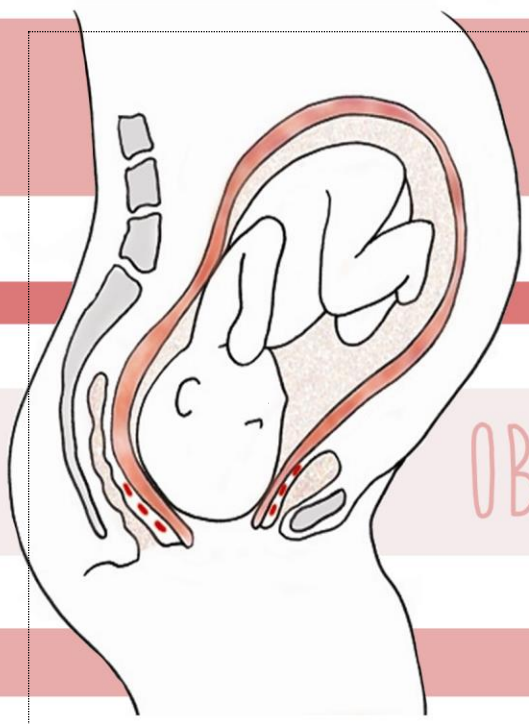


OBSTETRICS AND GYNECOLOGY

(24) CIN and Cervical Cancer

Leader: Alanoud Alyousef

Sub-leader: Dana ALdubaib

Done by: May Alorainy

Revised by: Razan Alhoqail

Doctor's note Team's note Not important Important 431 teamwork

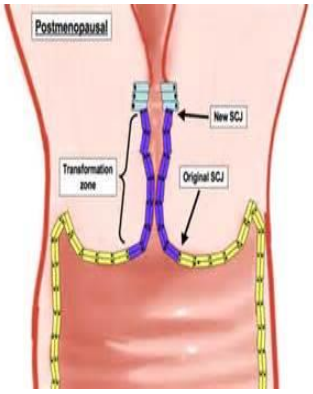
(431 teamwork do not highlight it in yellow, but put it in a yellow "box")

Objectives:

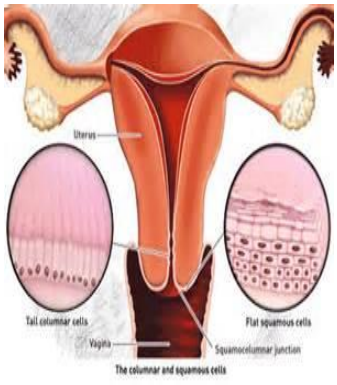
- Anatomy, Etiology & Epidemiology
  - SCJ
  - HPV
- Screening protocol
  - PAP
- Management of abnormal PAP
- Cervical intraepithelial lesion
  - Cancer related
  - Management
- Invasive cervical cancer
  - Clinical picture
  - Work-up
  - Staging & Management

Text in this color is from Hacker and Moore's Essentials of Obstetrics and Gynecology

Anatomy



- The ectocervix surface of the cervix that is visualized on vaginal speculum examination is covered in squamous epithelium, and the endocervix, including the cervical canal, is covered with glandular epithelium.
- SCJ is a dynamic point that change in response to puberty, pregnancy, menopause and hormonal stimulation.
- In neonate it is located on the exocervix, at menarche, the production of estrogen causes the vaginal epithelium filled with glycogen.
- Lactobacilli act on glycogen to lower the PH, stimulate the subcolumnar reserve cells to undergo metaplasia.
- **Further explanation:** At birth, the vagina is usually covered with squamous epithelium, and the columnar epithelium is limited to the endocervix and the central portion of the ectocervix. The embryologic squamous and columnar epithelia are designated the original and native squamous and columnar epithelia, respectively. The junction between them on the ectocervix is called the original squamocolumnar junction. Throughout life, but particularly during adolescence and a woman's first pregnancy, metaplastic squamous epithelium covers the columnar epithelium so that a new squamocolumnar junction is formed more proximally. This junction moves progressively closer to the external os and then up the endocervical canal. The transformation zone is the area of metaplastic squamous epithelium located between the original squamocolumnar junction and the new squamocolumnar junction.



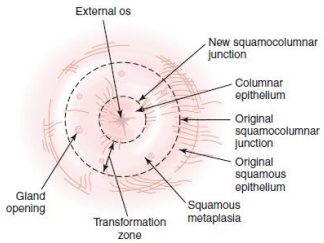


FIGURE 38-1 Schematic representation of the transformation zone.

HPV

- HPV is divided into two classes:
  1. Oncogenic
  2. Nononcogenic. E.g. HPV genotypes 11 and 6, which cause genital warts.
- Infection with oncogenic (or high-risk) HPV usually is a necessary but not sufficient factor for the development of squamous cervical neoplasia. Therefore, only a small fraction of women infected with HPV will develop significant cervical abnormalities and cancer.
- HPV attacks the cervical transformation zone.
- HPV 16 has the highest carcinogenic potential and accounts for approximately 55–60% of all cases of cervical cancer worldwide.
- HPV 18 is the next most carcinogenic genotype and is responsible for 10–15% of cases of cervical cancer.

- Approximately 10 other genotypes are associated with the remainder of cases of cervical cancer.
- The current model of cervical carcinogenesis posits that HPV infection results in either transient or persistent infection .
- Most HPV infection is transient and poses little risk of progression .
- Only a small fraction of infections are persistent, but persistent infection at 1 year and 2 years strongly predicts subsequent risk of cervical intraepithelial neoplasia (CIN) 3 or cancer regardless of age. → Persistence of the infection is the main concern in case of HPV infection as it carries the highest risk for progression to CIN.
- **Primary prevention:** Two prophylactic vaccines are presently available:
  - The quadrivalent vaccine Gardasil:
    - Protects against HPV types 6,11, 16 and 18.
    - Indicated for females aged 9-26 years.
  - The bivalent vaccine Cervarix:
    - protects against HPV types 16 and 18
    - Approved for females aged 9 to 45 years
  - The vaccine is most effective if performed before the onset of sexual activity and is less likely to be effective after HPV exposure.

Risk Factors

- **Cofactors that increase the likelihood of persistence infection include:**
  - Cigarette smoking and HPV infection have synergistic effects on the development of CIN and cervical cancer.
  - compromised immune system.
  - human immunodeficiency virus (HIV) infection.
- **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 affected by high risk HPV genotype. The excess risk of cervical cancer declines after discontinuation of oral contraceptives, and by 10 years, returns to the baseline risk in nonusers.
- **Herpes simplex virus and chlamydia**

  Infection with chlamydia, herpes simplex virus, or other sexually transmitted infections may be a surrogate marker of exposure to HPV rather than a causal factor itself.
  Alternatively, these infections may modulate host immunity, thereby facilitating persistence of oncogenic HPV.
- The risk of transmission of HPV correlates with the lifetime **number of sex partners**, but the prevalence of HPV infection is substantial (4 to 20 percent) even in those with one partner.

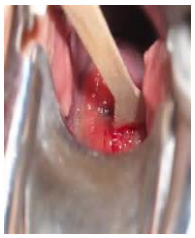
- In the United States (US), up to 50 percent of sexually active young women will have positive HPV tests within 36 months of first sexual activity, and up to 57 percent of sexually active female adolescents are infected with HPV at any one point in time.
- In our society, men married to multiple wives or women with multiple previous marriages are said to have multiple sexual partners.
- HPV is a sexually transmitted virus. It cannot be contracted from swimming pools or toilet seats.
- Human papillomavirus infection is most common in teenagers and women in their early 20s, with a decrease in prevalence as women age.
- Most young women, especially those younger than 21 years, have an effective immune response that clears the infection in an average of 8 months or reduces the viral load in 85–90% of women to undetectable levels in an average of 8–24 months. → If HPV is detected in women younger than 21 years of age, it is better not to intervene because she will clear the infection on her own in most cases.
- The adolescent cervix is believed to be more susceptible to carcinogenic stimuli because of the active process of squamous metaplasia, which occurs within the transformation zone during periods of endocrine change. This squamous metaplasia is normally a physiologic process, but under the influence of the HPV, cellular alterations occur that result in an atypical transformation zone. These atypical changes initiate CIN, which is the preinvasive phase of cervical cancer.

Screening (very important)

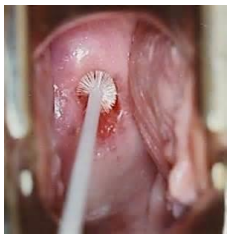
- Most cervical cancer occurs in women who were either never screened or were inadequately screened.
- Estimates suggest that 50% of the women in whom cervical cancer is diagnosed never had cervical cytology testing, and another 10% have not been screened within the 5 years before diagnosis.
- Thus, approximately 60% of diagnoses of cervical cancer are a result of inadequate screening.

When to Screen?

- Cervical cancer screening should begin at age 21 years → the reason behind this is the high prevalence of HPV infection in younger patients. This infection is expected to clear up by the time they are 21 and older.
- 21-29yrs → PAP every 3years.
- 30-65yrs → PAP and HPV every 5years. **(normal pap smear & negative HPV results → screen every 5 years)**
- Or PAP alone every 3years.
- Above 65 → no screening unless she had previous cervical abnormalities.
- Vaccinated women should continue age specific screening protocol because the vaccine does not protect against all high-risk HPV viral types.



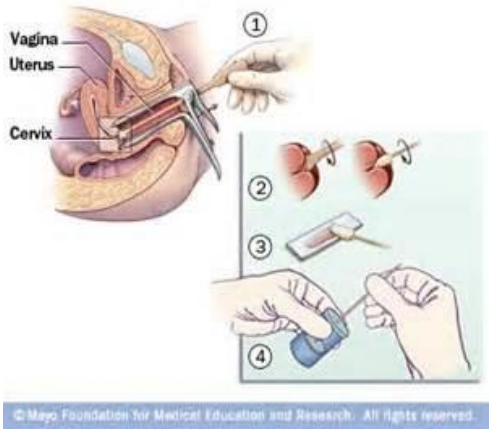
Spatula



Brush

Both the endocervical canal and the ectocervix should be sampled when taking the pap smear.

- **Coventional pap smear -3-:** The sample is spread on a glass slide.
- **Liquid-based cytology (LBC)-4-:** The sample is placed into a fixative solution that preserves cells.
- Both are equal in terms of sensitivity and specificity however, LBC has some advantages over the conventional method which include:
  - Ability to culture HPV from the same media.
  - Elimination of mucus, blood and cellular debris giving a clearer microscopic view.
  - Better conservation of cells.



Pap interpretation (Cytology) Important

Using Bethesda system classification:

Squamous cell abnormalities
in squamocolumnar junction

- ASC (**not** HPV related in 90%)
  - ASC-US
  - ASC-H
- LSIL → consistent with CIN 1
- HSIL → consistent with CIN2, CIN3, CIS
- SCC

*LSIL, HSIL and SCC are HPV related.

Glandular cell abnormalities
in cervical canal

- Atypical glandular cell
  - Atypical endocervical cell
  - Atypical endometrial call
  - No otherwise specific
- Atypical glandular cell favor neoplastic
  - Endocervical
  - No otherwise specific.
- Adenocarcinoma in situ (AIS)
- Adenocarcinoma

*If pap smear is positive for atypical glandular cells, an endometrial biopsy should be obtained.

Abbreviations: Atypical squamous cells of undetermined significance (ASC-US), ASC suggestive of high-grade lesion (ASC-H), Low-grade squamous intraepithelial lesions (LSIL), High-grade squamous intraepithelial lesion (HSIL), Squamous cell carcinoma (SCC).

Colposcopy

Next step in the management of an abnormal pap smear is colposcopy and direct biopsy.

- Steroscopic binocular microscope of low magnification.
  - 3% ascetic acid to remove adherent mucus & cellular debris. Acetic acid is used as a dye.
  - Green filter to accentuate the vascular changes.
  - Original squamous epithelium appears gray & homogenous.
  - The columnar epithelium appears red and grape like.
  - TZ glands opening that are not covered by the squamous metaplasia and by the paler color of the metaplastic epithelium.

Who needs colposcopy?

- Persistent atypical cells of undetermined significance (ASC-US) or ASC-US with positive high-risk human papillomavirus (HPV) subtypes.
- ASC suggestive of high-grade lesion (ASC-H).
- Atypical glandular cells (AGC).
- Low-grade squamous intraepithelial lesions (LSIL).
- High-grade squamous intraepithelial lesion (HSIL).
- Suspicious for invasive cancer → squamous carcinoma in situ or adenocarcinoma in situ.
- Malignant cells present.

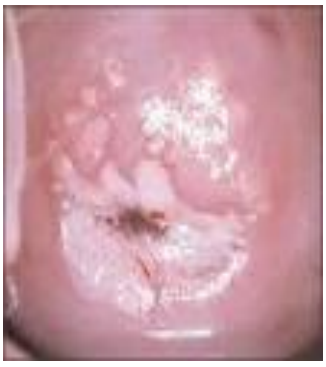
*Patient has ASC-US on her first pap smear? Observe then repeat pap smear after 1 year → if still ASC-US, it means that it is persistent → Do colposcopy.

Abnormal finding on colposcopy

1. Leucoplakia: glycogen deposits giving a white patchy appearance before adding acetic acid.
2. Aceto-white area: The colposcopic hallmark of CIN is an area of sharply delineated acetowhite epithelium, that is, epithelium that appears white after the application of acetic acid.
3. Mosaicism
4. Punctation

} Changes in vascular architecture

Punctate and mosaic patterns may be seen together within the same area of the cervix. The more dilated and irregular the punctate and mosaic capillaries and the greater the intercapillary distance, the more atypical is the tissue on histologic examination. Similarly, the whiter the lesion, the more severe the dysplasia.



Leucoplakia

Aceto-white area

Punctation

Mosaicism

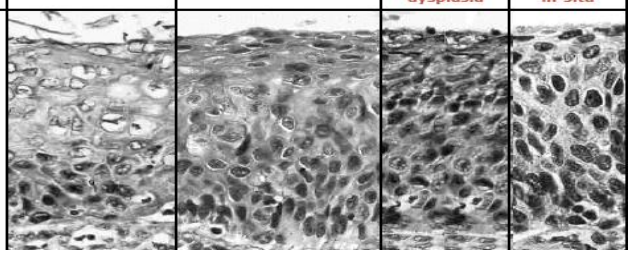
Biopsy and Endocervical curettage (ECC)

- The most abnormally appearing areas are biopsied. Biopsies are relatively contraindicated in patients on anticoagulation medication, who have a known bleeding disorder, or who are pregnant.
- Endocervical curettage or sampling is performed in patients with ASC-H, HSIL, AGC, adenocarcinoma in situ (AIS), LSIL but no visible lesion, if ablative treatment is contemplated, and those with an unsatisfactory colposcopy examination.
- If the borders of the lesion cannot be visualized, colposcopy is regarded unsatisfactory. Endocervical curettage is indicated in such case.

Histological definitions

- CIN represents a spectrum of disease, ranging from CIN I (mild dysplasia) to CIN III (severe dysplasia and carcinoma in situ). The disease is asymptomatic.
- CIN 1 is a low-grade lesion. It refers to mildly atypical cellular changes in the lower third of the epithelium (atypical changes are superficial). Human papillomavirus (HPV) cytopathic effect (koilocytotic atypia) is often present.HPV infected cells feature hyperchromatic nuclei and dcreased nuclear-cytoplasmic ratio which is referred to as *koilocytotic atypia.*
- 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.
- CIN 3 is 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 (previous terms were severe dysplasia or carcinoma in situ).

Note that ASC-US does not result in histopathological changes, while ASC-H and LSIL correspond to CIN on histology.

LAST System[1]	Cytology	LSIL	HSIL		
	Histology	LSIL	p16 staining should be performed*	HSIL	
Bethesda Classification System[2]	Cytology	LSIL	HSIL		
	Histology	CIN 1	CIN 2	CIN 3	
Previous terminology		Mild dysplasia	Moderate dysplasia	Severe dysplasia	Carcinoma in-situ
Histologic images					

No Pap! No colposcopy!

Any patient with grossly abnormal cervix should have a punch biopsy regardless of any previous result. Because pap smear is only a screening test!

CIN to Cancer

- The outcome of CIN 1 lesion depends upon the preceding cytology:
  - CIN 1 preceded by ASC-US or LSIL cytology –will be diagnosed with CIN 2,3 within 6 to 24 months of follow-up . No studies have reported invasive cervical cancer in this patient population within this follow-up period.
  - CIN 1 preceded by ASC-H or HSIL cytology, five-year risk of CIN 3+ of 15 percent
- For CIN 2 lesions, 40 to 58 percent of lesions will regress if left untreated, while 22 percent progress to CIN 3, and 5 percent progress to invasive cancer
- For CIN 3, the estimated spontaneous regression rate is 32 to 47 percent, with 12 to 40 percent progressing to invasive cancer if untreated.
- CIN 1 has a high chance of regression → **no** need for prompt treatment.
- CIN 2 & 3 have high risk of progression → need prompt treatment

Management of CIN

- **Loop Electrosurgical Excision Procedure (LEEP),** also known as Large Loop Excision of the Transformation Zone (LLETZ): This tissue is obtained for histologic evaluation.
- **Cryosurgery:** Not a first line treatment + Mainly useful for mild lesion like CIN 1 or previously treated patients. Has is a high failure rate for large lesions and for lesions extending down glandular crypts. The major side effect is a rather copious vaginal discharge that persists for several weeks.

- **Cone Biopsy:**
  - Cervical conization is mainly a diagnostic technique, but it may be used for treatment.
  - Removing the lesion extensively including the margins under GA
  - Complications: Bleeding, infection, cervical stenosis and cervical incompetence
  - Diagnostic cone is indicated in:
    - Colposcopy is unsatisfactory

        - ECC shows High grade lesion
        - Discrepancy between PAP and biopsy. Example: cytology result is HSIL but biopsy is CIN 1.
        - CIS or AIS on PAP
        - Biopsy confirm invasion
    - Cone as therapeutic in:
        - CIN 3
        - Stage IAI cancer

Examples:

- Young patient with ASC-H or LISL or HSIL → LEEP to reduce the risk of cervical incompetence and subsequent preterm labor in case she got pregnant.
- Old patient with CIN → Cone

Cervical Cancer

- **2008**
    - 530,000 new cases …275,000 deaths worldwide..
    - 8-6% in developing countries.
    - The tenth most common cause of death in developed countries 9 per 100,000 women
    - In the developing countries second most common type of cancer (17.8 per 100,000 women) and cause death 9.8 per 100,000 women.

- **In USA**
    - Over 12,000 new cases annually and 4000 cancer death
    - Third cause of death among gynecological cancer
- With effective screening program and vaccination 75% decrease in incidence and mortality had noticed in the past 50years in the developed countries.
- There are two main types of cervical cancer: squamous cell carcinoma and adenocarcinoma.
    - Squamous cell carcinoma of the cervix is more prevalent than adenocarcinoma.
    - Both types are found in sexually active women.
    - Infection with specific high-risk strains of human papillomavirus (HPV) is central to the pathogenesis of cervical cancer

- Of the approximately 30 to 40 HPV genotypes that infect the mucosa of the genital tract, eight (types 16, 18, 45, 31, 33, 52, 58, and 35) are responsible for 95 percent of cervical cancers, and two (types 16 and 18) are responsible for about 70 percent of cervical cancer [5]. Two low-risk types (6 and 11) cause about 90 percent of benign anogenital warts.

How to evaluate?

Symptoms

- Abnormal vaginal bleeding: Poscoital (mainly), intermenstrual, postmenopausal. (In patients who are not sexually active, bleeding from cervical cancer usually does not occur until the disease is quite advanced.)
- Persistent vaginal discharge
- Pelvic pain
- Leg swelling
- Urinary frequency
- Constipation and PR bleeding.

Clinical exam

- Rectovaginal exam is essential to determine the extent of the tissues invovlevement.
- Evaluate the vaginal fornices
- Evaluate the pelvic side wall

Physical finding

- Normal
- Weight loss? (not very pronounced and occurs late in the disease).
- Enlarged inguinal or supraclavicular LN with extensive disease.
- Lower limb edema. In case of parametrial extension and lymph node involvement leading to lymphatic obstruction.
- Local exam:
  - Normal cervix in microinvasive disease.
  - Lesion in endocervix → glandular lesion, detected only by ECC, LEEP or cone.
  - Ulcerative, exophytic, grannular or necrotic.
  - Friable cervix, bleeding to touch.

Pattern of Spread

- Direct invasion of
  - Cervical stroma
  - Corpus
  - Vagina
  - Parametrium: A band of fibrous tissue located between the uterus and pelvic side walls. It separates the supravaginal portion of the cervix from the bladder. The uterine artery and ovarian ligament are located in the parametrium. → parametrium is assessed clinically by rectovaginal examination.
- Lymphatic spread
  - Pelvic
  - Paraaortic: The status of para-aortic nodes is the single most impotant prognostic factor.
- Haematogenous
  - Lung
  - Liver
  - Bone

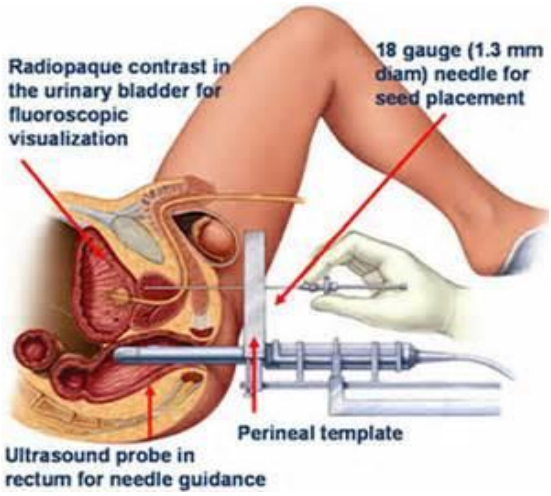
Work Up

- **History** **ALWAYS** ask about last pap smear when taking history from any OBGYN patient!
  - Ask about last PAP: When? Results? Any specific management?
- **Physical exam**
  - Biopsy for any gross lesion
  - PAP if no lesion seen
  - Sever bleeding → Packing
  - LN assessment →Supraclavicular and inguinal lymph node palpation.
- **Blood work**
  - CBC: Low HB in case of bleeding
  - KFT:
    - High creatinin in case of ureteric obstruction and subsequent AKI.
      - 30% in stage III disease.
      - 40% in stage IV disease.
    - Hypercalcemia indicate bone metastasis
  - LFT: Abnormal results indicate metastasis.

- **Images:**
  - CXR
  - IVP can be done to look for hydronephrosis but it has been replaced by MRI with IV contrast in clinical practice.
  - Abdominal CT: Upper abdominal organs are dynamic, which makes CT a better tool for assessment.
  - MRI pelvis may be helpful in planning management, but the results do not influence the FIGO stage. MRI is particularly helpful in defining the extent of the primary lesion, including any extension into the parametrium, bladder, or rectum.
  - PET is being increasingly used for detecting lymph node metastases.

Cervical cancer staging

- **Clinical exam…under anasthesia?**
  - Evaluation of the cervix
  - Upper and lower vagina
  - Rectovaginal exam to evaluate the parametria and pelvic side wall
- **Cystoscopy:** Bladder invasion
- **Proctoscopy:** Rectal invasion



FIGO Staging

The official International Federation of Gynecology and Obstetrics (FIGO) is a clinical staging method based on physical examination and non-invasive testing.

Stage I: The carcinoma strictly cofined to the cervix

- IA microscopic disease … no gross lesion → cone biopsy can detect the depth of invasion.
  - IA1… invasion </=3mm extension </=7mm
  - IA2 …invasion >3mm but not more than 5mm, extension not more than 7mm.
- IB microscopic disease more than stage IA or visible lesion
  - IB1 visible lesion </= 4cm in greatest dimension
  - IB2 visible lesion > 4cm in greatest dimension

Stage II: Extension beyond the cervix but not to the pelvic side wall or lower vagina.

- IIA…without parametrial invasion
  - IIA1 … clinically visible lesion </=4cm in greatest dimension.
  - IIA2… clinically visible lesion > 4cm in greatest dimension.
- IIB… with parametrial invasion.

Stage III: Tumor invade pelvic side wall & or lower third of the vagina & or causing hydronephrosis or non – functioning kidney.

- IIIA only lower third of the vagina
- IIIB invading pelvic side wall & or causing hydronephrosis or non – functioning kidney.

Stage IV: Tumor extended beyond the true pelvis or has invade the mucosa of the rectum or the bladder.

- IVA.. Tumor invading adjacent organ
- IV B.. Tumor invading distant organ.

Treatment

- Stage A1 is curable by cervical conization. It is the treatment of choice when childbearing is desired and for patients of a younger age group.
- Stage 1A2 & 1B: Radical hysterectomy. In this procedure, the uterus is removed along with adjacent portions of the vagina, cardinal ligaments, uterosacral ligaments, and bladder pillars. Repeat cervical conization could be an option for patients interested in preserving their uterus.
- 1B and above: Chemo-radiation → Cisplatin + 25 sessions external beam followed by 5 sessions of brachytherapy.

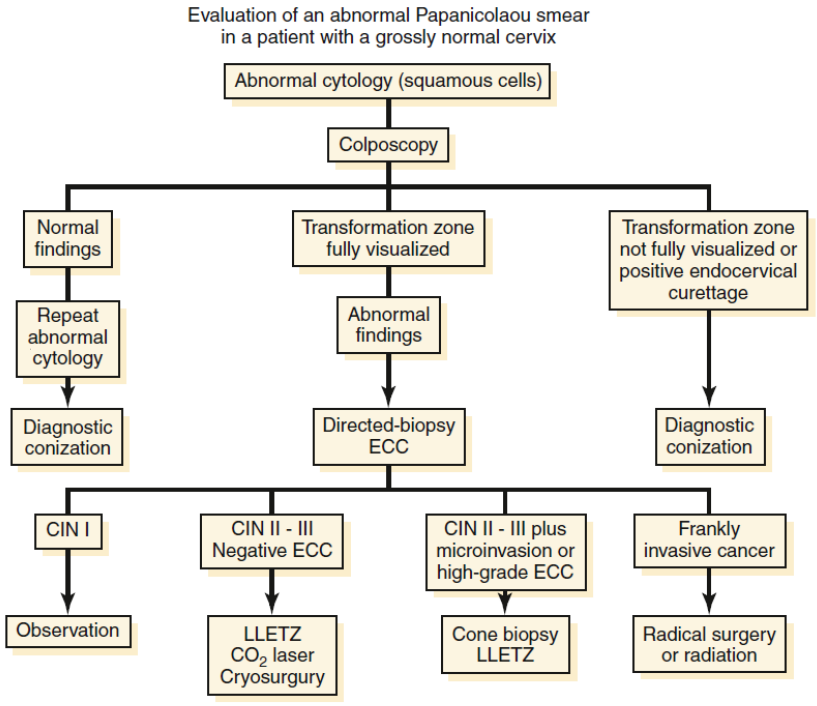


FIGURE 38-3 Algorithm for evaluation of patients with an abnormal Papanicolaou smear and a grossly normal-appearing cervix. CIN, cervical intraepithelial neoplasia; ECC, endocervical curettage; LLETZ, large loop excision of the transformation zone.

MCQ's :

1-the next step in patient with grossly abnormal cervix is ?

1- take a punch biopsy regardless of any previous result.

2- do pap smear

3-Sart chemo thereby

1-A

For mistakes or feedback

Obgynteam432@gmail.com