and Pecorelli S (2009). Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet. 105(2):103–4. http://dx.doi.org/10.1016/j.ijgo.2009.02.012 PMID:19367689, copyright (2009), with permission from Elsevier.

14.2 Compiled from Piver MS, Rutledge F, Smith JP (1974). Five classes of extended hysterectomy for women with cervical cancer. Obstet Gynecol. 44(2):265–72. PMID:4417035; and Querleu D, Morrow CP (2008). Classification of radical hysterectomy. Lancet Oncol. 9(3):297–303. http://dx.doi.org/10.1016/S1470-2045(08)70074-3 PMID:18308255

15.1 Rengaswamy Sankaranarayanan

16.1 Public Health England (2016). NHS Cervical Screening Programme: colposcopy and programme management. 3rd ed. London: PHE Screening. NHSCSP Publication No. 20. PHE Publications Gateway No.: 2015734. Available from: https://www.gov.uk/government/publications/cervical-screening-programme-and-colposcopy-management. © Crown copyright 2016.

18.1 Walter Prendiville

18.2 Compiled from Lawrence C, Block SS, editors (1968). Disinfection, sterilization, and preservation. 1st ed. Philadelphia: Wolters Kluwer.

18.3 Rengaswamy Sankaranarayanan

A3.1 Bornstein J, Bentley J, Bösze P, Girardi F, Haefner H, Menton M, et al. (2012). 2011 colposcopic terminology of the International Federation for Cervical Pathology and Colposcopy. Obstet Gynecol. 120(1):166–72. http://dx.doi.org/10.1097/AOG.0b013e318254f90c PMID:22914406

A4.1 Republished, with permission of Wiley, from Strander B, Ellström-Andersson A, Franzén S, Milsom I, Rådberg T (2005). The performance of a new scoring system for colposcopy in detecting high-grade dysplasia in the uterine cervix. Acta Obstet Gynecol Scand. 84(10):1013–7. http://dx.doi.org/10.1111/j.0001-6349.2005.00895.x PMID:16167921; permission conveyed through Copyright Clearance Center, Inc.

Text

Section 1.5.3.1 (page 8) Text quotation reprinted from Ronco G, Dillner J, Elfström KM, Tunesi S, Snijders PJ, Arbyn M, et al. (2014). Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet. 383(9916):524–32. http://dx.doi.org/10.1016/S0140-6736(13)62218-7 PMID:24192252, copyright (2014), with permission from Elsevier.

Section 1.6.3 (page 12) Text quotation reprinted from Song Y, Zhao YQ, Zhang X, Liu XY, Li L, Pan QJ, et al. (2015). Random biopsy in colposcopy-negative quadrant is not effective in women with positive colposcopy in practice. Cancer Epidemiol. 39(2):237–41. http://dx.doi.org/10.1016/j.canep.2015.01.008 PMID:25684646, copyright (2015), with permission from Elsevier.

Section 4.2.2 (page 34) Text quotation reprinted from Ikenberg H, Bergeron C, Schmidt D, Griesser H, Alameda F, Angeloni C, et al. (2013). Screening for cervical cancer precursors with p16/Ki-67 dual-stained cytology: results of the PALMS study. J Natl Cancer Inst. 105(20):1550–7. http://dx.doi.org/10.1093/jnci/djt235 PMID:24096620, by permission of Oxford University Press.

Section 11.14 (pages 98 and 99) Text quotation reprinted from Martin-Hirsch PP, Paraskevaidis E, Bryant A, Dickinson HO, Keep SL (2010). Surgery for cervical intraepithelial neoplasia. Cochrane Database Syst Rev. (6):CD001318. http://dx.doi.org/10.1002/14651858.CD001318.pub2 PMID:20556751

Index

A

acetic acid solution 41–43, 48, 55, 62–64, 70, 78, 79, 82

acetowhitening 62–64, 68, 70, 78, 79, 82, 83, 108

adenocarcinoma 29, 81, 101, 102, 104, 112, 118, 121

adenocarcinoma in situ 81, 101, 102, 104, 133, 134

adenosquamous carcinoma 112

adequacy 9, 45, 48, 52, 56, 59, 77, 140

American Society for Colposcopy and Cervical Pathology (ASCCP) 5, 25

atypical squamous cells of undetermined significance (ASCUS) 2, 5, 8, 97

atypical surface vessels 56, 79–83, 108

atypical transformation zone 20

B

Bethesda system 25

biopsy 8–12, 26, 42, 46–48, 51, 64, 70, 72, 73, 82, 88, 98, 102, 103, 108, 109, 113, 118, 136

blended cutting waveform 92, 95

brachytherapy 123–128

branching surface vessels 61, 63

C

carcinoma in situ 23, 24

cervical glandular intraepithelial neoplasia (CGIN) 101–105

cervical intraepithelial neoplasia (CIN) 1, 2, 7, 11, 20, 23, 24, 26, 27, 31, 32, 56, 59, 60, 79–83, 85–87, 89–92, 97–99, 131–137, 144

cervical stenosis 91, 132

cervicitis 67, 68, 70–73, 140

cervicovaginitis 67, 68, 70–73

chemotherapy 126–129

coagulation waveform 92, 95

coarse mosaic 55, 80, 81, 83, 108

coarse punctation 55, 80, 81, 83, 108

cold-knife conization 87, 91, 98, 118, 120

colposcope 8, 37–39, 45, 46, 48, 145

colposcopic terminology/nomenclature 51–53, 55, 56

colposcopy record/documentation 48, 77, 78, 85

columnar epithelium 14–19, 25, 59–62, 64, 80

concurrent chemoradiotherapy (CCRT) 126–128

condyloma 56, 79, 82

congenital transformation zone 20, 21, 56, 59, 64, 82

consent 47

contraception 25, 61, 136

cryotherapy (cryosurgery, cryo) 87–90, 98

crypts 15–18, 55, 59, 61, 63, 95

D

decontamination 142–145

desiccation 93

dual testing (p16/Ki-67) 5, 32, 34

dyskaryosis 4, 5, 24, 26, 27, 101

dysplasia 4, 23–25, 60, 77, 79, 80, 82, 101–104

E

ectocervix 6, 13–17, 19, 20, 26, 48, 52, 53, 59, 64

ectopy 16, 17

ectropion 16, 17, 135

electrosurgical unit (ESU) 39, 92–94, 142, 145

endocervical curettage 14

endocervix 13–17, 19, 41, 48, 51, 52, 56, 59–63, 73, 101–104, 109, 112

excision types 52, 53, 55, 95, 97, 103, 104, 109, 110, 118

external beam radiotherapy (EBRT) 123, 124, 126–128

F

fine mosaic 55, 64, 81, 82

fine punctation 55, 64, 70, 71, 80–82

fulguration 93

G

glandular dysplasia/disease/abnormality 86, 87, 97, 101–105, 134

H

high-grade squamous intraepithelial lesion (HSIL) 1, 5, 10, 26, 27, 31, 32, 63, 79, 80, 82, 97, 101, 108, 133, 135–137

high-level disinfection (HLD) 142–144

histopathology 26

hormone replacement therapy 137

human papillomavirus (HPV) 2, 7, 8, 19, 20, 23–26, 29, 30, 32, 34, 80, 82, 85, 99, 101, 102, 105, 128, 132–134

hyperkeratosis 82

hyperplasia 17, 18, 82

hysterectomy 87, 91, 105, 115, 117, 118, 120, 121, 134, 137

I

IFCPC/IARC training programme 46

immature squamous metaplasia 18, 19, 59, 61–64, 78, 82

inflammatory lesions 67, 68, 70–73, 79

inner border sign 55, 56, 108

instruments 37, 39–43, 46–48, 94, 141–144

International Federation of Cervical Pathology and Colposcopy (IFCPC) 9, 46, 51, 52, 55, 56

International Federation of Gynecology and Obstetrics (FIGO) staging system 107, 110, 113, 116

intracavitary radiotherapy (ICR) 123–128

intrauterine contraceptive device (IUCD) 67, 136, 137

K

keratinizing squamous cell carcinoma 112

koilocytosis 24, 26, 27

L

large loop excision of the transformation zone (LLETZ) 4, 40–43, 53, 55, 86, 87, 91–99, 103, 109, 136

leopard-skin appearance 71

leukoplakia 55, 56, 82

loop electrosurgical excision procedure (LEEP) 4, 40–43, 53, 55, 86, 87, 91–99, 103

low-grade squamous intraepithelial lesion (LSIL) 8, 26, 30, 32, 82, 136

Lugol's iodine solution 14–16, 41, 43, 48, 57, 64, 71

M

mature squamous metaplasia 18, 19, 59, 63

menopause 14, 15, 60–62, 64

microinvasive carcinoma 81, 101, 107–111, 113, 118, 133

molecular biomarkers (E6, E7, E4, MCM) 29–32, 34

Monsel's paste 42, 95

N

nabothian cyst/follicle 18, 55, 59, 61, 63

needle excision of the transformation zone (NETZ) 86

neoadjuvant chemotherapy 127

new squamocolumnar junction 14, 17, 25, 60–62

non-keratinizing squamous cell carcinoma 112

O

Objective Structured Clinical Examination (OSCE) 46

oncogenesis 24, 25

oncogenic (high-risk) HPV 2, 4, 5, 7, 8, 19, 20, 23–25, 29, 30, 32, 34, 105, 131–133

original squamocolumnar junction 13, 16–20, 55, 59–61

P

polyps 15, 16, 56, 57, 61, 63, 64, 72

pregnancy 14, 16, 62, 86, 90, 92, 95–97, 121, 135, 136, 140

proliferative HPV infection 27, 31

R

radiotherapy 113, 117, 118, 120, 121, 123–129, 133, 134

Reid Colposcopic Index 78

reproductive tract infection 67, 68, 70–73, 110, 111, 140, 141

ridge sign 55, 56, 108

S

saline solution 43, 48, 59–61

Schiller test 14, 64

screening 3–8, 34, 51, 85, 96, 99, 101, 105, 108, 131–136, 139, 140

squamocolumnar junction (SCJ) 13, 14, 16–19, 21, 48, 55, 56, 59–62, 79, 82, 97, 102–104, 131

squamous epithelium 13–21, 24, 26, 55, 59–64, 71, 80

squamous metaplasia 17–21, 55, 60, 62, 63, 80

sterilization 141–144

straight wire excision of the transformation zone (SWETZ) 53, 55, 91, 98, 109

stratified, non-keratinizing squamous epithelium 14, 15

strawberry appearance 68, 70–72

Swede score 9, 48, 55, 64, 77, 78, 81, 85, 108

T

thermal coagulation 87, 90, 91, 98, 99

transformation zone (TZ) 3, 4, 6, 9, 14, 18–21, 25, 48, 51–53, 55, 56, 59–61, 64, 70, 78, 82, 85–98, 101, 103, 104, 109, 118, 131, 135–137

transformation zone types (1, 2, and 3) 20, 41, 48, 52, 53, 56, 60, 77, 85–89, 95, 97, 98, 109, 131

transforming HPV infection 24–27, 29, 31, 34, 79

U

umbilication 81

United Kingdom National Health Service (NHS) 4, 25, 99, 105, 131, 139

V

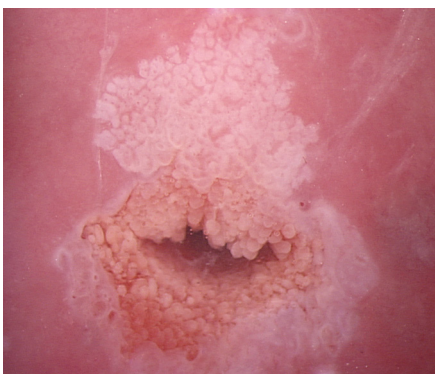
vaginal intraepithelial neoplasia 117, 137

viral proteins (E6, E7) 24, 30, 32

visual inspection with acetic acid (VIA) 2, 5, 6, 48, 55, 62–64, 70, 78, 79, 82

visual inspection with acetic acid using magnification 6

visual inspection with Lugol's iodine (VILI) 6, 14, 48, 64, 71



ISBN 978-92-832-2459-4