437 Team: Obstetrics and Gynecology

Cervical Disease & Neoplasia CIN

Objectives:

- 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

References:

- Kaplan USMLE step 2 CK - Obstetrics and Gynecology
- Online Meded videos
- Team 435

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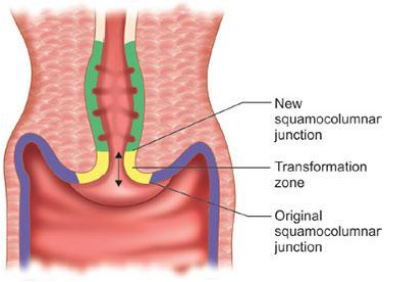
Color index: Important | Notes | Meded | Video-Case

Editing file link

Normal Lining of The Cervix



- **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.**
    - (Area between the old and new squamocolumnar junction)

Cervical Cancer

- **Premalignant lesions of the cervix are usually asymptomatic.** The progression from premalignant to invasive cancer has been reported to be **approximately 8–10 years.**
- Most lesions will spontaneously regress; others remain static, with only a minority progressing to cancer.

Etiology of Cervical Cancer

- The most common etiology of cervical cancer is the **human papillomavirus** (HPV).
- More than 75 subtypes of HPV have been identified.
- Takes 3-5 years for HPV to cause cellular changes in the tissue to develop precancer (CIN)
- HPV is the **most common sexually transmitted infection** (STI). Infects the lower genital tract, especially cervix in **the transformation zone.**

HPV 16, 18, 31, 33, 35 and 45

(high risk) are the most common HPV types associated with **premalignant and cancerous lesions of the cervix**. High risk are responsible for cancer (cervical, vagonal, head and neck cancer).

HPV 6 & 11

(low risk) are the most common HPV types associated with **benign condyloma acuminata** (genital warts).

Weather the HPV will result in cancer or not depends on 2 factors :

1. Weather it is high risk or low risk HPV type
2. Persistence of that infection (almost 80-90 of women will clear the virus by natural immunity)

Risk Factors (important to understand risk factors)

Cofactors that increase the likelihood of persistence HPV infection include:

- ❏ Multiple sexual partners
- ❏ Cigarette smoking Cause persistence of HPV by suppressing local immunity
- ❏ Immunosuppression. (most commonly transplant patients)
- ❏ HIV infection.
- ❏ Young age at first coitus. (coitus = sexual intercourse)
- ❏ Young age at first pregnancy.
- ❏ High parity.
- ❏ Lower socioeconomic status
- ❏ Multiparity and oral contraceptives

Primary Prevention of Cervical Cancer

Two prophylactic vaccines are presently available:

★ The **9 valent** vaccine

Gardasil-9	Recommend for all females age **9-45**, with target age 11-12. Protect against **9** HPV types (6,11, 16, 18, 31, 33, 45, 52, 58)

★ The **quadrivalent** vaccine

Gardasil	(also called tetravalent): 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.
- Continue regular Pap smears according to current guidelines because the vaccine **does not prevent against all HPV types** that can cause genital warts or cervical cancer.
- The vaccine is **not recommended for pregnant or immunosuppressed women.**
- **Abnormal Pap smear** should be followed by confirmatory **colposcopy** and direct biopsies, including an endocervical curettage (ECC). Pap test doesn't give you a diagnosis. For diagnosis, we need tissue, but we can't take tissue blindly, we need do colposcopy-guided cervical biopsy
- 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.

Secondary Prevention

Pap Smear (Screening)

The best screening test for premalignant lesions is cytology. Cytologic screening uses the Pap test. The most common site for cervical dysplasia is the **transformation zone** (T-zone).

How is it performed?

Two specimens are obtained with the Pap smear: an ectocervical sample performed by scraping the T-zone with a spatula and an endocervical sample obtained with a cytobrush in a nonpregnant woman or a cotton tip applicator in a pregnant woman.

What cytologic screening methods can be used?

- ➔ **With the conventional method,** the specimens are **smeared onto a glass slide**, which is placed in fixative and then microscopically examined.
- ➔ **With the thin-layer, liquid-based cytology**, the specimens are rinsed into a preserving solution and then deposited on a slide as a thin layer of processed cells.

Both methods are equivalent for cancer screening but the liquid-based method has the advantage of doing reflex HPV-DNA typing.

Pap smear should be **started** at the following ages:	➢ **Age less than 20**: no Pap test or screening for HPV, regardless of sexual activity. ➢ **Age 21:** Start Pap test with cytology alone without HPV testing; the recommendation is the same whether HPV vaccinated or not.
The **frequency** of recommended Pap smear is as follows:	➢ **Age 21–29**: repeat Pap every three years with cytology alone; do not perform HPV testing in this age group. ➢ **Age 30–65:** repeat Pap every three years with cytology but no HPV testing OR repeat Pap every five years if both cytology and HPV testing (the recommended option in this age group).
Pap smears should be **discontinued**:	➢ **After age 65** if negative cytology and/or HPV tests for past 10 years AND no history of CIN 2, CIN 3, or cervical carcinoma. ➢ **Any age if** total hysterectomy AND no history of cervical neoplasia.

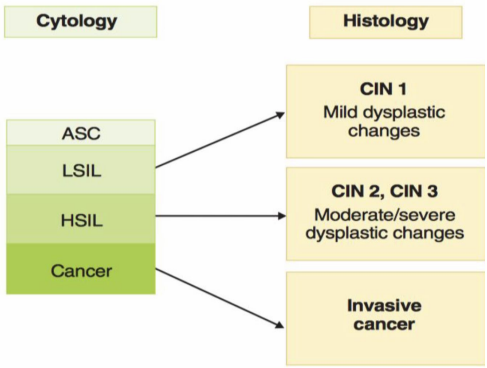
Classification of a Pap Smear

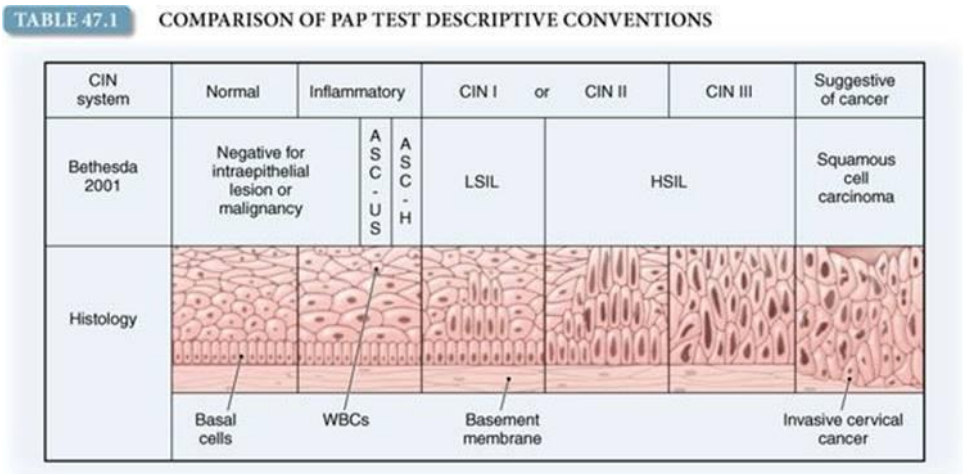
The Bethesda system is the current classification used in the United States.

Negative for intraepithelial lesion or malignancy; comments may report trichomoniasis, candida, BV, HSV, or atrophy.

Abnormal squamous cells (99% of abnormal Pap smears):

- **ASC-US (atypical squamous cells of undetermined significance):** changes suggestive of but not adequate to label LISL.
- **LSIL (low-grade squamous intraepithelial lesion)**: biopsy is expected to show histologic findings of HPV, mild dysplasia, or **CIN 1** (reflection of presence of HPV so when we have it we tend not to treat, just follow up)
- **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)** next step is colposcopy**:** biopsy is expected to show histologic findings of moderate–severe dysplasia, **CIN 2, CIN 3** (actual real pre cancer histopathology, we have to treat. If we leave it there is a good chance it is going to progress to cancer (but it will take years to progress), or CIS
- **Squamous cell carcinoma:** biopsy is expected to show histologic findings of **invasive cancer**





Bethesda			
Cytology	LISL	HSIL	
Colposcopy (Histo)	CIN 1	CIN 2	CIN 3
Histological Atypia	1/3	2/3	Full thickness

Diagnostic approach to an abnormal Pap smear

1. Accelerated repeat Pap:

an option for findings of ASC-US in patients of any age, and the preferred option with either **ASC-US or LSIL in patients age 21–24**. Repeat the Pap in 12 months.
-If repeat cytology is anything other than negative, proceed to colposcopy and biopsies.

2. HPV DNA testing:

the preferred option for findings of **ASC-US in patients age ≥25**. If liquid-based cytology was used on the initial Pap, one can use this specimen for DNA testing. . Perform colposcopy only if high-risk HPV DNA is identified.

3. Colposcopy:

- indicated for evaluation of **LSIL in patients age ≥25 and all patients with ASC-H and HSIL. Colposcopy is a magnification of the cervix** (10–12x); it is aided by acetic acid or iodine, which makes the vascular patterns **more visible**.
- Satisfactory or adequate colposcopy is diagnosed if the entire T-zone is visualized and no lesions disappear into the endocervical canal.
- Our main goal for colposcopy is to discover CIN 3

4. Endocervical curettage (ECC):

All nonpregnant patients undergoing colposcopy that shows metaplastic epithelium entering the endocervical canal will undergo an ECC to rule out endocervical lesions.

5. Ectocervical biopsy:

Lesions identified on the ectocervix by colposcopy (e.g., mosaicism, punctuation, white lesions, abnormal vessels) are biopsied and sent for histology.

6. Cone biopsy:

If the Pap smear is worse than the histology (suggesting the site of abnormal Pap smear cells was not biopsied), then a cone biopsy is performed. Deep cone biopsies can result in an incompetent cervix. Another risk of cone biopsy is cervical stenosis.

Other indications for cone biopsy :

- If you have persistent CIN1 (for more than 2 years) we do it for diagnostic reason, to see if there is CIN3 hidden or other serious pathology
- If you have micro invasive cervical cancer

Management according to histology

- **Observation and follow-up** without treatment are appropriate for **CIN 1** and include 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.

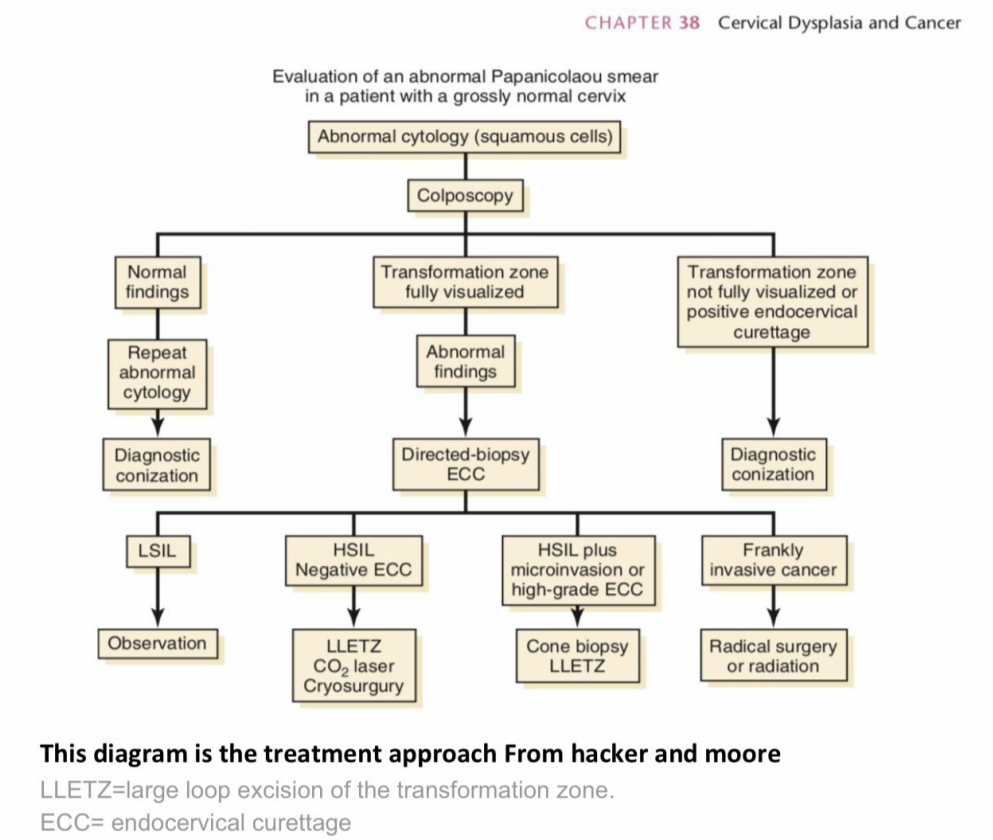
- **Ablative modalities** can be used for **CIN 1, 2, and 3**. These include **cryotherapy** (freezing), laser vaporization, and electrofulguration.

- **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**.

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 four to six months for two years.**



This diagram is the treatment approach From hacker and moore

LLETZ=large loop excision of the transformation zone.
ECC= endocervical curettage

Invasive cervical cancer

- ❏ **Invasive cervical cancer** is cervical neoplasia that has **penetrated through the basement membrane.**
- ❏ Cervical carcinoma is the **third** most common gynecologic malignancy; 50 is the mean age at diagnosis. Usually women acquire HPV in her 20s (when she becomes sexually active) and then comes with CIN in her late 20s early 30s and cancer will be in her 40s.
- ❏ Patients can present with **abnormal vaginal bleeding: Postcoital bleeding**. Other **symptoms** include **irregular vaginal bleeding and, in advanced stages, lower extremity pain and edema, pelvic pain, renal failure, vaginal discharge (very smelly).**
- ❏ Cervical cancer is usually disease of young women and it is the most common gynecological cancer worldwide (most common in developed countries is uterine 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**.

The initial diagnostic test

- ➔ **Cervical biopsy is the initial diagnostic test.** The most common diagnosis is squamous cell carcinoma.
- ➔ **Metastatic workup:** that includes pelvic examination, chest x-ray, intravenous pyelogram, cystoscopy, and sigmoidoscopy.
- ➔ **Imaging studies**: **Invasive cervical cancer is the only gynecologic cancer that is staged clinically.** an abdominal pelvic CT scan or MRI can **not** be used for clinical staging.
- ➔ Staging is clinical **based on pelvic examination and may include an intravenous pyelogram (IVP), cystoscopy, or proctoscopy.** It does not require surgical procedure other than a biopsy. Stage 1 is the most common stage.

EXTRA: Staging for Cervical Cancer

Stage 0:	Carcinoma in-situ (CIS). Spread limited to the cervix The basement membrane is intact.
Stage I: IA1. IA2. IB.	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. IIIC.	Spread further from the cervix • Involves lower one third of vagina • Extends to pelvic side wall or hydronephrosis -Involvement of pelvic or paraaortic lymph node
Stage IV: IVA. IVB.	Spread furthest from the cervix • Involves bladder or rectum or beyond true pelvis • Distant metastasis

Management

Patients treated surgically are evaluated for risk factors for metastatic disease and tumor recurrence. These include metastatic disease to the lymph nodes, tumor size >4 cm, poorly differentiated lesions, or positive margins. Patients with these findings are offered adjuvant therapy (radiation therapy and chemotherapy).

Specific by stage:

- ➔ **Stage Ia1** (when the tumor is confined to the cervix)**:** total simple hysterectomy, either vaginal or abdominal
- ➔ **Stage Ia2:** modified radical hysterectomy (we take the uterus and the tissue around the uterus)
- ➔ **Stage IB or IIA:** either radical hysterectomy with pelvic and paraaortic lymphadenectomy (if premenopausal) and peritoneal washings OR pelvic radiation (if postmenopausal); in those who can tolerate surgery, a radical hysterectomy is preferred, although studies have demonstrated equal cure rates with radiation or surgical treatment
- ➔ **Stage IIB, III, or IV:** radiation therapy and chemotherapy for all ages

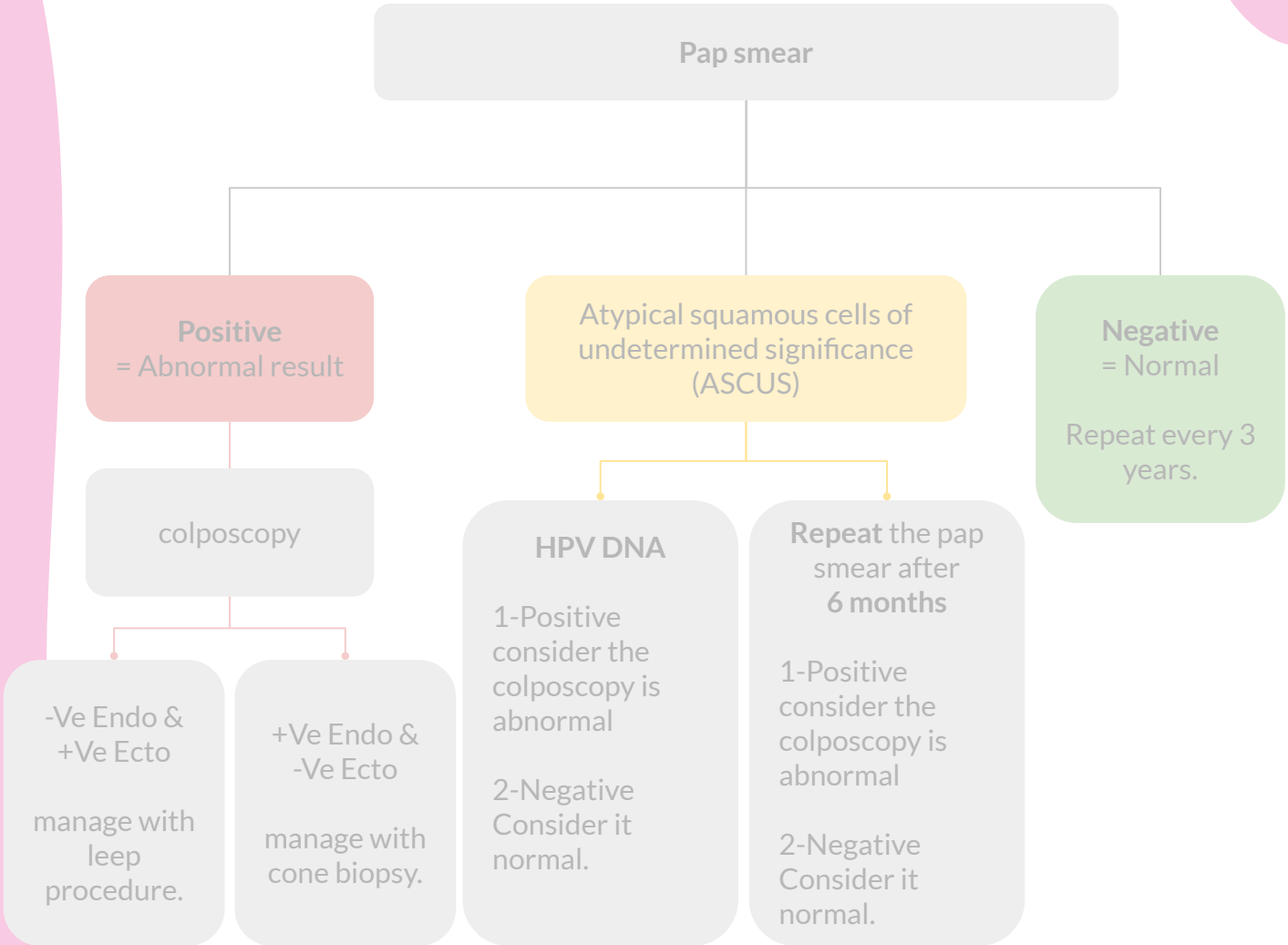
Follow up

All patients with invasive cervical cancer should be **followed up with Pap smear every three months for two years** after treatment, and **then every six months for the subsequent three years.**

Patients who have a local **recurrence** can be treated with radiation therapy; if they had received radiation previously, they might be considered candidates for a pelvic exenteration. Patients with distant metastases should be considered for chemotherapy treatment.

- Most common histopathology type in cervical cancer ? squamous cell carcinoma
- Most common site of extrapelvic disease is lung

1. HPV (16,18,30s) are the main causes of cervical cancer.
2. Cervical cancer occurs in the 30s and the 60s of age.
3. In the reproductive years the patient will present with postcoital bleeding or asymptomatic screening.
4. In the postmenopausal period the patient will present with bleeding
5. The risk factors of cervical cancer include anythings gives you HPV such as sex and STD, also smocking is a factor.
6. To screen for cervical cancer you have to use pap smear.
7. All women should have an asymptomatic screening by the age of 21, and repeat it every 3 years except HIV patient every year, and patients over 30 every 5 years.
8. In general we should stop screening at the age of 65, except patients who have positive screening.



Teaching case (video 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.

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: Secondary prevention means the pathological change already started, but that pathology still sub- clinical (pt doesn't have any symptoms)

- **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; "Co Testing" 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 she 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 immunosuppressive** therapies.
- **DES** (Diethylstilbestrol)exposure
- **HIV** infection

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

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 **totriage 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**.

Indications for HPV testing :

1. Screening at age of 25.
2. We can use it as a triage (when we have low grade cytology) (atypical squamous cells of undetermined significance ASCUS) if HPV is negative then patient is normal, if HPV is positive then ASCUS means there is something serious then we refer the patient to colposcopy.
3. Co testing (women above 30 we can combine it with cytology) we do it every 5 years.
4. Monitor response for treatment.