CERVICAL INTRAEPITHELIAL NEOPLASIA

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CERVICAL CANCER SCREENING TESTS

- INTRODUCTION

- Cervical cancer screening detects preinvasive neoplasia, thereby making treatment possible before the disease becomes invasive. Screening is performed using cervical cytology (Pap test), or a human papillomavirus (HPV) test, or a combination of the two tests.

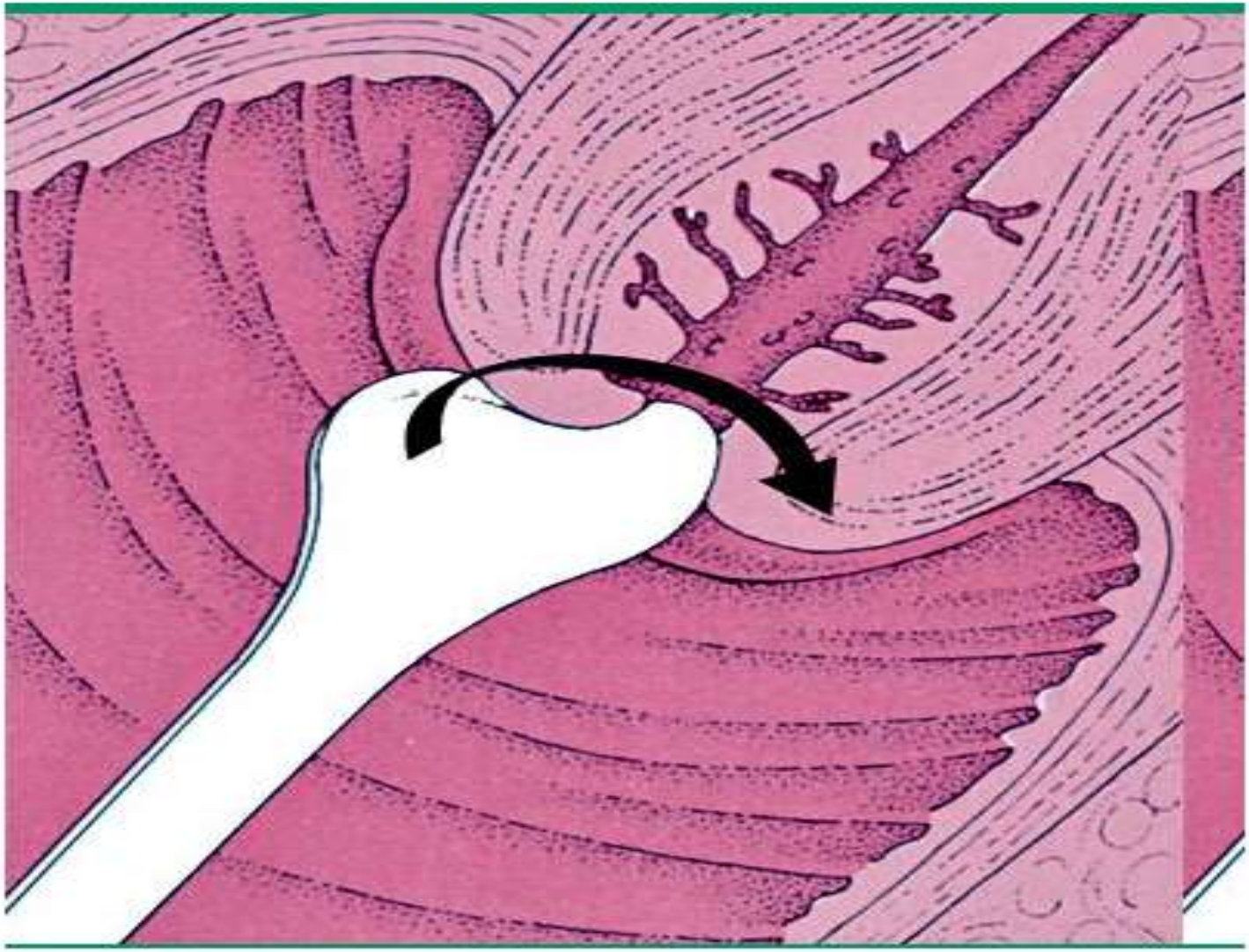
TECHNIQUES FOR OBTAINING SPECIMENS

- HOW TO OBTAIN A SAMPLE — Cell samples for cervical cytology and HPV testing are obtained during the speculum examination. The same specimen can be used for both tests or separate specimens can be obtained.
- Specimens for cytology — There are two methods for preparing a specimen for cervical cytology: the conventional Pap smear and the liquid-based, thin layer preparation (eg, ThinPrep®, SurePath™).
- For both methods, cells are obtained from the external surface of the cervix (ectocervix) and the cervical canal (endocervix) to evaluate the transformation zone , the area at greatest risk for neoplasia

COLLECTION DEVICE

- Several collection devices are available for cervical cytology sampling. It's suggested to use a spatula and a separate endocervical brush as this combination provides a specimen with more endocervical cells than when only a spatula is used. It is also slightly better for detecting any grade of cervical intraepithelial neoplasia (CIN) than the single device . Cotton tipped swabs should be avoided because they collect fewer endocervical cells and do not detect CIN as well as other devices.

Pap test Ayre spatula

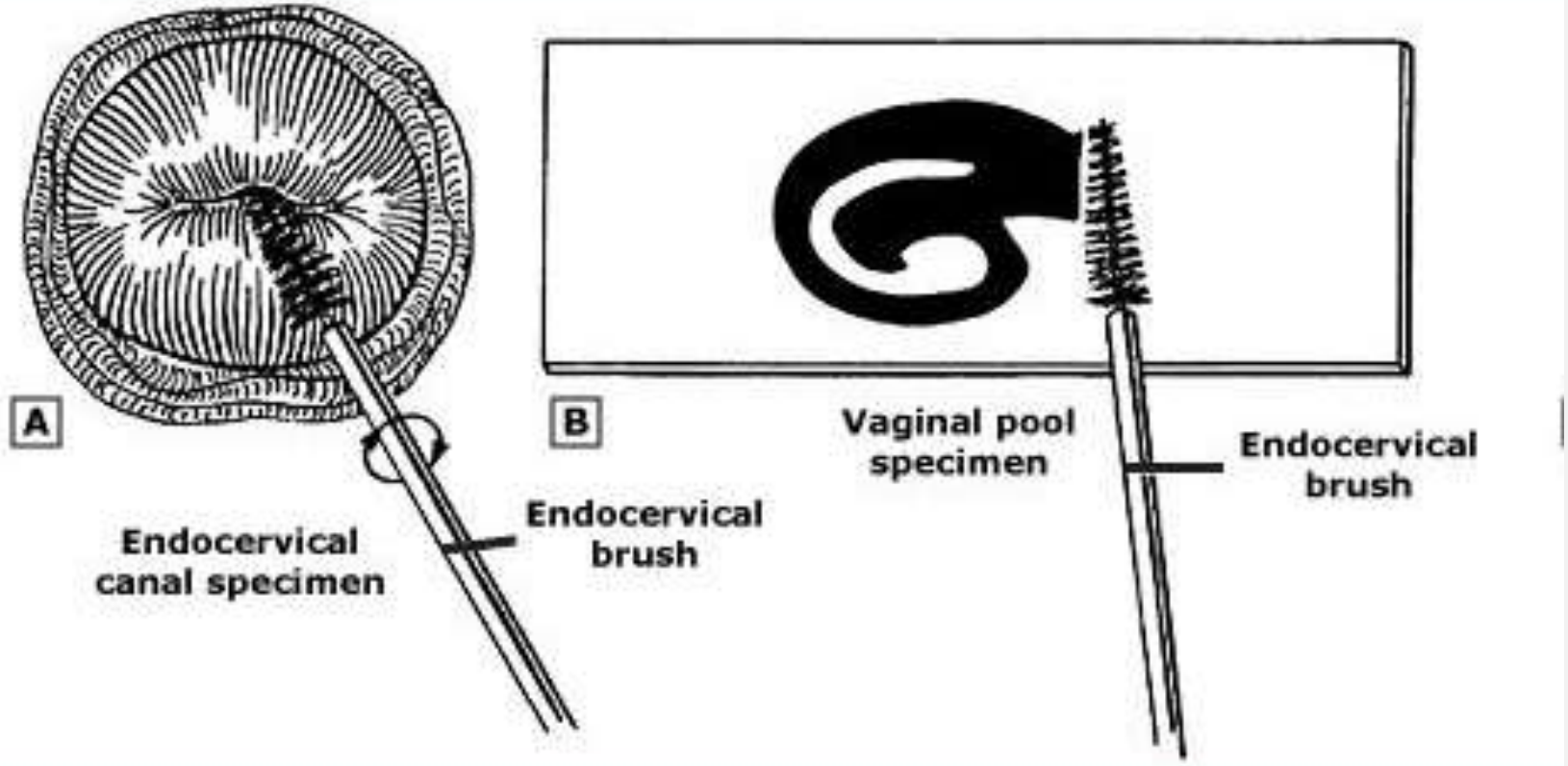


Close up view of cross section of upper vagina and cervix with wooden or plastic spatula pressed against cervix, longer end introduced slightly into os. Arrow indicates rotation to obtain ectocervical sample.

SAMPLE PREPARATION

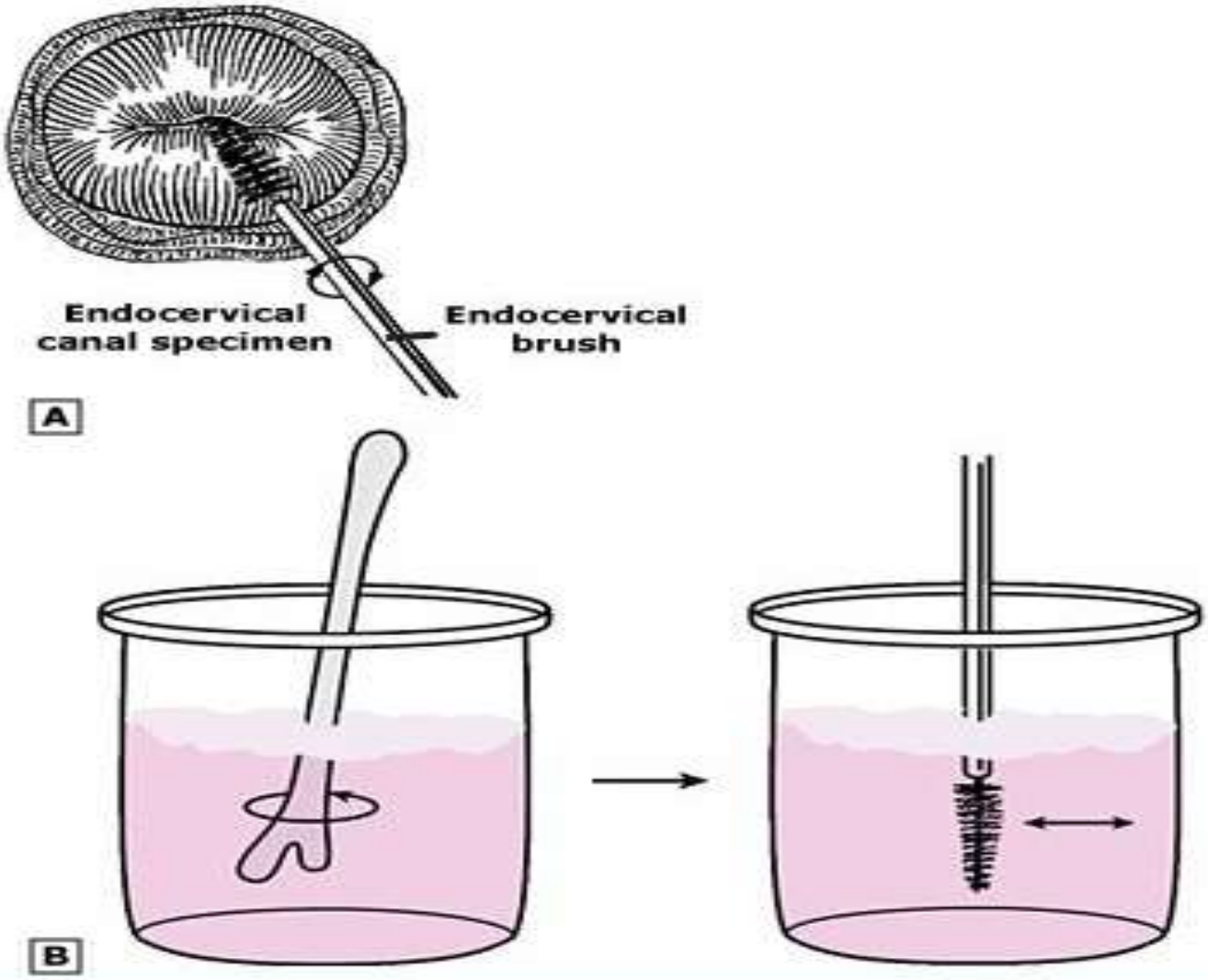
- For conventional Pap smears, the ectocervical spatula is smeared and the endocervical brush is rolled uniformly onto a single slide promptly after obtaining the specimens. The slide is then rapidly fixed to avoid air-drying; the usual fixatives are either ethyl ether plus 95 percent ethyl alcohol or 95 percent ethyl alcohol alone. If spray fixatives are used, the spray should be held at least 10 inches away from the slide to prevent disruption of cells by the propellant.
- For liquid-based thin layer cytology, the collecting device is placed into a liquid fixative solution and vigorously swirled or rotated ten times in the solution. When the liquid is processed by the cytology laboratory, loose cells are trapped onto a filter and then plated in a monolayer onto a glass slide.

Conventional Pap smear



A) Obtaining endocervical portion of Pap smear. B) Smearing specimen on slide.

Liquid-based cervical cytology



A) Obtaining endocervical portion of Pap test. B) Placement of specimens in liquid collection medium.

HPV TESTING

- Specimens for HPV testing can be collected from the endocervix using a Dacron swab or cervical brush, which is then placed in HPV test transport medium . If liquid-based cytology sampling is performed, the same specimen can be used for HPV testing and cytology.

- Commercial HPV assays, used with liquid based cytology sampling, only test for HPV types that have been associated with cancer. These HPV types are called oncogenic or high risk HPV

Risk of cervical cancer with human papillomavirus

High-risk (oncogenic or cancer-associated) types
Common types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 69, 82
Low-risk (non-oncogenic) types
Common types: 6, 11, 40, 42, 43, 44, 54, 61, 72, 81

SAMPLE INTERPRETATION

- Cytologic analysis — Cytopathologists review cervical cytology slides. The interpretation of cytologic smears is subject to considerable inter-observer variability, particularly in the case of non-diagnostic squamous and glandular atypias (atypical squamous cells of undetermined significance [ASCUS] and atypical glandular cells of undetermined significance).
- In some settings, cytotechnologists and/or automated slide interpretation devices perform initial review of the cytology slides to identify a subgroup of slides for subsequent evaluation by a cytopathologist. This subgroup consists of slides with specific abnormal characteristics.
- Standardized terminology for reporting cervical cytology results were introduced with the Bethesda System in 1988, which was last revised in 2001

Bethesda classification of cervical cytology

Specimen type
Conventional smear, liquid-based, or other technique
Specimen adequacy
Satisfactory for evaluation (description includes quality indicators, including endocervical/transformation zone component and obscuring blood or inflammation)
Unsatisfactory due to… (specify reason)
General categorization (optional)
Negative for intraepithelial lesion or malignancy
Epithelial cell abnormality (specify squamous or glandular)
Other: see interpretation/result (eg, endometrial cells in woman ≥age 40)
Automated review
If examined by a device, specify device and result
Ancillary testing
Describe method and result (eg, molecular testing)
Interpretation/result
Negative for intraepithelial lesion or malignancy (when there is absence of neoplasia this should be stated specifically, regardless of other findings)
In addition describe, if present:
Infection (Trichomonas vaginalis, Candida spp, shift in flora consistent with bacterial vaginosis, Actinomyces spp, cellular changes)
Other nonneoplastic findings, such as, but not limited to:
Reactive cellular changes associated with inflammation/cellular repair, radiation, or an intrauterine contraceptive device
Glandular cells post hysterectomy
Atrophy

Other

Endometrial cells (in a woman ≥age 40) and specify whether negative for squamous intraepithelial lesion

Epithelial cell abnormalities

Squamous cell

Atypical squamous cells (ASC)

of undetermined significance (ASC-US)

cannot exclude HSIL (ASC-H)

Low grade squamous intraepithelial lesion (LSIL) cellular changes consistent with HPV, mild dysplasia, CIN 1

High grade squamous intraepithelial lesion (HSIL) moderate/severe dysplasia, CIN 2, CIN 3, CIS

indicate if there are features suspicious for invasion (if invasion suspected)

Squamous cell carcinoma

Glandular cell

Atypical

Endocervical cells

Endometrial cells

Not otherwise specified

Atypical, favor neoplastic

Endocervical cells

Not otherwise specified

Endocervical adenocarcinoma in situ (AIS)

Adenocarcinoma

Other malignant neoplasms (specify)

Educational notes and suggestions

Suggestions should be concise and consistent with clinical follow-up guidelines published by professional organizations

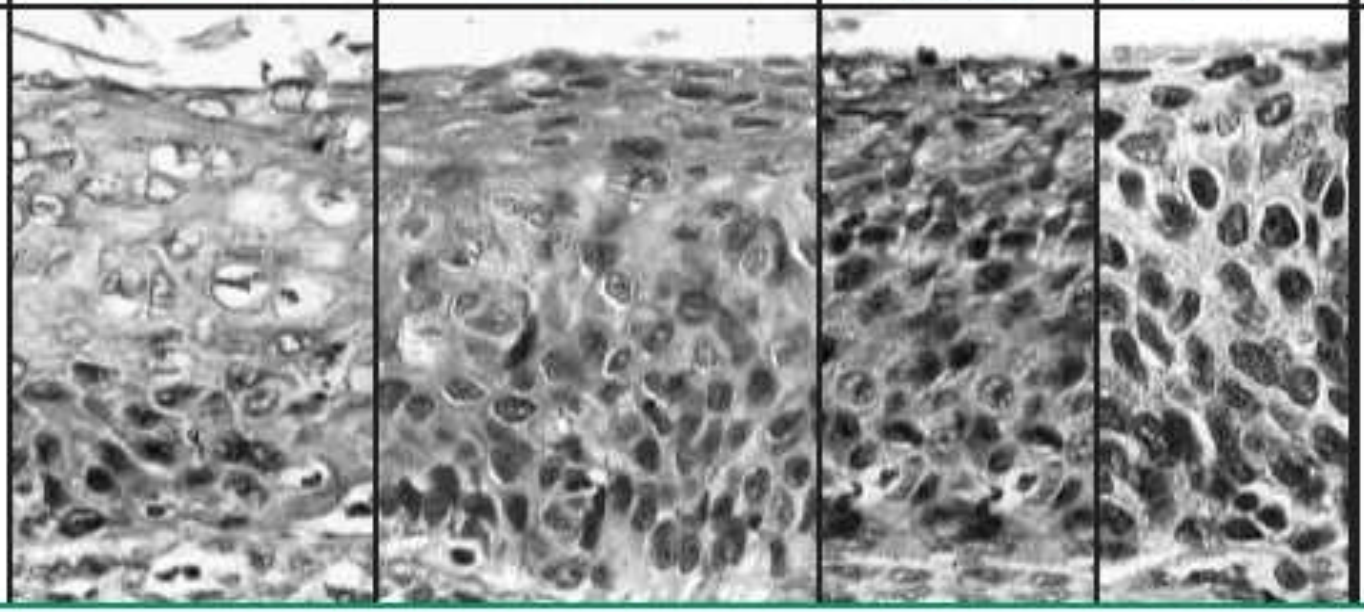
TERMINOLOGY

- Historically, mild, moderate, and severe dysplasia were the terms used to describe premalignant squamous cervical cellular changes. This nomenclature, although still in use, has generally been replaced by the term CIN, which is used to describe histologic changes (those detected with biopsy). CIN has three degrees of severity

1. CIN 1 is considered a low grade lesion. It refers to mildly atypical cellular changes in the lower third of the epithelium (formerly called mild dysplasia). HPV viral cytopathic effect (koilocytotic atypia) is often present.
2. CIN 2 is considered a high grade lesion. It refers to moderately atypical cellular changes confined to the basal two-thirds of the epithelium (formerly called moderate dysplasia) with preservation of epithelial maturation.

3. CIN 3 is also considered a high grade lesion. It refers to severely atypical cellular changes encompassing greater than two-thirds of the epithelial thickness, and includes full-thickness lesions (formerly called severe dysplasia or carcinoma in situ).

Terminology and histology of cervical intraepithelial neoplasia

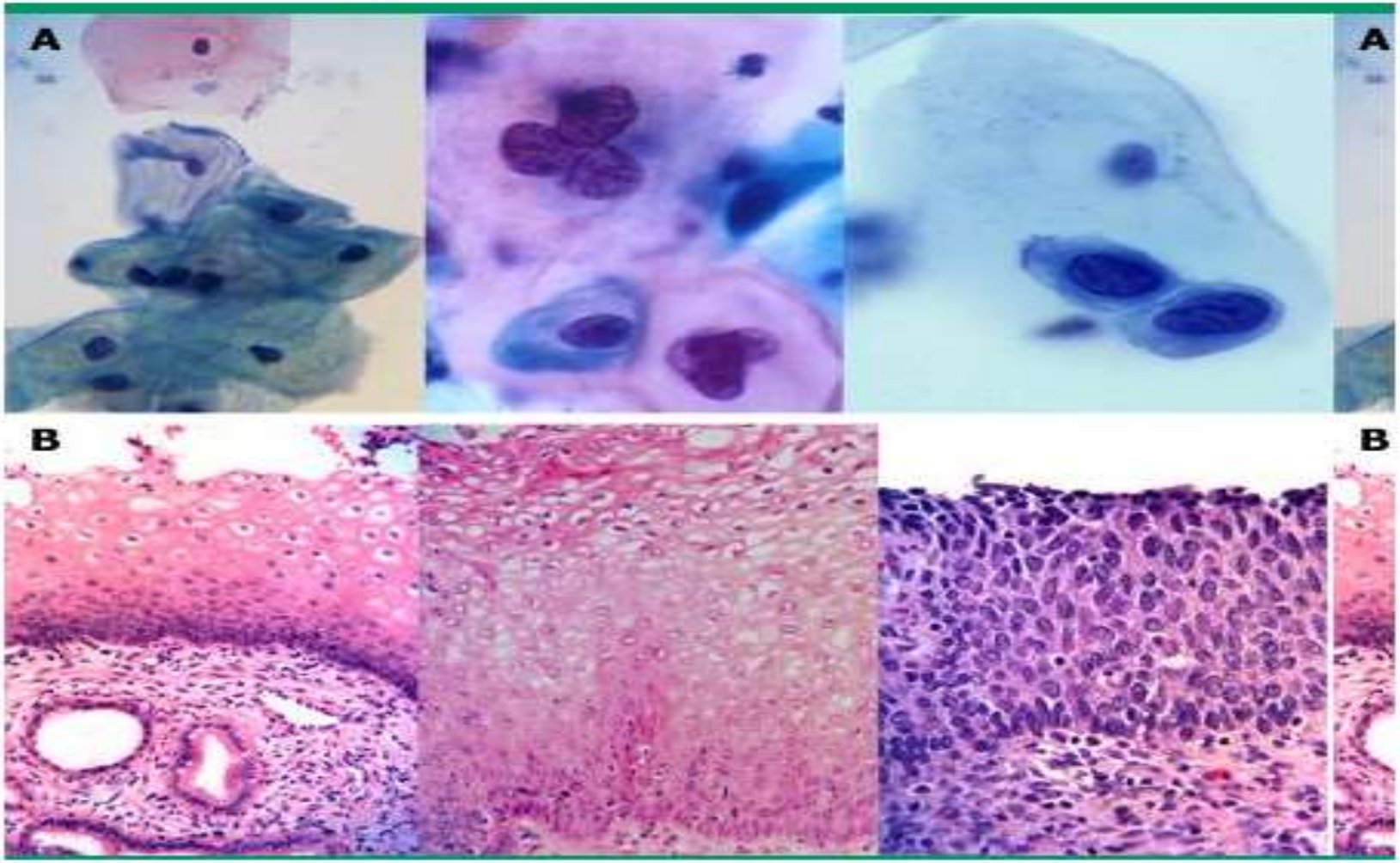
Bethesda Classification System[1]	Cytology	LSIL	HSIL		
	Histology	CIN 1	CIN 2	CIN 3	
Previous terminology		Mild dysplasia	Moderate dysplasia	Severe dysplasia	Carcinoma in-situ
Histologic images					

Terminology regarding cytologic and histologic precancerous changes of the uterine cervix. The corresponding terminology from the previous classification system to the current system (initiated with the Bethesda 1988 report) is shown. Images of the histologic correlates for each category are also shown.

LSIL: low grade squamous intraepithelial neoplasia; HSIL: high grade squamous intraepithelial neoplasia; CIN: cervical intraepithelial neoplasia.

References:

Comparison of normal, low grade and high grade lesions by cervical cytology findings and histology from colposcopically directed biopsies



A) Normal, low grade and high grade cervical cytology. B) Cervical intraepithelial neoplasia I, II, III.

HPV TESTING RESULT REPORTING

- In the United States, human papilloma virus (HPV) testing is used as primary screening for cervical cancer (as a co-test with cytology) in women over age 30 and for reflex testing after a cervical cytology result of atypical squamous cells of undetermined significance in women 21 years and older
- There are two types of available HPV tests

1. Tests that detect the presence or absence of any of 12 to 14 high-risk HPV subtypes that are associated with a high risk of cervical cancer. These tests do not report which of the individual subtypes are present. A negative test means that no oncogenic HPV types or only HPV types of low oncogenic risk were detected (however, the laboratory will report a negative test even if no cells are present.

2. Tests that perform HPV genotyping and report the presence or absence of HPV 16 or 18, which are the subtypes most commonly associated with high-grade cervical intraepithelial neoplasia and cervical cancer types. In addition, HPV 18 infection appears to be associated with an increased risk of cervical adenocarcinoma compared with other oncogenic types.

- Type-specific testing for HPV 16 and 18 is not useful for identifying women who should not receive HPV vaccination, since HPV infection can be transient and it is not known if previous HPV infection is protective against

- Patients with apparently normal immune systems may "reactivate" latent HPV infections and may develop new episodes of cervical, vulvar, or vaginal dysplasia, without a new exposure. For women with latent infections, the virus may remain dormant in the cytoplasm. In such cases, the HPV virus is still technically present, but the HPV test will be negative.

ROLE OF HUMAN PAPILLOMAVIRUS

- The terms transformation zone and squamocolumnar junction are frequently used interchangeably in the literature. However, these are two distinct entities. The squamocolumnar junction is the area in which the squamous epithelium of the ectocervix meets the columnar epithelium of the endocervix. The cervical transformation zone is a dynamic entity of metaplasia throughout a women's life and is histologically the area where the glandular epithelium has been replaced by squamous epithelium. Thus, the squamocolumnar junction is part of the transformation zone, but the transformation zone comprises a larger area than just the squamocolumnar junction

- HPV infection is endemic among sexually experienced individuals. The risk correlates with the lifetime number of sex partners, but is relatively high (4 to 20 percent) even in those with one partner. At least 80 percent of sexually active women will have acquired a genital HPV infection by age 50

- Most HPV infections occur in young women and are transient, over 50 percent of new infections are cleared in 6 to 18 months, and 80 to 90 percent will have resolved within two to five years. Transient infections are particularly common in young women in whom the average length of a newly diagnosed HPV infection is 8 to13 months. It is unclear whether HPV positive women who become HPV negative actually clear the virus from their bodies or retain the virus in an inactive or low-level state

SEQUELAE OF ACUTE INFECTION

- Latent infection without physical, cytological, or histological manifestations. This is the most common clinical sequelae of HPV infection, occurring in well over 90 percent of infected women.
- Active infection in which HPV undergoes vegetative replication, but not integration into the genome.
  Actively replicating HPV produces characteristic cellular changes, such as nuclear enlargement, multinucleation, hyperchromasia, and perinuclear cytoplasmic clearing (halos). On average, these changes occur two to eight months after the woman is first infected. The cytological findings are also the cytological characteristics of LSIL and ASC-US (atypical squamous cells of undetermined significance), thus LSIL and HPV positive ASC-US can be considered cytological manifestations of active HPV infection.

- Resolution of infection is associated with regression of the cytological changes. Resolution appears to be related, at least in part, to formation of HPV antibodies and recruitment of macrophage natural killer cells and activated CD4+ T-lymphocytes. In most women the immune response is a dominant process so the infection remains latent or is suppressed quickly; however, these antibodies can take months to develop, or never develop at all.
- Neoplastic transformation in which HPV integrates into the human genome. Possible clinical manifestations of this state include high grade lesions and cancer. This process occurs years after the acute infection

FACTORS ASSOCIATED WITH DEVELOPMENT OF HIGH GRADE LESIONS AND CANCER

1. Subtype

- Low-risk subtypes, such as HPV 6 and 11, do not integrate into the host genome and only cause low grade lesions (eg, LSIL and CIN 1) and benign condylomatous genital warts (Overall, HPV 6 and 11 account for 10 percent of low grade lesions and 90 percent of condylomatous genital warts).
- High risk HPV subtypes, such as 16 and 18, are strongly associated with high grade lesions (HSIL and CIN 2,3), persistence, and progression to invasive cancer, although they may also be associated with low grade lesions. HPV 16 and 18 account for 25 percent of low grade lesions, 50 to 60 percent of high grade lesions, and 70 percent of cervical cancers. High grade lesions are usually flat, but cancers can be nodular, ulcerative, exophytic, or endophytic.

2. Persistence: A persistent HPV infection is variably defined as one that is present at least 6 to 12 months
3. Viral load: The effect of HPV viral load is controversial

COFACTORS IN PATHOGENESIS

1. Immunosuppression
   - HIV infection — The incidence of CIN is increased in HIV-infected women
     In addition, cervical cancer is one of the most common AIDS-related malignancies in women.
   - Immunosuppressive therapy
2. Cigarette smoking — Cigarette smoking and HPV infection have synergistic effects on the development of CIN and cervical

3. Cigarette smoking — Cigarette smoking and HPV infection have synergistic effects on the development of CIN and cervical
4. Herpes simplex virus and chlamydia — Infection with chlamydia, herpes simplex virus (HSV), or other sexually transmitted diseases may be a surrogate marker of exposure to HPV, rather than a causal factor itself
5. Oral contraceptives — Long-term use of oral contraceptives has been implicated as a cofactor that increases the risk of cervical carcinoma in women who are HPV positive
6. Other — For the most part genetic, familial, dietary, and endogenous hormonal factors are not thought to play a role in development of CIN or cervical cancer

COLPOSCOPY

- Colposcopy is a diagnostic procedure in which a colposcope (a dissecting microscope with various magnification lenses) is used to provide an illuminated, magnified view of the cervix, vagina, and vulva.

- Colposcopic evaluation of the cervix and vagina is based on the finding that malignant and premalignant epithelium have specific macroscopic characteristics relating to contour, color, and vascular pattern that are recognizable by colposcopy.

- The improved visualization of epithelial surfaces enhances the colposcopist's ability to distinguish normal from abnormal areas and to obtain directed biopsies from suspicious tissue.

Colposcope on a rolling stand

INDICATIONS

- Specific cytological abnormalities:
  1. Persistent atypical cells of undetermined significance (ASC-US) or ASC-US with positive high-risk human papillomavirus (HPV) subtypes
  2. ASC suggestive of high-grade lesion (ASC-H)
  3. Atypical glandular cells (AGC)
  4. High-grade squamous intraepithelial lesion (HSIL)
  5. Suspicious for invasive cancer
  6. Malignant cells present

- Additional common indications for colposcopy include :
- Evaluation of patients with persistent (two consecutive years) positive testing for high-risk human papillomavirus and normal cytology.
- Assessment of women exposed to diethylstilbestrol (DES) exposure in utero.
- Evaluation of a palpably or visually abnormal cervix, vagina, or vulva (see individual topic reviews).
- In conjunction with laser or other treatment modalities to ensure that known lesions are completely removed or treated, to detect any other lesions in surrounding areas, and for posttreatment surveillance.
- Evaluation of a positive screening test for cervical neoplasia such as spectroscopy, cervicography, or speculoscopy

STEPS IN THE COLPOSCOPIC EXAM

- Examine cervix using low power (inflammation, infection, leukoplakia, punctation, mosaicism, abnormal vessels)
- Use green filter and normal saline
- Apply 5% acetic acid. Repeat Q 5 min if needed.
- Scan entire cervix with white light. Start with low power and move to higher magnification to document abnormal vascular patterns. Use endocervical speculum if needed to view entire transformation zone
- The ***entire TZ, including SCJ***, and borders of all lesions must be visualized in order for colposcopy to be satisfactory

5% ACETIC ACID APPLICATION

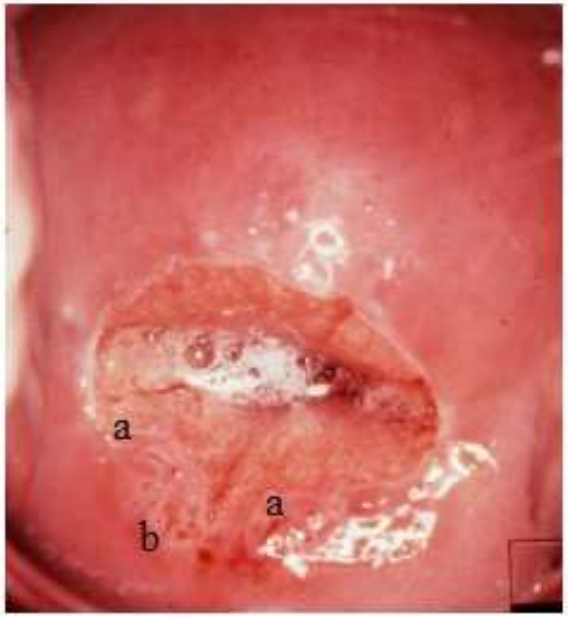


FIGURE 6.11: The prominent white line corresponds to the new squamocolumnar junction and tongues of immature squamous metaplasia (a) with crypt opening at 4-8 o'clock positions (b) (after application of 5% acetic acid).

- Apply Lugol's iodine solution to aid in delineating potential biopsy site
- Lugol's iodine consists of 5 g of iodine and 10 g of potassium iodide in 100 mL distilled water

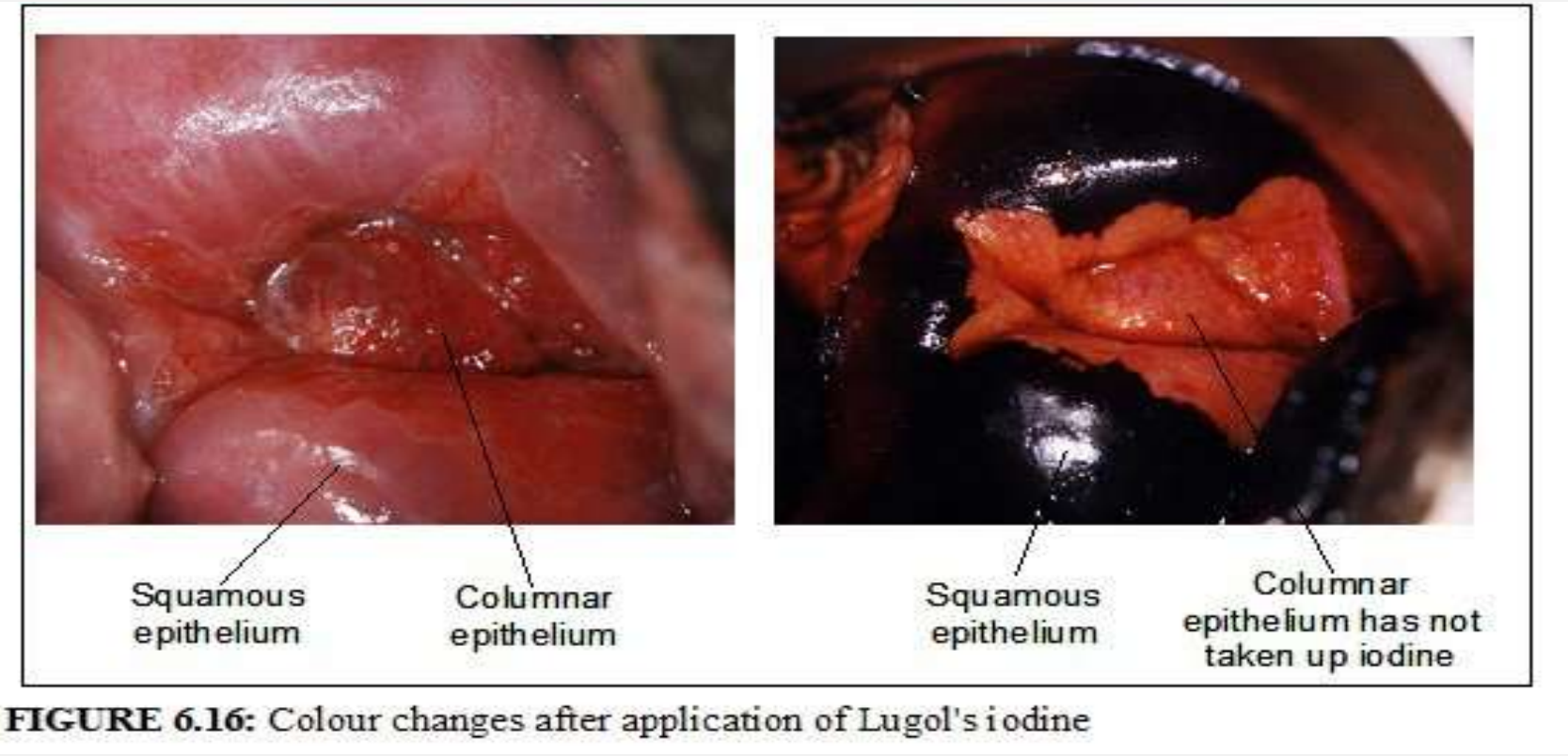
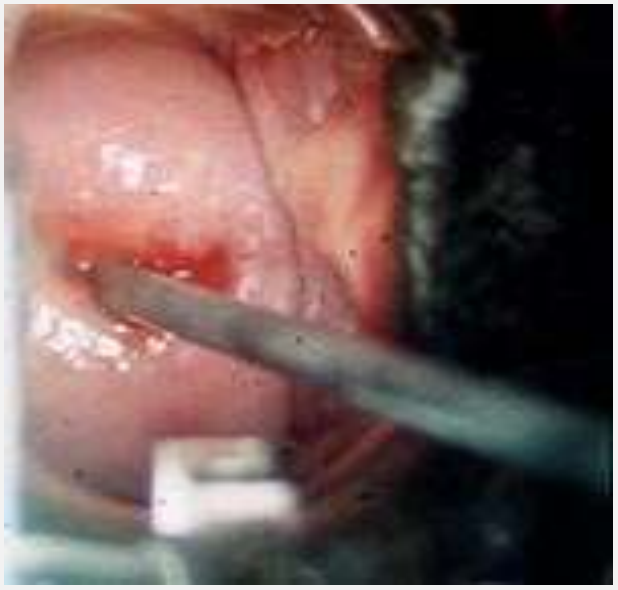


FIGURE 6.16: Colour changes after application of Lugol's iodine

STEPS IN THE COLPOSCOPIC EXAM

- Perform endocervical curettage, if indicated
  - ASC-H; HSIL
  - Adenocarcinoma in situ
  - Glandular lesion
  - Unsatisfactory colposcopy
  - ASC-US/LSIL but no visible lesion
  - CONTRAINDICATED in pregnancy or active cervicitis

FIGURE 4.7: Endocervical curette



STEPS IN THE COLPOSCOPIC EXAM

- Mentally map abnormal areas
  - Mild acetowhite < Intensely acetowhite
  - No blood vessel pattern < Punctation < Mosaicism
  - Diffuse vague borders < Sharply demarcated borders
  - Follows normal contours of the cervix < "humped up"
  - Leukoplakia – usually a very good (condylomata) or very bad sign
  - Atypical vessels – usually cancer
  - Normal iodine reaction (dark) < Iodine-negative epithelium (yellow)

STEPS IN THE COLPOSCOPIC EXAM

- Perform cervical biopsies, if necessary
  - Biopsy posterior areas first
  - A depth of 3 mm is adequate
  - Biopsy area of the lesion with worst features and closest to SCJ, include the area with atypical vessels

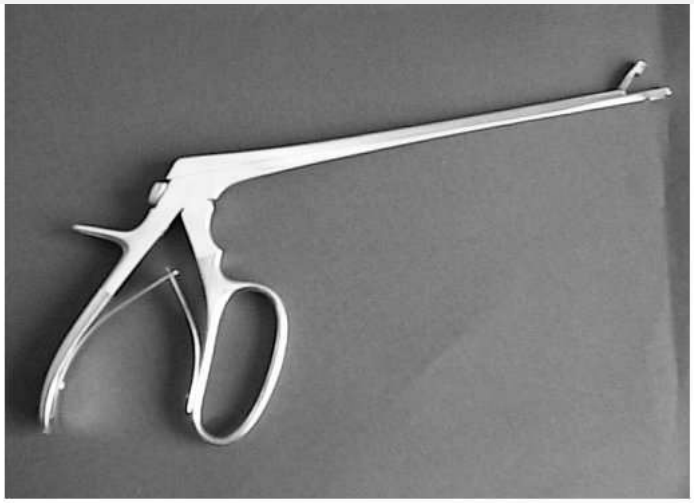


FIGURE 4.8: Cervical punch biopsy forceps with sharp, cutting edges

- Performing two or more biopsies appears to increase sensitivity .
- Options include performing additional biopsies
    1. from another part of the most abnormal appearing lesion,
    2. from more than one abnormal appearing area,
    3. randomly from normal appearing quadrants .
- Apply pressure to bleeding sites after biopsy
- Remove speculum and inspect vaginal walls, vulva, perineum, and perianal areas
- Allow patient to recover
- Document findings
- Discuss findings with patient and give post-procedure instructions

REID COLPOSCOPIC INDEX

Colposcopic Sign	Zero Points	One Point	Two Points
Margin	Condylomatous or micropapillary contour. Indistinct borders. Flocculated or feathered margins. Jagged, angular lesions. Satellite lesions, acetowhite lesions outside the transformation zone.	Regular lesions with smooth, straight outlines. Sharp peripheral margins.	Rolled, peeling edges. Internal borders between lesions of different severity.
Color	Shiny, snow white. Transient, indistinct acetowhite, semi-transparent.	Shiny, off-white. Intermediate white.	Dull, oyster grey. Persistent, dense acetowhite
Vessels	Fine punctation or fine mosaic. Uniform, fine caliber, nondilated capillary loops. Narrow intercapillary distance.	Absence of surface vessels following acetic acid application.	Coarse punctation or coarse mosaic. Individual vessels dilated. Wide intercapillary distance.
Iodine Staining	Positive iodine uptake, producing a mahogany brown color. Negative iodine uptake (mustard yellow) of a lesion recognized as low grade by above criteria (≤2/6)	Partial iodine uptake. Variegated, tortoise-shell appearance.	Negative iodine uptake (mustard yellow) of a lesion considered high grade by above (≥3/6).
Total Reid Colposcopic Index Score:	0-2 = HPV or CIN I	3-5 = CIN I or CIN II	6-8 = CIN II or CIN III

Name: _____ Colposcopy F/U office visit Date: _____

Clinical Impressions: _____

_____

Pathology report: BX _____ ECC _____

Repeat pap result:

_____

Plan:
- ❑ Discourage Smoking
- ❑ Quarterly pap
- ❑ Semiannual pap
- ❑ Annual pap

1. Lesion Limited to portio	❑ Yes	❑ No	❑ Pending
2. Colposcopy indicates only CIN	❑ Yes	❑ No	❑ Pending
3. ECC negative	❑ Yes	❑ No	❑ Pending
4. Cytology indicates no invasion	❑ Yes	❑ No	❑ Pending
5. Biopsy correlates with Pap	❑ Yes	❑ No	❑ Pending

Recommendations:

Medication: _____

Conization ❑ Yes ❑ No Leep ❑

Cryocautery ❑ Yes ❑ No

Referral ❑ Yes ❑ No _____

Follow-up: _____ weeks _____ month _____ yr _____ prn

_____ EXAMINER

_____ ATTENDING

EMORY FAMILY MEDICINE – Colposcopy Procedure Form

Date: ____ / ____ / ____

❑ Midtown: 490 Peachtree St., NE Suite 275-C, Atlanta, GA 30308 Tel: 404-686-8202 Fax: 404-686-4319
❑ South Dekalb: 2764 Candler Road, Decatur, GA 30034 Tel: 404-778-8600 Fax: 404-778-8695
❑ IDC: 341 Ponce de Leon Ave., Atlanta, GA 30308 Tel: 404-616-9833 Fax: 404-616-9700

PATIENT INSTRUCTIONS: Please complete questions in this box.

Date _____ Referring Physician _____

Name _____ Reason for Colposcopy _____

Phone (Home) _____ (Work) _____

HISTORY

Previous abnormal paps?	Y	N
History of previous cryocautery (freezing)?	Y	N
Personal history of cancer?	Y	N
Family history of cancer?	Y	N
History of venereal diseases (circle)	Y	N
• Goneorrhea AIDS herpes syphillis		
Do you desire testing for any of these diseases?	Y	N
History of genital warts?	Y	N
Visible warts now?	Y	N
Previously treated?	Y	N

If so, how? _____

Age _____
Number of pregnancies _____ Children _____
Date of last menstrual period _____
Type of contraception _____
Number of sexual partners (lifetime) _____
Age at first sexual intercourse _____
Do you smoke? _____
Partner(s) with warts? _____
History of sexual abuse? _____

VS: T: P: BP: /

PROCEDURE (Doctor will fill out)

Observation without staining: _____
Acetic acid staining/colposcopy: _____
Lugol's staining: _____

Pap repeated?	Y	N
SCJ seen?	Y	N
Endo spec needed?	Y	N
ECC done:	Y	N
Entire lesion seen?	Y	N

Vaginal Vault:

Urethra:

Labia:

Perineum:

Rectum:

LK = Leukoplakia
WE = White epihelium
PN = Punctation
MO = Mosaicism
ATZ = Abnormal Transformation zor
AV = Abnormal vessels
BE = Bulk effect
AG = Atypical glands
X = Biopsy site

RCI:
Margin _____
Color _____
Vessels _____
Iodine _____
Total _____

IMPRESSION: _____

PLAN: ❑ Biopsy Post-Care Instructions ❑ Need at least annual Paps for life, no matter what others may say.
❑ Followup 2 weeks ❑ Discourage smoking Other: _____

Examiner: _____

Attending: _____

MANAGEMENT

- CIN 1 — Given the high rate of spontaneous regression, it's suggested that expectant management rather than treatment of most patients with CIN 1

- CIN 2,3 — Given the low rate of spontaneous regression and high rate of progression, it's suggested that treatment rather than expectant management of patients with CIN 2,3 (except for adolescents and pregnant women)

- Treatment options fall into one of two main categories: procedures that ablate the abnormal tissue; these do not produce a specimen for additional histologic evaluation, and procedures that excise the area of abnormality; these allow further histologic study. Clinical trials comparing the different treatment modalities have not found that any treatment is significantly more successful than another .Regardless of the modality used, the entire transformation zone should be eliminated

ABLATIVE THERAPY

- Women are candidates for ablative therapy if they have no suspected glandular or invasive squamous disease and are compliant with follow-up.

1. Cryotherapy — Cryotherapy uses a refrigerant gas (carbon dioxide or nitrous oxide) to cool the ectocervix with a metal cryoprobe. The ectocervix must be cooled to -20°C to cause crystallization of intracellular water and destroy the lesion. This can be achieved by forming an ice ball in the cervical tissue that is at least 5 mm from the tip of the probe.

2. CO2 laser — Laser surgery should only be performed by physicians with specialized training. The laser is directed at the cervical lesion under colposcopic guidance. Water in the tissue absorbs the laser energy, which destroys the tissue by vaporization. To be effective, the lesion is typically ablated to a depth of 5 mm on the ectocervix and 8 to 9 mm around the endocervix.

3. Cold coagulation — Despite the term "cold" coagulation, this method uses heat to ablate the cervical stroma. The term "cold" coagulation is used because lower temperatures are used compared with electrocoagulation diathermy ablation (see below). Similar to cryotherapy, a probe (thermosound) is used to conduct heat to the cervix. Probe temperatures vary from 50°C to 120°C. Depth of penetration into the cervical stroma depends on the temperature of the probe and duration of probe application.

4. Diathermy — The term diathermy means "electrically induced heat". This technique uses a needle that is attached to an electrosurgical generator (cautery device) to destroy cervical tissue.

EXCISIONAL THERAPY

- Indications for excisional therapy are:
  1. Suspected microinvasion
  2. Unsatisfactory colposcopy (the transformation zone is not fully visualized)
  3. Lesion extending into the endocervical canal (including CIN 1)
  4. Endocervical curettage showing CIN or a glandular abnormality
  5. Lack of correlation between the cytology and colposcopy/biopsies
  6. Suspected adenocarcinoma in situ
  7. Colposcopist unable to rule out invasive disease
  8. Recurrence after an ablative or previous excisional procedure

- Excisional treatment can be performed by cold knife conization, laser conization, or the loop electrosurgical excision procedure (LEEP), also called large loop excision of the transformation zone (LLETZ).
- In general, with suspected microinvasion or adenocarcinoma in situ (AIS), cold knife conization is often recommended so that margins can be evaluated without cautery artifact.

HYSTERECTOMY

- Hysterectomy should not be performed as an initial treatment of CIN 2,3. The incidence of significant morbidity with hysterectomy is higher than with the less invasive modalities discussed above.
- There are, however, some indications for which hysterectomy remains a valid treatment option for CIN

1. Conization specimen margins that are positive for CIN 2,3, especially in the setting of completed childbearing and expected poor compliance with follow-up
2. Presence of coexistent gynecologic conditions requiring hysterectomy
3. Patient request and persistent or recurrent CIN 2,3