Managing HPV: A New Era in Patient Care

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Learning Objectives:
At the conclusion of this activity, participants should be able to:

- Describe the significance of infection with HPV to patients including prevalence, mode of transmission, and long-term consequences.
- Describe three provider-delivered treatments for external genital warts.
- Use national guidelines when screening patients for HPV-related cervical disease.
- Apply evidence-based guidelines when managing abnormal screening tests for cervical cancer, including those specific for adolescents.
- Compare and contrast the bivalent and quadrivalent HPV vaccines.
- Answer frequently asked questions about the clinical use of the HPV vaccines.

Supporter Acknowledgement
Funding for this publication was provided by educational grants from GlaxoSmithKline, Graceway Pharmaceuticals, Merck and Co. Inc., QIAGEN, and Roche Pharmaceuticals.

Clinical Advisors
Don Downing, RPh
Mary Rubin, RNC, PhD, CRNP
Richard Guido, MD

This publication is part of a joint Association of Reproductive Health Professionals (ARHP) and Planned Parenthood Federation of America (PPFA) program that also included the following clinical advisors: Nancy R. Berman, MSN, APRN, BC; Barbara Clark, MPAS, PAC; Francisco Garcia, MPh, MD; Sereni Shenfeld Gorin, PhD; Julie Hibben, UWSW, CFPS; Marie Savard, MD; Analidetia Tavares, MD; Maria Trent, MD; MPh; Jeff Waldman, MD; and Thomas C. Wright, Jr., MD.

Contributing Staff and Consultants
Shama Alam, MSsPH, ARHP Education Associate
Jennifer Baldwin, Consulting Designer
Caroline Brown, MPH, MS, MBA, Education Associate
Vanessa Cullins, MD, MPH, MBA, PPFA Vice President for Medical Affairs
Beth Jordan, MD, ARHP Medical Director
Kathryn Quissell, MPH, ARHP Program Manager
Diane Shannon, MD, MPH, Consulting Writer
Wayne C. Shields, ARHP President and CEO
Amy M. Swann, MA, ARHP Director of Education
Jeffrey Waldman, MD, PPFA Senior Director of Clinical Services and Medical Education
Sandy Worthington, MSN, WHNP-BC, CNM, PPFA Program Director

Financial Disclosure Information
The following committee members and/or contributing staff have a financial interest or affiliation with the manufacturers of commercial products possibly related to topics covered in this issue of Clinical Proceedings™. These financial interests or affiliations are in the form of grants, research support, speaker support, or other support. This support is noted to fully inform readers and should not have an adverse impact on the information provided within this publication.

Berman: Speaker for QIAGEN Corporation, Graceway Pharmaceuticals, and Merck and Co., Inc.; consultant for QIAGEN Corporation

Clark: Speaker for Ortho Women’s Health and Urology and Wyeth Pharmaceuticals

Cullins: Receives grants and research support from QIAGEN Corporation, Graceway Pharmaceuticals, Merck and Co., Inc., and Ortho Women’s Health, Urology Wyeth Pharmaceuticals; consultant for Merck and Co., Inc.; speaker for Ortho Women’s Health and Urology

Guido: Conducted research for Graceway Pharmaceuticals and Tigress Pharmaceuticals; speaker for Merck and Co., Inc.; consultant for GlaxoSmithKline

Rubin: Speaker for Merck and Co., Inc. GlaxoSmithKline Cervical Cancer Advisory Board

Savard: Speaker for QIAGEN Corporation and GlaxoSmithKline

Trent: Speaker for Merck and Co., Inc. Medical Forums

Waldman: Speaker for QIAGEN Corporation, Graceway Pharmaceuticals, and GlaxoSmithKline

Wright: Consultant for GlaxoSmithKline, Merck and Co., Inc. and Roche Molecular Systems, Inc.

Alam, Baldwin, Downing, Garcia, Gorin, Hibben, Jordan, Quissell, Shannon, Shields, Swann, Tavares, and Worthington have no affiliations to disclose.
Introduction

Despite the fact that cervical cancer is highly preventable with screening and early intervention, about 11,150 new cases of cervical cancer occur annually in the United States. Infection with high-risk types of human papillomavirus (HPV) is a necessary cause of cervical cancer, and evidence also suggests a strong association of high-risk HPV with cancer of the penis, vagina, vulva, anus, and oropharynx. Genital infection with HPV is ubiquitous among people who are sexually active. In fact, it is the most commonly diagnosed sexually transmitted infection in the United States. However, HPV infection, including infection with the high-risk types associated with cervical cancer and the low-risk types associated with external genital warts, is most often cleared by the body’s immune system.

Ideal management of cervical cytology abnormalities and positive HPV DNA testing must balance the need to identify and treat abnormalities likely to progress to invasive cancer with the need to avoid unnecessary treatment of abnormalities related to transient HPV infection unlikely to lead to invasive cancer. Guidelines on screening for and management of HPV-related disease can be challenging to interpret and may shift repeatedly as new research is reported.

Testing for HPV infection, screening for HPV-related disease, and managing HPV-associated conditions are complex topics about which some critical shifts in thinking recently have occurred. This Clinical Proceedings is not meant to provide a comprehensive study of HPV; it was created to highlight management areas for which expert guidelines have recently changed and to cover issues that tend to be perplexing for frontline providers. To close the gap between ideal and delivered care, it is essential that clinicians be familiar with these updates. We hope that this monograph illuminates important areas of concern, facilitates optimal screening for and management of HPV-related disease, and supports clinicians in counseling patients about HPV. To facilitate counseling, we have included “Counseling Points” boxes throughout the Clinical Proceedings.

Our sincere thanks to the members of our expert advisory committee for investing their remarkable insight and valuable time in this project.

Wayne C. Shields
President and CEO
Association of Reproductive Health Professionals

Vanessa E. Cullins, MD, MPH, MBA
Vice President for Medical Affairs
Planned Parenthood® Federation of America
Impact and Epidemiology

Impact

Genital human papillomavirus (HPV) infection is the most commonly diagnosed sexually transmitted infection in the United States and is a necessary cause of cervical cancer.1,2 HPV also is associated with external genital warts and cancer of the penis, vagina, vulva, anus, and oropharynx.2

Approximately 11,150 women are diagnosed with cervical cancer each year in the United States.3 Most cases of invasive cervical cancer and death due to cervical cancer occur in women who did not receive proper screening.4 Cervical cancer screening has not been equally accessible to all women, and the incidence of cervical cancer is higher among ethnic minorities and poor women.4

One hundred percent of the cervical cancer cases diagnosed each year are believed to be attributable to HPV.3 This means that essentially all cervical cancers are associated with persistent infection with “high-risk” HPV. High-risk types are associated with cervical and other cancers, whereas low-risk types are associated with external genital warts but not cancer. These HPV types (see Table 1) have been shown to be carcinogenic for the cervix.2

Prevalence

HPV infection is common among sexually active individuals, with a lifetime risk of about 75 percent.7 As shown in Figure 1, HPV prevalence varies by age and is highest for young women, decreasing in the middle age range (30 to 60 years old). Prevalence by type varies somewhat by region, for reasons that are not yet known. This figure compares data from cohorts in Portland, Oregon, and Guanacaste, a rural province in Costa Rica.

Transmission

Unlike most sexually transmitted infections (STIs), which spread via body fluids, HPV is transmitted through direct genital contact, most commonly by sexual intercourse.10 Genital contact in the absence of intercourse is a plausible means for HPV transmission, but the risk associated with such contact is much lower than that for intercourse.10,11 Transmission via inanimate objects such as clothing is thought to be unlikely, but the true risk is unknown.10

Natural History

Progression to precancer occurs when infection with high-risk HPV persists over time (see Figure 2). In most cases, HPV infection—with either a low- or high-risk type—is cleared by the body. Observational studies have shown that about 90 percent of women infected with a particular HPV type will clear the infection within two years.12 Less than half of women who develop HPV infection will have persistence of the same HPV type 12 months later.1 HPV type 16 combines high rates of persistence with carcinogenicity, resulting in a risk of CIN-3 of 40 percent at 5 years.12

The high prevalence of HPV infection among young women has been confirmed in several studies. A study of 603 female college students found that 19.7 percent of the women were already HPV DNA positive at study initiation.9 Over 2 years of follow-up, 39 percent of the women who were initially HPV DNA negative became HPV DNA positive. High-risk types of HPV such as HPV 16 and 18 were the types most commonly identified in these young college-aged women.

Table 1: HPV Types Associated with Cancer and External Genital Warts1,7

<table>
<thead>
<tr>
<th>High-Risk Types</th>
<th>Low-Risk Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selected types</td>
<td>6, 11, 40, 42, 43, 44, 54, 61, 72, 81</td>
</tr>
<tr>
<td>Associated</td>
<td>16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 82</td>
</tr>
</tbody>
</table>

Associated abnormalities

Low-grade cervical lesions
High-grade cervical lesions
Anogenital cancers
External genital warts

Figure 1: Age-Specific Prevalence of High-Risk HPV Types8

![Figure 1: Age-Specific Prevalence of High-Risk HPV Types](image-url)
Counseling Points

When counseling a patient about risk factors for HPV infection, make sure she understands these points before she leaves your office or clinic:

- The primary risk factor is sexual activity.
- Condom use reduces but does not completely prevent the spread of HPV.
- Long-term use of oral contraceptives may increase the risk for persistent HPV infection, but currently, the risk does not appear to be great enough to warrant discontinuing use of OCS.

References:

1. Trotter H, Franco EL. The epidemiology of genital human papillomavirus infection. Vaccine. 2006;24(suppl 1):S1-4.15
13. Figure Courtesy of M. Schiffman, National Cancer Institute.

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External genital warts (EGW), also called condyloma acuminata, are fleshy lesions located in the genital area that are caused by HPV. EGW are usually associated with low-risk HPV types—that is, those that have not been linked to anogenital cancers. Thus, the main consequence of EGW is aesthetic. Ninety percent of EGW lesions are associated with low-risk HPV types 6 and 11.

EGW are common, at any point in time affecting approximately 1 percent of sexually active adults in the United States. Genital warts are usually asymptomatic, but depending on the size and location, they can be pruritic, painful, or friable. Left untreated, genital warts may remain unchanged or entirely disappear. However, they often grow in size or number. During pregnancy, warts may proliferate and become friable.

Diagnosis
Genital warts are diagnosed by visual inspection. The lesions, which have a pedunculated, flat, or papular appearance, are located on the external genitalia of both women and men, on the cervix, or in the vagina, urethra, or anus. Application of vinegar or acetic acid may turn lesions white, but this technique is not recommended for diagnosis because of a lack of specificity for HPV-associated lesions. Diagnosis can be confirmed by biopsy if lesions are black, brown, or red in color, unresponsive to treatment, or worsen during treatment. HPV DNA testing is not indicated for evaluation of EGW. Similarly, examination of partners is not necessary, because data do not suggest that reinfection plays a role in recurrences.

Treatment
The exact impact of treatment on reducing infectivity is unknown. Therefore, the primary goal of EGW treatment is removal of lesions for cosmetic reasons. Recurrences are common, and most patients require a series of treatments rather than a single treatment.

Both provider-delivered and patient-applied treatments are available (see Table 2).

Evidence does not suggest that any one EGW treatment is superior to the others. Therefore, treatment choice should be based on size, number, and location of lesions and tailored to the needs and preference of the particular patient. In addition, clinicians should use the least invasive and least costly approach possible to address a particular patient’s needs.

Providers should consider these factors when selecting treatment:

- Lesions located on dry surfaces respond less readily to topical treatments than warts on moist surfaces or intertriginous areas.
- Small isolated lesions often respond to provider-applied therapy such as TCA.
- Large lesions or multiple-site involvement may be more amenable to other options.
- Podophyllin resin, imiquimod, and podofilox should NOT be used for treatment of EGW in pregnant women, because their safety during pregnancy has not been established.
- Imiquimod is not approved for the treatment of intravaginal warts.
- Intra-anal and intravaginal warts should not be treated with podophyllin resin; instead, warts in these locations can be treated with TCA, or surgical therapy if needed.
- Although employed in the past, 5-FU is rarely used now for treatment of EGW.

Counseling Points
When counseling a patient about external genital warts, make sure she understands these points before she leaves your office or clinic:

- The types of HPV that usually cause EGW do not cause cervical cancer.
- The purpose of removing EGW is aesthetic. Treatment of EGW does not appear to alter the risk of transmission.

Planned Parenthood® Federation of America (PPFA) has published a treatment algorithm for cost-effective treatment of EGW. Based on a retrospective chart review, PPFA investigators evaluated the cost of treatment modalities and time for clearance of lesions. They found that 47 percent of clinic resources were spent on the 26 percent of patients who required four or more clinic visits before clearance of EGW. These results informed the creation of the algorithm (see Figure 3).
Based on the algorithm, a first-time EGW patient with lesions in a single location would be treated with TCA or cryotherapy. If lesions clear in three visits or fewer, treatment would be considered complete. If lesions do not clear within three visits, patients would be provided with imiquimod for treatment at home, along with educational materials for proper use. Patients who have recurrent EGW lesions and first-time EGW patients with lesions in multiple locations would be provided with imiquimod for treatment at home, along with educational materials for proper use. Although it is not included in the algorithm, ablative therapy with a laser could be considered if lesions persist despite treatment.

References:
Screening for HPV-Related Cancer: Cytology

Although human papillomavirus (HPV) is now known to play a role in a number of different cancers, national screening guidelines exist only for cervical cancer. This chapter will focus on the current methods used for cytology-based screening for cervical cancer, with brief mention of emerging recommendations on screening for anal cancer.

Screening for Cervical Cancer: Conventional versus Liquid-Based Cytology Methods

Both conventional Papanicolaou tests and liquid-based cytology are acceptable screening methods. Recent well-controlled clinical trials have found little difference in performance of the two methods for identifying high-grade disease. An advantage of the liquid-based cytology is that the technique facilitates “reflex” HPV testing, as well as testing for other sexually transmitted infections (STIs).

Age to Initiate Screening

If used, aggressive screening of young women would result in the evaluation of many minor cytological abnormalities because of the high prevalence HPV infection. This practice would be expensive, cause considerable anxiety, and result in unnecessary treatment. For this reason, the recommended age for initiation of cervical cancer screening is based on two opposing factors:

- HPV infections are very common in young women and frequently result in abnormal Pap test results.
- The incidence of CIN-3 and invasive cancer increases with age.

Within the United States, expert committees from American Cancer Society (ACS), American College of Obstetricians and Gynecologists (ACOG), and United States Preventive Services Task Force (USPSTF) recommend starting cervical cancer screening 3 years after initiation of sexual intercourse or no later than 21 years old. In contrast, ACOG guidelines do not specify an age at which cervical cancer screening can be stopped, although they note that risk of cancer is low among older women who have adequate previous screening. USPSTF guidelines do not specify an age at which to stop screening but recommend against routine screening for women over age 65 who have had adequate recent screening and are not otherwise at high risk.

Screening Interval

The recommended frequency for cervical cancer screening varies by expert group but is in the range of every 2 to 3 years. ACS recommends annual screening if conventional Pap testing is used and screening every 2 years for liquid-based testing. The frequency of screening can be reduced to every 2 to 3 years at age 30 for women who have three normal consecutive Pap test results (unless there is a history of DES exposure or immunosuppression). Notice that recommendations on screening interval do not vary based on the number of sexual partners or other markers of sexual activity.

ACOG recommends annual screening for women who are less than 30 years old. The frequency of screening can be reduced to every 2 to 3 years at age 30 for women with three normal consecutive Pap tests (unless there is a history of DES exposure or immunosuppression). The ACOG guidelines also recommend that Pap testing with or without HPV testing can be used for screening for women age 30 or older. At age 30 if HPV and Pap test results are both negative, the screening interval can be changed to no more frequently than every 3 years.

The USPSTF guidelines state that cervical cancer screening should be conducted at least every 3 years. The guidelines note that there is no direct evidence to support the clinical utility of more frequent screening.

Counseling Points

When counseling a patient about screening, make sure she understands these points before she leaves your office or clinic:

- Health Care Professionals (HCPs) need to tell patients that the Pap test is to check for cervical cancer.
- For women with normal Paps, HCPs should talk with them about their sexual lives and screen them for STIs if at risk, even if they don’t need another Pap at that time.
Screening After Hysterectomy

Recognizing that high-grade neoplasia is uncommon in women who have had a hysterectomy, ACS, ACOG, and USPSTF all recommend against routine screening of women who have had a hysterectomy for benign disease.4,7

Screening for Anal Cancer

Anal cancer is associated with infection with high-risk HPV types. As with cervical cancer, HPV type 16 is most common, followed by type 18.8 In fact, HPV DNA is detected in 88 percent to 94 percent of anal cancers.8 Risk factors for developing anal cancer include:9,10

- 15 or more lifetime sexual partners
- Receptive anal intercourse
- Current smoking
- In women, history of CIN, VIN, or VAIN
- HIV infection

Many anal cancers appear to arise from high-grade precursor lesions called anal intraepithelial neoplasia (AIN). The prevalence of anal HPV infections and AIN is quite high in certain populations including men who have sex with men (MSM) and HIV-infected individuals. In one study, 95 percent of 357 gay males had anal HPV and 50 percent had high-grade AIN.11 The role of routine screening for AIN and anal cancer in high-risk individuals is controversial.

Advocates for screening believe that cytology is as effective for detecting anal disease as it is for cervical disease, but opponents point out that treatments for AIN often fail and there are no data suggesting that AIN treatment prevents cancer.12 Currently, national expert groups, including the Centers for Disease Control and Prevention, USPSTF, ACS, and the Infectious Diseases Society of America, do NOT recommend routine anal cytology screening. Similarly, the National Guidelines Clearinghouse maintains no guidelines for anal cytology screening. However, some local entities, such as the New York State Department of Health, recommend anal cytology for certain populations (in this case, HIV-infected individuals who are MSM, individuals who have had genital warts, or women who have had CIN or VIN).13

References:


Tests are available to identify current human papillomavirus (HPV) infection by detecting the presence of HPV DNA. Currently, three tests have been approved by the Food and Drug Administration (FDA) for this use. The Hybrid Capture II® HPV Test, detects 13 of the 14 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 but not 82)1 and Cervista™ HPV HR detects these same 13 HR types of HPV as well as Type 66.2 Cervista™ HPV 16/18, which detects just types 16 & 18, can be used alongside or as a follow up to HR HPV testing. Types 16 & 18 are the high risk types associated with 70% of all cervical cancers.3 The tests assess whether one or more of these types of high-risk HPV are present; they do not identify the individual HPV type. Testing for low-risk HPV types should not be performed because, according to national guidelines, “there is no clinical utility in testing for other (nononcogenic) types.”4 The laboratory request slip should be marked appropriately to ensure that only testing for high-risk HPV types is performed.

Use of HPV Testing

HPV testing to screen for cervical cancer has two main benefits:

• First, it allows for less frequent screening. A normal Pap test result and a negative HPV test result give a high assurance that cervical cancer is not present and is not likely to occur in the next few years. In fact, when both tests are negative, the chance is 1 in 1,000 that CIN-2,3 is present and less than 2 in 1,000 that CIN-2,3 will develop within three years.5

• Second, HPV DNA testing identifies women who need increased surveillance. A positive HR HPV test result paired with a normal Pap test result reflects either a false-negative Pap test result or increased risk for development of CIN-2,3 and cancer.6 For this reason, women who have these results require more frequent follow-up. Women who are found to be positive for type 16 or 18 are at highest risk and should proceed to immediate colposcopy.6

Counseling Points

When counseling a patient about HPV DNA testing, make sure she understands these points before she leaves your office or clinic:

• Testing detects whether or not you have a current infection with one of the high-risk types of HPV. Testing detects the majority of high-risk types, but does not detect the types that cause external genital warts (EGW).

• In women age 30 or older, HPV DNA testing can be used in combination with Pap testing to improve the sensitivity of screening for cervical cancer or precancer.

• HPV DNA testing should not be used in men, because research on the performance of the test in men is under way but has not yet been completed.

On the basis of these benefits, clinical uses of HPV DNA testing include:7

• Routine screening of women age 30 and older, when used in conjunction with Pap testing

• Triage of women age 21 or older with atypical squamous cells of undetermined significance (ASCUS)

• Triage of menopausal women with low-grade squamous intraepithelial lesion (LSIL)

• Postcolposcopy follow-up of women with abnormal cytology results

• Posttreatment follow-up of women (at least six months after treatment)
The HPV DNA test should NOT be used:

- For screening before HPV vaccination
- For men
- To check the HPV status of:
  - Pregnant women
  - Patients with sexually transmitted infections (STIs), including EGW, or their partners
  - Partners of patients with cervical cancer abnormalities
- To triage women with Pap test results other than ASCUS (with the exception of postmenopausal women with LSIL)
- As adjunct to Pap testing in primary screening of women:
  - Less than 30 years old (primary screening is not recommended in young women because of the high prevalence of HPV infection and the low prevalence of cervical cancer in this population)
  - For status after total hysterectomy for benign disease

Frequency of Screening

Research has shown that screening every 3 years with a combination of cytology and HPV testing in women age 30 years or older is equivalent to or better than cervical cancer screening with annual Pap testing. For this reason, national guidelines recommend that women who have negative HPV test results and negative cytology should be screened no more frequently than every three years.

Management of Results: Positive HPV and Negative Pap Test

Of the women who undergo screening with a combination of Pap testing and HPV DNA testing, many of those who test positive for HPV will have normal Pap test results. National guidelines recommend follow-up at 12 months with repeat Pap testing and HPV testing. Colposcopy is recommended for women who test positive for HPV or have LSIL or greater Pap results on repeat testing at 12 months. Rescreening in three years is recommended for women who test negative on both tests on repeat testing at 12 months.

References:

7. ASCCP Educate the Educators: HPV and the HPV Vaccines 2006, ASCCP [slide presentation].
Management of Abnormal Cervical Cancer Screening Results

The American Society for Colposcopy and Cervical Pathology (ASCCP) published updated national guidelines for the management of abnormal results from cervical cancer screening. These guidelines differ from those published in 2001 in several important ways, including the management of abnormal results in postmenopausal women and other specific populations. This chapter will discuss the current guidelines for most populations; a subsequent chapter will cover management of cervical cancer screening results in adolescents. Algorithms based on these guidelines are available at www.asccp.org/consensus.shtml. Table 3 provides a review of the clinical significance of cytology screening results.

Management of Atypical Squamous Cells of Undetermined Significance

National guidelines for management of ASCUS in premenopausal women remain unchanged from previous guidelines. ASCCP recommends three options for initial management in premenopausal women:4

- Human papillomavirus (HPV) DNA testing or
- Repeat cytology at six and 12 months or
- Colposcopy

Of these, HPV DNA testing is the preferred option if liquid-based cytology or co-collection is used.

For follow-up management of ASCUS in women who did not undergo colposcopy initially, the guidelines recommend that:4

- If HPV reflex testing was used initially and the results were negative, the Pap test should be repeated in 12 months. If HPV test results were positive, colposcopy should be performed.
- If repeat cytology was used initially and Pap tests are negative at both six and 12 months, the patient can return to routine screening. If either Pap test shows a result of ASC or greater, the woman should undergo colposcopy.

Table 3: Clinical Significance of Cervical Cytology Screening Results1-5

<table>
<thead>
<tr>
<th>Cytology Screening Results</th>
<th>Clinical Significance*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical squamous cells of undetermined significance (ASCUS)</td>
<td>7% to 15% have CIN-2,3; women with a cytological result of ASCUS require follow-up</td>
<td>Most common cytological abnormality in the United States; almost half of all cases of CIN-2,3 are diagnosed in women with ASCUS</td>
</tr>
<tr>
<td>Atypical squamous cells, cannot exclude HSIL (ASC-H)</td>
<td>26% to 68% have CIN-2,3; includes both HSIL and mimics</td>
<td>Relatively uncommon; relatively high frequency of CIN-2,3 in this population (therefore, all women with ASC-H should undergo colposcopy)</td>
</tr>
<tr>
<td>Low-grade squamous intraepithelial lesion (LSIL)</td>
<td>12% to 25% have CIN-2,3; usually represents self-limited HPV infection</td>
<td>Relatively common; found more commonly in liquid-based than conventional Pap specimens</td>
</tr>
<tr>
<td>High-grade intraepithelial lesion (HSIL)</td>
<td>Approximately 2% have invasive cancer; more often associated with persistent infection and progression than LSIL</td>
<td>Relatively uncommon; detecting CIN-2,3 has emerged as the central purpose of screening</td>
</tr>
<tr>
<td>Atypical glandular cells (AGC)</td>
<td>3% to 17% have invasive cancer — including adenocarcinomas of the cervix, endometrium, ovary, and fallopian tube</td>
<td>Relatively uncommon; more common in women &gt;40 years old</td>
</tr>
</tbody>
</table>

*CIN-2 = cervical intraepithelial neoplasia grade 2
For follow-up management of ASCUS in women who underwent colposcopy initially and had no CIN identified, the guidelines recommend:

- HPV DNA testing at 12 months (it is recommended that HPV DNA testing not be performed at intervals less than 12 months) or
- Repeat cytological testing at six and 12 months

If CIN is identified in women who underwent initial colposcopy for ASCUS management, follow-up should be directed by guidelines for CIN management, which will be discussed later in this chapter.

**Postmenopausal women and immunosuppressed women**

In contrast with the 2001 consensus guidelines, the updated guidelines recommend that ASCUS in postmenopausal women and immunosuppressed women should be managed in the same manner as for the general population.4,6

**Atypical Squamous Cells, Cannot Exclude HSIL**

The ASCCP guidelines recommend colposcopy for all women with ASC-H, based on the fact that a number of studies have reported high rates of CIN-2,3 in these women.4,6

**Low-Grade Squamous Intraepithelial Lesion**

The 2006 ASCCP guidelines recommend colposcopy for women with LSIL but with special provisions and other options for postmenopausal women and pregnant women. Recommendations for initial and follow-up management are shown in Tables 4 and 5.

The 2006 ASCCP guidelines differ from those published in 2001 in recommended management of LSIL for postmenopausal women and pregnant women.4

**Postmenopausal women**

The new guidelines recommend three options for LSIL management in postmenopausal women:4

- Reflex HPV DNA testing or
- Colposcopy or
- Repeat Pap test at six and 12 months

**Pregnant women**

The 2006 guidelines consider colposcopy to be preferred for nonadolescent pregnant women.4 The guidelines note that endocervical curettage is unacceptable for pregnant women and that deferring colposcopy until six weeks postpartum is an acceptable option. In addition, postpartum follow-up is recommended for pregnant women with no suspected CIN-2,3 or cancer at the initial colposcopy. The guidelines state that additional colposcopic and

cytological examinations during pregnancy are unacceptable management options for these women.4

**Management of Atypical Glandular Cells**

The 2006 ASCCP guidelines recommend colposcopy with endocervical sampling (i.e., endocervical curettage) for all women with AGC.4 Women age 35 or older should have endometrial sampling, colposcopy, and endocervical sampling. In addition, the guidelines recommend endometrial sampling for women of any age who have abnormal bleeding suggestive of a risk for neoplastic endometrial lesions. The ASCCP guidelines state that patients with AGC should have HPV testing at the time of colposcopy.4 Management after the colposcopy depends on the colposcopy, biopsy, endocervical sampling, and HPV test results.

After colposcopy, the ASCCP guidelines recommend that “atypical endocervical, endometrial, or glandular cells (NOS)” should be managed based on results of biopsies and endocervical sample.4

**Table 4: ASCCP Recommended Initial Management of LSIL**

<table>
<thead>
<tr>
<th>Results of Initial Testing</th>
<th>Recommended Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colposcopy was unsatisfactory</td>
<td>Endocervical sampling</td>
</tr>
<tr>
<td>No lesion visible on colposcopy</td>
<td>Endocervical sampling</td>
</tr>
<tr>
<td>Biopsy showed CIN-2,3</td>
<td>See ASCCP guidelines for CIN management (discussed later in this chapter)</td>
</tr>
<tr>
<td>Biopsy showed no CIN-2,3</td>
<td>Repeat Pap test at 6 and 12 months or HPV testing at 12 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 5: ASCCP Recommended Follow-up Management of LSIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results of Testing After Biopsy</td>
</tr>
<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td>Pap test result is normal x2 (at 6 and 12 months) or HPV test result (at 12 months) is negative</td>
</tr>
<tr>
<td>Pap test result is ASC or greater or HPV test result is positive</td>
</tr>
</tbody>
</table>
Management of Cervical Intraepithelial Neoplasia Grades 2, 3

ASCCP guidelines state that either excision or ablation is an acceptable option for the initial management of CIN-2,3, except in pregnant women and adolescents, if the colposcopy was deemed satisfactory. Recommended follow-up options after initial treatment include Pap testing alone or a combination of Pap testing and colposcopy at six-month intervals.

Pregnant women

If there is no evidence of invasive disease and the pregnancy is not advanced, additional colposcopy and Pap tests are acceptable (at intervals no more frequent than every 12 weeks). Biopsy should be repeated only if the lesion worsens or if Pap testing suggests invasive cancer. Deferring reevaluation until six or more weeks postpartum is an acceptable option.

Follow-up After Treatment of Cervical Intraepithelial Neoplasia

Follow-up is critical for women treated for CIN, because treatment failures occur and because these women remain at higher risk for invasive cervical cancer than the general population for at least 20 years. Although recommended follow-up has not yet been evaluated by randomized clinical trial, a reasonable option is HPV testing six months after treatment, with further management dependent on the results. Women who have negative HPV test results can return to annual screening, whereas women with positive results should undergo colposcopy.

References:

Guidelines for cervical cancer screening and management of abnormal results in adolescents differ in important ways from those recommended for nonadolescent women. These differences reflect the relatively low incidence of cervical cancer and the high incidence of human papillomavirus (HPV) infection in adolescents, compared with older females.1,2

Cervical Cancer Screening

National guidelines from ACOG, USPSTF, and ACS all recommend that cervical cancer screening begin three years after initial vaginal intercourse or by age 21, whichever occurs first.3-5

Management of Atypical Squamous Cells of Undetermined Significance

The prevalence of HPV infection is higher in adolescents than in older females. If HPV testing were used to manage ASCUS in adolescents, the practice would result in colposcopy referral for many women at low risk for cervical cancer.6 The ASCCP guidelines specifically state that HPV testing should not be used in management of ASCUS in adolescents. In fact, if the testing is performed for some reason, the results should not affect management. The guidelines recommend initial observation regardless of HPV status, with repeat cytology in 12 months.6

Subsequent management is dependent on the results of Pap testing:

- If the Pap test result at 12 months shows HSIL, the patient should be referred for colposcopy.
- If the Pap test result at 12 months shows any other result, the test should be repeated in 12 months. If the repeat Pap test result (at 24 months) shows ASC or greater, the patient should be referred for colposcopy. If the result is negative, she can return to routine screening.

Management of Low-Grade Squamous Intraepithelial Lesion

LSIL lesions will regress in more than 90 percent of adolescents and young women over the course of 36 months.7 For this reason, ASCCP guidelines recommend initial observation regardless of HPV status, with repeat cytology in 12 months.6 Subsequent management is identical to that for ASCUS, as outlined above.

- If the Pap test result at 12 months shows HSIL, the patient should be referred for colposcopy.
- If the Pap test result at 12 months shows any other result, the test should be repeated in 12 months. If the repeat Pap test result (at 24 months) shows ASC or greater, the patient should be referred for colposcopy. If the result is negative, she can return to routine screening.

Management of High-Grade Squamous Intraepithelial Lesion

In contrast with recommendations for older females, immediate loop electrosurgical excision (“see and treat”) is not an acceptable management option for HSIL in adolescents. Instead, ASCCP guidelines recommend colposcopy for all adolescents with HSIL.6

Subsequent follow-up depends on biopsy results:6

- If the colposcopy is unsatisfactory or endocervical curettage is positive, an excisional procedure is recommended.
- If the colposcopy is satisfactory and the biopsy shows no CIN-2,3, patients should have Pap testing and colposcopy every six months for up to 24 months. If both Pap test results are negative and the colposcopy is normal, she may return to routine screening.

Management of Cervical Intraepithelial Neoplasia Grade 1

ASCCP guidelines recommend initial observation regardless of HPV status, with repeat cytology in 12 months.8 Subsequent management is identical to that for ASCUS, as outlined above.
Management of Cervical Intraepithelial Neoplasia Grade 2 or 3

National guidelines recommend two management options for CIN-2,3 in adolescents: treatment or observation with colposcopy and cytology every six months for up to 24 months. If CIN-2 is specified, the guidelines suggest that observation is preferred, but treatment is acceptable. If CIN-3 is specified, treatment is recommended. Treatment also is recommended when colposcopy is deemed unsatisfactory.

Counseling Points

When counseling an adolescent patient about cervical cancer screening, make sure she understands these points before she leaves your office or clinic:

- HPV infection is very common among sexually active adolescents.
- Testing for HPV infection in adolescents would show positive results so frequently that it would not be helpful in determining whether cervical cell abnormalities are present.
- For this reason, other types of tests, such as the Pap test, are used to check for the effects of HPV infection.

References:
The two primary means for preventing the transmission of HPV and subsequent infection are minimizing exposure, by reducing the number of sexual partners and using condoms, and vaccination.

**Minimizing Exposure**

The number of sexual partners has been shown to be the most constant predictor of HPV infection.\(^1\) In fact, the number of partners is proportional to the risk of acquiring the infection.\(^2\)\(^-\)\(^4\) According to the Centers for Disease Control and Prevention, with the exception of abstaining from all genital contact, long-term mutually monogamous relationships are the most effective behavioral approach to HPV prevention.\(^5\) For women who are not in long-term mutually monogamous relationships, reducing the number of sex partners is likely to reduce the chance of acquiring HPV infection.\(^1\)

Condom use does not completely prevent transmission of HPV, because the virus is spread via skin contact, not body fluids.\(^1\) However, condoms appear to decrease the risk of transmission. A 2003 study documented that consistent condom use by their partners reduced the risk of HPV infection in female university students (adjusted hazard ratio = 0.3).\(^6\) Figure 4 illustrates the rate of HPV infection by frequency of condom use by partner in this study. Condom use also has been associated with higher rates of CIN regression and clearance of HPV infection in women, as well as regression of HPV-associated penile lesions in men.\(^7\)\(^-\)\(^8\)

**Counseling Points**

When counseling a patient about HPV prevention, make sure she understands these points before she leaves your office or clinic:

- HPV is spread through skin contact at the genital area.
- Condoms reduce the chance that HPV will spread but do not completely eliminate the risk.

**Vaccination**

A quadrivalent vaccine for HPV 6, 11, 16, and 18, (Gardasil™) which is manufactured by Merck, was approved for marketing in the United States by the FDA in June of 2006. Soon after its approval, the Advisory Committee on Immunization Practices (ACIP), which is an advisory committee of the Centers for Disease Control and Prevention, released recommendations for vaccination using the HPV vaccine. In November of 2006 the HPV quadrivalent vaccine was included in the Vaccines for Children Program, a federally funded vaccine program that provides vaccines for free to both children and adolescents through age 18 who are uninsured or underinsured.

GlaxoSmithKline has developed a bivalent vaccine (Cervarix™) for HPV 16 and 18, which is currently undergoing FDA review for approval. A comparison of the two vaccines is shown in Table 6.

**Frequently Asked Questions About the HPV Vaccine\(^1\)\(^\text{9}\)**

- **What is the target age for the vaccine?** According to ACIP recommendations, the target age is 11 to 12 years old for routine vaccination of females, although the series can be started as young as age 9 years.
• What about missed vaccines? Does it make sense for
24-year-olds to be vaccinated? “Catch-up” vaccines are
recommended for females age 13 to 26 who were not
previously vaccinated or who did not complete the full
series. Vaccinating a 24-year-old woman does make
sense. Even if she is already sexually active, she may
not yet have been exposed to all four of the HPV types
against which the vaccine offers protection.

• Who should not receive the vaccine? According to
ACIP recommendations, the HPV vaccine should not be
administered to:
— Pregnant women. The quadrivalent vaccine is designated
as Pregnancy Category B; its use has not been associated
with adverse outcomes of pregnancy or adverse events
to the developing fetus. However, because data on
vaccination in pregnancy are limited, it is recommended
that vaccination be postponed until after delivery.
— Individuals with moderate or severe acute illnesses
(although it can be administered to individuals with
minor acute illnesses, such as diarrhea or mild upper
respiratory infection).
— Individuals with a history of immediate hypersensitivity
to any vaccine component or to yeast.

The vaccine CAN be administered to immunocompromised
individuals; however, efficacy might be less than that in
immunocompetent individuals.

• How does previous HPV exposure affect the effectiveness
of the vaccine? The vaccine is not effective at preventing
HPV infection and related disease for HPV types to which an
individual has already been exposed. However, in clinical
studies to evaluate the quadrivalent vaccine, 74 percent of
HPV positive participants had evidence of exposure at entry to
just one of the four HPV types against which the vaccine offers
protection. The vaccine is effective at preventing HPV-related
disease associated with HPV types that have not yet infected
an individual.

• Should I test for HPV before vaccination?
Pap testing and screening for HPV DNA are not needed
before vaccination. Few women have been exposed to all
four HPV types present in the quadrivalent vaccine, making
pretesting irrelevant.

• My patients don’t understand why they need to continue
cervical cancer screening after vaccination. What should
I tell them? It is important for females who receive the HPV
vaccine to continue with regular cervical cancer screening
for three reasons:
— The vaccine does not protect against all of the HPV types
that cause cervical cancer.
— An individual may be at risk for HPV-related disease due
to infection with a high-risk HPV type before vaccination.
— An individual who does not complete the vaccine series
may not receive the full benefits of the vaccine, and thus
be at risk for HPV-related disease.
— The vaccine is not 100% effective at preventing infection
with the 4 HPV types, thus another reason to continue
screening for cervical cancer.

• Do the vaccines provide cross-protection to other HPV
types? There is some preliminary evidence that the bivalent
and quadrivalent vaccines may provide protection against
other HPV types. A 2006 clinical trial of the bivalent vaccine
found significantly lower rates of infection with HPV types 31
and 45, which it does not target. The clinical relevance of
these data is not yet known. In the quadrivalent vaccine, there
was a significant decrease in persistent infection with type 31
as well as CIN-1 and CIN-2,3 associated with type 31.

• Is the type of adjuvant a clinically important difference
between the bivalent and quadrivalent vaccines? The
adjuvant present in the bivalent vaccine increases immunity
in animal studies. The clinical relevance of these data is
not yet known.

• Does the quadrivalent vaccine provide protection against
external genital warts? Yes. In a combined analysis of three
clinical trials, the efficacy of the quadrivalent vaccine was
98.9 percent against EGVW that were associated with HPV
types 6, 11, 16, or 18.

• What about the use of the vaccine in males? The vaccine is
not FDA approved for males at this time, but Merck’s efficacy
studies indicate the vaccine is 90.4% effective at prevent-
ing HPV 6, 11, 16, 18 related EGW and 85.6% effective at
preventing persistent infection with HPV 6, 11, 16, 18 in men
who are vaccinated. In men who have sex with men (MSM)
the vaccine is 79% effective at preventing EGVW and 94.4%
effective at preventing persistent infection with HPV 6, 11, 16,
& 18. These studies don’t address whether vaccinating men
prevents HPV infection in their sex partners.

• Does the HPV vaccine help treat existing disease? No. The
HPV vaccine is not effective against existing disease, including
existing HPV infection, cervical cytological abnormalities, or
external genital warts.

• How safe is the HPV Vaccine? The CDC has been monitoring
the safety of Merck’s vaccine since it went on the market in
2006. As of the end of 2008 23 million doses of Gardasil
had been administered, and there had been 11,916 adverse
events reported, 6% of which were classified as serious. The
CDC has investigated these and has not found evidence
that they are caused by the vaccine. The CDC continues to
recommend that girls be vaccinated.
Counseling Points

When counseling a patient about HPV vaccination, make sure she understands these points before she leaves your office or clinic:

• The HPV vaccine currently available prevents infection from two of the most common types of HPV that cause cervical cancer and two of the most common types of HPV that cause external genital warts. It does not protect against the other, less common, types of HPV.

• The vaccine is most effective when given before a person becomes sexually active. For this reason, it is recommended that young girls (as young as age 9) receive the vaccine.

• Testing for HPV DNA is not recommended before vaccination.

• The HPV vaccine will not treat cervical precancer or cancer that is already present, and it will not treat external genital warts that are already present.

## Reference


### Table 6: Comparison of HPV Vaccines

<table>
<thead>
<tr>
<th>Quadrivalent (Gardasil®)</th>
<th>Bivalent (Cervarix®)</th>
</tr>
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<tbody>
<tr>
<td><strong>Targeted HPV types</strong></td>
<td>6, 11, 16, 18</td>
</tr>
<tr>
<td></td>
<td>16, 18</td>
</tr>
<tr>
<td><strong>HPV-related diseases potentially prevented</strong></td>
<td>Cervical cancer</td>
</tr>
<tr>
<td></td>
<td>External genital warts</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>Females ages 9–26 years for prevention of cervical cancer, cervical cancer precursors, vaginal and vulvar cancer precursors, and anogenital warts related to the four HPV types targeted by the vaccine.</td>
</tr>
<tr>
<td><strong>Dosing and administration</strong></td>
<td>Intramuscular injection of three separate 0.5-mL doses at 0, 2, and 6 months.</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>Among young women (ages 16–26 years) who previously had not been exposed to any of the four HPV types in the vaccine:</td>
</tr>
<tr>
<td></td>
<td>• 100% efficacy in preventing CIN-2/3 caused by the targeted HPV types</td>
</tr>
<tr>
<td></td>
<td>• nearly 100% efficacy in preventing vulvar and vaginal precancers and genital warts caused by the targeted HPV types</td>
</tr>
<tr>
<td></td>
<td>Among young women (15-25 years of age) who previously had not been exposed to any of the two HPV types in the vaccine:</td>
</tr>
<tr>
<td></td>
<td>• 90–100% efficacy in preventing CIN-2/3 caused by the targeted HPV types</td>
</tr>
<tr>
<td><strong>Local adverse events</strong></td>
<td>Injection site pain, swelling, erythema, pruritus</td>
</tr>
<tr>
<td><strong>Systemic adverse events</strong></td>
<td>Rate of events similar between placebo and treated groups</td>
</tr>
<tr>
<td></td>
<td>• Vaccine-related serious adverse events occurred in &lt;0.1% of participants in clinical trials</td>
</tr>
<tr>
<td></td>
<td>• Low rates of events</td>
</tr>
<tr>
<td></td>
<td>• No subject withdrawals due to serious adverse events</td>
</tr>
</tbody>
</table>


Over the past several years, a number of important developments have shifted the landscape of cervical cancer screening:

- It is now well accepted that persistent infection with high-risk human papillomavirus (HPV) is necessary for the development of cervical cancer.

- Technology is available to detect current HPV infection through testing for HPV DNA.

- Research has documented a high prevalence of HPV infection and has shown that the majority of these infections, and a proportion of those associated with cervical cytology abnormalities, will resolve without treatment.

These developments highlight the fact that screening and management can identify and treat women with early cervical cytology abnormalities and while minimizing unnecessary treatment of abnormalities related to transient infection. For optimal screening and management of HPV-related disease, clinicians must be familiar with these developments, apply the national guidelines for proper screening and management, and provide patients with appropriate counseling about HPV-related concerns.
1. Which statement is true about HPV infection?
   a. High-risk types of HPV have been associated with external genital warts.
   b. It is the third most common sexually transmitted infection in the United States.
   c. The lifetime risk of HPV infection among sexually active individuals is 75%.
   d. Cervical cancer is often, but not always, associated with HPV infection.

2. HPV transmission occurs most commonly through:
   a. Coughing or sneezing.
   b. Vaginal or anal intercourse.
   c. Exchange of body fluids.
   d. Nongenital skin contact.

3. Which statement is true about these provider-delivered treatments for external genital warts?
   a. Laser ablation should not be used for removal of EGW lesions.
   b. Trichloroacetic acid (TCA) application should be repeated no more frequently than once a month.
   c. To avoid systemic absorption, podophyllin resin 10% should not be used near open lesions or wounds.
   d. After application of TCA or bichloroacetic acid (BCA), the treated area should not be washed for at least 6 hours.

4. Which of the following is a recommendation on cervical cancer screening from national guidelines for women under 30?
   a. Screening should begin at the time of initiation of sexual intercourse.
   b. Cervical cancer screening should continue until the end of a woman’s life.
   c. Screening should continue after hysterectomy for benign disease.
   d. The American Cancer Society recommends annual screening if conventional Pap testing is used and testing every 2 years for liquid-based testing.

5. Which is true about HPV DNA testing?
   a. It can be used in routine screening of women who are younger than age 30.
   b. It is recommended for use in both men and women.
   c. Only tests that detect high-risk HPV are clinically useful.
   d. It should be used to check HPV status before vaccination.

6. Which is true about the management of ASCUS?
   a. Of the three recommended options for initial management in premenopausal, nonadolescent women, colposcopy is preferred.
   b. According to national guidelines, if repeat cytology is negative at 6 and 12 months during follow up of ASCUS in premenopausal, nonadolescent women, screening should continue every 6 months for a total of 36 months.
   c. HPV testing should not be used in the management of ASCUS in adolescents.
   d. The recommended guidelines for the management of ASCUS in premenopausal women changed significantly from the 2001 publication.

7. Observation with repeat Pap test at 12 months is the recommended initial management of LSIL for which group of women?
   a. The general population.
   b. Nonadolescent pregnant women.
   c. Postmenopausal women.
   d. Adolescents.

8. Which of the following statements is true about cervical cancer screening with a combination of Pap testing and HPV DNA testing?
   a. It is a recommended screening approach for adolescents.
   b. Those who test positive for HPV DNA and have a normal Pap test result should undergo immediate colposcopy.
   c. Those who test positive for HPV DNA and have a normal Pap test result should be followed up with repeat HPV testing alone at 3 months.
   d. Those who test positive for HPV DNA and have a normal Pap test result should be followed up with repeat Pap testing and HPV testing at 12 months.

9. Which is true about cervical cancer screening after vaccination?
   a. Its frequency can safely be reduced.
   b. Its frequency can be reduced only if concurrent HPV DNA testing is conducted.
   c. Its frequency can safely be reduced only if male partners have also been vaccinated.
   d. Its frequency should not be reduced.

10. Which is a true statement about the HPV vaccine?
    a. It is effective against existing cervical cytological abnormalities.
    b. It is effective against existing external genital warts.
    c. Both the bivalent and the quadrivalent vaccines target HPV types 16 and 18.
    d. Both the bivalent and the quadrivalent vaccines offer protection against external genital warts.
Evaluation Form

First Name: ____________________________
Last Name: ____________________________
Degree(s): ____________________________
E-mail address: _________________________
Phone number: _________________________
Mailing address: _________________________

Your professional category (choose one):
❍ Educator           ❍ Nurse Practitioner or Nurse Midwife
❍ Pharmacist         ❍ Physician Assistant
❍ Physician/Resident ❍ Registered Nurse
❍ Student            ❍ Other (please describe): _________________________

Do you interact with patients? ❍ Yes ❍ No

Continuing Medical Education
Credits Claimed __________

1. On a scale from 1 to 5, with 5 being best, please rate how competent you are after this training to:
   - Describe the significance of infection with HPV to patients including prevalence, mode of transmission, and long-term consequences. 1 2 3 4 5
   - Describe three provider-delivered treatments for external genital warts. 1 2 3 4 5
   - Use national guidelines when screening patients for HPV-related cervical disease. 1 2 3 4 5
   - Apply evidence-based guidelines when managing abnormal screening tests for cervical cancer, including those specific for adolescents. 1 2 3 4 5
   - Compare and contrast the bivalent and quadrivalent HPV vaccines. 1 2 3 4 5

2. On a scale from 1 to 5, with 5 being best, please rate the following by circling the one most appropriate answer:
   - Importance of this topic for improving reproductive health care 1 2 3 4 5
   - Use of evidence-based material in educational content 1 2 3 4 5
   - Fairness and balance of content 1 2 3 4 5

3. What recommendations would you have for improving any of the criteria above? ____________________________

4. I intend to use the information I have learned from this publication to enhance my personal clinical practice.
   ❍ Yes ❍ No ❍ N/A

5. I anticipate the following barriers in using the information from this course. (check all that apply)
   - Systemic resistance ❍ Patient resistance ❍ Clinician resistance ❍ Lack of resources
   - Lack of time ❍ Community resistance ❍ Funder/donor resistance ❍ N/A
   - Other (please describe): ____________________________

6. What can ARHP do to assist you to overcome these barriers and fully integrate this information into your practice?
   (check all that apply)
   - Develop patient education materials
   - Provide networking opportunities with colleagues to learn how they have integrated this information
   - Provide mentoring opportunities with experts on this topic
   - Develop additional continuing education materials, such as live sessions
   - Develop additional continuing education materials, such web-based sessions
   - Develop additional continuing education materials, such monographs/publications
   - Develop additional continuing education materials, such Mobile CME (CME on your PDA)
   - Other (please describe): ____________________________

7. What topics do you suggest for future medical education activities? ____________________________

To obtain credit, return the completed post-test and evaluation form by June 30, 2011 to:
Association of Reproductive Health Professionals, 1901 L Street, Suite 300, Washington, DC 20036