An Overview
Cervical Cancer Screening and Cervical Intraepithelial Neoplasia (CIN)

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Objectives

- Overview of Cervical Cancer Screening
- Incidents of Cervical Cancer
- Management of the Abnormal Pap
- Overview of Cervical Intraepithelial Neoplasia (CIN)
- Management of CIN
- Prevention: HPV vaccine
Cervical Cancer Incidence

- Worldwide, cervical cancer is common, and ranks third among all malignancies for women (Ferlay, 2010)

- Disparities are seen in African American women, African American women have the highest death rate from cervical cancer, Hispanic and Latino women have the highest incident rate
Cervical Cancer Incidence

- The mean age at diagnosis of cervical cancer in the United States is 48 years old.
- USA Incidence: ACS 2012: 11,270 cases
  - 4,070 deaths
- Worldwide an estimated 500,000 new cases of invasive cervical cancer are diagnosed annually
  - 275,000 deaths
- Developing countries have a much higher incidence rate
  - Account for 83% of cervical cancers
Papanicolaou (Pap) smear

- Cervical cytology became the standard screening test for cervical cancer and premalignant cervical lesions with the introduction of the Papanicolaou (Pap) smear in 1941.

- Liquid-based, thin layer preparation was a subsequent modification in technique (2000).

- Human papillomavirus (HPV) testing has now been incorporated into cervical cancer screening.
Case Study # 1

18 y.o. female comes to office for routine annual visit. She became sexually active at 17. Requests pill refill which she was started on by pediatrician 6 months ago.

*Do you need to do pap and pelvic?
Pap abnormality: How common?

- 5-7% abnormal paps/yr in U.S. (3.5 mil)
- 2.8% - Atypical Squamous Cells of Undetermined Significance (ASCUS)
- Low-grade squamous intraepithelial lesions 0.97% (LSIL)
- High-grade squamous intraepithelial lesions 0.21% (HSIL)
- Atypical glandular cells 0.21%
Pap Screening Interval

- 21 to 29 pap smear every 3 years

- ≥30 y.o. with normal “pap plus negative HPV” screen no more than q 3 yrs until age 65

- Continue more frequent screening for those at high risk such as HIV or other immunocompromised conditions, HPV positive, previous history of cin 2 or 3.
When to Stop

- ACOG - Consider stopping screening at age 65-70 for women with three or more consecutive, documented, negative Paps and no abnormal Paps within 10 years.
- American Geriatric Society 70 y.o.
- American Cancer Society 70 y.o.
- Post Hysterectomy for benign disease – stop screening
Recommendation

Case Study # 1

18 y.o. female comes to office for routine annual visit. She became sexually active at 17. Requests pill refill which she was started on by her pediatrician 6 months ago.

Do you need to do pap and pelvic?

- No pap needed
- GC/chlamydia screen – suggested.
Risk Factors

- Cervical cancer is primarily related to sexual activity and exposure to **HPV**
  - Detected in 99.7 percent of cervical cancers.
    - Subtypes HPV 16 and 18 are found in over 70 percent of all cervical cancers
- Early age of sexual activity
- h/o STI’s
- Multiple partners
- Cigarette smoking
- Immunodeficiency
Liquid based

- Increase detection of HSIL
- HPV testing
- Easier read for cytopathologist
- Decrease # of unsatisfactory
- Allows for automated screening
How Do We Screen

- Conventional
- Liquid based:
  - ThinPrep
  - SurePath
Case Study # 2

- 32 yo female g2p1 comes for annual preventive care. You perform pap and it returns with cytologic diagnosis:

  “Atypical squamous cells of undetermined significance” (ASCUS)

*What is the next step?
Interpreting Results of Cytology Report
Bethesda System

Description of specimen adequacy:

- Satisfactory
- Unsatisfactory
- “endocervical cells not present”

Interpretation:

- Negative
- Squamous cell abnormalities
- Glandular cell abnormalities
Cytology Report: Squamous Cell Abnormalities

- Atypical squamous cells (ASC)
- Low-grade squamous epithelial lesion (LSIL)
- High-grade intraepithelial lesion (HSIL)
- Carcinoma
<table>
<thead>
<tr>
<th>LAST System[1]</th>
<th>Cytology</th>
<th>LSIL</th>
<th>HSIL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Histology</td>
<td></td>
<td></td>
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</tbody>
</table>

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<thead>
<tr>
<th>Bethesda Classification System[2]</th>
<th>Cytology</th>
<th>LSIL</th>
<th>HSIL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Histology</td>
<td>CIN 1</td>
<td>CIN 2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Previous terminology</th>
<th>Mild dysplasia</th>
<th>Moderate dysplasia</th>
<th>Severe dysplasia</th>
<th>Carcinoma in-situ</th>
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| Histologic images | | | | |
|-------------------|---|---|---|
Management of Women ≥ Age 30, who are Cytology Negative, but HPV Positive

- **Repeat Cotesting**
  - @ 1 year
  - Acceptable
  - Cytology Negative and HPV Negative
  - Repeat cotesting @ 3 years

- **HPV DNA Typing**
  - Acceptable
  - ≥ASC or HPV positive
  - HPV 16 or 18 Positive
  - HPV 16 and 18 Negative
  - Repeat Cotesting @ 1 year

**Colposcopy**

- Manage per ASCCP Guideline
- Manage per ASCCP Guideline
Management of Women with Atypical Squamous Cells of Undetermined Significance (ASC-US) on Cytology*

- **Repeat Cytology**
  - @ 1 year
  - Acceptable
  - **Negative**
    - Routine Screening
      - (Cytology in 3 years)
  - ≥ ASC

- **HPV Testing**
  - Preferred
  - **HPV Positive**
    - (managed the same as women with LSIL)
  - **HPV Negative**
    - Repeat Cotesting
      - @ 3 years

- **Colposcopy**
  - Endocervical sampling preferred in women with no lesions, and those with inadequate colposcopy; it is acceptable for others

- **Manage per ASCCP Guideline**

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*Management options may vary if the woman is pregnant or ages 21-24.

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ASCUS Ages 21-24

Management of Women Ages 21-24 years with either Atypical Squamous Cells of Undetermined Significance (ASC-US) or Low-grade Squamous Intraepithelial Lesion (LSIL)

Women ages 21-24 years with ASC-US or LSIL

- Repeat Cytology @ 12 months Preferred

- HPV Positive
  - Reflex HPV Testing Acceptable for ASC-US only

- Negative, ASC-US or LSIL
  - Repeat Cytology @ 12 months
  - Negative x 2 ≥ ASC
    - Routine Screening
  - ASC-H, AGC, HSIL

- HPV Negative
  - Routine Screening
Absent or Insufficient Transformation Zone

Cytology NILM but EC/TZ Absent/Insufficient

Ages 21-29*

HPV negative

HPV testing (Preferred)

Routine screening

Age ≥30 years

HPV unknown

or

Repeat cytology in 3 years (Acceptable)

HPV positive

or

Genotyping

Cytology + HPV test in 1 year

Manage per ASCCP guideline

*HPV testing is unacceptable for managing women ages 21-29 years

Figure 2.
Special Populations

- Pregnant with ASCUS preferred to have colposcopy but acceptable to delay colposcopy till six weeks postpartum.
- Menopausal women with ASCUS trial of vaginal estrogen with repeat pap.
- > 60 yo HPV negative ASCUS should be considered abnormal and repeat pap and HPV co-testing in one year.
HPV 16 & 18 Genotyping

- Cytology neg/HR HPV positive (women ≥ 30 y.o.)
  - If HPV 16/18 positive refer directly to colpo
  - If HPV 16/18 negative, f/u current algorithm of repeating both pap and HR HPV in 1 year
HPV DNA Testing and Genotyping Are Not Recommended

- Adolescents, defined as women 20 years and younger (regardless of their cytology results)
- Women 21 years and older with ASC-H, LSIL, or HSIL cytology
- Routine screening in women before the age of 30 years
- In women considering vaccination against HPV
- For routine STI screening
- As part of a sexual assault workup
Cytology Report
Glandular Cell Abnormalities

- Atypical Glandular Cells of Undetermined significance
- AIS (adenocarcinoma in situ)
- Adenocarcinoma
- All are referred for colposcopy, ECC and endometrial biopsy
Case Study #2

- 32 yo female g2p1 for annual preventive care. You perform pap - it returns with cytologic dx:
  - Atypical squamous cells of undetermined significance” (ASCUS)

Next Steps:

- If liquid based testing used, Reflex HPV testing can be requested. If high risk subtype HPV positive refer for colposcopy. If high risk HPV negative return for routine annual screening.

*Other options - serial pap q6 months x 2 or immediate colpo
Colposcopy
Colposcopy
Colposcopy with Biopsy
Histologic Definitions
Cervical Intraepithelial Neoplasia

- CIN I (previously mild dysplasia)
  - Cytology LSIL
- CIN II (previously moderate)
  - -p16 LSIL
  - +p16 HSIL
- CIN III (previously severe and CIS)
  - Cytology HSIL
CIN 1

CIN 1 (mild dysplasia)

Regression rates:

- 2yrs 50%
- 5 yrs 74%

Progression to HGSIL

- 2 yr 2%-20%
Management of Women with No Lesion or Biopsy-confirmed Cervical Intraepithelial Neoplasia - Grade 1 (CIN1) Preceded by “Lesser Abnormalities”

Follow-up without Treatment

- Cotesting at 12 months
  - HPV (-)
  - Cytology Negative

  Age appropriate retesting
  3 years later

  - Cytology negative
    - **HPV (-)**
    - Routine screening

  - **HPV (-)**
    - Manage per ASCCP Guideline

≥ ASC or HPV (+)

- Cytology if age <30 years, cotesting if age ≥30 years

- Either ablative or excisional methods. Excision preferred if colposcopy inadequate, CIN2+ on ECC, or previously treated.

- Management options may vary if the woman is pregnant or ages 21-24.

- “Lesser abnormalities” include ASC-US or LSIL Cytology, HPV 16+ or 18+, and persistent HPV

Colposcopy

No CIN

- CIN2,3

- CIN1

If persists for at least 2 years

- Follow-up or Treatment
CIN 2

CIN 2 (moderate dysplasia)

- 50% regression
- 20% progression to CIN 3
- 5% to CA
CIN 3

CIN 3 (Severe dysplasia, Carcinoma in Situ)

- 40% regression
- Up to 35% progression to CA
- If colposcopy satisfactory:
  Excision or ablation
- Unsatisfactory colposcopy:
  Diagnostic excisional procedure
Management of Women with Biopsy-confirmed Cervical Intraepithelial Neoplasia - Grade 2 and 3 (CIN2,3) *

Adequate Colposcopy

Either Excision† or Ablation of T-zone *

Cotesting at 12 and 24 months

2x Negative Results

Repeat cotesting in 3 years

Routine screening

Inadequate Colposcopy or Recurrent CIN2,3 or Endocervical sampling is CIN2,3

Diagnostic Excisional Procedure †

Any test abnormal

Colposcopy With endocervical sampling

*Management options will vary in special circumstances or if the woman is pregnant or ages 21-24.
†If CIN2,3 is identified at the margins of an excisional procedure or post-procedure ECC, cytology and ECC at 4-6mo is preferred, but repeat excision is acceptable and hysterectomy is acceptable if re-excision is not feasible.
Case Study #3

22 y.o. sexually active female with previous abnormal pap smear which has resolved spontaneously. During her annual gyn exam she asks whether she should have HPV vaccine.
Prevention: HPV Vaccine

- HPV is essential to the development of Cervical cancer
- At least 40 types of HPV associated with the lower genital tract
- 20 million in U.S. are infected
- High Risk
  - 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68
- Low risk
  - 6, 11, 40, 42, 43, 44, 54, 61, 7
HPV Vaccine

Gardasil 9

- HPV subtypes 16, 18, 31, 33, 45, 52, 58 6,11
- Age 9-26
- Injection series at 0,2,6 months
- Adverse reaction: injection site only. No serious reactions.

- Vaccinate boys – FDA approved 10/2009
Case Study #3

22 y.o. sexually active female with previous abnormal pap smear which has resolved spontaneously. During her annual gyn exam she asks whether she should have HPV vaccine.

**YES. Although vaccine may not help to eradicate previous infection, it will provide protection against any of the 9 subtypes that she may not have immunity**
Summary

- Human papillomavirus (HPV) is central to the development of cervical neoplasia

- Risk factors:
  - Immune compromised (+HPV)
  - Early onset of sexual activity, multiple sexual partners
  - A high-risk sexual partner, history of sexually transmitted infections
Summary

- Cervical Cancer is the third most common cancer diagnosis and cause of death among gynecologic cancers in the United States.

- In countries that do not have access to cervical cancer screening and prevention programs, cervical cancer remains the second most common type of cancer and cause of cancer deaths among all types of cancer in women.
Summary

- The lifetime risk of developing cervical cancer for United States women is 0.76 percent. The mean age at diagnosis of cervical cancer in the United States is 48 years old.

- **Cytology results** (eg, ASC-US, LSIL, HSIL) from a Pap smear are distinct from **pathology results** (cervical intraepithelial neoplasia [CIN] 1,2,3) from colposcopy and biopsy.
Thank You for Your Attention