433 Teams

OBSTETRICS & GYNECOLOGY

CIN and Cervical Cancer

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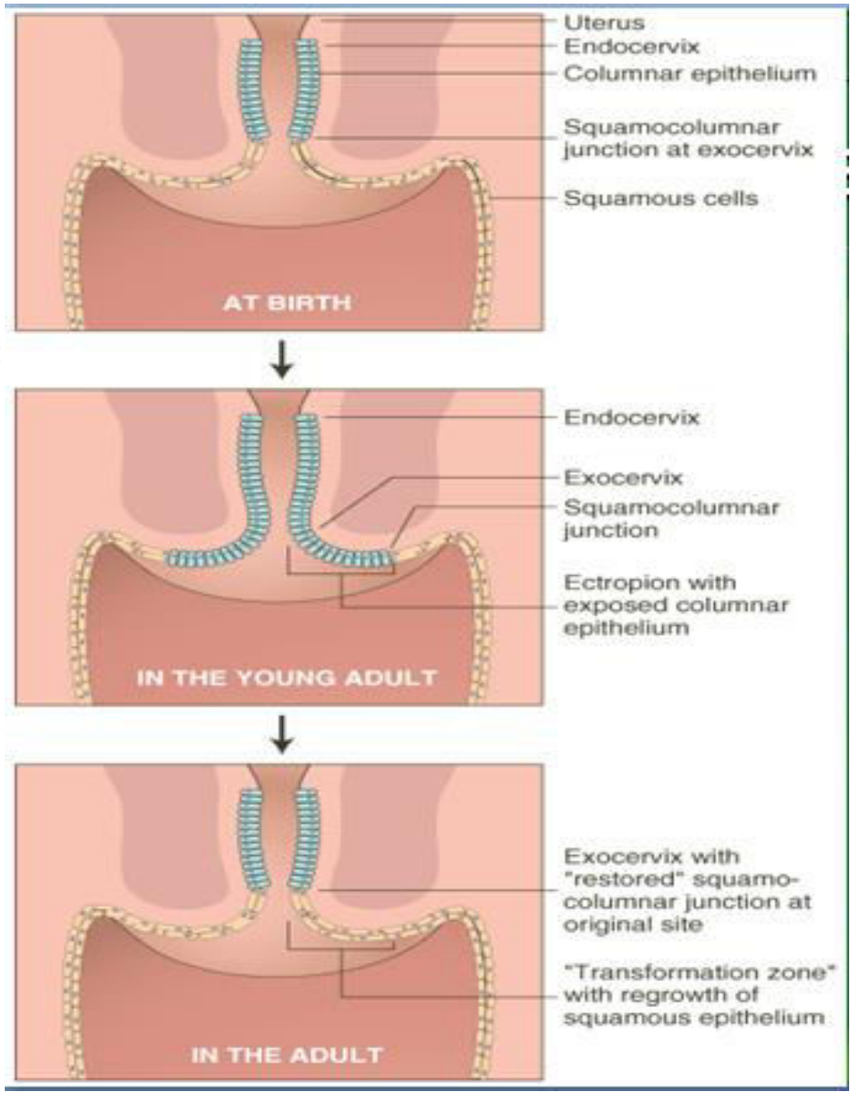
OBJECTIVES

- Determine the incidence and mortality of cervical cancer.
- Discuss the etiology of cervical cancer.
- List risk factors for cervical cancer.
- Describe the primary prevention methods for cervical cancer.
- List the guidelines for screening among asymptomatic women (The American College of Obstetrics & Gynecology).
- Discuss how to evaluate a patient with an abnormal Pap smear.
- Describe treatment options for cervical intraepithelial neoplasia and invasive cervical cancer according to stage.

Normal Lining of Cervix and possible changes:

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



Human papilloma virus (HPV) infection:

- The most common etiology of cervical cancer is the human papilloma virus (HPV).
- HPV is the most common sexually transmitted infection (STI).
- Infects the lower genital tract, esp cervix in the transformation zone.
- Some types of HPV can increase the risk of developing cervical cancer, particularly high risk HPV types 16, 18, 31, 33 and 45.
- 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 and human immunodeficiency virus (HIV) infection.
- Young age at first coitus.
- Young age at first pregnancy.
- Multiple sexual partners.
- Sexual partner with multiple sexual partners.
- High parity.
- Lower socioeconomic status.

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.

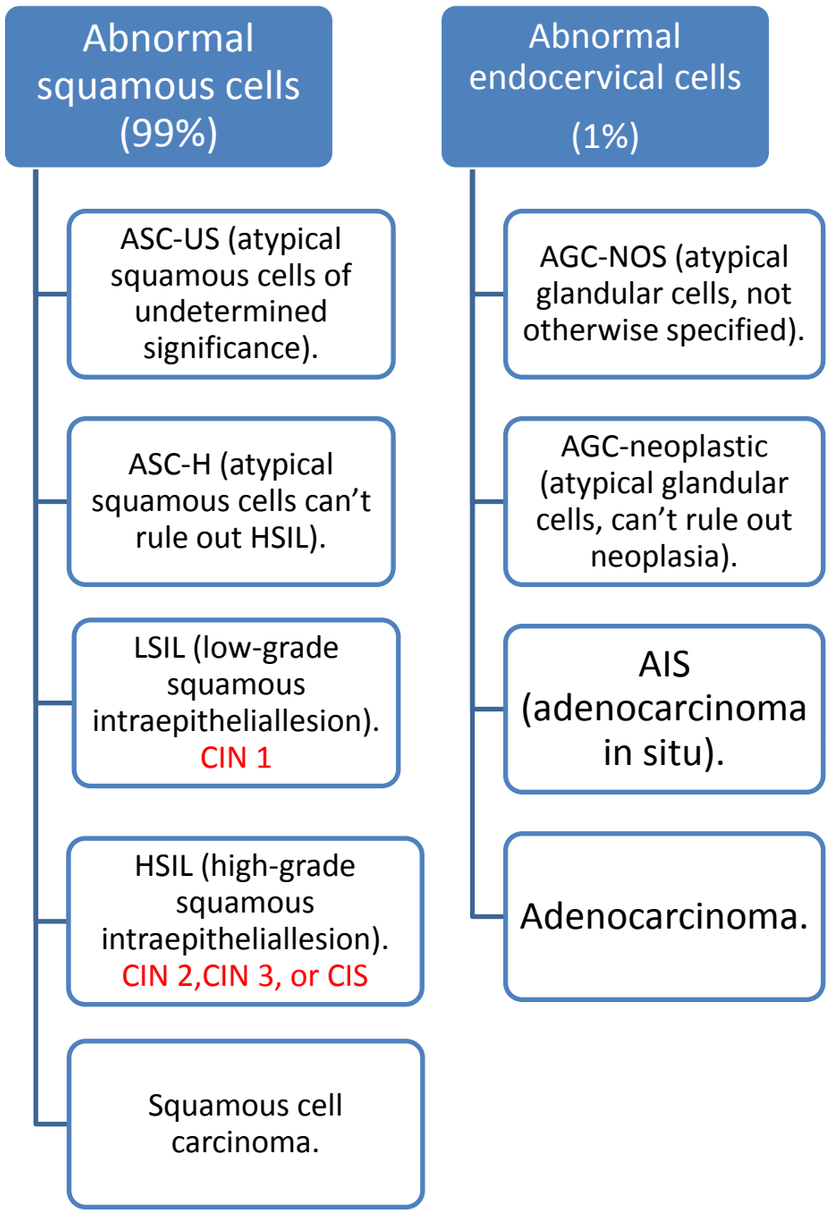
- The vaccine is most effective if performed before the onset of sexual activity.

Guidelines for cervical cancer screening:

- Pap smear is the gold standard for screening.
- ➢ Cervical cancer screening should start at age 21.
- ➢ For women between age 21 to 29: PAP should be done every 3 years.
- ➢ For women between age 30-64: PAP and HPV DNA test should be done every 5 years. **OR** PAP alone done every 3 years.
- ➢ For women 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.
- Abnormal Pap smear 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.

Pap Smear Classification (The Bethesda system):



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

Management of CIN:

- Observation and follow-up without treatment is appropriate for CIN 1 and includes any of the following:

repeat Pap in 6 and 12 months;

colposcopy and repeat Pap in 12 months;

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.
- Excisional procedures can be used for CIN 1, 2, and 3. These include LEEP (loop electrosurgical excision procedure) or cold-knife conization.
- Hysterectomy is only acceptable with biopsy-confirmed, recurrent CIN 2 or 3.

Invasive Cervical Cancer

- In 2013 (the most recent year numbers are available):
  - 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 45 years.
- 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 and urinary frequency are usually seen with advanced disease.

- Physical finding:

✓ Usually normal general physical examination.

✓ Weight loss occurs late in the disease.

✓ There may be Enlarged inguinal or supraclavicular LN, edema of the legs, or hepatomegaly.

✓ On pelvic examination, the cervix may be ulcerative or exophytic.

- Diagnostic Tests:

✓ **Cervical biopsy**: The initial diagnostic test should be a cervical biopsy.

✓ **Metastatic workup**: That 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 of Cervical Cancer:

Stage	Extent of disease	5-year survival
0	**Carcinoma in situ (CIN)**	~100%
I	**Limited to cervix**	
Ia1	Microscopic disease: stromal invasion <3mm, lateral spread <7mm	>95%
Ia2	Microscopic disease: stromal invasion <3mm and >5mm, lateral spread <7mm	
Ib1	Macroscopic lesion <4cm in greatest dimension	~90%
Ib2	Macroscopic lesion >4cm in greatest dimension	80-85%
II	**Extension to uterus/parametria/vagina**	~75-78%
IIa1	Involvement of upper two thirds of vagina *without* parametrial invasion, <4cm greatest diameter	
IIa2	Involvement of upper two thirds of vagina *without* parametrial invasion, >4cm greatest diameter	
IIb1	Involvement of upper two thirds of vagina *with* parametrial invasion	
III	**Extension to pelvic side wall and/or lower third of vagina**	~47-50%
IIIa	Involvement of lower third of vagina	
IIIb	Extension to pelvic side wall and/or hydronephrosis	
IV	**Extension to adjacent organs or beyond true pelvis**	~20-30%
IVa	Extension to adjacent organs e.g. bladder, bowel	
IVb	Distant metastases	

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.

TEACHING CASE

- **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 1⁄2 pack of cigarettes per day, does clerical work for a moving company, and is engaged to be married in 6 months.

- 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?
  - First cytology should be obtained at age 21 regardless of coitarche.
  - Between the ages of 21 and 29, there is no benefit to annual screening; screening with cytology alone eve-
  - ry 3 years is recommended. It leads to harm due to overtreatment of screen detected abnormalities.
  - Women ages 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 CIN2+
  - 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.
  - This patient should have had only two screening pap tests by now.

- **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 (< 19 years of age), and is a cigarette smoker
  - Abnormal Pap test is presumptive evidence of HPV infection
  - She is at risk of other sexually transmitted infections given her lack of barrier contraception, including
  - HIV/AIDS
  - Number of lifetime sexual partners
  - Low socio-economic status and poor access to healthcare
- **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 exposure
  - HIV infection

- What is meant by the term "high-grade squamous intraepithelial lesion"?
  - 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.
- Each category of abnormal cytologic reading encompasses a spectrum of possible correlating pathologic (histologic) diagnosis that should be further explored and identified. In this case, the finding of HGSIL encompasses moderate and severe dysplasia, carcinoma in situ (CIN 2 and CIN 3).
- 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.
- 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 re- quire 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 (see references).
  - Patient should also be counseled about STI testing (including HIV), smoking cessation, and use of barrier contraception.

- Would typing for the human papilloma virus (HPV) aid in the management of this patient?
  - HPV testing should not be used to screen women between the ages of 21-29, either as a stand-alone test or as a cotest with cytology. In this patient with HSIL, there is no role for HPV testing, as the result is expected to be positive. This patient requires colposcopic examination. For LSIL, 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.

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