

Cervical Cytology Screening: Navigating the ACOG and ASCCP 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

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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 have had sexual intercourse
 - 5.5% have had sex with four or more partners
- 4.9% had first intercourse before age 13

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.

Prevalence of HPV Infection – U.S. Females

Dunne et.al. JAMA 2007;297:813-819

HPV Infection from Time of First Sexual Intercourse

Winer Am J Epidemiol 2003

A New Paradigm for Cervical Screening in Adolescents

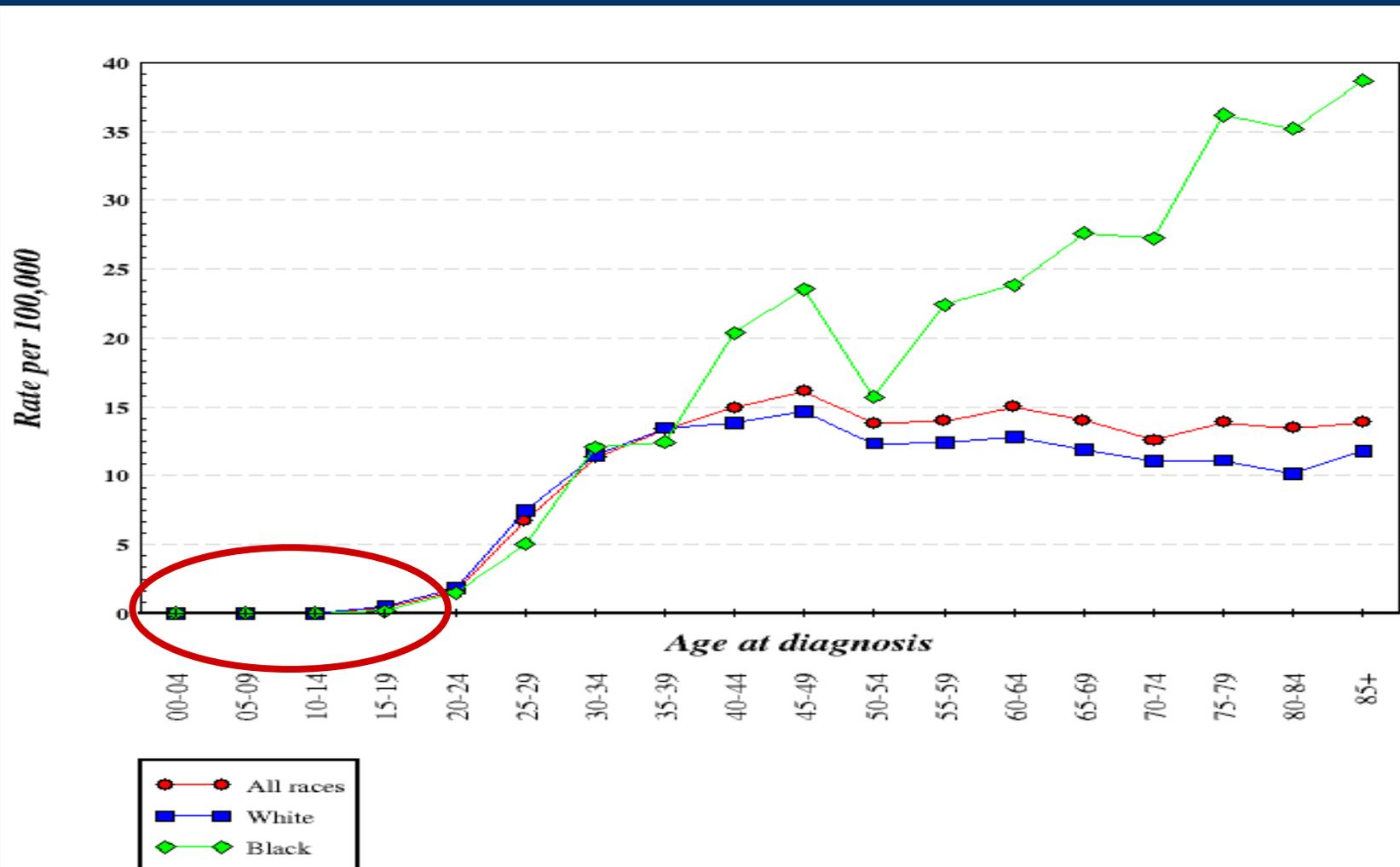
- HPV is widespread in adolescents

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



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

Rate of Progression, CIN 3 to Cancer

Moscicki, Cox, et al J Lower Genital Tract Dis 2010;14:73-80

- 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”
 - Sasieni P et.al BMJ 2009:339
 - 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

Cervical Cytology Screening

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Summary of Recommendations

- 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.”

Based on limited and inconsistent scientific evidence - Level B

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

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?

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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

What happens when adolescents get LSIL?

187 women aged 18-22 with LSIL followed without treatment

61% regressed in one year



91% regressed by three years

Only 3%
progressed
to CIN 3

Moscicki, *Lancet* 2004;364:1678-83

CIN 2 also tends to regress in adolescents and young women.

Author	N	Age	Mean f/u	Regression to neg	Progression to CIN3
Moore	23	≤ 21	18 mo	65%	13%
Fuchs	36 32	≤ 21	378 days 3 Yrs	39% 75%	8%
Moscicki	95	13-24	1 yr 2 yr 3 yr	38% 63% 68%	2% 12% 15%

No cases progressed to cancer in any study.

Moore K. et.al. Am J Obstet Gynecol 2007;197:141.e1-6

Fuchs J et.al. Ped Adoles 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 Kyrgiou, et al. Lancet 2006;367:489-498
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 \geq ASC-US
 - If both Paps are negative, return to routine screening

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

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.

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Summary of Recommendations

- Screening recommended every 2 years between age 21 and 29

Based on good and consistent scientific evidence - Level A

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Summary of Recommendations

- 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

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

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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

Based on good and consistent scientific evidence - Level A

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

Are we missing cancers by not screening every year?

- Markov model based on NBCCEDP data
- Assumed ≥ 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

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

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

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

Rate of CIN 3+ after baseline negative test

	<u>3 yrs</u>	<u>4 yrs</u>	<u>5yrs</u>	<u>6yrs</u>
Pap –	0.51%	0.69%	0.83%	0.97%
HPV-	0.12%	0.19%	0.25%	0.27%

Case 6. A 33 y.o. has Pap plus HPV co-testing. the Pap is negative, but the HPV is positive.

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

Case 6. A 33 y.o. has Pap plus HPV co-testing. the Pap is negative, but the HPV is positive.

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%

Her level of risk does not justify colposcopy.

5 yr cumulative risk of CIN 3+ in >300,000 women screened with Pap plus HPV cotesting .

Cumulative incidence of CIN 3+ reached 3.1% after 3 years, 5.9% after 6 years

We don't know what her prior screening was, but if 3 years previously she'd been both Pap and HPV negative, her risk would be even lower.

Cumulative incidence of CIN3+ after second visit in women negative for both HPV and Pap co-test at prior visit . If Pap negative / HPV +, risk of CIN 3+ = 1.8% after 3 years.

Fig. 3

Katki, Kinney, et al Lancet oncol.2011;12:663-72

ASSCP Recommendations for Management of HPV + / Pap Negative Patients

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



ASSCP Recommendations for Management of HPV + / Pap Negative Patients

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

There you have it!
Some of the newer
features of the *ACOG*
and *ASCCP* Pap guidelines

The guidelines 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