Another Change in Cervical Cytology Guidelines?

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Montana Nurses Association
Helena, MT – April 22-24, 2014

Learning Objectives
At the end of this presentation, the participant will be able to:
- Outline routine screening recommendations for women of different ages.
- Explain the principles underlying the differences between younger and older women in recommendations for management of biopsy-proven dysplasia.
- Describe the upcoming new terminology that is expected to replace the current CIN nomenclature.
- Outline the evaluation needed for abnormal cytologic test results and for dysplasia.

Principles Underlying Screening Recommendations
- Virtually every sexually active person will be exposed to HPV
- Most HPV infections are transient
- HR-HPV infections take longer (> 24 months) than low risk HPV
- Significant cervical dysplasia is caused by persistent HPV infection

U.S. Incidence of Cervical Cancer
- In US in 2014:
  - 12,360 new cases
  - 4,020 deaths
  - 70% reduction due to Pap smear screening
- Cervical cancer is disease of economically disadvantaged—elderly, minorities and low socioeconomic status
- Types of cervical carcinoma:
  - Squamous 85%
  - Adenocarcinoma 15%
Nelson: Another Change in Cervical Cytology Guidelines?

Risk Factors For Cervical Dysplasia and Cancer: Multiple Sexual Partners

<table>
<thead>
<tr>
<th>Number of Sexual Partners</th>
<th>Relative Risk Without Smoking</th>
<th>Relative Risk With Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>1.00</td>
<td>4.7</td>
</tr>
<tr>
<td>2</td>
<td>2.37</td>
<td>10.8</td>
</tr>
<tr>
<td>3-5</td>
<td>5.41</td>
<td>12.1</td>
</tr>
<tr>
<td>6+</td>
<td>6.07</td>
<td></td>
</tr>
</tbody>
</table>

Natural Course of HPV Infection

Prevalence of Minor Precursors, Major Precursors, and Invasive Cancer

Screening Recommendations

<table>
<thead>
<tr>
<th>Age/Condition</th>
<th>Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 21</td>
<td>No Screening</td>
</tr>
<tr>
<td>21 – 29</td>
<td>Cytology alone Q3 years</td>
</tr>
<tr>
<td>30 – 65</td>
<td>HPV and cytology “co-testing” Q 5 years OR</td>
</tr>
<tr>
<td>&gt; 65</td>
<td>Cytology alone Q 3 years</td>
</tr>
</tbody>
</table>

Cervical Cancer: Impact of Screening

- About 50% of US cervical cancers occur in:
  - Women never screened
  - Another 10% US cervical cancers
  - Women not screened in past 5 years
  - Screening fails
  - Low resource, medically underserved regions rates 7 times higher
  - Socioeconomic, geographic and/or racial disparities

Accuracy of Colposcopically-Directed Punch Biopsies: Meta-analysis

- 7,873 pairs of punch biopsy and excisional biopsies when excisional biopsy done immediately following punch biopsy
  - Sensitivity 81.4%
  - Specificity 63.3%
- Norwegian study 24% with negative biopsies found to have ≥ CIN 2 on follow-up biopsy
- Single punch biopsy/LEEP pairs in colposcopically CIN 1 failed to detect 71.4% of ≥ CIN 2

Contributions of ECC

- 13,115 colposcopic examination with guided biopsy
  - ECC increased diagnosis of CIN2+ by 1.01%
  - 99 ECC procedures needed to identify one new case of CIN2+
- Most valuable in:
  - Women ≥ 46 years old
  - High grade CIN, HSIL
  - Most of these women need excisional biopsy regardless of ECC


Random Cervical Biopsy and ECC in Low Risk Populations

- 4 quadrant random biopsies and ECC routinely added to colposcopically directed biopsies
- 4,677 women had colposcopy
  - 295 ≥ CIN 3
  - 61 (20.7%) diagnosed on random biopsy ± ECC
- Random biopsies increase yield
  - ECC not helpful in women < 25 years


Revised Terminology for Cervical Histopathology

- Consensus conference: Lower Anogenital Squamous Terminology (LAST)
  - 35 organizations
  - Uniform 2-tier terminology for all HPV-related squamous diseases
    - Vulva, vagina, cervix, penis, perianus, and anus
  - 2-tier classification similar to cytology results
    - Low-grade SIL (IN)
    - High-grade SIL (IN)
- Replaces CIN 1, CIN 2, CIN 3


Revised Terminology

- Problems with prior CIN 2
  - Poor reproducibility
    - Agreement in only 13-43% of cases
  - Not clear clinical meaning
    - Usually combined with CIN 3
    - Many represent mixture of cells
  - Intermediate diagnosis of CIN 2 now resolved into either high or low grade SIL


Use of Adjunctive Tests to Sort “CIN 2”

- Use of p16INK4a (p16) immunohistochemical stain to determine if high or low grade lesion
- Overexpression of P16 occurs in squamous cells
  - Cell cycle regulator (retinoblastoma protein)(pRB)
    - inactivated by E7 oncoprotein of high-risk HPV
  - Positive p16 immunostaining of squamous cells throughout epithelium correlates well with HSIL
- If CIN 2 lesion seen on hematoxylin and eosin dyes
  - P16 ⊕ → HSIL (histology)
  - P16 ⊝ → LSIL (histology)


Lost to Follow-Up Low-Income Colposcopy Clinic

- Compliance ≥ 1 return visit within 3-14 months
  - 54% appropriately timed repeat testing
  - 46% failed to return within 14 months
  - 45% of women with CIN 2 or 3 did not return
- Risk factors:
  - Referral from outside clinic, self or government funds, Spanish speaking, unmarried

Recurrence Rates After Treatment for CIN 1, 2, 3
- 37,142 women treated for CIN 1, 2, or 3 diagnosed in 1986-2000
- Recurrence rates depend on grade of CIN, treatment used and woman’s age
- In first 6 year after treatment, rate of CIN 2,3
  - 5.6% for original CIN 1
  - 9.3% for original CIN 2
  - 14.0% for original CIN 3
- After 6 years, annual rates were < 1%


Alternative Screening Methods
- High risk HPV testing of urine sample
  - Concordance with cervical cytology 80%
  - Sensitivity for HSIL 100%
  - Specificity for HSIL 80%
  - Positive predictive value 91%
- Blind vaginal swabs for HR-HPV
  - Acceptable yield of endocervical cells
- Self swabbing for cytology and HR-HPV samples


Future Developments: Cervical Adenocarcinoma
- HPV 16, 18 account for:
  - 70% squamous cell carcinoma
  - 80% adenocarcinoma
- HPV test-based screening may be more effective than cytology-based screening for adenocarcinoma
  - HPV 77.8% vs. PAP 17.4%
  - HPV adenocarcinoma detected earlier by HPV-tests


Vaccine for Cervical Dysplasia Cancer Treatment: Early Promise
- 10-25% of women with high grade dysplasia clear themselves
  - Tend to have higher levels of T cells against HPV genes E6 and E7
- New vaccine designed to trigger production of these T cells
  - 14 of 18 women responded for ≥ 2 years
  - T cells functional
  - Inserts specific DNA into patient’s cells using electroporation

www.reuters.com/assets/pring?aid=USBRE8991JS20121010

Treatment CIN 2-3
Topical Imiquimod: 16 Week Trial
- Randomized, double-blind, placebo-controlled phase 2 trial self applied vaginal imiquimod vs. placebo:

<table>
<thead>
<tr>
<th></th>
<th>Imiquimod</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>Reduced to ≤ CIN 1</td>
<td>73%</td>
<td>39%</td>
</tr>
<tr>
<td>Complete remission</td>
<td>47%</td>
<td>14%</td>
</tr>
<tr>
<td>HPV clearance</td>
<td>60%</td>
<td>14%</td>
</tr>
<tr>
<td>Complete remission HPV-16</td>
<td>47%</td>
<td>0</td>
</tr>
<tr>
<td>Microinvasive</td>
<td>0</td>
<td>5%</td>
</tr>
<tr>
<td>Erythema</td>
<td>37%</td>
<td>5%</td>
</tr>
<tr>
<td>Erosion</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Severe edema</td>
<td>13%</td>
<td></td>
</tr>
</tbody>
</table>


Role of ECC and Random Biopsy
- Retrospective analysis of 550 patients undergoing colposcopy
  - 42.1% single 1-quadrant lesion
  - 101 patients with no visible lesion; ≥ CIN 2 found
  - 26 patients on ECC only
  - 11 patients ECC + random biopsy
  - 63% of ASC-US on pap and no colposcopic lesion had on ≥ CIN 2 on random biopsy
  - Patients with no visible lesions were 4 times more likely to have ≥ CIN 2

ECC in Low Grade Cytology Improves Detection High Grade Disease

- 374 patients; 75 women ≥ CIN 2
  - 16 with ECC with high grade dysplasia
  - 12 high grade in ectocervical dysplasia
  - ASC-US + HR-HPV
  - LSIL
  - 4 on ECC alone
  - 4 in 374 = 1 in 93.5
  - Screen 93-94 to find 1 case

**Conclusion:** "Routine ECC at time of satisfactory colposcopy for low grade abnormality with a visible lesion does not significantly improve the diagnosis of high grade dysplasia"


Other Interpretations

Other Approaches

- However
  - 12 of 75 would have been suboptimally treated without ECC
  - Test 23 to find 1 case?
  - OR
  - Test 2.4 to find 1 case?

Pain Control (VAS) with Cervical Biopsy Forced Coughing vs 1% Lidocaine Injection

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Local Anesthetic</th>
<th>Forced Coughing</th>
<th>P Value</th>
<th>95% CI for Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speculum Insertion</td>
<td>1.7 (0-7.5)</td>
<td>1.4 (0-6.9)</td>
<td>.97</td>
<td>-0.8 to 0.8</td>
</tr>
<tr>
<td>Injection</td>
<td>1.4 (0-6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical Biopsy</td>
<td>1.5 (0-7.1)</td>
<td>1.9 (0-8.5)</td>
<td>.47</td>
<td>-0.4 to 1.3</td>
</tr>
<tr>
<td>Overall Score</td>
<td>2.3 (0-9)</td>
<td>3.0 (0-8.5)</td>
<td>.30</td>
<td>-0.5 to 1.5</td>
</tr>
<tr>
<td>Time needed (min)</td>
<td>7.0 (5-15)</td>
<td>5.0 (3-8)</td>
<td>&lt; .001</td>
<td>-2.8 to -1.6</td>
</tr>
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</table>


Role Of Primary LLETZ Therapy “Look and LEEP”

- Reserved for HSIL in Adults

<table>
<thead>
<tr>
<th>Pap smear</th>
<th>Histology</th>
<th>No dysplasia</th>
<th>CIN 1</th>
<th>CIN 2/3</th>
<th>Micro-invasive</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td></td>
<td>32.5%</td>
<td>26.5%</td>
<td>40.5%</td>
<td>0.5%</td>
</tr>
<tr>
<td>CIN 1</td>
<td></td>
<td>40.7%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIN 2,3</td>
<td></td>
<td>63.9%</td>
<td></td>
<td></td>
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Photodynamic Therapy

CN is a 21 year old G3P0Ab3 woman whose pap smear returns ASC-US. She had coarchitecture at age 13 and has had 6 lifetime partners. At age 14, she had EGW that required multiple treatments with TCA and cryotherapy to eradicate. She wants you to test to see if she has HPV. How do you manage her?

A 67 year old G7P7 woman who has never had a pap smear test is referred in for well woman care. She denies any recent abnormal bleeding, vaginal discharge or sexual contact for last 12 years. She has never smoked tobacco or consumed alcohol. What examinations and tests should she have to evaluate for pelvic organ carcinoma?

A. No tests
B. Cytology test
C. Cytology test + HP-HPV test
D. Colposcopy

What would you do if your examination revealed a 5 mm cervical polyp? What would you do if you found an exophytic lesion on the anterior lip of her cervix?

A 29 year old woman with LSIL on pap smear. No previously abnormal pap smears. New sex partner 9 months ago. No HPV test was done. What should we do next.

A. HPV testing
B. Colposcopy
C. Repeat testing in 12 months
Management of Women with Low-Grade LSIL

If colposcopy failed to identify any suspicious lesions and her ECC is negative, which of the following is recommended?

A. Repeat colposcopy with blind biopsies
B. Repeat pap every 6 months X 2
C. Cotesting at 12 months
D. Look and LEEP

39 year old woman with pap smear with ASC-H underwent colposcopy. No lesions were seen on inspection of the cervix and ECC showed no dysplasia. Would you do

A. Repeat pap in 6 and 12 months
B. Cotesting at 6 and 12 months
C. Repeat colposcopy, cervix and vagina blind biopsy
D. Other

Management of Women with No Lesions

A 23 year old woman with repeat pap smear with LSIL. At age 21 she had LSIL on pap smear. Her colposcopy exam at the time was reported as being satisfactory and a cervical biopsy showed CIN1. Last year her pap smear was ASC-US, so repeat pap was done this year. Now what do we do?

Now What?
Management of Women with No Lesions

What if . . .
- Her next biopsy returns as CIN1 again?
  - How long can this watch and wait process go on?
  - Why?

Climbing Higher, Higher
A 52 year old woman with HSIL after years without any screening. Colposcopic exam was unsatisfactory. Biopsy was CIN1 and ECC was negative. What are your treatment options? Choose all the apply:

- A. Cytology at 6 and 12 months
- B. Co-testing at 12 and 24 months
- C. Diagnostic excision procedure
- D. Review cytology, histological and colposcopic findings

No Lesion or Biopsy-Confirmed Management

Climbing Higher, Higher
What if her ECC were inadequate? What would your options be then? Check all the apply:

- A. Cytology at 6 and 12 months
- B. Co-testing at 12 and 24 months
- C. Diagnostic excision procedure
- D. Review cytology, histological and colposcopic findings

More About ECCs
A 22 year old with ASC-H has CIN1 biopsy and ECC with CIN1. What are her treatment options? Check all that apply:

- A. Cytology at 6 and 12 months
- B. Cytology and colposcopy every 6 months x 4
  - a. Biopsy if high grade lesion persists for > 1 year
- C. Cytology, colposcopy and ECC every 6 months x 4
  - a. Biopsy if high grade lesion persists for > 1 year
A 24 year old woman has a pap smear with LSIL. The following year, her pap smear is LSIL again. Now what do you do?

A. Repeat cytology in 1 year
B. Colposcopy

Management of Women with Low-Grade LSIL

A 47 year old woman presents with HSIL. Her colposcopy was not satisfactory. A diagnostic LEEP cone was performed as was an ECC above the LEEP site. Hemostasis was challenging. Her remaining cervical length is 2.5 cm. Her ECC was unsatisfactory. What are your treatment options?

Check all that apply:
A. Cytology at 6 and 12 months
B. Co-testing at 12 and 24 months
C. Cytology and ECC at 4-6 months
D. Repeat diagnostic excisional procedure
E. Hysterectomy

Colposcopic Principles in Pregnancy

- Limit biopsy to lesions suspicious for CIN2, 3 or cancer
- Biopsy not linked to fetal loss or preterm labor
- ECC is contraindicated in pregnancy
- CIN2 or CIN3 on biopsy rarely progress to invasive cancer during first months of pregnancy
- Re-evaluation during pregnancy may prompt needless intervention
- Observe until postpartum period safe and reasonable provided cancer has been ruled out
Management of ASC-US
Pregnant women > 20 years
• Reflex HR-HPV testing
• Repeat cytology
• Colposcopy may be deferred until at least 6 weeks postpartum
• If colposcopy done, biopsy only lesions suspicious for invasive carcinoma

Management of LSIL in Pregnancy
• Colposcopy is preferred
  • Biopsy only lesions suspicious for invasive disease
  • ECC unacceptable
  • If no high grade lesions seen, repeat evaluation 6 weeks postpartum
  • If high grade lesion seen, repeating colposcopy periodically until delivery may be helpful
• Deferring colposcopy until 6 weeks postpartum is acceptable

Management of HSIL in Pregnancy
• Colposcopy necessary to rule out invasive disease
• Biopsy lesions with features that can not confidentially exclude invasive disease
• Endocervical curettage not acceptable
• If colposcopy satisfactory and no invasive disease
  • Repeat colposcopy and cytology in 8-12 weeks
  • Anticipate vaginal delivery
  • Repeat full evaluation at 8-12 weeks postpartum
  • If lesion resolved, repeat 2 tests Q 6 months for 2 years

Details of Management of Abnormal Cytology Tests During Pregnancy
• AGC and AIS
  • Colposcopy recommended
  • Cervical biopsy of suspicious lesions
  • HR-HPV testing preferred at time of colposcopy for AGC-NOS
• Endocervical curettage and endometrial biopsy are unacceptable
• Postpartum re-evaluation at 6 weeks

Physiologic Effects of Pregnancy
Colposcopic Challenges
• Cervical mucus obscures visualization
• Cervical hyperemia
• Gland prominence
• Eversion of columnar epithelium
• SCJ difficult to visualize early
  • Everts later
Management of CIN or AIS During Pregnancy: Considerations

- Risk of progression of CIN 2,3 to invasive cancer during pregnancy is minimal
- Rate of regression postpartum is relatively high
- Treatment of CIN during pregnancy is associated with:
  - Complications—bleeding, infection, abortion
  - High rate of recurrence/persistence
- CIN and AIS should not affect route of delivery


Natural History Dysplasia in Pregnancy

- 65 women followed postpartum
  - Remission 40.0%
  - Partial remission 4.6%
  - Persistence 26.2%
  - Progression 3.0%
  - 4.4% miscarried
  - 71.1% Delivered vaginally


Colposcopy Indicated For:

- ASC-US + HPV women over 25
- LSIL women over 25
- ASC-H women all ages
- HSIL women all ages
- AGC (with ECC +/- EMB)
- AIS (with ECC +/- EMB)

Ablation or Excision for:

- Histology of CIN2, CIN3, CIN2, 3 with adequate colposcopy

Repeat Co-Testing for:

- HPV ≥ + and cytology ≤ in ≥ 30 years
- Negative colposcopy in HPV+ ASC-US
- CIN1 in women < 25 years with “lesser abnormalities” pap
- Repeat co-testing in 3 years
- ASC-US with HPV
- Follow-up negative co-testing, negative colposcopy in HPV+, ASC-US

Treatment CIN1 Unacceptable:

- Pregnant women
- Women 21-24 years
Repeat Cytology Only

- Repeat cytology in 12 months
  - Women 21-24
  - ASC-US
  - LSIL

Diagnostic Excision Procedure

- HSIL with inadequate colposcopy
  - Except in pregnancy
  - Except in women 21-24