Updated ASCCP Guidelines

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At Harbor-UCLA Medical Center

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

Conflict of Interest Disclosure
Anita L. Nelson, MD

<table>
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<tr>
<th>Grants/Research</th>
<th>Bayer, Merck, Pfizer, Teva</th>
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Learning Objectives
At the end of this presentation, the participant will be able to:
- Explain rationale for current cervical cancer screening recommendations
- Outline evaluation needed for cytological abnormalities in different age women
- Determine therapy and follow up of histological abnormalities considering antecedent cytological abnormality and patient age

U.S. Incidence of Cervical Cancer
- In US in 2014, 12,360 new cases and 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%

HPV and Cervical Carcinoma
- Cervical cancer—first major solid tumor to be virally induced in essentially every case
- HPV DNA present in more than 99% of cervical cancer. Also in metastases
- HPV genes E6 and E7 integrated into host genome. Transforming proteins encoded by these genes are tumorigenic
- Persistent HPV infection is associated with high relative risk for SIL, particularly for HPV types 16 and 18

Risk Factors For Cervical Dysplasia and Cancer: Multiple Sexual Partners

<table>
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<tr>
<th>Number of Sexual Partners</th>
<th>Relative Risk Without Smoking</th>
<th>Relative Risk With Smoking</th>
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<tbody>
<tr>
<td>0-1</td>
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</tr>
<tr>
<td>2</td>
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<td>4.7</td>
</tr>
<tr>
<td>3-5</td>
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<td>10.8</td>
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<td>6+</td>
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Passive Smoke Exposure and Abnormal Cytology

- Women 18-55 (73% Hispanic)
  - Results adjusted for age, prior abnormal pap, number sex partners, etc.
- Passive smoke exposure OR = 1.70 [95% CI: 1.14 - 2.52]
  - 67% of women
- Current active smoker OR = 1.45 [95% CI: 1.0 - 2.04]
  - 15.7% of women

Passive smoking exposure higher in women with LSIL than in women with normal pap
- Only 60% of women with abnormal pap results return for evaluation

Natural Course of HPV Infection

First Lesion - Incubation (1-8 Mo.)
Imune Response - Active Growth (3-6 Mo.)
Host Containment (3-6 Mo.)
Late Stage - Sustained clinical remission
Persistency or recurrent disease

Prevalence of Minor Precursors, Major Precursors, and Invasive Cancer

Screening Recommendations

<table>
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<tr>
<th>Age/Condition</th>
<th>Screening</th>
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<td>&lt; 21</td>
<td>No Screening</td>
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<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>
<tr>
<td>After hysterectomy</td>
<td>No screening if no prior ≥ CIN 2 in prior 20 years</td>
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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
  - 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


Unsatisfactory Cytology Tests

- With no, unknown or negative HPV test
- Repeat cytology testing in 2-4 months
- Special case: Women over 30 with + HPV
  - 2 Options
    - Repeat cytology in 2-4 months
    - Colposcopy
  - If 2 unsatisfactory cytology tests, coloscopy


Absent of Insufficient Endocervical Transformation Zone

- Negative Cytology test
  - Age 21-29, routing screening
  - ≥ 30 with no or unknown HPV
    - HPV testing preferred*
    - Repeat cytology in 3 years ok
  - Even women with past treatment high grade abnormalities, no increase in risk of high grade abnormalities

*See HPV cotesting follow up


Cotesting Women >30 Cytology Negative, HPV Positive

- Two options: (both acceptable)
  - Option 1: Repeat cotesting in 1 year
    - In both negative, repeat cotesting in 3 years
    - If either positive, colposcopy
  - Option 2: genotyping
    - If 16, 18, colposcopy
    - If no 16, 18, repeat cotesting in 1 year
    - See option 1 for follow-up


ASC-US Women > 25 Years

- Two options:
  - Option 1: (preferred): HPV testing reflex
    - If positive – colposcopy as with LSIL
    - If negative – repeat cotesting 3 years
  - Option 2: (acceptable): Repeat cytology 1 year
    - If positive – colposcopy
    - If negative – return to regular testing

ASC-US 21-24 Years
LSIL 21-24 Years

- Two options:
  1. Repeat cytology in 12 months (preferred)
     - If ASC-H, AGG or HSIL, coloscopy
     - In negative, ASC-US, LSIL - repeat cytology 12 months X 2
     - If ≥ ASC in either test, coloscopy
     - If negative X 2, routine screening
  2. Refer HPV testing (acceptable ASC-US only)
     - If positive - repeat cytology in 12 months
     - If negative - routine screening

ASC-H or HSIL

- Colposcopy is recommended
- HPV testing no recommended
  - Colposcopic directed biopsy
    - ECC recommended in nonpregnant
  - Women > 25 with HSIL
  - May have immediate LEEP

AGC and AIS

- All subtypes except atypical endometrial cells
  - Colposcopy with ECC
  - EMB (if ≥ 35 or endometrial cancer risk factor)
- Atypical endometrial cells
  - EMB + ECC
  - Colposcopy if no endometrial pathology

Putting It All Together

- Management of histological abnormalities depends upon
  - Patient age
  - Preceding pap smear
  - "Lesser abnormalities"
    - HPV 16 or HPV 18
    - Persistent untyped high risk HPV
  - ASC-US
  - LSIL

CIN 1* or No Lesion

- Age ≥ 25 with lesser abnormalities
  - Cotesting at 1 year
    - If both negative - age appropriate retesting 3 years
    - If testing negative - routine testing
    - If either positive - coloscopy
    - If CIN 1 persists – may treat or continue to follow
  - Diagnostic excisional procedure
    *Adequate colposcopy required
**CIN 1* No Lesion**

- Age 21-24 with lesser abnormalities
  - Repeat cytology at 1 year
    - If ASC-H, HSIL or greater, colposcopy
    - If ≤ ASC - repeat cytology at 2 years
    - If ≥ ASC at 2 years - colposcopy
    - If 2 negative cytology - routine screening
  *Adequate colposcopy

**CIN 1* Age 21-24 with ASC-H or HSIL

- Do not treat
- Repeat cytology and colpo Q 6 months for 24 months
  - If > CIN1 - treat
  - If HSIL or colpo persists ≥ 1 year - biopsy
  - If HSIL persists 24 months with normal biopsy - excisional procedure
  - If colpo inadequate or +ECC - excisional procedure
  *Adequate colpo and negative ECC required

**CIN1 or No Lesion Age >24 with ASC-h or HSIL, etc.

- Review cytology and biopsy specimen
  2 options:
    - Diagnostic excisional biopsy
    - Repeat testing at 12 and 24 months
      - If both negative at each time - retest in 3 years
      - If any test is abnormal - colposcopy
      - If repeat HSIL - diagnostic excisional biopsy
    - Also consider Lugol's solution with acetic acid to cervix and vagina
  *Adequate colposcopy and negative ECC

**CIN 1 on ECC

- With lesser pap, ≤ CIN1 on biopsy
  - Treat as if CIN 1, but add repeat ECC at 12 months
- With ASC-H, HSIL or AGC or ≥ CIN2
  - Treat according to abnormality
    - If conservative management, add repeat ECC

**CIN2, CIN3, CIN2,3

- Older women, nonpregnant with adequate colposcopy and ECC ≤ CIN1
  - Excision or ablation acceptable
  - Choose excision if
    - Inadequate colposcopy
    - ECC ≥ CIN2 or ungraded
  - Hysterectomy is unacceptable as primary therapy

**CIN2, CIN3, CIN2,3

- "Young" women with a adequate colposcopy - 2 options:
  - Repeat testing colposcopy + cytology Q6 months X 2 (if CIN2, preferred)
    - If colposcopy worsens or HSIL/colposcopy lesion persists 12 months - repeat biopsy
    - If CIN2, CIN, CIN2,3 persists 2 years – treat
    - If cytology negative *2, cotest at 24 months
    - If both negative – repeat cotest in 3 years
    - If any test positive - colposcopy

# Monitoring After Treatment ≥CIN2
- Cotesting at 12, 24 months
  - If all results negative - retest in 3 years
  - If any test positive - colposcopy with EC
  - Routine screening recommended for at least 20 years
- HIV infected women
  - After 2 negative co-tests - annual cytology

# AIS on Diagnostic Excision
- Hysterectomy preferred if childbearing complete
- Conservative management if desires fertility
  - If margin or ECC positive, 2 options:
    - Re-excision
    - Re-evaluate at 6 months with cotesting - colposcopy, ECC

# Positive Margin on Excisional Biopsy
- ≥ CIN2 on cone biopsy or ECC, 2 options:
  - Cytology + ECC at 4-6 months (preferred)
  - Repeat diagnostic excision (acceptable)
  - Hysterectomy or repeat diagnostic excision acceptable if recurrent or persistent ≥ CIN2

# CIN in Pregnancy
- ASC-US: Same as nonpregnant except defer colpo until 6 weeks postpartum (acceptable)
  - If no cytological, histological or colposcopic suspicion ≥ CIN2 - defer until postpartum
- LSIL – colpo preferred for women > 25
  - Maybe deferred until 6 weeks postpartum
  - No ECC
  - If no cytological, histological, or colposcopy suspected ≥ CIN2 - defer until postpartum

# Summary Recommendations: Level A
A. For women with ASC-US cytology test results, reflex HPV testing is preferred (unless <25)
B. For women with HPV-positive ASC-US, whether from reflex HPV testing or co-testing, colposcopy is recommended.
C. For women with LSIL cytology test results and no HPV test or a positive HPV test result, colposcopy is recommended.
D. For women with a histologic diagnosis of CIN2, CIN3, CIN2,3 and adequate colposcopic examination, both excision and ablation are acceptable treatment modalities, except in pregnant women and young women.
Summary Recommendations: Level B

A. For women 30 years of age and older with HPV-positive but cytology-negative co-test results, repeat co-testing at 1 year is acceptable. For women with HPV-negative ASC-US, whether from reflex HPV testing or co-testing, repeat co-testing at 3 years is recommended.

B. When colposcopy does not identify CIN in women with HPV-positive ASC-US, co-testing at 12 months is recommended. If the co-test result is HPV-negative and cytology negative, return for age-appropriate testing in 3 years is recommended.

C. For women aged 21-24 years with ASC-US cytology test results, cytology testing along at 12-month intervals is recommended. Colposcopy is not recommended.


Summary Recommendations: Level B, con’t

D. For women aged 65 years and older, HPV-negative ASC-US test results should be considered abnormal when considering discontinuation of screening.

E. For women aged 21-24 years with LSIL cytology test results, follow-up with cytology testing at 12-month intervals is recommended. Colposcopy is not recommended.

F. For pregnant women with LSIL, colposcopy is preferred.

G. For women with ASC-H cytology test results, colposcopy is recommended regardless of HPV result. Reflex HPV testing is not recommended.

H. For women with HSIL cytology test results, immediate LEEP or colposcopy is acceptable, except in special populations.


Summary Recommendations: Level B, con’t

I. A diagnostic excisional procedure is recommended for women with HSIL cytology test results when the colposcopic examination is inadequate, except during pregnancy.

J. For women aged 21-24 years with ASC-H or HSIL test results, colposcopy is recommended. Immediate treatment (ie, see-and-treat) is unacceptable.

K. For women with all subcategories of AGC and AIS except atypical endometrial cells, colposcopy with endocervical sampling is recommended regardless of HPV test result. Endometrial sampling is recommended in conjunction with colposcopy and endocervical sampling in women 35 years of age and older with all subcategories of AGC and AIS.


Summary Recommendations: Level B, con’t

L. No further evaluation is recommended for asymptomatic premenopausal women with benign endometrial cells, endometrial stromal cells, or histiocytes. For postmenopausal women with benign endometrial cells, endometrial assessment is recommended regardless of symptoms.

M. For women aged 25 years and older with CIN 1 or no lesion preceded by “lesser abnormalities,” co-testing at 1 year is recommended. If both the HPV test and cytology test results are negative, then age appropriate retesting 3 years later is recommended. If all test results are negative, considering discontinuation of screening.


Summary Recommendations: Level B, con’t

N. When CIN 1 is detected on endocervical sampling after lesser abnormalities but no CIN2+ is detected colposcopically directed biopsies, management should follow ASCCP management guidelines for CIN 1, with the addition of repeat endocervical sampling in 12 months.

O. For women aged 21-24 years with CIN 1 after an ASC-US or LSIL cytology test result, repeat cytology testing at 12-month intervals is recommended. Follow-up with HPV testing is unacceptable.


Summary Recommendations: Level B, con’t

P. Regardless of antecedent cytology test results, treatment of CIN 1 in women aged 21-24 years is not recommended.

Q. Treatment of pregnant women for CIN 1 in unacceptable.

R. Hysterectomy is unacceptable as primary therapy for CIN 2, CIN 3, or CIN 2,3.

S. For women treated for CIN 2, CIN 3, or CIN 2,3, co-testing at 12 months and 24 months is recommended. If both co-test results are negative, retesting in 3 years is recommended. If any test result is abnormal, colposcopy with endocervical sampling is recommended. If all test results are negative, routine screening is recommended for at least 20 years, even if this extends screening beyond 65 years of age.
Summary Recommendations: Level C

A. For women with an unsatisfactory cytology test result and no, unknown, or a negative HPV test result, repeat cytology testing in 2-4 months is recommended.

B. For women aged 21-29 years with negative cytology test results and absent or an insufficient endocervical-transformation zone component, routine screening is recommended. For women aged 30 years and older with cytology test results reported as negative and with an absent or insufficient endocervical-transformation zone component and no or unknown HPV test result, HPV testing is preferred.

C. Acceptable options for the management of postmenopausal women with LSIL and no HOP test include obtaining HPV testing, repeat cytology testing at 6 months and 12 months, and colposcopy.

D. For women aged 21-24 years with HSIL cytology test results, when CIN 2+ is not identified on histology testing, observation for up to 24 months using both colposcopy and cytology testing at 6-month intervals is recommended, provided the colposcopic intervals is recommended. In this circumstance, it is acceptable to review the cytologic, histologic, and colposcopic findings.

E. When CIN 2+ is not identified on histologic testing, either a diagnostic excisional procedure or observation with co-testing at 12 months and 24 months is recommended, provided in the latter case that the colposcopic examination is adequate and the endocervical sampling is negative. In this circumstance, it is acceptable to review the cytologic, histologic, and colposcopic findings.

F. For women aged 21-24 years with CIN 1 or no lesions after an ASC-H or HSIL cytology test result, observation for up to 24 months using both colposcopy and cytology testing at 6-month intervals is recommended, provided the colposcopic examination is adequate and endocervical assessment is negative.

G. If CIN 2, CIN 3 or CIN 2,3 is identified at the margins of a diagnostic excisional procedure or in tan endocervical sample obtained immediately after the procedure, reassessment using cytology testing with endocervical sampling at 4-6 months after treatment is preferred.

H. For young women with a histologic diagnosis of CIN 2,3 not otherwise specified, either treatment or observation for up to 12 months using both colposcopy and cytology testing at 6-month intervals is acceptable, provided the colposcopy finding is adequate. When a histologic diagnosis of CIN 2 is specified for a young woman, observation is preferred but treatment is acceptable. Hysterectomy is preferred for women who have completed childbearing and have a histologic diagnosis of AIS on a specimen from a diagnostic excisional procedure.

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:

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<th>Placebo</th>
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<td>Reduced to ≤ CIN 1</td>
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<tr>
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<td>Complete remission HPV-16</td>
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