Management of Abnormal Pap Findings & HPV Vaccine Update

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History

- 1943 – Papanicolau & Traut, USA, report exfoliative cytology as research tool
- c.1950 - PAP smears become used in clinical medicine
- 1964 - Early interest in colposcopy in U.S.A. American Society for Colposcopy and Cervical Pathology (ASCCP) established.
Cervical Cancer

- 500,000 new cases worldwide each year
- Leading cause of cancer-related death in women in underdeveloped countries
  - US: ~11,150 cases & 3,670 deaths (est. 2007)
  - Oregon: 110 cases (est. 2007)
- 93-100% association with HPV
  - HPV 16 associated with >60%

Pap Smears

- 50 million/year
- 3.5 million (7%) abnormal
  - 2 million – ASC-US and ASC-H
  - 1.25 million LSIL
  - 300,000 HSIL
Natural History of Cervical Cancer

HPV Infection → Low-Grade Cervical Dysplasia → High-Grade Cervical Dysplasia → Invasive Cancer

Source: PATH, 2001

Consensus Guidelines - Squamous cell types

- ASC-US - Atypical squamous cells of uncertain significance
- ASC-H - Atypical squamous cells, cannot exclude HSIL
- Low grade precursors: LSIL = CIN I
- High grade precursors: HSIL = CIN 2,3
Screening Guidelines

When to Start?
When to Stop?
Screening after hysterectomy
Screening Interval

When to Start

• Old Recommendations: age 18 or with sexual activity
What is the probability of developing invasive cervical cancer, by age?*

<table>
<thead>
<tr>
<th>Birth - 39</th>
<th>40-59</th>
<th>60-69</th>
<th>≥ 70</th>
<th>Birth - Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.16 %</td>
<td>0.29 %</td>
<td>0.14 %</td>
<td>0.20 %</td>
<td>0.73 %</td>
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<tr>
<td>(1 in 631)</td>
<td>(1 in 346)</td>
<td>(1 in 695)</td>
<td>(1 in 512)</td>
<td>(1 in 138)</td>
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*for those cancer-free at beginning of interval

CA Cancer J Clin 2007, 57: 61 (Table 12)

When to Stop

- No definitive data
  - ACS: age 70 with intact cervix and 3 or more nl. Paps in prior 10 years
  - USPSTF: age 65 if adequately screened and not at high risk
- If older women have not been screened, or if past screening info not available, then need nl Pap testing x 3 before can stop screening
Pap Tests After Hysterectomy

- USPSTF (2003):
  - If cervix removed as part of hysterectomy, no further Pap testing needed
  - UNLESS: hysterectomy was performed for cervical cancer or cervical dysplasia
- ACS: same. If CIN 2,3 reason for hysterectomy, may stop after 3 nl Paps q 6 m
- If hysterectomy performed for Ca-in-Situ, screen indefinitely

Frequency of Routine Cytologic Screening

- After a woman has had three or more consecutive annual exams with normal findings, the Pap test may be performed less frequently on a low risk woman
  - Issue: who is low risk?
- Estimates from models indicate that screening every 3 yrs would achieve 91-96% of the benefit of annual screening
HPV DNA Testing Methods

- Digene Hybrid Capture II HPV Test only FDA approved
- High risk viral test useful (not low-risk)
- Liquid based cytology for HPV Samples
  - Reflex: optimal

HPV Testing: Summary

- HPV infection is extremely common
- Most HPV infections are transient
  - Persistent infections with oncogenic types are associated with SIL, and progression
  - Viral load, immunosuppression are cofactors
- Most CIN1, some CIN2 regress spontaneously
- Cervical cancer is a slow-growing disease
- However, still cannot evaluate who will develop cervical cancer and who will not….
Management of Cytologic Abnormalities

(Everything you want to know about what to do when the Pap comes back ASCUS, LGSIL, HGSIL or AGUS…or don’t want to know)

Wright TC, Cox JT, Massad LS et al. 2001 Consensus guidelines for the management of women with cervical cytological abnormalities. JAMA 2002;287:2120-2129

Definitions of Terms Utilized in the Consensus Guidelines

Colposcopy is the examination of the cervix, vagina, and, in some instances the vulva, with the colposcope after the application of a 3-5% acetic acid solution coupled with obtaining colposcopically-directed biopsies of all lesions suspected of representing neoplasia.

Endocervical sampling includes obtaining a specimen for either histological evaluation using an endocervical curette or a cytobrush or for cytological evaluation using a cytobrush.

Endocervical assessment is the process of evaluating the endocervical canal for the presence of neoplasia using either a colposcope or endocervical sampling.

Diagnostic excisional procedure is the process of obtaining a specimen from the transformation zone and endocervical canal for histological evaluation and includes laser conization, cold-knife conization, loop electrosurgical excision (i.e., LEEP), and loop electrosurgical conization.

Satisfactory colposcopy indicates that the entire squamocolumnar junction and the margin of any visible lesion can be visualized with the colposcope.

Endometrial sampling includes obtaining a specimen for histological evaluation using an endometrial biopsy or a “dilatation and curettage” or hysteroscopy.
ASC-US - Atypical Squamous Cells - Uncertain Significance

- 5-10% harbor serious disease
- One third of HSIL identified from ASC-US
What is Colposcopy?

- Colposcopy is a method of magnifying the tissue being evaluated to identify abnormal tissue changes. Magnification can be 8 to 20 X, most commonly 12 X. The colposcope is essentially an operating microscope:
Mature Metaplasia

Punctation

- Puncta or “dots” are vascular changes seen in the epithelium which are usually associated with abnormal epithelial proliferation.
Punctation

Mild Mosaicim
Mosaicism on White Epithelium

Moderate to Mild Mosaicism
Severe Mosaicism

Vascular Changes of Cancer
ASC - H

- Colposcopy

- If no identified abnormality- repeat Pap at 6 & 12 mos or HPV testing at 12 mos.
AGC- Atypical Glandular Cells

- Rare - 0.5% all Paps = 1/200
- Risk of neoplasia significantly greater than ASC or LSIL
  - 9-54% have CIN by biopsy
  - 0-8% have AIS
  - 1-9% have invasive carcinoma
- Premenopausal women - higher risk of CIN 2,3, AIS
- Postmenopausal women - higher risk of endometrial hyperplasia and cancer

Management of Women with Atypical Glandular Cells (AGC)
Management of Women with Low-grade Squamous Intraepithelial Lesions (LSIL) *

Colposcopic examination *

- Satisfactory colposcopy and lesion identified
- Satisfactory colposcopy and NO lesion identified
- Unsatisfactory colposcopic examination

Endocervical sampling "acceptable"
Endocervical sampling "preferred"

No CIN / Cancer

Cytology @ 9 & 12 mos CN
HPV DNA testing @ 12 mos

≥ ASC or HPV (+)
Repeat Colposcopy

Negative
Routine Screening

≥ ASC
Manage per ASCCP Guidelines

CIN / Cancer

* Management options may vary if the woman is pregnant, postmenopausal, or an adolescent - see also:

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Management of Women with Low-grade Squamous Intraepithelial Lesions in Special Circumstances

Post-menopausal Women *

Intravaginal Estrogen therapy

Negative
Repeat Cytology

≥ ASC
HPV Positive (for high-risk HPV)
≥ ASC
Colposcopy

Negative
Repeat Cytology @ 4 - 8 mos

≤ ASC
HPV Negative (for high-risk HPV)
≤ ASC
Routine Screening

HPV DNA testing 12 mos after index Pap

≥ 6 mos after completion of therapy

* For low-risk, post-menopausal women with a history of negative screening - see also:

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**HSIL**

- Rare - 0.45% of all Paps
- 70-75% have biopsy confirmed CIN 2,3
- 1-2% have invasive cervical cancer
Management of Histologic Abnormalities
(Or..what to do after you’ve got the pathology results back from biopsies at colposcopy)

Changes in Treatment Guidelines for CIN

- Follow-up Paps Preferred for CIN 1
  - Unless Unsatisfactory Colpo, or;
  - Persistent CIN 1
- Treat CIN 2/3
Management of Women with Biopsy-confirmed Cervical Intraepithelial Neoplasia - Grade 1 (CIN 1) and Unsatisfactory Colposcopy

- Diagnostic Excisional Procedure
  - Preferred Approach

- Special Circumstances
  - Immunosuppressed, Pregnant, & Adolescent Women

- Follow-up without Treatment
  - Acceptable Approach

Management of Women with Biopsy-confirmed Cervical Intraepithelial Neoplasia - Grade 2 or 3 (CIN 2,3) *

- Satisfactory Colposcopy
  - Either Excision or Ablation of T-zone *
    - Acceptable Approach

- Unsatisfactory Colposcopy
  - Diagnostic Excisional Procedure
    - Recommended Approach

Acceptable follow-up approaches post-treatment

- Cytology @ 4 - 6 mos OR
  - Cytology & Colposcopy @ 4 - 6 mos

- HPV DNA Testing performed @ least 6 mos after treatment

- 3x Negative Results
- ≥ ASC (any repeat cytology)
- HPV Positive (for high-risk types)
- HPV Negative (for high-risk types)

Annual Cytologic Screening

Colposcopy

Annual Cytologic Screening

* Excisional modalities preferred for recurrent CIN 2,3

* Management options may vary if the woman is pregnant, immunosuppressed, or an adolescent - (see text)
Other Findings on Colposcopy

Cervical Inclusion Cysts
Condyloma of the Cervix

- Two types
  - Condyloma Accuminata
  - Condyloma Plana
Condyloma Plana

Normal or Abnormal?
Squamocolumnar Junction Not Seen

Endocervical Polyp

- Endocervical polyp can cause inflammatory PAP smear changes until removed.
**HPV Vaccine: The New Frontier**

- June 8, 2006: FDA approved an HPV vaccine for clinical use
- Quadrivalent vaccine consisting of recombinant viral-like particles (VLPs) of HPV 6, 11, 16, 18.
- Administered IM as 3 injections: 1, 2 and 6 months
- Bivalent vaccine for HPV 16 and 18 most likely to be approved in the near future

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**Human Papillomavirus: HPV**

- Approximately 20 million Americans and 630 million persons worldwide are infected with HPV
- Most common STI in the US with 6.2 million individuals acquiring a new infection each year
- CDC estimates that 80% of women will acquire an HPV infection by age 50
HPV Subtypes

- High risk due to strong association with cervical cancer
  - 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82
  - In US, HPV16 associated with 59% of cervical cancer cases, HPV18 with 18%, HPV 45 with 7%

- Low risk subtypes (6, 11) associated with low grade dysplasia, genital warts
Vaccine Indications

• “a vaccine indicated in girls and women 9-26 years of age for the prevention of the following diseases caused by HPV types 6, 11, 16, and 18:
  – Cervical cancer, genital warts, cervical adenocarcinoma in situ (AIS), cervical intraepithelial neoplasia grade 2 and grade 3, vulvar intraepithelial neoplasia grade 2 and grade 3, vaginal intraepithelial neoplasia grade 2 and grade 3, cervical intraepithelial neoplasia grade 1”

ACIP Recommendations

• Routine vaccination of 11-12 year old females
• Vaccination can begin as early as 9 years of age
• Also routine vaccination of 13-26 year old females
• Females who are sexually active should still be vaccinated
• CDC Advisory Committee on Immunization Practices:
  http://www.cdc.gov/od/oc/media/pressrel/r060629.htm
Vaccine Contraindications

- Hypersensitivity to the active substances of the vaccine
- Not recommended for use in pregnant patients, Pregnancy Category B
- Package insert available on FDA website: http://www.fda.gov/cber/products/hpvmer060806.htm

Lifetime Risk Reduction for Cervical Cancer after Vaccination

- 12-year-old girls: -62%
- 24-year-old women: -35%
- 30-year-old women: -17%

*Against the 2 most oncogenic HPV types

*Assumes 70% of age-group is vaccinated, vaccine is effective for 10 years, and both girls and boys are vaccinated.

Vaccine Issues

- Long term efficacy of vaccine not known
- “Gardisil” (Merck)
- Price quoted as $120 per dose ($360 for course)
- Some large primary insurers have okayed coverage, others awaiting formal approval of CDC
- OHP coverage: not anticipated

HPV Vaccine: Key Points to Remember

- NOT a cure for HPV infection or abnormal cervical findings
- NOT a replacement for other preventative strategies such as cervical screening
- Routine recommendations for cervical cancer screening still in order
- Do not need HPV test in sexually active patients prior to immunization BUT must address cytologic/histologic abnormalities prior to vaccination and document resolution of cervical disease
Questions?