SOGC / SCC Clinical Practice Guideline

Colposcopic Management of Abnormal Cervical Cancer Screening and Histology

These Clinical Practice Guidelines have been prepared and approved by the Executive and Council of the Society of Canadian Colposcopists (SCC). These guidelines have been approved by the SOGC/GOC/SCC Policy and Practice Guidelines Committee, the Society of Gynecologic Oncology of Canada (GOC) and the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

Principal Author
James Bentley, MB ChB, Halifax, NS

The Executive Council of the Society Of Canadian Colposcopists
James Bentley, MB ChB, Halifax, NS
Monique Bertrand, MD, London, ON
Lizabeth Brydon, MD, Regina, SK
Helene Gagne, MD, Ottawa, ON
Brian Hauck, MD, Calgary, AB
Marie-Helene Mayrand, MD, Montreal, QC
Susan McFaul, MD, Ottawa, ON
Patti Power, MD, St. John's,NL
Alexandra Schepanski, MD, Edmonton, AB

Special Contributors
Lucy Gilbert, MD, Montreal, QC
Jill Nation, MD, Calgary, AB
Michael Shier, MD, Toronto, ON
Laurette Geldenhuys, MD, Halifax, NS
Linda Kapusta, MD, Mississauga, ON
Terry Colgan, MD, Toronto, ON
Roberta Howlett, PhD, St Thomas, ON
Joan Murphy, MD, Toronto, ON
Rachel Kupets, MD, Toronto, ON

DISCLOSURE STATEMENT

Disclosure statements have been received from all members of the committee(s).

DISCLAIMER

ABSTRACT

Objective: To define a guideline for managing abnormal cytology results after screening for cervical cancer and to clarify the appropriate algorithms for follow-up after treatment.

Options: Women with abnormal cytology are at risk of developing cervical cancer; appropriate triage and treatment will reduce this risk.

Outcomes: A quality guideline will facilitate implementation of common standards across Canada, moving away from the current trend of individual guidelines in each province and territory.

Evidence: Published literature was retrieved through searches of PubMed or MEDLINE, CINAHL, and The Cochrane Library in October 2008 using appropriate controlled vocabulary (e.g., colposcopy, cervical dysplasia) and keywords (e.g., colposcopy management, CIN, AGC, cervical dysplasia, LEEP, LLETZ, HPV testing, cervical dysplasia triage). Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies. There were no date or language restrictions. Searches were updated on a regular basis and incorporated in the guideline to December 2011. Grey (unpublished) literature was identified through searching the Web sites of health technology assessment (HTA) and HTA-related agencies, clinical practice guideline collections, and from national and international medical specialty societies.
Expert opinion from published peer-reviewed literature and evidence from clinical trials (where available) is summarized. Consensus opinion is outlined where evidence is insufficient.

Values: The quality of the evidence is rated using the criteria described by the Canadian Task Force on Preventive Health Care (Table 1). The task force has recently reconvened and no new recommendations have been released.

Benefits, Harms and Costs: The intent is to promote the best possible care for women while ensuring efficient use of available resources.

Validation: This guideline has been reviewed for accuracy from content experts in

cytology, pathology and cervical screening programs. Guideline content was also compared to similar documents from other organizations including the American Society for Colposcopy and Cervical Pathology, British Society for Colposcopy and Cervical Pathology, and the European Cancer Network.

Sponsors: None

Key Words: Cervical Cytology, Cervical Cancer, Colposcopy, Treatment, Follow-up, Abnormalities, Guidelines

Recommendations

Wait Times for Colposcopy

1. Women with HSIL are ideally seen in a colposcopy clinic within 4 weeks of referral. (III-C)

2. Women with ASC-H or AGC should be seen in a colposcopy clinic within 6 weeks of referral. (III-C)

3. Women with a Pap test suggestive of carcinoma should be seen within 2 weeks of referral. (III-C)

4. Other results should be seen in a colposcopy clinic within 8 weeks of referral. (III-C)

The Colposcopy Exam

1. Colposcopic findings can be described according to the terminology defined by the International Federation for Cervical Pathology and Colposcopy. (III-C)

2. At colposcopy, two or more biopsies should be taken. (I-A)

3. An ECC should be performed when colposcopy is unsatisfactory, with an AGC pap and in older women with high-grade cytology. (II-2B)

4. Routine HR-HPV testing for all colposcopy referrals is discouraged. (III-C)

Managing women with ASCUS or LSIL on referral to Colposcopy

1. A colposcopically identified lesion should be biopsied. (III-C)

2. If no lesion is identified, a random biopsy of the transformation zone could be considered. (III-C)

Managing ASC-H

1. A woman with an ASC-H Pap test should have colposcopy to rule out CIN 2/3 and/or cancer. (II-2A)

2. With an ASC-H Pap test, the finding of negative colposcopy does not automatically warrant a diagnostic excisional procedure. (III-B)

Managing HSIL

1. All women with an HSIL test result should have colposcopy. (II-2A)

2. In the absence of an identifiable lesion at colposcopy and unsatisfactory colposcopy, a diagnostic excisional procedure should be performed. (III-B)

Managing Atypical Glandular Cytology (AGC-NOS, AGC-N, AIS)

1. The finding of an AGC Pap test warrants colposcopy. (II-2A)

2. An AGC-N Pap test without an identifiable lesion at colposcopy should be followed with a diagnostic excisional procedure. (II-2A)

Managing SCC and Adenocarcinoma

1. Women with a cytologic diagnosis suggestive of carcinoma, with or without a visible lesion, should have colposcopy. (III A)

Managing the Patient with Abnormal HPV Test and Normal Cytology

1. Women who test positive for HR-HPV and have negative cytology should have repeat testing at 12 months. Persistent positive HR-HPV tests warrant colposcopy. (I A)

Managing Abnormal Cytology in Pregnancy

1. Women with an ASCUS or LSIL test result during pregnancy should have repeat testing post pregnancy. (III-B)

2. Women with HSIL, ASC-H or AGC should be referred promptly for colposcopy in pregnancy. (III-B)

3. ECC is not recommended during pregnancy. (III-B)

Managing Abnormal Cytology in the Adolescent

1. Screening should not be initiated in women less than 21 years of age. (II-2A)

2. If screening is done, and an ASC-US or LSIL result is reported, cytology should be repeated in one year, with referral to colposcopy if a low-grade test result continues for 24 months. (III-B)

3. Cytology results of ASC-H, HSIL, and AGC in the adolescent should be referred to colposcopy. (III-B)

Managing Histological Abnormalities

Managing CIN 1

1. Biopsy proven CIN 1 should be observed with repeat colposcopy at 12-month intervals. Persistence beyond 24 months may be treated or observed with repeat cytology and/or colposcopy. (II-1B)

2. Biopsy-proven CIN 1 after HSIL or AGC cytology, an excisional procedure should be considered. (III-B)

Managing CIN 2/3

1. CIN 2 or 3 should be treated; excisional procedures are preferred for CIN 3. (II-1A)

2. Women who have positive margins should have close follow-up with retreatment with excision for persistent disease. (II-1B)

Managing CIN 2/3 in the Adolescent

1. CIN 2 in the adolescent patient should be observed with colposcopy at 6-month intervals for up to 24 months before treatment. (II-2B)

2. CIN 3 should be treated in the adolescent patient. (III-B)

Managing Adenocarcinoma in Situ (AIS)

1. If AIS is diagnosed, treatment needs to be done with a diagnostic excisional procedure, or type 3 TZ excision. (II-2A)

2. If margins are positive after diagnostic excisional procedure, a second excisional procedure should be performed. (II-2A)

3. If after treatment for AIS a woman has finished childbearing, a hysterectomy should be considered. (III-B)

4. If AIS is diagnosed after LEEP is performed for CIN in a woman who has not completed her family and margins are negative, it is unnecessary to perform a further diagnostic excisional procedure. (II-2A)

Managing Histological Abnormalities During Pregnancy

1. If CIN 2 or CIN 3 is diagnosed during pregnancy, treatment should be delayed until after delivery. (II-2A)

Follow-up Post Treatment

1. Post-treatment for CIN 2 or 3: women should be followed with cytology and colposcopy at 6 month intervals for two visits, as long as both cytology and any biopsies are negative. (II-2B)

2. Post-treatment for CIN 2 or 3: HPV testing at 6 or 12 months combined with cytology. If both cytology and HPV testing are negative, returning to annual or biannual cytology is a reasonable option. (II-2B)

Managing Histological Abnormalities in High-Risk Individuals

1. Immunocompromised women should be screened annually but not with colposcopy. (II-2B)

2. Immunocompromised women should be treated with an excisional procedure taking care to minimize positive margins. (II-2B)

Table 1: Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventative Health Care

Quality of Evidence Assessment*	Classification of Recommendations‡
I: Evidence obtained from at least one properly randomized controlled trial II-1: Evidence from well-designed controlled trials without randomization II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in the category III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	A. There is good evidence to recommend the clinical preventive action B. There is fair evidence to recommend the clinical preventive action C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making D. There is fair evidence to recommend against the clinical preventive action E. There is good evidence to recommend against the clinical preventive action L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making
* The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care. †Recommendations included in these guidelines have been adapted from the Classification of recommendations criteria described in The Canadian Task Force on Preventive Health Care.	

Introduction

Over the last 30 years cervical cancer morbidity and mortality rates have dropped significantly in Canada, from approximately 30 per 100,000 to 7 per 100,000

women (1). This change has been widely attributed to the availability of cervical screening via cytologic sampling (2).

Colposcopy has evolved to evaluate those with abnormal cytology and provide a histological sample by biopsy. Treatment of lesions can then be performed, usually preserving fertility and avoiding major surgery (3) (Ch1, p6). Numerous jurisdictions have developed guidelines (4-8) for colposcopy[1] and these have been reviewed in developing this document.

Cervical cancer screening is organized within each province and territory in Canada. Screening Programs issue screening and follow-up recommendations for abnormal screening results, including referral to colposcopy. The diversity and status of cervical screening in Canada has been summarized elsewhere (9).

The age for initial screening has been re-evaluated recently. This review of screening initiation was pioneered by the American Society of Colposcopy and Cervical Pathology (ASCCP), which convened a consensus practice improvement conference in June 2009. Stakeholders from the United States (USA) and Canada were included. Outcomes from this meeting included a recommendation to start screening at age 21 (10). This recommendation has been incorporated into new guidelines from Québec (11) and Alberta (12).

Canadian colposcopic practice is unique in several ways. Colposcopy is performed predominantly by gynecologists in both hospital clinics and private offices. Access to HPV testing is currently limited outside of teaching hospitals. The primary aim of these guidelines is to standardize the colposcopic care provided for women in Canada.

Methods

These guidelines were developed through the leadership of the Society of Canadian Colposcopy. Input was solicited from various organizations including; Society of Gynecologic Oncology of Canada (GOC); Society of Obstetricians and Gynecologists of Canada (SOGC); Canadian Association of Pathologists (CAP); Canadian Society of Cytopathology (CSC); and, representation from provincial screening programs. A face-to-face meeting of contributors was held in December 2008 for the following purpose. Relevant literature was reviewed, including guidelines related to colposcopic management of abnormal cytology and histology. Clinical questions were developed and discussed. Where evidence was incomplete, consensus opinion prevailed. Guidelines exist both as formally published and web-based documents; the most commonly referenced are those published by the American Society for Colposcopy and Cervical Pathology (ASCCP) for management of cytological and histological abnormalities (13,14).

[1] Guidelines from both within and outside Canada have been reviewed and will be referenced, where appropriate, throughout the document.

The Bethesda 2001 classification system (15) is the cytological terminology commonly used in Canada; this terminology was used here to represent cytological diagnoses and CIN terminology was employed for histological diagnoses. (See also Table 2)

Colposcopic Management of Cytological Abnormalities
Screening and colposcopy recommendations vary across provinces and territories and have been documented elsewhere (9). Current guidelines for colposcopic referrals can be summarized as follows: referral to colposcopy is recommended for persistent ASCUS, persistent or incident LSIL, ASC-H, HSIL, and AGC[2] as well as for Papanicolaou (Pap) tests that suggest squamous or glandular carcinoma. HPV testing is not widely available; however, when reflex HPV testing shows the presence of oncogenic (or high risk) HPV (HR-HPV) with ASCUS cytology, referral to colposcopy is recommended.

Wait Times for Colposcopy
Patients with abnormal screening tests should be seen in colposcopy within a reasonable time, given the risk of high-grade changes and psychological stress associated with an abnormal cytology result (16). Because of this, the SOGC wait times statement recommends colposcopic assessment within 3 weeks for HSIL cytology; 6 – 8 weeks for ASC-H or LSIL; and 6 weeks for an AGC cytology result (17) These recommendations are similar to the UK recommendation that 90% of cases with high-grade cytology should be seen within 4 weeks and 90% of all tests should be seen within 8 weeks of referral (7).

The importance of guidelines to direct referral times to colposcopy was illustrated in an Ontario population-based review (18). Referrals were reviewed for Pap test results of HSIL, AGC and ASC-H between 2000 and 2006. Women with HSIL results were seen in colposcopy at a median time of 67 days, AGC 108 days and ASC-H 80 days. Invasive disease of the lower genital tract was detected in 2.4 % of ASC-H cases, 3% of AGC and 3.12% of HSIL. Unfortunately in this population there was a 26% loss to follow-up, i.e., women who did not have colposcopy within 24 months.

It is recognized that these are guidelines and may be difficult to achieve; however, triage efforts should ensure that those with more significant cytologic abnormalities are seen first.

Recommendations:

1. Women with HSIL are ideally seen in a colposcopy clinic within 4 weeks of referral. (III-C)

2. Women with ASC-H or AGC should be seen in a colposcopy clinic within 6 weeks of referral. (III-C)

[2] See Table 2 for description of these terms.

3. Women with a Pap test suggestive of carcinoma should be seen within 2 weeks of referral. (III-C)

4. Other results should be seen in a colposcopy clinic within 8 weeks of referral. (III-C)

The Colposcopy Exam

Colposcopy is the examination of the lower genital tract and cervix using magnification from a colposcope with a good light source. The squamo-columnar junction and transformation zone should be identified, determining whether the exam is satisfactory or not. Acetic acid is then used to assess the size, shape, margin and location of any neoplastic lesion. These findings can then be described according to the nomenclature of the International Federation for Cervical Pathology and Colposcopy (19).

When any lesion is identified, recent evidence supports the practice of taking at least two biopsies to improve the accuracy of colposcopy. A biopsy should be taken of the most severe area found on colposcopic examination, either to confirm or rule out malignant lesions (20,21). Analysis of the ALTS data showed that, taking two biopsies for a low-grade cytology referral at initial colposcopy, improved the sensitivity (to detect CIN2 or greater) to 81.8%, compared to 68.3% with one biopsy (20).

A recent review of the utility of endocervical curettage was published using data from Calgary. Based on over 13,000 examinations, the authors showed that 99 ECC specimens had to be taken to detect one additional case of CIN 2 or higher grade lesion. The largest benefit was in older women referred after high-grade cytology (22). An ECC should thus be performed with unsatisfactory colposcopy, an AGC smear, and in older women with high-grade cytology

A low threshold is recommended for undertaking a biopsy. If any lesion is seen, biopsy should be completed. If only metaplasia is in question, a biopsy should be considered. Unless dictated by the appropriate algorithm, there is no role for routine HR-HPV testing in the colposcopy clinic.

Recommendations:

1. Colposcopic findings can be described according to the terminology defined by the International Federation for Cervical Pathology and Colposcopy. (III-C)

2. At colposcopy, two or more biopsies should be taken. (I-A)

3. An ECC should be performed when colposcopy is unsatisfactory, with an AGC pap and in older women with high-grade cytology. (II-2B)

4. Routine HR-HPV testing for all colposcopy referrals is discouraged. (III-C)

Managing women with ASCUS or LSIL on referral to Colposcopy
Management of low-grade abnormalities remains controversial. A large randomized trial in the USA concluded that women with LSIL cytology results were best managed by immediate referral to colposcopy; it was noted that 83% were positive for HR-HPV and thus HPV triage would not be effective (23). The same study reported that women with ASCUS results, but negative for HR-HPV, could safely be triaged away from colposcopy (23). This approach requires availability of reflex HPV testing; unfortunately, this is not widely available in Canada. A recent multicenter study in the UK evaluated the management of similar low grade cytology. Outcomes indicated that a policy of immediate colposcopy led to increased referrals to colposcopy with no clear benefit and potential harm (24).

With low-grade lesions, colposcopy is done to rule out potentially pre-malignant changes i.e., CIN 2 or 3; if this is detected, management is undertaken according to the appropriate protocol. A meta-analysis reported CIN 2+ rates of 10% and CIN 3+ of 6% with an ASCUS referral (25,26). With an LSIL referral, the rates of CIN 2+ are 17% and CIN 3+ 12% (27,28). If CIN 1 is the highest grade identified at colposcopy, conservative management is recommended. If no lesion is identified at colposcopy, a random biopsy at the transformation zone should be considered. As per consensus opinion, if no dysplasia is identified at colposcopy, annual screening with the referring health care provider is recommended, until three negative Pap tests have been reported. If all cytology is negative, women may then be followed every 2 to 3 years, consistent with provincial/territorial guidelines.

Recommendations:

1. A colposcopically identified lesion should be biopsied. (III-C)

2. If no lesion is identified, a random biopsy of the transformation zone could be considered. (III-C)

Managing ASC-H
With an ASC-H result on the Pap test, significant pathology is typically found in the majority of cases. In a study of 517 cases from Edmonton, Alberta, CIN2 or greater was detected in 70% of cases (29). Most cases were CIN2; however, invasive carcinoma was reported in 2.9% of cases and AIS in 1.7% (29). A similar Ontario study showed CIN2 or greater in 59.4% of cases with a stronger correlation in women younger than 40 years (30). All women with ASC-H should have colposcopy to rule out significant pathology. If colposcopy is negative, recommendations include colposcopy, repeat cytology and, ideally, HR-HPV testing twice, at six month intervals, to avoid missing a significant lesion. If these repeat tests are negative, women may return to regular screening, as per provincial/territorial protocol. The finding of ASC-H with negative colposcopy does not warrant a cone biopsy or diagnostic excisional procedure for diagnostic purposes.

Recommendations:

1. A woman with an ASC-H Pap test should have colposcopy to rule out CIN 2/3 and/or cancer. (II-2A)

2. With an ASC-H Pap test, the finding of negative colposcopy does not automatically warrant a diagnostic excisional procedure. (III-B)

Managing HSIL
The risk of a significant lesion is high with HSIL cytology. Studies have shown CIN2 or greater in 53-66% of cases when colposcopic biopsies are taken, and up to 90% if an immediate LEEP is performed (31,32). Because of this high rate of significant high-grade histology, all women with an HSIL result should have colposcopy. A visual assessment and LEEP approach may be appropriate in some circumstances, but a colposcopically directed biopsy and tailored treatment is preferred.

If a lesion is not detected at colposcopy, and colposcopy is not satisfactory, then a diagnostic excisional procedure should be done. This can be achieved with a cone biopsy, or LEEP using a large loop, or a second endocervical pass. However, if no lesion was detected, and colposcopy was satisfactory, combined colposcopy and cytology is appropriate at six-month intervals for two visits. This situation is rare. Among women who have finished childbearing, a diagnostic excisional procedure should be considered.

Recommendations:

1. All women with an HSIL test result should have colposcopy. (II-2A)

2. In the absence of an identifiable lesion at colposcopy and unsatisfactory colposcopy, a diagnostic excisional procedure should be performed. (III-B)

Managing Atypical Glandular Cytology (AGC-NOS, AGC-N, AIS)
The finding of AGC-NOS, AGC-N or AIS always warrants prompt referral to colposcopy in the absence of other symptomatology. Neoplastic lesions other than from the cervix, including endometrium, ovary and fallopian tube, have been identified with AGC cytology (33-35). In a Canadian report 456 cases of AGC or AGUS were identified out of a database of over 1 million Pap tests (0.043%) (34). On final histology 7% were found to have CIN 1, 36% CIN 2 or 3, AIS was identified in 20%, carcinoma of the cervix in 9%, and endometrial pathology in 29%, including carcinoma of the endometrium in 10%. It should be noted that CIN is consistently the most frequent finding across many studies (33,34,36,37). This high rate of pathology precludes any attempt to triage using repeat cytology or HPV testing.

The diagnosis of AGC-N is associated with higher rates of abnormalities and thus, in the absence of an abnormality found by colposcopy, a diagnostic excisional procedure should be performed (38,39). A diagnostic excisional procedure includes a cold knife cone biopsy, laser cone biopsy and may include a LEEP if the specimen is of sufficient size. A hysterectomy is not considered as a diagnostic excisional procedure. Endocervical curettage (ECC) should be done in all women, and endometrial sampling should be performed in women over 35 years or if there is a history of abnormal bleeding, including anovulation.

However, with AGC-NOS cytology and the absence of an identified lesion, women are still at risk of developing a lesion. In this situation, follow-up assessment every six months for two years includes repeat cytology, colposcopy and ECC. If HR-HPV testing is available and was done at the initial colposcopy visit, women who test negative for HR-HPV may have repeat assessment with colposcopy, cytology, ECC and HR-HPV testing at 12 months. If a lesion is identified, treatment is guided by the specific guideline. If a carcinoma is identified, referral should be made to a gynecologic oncologist. If all follow up is negative after two years, routine cytologic testing may be resumed.

Recommendations:

1. The finding of an AGC Pap test warrants colposcopy. (II-2A)
2. An AGC-N Pap test without an identifiable lesion at colposcopy should be followed with a diagnostic excisional procedure. (II-2A)

Managing SCC and Adenocarcinoma
Women should be referred promptly to colposcopy if their Pap test is suggestive of carcinoma, with or without a visible lesion. Assessment should include colposcopy and directed biopsy with consideration of ECC. If no abnormality is detected, a diagnostic excisional procedure is recommended to rule out occult carcinoma. Endometrial biopsy should also be contemplated in the work up of women with adenocarcinoma on a Pap test.

Recommendation:

1. Women with a cytologic diagnosis suggestive of carcinoma, with or without a visible lesion, should have colposcopy. (III A)

Managing the Patient with Abnormal HPV Test and Normal Cytology
For those women with ASCUS and positive reflex HR-HPV, women should be referred to colposcopy. However, no provincial guidelines address management of negative cytology findings combined with a positive HR-HPV result.

Women with negative cytology and positive HPV results should have repeats of both tests after twelve months (40,41), with their primary health care provider. If both tests are negative at 12 months, women should return to screening as per provincial/territorial guidelines. Women with a cytological abnormality should be managed according to the cytological diagnosis. If there is persistent HR-HPV on two tests one year apart, referral to colposcopy is recommended to rule out the possibility of a high-grade lesion.

Recommendation:

1. Women who test positive for HR-HPV and have negative cytology should have repeat testing at 12 months. Persistent positive HR-HPV tests warrant colposcopy. (I-A)

Managing Abnormal Cytology in Pregnancy
The indications for colposcopy during pregnancy are essentially the same as for non-pregnant women. If a low-grade lesion (ASCUS or LSIL) is found during pregnancy, the Pap test should be repeated at least six weeks postpartum. This practice is safe as the rate of cancer in this group is very low (42). If HSIL, ASC-H or AGC is found, prompt evaluation with colposcopy is essential. If colposcopy is unsatisfactory in the first trimester, it should be repeated after 20 weeks gestation when, because of the physiological changes, the cervix everts itself and the squamo-columnar junction may become visible.

If CIN3 or carcinoma is suspected, biopsy is recommended. There is evidence that biopsy in pregnancy is not harmful (43). Women with high-grade dysplasia in pregnancy should be seen by an experienced colposcopist.

Recommendations:

1. Women with an ASCUS or LSIL test result during pregnancy should have repeat testing post pregnancy. (III-B)

2. Women with HSIL, ASC-H or AGC should be referred promptly for colposcopy in pregnancy. (III-B)

3. ECC is not recommended during pregnancy. (III-B)

Managing Abnormal Cytology in the Adolescent
There is little evidence that screening by cytology in adolescents (less than 21 years old) is beneficial. The incidence of cervical cancer is very low. SEER data from the USA showed a rate of 0.1/100,000 in women 15-19 years old and 1.6/100,000 in women 20-24 years old, compared to 15.5/100,000 in women 40-45 years old (44). Although HPV infection and low-grade Pap tests are common in this age group, most of these infections, and related cytological changes, will resolve without intervention (45,46). Screening is invasive and can have adverse psychological sequelae especially if it leads to colposcopy referral (10,47).

If this screening leads to treatment, treatment by LEEP can later be associated with a slightly increased risk of premature rupture of membranes and preterm delivery (48,49). HPV vaccination has recently been instituted in Canada and the high efficacy against HPV 16 and 18 should likely result in fewer high grade lesions needing treatment (50-54). This collective evidence has led the American College of Obstetrics and Gynecology, as well as the provinces of Alberta and Québec to recommend an older age for screening initiation – until 21 years of age (11,12,55,56).

Among women younger than 21 years, if a Pap test has been done and abnormalities are detected at screening, management should be conservative to avoid harm. Low-grade changes, i.e., ASC-US and LSIL regress in up to 93% of cases with conservative management. Thus women less than 21 years with ASC-US and LSIL results should have repeat cytology in one year with referral to colposcopy only if abnormalities

persist for 24 months (10). Women younger than 21 years, with ASC-H, HSIL, or AGC results, should be referred to colposcopy.

Recommendations:

1. Screening should not be initiated in women less than 21 years of age. (II-2A)
2. If screening is done, and an ASC-US or LSIL result is reported, cytology should be repeated in one year, with referral to colposcopy if a low-grade test result continues for 24 months. (III-B)
3. Cytology results of ASC-H, HSIL, and AGC in the adolescent should be referred to colposcopy. (III-B)

Managing Histological Abnormalities

Once a lesion has been identified on colposcopy, and biopsy completed, a decision must be made regarding management. The aim of treatment is to remove a potentially precancerous lesion to avoid development of carcinoma. The initial classification of cervical intraepithelial neoplasia as CIN 1, 2 or 3 was proposed by Richart in 1973 and subsequently reinforced by the World Health Organization in 1994 (57). The rate of progression of these dysplastic lesions has been well reviewed by Ostor (58) (Table 3), and over time the therapeutic approach has been adapted to avoid harm when lesser CIN grades are unlikely to progress to invasive cancer.

Treatment modalities include either excisional or ablative approaches (cryotherapy or laser ablation). The favoured method in Canada is excisional - the loop electrosurgical excision procedure (LEEP). Although relatively easy to perform in the outpatient setting, there can be complications. A recent meta-analysis estimated that, after a LEEP procedure, the risk for preterm delivery in a subsequent pregnancy of less than 32-34 weeks gestation, was 1 in 143 treatments (48). The same research group suggested that a depth threshold of 10mm is also a variable in reducing harm. Consequently, if the colposcopist is able to adjust the procedure to the lesion, future negative sequelae in pregnancy may be minimized (59).

Treatment is tailored to the lesion identified on the cervix, by either removing or ablating the entire transformation zone. The International Federation of Cervical Pathology and Colposcopy (IFCPC) has classified the transformation zone (TZ) into three categories (60). A type 1 TZ is completely ectocervical, and fully visible. A type 2 TZ is fully visible, has an endocervical component and may have an ectocervical component. A type 3 TZ is predominantly endocervical, not fully visible and may have an ectocervical component (Figure 1).

Using this classification, ablative methods can be used for a type 1 or 2 TZ if recognized criteria are met (Table 4). If excision with LEEP is utilized the size of loop electrode must be adjusted depending on the lesion, i.e., a type 2 TZ requires a larger loop electrode than a type 1 TZ to ensure the lesion is fully excised. If the lesion is not seen in its entirety, colposcopy is unsatisfactory and ablative therapies should not be used (60,61). Care should be taken to avoid removal of excessive

cervical stroma which would predispose women to preterm delivery, especially if using very large loops or taking multiple passes.

A type 3 TZ with a lesion that extends into the endocervical canal, or a glandular lesion, requires a larger or longer excision for adequate evaluation or treatment. This document adopted the new IFCPC terminology to identify this procedure as a type 3 excision to avoid the current confusion in terminology (62). Currently, cone biopsy, diagnostic excisional procedure, laser excision and LEEP may be used but have different meanings to individual colposcopists (61).

Managing CIN 1

Evidence from the recent ALTS trial has confirmed significant inter-observer variability in the histological diagnosis of CIN 1, with the overlap often observed with benign HPV infection (63). Our current understanding is that CIN 1 seldom progresses to invasive disease and that it will regress without treatment within 2-5 years in 60-80% of all cases (58,64). Regression rates are even more pronounced in adolescents, with regression of low-grade squamous intra-epithelial lesions in up to 91% of cases over a three-year period (65). This knowledge has led to a change in the treatment philosophy for CIN 1.

Conservative management with observation is preferred for CIN 1. Women should be followed with repeat cytology and colposcopy at 12-month intervals; if no lesion is identified she may return to routine screening. If the lesion persists for 24 months or longer, treatment is acceptable. If colposcopy is satisfactory, treatment may be by ablative modalities. However in a compliant patient, longer follow-up is possible, especially in women who have not completed childbearing.

The exception to a conservative approach occurs when a diagnosis of CIN 1 is preceded by HSIL or AGC cytology. In these situations, histological findings have not adequately explained the abnormal cytology and an excisional procedure should be considered.

Recommendations:

1. Biopsy proven CIN 1 should be observed with repeat colposcopy at 12-month intervals. Persistence beyond 24 months may be treated or observed with repeat cytology and/or colposcopy. (II-1B)

2. Biopsy-proven CIN 1 after HSIL or AGC cytology, an excisional procedure should be considered. (III-B)

Managing CIN 2/3

Pathologically confirmed high grade dysplasia includes CIN 2 and CIN 3, these are treated in the same fashion in most jurisdictions (7,13,66-69). There are however differences in the rates of regression. The classical review by Ostor showed that CIN 2 regresses in 43% and progressed to CIN 3+ in 27% this compares to regression of 33% persistence of 52% and progression to invasion in at least 12% of CIN 3 cases (58). (See Table 3.) The true malignant potential of CIN 3 has been demonstrated in New Zealand by long-term follow-up of CIN 3 that was not treated. This showed that

the invasive risk in untreated CIN3 is 31% over 30 years, also noting that patients with documented persistent CIN3 for 2 years had a risk of subsequent invasion of 50% (70).

For these reasons most women with CIN 2 or 3 should be treated [3]. If colposcopy is satisfactory, i.e., a type 1 or 2 TZ, excision and ablative therapy are both acceptable; however, an excisional procedure is preferred for the treatment of CIN 3. If CIN 2 or 3 is identified and colposcopy is unsatisfactory, an excisional procedure should be performed. If at treatment, margins are positive for CIN, or the ECC (if done) is positive, these women are at increased risk of persistent dysplasia. In a meta-analysis of excisional treatment, the risk of post-treatment disease was 18% for incomplete excision and 3 % for complete excision (71). If the deep margins are involved, consideration should be made for repeat excision. Most women should be followed with repeat colposcopy at 6 months (72). Hysterectomy is not recommended as initial therapy for CIN 2 or 3 but may be performed for women with persistent CIN.

Recommendations:

1. CIN 2 or 3 should be treated; excisional procedures are preferred for CIN 3. (II-1A)

2. Women who have positive margins should have close follow-up with retreatment with excision for persistent disease. (BII-1B)

Managing CIN 2/3 in the Adolescent

As discussed earlier there is little evidence to justify routine screening in the adolescent patient. If however, Pap screening is completed, these patients may be referred for colposcopy. Management must be modified to avoid harm. Recent evidence suggests that regression of CIN2 in this population occurs at a rate similar to CIN1 (10,46,73,74).

Based on the evidence, this group's consensus opinion is that CIN2 in the adolescent can be observed with repeat colposcopy and cytology every 6 months for up to 24 months. If dysplasia persists the patient should be treated, either with ablative methods or a LEEP. This is conditional on a satisfactory colposcopy; if it is unsatisfactory, treatment should be performed with an excisional procedure. A recent study looked at regression rates of CIN 2 in women less than 25 years old, most were 20-25 years old, the overall regression rate over a median of 8 months was 62%. This suggests that observation may be reasonable in young women less than 25 years old (20). In some centers, high-grade histology is designated as HSIL, i.e., CIN terminology is not used. If the biopsy is reported as HSIL in an adolescent woman we suggest a review of the histology using CIN terminology. If reclassified as CIN 3, treatment by an excisional method is preferred.

---

[3] Remaining women – those who are younger or pregnant – are managed as outlined elsewhere in this document.

Recommendations:

1. CIN 2 in the adolescent patient should be observed with colposcopy at 6-month intervals for up to 24 months before treatment. (II-2B)

2. CIN 3 should be treated in the adolescent patient. (III-B)

Managing Adenocarcinoma in Situ (AIS)
In Canada the ratio of adenocarcinoma to squamous carcinoma of the cervix is increasing; adenocarcinoma comprises 20-25% of all cervical cancer (75). This is largely a function of a significant decrease in squamous cell cancers due to widespread availability of screening by Pap tests over several decades. Nevertheless, implementation of cytology quality assurance initiatives in recent years has been associated with a decrease in adenocarcinoma of the cervix.

In contrast, diagnosis of premalignant adenocarcinoma in situ (AIS) occurs at a ratio of 1:50, when compared with severe squamous dysplasia (76). Consequently a colposcopist will not often see AIS and the treatment remains controversial. Colposcopic features can be difficult to identify and lesions often extend high in the canal (77). Bertrand and colleagues showed that in 78% of cases the highest lesion in the canal was less than 20mm from the exocervix and none were higher than 29.9mm (78). Subsequent to a diagnosis of adenocarcinoma in situ either on punch biopsy or endocervical curretage, a diagnostic excisional procedure, or type 3 TZ excision should be performed. Margin status is an important predictor of residual disease, and thus the method chosen for treatment must preserve the ability to assess the endocervical margin. A recent meta-analysis of 33 studies showed that the risk of residual disease was 2.6% with negative margins and 19.4% with positive margins. Invasive carcinoma was also more frequently associated with positive margins (5.2%) compared with negative margins (0.1%) (79). Thus, if margins are positive, a second excision is required.

If AIS is diagnosed after completing a LEEP procedure (because of a CIN finding), the margins need to be carefully examined. If the AIS is small and margins are clear, there is no need to perform an excisional procedure unless childbearing is complete, when hysterectomy should be considered (80).

If fertility is not an issue or one cannot achieve negative margins, a hysterectomy is recommended (79).

After treatment for AIS, if the woman wishes to preserve her fertility, she can be closely observed in the colposcopy clinic. She should be seen for colposcopy, ECC and cytology every 6 to 12 months, for at least 5 years. HR-HPV testing can be utilized to aid reassurance. Thereafter the patient should have annual cytology.

Recommendations:

1. If AIS is diagnosed, treatment needs to be done with a diagnostic excisional procedure, or type 3 TZ excision. (II-2A)

2. If margins are positive after diagnostic excisional procedure, a second excisional procedure should be performed. (II-2A)

3. If after treatment for AIS a woman has finished childbearing, a hysterectomy should be considered. (III-B)

4. If AIS is diagnosed after LEEP is performed for CIN in a woman who has not completed her family and margins are negative, it is unnecessary to perform a further diagnostic excisional procedure. (II-2A)

Managing Histological Abnormalities During Pregnancy

The aim of colposcopy in pregnancy is to rule out a diagnosis of invasive or micro-invasive carcinoma. If diagnosed, these cases should be promptly referred to a gynecologic oncologist. If CIN 2 or CIN 3 is diagnosed during pregnancy, the available evidence would suggest that treatment can be delayed until after delivery. The risk of progression is not affected by the pregnancy and regression to CIN 1 or normal post pregnancy is between 31 and 47% (81,82).

Recommendations:

1. If CIN 2 or CIN 3 is diagnosed during pregnancy, treatment should be delayed until after delivery. (II-2A)

Follow-up Post Treatment

Once treated for CIN or AIS, a woman remains at risk of persistence or recurrence and at long-term risk of invasive carcinoma (13,83,84). Failure rates following treatment for CIN do not vary significantly with the treatment method used and in published series are between 5% and 13 % (85,86). The aim of follow-up is to detect persistent or recurrent dysplasia.

Conventionally in Canada, women are followed after treatment with colposcopy and cytology at 6 month intervals for 1 to 2 years, prior to returning to cytology on an annual basis with their primary healthcare provider. In recent years the availability of HR-HPV testing has raised the possibility of its use to follow women and potentially detect recurrence or persistence earlier. Reviews and meta-analyses have evaluated this approach and demonstrate that HPV testing may be more sensitive for detecting recurrence (87-91). It has been noted that an adequately powered prospective trial is needed to truly evaluate this issue (91,92). Such a trial is underway in several Canadian centers (93).

Recommendations:

1. Post-treatment for CIN 2 or 3: women should be followed with cytology and colposcopy at 6 month intervals for two visits, as long as both cytology and any biopsies are negative. (II-2B)

2. Post-treatment for CIN 2 or 3: HPV testing at 6 or 12 months combined with cytology. If both cytology and HPV testing are negative, returning to annual or biannual cytology is a reasonable option. (II-2B)

Managing Histological Abnormalities in High-Risk Individuals
Numerous medical conditions reportedly affect the ability to limit progression of HPV infection to dysplasia, and hence are associated with dysplasia. These include transplantation with associated immunosuppression, medication for conditions such as Crohn's Disease, rheumatoid arthritis, diabetes or HIV infection. Most available information relates to transplant and HIV patients. In a review from 1995, 144 women were followed after renal transplant. There was a 17.5% incidence of dysplasia (94). Similar outcomes were reported after liver transplant as well as 13% incidence of HSIL (95).

The link between cervical cancer and HIV is well documented. The rate of cervical cancer is up to 4-6 times higher in HIV-positive women (96). In recent years improved survival has been attributed to the availability of highly active antiretroviral therapy (HAART) (96). In a review of 400 women who were HIV-positive in Cape Town, high-risk HPV was present in 68% of these women and 55% had abnormal Pap smears. Most Pap test results were low-grade changes, of which only 4% progressed, 13% were HSIL (97). In one review from North America the rates of CIN2+ with an ASC US/LSIL referral were 13.3% in HIV-negative women and 15.3 in HIV-positive women (98).

There is no good evidence to recommend routine colposcopy in this group and they can be screened with annual Pap tests (99). If at colposcopy CIN 1 is diagnosed these women can be observed and treated for persistent disease. CIN 2/3 need to be treated and excisional methods are preferred. There is a high rate of recurrence thus a wide excision should be used (100). HAART therapy seems to decrease recurrence.

Recommendations:

1. Immunocompromised women should be screened annually but not with colposcopy. (II-2B)
2. Immunocompromised women should be treated with an excisional procedure taking care to minimize positive margins. (II-2B)

Recommendations

Wait Times for Colposcopy

5. Women with HSIL are ideally seen in a colposcopy clinic within 4 weeks of referral. (III-C)
6. Women with ASC-H or AGC should be seen in a colposcopy clinic within 6 weeks of referral. (III-C)
7. Women with a Pap test suggestive of carcinoma should be seen within 2 weeks of referral. (III-C)

8. Other results should be seen in a colposcopy clinic within 8 weeks of referral. (III-C)

The Colposcopy Exam

5. Colposcopic findings can be described according to the terminology defined by the International Federation for Cervical Pathology and Colposcopy. (III-C)

6. At colposcopy, two or more biopsies should be taken. (I-A)

7. An ECC should be performed when colposcopy is unsatisfactory, with an AGC pap and in older women with high-grade cytology. (II-2B)

8. Routine HR-HPV testing for all colposcopy referrals is discouraged. (III-C)

Managing women with ASCUS or LSIL on referral to Colposcopy

3. A colposcopically identified lesion should be biopsied. (III-C)

4. If no lesion is identified, a random biopsy of the transformation zone could be considered. (III-C)

Managing ASC-H

3. A woman with an ASC-H Pap test should have colposcopy to rule out CIN 2/3 and/or cancer. (II-2A)

4. With an ASC-H Pap test, the finding of negative colposcopy does not automatically warrant a diagnostic excisional procedure. (III-B)

Managing HSIL

3. All women with an HSIL test result should have colposcopy. (II-2A)

4. In the absence of an identifiable lesion at colposcopy and unsatisfactory colposcopy, a diagnostic excisional procedure should be performed. (III-B)

Managing Atypical Glandular Cytology (AGC-NOS, AGC-N, AIS)

3. The finding of an AGC Pap test warrants colposcopy. (II-2A)

4. An AGC-N Pap test without an identifiable lesion at colposcopy should be followed with a diagnostic excisional procedure. (II-2A)

Managing SCC and Adenocarcinoma

2. Women with a cytologic diagnosis suggestive of carcinoma, with or without a visible lesion, should have colposcopy. (III A)

Managing the Patient with Abnormal HPV Test and Normal Cytology

2. Women who test positive for HR-HPV and have negative cytology should have repeat testing at 12 months. Persistent positive HR-HPV tests warrant colposcopy. (I A)

Managing Abnormal Cytology in Pregnancy

4. Women with an ASCUS or LSIL test result during pregnancy should have repeat testing post pregnancy. (III-B)

5. Women with HSIL, ASC-H or AGC should be referred promptly for colposcopy in pregnancy. (III-B)

6. ECC is not recommended during pregnancy. (III-B)

Managing Abnormal Cytology in the Adolescent

4. Screening should not be initiated in women less than 21 years of age. (II-2A)

5. If screening is done, and an ASC-US or LSIL result is reported, cytology should be repeated in one year, with referral to colposcopy if a low-grade test result continues for 24 months. (III-B)

6. Cytology results of ASC-H, HSIL, and AGC in the adolescent should be referred to colposcopy. (III-B)

Managing Histological Abnormalities

Managing CIN 1

3. Biopsy proven CIN 1 should be observed with repeat colposcopy at 12-month intervals. Persistence beyond 24 months may be treated or observed with repeat cytology and/or colposcopy. (II-1B)

4. Biopsy-proven CIN 1 after HSIL or AGC cytology, an excisional procedure should be considered. (III-B)

Managing CIN 2/3

3. CIN 2 or 3 should be treated; excisional procedures are preferred for CIN 3. (II-1A)

4. Women who have positive margins should have close follow-up with retreatment with excision for persistent disease. (II-1B)

Managing CIN 2/3 in the Adolescent

3. CIN 2 in the adolescent patient should be observed with colposcopy at 6-month intervals for up to 24 months before treatment. (II-2B)

4. CIN 3 should be treated in the adolescent patient. (III-B)

Managing Adenocarcinoma in Situ (AIS)

5. If AIS is diagnosed, treatment needs to be done with a diagnostic excisional procedure, or type 3 TZ excision. (II-2A)

6. If margins are positive after diagnostic excisional procedure, a second excisional procedure should be performed. (II-2A)

7. If after treatment for AIS a woman has finished childbearing, a hysterectomy should be considered. (III-B)

8. If AIS is diagnosed after LEEP is performed for CIN in a woman who has not completed her family and margins are negative, it is unnecessary to perform a further diagnostic excisional procedure. (II-2A)

Managing Histological Abnormalities During Pregnancy

2. If CIN 2 or CIN 3 is diagnosed during pregnancy, treatment should be delayed until after delivery. (II-2A)

Follow-up Post Treatment

3. Post-treatment for CIN 2 or 3: women should be followed with cytology and colposcopy at 6 month intervals for two visits, as long as both cytology and any biopsies are negative. (II-2B)

4. Post-treatment for CIN 2 or 3: HPV testing at 6 or 12 months combined with cytology. If both cytology and HPV testing are negative, returning to annual or biannual cytology is a reasonable option. (II-2B)

Managing Histological Abnormalities in High-Risk Individuals

3. Immunocompromised women should be screened annually but not with colposcopy. (II-2B)

4. Immunocompromised women should be treated with an excisional procedure taking care to minimize positive margins. (II-2B)

References

(1) Canadian Cancer Society's Steering Committee. Canadian Cancer Statistics. 2009.

(2) International Agency for Research on Cancer, World Health Organization. IARC Handbooks of Cancer Prevention: Cervix Cancer Screening. Lyon: IARC Press; 2005.

(3) Ferris DG, Cox JT, O'Connor DM, Wright VC, Foerster J. Modern Colposcopy Textbook and Atlas. : Kendall/Hunt Publishing Company; 2004.

(4) Working Group of Cervical Screen Singapore. Management Guidelines for Abnormal Pap Smear & Invasive Disease of the Cervix. 2002.

(5) Australian National Health and Medical Research Council. Screening to prevent cervical cancer: guidelines for the management of asymptomatic women with screen detected abnormalities. 2005.

(6) Wright TC,Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D, et al. 2006 Consensus Guidelines for the Management of Women with Cervical Intraepithelial Neoplasia Or Adenocarcinoma in Situ. J Low Genit Tract Dis 2007 Oct;11(4):223-239.

(7) National Health Service. Colposcopy and Programme Management: Guidelines for the NHS Cervical Screening Programme, 2nd Edition. 2010; Available at:

http://www.cancerscreening.nhs.uk/cervical/publications/nhscsp20.html. Accessed 02/28, 2011.

(8) Arbyn M, Anttila A, Jordan J, Ronco G, Schenck U, Segnan N, et al. European Guidelines for Quality Assurance in Cervical Cancer Screening. Second edition--summary document. Ann Oncol 2010 Mar;21(3):448-458.

(9) Murphy KJ, Howlett RI. Screening for Cervical Cancer. JOGC 2007;29(8):S27-S36.

(10) Moscicki AB, Cox JT. Practice improvement in cervical screening and management (PICSM): symposium on management of cervical abnormalities in adolescents and young women. J Low Genit Tract Dis 2010 Jan;14(1):73-80.

(11) Institut nationale de sante publique Quebec. Recommendations on optimizing cervical cancer screening in Québec. 2009; Available at: http://www.inspq.qc.ca/pdf/publications/1081_CervicalScreening.pdf. Accessed 03/11, 2011.

(12) Alberta Health Services. Alberta Cervical Cancer Screening: Clinical Practice Guidelines and Management of Abnormal Cytology. 2009; Available at: http://www.screeningforlife.ca/_files/file.php?fileid=filenrNvasUkRV&filename=file_CC_CPG_Summary_Chart_LowR_Mar_2010.pdf. Accessed 03/11, 2011.

(13) Wright TC,Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D, et al. 2006 Consensus Guidelines for the Management of Women with Abnormal Cervical Cancer Screening Tests. Am J Obstet Gynecol 2007 Oct;197(4):346-355.

(14) Wright TC,Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D, et al. 2006 Consensus Guidelines for the Management of Women with Cervical Intraepithelial Neoplasia Or Adenocarcinoma in Situ. Am J Obstet Gynecol 2007 Oct;197(4):340-345.

(15) Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA 2002 Apr 24;287(16):2114-2119.

(16) Le T, Hopkins L, Menard C, Hicks-Boucher W, Lefebvre J, Fung Kee Fung M. Psychologic morbidities prior to loop electrosurgical excision procedure in the treatment of cervical intraepithelial neoplasia. Int J Gynecol Cancer 2006 May-Jun;16(3):1089-1093.

(17) Farrell S, Roye C, Crane J, Davis D, Heywood M, Lalonde A, et al. Statement on wait times in obstetrics and gynaecology. J Obstet Gynaecol Can 2008 Mar;30(3):248-270.

(18) Kupets R, Paszat L. How are women with high grade Pap smear abnormalities managed? A population based study. Gynecol Oncol 2011 Jun 1;121(3):499-504.

(19) Walker P, Dexeus S, De Palo G, Barrasso R, Campion M, Girardi F, et al. International terminology of colposcopy: an updated report from the International

Federation for Cervical Pathology and Colposcopy. Obstet Gynecol 2003 Jan;101(1):175-177.

(20) Gage JC, Hanson VW, Abbey K, Dippery S, Gardner S, Kubota J, et al. Number of cervical biopsies and sensitivity of colposcopy. Obstet Gynecol 2006 Aug;108(2):264-272.

(21) Zuchna C, Hager M, Tringler B, Georgoulopoulos A, Ciresa-Koenig A, Volgger B, et al. Diagnostic accuracy of guided cervical biopsies: a prospective multicenter study comparing the histopathology of simultaneous biopsy and cone specimen. Am J Obstet Gynecol 2010 Oct;203(4):321.e1-321.e6.

(22) Gage JC, Duggan MA, Nation JG, Gao S, Castle PE. Detection of cervical cancer and its precursors by endocervical curettage in 13,115 colposcopically guided biopsy examinations. Am J Obstet Gynecol 2010 Aug 26.

(23) ASCUS-LSIL Triage Study (ALTS) Group. A randomized trial on the management of low-grade squamous intraepithelial lesion cytology interpretations. Am J Obstet Gynecol 2003 Jun;188(6):1393-1400.

(24) TOMBOLA Group. Cytological surveillance compared with immediate referral for colposcopy in management of women with low grade cervical abnormalities: multicentre randomised controlled trial. BMJ 2009 Jul 28;339:b2546.

(25) Arbyn M, Dillner J, Van Ranst M, Buntinx F, Martin-Hirsch P, Paraskevaidis E. Re: Have we resolved how to triage equivocal cervical cytology? J Natl Cancer Inst 2004 Sep 15;96(18):1401-2; author reply 1402.

(26) Arbyn M, Buntinx F, Van Ranst M, Paraskevaidis E, Martin-Hirsch P, Dillner J. Virologic versus cytologic triage of women with equivocal Pap smears: a meta-analysis of the accuracy to detect high-grade intraepithelial neoplasia. J Natl Cancer Inst 2004 Feb 18;96(4):280-293.

(27) Arbyn M, Paraskevaidis E, Martin-Hirsch P, Prendiville W, Dillner J. Clinical utility of HPV-DNA detection: triage of minor cervical lesions, follow-up of women treated for high-grade CIN: an update of pooled evidence. Gynecol Oncol 2005 Dec;99(3 Suppl 1):S7-11.

(28) Arbyn M, Sasieni P, Meijer CJ, Clavel C, Koliopoulos G, Dillner J. Chapter 9: Clinical applications of HPV testing: a summary of meta-analyses. Vaccine 2006 Aug 31;24 Suppl 3:S3/78-89.

(29) Barreth D, Schepansky A, Capstick V, Johnson G, Steed H, Faught W. Atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion (ASC-H): a result not to be ignored. J Obstet Gynaecol Can 2006 Dec;28(12):1095-1098.

(30) Mokhtar GA, Delatour NL, Assiri AH, Gilliatt MA, Senterman M, Islam S. Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion:

cytohistologic correlation study with diagnostic pitfalls. Acta Cytol 2008 Mar-Apr;52(2):169-177.

(31) Massad LS, Collins YC, Meyer PM. Biopsy correlates of abnormal cervical cytology classified using the Bethesda system. Gynecol Oncol 2001 Sep;82(3):516-522.

(32) Dunn TS, Burke M, Shwayder J. A "see and treat" management for high-grade squamous intraepithelial lesion pap smears. J Low Genit Tract Dis 2003 Apr;7(2):104-106.

(33) Tam KF, Cheung AN, Liu KL, Ng TY, Pun TC, Chan YM, et al. A retrospective review on atypical glandular cells of undetermined significance (AGUS) using the Bethesda 2001 classification. Gynecol Oncol 2003 Dec;91(3):603-607.

(34) Daniel A, Barreth D, Schepansky A, Johnson G, Capstick V, Faught W. Histologic and clinical significance of atypical glandular cells on pap smears. Int J Gynaecol Obstet 2005 Dec;91(3):238-242.

(35) Castle PE, Fetterman B, Poitras N, Lorey T, Shaber R, Kinney W. Relationship of atypical glandular cell cytology, age, and human papillomavirus detection to cervical and endometrial cancer risks. Obstet Gynecol 2010 Feb;115(2 Pt 1):243-248.

(36) Zhao C, Florea A, Onisko A, Austin RM. Histologic follow-up results in 662 patients with Pap test findings of atypical glandular cells: results from a large academic womens hospital laboratory employing sensitive screening methods. Gynecol Oncol 2009 Sep;114(3):383-389.

(37) Castle PE, Fetterman B, Poitras N, Lorey T, Shaber R, Kinney W. Relationship of atypical glandular cell cytology, age, and human papillomavirus detection to cervical and endometrial cancer risks. Obstet Gynecol 2010 Feb;115(2 Pt 1):243-248.

(38) Schnatz PF, Guile M, O'Sullivan DM, Sorosky JI. Clinical significance of atypical glandular cells on cervical cytology. Obstet Gynecol 2006 Mar;107(3):701-708.

(39) Ullal A, Roberts M, Bulmer JN, Mathers ME, Wadehra V. The role of cervical cytology and colposcopy in detecting cervical glandular neoplasia. Cytopathology 2009 Dec;20(6):359-366.

(40) Cuzick J, Szarewski A, Cubie H, Hulman G, Kitchener H, Luesley D, et al. Management of women who test positive for high-risk types of human papillomavirus: the HART study. Lancet 2003 Dec 6;362(9399):1871-1876.

(41) Castle PE, Fetterman B, Thomas Cox J, Shaber R, Poitras N, Lorey T, et al. The age-specific relationships of abnormal cytology and human papillomavirus DNA results to the risk of cervical precancer and cancer. Obstet Gynecol 2010 Jul;116(1):76-84.

(42) Wetta LA, Matthews KS, Kemper ML, Whitworth JM, Fain ET, Huh WK, et al. The management of cervical intraepithelial neoplasia during pregnancy: is colposcopy necessary? J Low Genit Tract Dis 2009 Jul;13(3):182-185.

(43) Kohan S, Beckman EM, Bigelow B, Klein SA, Douglas GW. The role of colposcopy in the management of cervical intraepithelial neoplasia during pregnancy and postpartum. J Reprod Med 1980 Nov;25(5):279-284.

(44) Ries L, Melbert D, Krapcho, M. (eds.), et al. SEER Cancer Statistics Review, 1975-2004. 2007.

(45) Mount SL, Papillo JL. A study of 10,296 pediatric and adolescent Papanicolaou smear diagnoses in northern New England. Pediatrics 1999 Mar;103(3):539-545.

(46) Moscicki AB, Ma Y, Wibbelsman C, Darragh TM, Powers A, Farhat S, et al. Rate of and risks for regression of cervical intraepithelial neoplasia 2 in adolescents and young women. Obstet Gynecol 2010 Dec;116(6):1373-1380.

(47) Le T, Hopkins L, Menard C, Hicks-Boucher W, Lefebvre J, Fung Kee Fung M. Psychologic morbidities prior to loop electrosurgical excision procedure in the treatment of cervical intraepithelial neoplasia. Int J Gynecol Cancer 2006 May-Jun;16(3):1089-1093.

(48) Arbyn M, Kyrgiou M, Simoens C, Raifu AO, Koliopoulos G, Martin-Hirsch P, et al. Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis. BMJ 2008 Sep 18;337:a1284.

(49) Samson SL, Bentley JR, Fahey TJ, McKay DJ, Gill GH. The effect of loop electrosurgical excision procedure on future pregnancy outcome. Obstet Gynecol 2005 Feb;105(2):325-332.

(50) FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007 May 10;356(19):1915-1927.

(51) Kohli M, Ferko N, Martin A, Franco EL, Jenkins D, Gallivan S, et al. Estimating the long-term impact of a prophylactic human papillomavirus 16/18 vaccine on the burden of cervical cancer in the UK. Br J Cancer 2007 Jan 15;96(1):143-150.

(52) Cutts FT, Franceschi S, Goldie S, Castellsague X, de Sanjose S, Garnett G, et al. Human papillomavirus and HPV vaccines: a review. Bull World Health Organ 2007 Sep;85(9):719-726.

(53) Rogoza RM, Ferko N, Bentley J, Meijer CJ, Berkhof J, Wang KL, et al. Optimization of primary and secondary cervical cancer prevention strategies in an era of cervical cancer vaccination: a multi-regional health economic analysis. Vaccine 2008 Sep 15;26 Suppl 5:F46-58.

(54) Paavonen J, Naud P, Salmeron J, Wheeler CM, Chow SN, Apter D, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical

infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet 2009 Jul 25;374(9686):301-314.

(55) ACOG Committee on Gynecological Practice. ACOG committee opinion No. 431: routine pelvic examination and cervical cytology screening. Obstet Gynecol 2009 May;113(5):1190-1193.

(56) ACOG Committee on Practice Bulletins--Gynecology. ACOG Practice Bulletin no. 109: Cervical cytology screening. Obstet Gynecol 2009 Dec;114(6):1409-1420.

(57) Scully RE. Histological typing of female genital tract tumours 1994:189.

(58) Ostor AG. Natural history of cervical intraepithelial neoplasia: a critical review. Int J Gynecol Pathol 1993 Apr;12(2):186-192.

(59) Kyrgiou M, Tsoumpou I, Vrekoussis T, Martin-Hirsch P, Arbyn M, Prendiville W, et al. The up-to-date evidence on colposcopy practice and treatment of cervical intraepithelial neoplasia: the Cochrane colposcopy & cervical cytopathology collaborative group (C5 group) approach. Cancer Treat Rev 2006 Nov;32(7):516-523.

(60) Walker P, Dexeus S, De Palo G, Barrasso R, Campion M, Girardi F, et al. International terminology of colposcopy: an updated report from the International Federation for Cervical Pathology and Colposcopy. Obstet Gynecol 2003 Jan;101(1):175-177.

(61) Prendiville W. The treatment of CIN: what are the risks? Cytopathology 2009 Jun;20(3):145-153.

(62) Bornstein J. Personal Communication Regarding Manuscript Submitted for Publication. July 2011.

(63) Stoler MH, Schiffman M, Atypical Squamous Cells of Undetermined Significance-Low-grade Squamous Intraepithelial Lesion Triage Study (ALTS) Group. Interobserver reproducibility of cervical cytologic and histologic interpretations: realistic estimates from the ASCUS-LSIL Triage Study. JAMA 2001 Mar 21;285(11):1500-1505.

(64) Petry KU. Management options for cervical intraepithelial neoplasia. Best Pract Res Clin Obstet Gynaecol 2011 Oct;25(5):641-651.

(65) Moscicki AB, Shiboski S, Hills NK, Powell KJ, Jay N, Hanson EN, et al. Regression of low-grade squamous intra-epithelial lesions in young women. Lancet 2004 Nov 6-12;364(9446):1678-1683.

(66) The Society for Colposcopy and Cervical Pathology of Singapore. Structured colposcopy training programme and registration forms. Available at: http://www.sccps.org/training.htm. Accessed 02/13, 2006.

(67) Jones RW, Best DV, Cox B, Fitzgerald NW, Hill M, Jennings P, et al. Guidelines for the management of women with abnormal cervical smears 1998. N Z Med J 2000 May 12;113(1109):168-171.

(68) Royal College of Obstetricians and Gynaecologists. Standards in colposcopy. Available at: http://www.rcog.org.uk/index.asp?PageID=1170. Accessed 02/13, 2006.

(69) National Cervical Screening Program (Australia). Screening to Prevent Cervical Cancer: Guidelines for the Management of Asymptomatic Women with Screen Detected Abnormalities. 2005; Available at: http://www.health.gov.au/internet/screening/publishing.nsf/Content/guide. Accessed 03/16, 2011.

(70) McCredie MR, Sharples KJ, Paul C, Baranyai J, Medley G, Jones RW, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. Lancet Oncol 2008 May;9(5):425-434.

(71) Ghaem-Maghami S, Sagi S, Majeed G, Soutter WP. Incomplete excision of cervical intraepithelial neoplasia and risk of treatment failure: a meta-analysis. Lancet Oncol 2007 Nov;8(11):985-993.

(72) Ghaem-Maghami S, Soutter WP. Re: Effect of margin status on cervical intraepithelial neoplasia recurrence following LLETZ in women over 50 years. BJOG 2009 Feb;116(3):465.

(73) ASCUS-LSIL Triage Study (ALTS) Group. Results of a randomized trial on the management of cytology interpretations of atypical squamous cells of undetermined significance. Am J Obstet Gynecol 2003 Jun;188(6):1383-1392.

(74) Moore K, Cofer A, Elliot L, Lanneau G, Walker J, Gold MA. Adolescent cervical dysplasia: histologic evaluation, treatment, and outcomes. Am J Obstet Gynecol 2007 Aug;197(2):141.e1-141.e6.

(75) Howlett RI, Marrett LD, Innes MK, Rosen BP, McLachlin CM. Decreasing incidence of cervical adenocarcinoma in Ontario: is this related to improved endocervical Pap test sampling? Int J Cancer 2007 Jan 15;120(2):362-367.

(76) Etherington IJ, Luesley DM. Adenocarcinoma in situ of the cervix-controversies in diagnosis and treatment. J Low Genit Tract Dis 2001 Apr;5(2):94-98.

(77) Cullimore JE, Luesley DM, Rollason TP, Byrne P, Buckley CH, Anderson M, et al. A prospective study of conization of the cervix in the management of cervical intraepithelial glandular neoplasia (CIGN)--a preliminary report. Br J Obstet Gynaecol 1992 Apr;99(4):314-318.

(78) Bertrand M, Lickrish GM, Colgan TJ. The anatomic distribution of cervical adenocarcinoma in situ: implications for treatment. Am J Obstet Gynecol 1987 Jul;157(1):21-25.

(79) Salani R, Puri I, Bristow RE. Adenocarcinoma in situ of the uterine cervix: a metaanalysis of 1278 patients evaluating the predictive value of conization margin status. Am J Obstet Gynecol 2009 Feb;200(2):182.e1-182.e5.

(80) Bryson P, Stulberg R, Shepherd L, McLelland K, Jeffrey J. Is electrosurgical loop excision with negative margins sufficient treatment for cervical ACIS? Gynecol Oncol 2004 May;93(2):465-468.

(81) Serati M, Uccella S, Laterza RM, Salvatore S, Beretta P, Riva C, et al. Natural history of cervical intraepithelial neoplasia during pregnancy. Acta Obstet Gynecol Scand 2008;87(12):1296-1300.

(82) Fader AN, Alward EK, Niederhauser A, Chirico C, Lesnock JL, Zwiesler DJ, et al. Cervical dysplasia in pregnancy: a multi-institutional evaluation. Am J Obstet Gynecol 2010 Aug;203(2):113.e1-113.e6.

(83) Soutter WP, Sasieni P, Panoskaltsis T. Long-term risk of invasive cervical cancer after treatment of squamous cervical intraepithelial neoplasia. Int J Cancer 2006 Apr 15;118(8):2048-2055.

(84) Melnikow J, McGahan C, Sawaya GF, Ehlen T, Coldman A. Cervical intraepithelial neoplasia outcomes after treatment: long-term follow-up from the British Columbia Cohort Study. J Natl Cancer Inst 2009 May 20;101(10):721-728.

(85) Soutter WP, de Barros Lopes A, Fletcher A, Monaghan JM, Duncan ID, Paraskevaidis E, et al. Invasive cervical cancer after conservative therapy for cervical intraepithelial neoplasia. Lancet 1997 Apr 5;349(9057):978-980.

(86) Mitchell MF, Tortolero-Luna G, Cook E, Whittaker L, Rhodes-Morris H, Silva E. A randomized clinical trial of cryotherapy, laser vaporization, and loop electrosurgical excision for treatment of squamous intraepithelial lesions of the cervix. Obstet Gynecol 1998 Nov;92(5):737-744.

(87) Paraskevaidis E, Arbyn M, Sotiriadis A, Diakomanolis E, Martin-Hirsch P, Koliopoulos G, et al. The role of HPV DNA testing in the follow-up period after treatment for CIN: a systematic review of the literature. Cancer Treat Rev 2004 Apr;30(2):205-211.

(88) Arbyn M, Paraskevaidis E, Martin-Hirsch P, Prendiville W, Dillner J. Clinical utility of HPV-DNA detection: triage of minor cervical lesions, follow-up of women treated for high-grade CIN: an update of pooled evidence. Gynecol Oncol 2005 Dec;99(3 Suppl 1):S7-11.

(89) Cuzick J, Arbyn M, Sankaranarayanan R, Tsu V, Ronco G, Mayrand MH, et al. Overview of human papillomavirus-based and other novel options for cervical

cancer screening in developed and developing countries. Vaccine 2008 Aug 19;26 Suppl 10:K29-41.

(90) Meijer CJ, Berkhof J, Castle PE, Hesselink AT, Franco EL, Ronco G, et al. Guidelines for human papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older. Int J Cancer 2009 Feb 1;124(3):516-520.

(91) Chan BK, Melnikow J, Slee CA, Arellanes R, Sawaya GF. Posttreatment human papillomavirus testing for recurrent cervical intraepithelial neoplasia: a systematic review. Am J Obstet Gynecol 2009 Apr;200(4):422.e1-422.e9.

(92) Kitchener HC, Walker PG, Nelson L, Hadwin R, Patnick J, Anthony GB, et al. HPV testing as an adjunct to cytology in the follow up of women treated for cervical intraepithelial neoplasia. BJOG 2008 Jul;115(8):1001-1007.

(93) Mayrand MH, Abrahamowicz M, James Bentley J, Bessette P, Coutlée F, Ehlen T, Elit L, Fung-Kee-Fung M, Lau S, Plante M. Colposcopy vs. HPV testing to identity persistent pre-cancers post treatment: the CoHIPP trial. HPV 2010 Conference 2010 June 2010.

(94) ter Haar-van Eck SA, Rischen-Vos J, Chadha-Ajwani S, Huikeshoven FJ. The incidence of cervical intraepithelial neoplasia among women with renal transplant in relation to cyclosporine. Br J Obstet Gynaecol 1995 Jan;102(1):58-61.

(95) David M, Olbrich C, Neuhaus R, Lichtenegger W. Occurrence of suspicious changes in cervix cytology in women after liver transplantation. Geburtshilfe Frauenheilkd 1995 Aug;55(8):431-434.

(96) Clifford GM, Franceschi S. Cancer risk in HIV-infected persons: influence of CD4(+) count. Future Oncol 2009 Jun;5(5):669-678.

(97) Denny L, Boa R, Williamson AL, Allan B, Hardie D, Stan R, et al. Human papillomavirus infection and cervical disease in human immunodeficiency virus-1-infected women. Obstet Gynecol 2008 Jun;111(6):1380-1387.

(98) Boardman LA, Cotter K, Raker C, Cu-Uvin S. Cervical intraepithelial neoplasia grade 2 or worse in human immunodeficiency virus-infected women with mildly abnormal cervical cytology. Obstet Gynecol 2008 Aug;112(2 Pt 1):238-243.

(99) Kitchener H, Nelson L, Adams J, Mesher D, Sasieni P, Cubie H, et al. Colposcopy is not necessary to assess the risk to the cervix in HIV-positive women: an international cohort study of cervical pathology in HIV-1 positive women. Int J Cancer 2007 Dec 1;121(11):2484-2491.

(100) Foulot H, Heard I, Potard V, Costagliola D, Chapron C. Surgical management of cervical intraepithelial neoplasia in HIV-infected women. Eur J Obstet Gynecol Reprod Biol 2008 Dec;141(2):153-157.

Table 2: The 2001 Bethesda System Terminology for Cytology (permission requested)

Adapted from Solomon D et al. (15)

Squamous Cell

- ☐ Atypical squamous cells
    - Of undetermined significance
    - Cannot exclude high-grade squamous intraepithelial lesions
- ☐ Low-grade squamous intraepithelial lesions-encompassing human papillomavirus, mild dysplasia and CIN 1
- ☐ High-grade squamous intraepithelial lesions- encompassing moderate and severe dysplasia, carcinoma in situ, CIN 2 and CIN 3
- ☐ Squamous cell carcinoma

Glandular Cell

- ☐ Atypical glandular cells (specify endocervical, endometrial, or not otherwise specified)
- ☐ Atypical glandular cells, favor neoplasia (specify endocervical or not otherwise specified)
- ☐ Adenocarcinoma

Table 3: Evolution of Cervical Cancer Precursors (58)

CIN grade	Regression	Persistence	Progression to CIN 3	Progression towards invasive cancer
CIN 1	57%	32%	11%	1%
CIN 2	43%	35%	22%	5%
CIN 3	32%	<56%	-	>12%

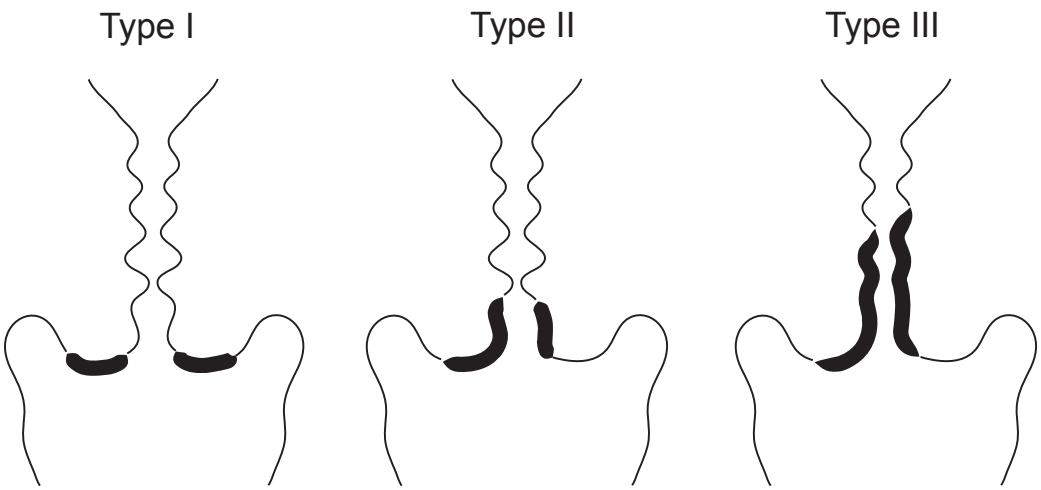
Table 4. Criteria for Ablative Methods of CIN Treatment

Modified from Prendiville 2009 (61) (permission requested)

- The transformation zone (TZ) must be fully visible
- A colposcopically directed diagnostic biopsy must be taken from the most dysplastic area in the TZ
- There must be no suspicion of invasive disease
- There must be no suspicion of glandular disease
- There should not be cytological/histological disparity
- The patient should not have had previous treatment

Cryotherapy is not recommended for treatment of CIN 3

Figure 1. Transformation Zone Categories



Glossary

AC	Adenocarcinoma
AGC-N	Atypical glandular cells-favor neoplasia
AGC-NOS	Atypical glandular cells-not otherwise specified
AGUS	Atypical glandular cells of undetermined significance
AIS	Adenocarcinoma in situ
ASC-H	Atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion
ASCUS	Atypical squamous cells of undetermined significance
CIN (1,2,3)	Cervical intraepithelial neoplasia (1,2,3)
ECC	Endocervical curettage
HPV	Human papillomavirus
HSIL	High-grade squamous intraepithelial lesion
LEEP/ LLETZ	Loop electrosurgical excision procedure / large loop excision of the transformation zone
LSIL	Low grade squamous intraepithelial lesion
SCC	Squamous cell carcinoma