COLPOSCOPY AND PROGRAMME MANAGEMENT

Guidelines for the NHS Cervical Screening Programme

NHSCSP Publication No 20
April 2004

Published by:

NHS Cancer Screening Programmes
The Manor House
260 Ecclesall Road South
Sheffield S11 9PS

Tel: 0114 271 1060
Fax: 0114 271 1089
Email: nhs.screening@sheffield-ha.nhs.uk
Website: www.cancerscreening.nhs.uk

ISBN 1 84463 014 5

Further copies of this publication can be ordered from the Department of Health Publications Orderline, quoting NHSCSP Publication No 20:

Tel: 08701 555 455
Fax: 01623 724 524
Email: doh@prolog.uk.com

A copy is also available as a PDF file on the NHS Cancer Screening Programmes website.

Typeset by Prepress Projects Ltd, Perth (www.prepress-projects.co.uk)
Printed by Cambrian Printers

CONTENTS

ACKNOWLEDGEMENTS

Editors	David Luesley, Simon Leeson
Editorial group	Ian Duncan, Henry Kitchener, Julietta Patnick, Charles Redman, Peter Smith, Patrick Soutter, Patrick Walker
Contributors	Caroline Bradbeer, Maggie Cruickshank, John Cullimore, Gabrielle Downey, Paola Dey, Grainne Flannelly, Theresa Freeman-Wang, Tito Lopez, Pierre Martin-Hirsch, Antonia Moore, John Murdoch, Peter Saseini, Tracy Smith, Glyn Teale, John Tidy

1. INTRODUCTION

1.1 Evidence based guidelines

Guidelines are a means of attempting to set standards of care. By definition they are a form of guidance and are not intended to be rules for practice. Not only will new information become available, which will necessitate change, but also there will be local or regional factors that may have a strong influence on practice.

Ideally, guidelines for practice should be based on robust evidence. In this particular area of healthcare, as in most others, evidence is patchy and incomplete and there remains a heavy reliance on professional consensus. In this publication, we have attempted to use as much evidence as possible and have indicated where we have relied on consensus. These weaknesses should serve as stimuli for research to provide the evidence that may allow successive editions to become more evidence based.

1.2 How were these guidelines developed?

Two previous publications have formed the basis for practice until now: *Guidelines for Clinical Practice and Programme Management*[1] and *Standards and Quality in Colposcopy*.[2] These publications have been amalgamated and the resulting hybrid constituted the starting point. An editorial group was convened to decide upon content and structure. Areas of previous omission were identified and areas of possible duplication removed. Contributions were commissioned from individuals or groups known to be active or recently active in the field of interest. These contributors worked closely with one of the editorial team to produce an individual guideline, as evidence based as is possible. All of the reference material has been included. The guidelines also include standards that can be used for audit purposes. These standards are shown throughout the text in bold and are also summarised in Appendix 1. Prior to the final draft being formatted, a wider consensus was invited by making the penultimate draft available on the internet. These additional comments have, where possible, been included.

1.3 Objectives

Guidelines are at best transient and have a limited life span. It is also recognised that the clinical skills required to deliver high quality care in this area are very subjective and do not lend themselves easily to quantification. There is no such thing as a standard colposcopy service but, with positive guidance and commitment from those charged with delivering the service, a high quality service can be maintained and improved. This was one of the objectives.

A second and equally important goal was to ensure that the colposcopy service becomes more focused on women with abnormalities. Women who are at very low risk of developing cervical cancer should not be brought into the colposcopy service. The guidelines have been developed with the aim of ensuring that these women are either not referred to colposcopy clinics or at the very least returned to community surveillance as quickly as possible. This not only is an efficient use of resources but also recognises the possible negative health impact of unnecessary colposcopy in women who have a very low risk of developing cervical cancer.

1.4 Changes from previous guidelines

Sections have been included to address issues that have generated constant query over the last decade. Such areas include hysterectomy, contraception and the menopause, immunosuppression and human immunodeficiency virus (HIV) infection. There is also a separate section on glandular abnormalities.

The major changes in the core of the programme include a recommendation for referral after one mildly dyskaryotic sample. This might be seen as increasing the workload and thus jeopardising one of the objectives. It is important to take this particular change of practice in context. A rapid return to community based cytology surveillance is also recommended for all women who have normal colposcopy and low grade abnormalities. Taken together, it is judged that this strategy offers both safety and eventually efficiency.

The concept of linking risk to practice continues in the changes in follow-up policy that are proposed. Patients at low risk will be returned to routine recall more quickly, whereas those at high risk will be maintained on follow-up for up to 10 years after treatment.

The value of training, audit and team working has been emphasised and standards have been set. Previous standards that relate to quality in the colposcopy clinic such as changing facilities, privacy, etc. have been made more stringent. A modern colposcopy service should not only be delivered in an environment that is properly designed and equipped but also take into account the views of women. This, and some of the other changes, may have resource implications, but if healthcare is to be quality driven then this is unavoidable in some cases. This document will have a positive effect in terms of quality on the NHS Cervical Screening Programme (NHSCSP) and will lay a solid foundation for future development.

2. SCREENING PROGRAMME POLICY

2.1 Frequency of screening

2.1.1 Screening intervals

Recently published evidence has indicated that a more effective screening programme can be offered to women by changing the frequency of screening according to a woman's age.[3] The recommendations made have been accepted by the Advisory Committee on Cervical Screening and by Ministers and will be implemented in the national programme. The recommendations are as follows:

Age group (years)	Frequency of screening
25	First invitation
25–49	Three yearly
50–64	Five yearly
65+	Only screen those who have not been screened since age 50 or those who have had recent abnormal tests

Evidence: Although, the meta-analysis[4] carried out by the IARC (International Agency for Research on Cancer) would suggest that five-yearly screening is almost as effective as three-yearly screening, this has not been borne out by more recent studies from the UK.[5,6] These two studies both suggest that three-yearly screening could prevent substantially more cancers than five-yearly screening and that the cost per cancer prevented may be no greater. Evidence from the recent UK audit of screening histories[3] stresses the value of screening in middle-aged women and recommends that the frequency of screening should depend on a woman's age.

2.1.2 Maximum screening interval

Cytological screening should be undertaken at least every five years.

Evidence: Cytological screening in the UK has always been offered at least every five years, and there is no new evidence to suggest that longer intervals would be as safe. However, there was no evidence in the study[4] carried out by the IARC to suggest that six-yearly screening is any less effective than five-yearly screening.

2.1.3 Invitations for routine screening and rescreening

All letters of routine invitation should be sent to women three months before the date that the test is due, and in no case later than the test due date; ie three months before a woman's twenty-fifth birthday, 33 months after a previous test for women aged 25–49, and 57 months after the previous test for women aged 50–64.

Evidence: There is (unpublished) evidence that a delay of several months may occur between inviting women and their actual screening test.

2.1.4 *Monitoring the screening interval*

The actual screening interval should be monitored.

Evidence: Good practice. The numbers of women screened within the previous three and five years do not correspond to the number regularly screened at intervals of three and five years. As a proportion of women will be screened just once in their lifetime, or less frequently than every screening round, the number of women screened in the last 3–5 years does not necessarily correspond to the number undergoing regular screening. Estimation of the proportion of the population screened at different intervals should also be undertaken.

2.1.5 *Screening interval of less than three years*

Routine screening at intervals of less than three years should not be considered without strong evidence to support such a move.

Evidence: Screening every two years is approximately 50% more expensive than screening every three years, and there is little evidence to support such a move. The IARC meta-analysis[4] found no significant difference in the rate of cancers diagnosed 12–23 months and 24–35 months after a negative smear. A more recent UK study[6] found a small advantage of two-yearly screening in women aged under 40, but it was not sufficient to warrant the extra cost and the greater number of insignificant abnormalities that would be identified. A recent US study[7] concluded that, in well screened women, three-yearly screening would prevent virtually all cancers prevented by annual screening: an additional 70 000 smears and 4000 colposcopies are needed to prevent one extra cancer.

2.2 Age at starting screening

Recently published research and experience from the cervical screening programme have shown that screening women under the age of 25 years may do more harm than good.[3] Cervical cancer is very rare in women under 25. In 2002, five deaths from cervical cancer were registered among women aged between 15 and 24. In total, 26 cases of cervical cancer were registered. By contrast, there were 55 000 women aged 20–24 with abnormal (borderline or worse) smears.[8]

Evidence: The incidence of cervical cancer in the under 25 age group is low,[9] and the prevalence of transient human papillomavirus (HPV) infection after coitarche is high.[10] One in six smears taken in this age group is abnormal. Much of this prevalent low grade disease would resolve spontaneously if screening were started at

a later age.[11] Hence, screening in this age group would result in unnecessary attendances at colposcopy, with the resultant possible negative consequences of increased anxiety and possible overtreatment. In addition, screening has not been shown to be effective at reducing the incidence of invasive cancer in women under the age of 20[12] or indeed under the age of 25.

The evidence confirms that women aged under 25 should not be screened in the context of a national programme with computerised call and recall. Women under 25 who are concerned about their sexual health or who are at risk of developing cervical cancer should contact their GP or the local genitourinary medicine (GUM) clinic.

2.3 Age at finishing screening

In England and Wales, routine screening ends at the age of 65 years. Although it is possible that it may be safe to withdraw well screened women with a negative smear history (three consecutive negative screening smears) from the cervical screening programme at age 50 years, there is insufficient robust evidence to withdraw this level of healthcare.[13]

The effectiveness of screening women over the age of 50 years will continue to be kept under review. It is clear that screening women aged 50–64 who have had at most one or two previous smears is an extremely effective policy.[3]

Evidence: The exit age of 65 has been questioned particularly on reducing the age of screening to 50 in women who have been well screened with a satisfactory negative history. Cervical screening is less efficient at detecting cervical intraepithelial neoplasia 3 (CIN 3) in older women – more smears are required to detect a case of CIN 3 after the age of 50,[14] but it is more efficient at preventing invasive cancer.[3]

The prevalence of CIN 3 and invasive cancer in women over the age of 50 is low: 11 in 100 000 in well screened women compared with a prevalence rate of 59 in 100 000 women in the population as a whole.[15] Women who were diagnosed with invasive cancer after the age of 50 had not participated adequately in the cervical screening programme.[16] Evidence from the USA suggests that screening women over the age of 65 who have been poorly screened previously still results in a reduction in the subsequent rate of cervical cancer.[17]

Early withdrawal of women from the cervical screening programme could lead to a substantial reduction in the resources devoted to screening, which could be channelled more effectively into other aspects of healthcare. However, this is likely to increase the overall incidence of cervical cancer unless other steps are taken to compensate.[18]

HPV tests may be a useful adjunct. A combined screening test offers the possibility of greater protection and/or longer screening intervals, which could reduce the overall cost of the screening programme.[19]

No study has shown that cervical cancer rates in women aged 60–70 years would not increase dramatically if screening were only offered up to the age of 50.

2.4 Unscheduled cervical screening

Additional cervical screening is not justified in any of the following situations, providing that the woman is in the age group to be screened and has had a screening test within the previous 3–5 years:

- on taking or starting to take an oral contraceptive
- on insertion of an intrauterine contraceptive device (IUCD)
- on taking or starting to take hormone replacement therapy
- in association with pregnancy – either antenatally or postnatally or after termination unless a previous screening test was abnormal (see section 10.1.1)
- in women with genital warts
- in women with vaginal discharge
- in women with infection
- in women who have had multiple sexual partners
- in women who are heavy cigarette smokers.

In a mathematical simulation model, the practice of routinely taking a second smear one year after the first ever smear conferred no additional benefit in terms of person–years life saved.[20] This practice should not be pursued providing that the first smear was negative and it was taken in a quality controlled programme.

Evidence: There is no available evidence to suggest that social or behavioural risk factors reduce the length of the preclinical detectable phase of cervical neoplasia. The strength of the association with sociosexual correlates is insufficient to reliably predict women with high grade CIN.[21,22] More intensive screening of women with a history of multiple sexual partners and early onset of first intercourse is not cost-effective.[22]

The issue of cervical screening in HIV positive women receiving antiretroviral treatment and in chronically immunosuppressed women has not been fully evaluated and is covered elsewhere in this document.

2.5 Cervical sampling in genitourinary medicine clinics

Cervical cytology in GUM clinics should be reserved for those with a cytological indication or those who have not been screened in the previous routine screening interval (three years for women under the age of 50).

Evidence: A case–control study of women attending GUM clinics in the UK suggested that they were as likely to attend for routine screening as women in the general population.[23] Higher rates of cytological abnormality were mainly due to an excess of smears containing low grade abnormalities. This has been confirmed in a survey of UK sexually transmitted infection clinics.[24,25] Audits of cervical screening in GUM clinics suggest that a greater proportion of smears are reported as inadequate or exhibit inflammatory changes owing to the presence of infection.[26–28] A cervical smear is an inappropriate test for the detection of genital infection.[29–31]

2.6 Summary of standards

1. Cervical screening should take place between the ages of 25 and 64 years, at intervals of three or five years depending on the woman's age.

2. Women must be called on or around their 25th birthday and subsequently recalled at three-yearly intervals between the ages of 25 and 49 years, and at five-yearly intervals between the ages of 50 and 64 years.

3. SCREENING STRATEGIES

3.1 Current screening method

Cervical cytology on samples obtained using conventional smear taking techniques is the current standard method of screening in the NHS Cervical Screening Programme (NHSCSP).

Evidence: A recent systematic review[32] has reported that, in 12 studies with the least biased estimates, sensitivity ranged from 30% to 87% and specificity from 86% to 100%. This means that there is a need to identify new methods that may increase the sensitivity and specificity and hence improve performance in the detection of cancer precursors. Any change in screening modalities must show an improvement in effectiveness and/or cost-effectiveness before the NHSCSP will recommend its use.

3.2 Liquid based cytology

Liquid based cytology (LBC) is a technology whereby a Cervex® brush sample (or other broom-like device) is suspended in buffer and processed such that a thin layer of cells is produced in a slide without contamination by blood cells and debris. It achieves 'cleaner' preparations, which are generally easier to read. Its advantage is a reduction in inadequate samples and there may be gains in reducing borderline results and increasing sensitivity.

In 2000, the National Institute for Clinical Excellence (NICE) recommended that NHS funded pilot studies should be set up to evaluate the use of LBC for cervical screening in England and Wales. A pilot study in Scotland had already been completed and liquid based cytology is now being implemented there. The NICE appraisal of the pilot studies in England was published in October 2003.[33] It recommended that LBC should be introduced as the primary means of processing samples in the cervical screening programme in England and Wales. Arrangements are now being put in place to implement the recommendation in the NHSCSP. The timescale is determined by the need to train laboratory staff and primary care sample takers and to install the necessary equipment in laboratories. This will take up to five years to complete nationally.

3.3 Colposcopic screening

There are a few circumstances in which colposcopic screening should replace cytology for routine cervical screening. Certain very high risk groups of women who are at increased risk of CIN, particularly immunosuppressed women such as transplant recipients and HIV positive women, could be considered for colposcopic screening (see Chapter 11). Women whose samples are repeatedly reported as inadequate should be referred for colposcopy as part of routine screening (see Chapter 4).

Evidence: There is evidence that in HIV positive women there is an increased risk of false negative cytology[34] and colposcopic screening could be recommended. In other high risk groups, for

example women with genital warts or cigarette smokers, there is no evidence to suggest that three-yearly cervical cytology is less protective than for other women, but in HIV positive women annual screening by cytology is recommended.

3.4 Other screening strategies

Other screening strategies are being researched and the following technologies are under investigation:

- human papillomavirus (HPV) testing as a form of risk assessment
- immunoenhanced testing using antibodies to cell cycle proteins
- electro-optical technologies.

Only HPV testing is being evaluated for implementation into the NHSCSP.

3.5 HPV testing

3.5.1 HPV triage for borderline and mildly abnormal results

The potential for the introduction of HPV testing to triage women with borderline and mildly abnormal results is under investigation.

Evidence: A systematic review[35] commissioned by the Health Technology Assessment (HTA) programme recommended controlled introduction of HPV testing as a triage for women with borderline and mildly abnormal screening results. This is being assessed by means of a large pilot study in England. The rationale is that women with borderline and mildly abnormal results will be divided into those at very low risk (HPV negative) and those at higher risk (HPV positive) for whom colposcopy would be appropriate.[36] This secondary screening role for HPV testing could potentially reduce the increasing number of women being referred for colposcopy with borderline or mildly abnormal results. This could be highly cost-effective, reduce the burden on colposcopy clinics and reduce patient anxiety associated with colposcopy.

HPV testing in this setting is also being evaluated in the Medical Research Council (MRC) Trial of Management of Borderline and Other Low grade Abnormal smears (TOMBOLA), which is expected to report in 2006.

3.5.2 HPV testing for follow up of treated CIN

There is the potential for women who are both cytology negative and HPV negative at six-month follow-up to be returned to routine recall. Before this can be recommended, there needs to be evidence of successful implementation of a suitable protocol for the NHSCSP. A pilot study is in progress.

Evidence: A number of non-randomised studies have been reported which have shown that HPV testing may improve the prediction of treatment failure.[37] This is probably based on the fact that HPV testing will have a high negative predictive value for any residual disease, which is the commonest reason for treatment failure. One of the published studies controlled for margin status and HPV was still significantly associated with treatment failure.[38]

3.5.3 Population screening with HPV testing

The high sensitivity of HPV testing for detecting high grade CIN makes it a candidate for improving population cervical screening. Sensitivity with cytology alone is probably not greater than 70% and this could rise significantly with HPV testing. Randomised trials are being undertaken in Sweden and the Netherlands, neither of which has yet reported, and a randomised trial began in mid-2001 in Manchester. Non-randomised studies suggest that HPV testing will improve the detection of underlying CIN. Longer term follow-up of these screened cohorts will provide further evidence of the effectiveness of HPV testing, particularly its negative predictive value. It is likely that HPV testing will prove sufficiently cost-effective to play a role in the NHSCSP, but any introduction into the national programme requires rigorous evaluation and a convincing evidence base. HPV testing is not recommended for routine use.

4. REFERRAL GUIDELINES FOR COLPOSCOPY

4.1 Inadequate samples

Women should be referred for colposcopy after three consecutive inadequate samples.

Evidence: Professional consensus. Invasive cancers may be associated with inflammatory processes and bleed on contact. Women with persistent inadequate samples should undergo colposcopy to exclude invasive cancer.

4.2 Borderline nuclear change

4.2.1 Squamous cell changes

Women should be referred for colposcopy after three tests in a series reported as borderline nuclear change in squamous cells without the woman being returned to routine recall.

Evidence: In a randomised trial of women with an atypical squamous cells of undetermined significance (ASCUS) smear, performed in the USA, the incidence of high grade CIN after a single smear reporting borderline nuclear change was low (11%).[39] In a UK prospective series, the incidence of CIN 2/3 was 36%.[40] Women with persistent borderline nuclear change are at increased risk of developing high grade CIN over time.[41]

4.2.2 Endocervical cell changes

Women should be referred for colposcopy after one test reported as borderline nuclear change in endocervical cells.

Evidence: Case series of women with smears reported as borderline glandular cells have increased rates of malignant (4–16%) and preinvasive disease (17–40%).[42–45]

4.3 Abnormal results of any grade

Women should be referred for colposcopy if they have had three tests reported as abnormal at any grade in a 10-year period, even if returned to routine recall on one or more occasions in that period.

Evidence: Professional consensus.

4.4 Mild dyskaryosis

Ideally, women should be referred for colposcopy after one test reported as mild dyskaryosis, but it remains acceptable to recommend a repeat test. Women must be referred after two tests reported as mild dyskaryosis without a return to routine recall.

Evidence: There are no reported randomised trials triaging women to immediate colposcopy or community based cytological follow-up. A randomised trial in the hospital based management of mild dyskaryosis comparing four periods of surveillance, which included immediate colposcopy, found 68% of women with high grade CIN after a single mild or moderately dyskaryotic smear.[46] Other case series have shown the percentage of women found with high grade CIN after a mild dyskaryotic smear is about 40%.[40,47] Retrospective case series of women followed in the community report varying rates of referral to colposcopy (14–64%) and these women are at increased risk of developing invasive cancer.[48] There is a high non-attendance rate for women who are followed up for more than 24 months.[49] An economic model suggested that immediate colposcopy was cheaper that cytological follow-up.[50] Since this publication, the recommendations for cytological follow-up after a mild dyskaryotic smear have changed: three normal results are required before return to routine screening instead of two.[51] This change will make cytological surveillance more expensive and make immediate colposcopy a better option. In two studies, only 25% of women with a smear showing mild dyskaryosis achieved regression to a normal smear.[49,52]

Women with a mild dyskaryotic result should be seen and assessed but not necessarily treated. To prevent possible overtreatment, they should not be managed in a 'see and treat' scenario. There will be an initial increase in referral to colposcopy clinics as a result of this guideline but with time this should decrease.

This guideline should not alter the management of women enrolled in studies that will further improve our understanding of management of minor cytological abnormalities. The debate about this area of practice needs to be informed by the outcomes of those studies.

4.5 Moderate dyskaryosis

Women must be referred for colposcopy after one test reported as moderate dyskaryosis (**100%**).

Evidence: A randomised trial of the management of women with a moderate dyskaryotic smear found 74% of women to have CIN 2/3.[46] Case series also report a high incidence (74–77%) of CIN 2/3 at time of colposcopy.[47,53]

4.6 Severe dyskaryosis

Women must be referred for colposcopy after one test reported as severe dyskaryosis (**100%**).

Evidence: Case series report a high incidence (80–90%) of CIN 2/3 at time of colposcopy.[48,53]

4.7 Possible invasion

Women must be referred for colposcopy after one test reported as possible invasion (**100%**). They should be seen urgently within two weeks of referral (**90%**).

Evidence: The correlation between a smear showing features of invasion and the histological diagnosis of invasive cancer is high. The positive predictive value in one series was 56% for all cancers.[54]

4.8 Glandular neoplasia

Women must be referred for colposcopy after one test reported as glandular neoplasia (**100%**). They should be seen urgently within two weeks of referral (**90%**).

Evidence: The natural history of this condition remains unclear. Case series of women referred to colposcopy with a single smear reporting glandular neoplasia are associated with high levels of invasive (40–43%) and preinvasive (20–28%) disease. [42,55]

4.9 Abnormal cervix

Women with an abnormal cervix should be referred for gynaecological examination and onward referral for colposcopy if cancer is suspected.

Evidence: Professional consensus. An abnormal cervix may be associated with invasive cancer.

4.10 Women with symptoms

Women presenting with symptoms of cervical cancer, ie postcoital bleeding in women over 40 years, intermenstrual bleeding and persistent vaginal discharge, should be referred for gynaecological examination and onward referral for colposcopy if cancer is suspected.

Referral of younger women with postcoital bleeding to GUM clinics should be considered.

Contact bleeding at the time of cervical sampling may often occur and is not an indication for referral for colposcopy in the absence of other symptoms or an abnormal result.

Evidence: Professional consensus. A case series reported a high incidence of cervical neoplasia in women with postcoital bleeding.[56]

Although postcoital bleeding is a significant symptom with regard to cervical neoplasia, the majority of cases are not malignant. In younger women, chlamydial infection and problems with family planning are more likely causes. These women require appropriate assessment and referral for colposcopy if cancer is suspected.

4.11 Previous treatment for CIN

Women should be referred for colposcopy if they have been treated for CIN and have not been returned to routine recall and a subsequent test is reported as mild dyskaryosis or worse (**100%**).

Evidence: Women treated for CIN are at increased risk of developing cervical cancer.[57]

4.12 Waiting times for colposcopy

At least **90%** of women with an abnormal test result should be seen in a colposcopy clinic within eight weeks of referral.

Evidence: Professional consensus.

At least **90%** of women with a test result of moderate or severe dyskaryosis should be seen in a colposcopy clinic within four weeks of referral.

Evidence: Professional consensus.

4.13 Summary of standards

1. Women should be referred for colposcopy after three consecutive inadequate samples.
2. Women should be referred for colposcopy after three tests reported as borderline nuclear change in squamous cells in a series, without the woman being returned to routine recall.
3. Women should be referred for colposcopy after one test reported as borderline nuclear change in endocervical cells.
4. Women should be referred for colposcopy if they have had three tests reported as abnormal at any grade in a 10-year period.
5. Ideally, women should be referred for colposcopy after one test reported as mild dyskaryosis, but it remains acceptable to recommend a repeat test. Women must be referred after two tests reported as mild dyskaryosis without a return to routine recall.
6. Women must be referred for colposcopy after one test reported as moderate dyskaryosis (**100%**).
7. Women must be referred for colposcopy after one test reported as severe dyskaryosis (**100%**).
8. Women must be referred for colposcopy after one test reported as possible invasion (**100%**). They should be seen urgently within two weeks of referral (**90%**).

9. Women must be referred for colposcopy after one test reported as glandular neoplasia (**100%**). They should be seen urgently within two weeks of referral (**90%**).

10. Women should be referred for colposcopy if they have been treated for CIN and have not been returned to routine recall and a subsequent test is reported as mild dyskaryosis or worse (**100%**).

11. At least **90%** of women with an abnormal test result should be seen in a colposcopy clinic within eight weeks of referral.

12. At least **90%** of women with a test result of moderate or severe dyskaryosis should be seen in a colposcopy clinic within four weeks of referral.

5. QUALITY STANDARDS FOR COLPOSCOPY CLINICS

5.1 Good working practices

5.1.1 Quality assurance

Colposcopy should be organised as a quality assured service whatever the setting, whether in a gynaecological clinic or GUM clinic or in primary care. A protocol that gives guidance on good working practices is in Appendix 2. The colposcopy service should be run by a team, using protocols based on these guidelines, and should aim to meet the quality standards outlined in this document. Any problems arising in connection with colposcopy practice should be addressed in a confidential and supportive manner.

The team should be led by a lead colposcopist. The role of the lead colposcopist is to ensure good practice, compliance with protocols, data collection to comply with KC65 and audit. It is also a responsibility of the lead colposcopist to ensure that the quality standards in this document are attained. An example job description for lead colposcopists is shown in Appendix 3.

The attainment of quality assured colposcopy in the UK has been a considerable achievement and requires continued efforts to ensure that standards remain uniformly high. The mandatory Department of Health (DoH) return, KC65, is one task that underpins this process. This return is required quarterly but will probably become an annual return in the future. This return requires clinics to have and to maintain computerised data based on the British Society for Colposcopy and Cervical Pathology (BSCCP) minimum dataset.

A hospital based programme coordinator should be identified. He or she should take responsibility for ensuring that quality assurance targets are monitored, including non-attendance.

5.1.2 Certification

All colposcopists in the team should be certificated through the BSCCP/ Royal College of Obstetricians and Gynaecologists (RCOG) scheme and should comply with the recertification process every three years, thus indicating continued practice of a sufficient caseload. It is considered by the NHSCSP that independent colposcopy should not be conducted in the NHS unless by certificated practitioners.

It is a requirement of recertification that continued medical education (CME) is pursued by all colposcopists in order to keep abreast of scientific knowledge and clinical practice developments. Suitable CME opportunities are available from advanced colposcopy courses and the BSCCP Annual Meeting (see section 5.7).

5.1.3 Clinic staffing and facilities

The service requires at least one colposcopy nurse whose duties are to ensure smooth running of the clinic and provision of support to the patient.

A second nurse will be needed to assist in the preparation between patients for cervical sampling, biopsies and treatment (see section 5.4).

The colposcopy service requires adequate clerical and secretarial support to ensure timely communication with patients and the GP. In addition, this support is required for data collection and ensuring that failsafe mechanisms are effective.

The clinic's facilities should protect the patient's dignity, and patients should be given time to discuss their care both before and after the colposcopy examination and/or treatment.

5.1.4 Team meetings

The colposcopy team should meet at least twice a year to discuss clinic policy, any protocol problems that may have arisen and the findings of audit and peer review visits as well as comparing any shortcomings against quality standards. Multidisciplinary meetings that include cytopathology, histopathology and colposcopy staff should be held at least twice a year to discuss operational issues relevant to the colposcopy service (see section 5.6).

5.2 Reducing anxiety for women

5.2.1 Information and communication

Reducing anxiety – information and communication:

- each woman should be offered verbal information and should be sent written information before and after a cervical sampling and before colposcopy (**95%**)
- counselling must be available as an integral part of colposcopy
- women must be sent an appropriately worded invitation with a contact name, telephone number and clinic times
- information with regard to visits and results of investigations should be communicated to the patient within four weeks of her attendance (**best practice 90%**) or eight weeks (**minimum standard 100%**)
- results and management plans should be communicated to the referring practitioner within four weeks of the patient's attendance at the clinic (**best practice 90%**) or eight weeks (**minimum standard 100%**)
- information leaflets should be individualised to each clinic.

Evidence: There is compelling evidence[58–64] that many women suffer significant negative psychological effects from receiving an abnormal smear result and the need for subsequent investigation and psychological sequelae is often more likely to discourage compliance with subsequent screening and follow-up. The provision of accurate and clear information reduces anxiety and improves patients' experiences.

5.2.2 Ethnic minority groups

Culturally appropriate information should be made available for ethnic minority groups.

Evidence: Coverage is low among many ethnic minority and refugee groups. There are significant differences in awareness about cervical cancer across different ethnic groups. Providing information and visiting community centres to explain the concept of screening improves compliance.[65–67]

5.2.3 'See and treat' clinics

Clinics providing a 'see and treat' policy must ensure that women who are offered treatment at their first visit are sent adequate and appropriate information in advance of their appointment (**100%**).

Evidence: Anxiety is greater in women attending 'see and treat' clinics if they are not adequately informed of the potential for treatment at their first visit.[68–70]

5.2.4 History taking

Appropriate and sensitive enquiries regarding sexual history may be made only if there is a specific indication with regard to presentation or under the auspices of an ethically approved study.

Evidence: Questions regarding sexual history may cause embarrassment, resentment and distress to women. This may result in poor compliance if the woman feels she is being judged.[59,71]

5.2.5 Clinic facilities

With respect to clinic facilities, there must be:

- a private area with changing facilities
- toilet facilities
- a permanently sited room specifically used for colposcopy (**100%**)
- refreshments available
- separate waiting and recovery areas.

Evidence: Professional consensus and patients' opinions.

5.2.6 Visitors to the clinic

Visitors to the unit should be limited as follows:

- women should be able to have a friend or relative present if they wish
- the woman's permission should be sought prior to colposcopy if any additional staff non-essential for the purposes of performing colposcopy are present (ie trainees, undergraduates, visitors).

Evidence: Women have strong negative reactions to the intrusiveness of a gynaecological examination. Those attending for colposcopy are often particularly anxious. Being sensitive to their concerns helps to improve their experience of the service.[59,62]

5.3 Colposcopy equipment

With regards to equipment for the colposcopy clinic, there must be:

- a permanent couch and colposcope
- appropriate sterilising facilities in accordance with local and national health and safety recommendations
- automatic referral (in units offering a diagnostic service) to a unit where treatment is available if required
- clinic staff familiarity with the treatment method(s) used (**100%**)
- adequate safety guidelines if laser or diathermy equipment is in use, with all staff trained in their use and clearly written and easily available emergency guidelines in each clinic in line with individual trust recommendations
- adequate resuscitation equipment immediately available and staff involved in the clinical care of patients must be familiar with its use
- suitable information technology equipment and software to facilitate collection of data for the BSCCP minimum dataset and for submission of the statutory quarterly KC65
- television monitoring facilities for patients who wish to watch the procedure are desirable.

Evidence: Professional consensus.

5.4 Clinic staffing

With respect to staffing of the colposcopy unit:

- all clinics must have a named colposcopist with appropriate skills who leads the service, with a specialist team specific to the colposcopy unit; the named lead colposcopist must have a job description
- there must be at least two nurses for each clinic
  - the primary nurse should be a registered nurse trained in counselling; she/he should be the named nurse dedicated to the unit and should not have other concurrent outpatient duties
  - the second nurse should be for the support of the patient, and would not need to be a fully trained nurse
- nurse colposcopists working in a clinic role must be supported by another registered nurse
- there must be adequate dedicated clerical support for the clinic.

Evidence: Having a specialist team specific to the colposcopy unit provides continuity of care and allows women to gain confidence in individual members of staff.[59] This in turn helps to reduce their anxiety and improves both attendance and their satisfaction with the service. The extended role of the nurse in respect to nurse colposcopy may be of particular benefit in this regard.[69,72]

5.5 Non-attenders

With respect to patient non-attendance:

- there must be written protocols for the management of non-attenders
- audit should include analysis of the records of defaulters to discern any patterns that could be addressed to reduce the default rate
- the default rate should be less than **15%**.

Evidence: In total, 20% of women fail to attend for fear of cancer or the procedure. There are multiple other reasons why women default on their appointments, including forgetting the appointment, menstruation, work, childcare, transport constraints and long waiting times.

There is an administrative cost to departments in terms of wasted appointments. Following reminders, most women will eventually be seen within one year of their first non-attendance. Strategies to improve patterns of attendance should be explored.[73–78]

5.6 Liaison with other units

Liaison with other units:

- colposcopy clinics in GUM must have established protocols for liaison with gynaecological services[79] (**100%**)
- multidisciplinary audit must be an integral part of the service
- there should be well established clinical and computer links with cytological and histological services to support multidisciplinary working
- details of the referral cytology report (if performed) should be available at time of colposcopy
- colposcopy clinics in gynaecology should have established protocols for liaison with GUM services.

Multidisciplinary meetings should include histopathology, cytopathology and colposcopy and should be held at least twice a year to discuss difficult cases, cases where there is significant mismatch between cytopathology, histology and colposcopy, and borderline glandular and glandular smears.

5.7 Training and certification of colposcopists

5.7.1 Training requirements

All practising colposcopists must be able to demonstrate that they have received an adequate training. The evidence required depends on when training commenced:

- for those who commenced training after April 1998: BSCCP/RCOG Diploma in Colposcopy
- for those who commenced training prior to April 1998 but had not completed training by the end of April 1998: BSCCP Completion of Training Certificate
- for those who completed training before April 1998: self-certification.

Training must be conducted according to the requirements determined by the BSCCP Certification and Training Committee. The BSCCP/RCOG training programme is the only recognised colposcopy training and certification programme for colposcopists wishing to practise within the NHSCSP and who commenced training after April 1998.

5.7.2 Maintenance of clinical skill and continued medical education (CME)

Colposcopists practising within the NHSCSP must see at least 50 new abnormal cytology referrals per year. All colposcopists must attend at least one BSCCP recognised colposcopy meeting every three years.

5.8 Summary of standards

1. Each woman should be offered verbal information and should be sent written information before and after cervical sampling and before colposcopy (**95%**).

2. Counselling must be available as an integral part of colposcopy.

3. Women must be sent an appropriately worded invitation with a contact name, telephone number and clinic times.

4. Information with regard to the visit and results of investigations should be communicated to the patient within four weeks of her attendance (**best practice 90%**) or eight weeks (**minimum standard 100%**).

5. Results and management plans should be communicated to the referring practitioner within four weeks of the patient's attendance at the clinic (**best practice 90%**) or eight weeks (**minimum standard 100%**).

6. Clinics providing a 'see and treat' policy must ensure that women who are offered treatment at their first visit are sent adequate and appropriate information in advance of their appointment (**100%**).

7. There must be a private area with changing facilities. There must also be toilet facilities.

8. There must be a permanently sited room specifically used for colposcopy (**100%**).

9. Refreshments must be available.

10. There must be separate waiting and recovery areas.

11. There must be a permanent couch and colposcope.

12. Appropriate sterilising facilities must be available in accordance with local and national health and safety recommendations.

13. In units offering a diagnostic service there must be automatic referral to a unit where treatment is available if required.

14. Clinic staff must always be familiar with the treatment method(s) used (**100%**).

15. If laser or diathermy equipment is in use, there must be adequate safety guidelines in place with all staff trained in their use; emergency guidelines must be available in each clinic.

16. Adequate resuscitation equipment must be immediately available and staff involved in the clinical care of patients must be familiar with its use.

17. There must be suitable information technology equipment and software to facilitate collection of data for the BSCCP minimum dataset and for submission of the statutory quarterly KC65.

18. All clinics must have a named colposcopist with appropriate skills who leads the service, with a specialist team specific to the colposcopy unit. The named lead colposcopist must have a job description.

19. There must be at least two nurses for each clinic.

20. Nurse colposcopists working in a clinic role must be supported by another registered nurse.

21. There must be adequate dedicated clerical support for the clinic.

22. There must be written protocols for the management of non-attenders.

23. The default rate should be less than **15%**.

24. Colposcopy clinics in GUM must have established protocols for liaison with gynaecological services (**100%**).

25. Multidisciplinary audit must be an integral part of the service.

26. All colposcopists in the team should be certificated through the BSCCP/RCOG scheme and should comply with the recertification process every three years.

27. All practising colposcopists must be able to demonstrate that they have received adequate training.

28. Colposcopists practising within the NHSCSP must see at least 50 new abnormal cytology referrals per year.

29. All colposcopists must attend at least one BSCCP recognised colposcopy meeting every three years.

6. DIAGNOSTIC STANDARDS FOR COLPOSCOPY

6.1 Cytology results

The cytology result should be available to the colposcopist prior to commencing the colposcopic examination.

Evidence: Knowledge of the cytological result improves the identification of colposcopic images of high grade CIN[80] and, when combined with colposcopic findings, improves the sensitivity of diagnosis of high grade CIN.[81,82]

6.2 Colposcopic examination

The following data should be recorded at the colposcopic examination:

- reason for referral (**100%**)
- grade of cytological abnormality (**90%**)
- whether the examination is satisfactory; this is defined as the entire squamocolumnar junction having been seen and the upper limit of any cervical lesion also being seen (**100%**)
- the presence or absence of vaginal and/or endocervical extension
- the colposcopic features should be recorded
- the colposcopic impression of lesion grade.

6.3 Invasive disease

Care should be taken not to overlook invasive disease. An excisional form of biopsy is recommended (**95%**) in the following circumstances:

- when colposcopic appearances indicate high grade abnormality
- when low grade colposcopic change is associated with severe dyskaryosis or worse
- when a lesion extends into the canal (sufficient canal must be removed in these situations).

In the situations mentioned above, punch biopsies are not considered to be reliably informative. The colposcopist should be cognisant of the small risk of inappropriate or inadvertent destruction of invasive or glandular lesions. This situation is most often encountered in association with high grade cytological or colposcopic change (CIN 3).

There may be pressing reasons for delay in biopsy, such as pregnancy. Reasons for not performing a biopsy must be recorded (**100%**).

Evidence: The evidence sources are one systematic review[83] and further subsequent retrospective reviews[84,85] of cases of invasion identified through cervical screening and colposcopic examination. The relevant findings were that 56% of microinvasive and 30% of invasive lesions are missed by colposcopy.[83] The retrospective reviews[84,85] suggest that approximately two-thirds of missed cancers

are due to colposcopist error, whereas one-third are due to the limitations of technique. Common cytological and colposcopic findings in cases of missed disease included one or more of the following:

- high grade cytological abnormality
- endocervical extension of lesions, even when examination was 'satisfactory'
- large, complex lesions with raised irregular surfaces
- underevaluation of lesions by colposcopically directed biopsy. [86–88]

Systematic review has shown that unsatisfactory colposcopy is a more frequent finding in invasive disease (61% of microinvasive, 71% of invasive disease) than CIN (14% of CIN). Atypical vessels are found in 44% of microinvasion and 84% of invasion.[83,89]

6.4 Local destruction

All patients must have a biopsy or biopsies taken prior to local destructive treatment (**100%**). Unless there are special circumstances, the result of the biopsy should be available (best practice).

Evidence: Accepted practice dictates that the decision to perform destructive treatments should only be reached after the available cytological, colposcopic and directed biopsy evidence indicate a high degree of confidence that invasion is absent. Retrospective studies of invasive disease presenting after destructive treatments indicate that failure to exclude invasive carcinoma prior to treatment is the most important aetiological factor.[90,91] Nevertheless, large observational studies of local destructive therapies conducted in regional centres with rigorous colposcopic assessment indicate high success rates with only a small risk of inadvertent/inappropriate treatment of invasive or glandular lesions.[92–94]

6.5 Colposcopically directed punch biopsy

Biopsy should be carried out unless an excisional treatment is planned, when the cytology indicates persisting moderate dyskaryosis or worse and always when a recognisably atypical transformation zone is present (**100%**). Pregnancy is an exception.

Low grade cytological abnormality (mild dyskaryosis or less) **and** negative colposcopic examination may not require colposcopic biopsy.

Evidence: A retrospective study[95] showed that in women with low grade cytological abnormalities and a normal colposcopic examination only 7.8% had CIN 2 or 3 on loop excision.

6.5.1 Treatment decisions

In deciding on treatment (and especially if destructive methods are being considered) associated cytological and colposcopic findings are as important as the result of directed biopsy.[83,86,96]

Evidence: Colposcopically directed biopsy (CDB) can only be considered as a sampling of the lesion, by convention the most atypical area, and thus can only give a provisional histological diagnosis. Systematic review[83] of studies comparing CDB with reference histology from cones or hysterectomy specimens shows a lower positive predictive value (PPV) for CIN 1 and 2 (16% and 32% respectively) than for CIN 3 (86%). PPV for microinvasion was 59% and for invasion 83%. Additional retrospective studies show that, although CDB may correctly 'overestimate' the grade of lesion compared with reference histology when the lesion is small, CDB has been shown frequently to underestimate the severity of the lesion. High grade CIN is underestimated in 4.3–57.1% of cases.[81,97–100] Cases of early invasive disease have been underevaluated as CIN 3.[85,86,97] Subjectivity in colposcopic opinion is also reflected in selection of site for biopsy.[101]

6.5.2 Destructive treatment

Of all biopsies taken (directed and excisional) > **90%** should be suitable for histological interpretation.

The colposcopist should analyse the results of cytology, colposcopy and biopsy before selecting a destructive method for treatment.

Evidence: Good practice dictates that the decision to perform destructive treatments should only be reached after the available cytological, colposcopic and directed biopsy evidence indicate a high degree of confidence that invasion is absent.

If colposcopically directed biopsy is reported as inadequate for histological interpretation, it should be repeated if there is a residual colposcopic lesion (**95%**).

Evidence: Good practice.

6.6 Accuracy of colposcopic diagnosis

For those with satisfactory colposcopic examination, the predictive value of a colposcopic diagnosis of a high grade lesion (CIN 2 or worse) should be at least **65%**.

It is desirable that colposcopists should be able to differentiate high grade (CIN 3 and CIN 2) lesions (intraepithelial or otherwise) from low grade in order to avoid missing advanced disease and to reduce overtreatment

for low grade lesions. A variety of factors influence the precision of colposcopic diagnosis.

Specific colposcopic appearances such as acetowhite epithelium, punctation and mosaicism, and glandular cuffing have been related to histology in few studies[83] and any statistical analysis is unreliable. Furthermore, punctation and mosaicism are noted in benign circumstances.[83] Scoring systems have been published but these are not recommended for routine clinical use. They do not readily facilitate the confirmation or exclusion of high grade disease, which is the most important and reproducible colposcopic criterion (see below). Among experienced colposcopists, there is a lower level of agreement for diagnosing low grade lesions (CIN 1) compared with high grade,[80,101] and for low grade abnormalities agreement is poor.[80] Not all CIN lesions may demonstrate colposcopic abnormality.[102]

There is an association between increasing severity of CIN and lesion size. Furthermore, the accuracy of colposcopic diagnosis in women with proven 'high grade' CIN is related to lesion size.[82] Invasive cancer and high grade CIN are usually accepted as reproducible endpoints for significant disease in assessing cervical screening and diagnosis. Although it has been noted that there is considerable subjectivity and interobserver variability in the grading of CIN by expert pathologists, this is less so for high grade lesions. The histological presence or absence of high grade CIN seems the most valid way of assessing the performance of colposcopic diagnosis (colposcopic impression).

For guidance in relation to cervical glandular intraepithelial neoplasia, see Chapter 12.

Evidence: One meta-analysis[103] of the ability of colposcopy to differentiate high grade lesions (CIN 2/3) from all others (normal and low grade). Additional retrospective studies were identified from which sensitivity and positive predictive value (PPV) for high grade lesions could be calculated.[81,86,104] One systematic review calculated the PPV of colposcopic impression.[83] Meta-analysis suggests high sensitivity of colposcopy, with average weighted sensitivity 85%, but low specificity, average weighted specificity 69%, confirming a high rate of false positive diagnosis of high grade lesions. Further analysis showed that high grade lesions had colposcopic characteristics that allowed them to be reasonably accurately separated from low grade lesions. However, attempting to distinguish low grade lesions from benign was much less accurate.[103] Analysis of three other retrospective studies indicated broadly similar results. One study showed improvement in diagnostic sensitivity of 8%[81] by considering the cytology result, at the expense of a similar reduction in specificity. The systematic review demonstrated a PPV of a colposcopic impression of CIN 3 of 78%. PPV declined as severity of CIN decreased.[83]

6.7 Summary of standards

1. The following data should be recorded at the colposcopic examination:

   - reason for referral (**100%**)
   - grade of cytological abnormality (**90%**)
   - whether the examination is satisfactory; this is defined as the entire squamocolumnar junction having been seen, and the upper limit of any cervical lesion also being seen (**100%**).

2. An excisional form of biopsy is recommended (**95%**):

   - when colposcopic appearances indicate high grade abnormality
   - when low grade colposcopic change is associated with severe dyskaryosis or worse
   - when a lesion extends into the canal (sufficient canal must be removed in these situations).

3. Reasons for not performing a biopsy must be recorded (**100%**).

4. All patients must have a biopsy or biopsies taken prior to local destructive treatment (**100%**). Unless there are special circumstances, the result of the biopsy or biopsies should be available (best practice).

5. Biopsy should be carried out unless an excisional treatment is planned, when the cytology indicates persisting moderate dyskaryosis or worse, and always when a recognisably atypical transformation zone is present (**100%**). Pregnancy is an exception.

6. Of all biopsies taken (directed and excisional), **>90%** should be suitable for histological interpretation.

7. If colposcopically directed biopsy is reported as inadequate for histological interpretation, it should be repeated if there is a residual colposcopic lesion (**95%**).

8. For those with satisfactory colposcopic examination, the predictive value of a colposcopic diagnosis of a high grade lesion (CIN 2 or worse) should be at least **65%**.

7. INFECTIONS AND COLPOSCOPY

7.1 Asymptomatic women

There is no indication to routinely test for *Chlamydia* and other infections in asymptomatic patients when attending for colposcopy. If a patient complains of vaginal discharge or soreness then high vaginal and endocervical sampling is indicated after gaining verbal consent for *Chlamydia*/*Gonococcus* testing.

Evidence: Screening for *Chlamydia* has been recommended for women attending genitourinary clinics (prevalence 16%), having termination of pregnancy (prevalence 8%), for sexually active women under 25 years of age or those with a new partner or more than two partners in the previous year. Prevalence of asymptomatic infection in general practice and family planning clinics is 5%.[105,106] Colposcopy clinics have not been included as a high risk group but a prevalence rate of 3–10% has been quoted in studies of women attending for cervical smears in general practice in Wales and a low risk urban population in the USA.[107,108] Similarly, evidence fails to support testing for *Gonococcus* in asymptomatic women.[108]

7.2 *Actinomyces*-like organisms

Actinomyces-like organisms (ALOs) require no specific intervention in the vast majority of patients and are usually seen in patients using an intrauterine contraceptive device (including the Mirena IUS).

If asymptomatic then:

- the coil does not need to be removed and antibiotics are not required
- the patient should have an abdominal and pelvic examination
- the patient should be warned of the small possibility of developing pelvic actinomycosis and advised to return should she develop symptoms
- family planning follow-up should be arranged every six months and should include enquiry regarding new symptoms and a pelvic examination
- repeat cytology is not required unless the smear was graded inadequate/abnormal
- if the asymptomatic patient wishes the device to be removed or it is due for removal then it need not be sent for culture.

If the patient complains of specific symptoms the device may need to be removed, after first ensuring that the patient has not had sexual intercourse in the preceding five days.

These symptoms include:

- pelvic pain
- deep dyspareunia
- intermenstrual bleeding (after six months of a device being in situ)

- vaginal discharge, dysuria or significant pelvic tenderness.

If the device is removed because the woman has any of the above symptoms:

- the device should be sent for culture and alternative contraception advised
- a course of antibiotics (such as amoxicillin 250 mg three times daily for two weeks in penicillin sensitive patients or erythromycin 500 mg three times daily for two weeks in penicillin resistant patients) should be given and a gynaecological opinion arranged to ensure that the symptoms or signs have resolved.[109]

Evidence: Good practice.

7.3 Incidental infections

Incidental infections may be detected in cervical samples. Some may require specific treatment or defined management.

Bacterial vaginosis
If the patient does not complain of a vaginal discharge and is not pregnant then treatment is not required.

Candidiasis (moniliasis)
This should be treated if symptomatic.

Herpes simplex
Patients with a herpes simplex virus infection may present with symptoms long before the cervical cytology report is available. All patients should be referred to a local GUM clinic. *Aciclovir* (200 mg five times daily for five days) is started if active infection is suspected. There is no evidence that this drug is teratogenic, so it can be safely prescribed in pregnancy.[110]

Trichomonas vaginalis *(TV)*
Asymptomatic detection of this protozoon merits treatment in all cases. All patients should be referred to a local GUM clinic. The patient and her partner should be treated with *metronidazole* (400 mg three times daily for one week). Samples with *Trichomonas* present may often be unsatisfactory owing to the marked inflammation. TV should be first treated if a repeat test is required.

Evidence: Good practice.

8. TREATMENT OF CERVICAL INTRAEPITHELIAL NEOPLASIA

8.1 Treatment standards

- All women needing treatment must be informed that treatment will be required and their consent, either written or verbal, recorded (**100%**).
- All women needing treatment must have had a colposcopic assessment (**100%**).
- All treatments must be recorded (**100%**).
- All women must be treated in properly equipped and staffed clinics (**100%**).
- All women must have had their histological diagnosis established prior to destructive therapy (**100%**).
- The proportion of women treated at the first visit that have evidence of CIN on histology must be ≥**90%**.
- Proportion of treatment associated with primary haemorrhage that requires a haemostatic technique in addition to the treatment method applied (<**5%**).
- The proportion of cases admitted as inpatients due to treatment complications (<**2%**).

8.2 Surgical techniques

There is no obviously superior conservative surgical technique for treating and eradicating cervical intraepithelial neoplasia (CIN). However ablative techniques are only suitable when:

- the entire transformation zone is visualised (**100%**)
- there is no evidence of glandular abnormality (**100%**)
- there is no evidence of invasive disease (**100%**)
- there is no major discrepancy between cytology and histology.

Evidence: Cochrane review of 28 randomised controlled trials comparing seven surgical techniques, namely knife cone biopsy, laser conisation, large loop excision of the transformation zone (LLETZ), laser ablation, cryocautery, cold coagulation and radical diathermy.[111] One recent prospective randomised trial of excision versus destruction has indicated a lower rate of moderately dyskaryotic smears after excision.[112]

CIN 1 does not necessarily require treatment. If CIN 1 is not treated, cytological and colposcopic follow-up should be performed until spontaneous regression has occurred or treatment is required.

8.3 Cryocautery

Cryocautery should only be used for low grade CIN, and a double freeze thaw–freeze technique must be used (**100%**).

Evidence: The rate of clearance of CIN 3 is poor.[113,114] The double freeze technique has a lower incidence of residual disease compared with a single freeze technique.[115,116]

8.4 Excision

8.4.1 Removal of specimen

When excision is used, at least **80%** of cases should have the specimen removed as a single sample. Removing the transformation zone in multiple fragments can increase the difficulties encountered in histopathological assessment. Furthermore, if microinvasive disease is present, it may be impossible to allocate a substage or define completeness of excision in fragmented excisional specimens.

Evidence: Good practice.

8.4.2 Histology report

The histology report should record the dimensions of the specimen and the status of the resection margins with regard to intraepithelial or invasive disease.

Evidence: Professional consensus.

8.4.3 Ectocervical lesions

For ectocervical lesions, excisional techniques should remove tissue to a depth of greater than 7 mm (**95%**).

Evidence: Histological assessment of the depth of crypt involvement by CIN 3 has shown a mean depth of 1–2 mm with a maximum of 5.22 mm and a mean ± three standard deviations (99.7%) of 3.80 mm.[117,118]

8.5 'See and treat' policy

Treatment at first visit for a referral of borderline or mild dyskaryosis should only be used in exceptional cases, and only when audit has identified that CIN is present in ≥**90%** of the excised specimens.

Evidence: It is inappropriate to adopt 'see and treat' if the proportion of specimens with no CIN is high, as these women will have received unnecessary treatment. Clinics undertaking treatment at the first visit must audit the proportion of cases with CIN. A target of ≥90% can be achieved with a selective policy.[119]

8.6 Repeat excision

8.6.1 CIN extending to margins

CIN extending to the margins at excision results in a higher incidence of recurrence but does not justify routine repeat excision as long as:

- there is no evidence of glandular abnormality
- there is no evidence of invasive disease
- the woman is under 50 years of age.

Evidence: CIN extending to the resection margins of a LLETZ has been shown to be a risk factor for recurrent CIN both in the short and long term.[120–122] This risk appears to be predominantly due to the presence of CIN at the endocervical margin.[123] Despite the increased incidence of recurrence, the majority of women in the above studies had no evidence of residual disease and the recommendation is that these women have colposcopy and cytology at first follow-up.

8.6.2 Women over the age of 50 years

All women over the age of 50 who have CIN 3 at the endocervical margin and in whom satisfactory cytology and colposcopy cannot be guaranteed must have a repeat excision performed to try and obtain clear margins (**100%**).

Evidence: In a series of 3426 LLETZ procedures, women aged ≥50 with CIN at the margins of excision constituted a minority high risk group. It was suggested that these women should be offered retreatment rather than surveillance.[123]

8.7 Local excision

8.7.1 Women with adenocarcinona in situ/cervical glandular intraepithelial neoplasia

Women with adenocarcinoma in situ/cervical glandular intraepithelial neoplasia (cGIN) can be managed by local excision for those wishing to retain fertility. Incomplete excision at the endocervical margin requires a further excisional procedure to obtain clear margins and exclude occult invasive disease (**95%**) (see Chapter 12).

Evidence: Several studies have shown that women with adenocarcinoma in situ with negative margins can be managed conservatively.[124–127] One study has suggested that up to 15% of these women will require further treatment by four years because of recurrent cytological abnormalities.[126]

8.7.2 Microinvasive squamous cancer FIGO stage Ia1

Microinvasive squamous cancer FIGO stage Ia1 can be managed by local excisional techniques if:

- the excision margins are free of CIN and invasive disease

- the gynaecological cancer centre pathologist and multidisciplinary team have reviewed the histology.

If the invasive lesion is excised but CIN extends to the excision margin then a repeat excision should be performed to confirm excision of the CIN and to exclude further invasive disease. This should be performed even in those cases planned for hysterectomy to exclude an occult invasive lesion requiring radical surgery.

Evidence: Several studies have suggested that FIGO stage Ia1 disease can be managed conservatively.[119,128] Variation in histological diagnosis of microinvasive disease is well recognised and all cases should be reviewed by an independent pathologist with an interest in gynaecological oncology.

8.8 Anaesthesia

Treatment should be performed with adequate pain control and should include pretreatment counselling. Treatment should be offered with local analgesia but, when this is inappropriate, general anaesthesia should be offered. Reasons for treating under general anaesthesia should be recorded in the colposcopy record. The proportion of women managed as outpatients with local analgesia should exceed **80%**.

8.9 Summary of standards

1. All women needing treatment must be informed that treatment will be required and their consent, either written or verbal, recorded (**100%**).

2. All women needing treatment must have had a colposcopic assessment (**100%**).

3. All treatments must be recorded (**100%**).

4. All women must be treated in properly equipped and staffed clinics (**100%**).

5. All women must have had their histological diagnosis established prior to destructive therapy (**100%**).

6. The proportion of women treated at the first visit who have evidence of CIN on histology must be ≥**90%**.

7. The proportion of treatment associated with primary haemorrhage that requires a haemostatic technique in addition to the treatment method applied must be <**5%**.

8. The proportion of patients admitted as inpatients owing to treatment complications must be <**2%**.

9. Ablative techniques are only suitable when:

   - the entire transformation zone is visualised (**100%**)
   - there is no evidence of glandular abnormality (**100%**)
   - there is no evidence of invasive disease (**100%**).

10. Cryocautery should only be used for low grade CIN and a double freeze thaw–freeze technique must be used (**100%**).

11. When excision is used, at least **80%** of cases should have the specimen removed as a single sample.

12. For ectocervical lesions, excisional techniques should remove tissue to a depth of greater than 7 mm (**95%**).

13. Treatment at first visit for a referral of borderline or mild dyskaryosis should only be used in exceptional cases, and only when audit has identified that CIN is present in ≥**90%** of the excised specimens.

14. All women over the age of 50 years who have CIN 3 at the endocervical margin and in whom satisfactory cytology and colposcopy cannot be guaranteed must have a repeat excision performed to try and obtain clear margins (**100%**).

15. Among women with adenocarcinoma in situ/cGIN, those wishing to retain fertility can be managed by local excision. Incomplete excision at the endocervical margin requires a further excisional procedure to obtain clear margins and exclude occult invasive disease (**95%**).

16. The proportion of women managed as outpatients with local analgesia should exceed **80%**.

9. FOLLOW-UP OF WOMEN ATTENDING FOR COLPOSCOPY

9.1 Treated women

All women remain at risk following treatment and must be followed up (**100%**).

There is no obviously superior conservative surgical technique for the treatment of cervical intraepithelial neoplasia.[111] Excisional treatments permit histological assessment of biopsy and can determine risk factors for residual disease. Women at increased risk of residual/recurrent disease should be considered for more intensive surveillance following treatment.

Evidence: Several retrospective studies[120,123,129–137] of residual disease rates after LLETZ or knife cone biopsy 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. Studies have demonstrated that disease at the endocervical resection margin is associated with increased risk of residual disease compared with involved ectocervical margins.[120,123,136,138,139] Women aged 50 years or more[123,140] are particularly at risk of persistent/recurrent disease.

9.2 Standards for follow-up of treated women

- Follow-up should start at six months following treatment and not later than eight months following treatment (**>90%**).
- Cytology alone is recommended for follow-up and samples should be taken by appropriately trained staff.
- Initial follow-up cytology (six month test) is ideally performed in the treatment centre (best practice); alternatively, follow-up cytology can be performed in the primary care sector (minimum standard).
- All women who do not have negative test results after treatment should be recolposcoped at least once within 12 months (**100%**).
- The proportion of treated women with no dyskaryosis six months after treatment should exceed **90%**.
- The proportion of confirmed histological treatment failures should not exceed **5%** within 12 months of treatment.

9.3 Duration of follow-up

Women should have annual follow-up for at least 10 years after the treatment of CIN 2 or worse before returning to the routine screening interval. Women treated for CIN 1 can be returned to routine recall after two years of negative post-treatment cytology.

Evidence: The majority of persistent/recurrent disease is detected within the first 24 months.[123,141] However, there is clear evidence that there is persistent long term risk of invasive cancer for at least 10 years after treatment and possibly for 20 years.[57,142] Annual follow-up cytology is therefore justified after the treatment of CIN

2 or worse. Although the risk of invasive recurrence is likely to be greater after treatment of high grade disease, there are no reliable data that examine the relative risks for different grades of CIN.

9.4 Frequency of follow-up

Recommendations for follow-up protocols have to be determined by expert consensus opinion:

- women treated with high grade disease (CIN 2, CIN 3, cGIN) require 6 and 12 month follow-up cytology and annual cytology for the subsequent nine years at least, before returning to screening at the routine interval (high risk follow-up)
- women treated for low grade disease require 6, 12 and 24 month follow-up cytology. If all results are negative, then women may be returned to screening at the routine interval (low risk follow-up).

Evidence: There is no clear evidence suggesting that diagnostic performance of cytology in combination with colposcopy for the detection of persistent disease after treatment for CIN is superior to cytology alone.

Current opinion is mixed on the value of cytology combined with colposcopy for follow-up. Some authors suggest that colposcopy does not increase the detection of disease.[133,143] Other authors[144–147] suggest that an initial follow-up colposcopy marginally enhances early detection of disease and reduces the false negative rate.

Women treated for cGIN are at somewhat higher risk of developing recurrent disease than those with high grade CIN.[126] In addition, recurrent disease is more difficult to detect cytologically. Cytology should continue for the same duration with the same frequency as after treatment of CIN 2 and CIN 3 (minimum standard). Ideally, six-monthly samples would be taken for five years followed by annual samples for a further five years (best practice).

9.5 Samples for follow-up cytology

Extended tip sampling devices should be used for taking samples for follow-up by conventional cytology; brush devices such as the Cervex-Brush® should be used for liquid based samples:

- after surgical treatment, particularly excisional treatment, the squamocolumnar junction can retract into the cervical canal; ideally, a cervical sample should be taken with an extended tip device
- after treatment for cGIN, follow-up samples must contain endocervical cells (see section 12.3).

9.6 Follow-up after hysterectomy

Women who have had a hysterectomy with CIN present are potentially at risk of developing vaginal intraepithelial neoplasia (VaIN) and invasive vaginal disease. There is no clear evidence that colposcopy increases the detection of disease on follow-up. Expert consensus opinion recommends that:

- for women on routine recall for at least 10 years prior to hysterectomy and no CIN in the sample at hysterectomy, no vault cytology is required
- for women with less than 10 years' routine recall and no CIN at hysterectomy, a sample should be taken from the vault six months after surgery and there should be no further cytology follow-up if it is negative
- for women with completely excised CIN at hysterectomy, a sample should be taken from the vault at 6 and 18 months after surgery and there should be no further cytology follow-up if both are negative
- for women with incomplete or uncertain excision of CIN, follow-up should be conducted as if the cervix were still in situ (ie as for low and high risk follow-up in section 9.4 above).

It should be emphasised that these clinical guidelines for follow-up of women treated by hysterectomy are not part of the cervical screening programme and data on cytology from vault samples are not collected routinely.

Evidence: The incidence of VaIN after hysterectomy diagnosed with CIN was in the order of 1% in a series of 341 women,[148] with no subsequent cases of invasive disease. In a similar series of 177 women,[149] 4% developed VaIN, with 0.6% developing subsequent invasive disease. A meta-analysis of long term results suggests that, although recurrent intraepithelial disease is less common after hysterectomy for CIN than after local treatments of the cervix (522 versus 1587 per 100 000 woman–years), the risk of invasive recurrence is similar in both groups (57 versus 67 per 100 000 woman–years).[150]

It is accepted that, even after hysterectomy, there is a risk of developing cancer similar to that after conisation or local destruction. It is not clear whether this is due to incomplete treatment or recurrent disease, although the latter would seem unlikely if the whole cervical transformation zone (along with the cervix) has been removed. Although supporting evidence is lacking, it seems reasonable to assume that if there is complete excision with no transformation zone remaining and two follow-up cytology tests confirm no dyskaryosis then the risk of developing cancer must be very small indeed and does not justify surveillance beyond the suggested 18 months.

9.7 Role of HPV testing during post-treatment follow-up

HPV testing after treatment has the potential to enhance the detection of persistent/recurrent disease.[37,38,151–155] These preliminary studies suggest that there is a role for HPV DNA testing during follow-up. These studies suggest that:

- a positive HPV test, even in the presence of normal cytology, can detect treatment failure more quickly and more accurately
- some treatment failures have a negative HPV test in the presence of abnormal cytology; a combined cytological evaluation together with

an HPV test will significantly increase the safety of the follow-up surveillance
- a proportion of women have a positive HPV test in the presence of normal cytology, without eventually developing failure/recurrence; as it is not possible to distinguish which of them is likely to be a failure, they should undergo colposcopic evaluation
- further larger studies are required to assess the true diagnostic accuracy of HPV testing during the follow-up period.

9.8 Follow-up of untreated women

9.8.1 Women referred with moderate or severe dyskaryosis

Women referred with moderate or severe dyskaryosis (high grade) on their test result are at significant risk of CIN 2 or 3, even in the presence of normal colposcopy. Biopsy should be undertaken in >**95%** of women with high grade abnormalities (see section 6.3). If treatment is not undertaken, close surveillance with colposcopy and cytology every six months is advised. If at follow-up a high grade cytological abnormality persists, excisional treatment is recommended (**90%**).

Evidence: The overall specificity for distinguishing normal from abnormal tissue at colposcopy in a meta-analysis was only 48%.[156] The specificity of high grade cytology is over 90% in several studies.[157,158] This evidence suggests that high grade cytological abnormalities have a high likelihood of being associated with CIN 2 or CIN 3. Follow-up studies[159,160] also support the relatively high likelihood of CIN 2 or CIN 3 in this group, and thus the presence of persistent high grade abnormalities, even in the face of normal colposcopy, warrants treatment.

9.8.2 Women referred with moderate dyskaryosis or worse

Women referred with moderate dyskaryosis or worse cytological abnormalities who have a colposcopically low grade lesion and who are not treated should have multiple biopsies (**90%**). If CIN 1 or less is confirmed, close colposcopic and cytological follow-up is advised. Cases with unexplained severe dyskaryosis should be discussed at multidisciplinary meetings.

Evidence: The positive predictive value of colposcopy for distinguishing low grade from high grade lesions is only 57%.[156] As the specificity of high grade cytology is over 90%, the likelihood of an underlying high grade lesion in this situation is extremely high. If treatment is not undertaken as a result of colposcopic diagnosis of a low grade lesion, histological assessment is recommended by way of multiple directed biopsies.[158,161] If there is high grade cytology at follow-up, treatment is recommended.

9.8.3 Women referred with mild dyskaryosis or less

Women referred with mild dyskaryosis or less who have a satisfactory and normal colposcopic examination are at low risk of developing cervi-

cal cancer. Their management is best determined by repeat cytological assessment six months after the referral sample:

- if this is normal they can be returned to recall
- if this is borderline, repeat test in 12 months
- if this is mild dyskaryosis, a colposcopy with another test within 12 months is recommended
- any other test result warrants further colposcopy with or without biopsies.

Evidence: Three studies[159,160,162] indicate that the risk of significant disease is extremely small when low grade cytology (mild dyskaryosis or less) is associated with normal colposcopy. The risk probably does not warrant intensive surveillance with its attendant costs and anxieties. In each of these studies, follow-up cytology identified women with significant disease and this should form the main part of follow-up. In one study,[162] the smear at first colposcopy visit distinguished those who were at risk. If this repeat smear was normal or borderline, the risk was minimal and referral back to community screening was advised. There is evidence to suggest that the routine practice of repeating smears at first attendance at the clinic does not add significantly to management and certainly repeating a smear within three months of an index smear is unlikely to be helpful. However, in the face of a low grade referral smear there is a 50% chance of normal colposcopy, and in this group the repeat smear at first visit offers the chance of discharging the woman to her GP if the result is normal or borderline.

9.8.4 Women referred with a report of mild dyskaryosis or less

Women referred with a result of mild dyskaryosis or less who have a colposcopically low grade lesion may be treated or followed up at six-monthly intervals in the colposcopy clinic.

If the lesion has not resolved within two years of referral to colposcopy, at least a biopsy is warranted (>**90%**). In practice, many women are offered treatment at this point, as persistent surveillance risks default.

Evidence: Approximately 50% of women with a low grade cytological abnormality who are not treated at first visit will eventually revert to normal cytology and colposcopy.[162] Those who are identified to have a colposcopically low grade lesion may be followed up.[1] Prospective randomised data suggest that such a policy does not alter the number of women with high grade lesions who are treated but does reduce the number of low grade lesions treated.[52] However, in this study over one-fifth of women defaulted from follow-up. Therefore, the decision to follow up rather than treat in the presence of an apparent low grade lesion must incorporate analysis of the likelihood of default. Furthermore, the positive predictive value for distinguishing low grade from high grade lesions is only 57%.[156] Therefore, follow-up is warranted as a result of the

inherent poor colposcopic discrimination between high and low grade lesions. The ongoing management decisions for this group will often be influenced by the woman's choice.

9.9 Summary of standards

1. All women remain at risk following treatment and must be followed up (**100%**).
2. Follow-up should start at six months following treatment and not later than eight months following treatment (>**90%**).
3. All women who do not have negative test results after treatment must be recolposcoped at least once within 12 months (**100%**).
4. The proportion of treated women with no dyskaryosis six months following treatment should exceed **90%**.
5. The proportion of confirmed histological treatment failures should not exceed **5%** within 12 months of treatment.
6. Biopsy should be undertaken in >**95%** of women with high grade abnormalities.
7. If at follow-up a high grade cytological abnormality persists, excisional treatment is recommended (**90%**).
8. Women referred with moderate dyskaryosis or worse cytological abnormalities who have a colposcopically low grade lesion and who are not treated should have multiple biopsies (**90%**).
9. If a low grade lesion has not resolved within two years of referral to colposcopy, at least a biopsy is warranted (>**90%**).

10. PREGNANCY, CONTRACEPTION, MENOPAUSE AND HYSTERECTOMY

10.1 Pregnant women

10.1.1 Cervical screening in pregnancy

- Unless a pregnant woman with negative history has gone beyond three years without having cervical screening then the test should be postponed.
- If a woman has been called for routine screening and she is pregnant then the test should be deferred.
- If a previous test was abnormal, and in the interim the woman becomes pregnant, then the test should not be delayed but should be taken in mid-trimester unless there is a clinical contraindication.

10.1.2 Colposcopy in pregnancy

A woman who meets the criteria for colposcopy still needs colposcopy if she is pregnant. The primary aim of colposcopy for pregnant women is to exclude invasive disease and to defer biopsy/treatment until the woman has delivered. Women seen in early pregnancy may require a further assessment in the late second trimester at the clinician's discretion.

Evidence: The safety of delaying treatment of pregnant women has been shown in a number of cohort and retrospective uncontrolled studies.[163,165] The incidence of invasive cervical cancer in pregnancy is low and pregnancy itself does not have an adverse effect on the prognosis.[166]

If colposcopy has been performed during pregnancy, postpartum assessment of women with an abnormal smear or biopsy proven CIN is essential (**100%**). Excision biopsy in pregnancy cannot be considered therapeutic and these women should be seen for colposcopy post partum. This requires a system to ensure that women are given an appointment after delivery.

Evidence: Regression rates for preinvasive cervical disease during pregnancy and following delivery are low from retrospective uncontrolled studies and regression is not related to mode of delivery.[167] A retrospective study of pregnant women treated by cone biopsy for high grade CIN and microinvasion reported high rates of disease persistence.[168]

10.1.3 Colposcopic evaluation of the pregnant woman

Colposcopic evaluation of the pregnant woman requires a high degree of skill:

- if CIN 1 or less is suspected, repeat the examination three months following delivery

- if CIN 2 or 3 is suspected, repeat colposcopy at the end of the second trimester or, if the pregnancy has already advanced beyond that point, three months following delivery
- if invasive disease is suspected clinically or colposcopically, a biopsy adequate to make the diagnosis is essential (**100%**). Cone, wedge and diathermy loop biopsies are all associated with a risk of haemorrhage and such biopsies should be taken where appropriate facilities to deal with haemorrhage are available. Punch biopsy suggesting only CIN cannot reliably exclude invasion.

Evidence: Case series of biopsies taken by diathermy loop in pregnancy have shown that the risk of haemorrhage is in the order of 25%.[169]

10.2 Use of contraceptives

10.2.1 Women with abnormal cervical screening results

Women with abnormal cervical screening results should not be advised to change from the oral contraceptive pill (OCP) if it is a successful method of contraception. An abnormal result should not influence the choice of contraception.

Evidence: Nested case–control studies indicate a small increase in the relative risk of CIN after compensating for HPV infection with long term use of the OCP.[170–172] However, we do not have evidence that stopping the OCP will alter the natural history of the disease. A large prospective cohort study confirms no significant association between the use of the OCP ever and cervical cancer.[173]

10.2.2 Women with an IUCD

It is not necessary to remove an intrauterine contraceptive device (IUCD) to perform local treatment. Women with an IUCD should be given clear information on the clinic's management policy regarding whether her IUCD will be removed or not. She will need to know if she has to use alternative methods of contraception and if she has to schedule her treatment to coincide with the first half of her cycle.

Evidence: Professional consensus.

10.3 Menopause and the use of hormone replacement therapy

10.3.1 Postmenopausal women

The incidence of abnormal cytology is low in postmenopausal women with previous normal results. The use of systemic hormone replacement therapy (HRT) is not known to alter the risk of cervical disease.

Evidence: One randomised controlled trial and two case–control studies demonstrated no increase in relative risk from the use of systemic HRT.[174–176]

10.3.2 Postmenopausal bleeding

In an adequately screened woman, postmenopausal bleeding (PMB) is NOT an indication to take a cervical sample. The investigation of abnormal bleeding after the menopause must include direct visual inspection of the cervix. A cervical sample is not an appropriate test for investigating PMB. All unexplained bleeding should be referred to a gynaecologist.

Evidence: Professional consensus.

10.4 Hysterectomy

10.4.1 Women undergoing a hysterectomy for other reasons

All women in the cervical screening age range undergoing a hysterectomy for other gynaecological reasons should have a negative test result within the screening interval. Otherwise, a cervical sample should be taken as part of their preoperative investigations (**100%**).

Evidence: Professional consensus.

10.4.2 Women being considered for hysterectomy

All patients being considered for hysterectomy who have an undiagnosed abnormal test result or symptoms attributable to cervical cancer should have diagnostic colposcopy and an appropriate biopsy[177] (**100%**).

Evidence: Professional consensus suggests that the nature and extent of cervical neoplasia is defined to avoid inadvertent non-radical treatment of cervical cancer or inadvertent inadequate excision of VaIN.[177,178]

10.4.3 Hysterectomy as treatment for histologically proven cervical intraepithelial neoplasia

Hysterectomy is a recognised treatment for histologically proven CIN if there are coexisting conditions appropriately treated by hysterectomy.

Evidence: Professional consensus.

10.4.4 Hysterectomy as treatment of persistent abnormal endocervical cytology

Hysterectomy is an acceptable form of treatment of persistent abnormal endocervical cytology despite a prior excisional biopsy of adequate size. This is provided that all measures to exclude occult invasion have been applied.[179]

Evidence: Professional consensus.

10.4.5 Mapping vaginal abnormalities

Patients with CIN should have any abnormality on the vagina mapped by colposcopy or Lugol's iodine at the time of surgery to ensure that any coexisting VaIN is recognised and excised at the time of the hysterectomy.[179]

Evidence: Observational data.

10.4.6 Correlation of histology with cytology

The histology of the resected uterus should be correlated with prior cervical cytology as part of the quality assurance process.

Evidence: Professional consensus.

10.4.7 Follow-up after hysterectomy

After hysterectomy, follow-up is advised as suggested in section 9.6.

Evidence: Professional consensus.

10.5 Summary of standards

1. If colposcopy has been performed during pregnancy, postpartum assessment of women with an abnormal cervical sample or biopsy proven CIN is essential (**100%**).

2. Colposcopic evaluation of the pregnant woman requires a high degree of skill. If invasive disease is suspected clinically or colposcopically, a biopsy adequate to make the diagnosis is essential (**100%**).

3. The investigation of abnormal bleeding after the menopause must include direct visual inspection of the cervix.

4. 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 (**100%**).

5. 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 (**100%**).

11. SCREENING AND MANAGEMENT OF IMMUNOSUPPRESSED WOMEN

11.1 Immunosuppressed women

This includes women on immunosuppressing medication, transplant recipients and all other forms of immunosuppression. The screening and management of the immunosuppressed woman is a complex area of assessment and management. All patients who are immunosuppressed must be managed in a centre with demonstrable skill and expertise, with sufficient access to patient numbers to maintain that expertise. There must be a compromise between the increased risk of CIN and the additional psychological and physical trauma of assessment and treatment, with due consideration to the comorbidity of the underlying disease process.

11.2 Women with renal failure requiring dialysis

All women aged 25–65 years with renal failure requiring dialysis must have cervical cytology performed at, or shortly after, diagnosis.

Colposcopy should be performed if resource permits. Any cytological abnormality should be treated as a high grade abnormality requiring prompt colposcopic referral. All women about to undergo renal transplantation should have had cervical cytology performed within one year. Coexisting CIN should be managed according to national guidelines.

Evidence: There is good evidence that women who have renal failure requiring dialysis or renal transplantation are at an increased risk of CIN and cervical cancer.[180,181] The range of incidence of abnormal cervical cytology in the renal transplant population has been quoted as between 8.7% and 70%; a realistic figure of around 15% represents a fivefold increase from that of the normal population.[182] There is some evidence that cervical cytology is relatively insensitive and coexisting CIN could be missed, hence early recourse to colposcopy.[183,184] Most publications inform on cytology taken in a research/colposcopy clinic setting and thus there is no information regarding cytology obtained on routine screening.

11.3 Women taking maintenance immunosuppression medication post transplantation

Women taking maintenance immunosuppression medication post transplantation, who have no history of CIN, should have cervical screening as per the national guidelines for the non-immunosuppressed.

Any abnormal cervical cytology result should prompt colposcopic referral. Any woman with a previous history of CIN should have routine follow-up as recommended for the immunocompetent population.

Evidence: There are insufficient data on the assessment and management of these patients long term. All studies bar one were cross-sectional, whereas the only published longitudinal study has insufficient numbers to be useful in dictating national guidelines.[185] There is no evidence that women who are immunosuppressed after

renal transplantation have an accelerated natural history of CIN, and thus decreasing the screening interval has no demonstrable benefit.

11.4 Women with multifocal disease

Patients with multifocal disease will require expert assessment and management in a centre with expertise in this area. The patients should be assessed by cytology, colposcopy, vulvoscopy and biopsy where indicated, at least six-monthly.

Evidence: In renal patients, the risk of intraepithelial disease, and therefore cancer, appears to be temporally related, ie the risk increases with time. There is little information in the literature regarding multifocal disease and renal transplantation. The only longitudinal study demonstrated the presence of 'high risk' oncogenic HPV type infection in all patients with vulval intraepithelial neoplasia (VIN).[185] There is good evidence that infection with 'high risk' HPV types and persistence of viral infection increases the risk of subsequent CIN and cervical cancer.[186–188] However, the value of HPV screening has yet to be determined.

11.5 Women receiving cytotoxic drugs for rheumatological disorders

Women receiving long term cytotoxic drugs for rheumatological disorders should have regular cytological screening as per national guidelines.

If the screening history is incomplete at commencement of cytotoxic drugs then a cervical sample should be taken with referral to colposcopy for any cytological abnormality.

Evidence: There is an increased incidence of CIN in women with systemic lupus erythematosus treated with long term chemotherapy.[189,190] The data in other rheumatological disorders are lacking but safe practice dictates adequate screening histories as a minimum requirement.

11.6 Other women who are immunosuppressed

There is no indication for increased surveillance in the following situations:

- women receiving cytotoxic chemotherapy for non-genital cancers
- women receiving long term steroids
- women receiving oestrogen antagonists such as tamoxifen.

Such women should have cytological screening in accordance with national guidelines.

Evidence: There is a theoretical risk that folate deficiency acts as a cocarcinogen during the initiation of cervical dysplasia. Folic

acid supplements neither alter the course of established disease nor decrease the risk of developing CIN.[191] There is no evidence to suggest that women who receive chemotherapy with cytotoxic drugs or tamoxifen are at increased risk of CIN.[192–194]

11.7 HIV positive women

All women newly diagnosed with HIV should have cervical surveillance performed by, or in conjunction with, the medical team managing the HIV infection. Annual cytology should be performed with an initial colposcopy if resources permit. Subsequent colposcopy for cytological abnormality should follow national guidelines. The age range screened should be the same as for HIV negative women.

Despite the higher cervical treatment failure rate, high grade CIN should be managed according to national guidelines. Lesions less severe than CIN 2 should probably not be treated as these are likely to represent persistent HPV infection of the cervix, which may ultimately clear and responds poorly to treatment. Regular cytological surveillance will detect progression.

Evidence: Whereas the estimated prevalence of cervical disease in HIV seronegative women is approximately 3%,[195] a number of reports including cross-sectional, case–control and cohort studies have indicated a greatly increased prevalence of squamous intraepithelial lesions, ranging from 20% to 40%,[196–199] and increased incidence in HIV infected women.[200] Furthermore, regression of low grade lesions is rare and high grade lesions may respond poorly to standard therapies.[201,202] In one study, the recurrence rate in women with CD4 counts $< 200/mm^3$ was 87%,[202] compared with less than 10% in immunocompetent women.

The reason for this high incidence of CIN and recurrence after treatment is thought to be the lack of immune activity against HPV. Even in cohorts with a high use of highly active antiretroviral therapy (HAART), there is a high risk of abnormal cytology, although HAART may increase the regression of low grade lesions.[203] Early data from a European cohort study show a 33% prevalence of abnormal cytology, ASCUS or worse, among 859 women recruited so far. This was despite the fact that a large proportion of the women were on HAART (Mach 1 Study Group).

Use of HAART reduces HIV viral load, and may reduce HPV viral load. As a consequence, the prevalence and incidence of cervical abnormality may also be reduced. However, the evidence for this is inconsistent to date and thus there is a need for more intense surveillance of these women to detect preinvasive cervical lesions.

11.8 Summary of standards

1. All patients who are immunosuppressed must be managed in a centre with demonstrable skill and expertise, with sufficient access to patient numbers to maintain that expertise.

2. All women aged 25–65 years with renal failure requiring dialysis must have cervical cytology performed at or shortly after diagnosis.

12. MANAGEMENT OF GLANDULAR ABNORMALITIES

12.1 Cervical glandular epithelial abnormalities

Cervical cytological screening can predict the presence of cervical glandular intraepithelial abnormalities, including cervical adenocarcinoma and high grade intraepithelial glandular neoplasia.

Evidence: Observational studies of women with abnormal glandular cytology with histological correlation. The data indicate that premalignancy and malignancy account for a variable proportion of pathology, with high grade CIN, cervical adenocarcinoma, endometrial cancer and high grade glandular intraepithelial neoplasia being the pathological conditions most commonly diagnosed.[42,55,204,205]

12.2 Reporting of abnormal glandular samples

12.2.1 Written reports

Reporting of any abnormal glandular sample must be supplemented by a written descriptive report (**100%**).

Evidence: The written report should indicate the likely source of the glandular cells wherever possible. Although not expected to be 100% accurate, the finding of abnormal endometrial cells can facilitate the diagnosis of endometrial carcinoma.

12.2.2 Colposcopic assessment

Colposcopic assessment is essential in the presence of cytological glandular abnormality (**100%**).

Evidence: There is a high prevalence of invasive adenocarcinoma, cGIN and CIN in this population.[42,43] Although there are no specific colposcopic indicators of glandular abnormality, villous fusion and acetowhite changes proximal to the squamocolumnar junction have been noted.[42,206] However, colposcopy lacks sensitivity for the diagnosis of glandular lesions[207] and punch biopsy has little role in their precise diagnosis. Colposcopy demonstrates concomitant CIN in 50% of cases, provides an assessment of the anatomy of the cervix and vagina, and helps to decide on the most appropriate method and extent of biopsy.

12.2.3 Further investigation of ?glandular neoplasia

Women with samples reported as ?glandular neoplasia should be referred for urgent investigation by colposcopy to exclude significant cervical and endometrial neoplasia.

Evidence: For high grade glandular cytological abnormality, reports suggest variations in positive predictive value (PPV) between 17% and 96% for premalignant or malignant pathology.[42,55,204,205,208] Furthermore, the predictive value of abnormal glandular cytology is compromised by the occurrence of several benign conditions that mimic cervical glandular neoplasia cytologically.[209] Endocervical brush artefact can give rise to such samples.[210] Other non-cervical/endometrial neoplastic lesions of the genital tract and intraperitoneal organs sometimes present in this way. Although larger datasets are desirable, expert opinion and the limited data available support a rigorous investigative protocol for this grade of abnormality.[42,52,204,205]

12.2.4 Borderline glandular samples

Women with borderline glandular samples should be referred promptly for investigation by colposcopy, any appropriate cervical biopsy and selective use of endometrial biopsy.

Evidence: For predictions with less certainty of glandular neoplasia, the borderline classification is used. Most available studies, however, report atypical glandular cells of undetermined significance (AGUS) samples representing the Bethesda convention,[212] which differs from the UK in respect of glandular samples. Although the data are somewhat unreliable, high grade squamous intraepithelial lesions are those most commonly diagnosed in 27–37% of cases.[210,213] However, invasive lesions have been noted to present in this way.[214] Limited UK data indicate that a borderline classification of those examples of abnormal glandular cells is associated with a low, but still significant, incidence of pathology (33–57%). Intraepithelial glandular lesions very infrequently present with this grade of abnormality.[42,43]

The above guideline conforms with the suggestions of a Joint College working party,[215] which did not suggest a need for radical excision of the endocervix.

12.2.5 Punch biopsy

Punch biopsy is an unreliable investigation in the management of high grade cytological glandular abnormality.

Evidence: Invasive neoplasia cannot be excluded on the basis of a punch biopsy.[216] Punch biopsy is of low sensitivity for diagnosis of glandular lesions.[217,218] Expert opinion indicates that a reliable diagnosis of high grade cGIN and distinction from invasive adenocarcinoma can only be achieved in the histopathology laboratory, and an excisional biopsy including the endocervical canal is required for this purpose. Endometrial carcinoma has been detected through the screening process under the circumstances described above.[42,43,214]

12.2.6 Endometrial biopsy

Selective use of endometrial biopsy is recommended for women of perimenopausal age and above, or for those with irregular vaginal bleeding or if the atypical cells appear to be of endometrial origin. Postmenopausal women with atypical endometrial cells on a sample must be referred to a gynaecologist. Although it is accepted that cervical assessment may be required in such cases, the majority do not have cervical disease and should have an endometrial assessment in the first instance.

Evidence: Professional consensus.

12.3 Clinical management of cervical glandular intraepithelial neoplasia

12.3.1 Conservative management of cervical glandular intraepithelial neoplasia lesions

Cervical glandular intraepithelial neoplasia (cGIN) often occurs in young women who wish to retain fertility. The weight of expert opinion has moved from radical towards conservative methods. In selected cases, a conservative cone type excision (using a cylindrical rather than a conical specimen) is considered appropriate. Expert histopathological opinion[216] favours techniques that either avoid or minimise thermal artefact to improve assessment of the excision margins.

For women with suspected cGIN or early invasive adenocarcinoma, the extent of cervical excision can be individualised. In younger women and/or women desirous of fertility who have a colposcopically visible squamocolumnar junction (SCJ), a cylindrically shaped cervical excisional biopsy including the whole transformation zone (TZ) and at least 1 cm of endocervix above the SCJ is appropriate. In older women, or where the SCJ is not visible at colposcopy, cylindrical biopsy including all of the visible TZ and about 20–25 mm of the endocervical canal should be removed.

Evidence: Retrospective and prospective clinical studies[207,217–222] and histomorphometric studies[218,222] support the use of cone biopsy for the management of cGIN, provided that the conditions below are met.

Despite columnar cell origins, this lesion is found in the TZ in 85% of cases.[219,223] TZ involvement is usually accompanied by endocervical columnar disease. Bertrand et al[219] emphasised that deep clefts of up to 5 mm from the margin of the canal could be involved with disease. Although theoretically any site within the endocervix can be affected, multifocal disease is found in only 13–17% of cases and the lesion is usually contiguous with the SCJ, extending up the canal as a unicentric lesion for variable distances. A similar distribution of early invasive adenocarcinoma has been described.[224] Overall, 95% of cGIN extends within 25 mm of the anatomical external os.[219] Further data[225] show a relationship between age and

proximal linear extent of disease, suggesting that more limited excision of the endocervix, ie 1 cm above the SCJ, may be reasonable in women aged <36 years. Such an approach would also allow accurate diagnosis of early invasive adenocarcinoma.[224] A trend for a greater extent of glandular disease has been noted in older women.[125] Similarly, it is well established that the SCJ retreats into the canal with increasing age and thus older women require deeper excisions. Thus, colposcopic examination can help to individualise the requisite extent of the excisional specimen.

In advising expectant management for cGIN, the clinician should be satisfied that:

- the margins of the specimen are free of disease; if the margins of the first excision are not free, it is reasonable to offer a further attempt at conservative excision in order to confidently exclude invasion and obtain negative margins
- the specimen submitted has been thoroughly sampled in the laboratory.

Women to be managed conservatively after cone biopsy should be counselled that expectant management appears safe if careful follow-up is carried out (see below). Recent data indicate a recurrence rate of 15% at four years, although a slightly higher proportion will require further surgical investigation for abnormalities detected during follow-up. Follow-up of conservatively treated cGIN should consist of cytology and such follow-up is best managed in the colposcopy clinic (see section 9.4).

Evidence: Follow-up cytology must include endocervical cells (see section 9.5).[218] Such samples can detect the presence of residual glandular lesions.[218] There are recognised difficulties in assessing atypical glandular cells in samples after cone biopsy for cGIN. Lower segment sampling has been misinterpreted as glandular abnormality, leading to further surgical intervention.[225] The increased awareness of the possibility of glandular neoplasia introduces bias into the diagnosis with increased risks of false positive reporting due to benign mimics.[226]

Although evidence is lacking, colposcopy may be indicated because of the need to monitor the possible recurrence of cGIN, CIN and invasion. However, some form of heightened surveillance and easy access to cytologists is required.

If cervical histology is negative, consider other gynaecological/non-gynaecological conditions that could yield abnormal glandular cells.

Evidence: Observational retrospective studies.[42,55,126,204,205,211]

12.4 Hysterectomy for cervical glandular intraepithelial neoplasia

Simple hysterectomy might be considered in the following circumstances:

- if fertility is not required
- if there are positive margins after an adequate excisional procedure
- if treatment by cone biopsy is followed by further high grade cytological abnormality
- for those who are unwilling to undergo conservative management
- failure to achieve adequate cytological follow-up, eg because of cervical stenosis
- for those with other clinical indications for the procedure
- only when invasive disease has been confidently excluded.

12.5 Summary of standards

1. Reporting of any abnormal glandular sample must be supplemented by a written descriptive report (**100%**).

2. Colposcopic assessment is essential in the presence of cytological glandular abnormality (**100%**).

3. Postmenopausal women with atypical endometrial cells on a sample must be referred to a gynaecologist.

APPENDIX 1: SUMMARY OF STANDARDS

1. To ensure that women are adequately informed about colposcopy and treatment
   - Each woman should be offered verbal and be sent written information before and after a smear and before colposcopy (**95%**) (section 5.2.1).
   - Counselling must be available as an integral part of colposcopy (section 5.2.1).
   - Women must be sent an appropriately worded invitation with a contact name, telephone number and clinic times (section 5.2.1).
   - Information with regard to visit and results of investigations should be communicated to the patient within four weeks of her attendance (**best practice 90%**) or eight weeks (**minimum standard 100%**) (section 5.2.1).
   - Clinics providing a 'see and treat' policy must ensure that women who are offered treatment at their first visit are sent adequate and appropriate information in advance of their appointment (**100%**) (section 5.2.3).
   - All women needing treatment must be informed that treatment will be required and their consent, either written or verbal, recorded (**100%**) (section 8.1).

2. To provide an adequate clinic environment
   - There must be a private area with changing facilities. There must also be toilet facilities (section 5.2.5).
   - There must be a permanently sited specific room for colposcopy (**100%**) (section 5.2.5).
   - Refreshments must be available (section 5.2.5).
   - There must be separate waiting and recovery areas (section 5.2.5).
   - There must be a permanent couch and colposcope (section 5.3).
   - Appropriate sterilising facilities must be available in accordance with local and national health and safety recommendations (section 5.3).
   - In units offering a diagnostic service, there must be automatic referral to a unit where treatment is available if required (section 5.3).
   - If laser or diathermy equipment is in use, there must be adequate safety guidelines in place with all staff trained in their use and emergency guidelines must be available in each clinic (section 5.3).
   - Adequate resuscitation equipment must be immediately available and staff involved in the clinical care of patients must be familiar with its use (section 5.3).

3. To provide appropriate clinic staff
   - All clinics must have a named colposcopist with appropriate skills who leads the service with a specialist team specific to the colposcopy unit. The named lead colposcopist must have a job description (section 5.4).
   - There must be at least two nurses for each clinic (section 5.4).
   - Nurse colposcopists working in a clinic role must be supported by another registered nurse (section 5.4).
   - There must be adequate dedicated clerical support for the clinic (section 5.4).

4. To ensure appropriate and accurate data collection
   - There must be suitable information technology equipment and software to facilitate collection of data for the BSCCP minimum dataset and for submission of the statutory quarterly KC65 (section 5.3).
   - Multidisciplinary audit must be an integral part of the service (section 5.6).

5. To reduce default
   - There must be written protocols for the management of non-attenders (section 5.6).
   - The default rate should be less than **15%** (section 5.6).

6. To reduce failure of diagnosis of early cancers
   - All women needing treatment must have had a colposcopic assessment (**100%**) (section 8.1).
   - An excisional form of biopsy is recommended (**95%**) (section 6.3):
     - when colposcopic appearances indicate high grade abnormality
     - when low grade colposcopic change is associated with severe dyskaryosis or worse
     - when a lesion extends into the canal (sufficient canal must be removed in these situations).
   - Reasons for not performing a biopsy must be recorded (**100%**) (section 6.3).
   - All measures including biopsy must be taken to exclude invasion prior to treating with local destruction (**100%**) (section 6.4).

7. To improve the quality, accuracy and timeliness of diagnosis
   - Cervical screening should take place between the ages of 25 and 64 at intervals of three or five years, depending on the woman's age (section 2.1.1).
   - Women must be called on or around their 25th birthday and subsequently recalled at three-yearly intervals between the ages of 25 and 49 years, and at five-yearly intervals between the ages of 50 and 64 years (section 2.1.3).
   - Women should be referred for colposcopy after three consecutive inadequate samples (section 4.1).
   - Women should be referred for colposcopy after three tests in a series reported as borderline nuclear change in squamous cells

without the woman being returned to routine recall (section 4.2.1).

- Women should be referred for colposcopy after one test reported as borderline nuclear change in endocervical cells (section 4.2.2).
- Women should be referred for colposcopy if they have had three tests reported as abnormal of any grade in a 10-year period (section 4.3).
- Ideally, women should be referred for colposcopy after one test reported as mild dyskaryosis, but it remains acceptable to recommend a repeat test. Women must be referred after two tests reported as mild dyskaryosis without a return to routine recall (section 4.4).
- Women must be referred for colposcopy after one test reported as moderate dyskaryosis (**100%**) (section 4.5).
- Women must be referred for colposcopy after one test reported as severe dyskaryosis (**100%**) (section 4.6).
- Women must be referred for colposcopy after one test reported as possible invasion (**100%**). They should be seen urgently within two weeks of referral (**90%**) (section 4.7).
- Women must be referred for colposcopy after one test reported as glandular neoplasia (**100%**). They should be seen urgently within two weeks of referral (**90%**) (section 4.8).
- Women should be referred for colposcopy if they have been treated for CIN and have not been returned to routine recall and a subsequent test is reported as mild dyskaryosis or worse (**100%**) (section 4.11).
- At least **90%** of women with an abnormal test result should be seen in a colposcopy clinic within eight weeks of referral (section 4.12).
- At least **90%** of women with a test result of moderate or severe dyskaryosis should be seen in a colposcopy clinic within four weeks of referral (section 4.12).
- The following data should be recorded at the colposcopic examination (section 6.2):
  - reason for referral (**100%**)
  - grade of cytological abnormality (**90%**)
  - whether the examination is satisfactory; this is defined as the entire SCJ having been seen, and the upper limit of any cervical lesion also being seen (**100%**).
- Of all biopsies taken (directed and excisional), >**90%** should be suitable for histological interpretation (section 6.5.2).
- If a colposcopically directed biopsy is reported as inadequate for histological interpretation, it should be repeated if there is a residual colposcopic lesion (**95%**) (section 6.5.2).
- For those with satisfactory colposcopic examination, the predictive value of a colposcopic diagnosis of a high grade lesion (CIN 2 or worse) should be at least **65%** (section 6.6).
- Biopsy should be undertaken in >**95%** of women with high grade abnormalities (section 9.8.1).
- Women referred with moderate dyskaryosis or worse cytological abnormalities who have a colposcopically low grade lesion and

who are not treated should have multiple biopsies (**90%**) (section 9.8.1).

- All patients who are immunosuppressed must be managed in a centre with demonstrable skill and expertise, with sufficient access to patient numbers to maintain that expertise (section 11.1).
- All women aged 25–65 years with renal failure requiring dialysis must have cervical cytology performed at or shortly after diagnosis (section 11.2).
- Reporting of any abnormal glandular smear must be supplemented by a written descriptive report (**100%**) (section 12.2.1).
- Postmenopausal women with atypical endometrial cells on a smear must be referred to a gynaecologist (section 12.2.6).
- The investigation of abnormal bleeding after the menopause must include direct visual inspection of the cervix (section 10.3.2).
- Colposcopic assessment is essential in the presence of cytological glandular abnormality (**100%**) (section 12.2.2).
- If colposcopy has been performed during pregnancy, postpartum assessment of women with an abnormal smear or biopsy proven CIN is essential (**100%**) (section 10.1.2).
- Colposcopic evaluation of the pregnant woman requires a high degree of skill. If invasive disease is suspected clinically or colposcopically, a biopsy adequate to make the diagnosis is essential (**100%**) (section 10.2.3).
- All patients in the cervical screening age range undergoing a hysterectomy for other gynaecological reasons should have a negative smear within the screening interval or as part of their preoperative investigations (**100%**) (section 10.4.1).
- All patients being considered for hysterectomy who have an undiagnosed abnormal smear or symptoms attributable to cervical cancer should have diagnostic colposcopy and an appropriate biopsy (**100%**) (section 10.4.2).

8. To ensure appropriate selection for and quality of treatment
   - Colposcopy clinics in GUM must have established protocols for liaison with gynaecological services (**100%**) (section 5.6).
   - Clinic staff must always be familiar with the treatment method(s) used (**100%**) (section 5.3).
   - Biopsy should be carried out unless an excisional treatment is planned, when the cytology indicates persisting moderate dyskaryosis or worse, and always when a recognisably atypical TZ is present (**100%**). Pregnancy is an exception (section 6.5).
   - All patients must have a biopsy or biopsies taken prior to local destructive treatment (**100%**). Unless there are special circumstances, the result of the biopsy should be available (best practice) (section 6.5.2).
   - All women needing treatment must be informed that treatment will be required and their consent, either written or verbal, recorded (**100%**) (section 8.1).
   - All women needing treatment must have had a colposcopic assessment (**100%**) (section 8.1).

- All treatments must be recorded (**100%**) (section 8.1).
- All women must be treated in properly equipped and staffed clinics (**100%**) (section 8.1).
- All women must have had their histological diagnosis established prior to destructive therapy (**100%**) (section 8.1).
- The proportion of women treated at the first visit who have evidence of CIN on histology must be ≥**90%** (section 8.1).
- The proportion of treatment associated with primary haemorrhage that requires a haemostatic technique in addition to the treatment method applied must be **<5%** (section 8.1).
- The proportion of patients admitted as inpatients owing to treatment complications must be <**2%** (section 8.1).
- Ablative techniques are only suitable when (section 8.2):
  - the entire transformation zone is visualised (**100%**)
  - there is no evidence of glandular abnormality (**100%**)
  - there is no evidence of invasive disease (**100%**)
- Cryocautery should only be used for low grade CIN and a double freeze thaw–freeze technique must be used (**100%**) (section 8.3).
- When excision is used, at least **80%** of cases should have the specimen removed as a single sample (section 8.4.1).
- For ectocervical lesions, excisional techniques should remove tissue to a depth of greater than 7 mm (**95%**) (section 8.4.3).
- Treatment at first visit for a referral of borderline or mild dyskaryosis should only be used in exceptional cases, and only when audit has identified that CIN is present in ≥**90%** of the excised specimens.
- All women over the age of 50 years who have CIN 3 at the endocervical margin, and in whom satisfactory cytology and colposcopy cannot be guaranteed, must have a repeat excision performed to try and obtain clear margins (**100%**) (section 8.6.2).
- Women with adenocarcinoma in situ/cGIN can be managed by local excision for those wishing to retain fertility. Incomplete excision at the endocervical margin requires a further excisional procedure to obtain clear margins and exclude occult invasive disease (**95%**) (section 8.7.1).
- The proportion of women managed as outpatients with local analgesia must be >**80%** (section 8.8).

9. To ensure appropriate and adequate follow-up
   - All women are at risk after treatment and must be followed up (**100%**) (section 9.1).
   - Follow-up should start at six months after treatment and not later than eight months after treatment (>**90%**) (section 9.2).
   - All women who do not have negative test results after treatment must be recolposcoped at least once within 12 months (**100%**) (section 9.2).
   - The proportion of treated women with no dyskaryosis six months after treatment should exceed **90%** (section 9.2).
   - The proportion of confirmed histological treatment failures should not exceed **5%** within 12 months of treatment (section 9.2).

- If at follow-up a high grade cytological abnormality persists, excisional treatment is recommended (**90%**) (section 9.8.1).
- If a low grade lesion has not resolved within two years of referral to colposcopy, at least a biopsy is warranted (>**90%**) (section 9.8.4).

10. To ensure adequate communications with the referring practitioner
    - Results and management plans should be communicated to the referring practitioner within four weeks of the patient's attendance at the clinic (**best practice 90%**) or eight weeks (**minimum standard 100%**) (section 5.2.1).

11. To maintain skill levels
    - All practising colposcopists must be able to demonstrate that they have received an adequate training (section 5.7.1).
    - All colposcopists in the team should be certificated through the BSCCP/RCOG scheme and should comply with the recertification process every three years (section 5.7.1).
    - Colposcopists practising within the NHSCSP should see at least 50 new abnormal cytology referrals per year (section 5.7.2).
    - All colposcopists must attend one colposcopy meeting recognised by the BSCCP every three years (section 5.7.2).

APPENDIX 2: GUIDANCE ON WORKING PRACTICES FOR COLPOSCOPY UNITS

The following guidance has been agreed by the NHSCSP Colposcopy Quality Assurance (QA) Group.

1. There needs to be a clear structure for managing NHS colposcopy services, whatever the setting. There should be a designated lead colposcopist, ideally at consultant level, who is a practising colposcopist certificated through the BSCCP/RCOG scheme.

2. The lead colposcopist will be required to ensure that the defined standards are being met and maintain data collection, which will allow audit to be conducted against these standards. The agreed national minimum dataset and the required quarterly return should be collected. The required annual return will be the responsibility of the lead colposcopist.

3. The data collected will serve as a means of comparing performance between colposcopy units. All colposcopic practice, whether in trusts or in the community, should be measured against uniform national standards. Regional arrangements should be in place to ensure that colposcopy clinics are running effectively. A scheme of regular visits (eg every 3–4 years) may provide an effective process for identifying deficiencies before problems arise and encourage good practice.

4. Where concerns arise about colposcopic practice, there must be a means of open discussion between colleagues. The best way of ensuring this is a culture of audit within the unit. This should comprise regular multidisciplinary meetings. Quality assurance is a means of ensuring that standards are improved, where necessary, using a constructive approach rather than a critical one.

5. Where concerns arise about an individual's clinical performance in colposcopy, these require to be handled sensitively and should be the responsibility of the lead colposcopist. There must be a speedy resolution and if this fails, or the lead colposcopist is under scrutiny, the medical director (or equivalent) should take responsibility. The regional QA colposcopy representative should also be involved at this stage.

6. Individual practice often cannot be judged on the basis of a small sample of cases with poor outcomes, unless these are extreme. Large truly representative samples may be required using valid outcomes in order to reach reliable conclusions. Only when matters cannot be satisfactorily resolved 'in house' should consideration be given to the need for external review. The external reviewer should assist in determining the extent and nature of the review. Under these circumstances the regional QA director will be informed.

7. All NHS colposcopy units must comply with the nationally agreed QA measures, and trusts and primary care trusts (PCTs) should regard maintenance of quality in colposcopy as an essential part of the framework of clinical governance.

APPENDIX 3: EXAMPLE JOB DESCRIPTION FOR LEAD COLPOSCOPISTS

Introduction

The NHSCSP requires that each hospital trust providing colposcopy services should have a named lead colposcopist. In trusts where more than one colposcopy unit provides services, there should be one lead colposcopist to coordinate the KC65 statutory return, but there may be lead clinicians in separate colposcopy clinics within a single trust.

The National Quality Assurance Group in Colposcopy of the NHSCSP and the Royal College of Obstetricians and Gynaecologists (RCOG) have published guidance previously on the roles and responsibilities for lead colposcopists.

The national quality assurance group has devised this job description for lead colposcopists. Both the RCOG and the NHSCSP Quality Assurance Group believe that the roles and responsibilities of the lead colposcopist should be recognised by a sessional commitment of at least one notional half day per week (or programmed activity). The lead colposcopist should be supported by at least one session of designated administrative/secretarial time for the tasks associated with the position.

Responsibilities of the post

The lead colposcopist is responsible for:

- Ensuring that written protocols are in place for the service and that these include recommended national guidelines.
- Ensuring that the protocols are regularly reviewed so that the needs of the commissioners and the users of the service are met. The lead colposcopist will be required to ensure that the defined quality assurance standards are being met. The agreed national minimum dataset and the required quarterly KC65 return should be collected.
- Ensuring that regular audit of the service takes place to compare practice with the local protocols and national targets.
- Liaising with those within the trust responsible for providing the facilities for the service to ensure that the service is adequately staffed by appropriately trained individuals (medical and non-medical) in order that the service needs can be met in a timely and consumer sensitive fashion.
- Coordinating training and liaising with the BSCCP Certification and Training Committee as appropriate.
- Facilitating the maintenance of continued certification of practising colposcopists within the unit.
- Informing those in the trust management about the need to ensure that procedures are in place to facilitate care and rapid communication with patients, other hospital departments, primary care agencies and cytopathology and histopathology services.

- With the hospital based programme coordinator, convening regular multidisciplinary meetings, including cytology and histology services for case discussion and protocol review.
- Working with the hospital based programme coordinator to alert the PCT screening commissioner of any shortcomings of any aspect of the ability of the colposcopy services to respond to issues in primary care.
- Conducting regular dialogue with users, providers and purchasers of care to ensure that service and development are both appropriate and meet with the needs of the local population.

Person specification

Essential:

- BSCCP/RCOG certification
- commitment to the colposcopy service and readiness to take responsibility for it
- organisational skills
- team management skills
- training skills

Desirable:
Experience of:

- information technology
- data analysis
- conducting research

REFERENCES

1. Duncan ID (ed). *Guidelines for Clinical Practice and Programme Management*, 2nd edn. NHS Cervical Screening Programme, 1997 (NHSCSP Publication No 8).
2. Luesley D (ed). *Standards and Quality in Colposcopy*. NHS Cervical Screening Programme, 1996 (NHSCSP Publication No 2).
3. Sasieni P, Adams J, Cuzick J. Benefit of cervical screening at different ages: evidence from the UK audit of screening histories. *British Journal of Cancer*, 2003, 89(1): 88–93.
4. IARC Working Group on Evaluation of Cervical Cancer Screening Programmes. Screening for squamous cervical cancer: duration of low risk after negative results of cervical cytology and its implication for screening policies. *British Medical Journal*, 1986, 293: 659–664.
5. Sasieni PD, Cuzick J, Lynch-Farmery E. Estimating the efficacy of screening by auditing smear histories of women with and without cervical cancer. The National Co-ordinating Network for Cervical Screening Working Group. *British Journal of Cancer*, 1996, 73: 1001–1005.
6. Herbert A, Stein K, Bryant TN et al. Relation between the incidence of invasive cervical cancer and the screening interval: is a five year interval too long? *Journal of Medical Screening*, 1996, 3: 140–145.
7. Sawaya GF, McConnell KJ, Kulasingam SL et al. Risk of cervical cancer associated with extending the interval between cervical cancer screenings. *New England Journal of Medicine*, 2003, 349: 1501–1509.
8. *Statistical Bulletin. Cervical Screening Programme*, *England: 2002–2003*. Department of Health, 2003 (Bulletin 2003/24).
9. Sasieni P, Adams J. Effect of screening on cervical cancer mortality in England and Wales: analysis of trends with an age cohort model. *British Medical Journal*, 1999, 318: 1244–1245.
10. Adelstein AM, Husain OAN, Spriggs AI. Cancer of the cervix and screening. *British Medical Journal*, 1981, 282: 564.
11. Collins S, Mazloomzadeh S, Winter H et al. High incidence of cervical human papillomavirus infection in women during their first sexual relationship. *British Journal of Gynaecology*, 2002, 109: 96–98.
12. Wright VC, Riopelle MA. Age at beginning of coitus versus chronologic age as a basis for Papanicolaou smear screening: an analysis of 747 cases of preinvasive disease. *American Journal of Obstetrics and Gynecology*, 1984, 149: 824–830.
13. Quinn M, Babb P, Jones J et al. Effect of screening on the incidence of and mortality from cancer of the cervix in England, Evaluation based on routinely collected statistics. *British Medical Journal*, 1999, 318: 904–908.
14. Gustafsson L, Sparen P, Gustafsson M et al. Low efficiency of cytologic screening for cancer in situ of the cervix in older women. *International Journal of Cancer*, 1995, 63: 804–809.
15. Cruickshank ME, Angus V, Kelly M et al. The case for stopping cervical screening at age fifty. *British Journal of Obstetrics and Gynaecology*, 1997, 104: 586–589.
16. Van Winjngaarden W, Duncan ID. Rationale for stopping cervical screening in women over fifty. *British Medical Journal*, 1993, 306: 967–971.
17. Cornelison TL, Montz FJ, Bristow RE et al. Decreased incidence of cervical cancer in Medicare-eligible California women. *Obstetrics and Gynaecology*, 2002, 100(1): 79–86.
18. Sherlaw C, Johnson S, Gallivan S et al. Withdrawing low risk women from cervical screening programmes: mathematical modelling study. *British Medical Journal*, 1999, 318: 356–361.

19. Cuzick J, Beverley E, Ho L et al. HPV testing in primary screening of older women. *British Journal of Cancer*, 1999, 81: 554–558.
20. Shun-Zhang Y, Miller AB, Sherman GJ. Optimising the age, number of tests and test interval for cervical screening in Canada. *Journal of Epidemiology and Community Health*, 1982, 36: 1–10.
21. Blomfield PI, Lancashire RJ, Woodman CBJ. Can women at risk of cervical abnormality be identified? *British Journal of Obstetrics and Gynaecology*, 1998, 105: 486–492.
22. Hakama M, Pukkala E, Saastamoinen P. Selective screening: theory and practice based on high-risk groups of cervical cancer. *Journal of Epidemiology and Community Health*, 1979, 33: 257–261.
23. Stedman Y, Woodman CBJ, Donnelly BJ. Is a policy of screening for all women attending a genitourinary medicine clinic justified? *Journal of Public Health Medicine*, 1995, 17(1): 90–92.
24. Wilson JD, Parsons W. On behalf of the British Co-operative Clinical Group. Cervical cytology smears in sexually transmitted infection clinics in the United Kingdom. *Sexually Transmitted Infections*, 2001, 77: 107–110.
25. Foley E, Harinda V. Cervical cytology: are national guidelines adequate for women attending genito-urinary medicine clinics. *Sexually Transmitted Infections*, 1999, 75: 349–351.
26. Edwards SK, Sonnex C. Influence of genital infection on cervical cytology. *Sexually Transmitted Infections*, 1998, 74: 271–273.
27. Schwebke JR, Zajackowski ME. Effects of concurrent lower genital tract infections on cervical cancer screening. *Genitourinary Medicine*, 1997, 73: 383–386.
28. Brady M, Brook G. Influence of genital infection on cervical cytology. *Sexually Transmitted Infections*, 1998, 74: 457–458 (letter).
29. Burja IT, Shurbaji MS. Clinical impact of identifying *Trichomonas vaginalis* on cervicovaginal (Papanicolaou) smears. *Diagnostic Cytopathology*, 2000, 24: 195–199.
30. Vinette-Leduc D, Yazdi HM, Jessamine P et al. Reliability of cytology to detect chlamydial infection in asymptomatic women. *Diagnostic Cytopathology*, 1997, 17: 258–261.
31. Dimian C, Nayagam M, Bradbeer C. The association between sexually transmitted diseases and inflammatory cervical cytology. *Genitourinary Medicine*, 1992, 68: 305–306.
32. Nanda K, McCrory DC, Myers ER et al. Accuracy of the Papanicolaou Test in screening for and follow-up of cervical cytologic abnormalities: a systemic review. *Annals of Internal Medicine*, 2000, 132: 810–819.
33. *Guidance on the Use of Liquid-based Cytology for Cervical Screening*. National Institute for Clinical Excellence (NICE), 2003 (Technology Appraisal Guidance 69).
34. Maiman M, Fruchter RG, Sedlis A et al. Prevalence, risk factors, and accuracy of cytologic screening for cervical intraepithelial neoplasia in women with the human immunodeficiency virus. *Gynecology and Oncology*, 1998, 68: 233–239.
35. Cuzick J, Sasieni P, Davies P et al. *A Systematic Review of the Role of Human Papilloma Virus Testing (HPV) in the Cervical Screening Programme.* Health Technology Assessment, 1999.
36. Manos MM, Kinney WK, Hurley LB et al. Identifying women with cervical neoplasia: using human papillomavirus DNA testing for equivocal Papanicolaou results. *Journal of the American Medical Association*, 1999, 281: 1605–1610.
37. Nobbenhuis MA, Meijer CJ, van den Brule AJ et al. Addition of high-risk HPV testing improves the current guidelines on follow-up after treatment for cervical intraepithelial neoplasia. *British Journal of Cancer*, 2001, 84: 796–801.

38. Paraskevaidis E, Koliopoulos G, Alamonos Y et al. Human papillomavirus testing and the outcome of treatment for cervical intraepithelial neoplasia. *Obstetrics and Gynaecology*, 2002, 98: 833–836.
39. Solomon D, Schiffman M, Tarone R. Comparison of three management strategies for patients with atypical squamous cells of undetermined significance: baseline results from a randomized trial. *Journal of the National Cancer Institute*, 2001, 93: 293–299.
40. Bolger BS, Lewis BV. A prospective study of colposcopy in women with mild dyskaryosis or koilocytosis. *British Journal of Obstetrics and* Gynaecology, 1988, 95: 1117–1119.
41. Hirschowitz L, Raffle AE, Mackenzie EFD et al. Long term follow up of women with borderline cervical smear test results: effects of age and viral infection on progression to high-grade dyskaryosis. *British Medical Journal*, 1992, 304: 1209–1212.
42. Cullimore J, Scurr J. The abnormal glandular smear: cytologic prediction, colposcopic correlation and clinical management. *Journal of Obstetrics and Gynaecology*, 2000, 20: 403–407.
43. Mohammed DKA, Lavie O, Lopes A de B et al. A clinical review of borderline glandular cells on cervical cytology. *British Journal of Obstetrics and Gynaecology*, 2000, 107: 605–609.
44. Zweizig S, Noller K, Reale F et al. Neoplasia associated with atypical glandular cells of undetermined significance on cervical cytology. *Gynecology and Oncology*, 1997, 65: 314–318.
45. Kennedy AW, Salmieri SS, Wirth SL et al. Results of the clinical evaluation of atypical glandular cells of undetermined significance (AGCUS) detected on cervical cytology screening. *Gynecology and Oncology*, 1996, 63: 14–18.
46. Anderson DJ, Flannelly GM, Kitchener HC et al. Mild and moderate dyskaryosis; can women be selected for colposcopy on the basis of social criteria? *British Medical Journal*, 1992, 305: 84–87.
47. Soutter WP, Wisdom S, Brough AK et al. Should patients with mild atypia in a cervical smear be referred for colposcopy? *British Journal of Obstetrics and Gynaecology*, 1986, 93: 70–74.
48. Soutter WP, Fletcher A. Invasive cancer of the cervix in women with mild dyskaryosis followed up cytologically. *British Medical Journal*, 1994, 308: 1421–1423.
49. Flannelly G, Anderson D, Kitchener HC et al. Management of women with mild and moderate cervical dyskaryosis. *British Medical Journal*, 1994, 308: 1399–1403.
50. Johnson N, Sutton J, Thornton JG et al. Decision analysis for best management of mildly dyskaryotic smear. *Lancet*, 1993, 343: 91–96.
51. *Achievable Standards, Benchmarks for Reporting, and Criteria for Evaluating Cervical Cytopathology*, 2nd edn. NHS Cancer Screening Programmes, 2000 (NHSCSP Publication No 1).
52. Shafi MI, Luesley DM, Jordan JA et al. Randomised trial of immediate versus deferred treatment strategies for the management of minor cervical cytological abnormalities. *British Journal of Obstetrics and Gynaecology*, 1997, 104: 590–594.
53. Bigrigg MA, Codling BW, Pearson P et al. Colposcopic diagnosis and treatment of cervical dysplasia at a single clinic visit. Experience of low-voltage diathermy loop in 1000 patients. *Lancet*, 1990, 336: 229–231.
54. Johnson SJ, Wadehra V. How predictive is a cervical smear suggesting invasive squamous cell carcinoma? *Cytopathology*, 2001, 12: 144–150.
55. Leeson SC, Inglis TCM, Salman WD. A study to determine the underlying reason for abnormal glandular cytology and the formulation of a management protocol. *Cytopathology*, 1997, 8: 20–26.

56. Rosenthal AN, Panoskaltsis T, Smith T et al. The frequency of significant pathology in women attending a general gynaecological service for postcoital bleeding. *British Journal of Obstetrics and Gynaecology*, 2001, 108: 103–106.
57. Soutter WP, de Barros Lopes A, Fletcher A et al. Invasive cervical cancer after conservative therapy for cervical intraepithelial neoplasia. *Lancet*, 1997, 349: 978–980.
58. Austoker J, Davey C, Jansen C. *Improving the Quality of the Written Information Sent to Women About Cervical Screening.* NHS Cancer Screening Programmes, 1997 (NHSCSP Publication No 5).
59. Posner T, Vessey M. *Prevention of Cervical Cancer: The Patient's View.* King Edward's Hospital Fund for London, 1988.
60. Marteau TM. Reducing anxiety in women referred for colposcopy using an information booklet. *British Journal of Health Psychology*, 1996, 1: 181–189.
61. Marteau TM, Bekker H. The development of a six-item short-form of the State Scale of the Spielberger State–Trait Anxiety Inventory. *British Journal of Clinical Psychology*, 1992, 31: 301–306.
62. Marteau T, Walker P, Giles J et al. Anxieties in women undergoing colposcopy. *British Journal of Obstetrics and Gynaecology*, 1990, 97: 859–861.
63. Lerman C, Miller S, Scarborough R et al. Adverse psychologic consequences of positive cytologic cervical screening. *American Journal of Obstetrics and Gynecology*, 1991, 163: 658–662.
64. Gath D, Hallam N, Mynors-Wallis L et al. Emotional reactions in women attending a UK colposcopy clinic. *Journal of Epidemiology and Community Health*, 1995, 49: 79–83.
65. Schwartz M, Savage W, George J et al. Women's knowledge and experience of cervical screening: a failure of health education and medical organisation. *Community Medicine*, 1989, 46: 499–507.
66. Fylan F. Screening for cervical cancer: a review of women's attitudes, knowledge, and behaviour (see comments). *British Journal of General Practice*, 1998, 48: 1509–1514 (review).
67. Kernohan EEM. Evaluation of a pilot study for breast and cervical cancer screening with Bradford's minority ethnic women; a community development approach 1991–1993. *British Journal of Cancer*, 1996, 74 (Suppl XXIX): S42–S46.
68. Freeman-Wang T, Walker P, Linehan J et al. Anxiety levels in women attending colposcopy clinics for treatment for cervical intraepithelial neoplasia: a randomised trial of written and video information. *British Journal of Obstetrics and Gynaecol*ogy, 2001, 5: 482–484.
69. Smith T. Colposcopy. *Nursing Standard*, 1997, 11(45): 49–54.
70. Howells REJ, Lockett J, Dunn PDJ et al. Do women referred for colposcopy receive adequate information from the primary care team? *Journal of Obstetrics and Gynaecology*, 1999, 19(1): 59–60.
71. Meerabeau J. The management of embarrassment and sexuality in health care. *Journal of Advanced Nursing*, 1999, 29(6): 1507–1513.
72. Wilson JD, Hines B. Nurse counselling for women with abnormal cervical cytology improves colposcopy and cytology follow up attendance rates. *Sexually Transmitted Infections*, 2000, 76(4): 322.
73. Lester H, Wilson S. Is default from colposcopy a problem, and if so what can we do? A systematic review of the literature. *British Journal of Gynaecological Procedures*, 1999, 49: 223–229.
74. Sanders G, Craddock C, Waggstaff I. Factors influencing default at a colposcopy clinic. *Quality Health Care*, 1992, 1: 236–240.
75. Patterson T, Roworth M, Hill M. An investigation into the default rate at the Fife colposcopy clinic. *Journal of Reproductive Medicine*, 1995, 17(1): 65–69.
76. Freeman-Wang T, Coffey C, Walker PG. Non attendance for colposcopy: is it really a problem? *Poster Presentation BSCCP Annual General Meeting, Harrogate*, 2001.

77. Miller S, Seijak KK, Schroeder CM et al. Enhancing adherence following abnormal pap smears among low income women: a preventive telephone counselling strategy. *Journal of the National Cancer Institute*, 1997, 89: 703–708.
78. Lerman C, Hanjani P, Caputo C et al. Telephone counselling improves adherence to colposcopy in lower income minority women. *Journal of Clinical Oncology*, 1992, 10: 330–333.
79. Shen RN, Hicks DA, Cruickshank ME. Colposcopy services provided by genito-urinary medicine clinics in the United Kingdom. BSCCP/National Co-ordinating Network Survey 1993. *International Journal of Sexually Transmitted Diseases and AIDS*, 1996, 7: 98–101.
80. Etherington IJ, Luesley DM, Shafi MI et al. Observer variability among colposcopists from the West Midlands region. *British Journal of Obstetrics and Gynaecology*, 1997, 104: 1380–1384.
81. Kierkegaard O, Byrjalsen C, Frandsen KH et al. Diagnostic accuracy of cytology and colposcopy in cervical squamous intraepithelial lesions. *Acta Obstetrica et Gynecologica Scandinavica*, 1994, 738: 648–651.
82. Pretorius RG, Belinson JL, Zhang WH et al. The colposcopic impression. Is it influenced by the colposcopist's knowledge of the findings on the referral Papanicolaou smear? *Journal of Reproductive Medicine*, 2001, 46(8): 724–728.
83. Hopman EH, Kenemans P, Helmerhorst TJ. Positive predictive rate of colposcopic examination of the cervix uteri: an overview of literature. *Obstetrics and Gynecology Survey*, 1998, 53: 97–106.
84. Benedet JL, Anderson GH, Boyes DA. Colposcopic accuracy in the diagnosis of microinvasive and occult invasive carcinoma of the cervix. *Obstetrics and Gynecology*, 1985, 65: 557–662.
85. Liu WM, Chao KC, Wang KI et al. Colposcopic assessment in microinvasive carcinoma of the cervix. *Chung Hua I Hsueh Tsa Chih (Taipei)*, 1989, 43: 171–176.
86. Skehan M, Soutter WP, Lim K et al. Reliability of colposcopy and directed punch biopsy. *British Journal of Obstetrics and Gynaecology*, 1990, 97: 811–816.
87. Buxton EJ, Luesley DM, Shafi MI et al. Colposcopically directed punch biopsy: a potentially misleading investigation. *British Journal of Obstetrics and Gynaecology*, 1991, 98: 1273–1276.
88. Ang MS, Kaufman RH, Adam E et al. Colposcopically directed biopsy and loop excision of the transformation zone. Comparison of histologic findings. *Journal of Reproductive Medicine*, 1995, 40: 167–170.
89. Sillman F, Boyce J, Fruchter R. The significance of atypical vessels and neovascularization in cervical neoplasia. *American Journal of Obstetrics and Gynecology*, 1981, 139: 154–159.
90. Anderson MC. Invasive carcinoma of the cervix following local destructive treatment for cervical intraepithelial neoplasia. *British Journal of Obstetrics*, 1993, 100: 657–663.
91. Shumsky AG, Stuart GC, Nation J. Carcinoma of the cervix following conservative management of cervical intraepithelial neoplasia. *Gynecologic Oncology*, 1994, 53(1): 50–54.
92. Duncan ID. Cold coagulation. *Baillière's Clinical Obstetrics and Gynaecology*, 1995, 9: 145–155.
93. Loobuyck HA, Duncan ID. Destruction of CIN1 and 2 with the Semm cold coagulator: 13 years' experience with a see-and-treat policy. *British Journal of Obstetrics and Gynaecology*, 1993, 100: 465–468.
94. Gordon HK, Duncan ID. Effective destruction of cervical intraepithelial neoplasia (CIN) 3 at 100°C using the Semm cold coagulator: 14 years' experience. *British Journal of Obstetrics and Gynaecology*, 1991, 98: 14–20.

95. Howells RE, O'Mahoney F, Tucker H et al. How can the incidence of negative specimens resulting from large loop excision of the cervical transformation zone (LLETZ) be reduced? An analysis of negative LLETZ specimens and development of a predictive model. *British Journal of Obstetrics and Gynaecology*, 2000, 107: 1075–1082.
96. Parham DM, Wiredu EK, Hussein KA. The cytological prediction of cervical intraepithelial neoplasia in colposcopically directed biopsies. *Cytopathology*, 1991, 2: 285–290.
97. Jones MH, Jenkins D, Singer A. Regular audit of colposcopic biopsies from women with a mildly dyskaryotic or borderline cervical smear results in fewer cases of CINIII. *Cytopathology*, 1996, 7(1): 17–24.
98. Cinel A, Oselladore M, Insacco E et al. The accuracy of colposcopically directed biopsy in the diagnosis of cervical intraepithelial neoplasia. *European Journal of Gynaecological Oncology*, 1990, 11(6): 433–437.
99. Baldauf JJ, Dreyfus M, Ritter J et al. An analysis of the factors involved in the diagnostic accuracy of colposcopically directed biopsy. *Acta Obstetrica et Gynecologica Scandinavica*, 1997, 76: 468–473.
100. Heatley MK, Bury J. The correlation between the grade of dyskaryosis on cervical smear, grade of cervical intraepithelial neoplasia (CIN) on punch biopsy and the final histological diagnosis on cone biopsies of the cervix. *Cytopathology*, 1998, 9: 93–99.
101. Hopman EH, Voorhoorst FJ, Kenemans P et al. Observer agreement on interpreting colposcopic images of CIN. *Gynecologic Oncology*, 1995, 58: 206–209.
102. McCord ML, Stovall TG, Summitt RL Jr et al. Discrepancy of cervical cytology and colposcopic biopsy: is cervical conization necessary? *Obstetrics and Gynecology*, 1991, 77: 715–719.
103. Mitchell MF, Schottenfeld D, Tortolero-Luna G et al. Colposcopy for the diagnosis of squamous intraepithelial lesions: a meta-analysis. *Obstetrics and Gynecology*, 1998, 91: 626–631.
104. Rokyta Z. Diagnostic reliability of prebioptic methods in the prediction of a histological basis of cervical lesions and its correlation with accuracy of colposcopically directed biopsy in patients with cervical neoplasia. *European Journal of Gynaecological Oncology*, 2000, 215: 484–486.
105. Pimenta J, Catchpole M, Gray M et al. Screening for genital chlamydial infection. *British Medical Journal*, 2000, 321: 629–631.
106. Chief Medical Officer's Expert Advisory Group. *Main Report of the CMO's Expert Advisory Group on* Chlamydia trachomatis. London: Department of Health, 1998.
107. Lewis LS, Bushell A, Read K. Chlamydia and cervical smear testing. *British Medical Journal*, 1991, 302: 413–414.
108. Eltabbakh GH, Eltabbakh GD, Broekhuizen FF et al. Value of wet mount and cervical cultures at the time of cervical cytology in asymptomatic women. *Obstetrics and Gynecology*, 1995, 85: 499–503.
109. Cayley J, Fotherby K, Guillebaud J et al. *Recommendations for Clinical Practice: Actinomyces like Organisms and Intrauterine Contraceptives*. Faculty of Family Planning and Reproductive Health Care, RCOG, 1998.
110. RCOG. *Management of Genital Herpes in Pregnancy*. Clinical Guideline No 30, RCOG, 2002.
111. Martin-Hirsch PL, Paraskevaidis E, Kitchener H. Surgery for cervical intraepithelial neoplasia. *Cochrane Database of Systematic Reviews (computer file)*, 2000(2): CD001318.
112. Dey P, Gibbs A, Arnold DF et al. Loop diathermy excision compared with cervical laser vaporisation for the treatment of intraepithelial neoplasia: a randomised controlled trial. *British Journal of Obstetrics and Gynaecology*, 2002, 109: 381–385.

113. Ostergard DR. Cryosurgical treatment of cervical intraepithelial neoplasia. *Obstetrics and Gynecology,* 1980, 56(2): 231–233.
114. Walton LA, Edelman DA, Fowler WC Jr, Photopulos GJ. Cryosurgery for the treatment of cervical intraepithelial neoplasia during the reproductive years. *Obstetrics and Gynaecology*, 1980, 55: 353–357.
115. Creasman WT, Hinshaw WM, Clarke-Pearson DL. Cryosurgery in the management of cervical intraepithelial neoplasia. *Obstetrics and Gynecology*, 1984, 63: 145–149.
116. Schantz A, Thormann L. Cryosurgery for dysplasia of the uterine ectocervix. A randomized study of the efficacy of the single- and double-freeze techniques. *Acta Obstetrica et Gynecologica Scandinavica*, 1984, 63: 417–420.
117. Anderson MC, Hartley RB. Cervical crypt involvement by intraepithelial neoplasia. *Obstetrics and Gynecology*, 1980, 55: 546–550.
118. Boonstra H, Aalders JG, Koudstaal J et al. Minimum extension and appropriate topographic position of tissue destruction for treatment of cervical intraepithelial neoplasia. *Obstetrics and Gynecology*, 1990, 75: 227–231.
119. Morgan PR, Anderson MC, Buckley CH et al. The Royal College of Obstetricians and Gynaecologists micro-invasive carcinoma of the cervix study: preliminary results. *British Journal of Obstetrics and Gynaecology*, 1993, 100: 664–668.
120. Murdoch JB, Morgan PR, Lopes A et al. Histological incomplete excision of CIN after large loop excision of the transformation zone (LLETZ) merits careful follow up, not retreatment. *British Journal of Obstetrics and Gynaecology*, 1992, 99: 990–993.
121. Dobbs SP, Asmussen T, Nunns D et al. Does histological incomplete excision of cervical intraepithelial neoplasia following large loop excision of transformation zone increase recurrence rates? A six year cytological follow up. *British Journal of Obstetrics and Gynaecology*, 2000, 107: 1298–1301.
122. Zaitoun AM, McKee G, Coppen MJ et al. Completeness of excision and follow up cytology in patients treated with loop excision biopsy. *Journal of Clinical Pathology*, 2000, 53: 191–196.
123. Flannelly G, Bolger B, Fawzi H et al. Follow up after LLETZ: could schedules be modified according to risk of recurrence? *British Journal of Obstetrics and Gynaecology*, 2001, 108: 1025–1030.
124. McHale MT, Le TD, Burger RA et al. Fertility sparing treatment for in situ and early invasive adenocarcinoma of the cervix. *Obstetrics and Gynecology*, 2001, 98: 726–731.
125. Shin CH, Schorge JO, Lee KR et al. Conservative management of adenocarcinoma in situ of the cervix. *Gynecologic Oncology*, 2000, 79(1): 6–10.
126. Soutter WP, Haidopoulos D, Gornall RJ et al. Is conservative treatment for adenocarcinoma in situ of the cervix safe? *British Journal of Obstetrics and Gynaecology*, 2001, 108: 1184–1189.
127. Maini M, Lavie G, Comerci PA et al. The management and follow up of women with high grade cervical glandular intraepithelial neoplasia. *International Journal of Gynecologic Cancer*, 1998, 8: 287–291.
128. Winter R. Conservative surgery for microinvasive carcinoma of the cervix. *Journal of Obstetrics and Gynaecology Research*, 1998, 24: 433–436.
129. Andersen ES, Nielsen K, Larsen G. Laser conization: follow-up in patients with cervical intraepithelial neoplasia in the cone margin. *Gynecologic Oncology*, 1990, 39: 328–331.
130. Andersen ES, Pedersen B, Nielsen K. Laser conization: the results of treatment of cervical intraepithelial neoplasia. *Gynecologic Oncology*, 1994, 54: 201–204.
131. Chang DY, Cheng WF, Torng PL et al. Prediction of residual neoplasia based on histopathology and margin status of conization specimens. *Gynecologic Oncology*, 1996, 63: 53–56.

132. Dobbs SP, Asmussen T, Nunns D et al. Does histological incomplete excision of cervical intraepithelial neoplasia following large loop excision of transformation zone increase recurrence rates? A six year cytological follow up. *British Journal of Oncology and Gynaecology*, 2000, 107: 1298–1301.
133. Gardeil F, Barry-Walsh C, Prendiville W et al. Persistent intraepithelial neoplasia after excision for cervical intraepithelial neoplasia grade III. *Obstetrics and Gynecology*, 1997, 89: 419–422.
134. Gold M, Dunton CJ, Murray J et al. Loop electrocautery excisional procedure: therapeutic effectiveness as an ablation and a conization equivalent. *Gynecologic Oncology*, 1996, 61: 241–244.
135. Husseinzadeh N, Shbaro I, Wesseler T. Predictive value of cone margins and post-cone endocervical curettage with residual disease in subsequent hysterectomy. *Gynecologic Oncology*, 1989, 33: 198–200.
136. Lopes A, Morgan P, Murdoch J et al. The case for conservative management of 'incomplete excision' of CIN after laser conization. *Gynecologic Oncology*, 1993, 49: 247–249.
137. Moore BC, Higgins RV, Laurent SL et al. Predictive factors from cold knife conization for residual cervical intraepithelial neoplasia in subsequent hysterectomy. *American Journal of Obstetrics and Gynecology*, 1995, 173: 361–366, discussion 366–368.
138. Lapaquette TK, Dinh TV, Hannigan EV et al. Management of patients with positive margins after cervical conization. *Obstetrics and Gynecology*, 1993, 82: 440–443.
139. Paterson-Brown S, Chappatte OA, Clark SK et al. The significance of cone biopsy resection margins. *Gynecologic Oncology*, 1992, 46: 182–185.
140. Paraskevaidis E, Lolis ED, Koliopoulos G et al. Cervical intraepithelial neoplasia outcomes after large loop excision with clear margins. *Obstetrics and Gynecology*, 2000, 95: 828–831.
141. Chew GK, Jandial L, Paraskevaidis E et al. Pattern of CIN recurrence following laser ablation treatment: long-term follow-up. *International Journal of Gynecology and Cancer*, 1999, 9: 487–490.
142. Pettersson F, Malker B. Invasive carcinoma of the uterine cervix following diagnosis and treatment of in situ carcinoma. Record linkage study within a National Cancer Registry. *Radiotherapy and Oncology*, 1989, 16: 115–120.
143. Lopes A, Mor-Yosef S, Pearson S et al. Is routine colposcopic assessment necessary following laser ablation of cervical intraepithelial neoplasia? *British Journal of Obstetrics and Gynaecology*, 1990, 97: 175–177.
144. Baldauf JJ, Dreyfus M, Ritter J et al. Cytology and colposcopy after loop electrosurgical excision: implications for follow-up. *Obstetrics and Gynecology*, 1998, 92: 124–130.
145. Flannelly G, Langhan H, Jandial L et al. A study of treatment failures following large loop excision of the transformation zone for the treatment of cervical intraepithelial neoplasia. *British Journal of Obstetrics and Gynaecology*, 1997, 104: 718–722.
146. Mahadevan N, Horwell DH. Histological incomplete excision of CIN after large loop excision of the transformation zone (LLETZ) merits careful follow up, not retreatment. *British Journal of Obstetrics and Gynaecology*, 1993, 100: 794–795.
147. Paraskevaidis E, Jandial L, Mann EM et al. Pattern of treatment failure following laser for cervical intraepithelial neoplasia: implications for follow-up protocol. *Obstetrics and Gynaecology*, 1991, 78: 80–83.
148. Gemmell J, Holmes DM, Duncan ID. How frequently need vaginal smears be taken after hysterectomy for cervical intraepithelial neoplasia? *British Journal of Obstetrics and Gynaecology*, 1990, 97: 58–61.
149. Burghardt E, Holzer E. Treatment of carcinoma in situ: evaluation of 1609 cases. *Obstetrics and Gynecology*, 1980, 55: 539–545.
150. Soutter WP, Saseini P, Panoskaltsis T. (submitted).

151. Acladious NN, Sutton C, Mandal D et al. Persistent human papillomavirus infection and smoking increase risk of failure of treatment of cervical intraepithelial neoplasia (CIN). *International Journal of Cancer*, 2002, 98: 435–439.
152. Bollen LJ, Tjong AHSP, van der Velden J et al. Prediction of recurrent and residual cervical dysplasia by human papillomavirus detection among patients with abnormal cytology. *Gynecologic Oncology*, 1999, 72: 199–201.
153. Chua KL, Hjerpe A. Human papillomavirus analysis as a prognostic marker following conization of the cervix uteri. *Gynecologic Oncology*, 1997, 66: 108–113.
154. Elfgren K, Bistoletti P, Dillner L et al. 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. *American Journal of Obstetrics and Gynecology*, 1996, 174: 937–942.
155. Nagai Y, Maehama T, Asato T et al. Persistence of human papillomavirus infection after therapeutic conization for CIN 3: is it an alarm for disease recurrence? *Gynecologic Oncology*, 2000, 79: 294–299.
156. Mitchel MF, Schottenfeld D, Tortolero-Luna G et al. Colposcopy for the diagnosis of squamous intraepithelial lesions: a meta-analysis. *Obstetrics and Gynecology*, 1998, 91: 626–631.
157. DiBonito L, Falconieri G, Bonifacio-Gori D. Multicentric papillomavirus infection of the female genital tract. A study of morphologic pattern, possible risk factors and viral prevalence. *Pathology*, *Research and Practice*, 1993, 189: 1023–1029.
158. Soost HJ, Lange H, Lehmacher W et al. The validation of cervical cytology. Sensitivity, specificity and predictive values. *Acta Cytologica*, 1991, 35(1): 8–14.
159. Hellberg D, Nilsson S, Valentin J. Positive cervical smear with subsequent normal colposcopy and histology: frequency of CIN in a long-term follow-up. *Gynecologic Oncology*, 1994, 53(2): 148–151.
160. Milne DS, Wadehra V, Mennim D et al. A prospective follow up study of women with colposcopically unconfirmed positive cervical smears. *British Journal of Obstetrics and Gynaecology*, 1999, 106: 38–41.
161. DiBonito L, Falconieri G, Tomasic G et al. Cervical cytopathology. An evaluation of its accuracy based on cytohistologic comparison. *Cancer*, 1993, 72(10): 3002–3006.
162. Teale GR, Moffitt DD, Mann CH et al. Management guidelines for women with normal colposcopy after low grade cervical abnormalities: population study. *British Medical Journal*, 2000, 320: 1693–1696.
163. Coppola A, Sorossky J, Casper R et al. The clinical course of cervical carcinoma in situ diagnosed during pregnancy. *Gynecologic Oncology*, 1997, 67: 162–165.
164. Palle C, Bangsboll S, Andreasson B. Cervical intraepithelial neoplasia in pregnancy. *Acta Obstetrica et Gynecologica*, 2000, 79: 306–310.
165. Woodrow N, Permezel M, Butterfield L et al. Abnormal cytology in pregnancy. *Australia and New Zealand Journal of Obstetrics and Gynaecology*, 1998, 38: 161–165.
166. Nevin J, Soeters R, Dehaeck CM et al. Cervical carcinoma associated with pregnancy. *Obstetrics and Gynecology Survey*, 1995, 50: 228–239.
167. Yost NP, Santoso IT, McIntire DD et al. Postpartum regression rates of antepartum cervical intraepithelial neoplasia II and III lesions. *Obstetrics and Gynecology*, 1999, 93: 359–362.
168. Lapolla IP, O'Neill C, Wetrich DJ. Colposcopic management of abnormal cervical cytology in pregnancy. *Reproductive Medicine*, 1988, 33: 301–306.

169. Robinson WR, Webb S, Tirpack J et al. Management of cervical intraepithelial neoplasia during pregnancy with loop excision. *Gynecologic Oncology*, 1997, 64(1): 153–155.
170. Clarke EA, Hatcher J, McKeown-Eyssen GE et al. Cervical dysplasia: association with sexual behaviour, smoking and oral contraceptive use? *American Journal of Obstetrics and Gynecology*, 1985, 151: 612–616.
171. Negrini BP, Schiffman MH, Kurman RJ et al. Oral contraceptive use, human papillomavirus infection, and risk of early cytological abnormalities of the cervix. *Journal of Cancer Research*, 1990, 50: 4670–4675.
172. Ylitalo N, Sorensen P, Josefsson A et al. Smoking and oral contraceptives as risk factors for cervical carcinoma in situ. *International Journal of Cancer*, 1999, 81: 357–365.
173. Hannaford P, Clifford RK. The risk of serious illness among oral contraceptive users: evidence for the RCGP's oral contraceptive study. *British Journal of General Practice*, 1998, 48: 1657–1662.
174. Sawaya GF, Grady D, Kerlikowske K et al. The positive predicative value of cervical smears in previously screened postmenopausal women: the Heart and Estrogen/progestin Replacement Study (HERS). *American Internal Medicine*, 2000, 133(12): 942–950.
175. Parazzini F, La Vecchia C, Negri E et al. Case–control study of oestrogen replacement therapy and risk of cervical cancer. *British Medical Journal*, 1997, 315: 85–88.
176. Cruickshank ME, Chambers G, Murray GI et al. *HPV Testing: Age Restricted Cervical Screening*. British Society for Colposcopy and Cervical Pathology, Sunderland, 1999.
177. Roman LD, Morris M, Eifel PJ et al. Reasons for inappropriate simple hysterectomy in the presence of invasive cancer of the cervix. *Obstetrics and Gynecology*, 1992, 79: 485–489.
178. Chen RJ, Chang DY, Yen M et al. Independent clinical factors which correlate with failures in diagnosing early cervical cancer. *Gynecology and Oncology*, 1995, 58: 356–361.
179. Mohamed-Noor K, Quinn MA, Tan J. Outcomes after cervical knife conisation with complete and incomplete excision of abnormal epithelium. *Gynecologic Oncology*, 1997, 67(1): 34–38.
180. Fairley CK, Sheil AG, McNeil JJ et al. The risk of ano-genital malignancies in dialysis and transplant patients. *Clinical Nephrology*, 1994, 41: 101–105.
181. Cochrane R, Regan L. Undetected gynaecological disorders in women with renal disease. *Human Reproduction*, 1997, 12: 667–670.
182. Ter Haar-Van Eck SA, Rischen-Vos J, Chadha-Ajwani S et al. The incidence of cervical intraepithelial neoplasia among women with renal transplant in relation to cyclosporine. *British Journal of Obstetrics and Gynaecology*, 1995, 102: 58–61.
183. Alloub MI, Barr B, Laren KM et al. Human papillomavirus infection and cervical intraepithelial neoplasia in women with renal allografts. *British Medical Journal*, 1989, 298: 153–156.
184. Sheil PW, Daunter B, Wright RG. The pap smear revisited. *Australia and New Zealand Journal of Obstetrics and Gynaecology*, 1987, 27: 269–282.
185. Downey GP, Emery VC, Walker PG. A longitudinal study of human papillomavirus positivity in the development of lower genital intraepithelial neoplasia in immunosuppressed women. *Journal of Lower Genital Tract Disease*, 1999, 3: 163–170.
186. Sillman FH, Stanek A, Sedlis A et al. The relationship between human papillomavirus infection and lower genital tract intraepithelial neoplasia in women with renal allografts. *American Journal of Obstetrics and Gynecology*, 1984, 150: 300–308.

187. Le T, Guijon F. Human papillomavirus infection and cervical intraepithelial neoplasia in renal transplant patients. *Journal of Lower Genital Tract Disease*, 1999, 3: 155–158.
188. Fairley CK, Chen S, Tabrizi SN et al. Prevalence of HPV DNA in cervical specimens in women with renal transplants: a comparison with dialysis-dependent patients and patients with renal impairment. *Nephrology Dialysis and Transplantation*, 1994, 9: 416–420.
189. Nyberg G, Eriksson O, Westberg NG. Increased incidence of cervical atypia in women with systemic lupus erythematosus treated with chemotherapy. *Arthritis Rheumatism*, 1981, 24: 648–650.
190. Dhar JP, Kmak D, Bhan R et al. Abnormal cervical cytology in women with lupus: a retrospective cohort study. *Gynecologic Oncology*, 2001, 82(1): 4–6.
191. Goodman MT, McDuffier K, Hernandez B et al. Association of methylenetetra hydrofolate reductase polymorphism C 677T and dietary folate with the risk of cervical dysplasia. *Cancer Epidemiology and Biomarkers Preview*, 2001, 10: 1275–1280.
192. Liu K, Marshall J, Shaw HS et al. Effects of chemotherapy and tamoxifen on cervical and vaginal smears in bone marrow transplant recipients. *Acta Cytologica*, 1999, 43: 1027–1033.
193. Abadi MA, Barakat RR, Saigo PE. Effects of tamoxifen on cervico-vaginal smears from patients with breast cancer. *Acta Cytologica*, 2000, 44: 141–146.
194. Schachter A, Kopmar A, Avram E et al. Hormonal and cytopathological changes in vaginal and cervical smears from women undergoing chemotherapy for extragenital malignant diseases. *Acta Obstetrica et Gynecologica Scandinavica*, 1983, 62: 621–624.
195. Schiffman M, Brinton LA. The epidemiology of cervical carcinogenesis. *Cancer*, 1995, 76: 1888–1901.
196. Wright TC Jr, Koulas J, Schnoll F et al. Cervical intraepithelial neoplasia in women infected with human immunodeficiency virus: prevalence, risk factors and validity of Papanicolaou smears. *Obstetrics and Gynecology*, 1994, 84: 591–597.
197. Smith JR, Kitchen VS, Botcherby M et al. Is HIV infection associated with an increase in the prevalence of cervical neoplasia? *British Journal of Gynaecology*, 1993, 100: 149–153.
198. Schafer A, Friedmann W, Mielke M et al. The increased frequency of cervical dysplasia-neoplasia in women infected with human immunodeficiency virus is related to the degree of immunosuppression. *American Journal of Obstetrics and Gynecology*, 1991, 164: 593–599.
199. Mandelblatt JS, Fahs M, Garibaldi K et al. Association between HIV infection and cervical neoplasia: implication for clinical care of women at risk of both conditions. *AIDS*, 1992, 6: 173–178.
200. Ellerbrock TV, Chiasson MA, Bush TJ et al. Incidence of cervical squamous intraepithelial lesions in HIV infected women. *Journal of the American Medical Association*, 2000, 283: 1031–1037.
201. Heard I, Bergeron C, Jeannel D et al. Papanicolaou smears in human immunodeficiency virus-seropositive women during follow up. *Obstetrics and Gynecology*, 1995, 85: 749–753.
202. Fruchter RG, Maiman M, Sedlis A et al. Multiple recurrences of cervical intraepithelial neoplasia in women with the human immunodeficiency virus. *Obstetrics and Gynecology*, 1996, 87: 338–344.
203. Heard I, Schmitz V, Costagliola D et al. Early regression of cervical lesions in HIV seropositive women receiving highly active with retroviral therapy. *AIDS*, 1998, 12: 1459–1464.
204. Jackson SR, Hollingworth TA, Anderson MC et al. Glandular lesions of the cervix: cytological and histological correlation. *Cytopathology*, 1996, 7(1): 10–16.

205. Laverty CR, Farnsworth A, Thurloe J et al. The reliability of a cytological prediction of cervical adenocarcinoma in situ. *Australia and New Zealand Journal of Obstetrics and Gynaecology*, 1988, 28: 307–312.
206. Lickrish GM, Colgan TJ, Wright VC. Colposcopy of adenocarcinoma in situ and invasive adenocarcinoma of the cervix. *Obstetrics and Gynecology Clinics of North America*, 1993, 20(1): 111–122.
207. Ostor AG, Duncan A, Quinn M et al. Adenocarcinoma in situ of the uterine cervix: an experience with 100 cases. *Gynecologic Oncology*, 2000, 79: 207–210.
208. Waddell CA. Glandular abnormalities: dilemmas in cytological prediction and clinical management. *Cytopathology*, 1997, 8(1): 27–30.
209. Valente PT, Schantz HD, Schultz M. Cytologic atypia associated with microglandular hyperplasia. *Diagnostic Cytopathology*, 1994, 10: 326–331.
210. Lee KR, Manna EA, St John T. Atypical endocervical glandular cells: accuracy of cytologic diagnosis. *Diagnostic Cytopathology*, 1995, 13: 202–208.
211. Ng AB, Teeple D, Lindner EA et al. The cellular manifestations of extrauterine cancer. *Acta Cytologica*, 1974, 18: 108–117.
212. The Bethesda System for reporting cervical/vaginal cytologic diagnoses: revised after the second National Cancer Institute Workshop, April 29–30, 1991. *Acta Cytologica*, 1993, 37: 115–124.
213. Korn AP, Judson PL, Zaloudek CJ. Importance of atypical glandular cells of uncertain significance in cervical cytologic smears. *Journal of Reproductive Medicine*, 1998, 43: 774–778.
214. Zweizig S, Nollar K, Reale F et al. Neoplasia associated with atypical glandular cells of undetermined significance on cervical cytology. *Gynecologic Oncology*, 1997, 65: 314–318.
215. National Coordinating Network (National Cervical Screening Programme), British Society for Clinical Cytology, and Royal College of Pathologists' Working Party. Borderline nuclear changes in cervical smears: guidelines on their recognition and management. *Journal of Clinical Pathology*, 1994, 47: 481–492.
216. Fox HBCH. Working party of the Royal College of Pathologists and the NHS Cervical Screening Programme. *Histopathological Reporting in Cervical Screening.* NHS Cervical Screening Programme, 1999: 16–36 (NHSCSP Publication No 10).
217. Luesley DM, Jordan JA, Woodman CB et al. A retrospective review of adenocarcinoma-in-situ and glandular atypia of the uterine cervix. *British Journal of Obstetrics and Gynaecology*, 1987, 94: 699–703.
218. Cullimore JE, Luesley DM, Rollason TP et al. A prospective study of conization of the cervix in the management of cervical intraepithelial glandular neoplasia (CIGN): a preliminary report. *British Journal Obstetrics and Gynaecology*, 1992, 99: 314–318.
219. Bertrand M, Lickrish GM, Colgan TJ. The anatomic distribution of cervical adenocarcinoma in situ: implications for treatment. *American Journal of Obstetrics and Gynecology*, 1987, 157(1): 21–25.
220. Poyner EA, Barakat RR, Hoskins WJ. Management and follow up of patients with adenocarcinoma in situ of the uterine cervix. *Gynecologic Oncology*, 1995, 57: 158–164.
221. Widrich T, Kennedy AW, Myers TM et al. Adenocarcinoma in situ of the uterine cervix: management and outcome. *Gynecologic Oncology*, 1996, 61: 304–308.
222. Denehy TR, Gregori CA, Breen JL. Endocervical curettage, cone margins, and residual adenocarcinoma in situ of the cervix. *Obstetrics and Gynecology*, 1997, 90(1): 1–6.
223. Colgan TJ, Lickrish GM. The topography and invasive potential of cervical adenocarcinoma in situ, with and without associated squamous dysplasia. *Gynecologic Oncology*, 1990, 36: 246–249.

224. Teshima S, Shimosato Y, Kishi K et al. Early stage adenocarcinoma of the uterine cervix. Histopathologic analysis with consideration of histogenesis. *Cancer*, 1985, 56(1): 167–172.
225. Nicklin JL, Wright RG, Bell JR et al. 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. *Australia and New Zealand Journal of Obstetrics and Gynaecology*, 1991, 31: 179–183.
226. Roberts JM, Thurlow JK, Bowditch RC et al. Subdividing atypical glandular cells of undetermined significance according to the Australian modified Bethesda system: analysis of outcomes. *Cancer*, 2000, 90: 87–95.

INDEX