Cervical Cancer Prevention and Screening: Update 2010

Michael S. Policar, MD, MPH
Clinical Professor of Ob, Gyn, and RS
UCSF School of Medicine
policarm@obgyn.ucsf.edu

No commercial disclosures for this lecture

GUIDELINE SHOCK

- New guidelines released before older ones fully implemented
- May be the opposite of traditional practice
- Organizations may differ in content and timing
- Rationale often not well explained
- No one tells the consumer!!

The BIG Picture
ACOG Practice Bulletin No. 109, Dec 2009

- Half of women in whom cervical cancer is diagnosed each year have never had cervical cytology testing
  - Another 10% had not been screened within the 5 years before diagnosis
- One approach to reducing the incidence and mortality of cervical cancer is to increase screening rates among women who are not screened or screened infrequently
  - Women who are immigrants from countries where cervical cytology screening is not the norm are an especially high-risk group
The central purpose of screening is to detect high grade lesions (HSIL). Most LSIL, especially in young women, is due to acute HPV infection, which itself is not dangerous. >90% LSIL lesions resolve without treatment. Evaluate ASC, LSIL Paps because HSIL may exist. Focus on high grade lesions as progression to cancer is more likely, regression is less likely. Detect glandular lesions likely to progress.

Designing Pap Smear Intervals

- Screening interval depends upon:
  - Error rate of screening test
  - Progression rate of disease
- Cervical cancer risk factors don’t impact interval:
  - (Slow) rate of growth is the same, irrespective of behavioral risk factors
  - If rapid growth is more likely (HIV positive, immunocompromised), screen more often
- Balance of benefit (cancer prevention) and hazards (excess false positives → unnecessary treatment)

Cervical Cancer Screening

<table>
<thead>
<tr>
<th></th>
<th>ACS 2002</th>
<th>USPSTF 2003</th>
<th>ACOG 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiate Paps</td>
<td>SD + 3yrs or 21 yrs old</td>
<td>SD + 3yrs or 21 yrs old</td>
<td>21 yrs old</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>not recommended</td>
<td>not recommended</td>
<td>not recommended</td>
</tr>
<tr>
<td>(benign disease)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper age limit*</td>
<td>70 yrs old</td>
<td>65 yrs old</td>
<td>65-70 yrs old</td>
</tr>
<tr>
<td>Pap interval</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21-29 yrs old</td>
<td>annual (glass) Q2 yr (LBC)</td>
<td>at least every 3 years</td>
<td>every 2 years</td>
</tr>
<tr>
<td>≥ 30 yrs old</td>
<td>every 2-3 years at least every 3 years</td>
<td>every 3 years</td>
<td></td>
</tr>
</tbody>
</table>

* If 3 normal and no abnormal pap results in the prior 10 yrs
• SD: sexual debut (age at first vaginal intercourse)
• LBC: liquid based cytology
**Cervical Cytologic Screening Guidelines from the American College of Obstetricians and Gynecologists, 2009.**

<table>
<thead>
<tr>
<th>Age</th>
<th>Recommendation for Cytologic Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 21 yr</td>
<td>Avoid screening</td>
</tr>
<tr>
<td>21 to 29 yr</td>
<td>Screen every 2 yr</td>
</tr>
<tr>
<td>30 to 65 or 70 yr</td>
<td>May screen every 3 yr</td>
</tr>
<tr>
<td>Between 65 and 70 yr</td>
<td>May discontinue screening†</td>
</tr>
</tbody>
</table>

---

**Has Your Practice Adopted The 2009 ACOG Pap Guidelines?**

1. We have, and all clinicians are following them
2. We have, but they are followed inconsistently
3. We have discussed them but have taken no action
4. We have discussed them and have rejected them
5. There has been no discussion of this topic
6. Didn’t know that they existed

---

**Why Wait Until 21 To Start Paps?**

- Most HPV infections are transient
- In the few in whom HPV persists, the natural history of carcinogenesis is quite long
  - Detection of CIN 3 peaks in the late 20s and microinvasive cancer does not peak until early 40s
  - When CIN 3 persists, >10 years are required for the lesion to acquire the capacity to become invasive
- Spontaneous regression is common
  - 65% rate of regression of CIN 2 after 18 months; 75% after 36 months

---

**Why Wait Until 21 To Start Paps?**

- Invasive cervical cancer is a very rare event in women 15-19 years old. In the US from 1998-2006...
  - 14 cervical cancers annually
  - 1-2 cases per 1 million women
- In teens, *screening does not reduce mortality*
  - Cervical cancer rates have not changed since 1973-1977, before the recommendation to screen at 18 or first intercourse

---

ACOG Practice Bulletin No. 109, Dec 2009
Why Wait Until 21 To Start Paps?
- The adverse consequences of over-screening and over-management of adolescents who have CIN
  - Psychological effects of screening, abnormal results, and treatment, including effects on sexual function
  - Pregnancy outcomes following LEEP show a doubling or tripling of the rate of preterm birth
- Screening women under 21 may be harmful and lacks benefit
  - Don’t begin until 21, regardless of age of first intercourse

ACOG Practice Bulletin No. 109, Dec 2009

Pap Screening of Women 21 and Older
Cervical cancer screening is recommended
- Every 2 years for women aged 21-29
- Every 3 years for women 30 years and older if they...
  - Have had 3 consecutive negative cytology screening test results and no history of CIN 2-3, are not HIV-infected, are not immunocompromised, and were not exposed to DES in utero, OR
  - Received negative test co-test results on both cervical cytology screening and HPV DNA testing and are considered low risk

Discontinuation of Screening in Women with a Cervix
- Screening may be discontinued at age 70 years (ACS) or 65 years (USPSTF) in low risk women after 3 consecutive negative screening tests in the prior decade
- Continue routine cervical cytology examinations
  - Sexually active older women with multiple partners, as there is some risk for new HPV infection and CIN
  - Women with a previous history of abnormal cytology
- If discontinued, assess risk factors periodically to determine the need to reinitiate screening

Screening in High Risk Women
- Do not increase the screening interval beyond annual testing for women who are
  - HIV-positive
  - Immunosuppressed (e.g., transplant)
  - Were exposed in utero to diethylstilbestrol
- Follow guidelines for women who have been treated for CIN 2 or 3 or adenocarcinoma in situ

ACOG Practice Bulletin No. 109, Dec 2009
**Discontinuation of Screening in Women with Total Hysterectomy**

- If the hysterectomy was for benign indications and no history of high-grade CIN, discontinue routine screening.
- Women who had high-grade CIN lesions before hysterectomy can develop VaIN or carcinoma years later.
- If a history of CIN 2–3 cannot be documented, should continue to be screened even after their period of post-treatment surveillance.
- The screening interval may be extended; there are no good data to support or refute discontinuing screening.

**Most Cytopathology Laboratories Have Switched to LBC Because**

1. Liquid based cytology is more accurate than glass Pap smears and finds more HGSIL and cancer.
2. Collected specimens can be tested for a variety of pathogens.
3. They are easier for laboratory staff to process.
4. a. and b. are true.
5. b. and c. are true.
6. All are true.

**Is Liquid Based Cytology Better?**

- **Advantages**
  - Testing for HPV, GC, and Ct from the residual sample.
  - Cytotechnologists find liquid-based tests easier to read.
- **Disadvantages**
  - Higher cost.
  - Decreased specificity (more false positives).
- Whether LBC tests are more sensitive or specific is unclear.
  - A meta-analysis of 8 studies found no difference in sensitivity or specificity in diagnosing CIN 2+.
  - If the threshold for colposcopy was lowered to ASC-US, the LBC had a significantly lower specificity.
**Caveats**
- Inform women *in advance* of HPV screening
- Mgt of Pap neg/HPV pos women is uncertain
- Women who are Pap negative, HPV negative should be screened *no earlier* than 3 years

**Indications**
- Women 30 years old and older
- Immunocompetent
- Cervix in place

**HPV+Pap**
Wright, Obstet Gynecol 2004;103:304

**HPV+ Pap Co-testing: Concerns**
- For women who are HPV neg/Pap neg, and who are re-screened *earlier* than 3 years, there is risk of
  - More false positive tests, leading to unnecessary colposcopies, biopsies, and treatments
  - Default to a less cost-effective screening strategy ($2.215 million/year of life saved if done annually)
- Neither providers nor consumers have a motive to limit utilization as recommended by guidelines
- Most healthcare systems have no mechanism to enforce the guidelines unless a robust EMR is available

**Common Questions About Pap Intervals**
- Do virginal women need Pap smears?
- Are the intervals any different for women
  - With multiple sexual partners?
  - Using hormonal contraceptives, menopausal hormone therapy?
  - Who only have female partners?
  - Who are pregnant?
- If a Pap is *not* scheduled or necessary, what about the need to perform a bimanual pelvic exam?

**Implications of ACOG 2009 Guidelines**
In sexually active asymptomatic adolescents (under 21 years old), evidence-based screening (aka well-woman or annual) exams should consist of
- Blood pressure check, BMI, and PNP
- PNP= Pee, not Pap
- Pee: Chlamydia NAAT (PCR, LCR, etc)
- Pap: not until 21 years old
- Pelvic exam: not until 21 years old, unless symptomatic
2004 WHO Selected Practice
Recommendations for Contraceptive Use

- Not recommended as “contributing substantially to safe and effective use of contraceptive method”
  - Breast or genital tract examination
  - Cervical cancer screening
  - STI assessment or lab test screening
  - Hemoglobin determination
  - Other routine lab tests
- Blood pressure measurement before initiation of
  - OCs, POPs, DMPA, and implants

So What’s The Problem?

- Consumers either don’t know about the guidelines or believe that they are financially motivated
- Providers are...
  - Skeptical of abandoning Paps for their “girls” (under 21)
  - Fearful of encountering a patient with an interval cancer
  - Concerned that annual well-woman visits will be skipped
- When adopted, how to apply the “3 consecutive negative results” rule before extending the interval to 3 years
  - Can the patient’s history be trusted or must all negative Pap results be documented?

High Risk HPV DNA Testing
ASCCP Clinical Update 2009 @ ASCCP.org

Clinically useful for

- Primary screening (HPV+Pap), age 30 and over
- Triage of ASC-US or AGC Paps (≥ 21 years old)
- Postmenopausal women with LSIL
- Post-colposcopy and post-treatment follow-up, in lieu of Pap smears
- Triage of women who are HPV HR pos/Pap negative with HPV 16/18 genotyping (Cervista™ HPV 16/18)

High Risk HPV DNA Testing
ASCCP Clinical Update 2009

HR HPV testing and genotyping not recommended

- Any application in women under 21 years old
  - If inadvertently done, a positive result should not influence management
- (Reflex) triage of ASC-H, LSIL, HSIL Paps
- Routine screening in women before 30 years old
- In women considering vaccination against HPV
- For routine STD screening
- Evaluation of patients with genital warts
- Evaluation of sex partners
- As part of a sexual assault evaluation
How Can My Practice Prepare?

- Meet with your colleagues and determine the screening policies for your practice
  - All staff must be aware of the policy and follow it
- Inform your patients of changes that apply to them
  - During transition, leave decisions to patient
  - Educate patients with a personal letter or newsletter
- Verify prior negative Pap results rather than requiring that “3 consecutive negatives” occur in your practice
- Keep track of benefit changes made by your payers
  - Few have changed screening benefits yet

**HPV Vaccines**

<table>
<thead>
<tr>
<th>Brand name</th>
<th>HPV types</th>
<th>3 doses</th>
<th>Age range</th>
<th>US Licensure</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV4 Gardasil™ (Merck)</td>
<td>16, 18, 6, 11</td>
<td>0, 2, 6 mos</td>
<td>16-26</td>
<td>2006</td>
</tr>
<tr>
<td>HPV2 Cervarix™ (GSK)</td>
<td>16, 18</td>
<td>0, 1, 6 mos</td>
<td>15-25</td>
<td>2009</td>
</tr>
</tbody>
</table>


**HPV L1 Virus-Like-Particle (VLP) Vaccine Synthesis**

**HPV4 Study Design**

- Four placebo-controlled double blind randomized clinical trials of Gardasil
- Multinational study sites; 20,541 women enrolled
- Baseline testing
  - Sero-status for HPV 6/11/16/18: prior infection
  - Virus detection (HPV-DNA): current infection
  - Pap smear
- Inclusion criteria
  - 16-26 years old at enrollment
  - ≤ 4 lifetime sexual partners

**HPV Vaccines**

<table>
<thead>
<tr>
<th>Brand name</th>
<th>HPV types</th>
<th>3 doses</th>
<th>Age range</th>
<th>US Licensure</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV4 Gardasil™ (Merck)</td>
<td>16, 18, 6, 11</td>
<td>0, 2, 6 mos</td>
<td>16-26</td>
<td>2006</td>
</tr>
<tr>
<td>HPV2 Cervarix™ (GSK)</td>
<td>16, 18</td>
<td>0, 1, 6 mos</td>
<td>15-25</td>
<td>2009</td>
</tr>
</tbody>
</table>

**HPV4 Study Design**

**“Best Case Scenario”**
- **Per Protocol Efficacy**
  - Seronegative at entry to HPV type being followed
  - HPV-DNA negative during vaccination phase
  - All 3 injections completed
  - No protocol violation
  - Case counting 1 month after dose 3

**“Average Case Scenario”**
- **General Population Impact**
  - Serostatus on day 1
    - 73% negative for all 4 types
    - 20% positive for 1 type
    - <1% positive for all 4 types
  - Any HPV-DNA + during vaccination phase
  - Any Pap > ASC-US on day 1
  - Protocol violators

---

**HPV4 Efficacy* Studies**

**Vaccinated vs. Placebo**

<table>
<thead>
<tr>
<th>Efficacy against lesions at 3-4 years</th>
<th>Per Protocol</th>
<th>General population</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN 2/3 + AIS</td>
<td>100%</td>
<td>39.0%</td>
</tr>
<tr>
<td>High grade vulvar (VIN), vaginal (VaIN) lesions</td>
<td>100%</td>
<td>69.1%</td>
</tr>
<tr>
<td>All CINs + AIS</td>
<td>95.2%</td>
<td>46.4%</td>
</tr>
<tr>
<td>Genital Warts</td>
<td>98.9%</td>
<td>68.5%</td>
</tr>
</tbody>
</table>

*Only lesions due to vaccine HPV types; does not include disease due to non-vaccine HPV types*

AIS: adenocarcinoma in situ

---

**HPV Vaccines: Safety Issues**

- Since VLP antigen (not virus), expect few problems
- Injection-site pain, swelling, redness are common
  - Can be more severe than with other vaccines
- Pregnancy category B; no ▲ in congenital anomalies
- Can be used in immunocompromised patients
- Do not pre-screen for HPV-DNA shedding
- Continue routine Pap smears after completion of vaccination series to screen for SILS due to non-vaccine strains of HPV (i.e., other than HPV 16/18)

---

**Benefits of HPV Vaccines**

- Decrease cervical cancer cases and death rates
  - Reduce hysterectomies, radiation tx, infertility
  - Reduce loss of productive years of life
- Decrease need for colposcopy, treatment of SIL
  - Fewer false positive Paps
  - Less detection and treatment of pseudodisease (non-progressive high grade CIN)
- Decrease cases of external genital warts (HPV4 only)
  - Less physical discomfort, stigmatization, cost
Decrease Cervical Cancer Rates

- 2009 US rates of cervical cancer
  - Incident cases per year: 9,710
  - Deaths: 3,700
- HPV vaccine will not prevent all of these cases
  - Some US women will choose not be vaccinated
  - Many immigrant women will not be vaccinated
  - Some develop cervical cancer even if vaccinated
- Conclusions
  - “Vaccine saves women’s lives”
  - “Vaccine for a cancer that already has been successfully controlled in the US”

Reduce (Unnecessary) Evaluation and Treatment

- False positive Pap smears
  - ASC-US: 3-10% have CIN 2/3+
  - LSIL: 10-20% have CIN 2/3+
- Vaccine expected to sharply reduce transient HR-HPV infections that cause abnormal Paps
  - But, the false positives do not become cancer
- Conclusions
  - “Vaccine prevents invasive diagnostic evaluation”
  - “Vaccine prevents a false positive test result”

Decrease External Genital Warts

- Prevalence: 1% reproductive aged women
- US Incidence: 0.4% (1 case /250 persons/ year)
- Burden of illness
  - Many asymptomatic cases; no treatment needed
  - Can be cosmetically ugly; anxiety-provoking
  - Rare case requires surgery
- Conclusions
  - “Vaccine prevents a common, significant infectious disease and clinical problem”
  - “Vaccine prevents a cosmetic condition”

HPV Vaccine: ACIP Recommendations

- Routine vaccination with 3 doses of quadrivalent HPV vaccine for females 11–12 years of age
  - Can be started as young as 9 years of age
- Catch-up vaccination for females 13–26 years of age not previously vaccinated or have not completed the full series
  - Ideally, vaccine should be administered before potential exposure to HPV

MMWR 2007;56 (RR-2):1-24
HPV Vaccine: ACIP Recommendations
MMWR 2007;56 (RR-2):1-24

- Administered in a 3-dose schedule
  - Each dose is 0.5 mL, administered IM
  - The second and third doses should be administered 2 and 6 months after the first dose
- HPV vaccine can be given at the same visit as other vaccines, such as Tdap, Td, and MCV4
- HPV vaccine is contraindicated in people with a history of immediate hypersensitivity to yeast or to any vaccine component

HPV Vaccine: ACIP Recommendations
MMWR 2007;56 (RR-2):1-24

- Candidates for HPV vaccination
  - Women who have abnormal Pap tests, a positive HPV DNA test, or genital warts
  - Lactating women
  - Immunocompromised females
    » But, immune response and vaccine effectiveness might be less than in immunocompetent women

HPV Vaccine: ACIP Recommendations
MMWR 2007;56 (RR-2):1-24

- HPV vaccine is not recommended for use in pregnancy
  - Report any exposure to the vaccine during pregnancy to the pregnancy vaccine registry
- HPV vaccine can be administered to females with minor acute illnesses
  - Vaccination of people with moderate or severe acute illnesses should be deferred until after the illness improves.

American Cancer Society: 2007
CA Cancer J Clin 2007;57:7

- Routine vaccination recommended for girls 11-12 yo
- Females as young as 9 can receive HPV vaccination
- HPV vaccination also is recommended women 13-18 to catch-up missed vaccine or to complete the series
- Not recommended for women >26 years old or men
- Insufficient data to recommend for or against universal vaccination of females 19-26 years old*

* Studies showed limited reduction in CIN 2+; no data in women with >4 lifetime sexual partners; and lack of cost-effectiveness analyses
HPV Vaccine: Controversies

- Immunization of boys and men
  - HPV4 was FDA approved in 2009 for prevention of genital warts in men
  - Value of vaccinating men to prevent transmission to women depends upon prevalence of immunity in ♀
- Long term safety and durability
- Abandonment on “routine” Pap screening by vaccinated women
- State HPV vaccination mandates
- Cost to healthcare system; what is being traded off?