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Cervical Disease and Neoplasia (CIN)

Objectives:

A student should be able to:

- Describe the pathogenesis of cervical cancer
- Identify the risk factors for cervical neoplasia and cancer
- List the guidelines for cervical cancer screening
- Describe the initial management of a patient with an abnormal Pap smear
- Describe the symptoms and physical findings of a patient with cervical cancer

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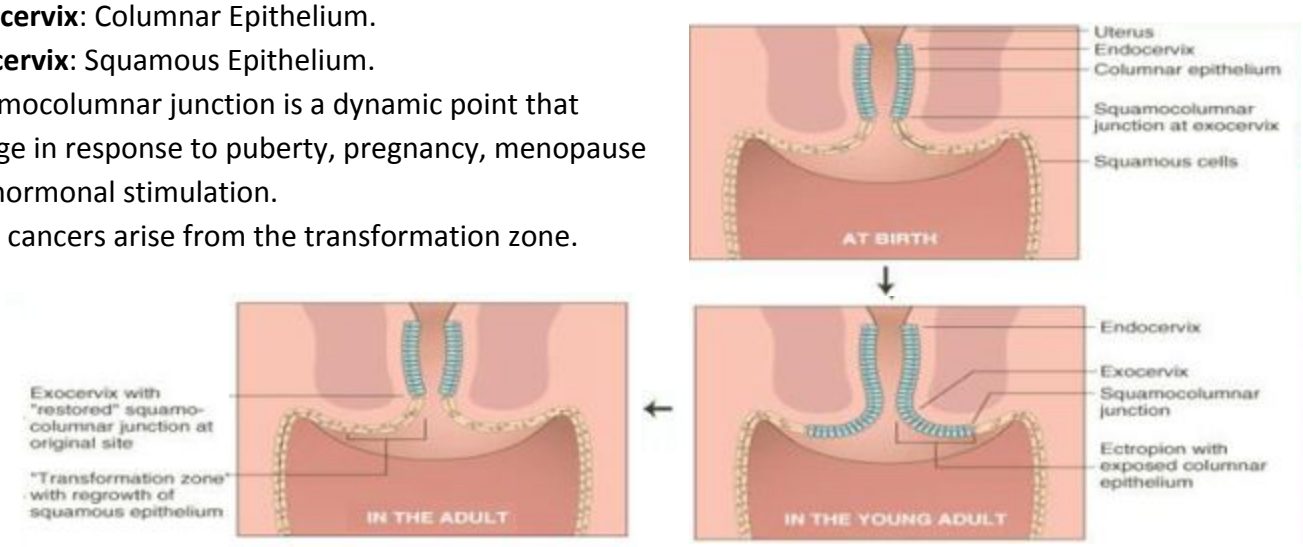
Normal Lining of Cervix and possible changes

Endocervix: Columnar Epithelium.
Ectocervix: Squamous Epithelium.
Squamocolumnar junction is a dynamic point that change in response to puberty, pregnancy, menopause and hormonal stimulation.
Most cancers arise from the transformation zone.



Transformation zone is the cervical area between the old and new squamocolumnar junctions

Human papillomavirus (HPV) infection

The most common etiology of cervical cancer is the human papillomavirus (HPV).
• HPV is the most common sexually transmitted infection (STI). Infects the lower genital tract, especially cervix in the transformation zone.
• There are 100 types of HPV and 30 of them affects the anogenital tract 15 of them have high risk and the other 15 are low risk
• HPV types **16**, **18**, **31**, 33 and **45** carry particularly high risk of developing cervical cancer.
• Types 16 and 18 are responsible for 70% of cervical cancers.
• **Low risk** HPV types 6 and 11 are non-oncogenic, associated with genital wart (condylomas).
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.

Risk factors

Cofactors that increase the likelihood of persistence HPV infection include:
•**Cigarette smoking**
•**compromised immune system**
•**human immunodeficiency virus (HIV) infection.**
• **Young age at first coitus**.(coitus = sexual intercourse)
• **Young age at first pregnancy**.
• **Multiple sexual partners.**
• **High parity.**
• **Lower socioeconomic status.**

Primary prevention

- **Two** prophylactic vaccines are presently available:
  - ★ The **quadrivalent** vaccine (a quadrivalent vaccine covers 4 types and is also called tetravalent) **Gardasil**, which 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.
  - Vaccinated women should continue age specific screening protocol because the vaccine does not protect against all high-risk HPV viral types.

•Abnormal Pap smear should be followed by **confirmatory colposcopy** and **direct biopsies**, including an **endocervical curettage** (**ECC**).

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

•Any patient with grossly abnormal cervix should have a punch biopsy regardless of any previous result.

Screening see question number1

1. Screening should start at age 21 pap test should be performed alone
2. For older women 30-65 pap test and HPV each 5 years or pap test alone each 3 years
3. Above 65 pap test can stop if no history if there is adequate screening and no cervical dysplasia greater than CIN ll within the last 20 years

•**Women should have regular cervical screening even if they have received the HPV vaccine,**because the vaccine does not protect against all high-risk HPV viral types.

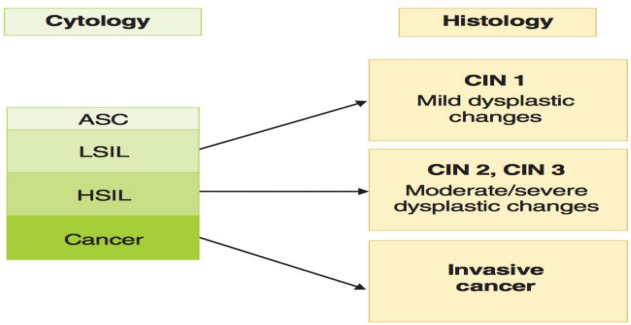
•**HPV deoxyribonucleic acid (DNA) testing is much more sensitive than cervical cytology, but less specific.**

•**50% of patients with cervical cancer have never had a pap test**

Pap Smear Classification

Using **The Bethesda system**

- ASC-US (atypical squamous cells of undetermined significance): changes suggestive of but not adequate to label LSIL
- **LSIL** (low-grade squamous intraepithelial lesion): biopsy is expected to show histologic findings of HPV, mild dysplasia, or **CIN 1** LSIL= CIN1
- ASC-H (atypical squamous cells can't rule out HSIL): changes suggestive of but not adequate to label HSIL
- **HSIL** (high-grade squamous intraepithelial lesion): biopsy is expected to show histologic findings of moderate–severe dysplasia, **CIN 2, CIN 3**, or CIS HSIL=CIN2 or 3 except for CIN2 with negative p16 then it is LSIL
- **Squamous cell carcinoma:** biopsy is expected to show histologic findings of **invasive cancer**



Bethesda			
Cytology	LSIL	HSIL	
Colposcopy (histology)	CIN1	CIN 2	CIN 3
Histological atypia	1/3	2/3	Full thickness

Management of CIN

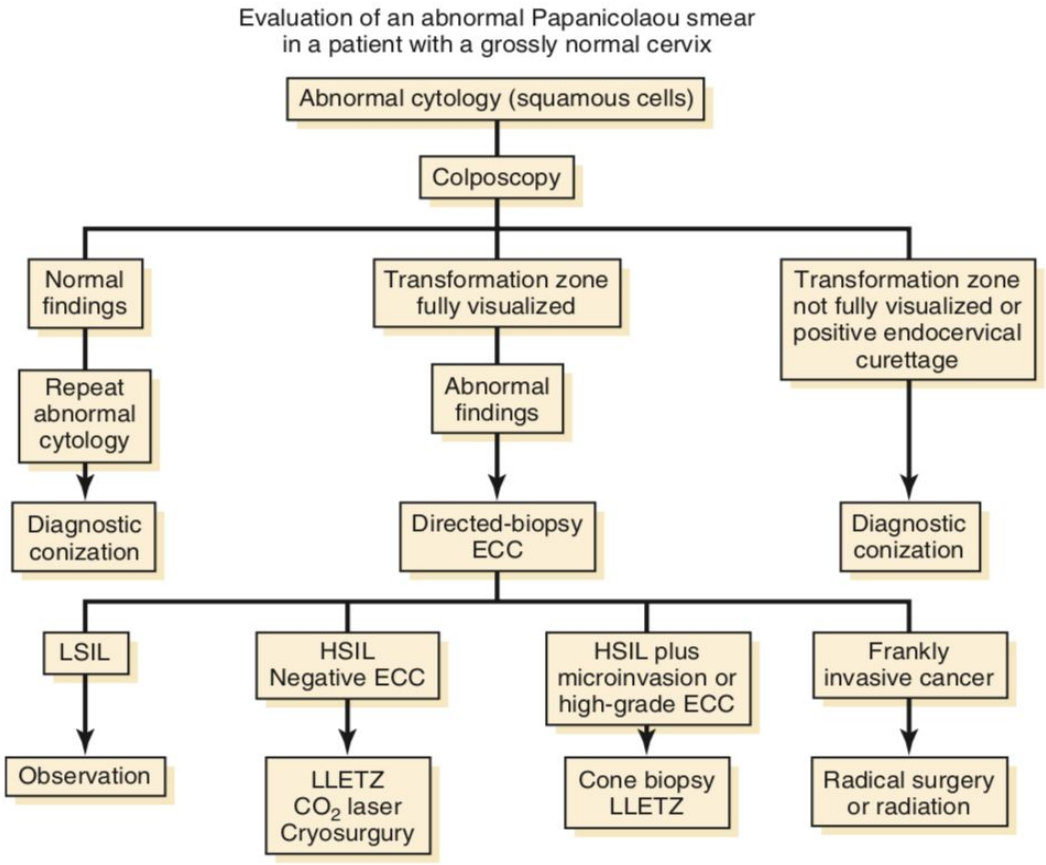
From kaplan

- **Observation and follow-up** without treatment is appropriate for **CIN 1** and includes any of the following:
  1. **repeat Pap in 6 and 12 months;**
  2. **colposcopy and repeat Pap in 12 months;**
  3. **or HPV DNA testing in 12 months.**
- **Ablative modalities*** can be used for **CIN 1, 2, and 3**. These include **cryotherapy** (freezing), **laser vaporization**, and electrofulguration.
  Ablation do not provide diagnostic information in comparison to excisional procedures.

Electrofulguration is a type of electrosurgery. Also called electrocautery, electrocoagulation, and fulguration. The electric current passes through an electrode that is placed on or near the tissue. The tip of the electrode is heated by the electric current to burn or destroy the tissue.

- **Excisional** procedures* can be used for CIN 1, 2, and 3.
  These include **LEEP** (loop electrosurgical excision procedure) or **cold-knife conization.**
  ***According to APGO video only CIN 2,3 (HSIL) treated with either ablation or exison**
- **Hysterectomy** is only acceptable with **biopsy-confirmed**, recurrent **CIN 2 or 3**.

childbearing and patient future compliance should be considered in treatment



This diagram is the treatment approach From hacker and moore

LLETZ=large loop excision of the transformation zone.

ECC= endocervical curettage

- Colposcopy is how we clinically visualize a cervical anatomy a colposcope is a binocular stereo microscope with magnification > acetic acid is then applied on the cervix which dehydrates cells causing those with large nuclei to appear white those white are undergoing metaplasia or dysplasia

- **To perform a colposcopic examination, an appropriately sized speculum is inserted to expose the cervix, which is cleansed with a cotton pledget soaked in 3% acetic acid to remove adherent mucus and cellular debris.**At colposcopy, the original or native squamous epithelium appears gray and homogeneous. The columnar epithelium appears red and grapelike.. Normal blood vessels branch like a tree.
- **the whiter the lesion, the more severe the dysplasia.**

Follow-Up: Patients treated with either ablative or excisional procedures require follow-up repeat Pap smears, colposcopy and Pap smear, or HPV DNA testing every 4 to 6 months for 2 years.

Invasive Cervical Cancer

In 2013:
– 11,955 women in the United States were diagnosed with cervical cancer.
– 4,217 women in the United States **died** from cervical cancer.
• **Cervical carcinoma** is the **third most common gynecologic malignancy** with a **mean age at diagnosis of 50 years**.

Symptoms of Cervical Cancer

-Abnormal vaginal bleeding: Postcoital bleeding (is a type of bleeding which occurs after sexual intercourse)(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 watery vaginal discharge,intermittent spotting, **pelvic pain**, **leg swelling** and **urinary frequency** are usually seen with **advanced disease**.

Physical finding in Cervical Cancer

Usually normal general physical examination. **Weight loss occurs late in the disease**. There may be **enlarged inguinal** or **supraclavicular** lymph Node, **edema** of the legs, or **hepatomegaly**. On pelvic examination, the cervix may be **ulcerative** or **exophytic**.

Diagnostic Tests to confirm Cervical Cancer

Cervical biopsy is the initial diagnostic test.

Metastatic workup, which includes pelvic examination, chest x-ray, intravenous pyelogram, cystoscopy, and sigmoidoscopy.

Invasive cervical cancer is the only gynecologic cancer that is staged clinically; an abdominal pelvic CT scan or MRI cannot be used for clinical staging.

Staging for Cervical Cancer

Stage 0:	**Carcinoma in-situ (CIS). The basement membrane is intact.**
Stage I: **IA1.** **IA2.** **IB.**	**Spread limited to the cervix. This is the most common stage at diagnosis.** ● Invasion is ≤3 mm deep (minimally invasive) ● Invasion is >3 but ≤5 mm deep (microinvasion) ● Invasion is >5 mm deep (frank invasion)
Stage II: **IIA.** **IIB.**	**Spread adjacent to the cervix Involves** ● upper two thirds of vagina ● Invasion of the parametria
Stage III: **IIIA.** **IIIB**	**Spread further from the cervix** ● Involves lower one third of vagina ● Extends to pelvic side wall or hydronephrosis
Stage IV: **IVA.** **IVB.**	**Spread furthest from the cervix** ● Involves bladder or rectum or beyond true pelvis ● Distant metastasis

Management of Cervical cancer

- **Stage Ial:** Total simple hysterectomy, either vaginal or abdominal.
- **Stage Ia2:** Modified radical hysterectomy.
- **Stage IB or IIA:** Either radical hysterectomy with pelvic and paraaortic lymphadenectomy (if premenopausal) and peritoneal washings or pelvic radiation (if postmenopausal). In patients who can tolerate surgery, a radical hysterectomy is preferred; however, studies have demonstrated equal cure rates with radiation or surgical treatment.
- **Stage IIB,III, or IV:** Radiation therapy and chemotherapy for all ages.

RADICAL HYSTERECTOMY. In this procedure, the uterus is removed along with adjacent portions of the vagina, cardinal ligaments, uterosacral ligaments, and bladder pillars.

The most common complication of radical hysterectomy is bladder dysfunction

The most serious complication of radical hysterectomy is ureteric fistula or stricture,

A less common but life-threatening complication is **deep venous thrombosis,**

Case

A generally healthy 26 year-old G1P0 woman with a last menstrual period approximately 16 weeks ago is referred for the management of an abnormal Pap test showing High Grade Squamous Intraepithelial Lesion (HGSIL). This Pap test was obtained 10 weeks ago when she underwent an elective termination of an unplanned pregnancy at approximately six weeks of gestation. She has not had any prior Pap tests. She has never been tested for sexually transmitted infections. The combination of the undesired pregnancy and the abnormal Pap test, however, has been a "wake-up call" and today she requests testing for "everything." She received Depo-Provera at the time of the termination, and has not had a period yet. She reports a history of normal, regular menses and has used oral contraceptives inconsistently in the past. She began having sexual intercourse at the age of 17, and has had 4 lifetime partners. She is on no other medications and has no known drug allergies. Her family history is notable for a grandmother with breast cancer. She smokes ½ pack of cigarettes per day, does clerical work for a moving company, and is engaged to be married in 6 months.

Questions

1. According to recent guidelines published by the American College of Obstetricians and Gynecologists (2012), how many Pap tests should this patient have had given her age and clinical history?

– This patient should have had only two screening pap tests by now.

Screening guidelines\

- ★ First cytology should be obtained at age 21 regardless of coitarche.
- ★ Between the ages of 21 and 29, there is no benefit of annual screening; screening with cytology alone every 3 years is recommended. It leads to harm due to overtreatment of screen detected abnormalities.
- ★ Women aged 30–65 years should be screened with cytology and HPV testing; "Cotesting" every 5 years (preferred), or cytology alone every 3 years.
- ★ Women over 65 years of age with evidence of adequate negative prior screening and no history of CIN within the last 20 years should not be screened for cervical cancer with

any modality. Once screening is discontinued it should not resume for any reason, even if a woman reports having a new sexual partner.

2. Which historical risk factors does this patient have, for having cervical dysplasia or for having cervical dysplasia progress to cervical cancer?

– She has **poor compliance** with screening, **early age of coitarche** (< 17 years of age), and is a cigarette **smoker.**
– **Abnormal Pap test** is presumptive evidence of **HPV infection.**
– She is at risk of other **STIs** given her lack of barrier contraception, including HIV/AIDS.
– **relatively high number of lifetime sexual partners.**
– **Low socio-economic status** and **poor access to healthcare.**

3. What are other possible risk factors for development of cervical dysplasia?

– She probably does not have an **autoimmune disease**, given her generally healthy medical history. Other diagnoses that would increase her risk of cervical neoplasia include **SLE**, and history of **organ transplantation** on **immunosuppressive** therapies.
– **DES** (Diethylstilbestrol) exposure
– **HIV** infection

4. What is meant by the term "high-grade squamous intraepithelial lesion"?

It indicates **moderate or severe cervical intraepithelial neoplasia or carcinoma in situ(CIN2 and CIN3)**. Of all women with HGSIL results, **2% or less have invasive cervical cancer at that time,** however about **20% would progress to** having invasive cervical **cancer** without treatment.
• Cells were identified on cytology (Pap test) suggesting abnormal cellular maturation between 1/3 and full thickness of the squamous epithelial layer of the cervix.
•Each Pap test report should have a statement of **specimen adequacy** (satisfactory, unsatisfactory), general **categorization** (negative for intraepithelial lesion or malignancy, epithelial cell abnormality, other), and **interpretation/result** (negative for intraepithelial lesion or malignancy, epithelial cell abnormalities). Possible Pap test results include: **ASCUS, ASC-H, LGSIL, HGSIL, AGC, AIS, and squamous cell carcinoma.**
***This is called Bethesda system,** it's for reporting cervical or vaginal cytologic diagnoses

ASC-US	**A**typical **s**quamous **c**ells of **u**ndetermined **s**ignificance
ASC-H	**A**typical **s**quamous **c**ells – cannot exclude HGSIL
LGSIL	**L**ow **g**rade **s**quamous **i**ntraepithelial **l**esion
HGSIL	**H**igh **g**rade **s**quamous **i**ntraepithelial **l**esion
AGC	**A**typical **G**landular **C**ells, suspicious for AIS or cancer.
AIS	**A**denocarcinoma **i**n **s**itu

• Each category of abnormal cytologic reading encompasses a **spectrum** of possible correlating pathologic (histologic) **diagnosis** that should be further explored and identified.

5. What would you recommend as the next step in the evaluation of this patient's abnormal Pap test?

– Abnormal Pap test results require **further work-up**, typically to **establish a diagnosis.** This patient will require **colposcopy** and **directed biopsies**, including an **endocervical curettage (ECC)**. Once a diagnosis is made based on these findings, appropriate treatment can then be recommended.
– Available algorithms for abnormal cytologic and pathologic cervical neoplasia are detailed from **ASCCP** (American Society for Colposcopy and Cervical Pathology).
– Patient should also be **counseled** about **STI** testing (including HIV), **smoking cessation**, and **use of barrier** contraception.

6. Would typing for the human papillomavirus (HPV) aid in the management of this patient?

–This patient requires **colposcopic examination**. In this patient with **HGSIL**, there is **no role for HPV testing**, as the result is **expected to be positive.**
–For **LGSIL**, **HPV** can be expected to be **positive in 77%** of cases, making this test **impractical** in deciding to **triage to colposcopy.**
– **Low risk HPV types include 6 and 11**, are associated with **cervical warts**. **High risk HPV types include 16 and 18**, are associated with high grade **cervical dysplasia and cervical cancer**.