Cervical Cytology Screening: The Impact of the New ACOG Guidelines

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DISCLOSURE STATEMENT

• I have no real or perceived commercial interests that relate to this presentation nor do I have any relationships with pharmaceutical companies, biomedical device manufacturers, and/or other corporations whose products or services are related to pertinent therapeutic areas.

• I am on the Board of Directors for the American Society for Colposcopy and Cervical Pathology (ASCCP) and lecture on this and related subjects for them and other academic and professional organizations.
Objectives

• List three ways current screening and management guidelines treat adolescents different from older women.

• Discuss the rationale for no longer performing Pap test annually.

• Appropriately manage women whose Pap test is negative but who test positive for high-risk HPV.
Case 1: A 16 year old G0, sexually active for 3 years. She’s had four sexual partners. She presents for contraceptive counseling.

How will you assess her this visit?

A. Pap test / GC, Chlamydia with Pap / Pelvic exam
B. Pap test / Pelvic exam / Urine for GC, Chlamydia
C. No Pap test / Pelvic exam / Urine for GC, Chlamydia
D. No Pap / No pelvic exam / Urine for GC, Chlamydia
Wait a second, Do you mean she’s been sexually active since age 13?

- 27% of 9th grade girls (age 14-15) admit to having had sexual intercourse
  - 5.5% have had sex with four or more partners
- 4.9% had first intercourse before age 13

*CDC Youth Risk Behavior Surveillance, United States 2007  MMWR. 2008;57 No.SS-4*
Cervical Cytology Screening
ACOG Practice Bulletin #109
Summary of Recommendations

• Begin cervical cancer screening at age 21
  – Avoid screening before age 21.
  – “…earlier screening may lead to unnecessary and harmful evaluation and treatment in women at very low risk of cancer.”

Based on good and consistent scientific evidence - Level A
But we've always timed Pap testing with the onset of intercourse. Aren't we putting young women at risk by disregarding when they first had sex?
Before we discuss this one, let’s look at the risk of HPV and cancer, and the natural history of dysplasia in adolescents.
Adolescents and young women acquire HPV very efficiently.

- A 2007 NHANES survey found 24.5% of adolescents aged 14-19 positive for HPV and 17.5% positive for high risk HPV.
- 44.8% of women aged 20-24 tested positive for HPV.
  - 28% positive for high risk types.

Dunne et.al. JAMA 2007;297:813-819
Adolescents and young women acquire HPV very efficiently.

- A university based study in Washington State followed 603 women from their act of sexual intercourse and found that by 12 months, 30% had been HPV positive at least once
  - 40% by 24 months
  - 50% by 48 months

Winer Am J Epidemiol 2003
A New Paradigm for Cervical Screening in Adolescents

• HPV is widespread in adolescents
Young women are also very efficient at clearing the infection
Ho et.al. NEJM 1998;338:423-8

• Median duration of incident HPV infection: 8 months
  – 70% no longer infected by 12 months
  – 81% no longer infected by 24 months
Invasive Cervical Cancer is Exceedingly Rare in Adolescents

Age-specific incidence of invasive cervical cancer per 100,000 women – 1992-2008

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Incidence</th>
</tr>
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<tbody>
<tr>
<td>0-14 years</td>
<td>0</td>
</tr>
<tr>
<td>15-19 years</td>
<td>0.24</td>
</tr>
<tr>
<td>20-24 years</td>
<td>1.81</td>
</tr>
<tr>
<td>25-29 years</td>
<td>6.02</td>
</tr>
</tbody>
</table>

Invasive Cervical Cancer in Adolescents (Age <21)

- 0.1% of cervical cancers in U.S.
- Rate ~1/1,000,000 adolescents
- Ave 14 cases per year in 15-19 year olds.
  - Too rare to report under age 15
  - Rate unchanged between 1973-77 and 1998-2006
- Recommendation to start screening at age 18 or with onset of intercourse made in 1980s

Moscicki, Cox, et al J Lower Genital Tract Dis 2010;14:74
(Data from SEER and CDC)
Rate of Progression, CIN 3 to Cancer

• Increases with age
  – Age 80: 10% per year
  – Age 20-24: 0.5% per year
  – Adolescents: negligible
A New Paradigm for Cervical Screening in Adolescents

- HPV is widespread in adolescents
- Cervical cancer is very rare in adolescents
The Pap May Be Less Protective at Younger Ages

- Large British study looked at odds of developing cancer based on whether or not women had Pap in prior 3 yr interval
  - “Cervical screening in women ages 22-24 had little or no impact on the rates of invasive cervical cancer up to age 30”
  - No data showing screening women less than 21 years old impacts future rates of CIN 2,3
    - Moscicki, Cox J Lower Genital Tract Dis 2010;14:73-80
• Avoid screening before age 21”
  — “...may lead to unnecessary and harmful evaluation and treatment in women at very low risk of cancer.”

• Critical that sexually active adolescents be counseled and tested for STDs and counseled regarding sex and contraception.
  — “…may be carried out without cervical cytology screening and in the asymptomatic patient, without the use of a speculum.”
Case 2: A 17 year old G0, sexually active for 4 years, has ASC-US on a Pap test performed by your colleague. Now, what should you do?

A. Triage based on Reflex HPV result
B. Immediate colposcopy
C. Repeat the Pap test in 6 and 12 months
D. Repeat the Pap test in one year
Why not do “Reflex” HPV DNA testing in adolescents?

Sherman, J Natl Cancer Inst 2002;94:102-7

• NCI ALTS study
• Proportion of women with ASCUS who tested positive for HR HPV varied widely with age.

• Overall: 56%
• Age >29: 31%
• Ages 23-28: 65%
• Ages 18-22: 71%

• Unacceptably high percentage of younger women would be referred to colposcopy.
Why not do “Reflex” HPV DNA testing in adolescents?

Boardman, Obstet Gynecol 2005;105;741-6

• 530 women with ASC-US and known high-risk HPV results
  • 359 (67%) HR HPV positive
    • Age >25: 59% positive
    • Age <20: 77% positive

P<.01
So, adolescents with ASC-US are so likely to be HPV positive that reflex testing is not an efficient way to triage who should have colposcopy. In fact if HPV is ordered in a woman under age 21, the result should be disregarded.
OK, So how do we manage this 17 y.o. with ASC-US??
Not so fast. First we need to consider the natural history of dysplasia in adolescents.
LSIL has a very high spontaneous regression rate in adolescents.

- **Winer et al. JID 2005**
  - 112 women 18-20 y.o. (mean age 19.2) followed q 4 months X 4 yrs
  - 96 (85.7%) cleared spontaneously over 4 yrs
  - Median time to clearance 5.5 months
  - 10 (8.9%) developed CIN 2-3

- **Moscicki et.al. Lancet 2004**
  - 187 young women aged 18-22 with LSIL
  - 61% regressed over first year
  - 91% regressed by 3 years
  - 3% progressed to CIN 3
CIN 2 also tends to regress in adolescents and young women.

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Age</th>
<th>Mean f/u</th>
<th>Regression to neg</th>
<th>Progression to CIN3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moore</td>
<td>23</td>
<td>≤ 21</td>
<td>18 mo</td>
<td>65%</td>
<td>13%</td>
</tr>
<tr>
<td>Fuchs</td>
<td>36</td>
<td>≤ 21</td>
<td>378 days 3 Yrs</td>
<td>39% 75%</td>
<td>8%</td>
</tr>
<tr>
<td>Moscicki</td>
<td>95</td>
<td>13-24</td>
<td>1 yr 2 yr 3 yr</td>
<td>38% 63% 68%</td>
<td>2% 12% 15%</td>
</tr>
</tbody>
</table>

No cases progressed to cancer in any study.

Fuchs J et.al. Ped Adolesc Gynecol 2007;20:269-74
Moscicki AB et.al Obstet Gynecol 2010;116:1373-80
A New Paradigm for Cervical Screening in Adolescents

- HPV is widespread in adolescents
- Cervical cancer is very rare in adolescents
- Most SIL regresses spontaneously in adolescents.
Obstetric Outcomes after LEEP: Results of two meta-analyses

- Significant increase in
  - Late preterm births (>32 / 34 wks)
  - pPROM
  - Low birth weight infants

- No significant increase in
  - Preterm births <32/34 weeks
  - Cesarean section
  - NICU admissions
  - Perinatal mortality

M Arbyn et.al. BMJ 2008;337: a1284
A New Paradigm for Cervical Screening in Adolescents

- HPV is widespread in adolescents
- Cervical cancer is very rare in adolescents
- Most SIL regresses spontaneously in adolescents.
- Treatment of cervical dysplasia is associated with perinatal risk.
A New Paradigm for Cervical Screening in Adolescents

- HPV is widespread in adolescents
- Cervical cancer is very rare in adolescents
- Most SIL regresses spontaneously in adolescents.
- Treatment of cervical dysplasia is associated with perinatal risk.
- How can we combine these concepts and devise a screening strategy that prevents cancer, protects the cervix, and reduces the anxiety, discomfort, and cost of doing colposcopy in adolescents?
How about if we delay the first Pap test until age 21?
But if a Pap is done, be conservative in your management.
ACOG and ASCCP Recommended Management of Adolescents (<21) with ASC-US or LSIL on Pap.

- Repeat cytology twice at 12 month intervals
  - At 12 months
    - Colposcopy if HSIL or worse
    - If Pap is <HSIL, repeat cytology again in 12 months
  - At 24 months
    - Colposcopy if ≥ASC-US
- If both Paps are negative, return to routine screening

www.asccp.org
Management of Adolescents (<21) and Young Women with CIN 2 on Biopsy

- If colposcopy is satisfactory
  - Conservative management is preferred
    - Cytology and colposcopy q 6 months for up to 2 years
    - Excision if CIN 3 or unsatisfactory
  - Treatment is acceptable
- If colposcopy is unsatisfactory or CIN 3
  - Excision
- If biopsy “CIN 2,3”
  - Either conservative management or treatment acceptable

www.asccp.org
Case 3: A 25 y.o. woman has had negative Pap tests every year for the past 3 years. Her clinic only used conventional Pap tests. Her last Pap was 1 year ago. She has transferred her care to you.

What will you do regarding cervical cancer screening this visit?

A. Another conventional pap test
B. A liquid based Pap test with reflex HPV DNA testing
C. A liquid based Pap test plus HPV DNA co-testing
D. No Pap test until next year.
Cervical Cytology Screening
ACOG Practice Bulletin #109
Summary of Recommendations

• Screening recommended every 2 years between age 21 and 29

Based on good and consistent scientific evidence - Level A
Both liquid-based and conventional methods of cervical cytology are acceptable.

Based on good and consistent scientific evidence - Level A
Meta-analysis Comparing Liquid-based and Conventional Pap Tests
Arbyn et al Obstet Gynecol 2008 111:167-77

• Eight studies- Pooled data
• Cytology threshold ASC-US+ to detect histologic CIN 2 +
• No difference in sensitivity
  – Liquid based 90.4 (CI 82.5-95.0)
  – Conventional 88.2 (CI 80.2 -93.2)
• No difference in specificity
  – Liquid based 64.6 (CI 50.1-76.8)
  – Conventional 71.3 (CI 58.3-81.6)
• Relative specificity of liquid based cytology lower at ASC-US threshold (LB/C)
  – 0.91 (CI 0.84-0.98)
Why not Pap plus HPV co-testing?

- HPV DNA testing not FDA approved for use in screening with Cytology before age 30
- Unacceptable false positive rate < age 30
  - Prevalence of HR HPV peaks ages 20-24
    - 20-24%
Case 4: Her 44 y.o. mother is your next patient. All her Paps have been negative except for one LSIL in her 20s. Today’s report is also negative. When should she have her next Pap test?

A. One year
B. Two years
C. Three years
D. Two or three years
Cervical Cytology Screening
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Summary of Recommendations

• Screening recommended every 2 years between age 21 and 29
• Interval may be extended to every three years aged 30 and older
  – Provided
    • 3 consecutive negatives
    • No history of CIN 2 or 3
    • HIV negative, not immunocompromised
    • Not DES exposed in utero
Wait a second! Does this mean the annual Pap test is dead??
How much protection do we lose by not doing Pap tests every year?

- Percentage reduction in rate of invasive cervical cancer in cohort of women aged 35 - 64 with different frequencies of screening
  - Assumes at least negative Pap prior to age 35
  - Next Pap 1 yr: 93.5%
    - 30 Paps required over 30 years
  - Next Pap 2 yrs: 92.5%
    - 15 Paps required over 30 years
  - Next Pap 3 yrs: 90.8%
    - 10 Paps required over 30 years
  - Next Pap 5 yrs: 83.6%
    - 8 Paps required over 30 years

IARC Br. Med Jl. 293:1986
Are we missing cancers by not screening every year?

- Markov model based on NBCCEDP data
- Assumed $\geq 3$ prior consecutive negative Paps
- Cancers prevented by doing Pap annually instead of every 3 years
  - Age 30 – 44: 3 / 100,000 women
  - Age 45 – 59: 1 / 100,000 women
- Additional tests needed to find each incremental cancer
  - Age 30 – 44: 69,665 Paps plus 3,861 colpos
  - Age 45-59: 209,324 Paps plus 11,502 colpos

Sawaya et.al. NEJM 2003;349:1501-9
Why screen every 3 years after age 30 instead of every 2-3 years?

• Low risk of developing CIN 3 or cancer within 3 years of negative Pap in women with multiple previous negatives.
  – In women aged 30 – 64 with \( \geq 3 \) prior consecutive negative paps, risk of CIN 3 in next 3 yrs = 0.019%  
    • Sawaya et al NEJM 2003;349:1501-9

• No difference in relative risk of cancer with screening at 2 vs 3 yr intervals.
  – Miller et al Obstet Gynecol. 2003; 101:2-37

• Screening at 3 year intervals in women with prior negative screening most cost-effective strategy  
Case 5: A 46 year old presents for her annual exam. One year ago, her Pap and HR HPV test were both negative.

What will you do regarding cervical cancer screening this visit?

A. A Pap test
B. A Pap test with HR HPV testing
C. HPV testing alone
D. No cervical cancer screening this visit
Negative Predictive Value of Cytology, HPV DNA Testing, and Pap plus HPV Combined

- Cohort of 20,810 women followed for up to 122 months
- Negative Predictive Value for CIN 3+ after 45 months
  - Pap alone 99.47
  - HPV DNA 99.76
  - Pap + HPV 99.84

Sherman et.al. JNCI 2003;95:46-52
A negative HPV DNA test offers better protection after 6 years than a negative Pap does after 3 years.

- Joint European Cohort Study compared HPV testing with conventional Pap in 6 countries
- N=24,295

<table>
<thead>
<tr>
<th></th>
<th>3 yrs</th>
<th>4 yrs</th>
<th>5 yrs</th>
<th>6 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pap –</td>
<td>0.51%</td>
<td>0.69%</td>
<td>0.83%</td>
<td>0.97%</td>
</tr>
<tr>
<td>HPV-</td>
<td>0.12%</td>
<td>0.19%</td>
<td>0.25%</td>
<td>0.27%</td>
</tr>
</tbody>
</table>

Dillner, J. et al. BMJ 2008;337:a1754
She is screened again three years after her negative Pap and HPV. This time the Pap is negative, but the HPV is positive.

Now how would you manage her?

A. Repeat Pap and HPV in 3 years
B. Repeat Pap and HPV in 1 year
C. Order HPV 16/18 assay
D. Colposcopy with biopsy as indicated
How often is the HPV test positive when the Pap is negative?

- Review of 580,289 women in prepaid health plan with negative cytology and positive HPV
- Occurred in 4% of cases overall
  - Varied by age
    - Age 30-34: 6.8%
    - Age 40-44: 3.81%
    - Age 50-54: 2.89%
    - Age 60-69: 2.6%
    - Age 70-74: 2.94%

Castle et al. Obstet Gynecol 2009;113:595-600
If the Pap is negative, what is the impact of a positive HPV DNA test?

- Cohort of 20,810 women followed for up to 122 months Pap negative HPV positive at baseline
  - Cumulative incidence of CIN 3+
    - After 39 months: 3%
    - After 120 months: 5%

  *Sherman et.al. JNCI 2003;95:46-52*

- Subsequent analysis selected out HPV 16/18 positive
  - Cumulative incidence of CIN 3+
    - After 39 months HPV 16 and/or 18+: 12%
    - After 122 months HPV 16+: 21% / HPV 18+: 17%
      - HPV + non 16/18 types: 2%

  *Khan et al., JNCI, 2005*
HPV Type does make a difference.

1,222 Danish women, ave age 28 yrs followed 14.3 yrs.
– Cytology negative at baseline

<table>
<thead>
<tr>
<th>HPV Type at Baseline</th>
<th>CIN 3+ within 12 yrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>26.7%</td>
</tr>
<tr>
<td>18</td>
<td>19.1%</td>
</tr>
<tr>
<td>31</td>
<td>14.3%</td>
</tr>
<tr>
<td>33</td>
<td>14.9%</td>
</tr>
<tr>
<td>HR HPV not 16,18,31,33</td>
<td>6.0%</td>
</tr>
<tr>
<td>HR HPV negative</td>
<td>3.0%</td>
</tr>
</tbody>
</table>

• If HPV 16 positive X2, 2 yrs apart- risk of CIN 3+ 47.4%
  – CIN 2+ 50.9%

Kjaer SK et al JNCI 2010;109:1478-88
Wouldn’t it be neat if there was a test you could do to look for just HPV 16 and 18 instead of the whole pool of 13 or 14 types?
There are two HPV16/18 diagnostic tests. FDA approved March 2009 and April 2011

- Recommended for use:
  - When screening with Pap test plus HPV test that includes 13 or 14 high-risk types

Cytology Negative, HR HPV Positive

- HPV 16/18 Positive
  - Colposcopy

- HPV 16/18 Negative or not available
  - Repeat Pap plus HR HPV Test in One Year
When the algorithm calls for repeating cytology and HR HPV* in 12 months.

- If HPV still positive, then Colposcopy

**If HPV Negative and...**

- Cytology LSIL+, then Colposcopy
- Cytology ASC-US, then Repeat Pap in one year
- Cytology negative, then Repeat Pap in 3 years

*HR HPV is test for 13-14 HR types*
Would these new tests for HPV 16/18 be helpful in triaging ASC-US?

<table>
<thead>
<tr>
<th></th>
<th>HPV 16/18 +</th>
<th>HPV + (16/18 -)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute risk (Cross sectional)</td>
<td>24.4%</td>
<td>8.6%</td>
</tr>
<tr>
<td>2 year cumulative risk</td>
<td>40%</td>
<td>20%</td>
</tr>
</tbody>
</table>

- Most of risk is from HPV 16

ASCCP: since risk of CIN 2+ with HPV +/16/18 – is high enough to warrant colposcopy, use of 16/18 genotyping not recommended as ASC-US triage.

Stoler et al. More aggressive post-colposcopy follow-up may be justified if colposcopy neg but positive for HPV 16.

ASCCP.org 2009
In the future, look for broader applications of type specific HPV genotype testing, and probably new tests as well.
Those are some of the newer features of the ACOG and ASCCP Pap guidelines
The changes are designed to maintain the benefits of prior regimens and minimize risks:
- Anxiety
- Expense
- False positives
- Morbidity from overtreatment
References

ACOG Practice Bulletin No. 109 Cervical Cytology Screening (December, 2009)

ACOG Practice Bulletin No. 99 Management of abnormal cervical cytology and histology (December, 2008)

Algorithms available at: www.asccp.org