Genital Human Papillomavirus (HPV)

Learning Objectives

Upon completion of this content, the learner will be able to:

1. Describe the epidemiology of genital HPV infection in the U.S.
2. Describe the pathogenesis of genital HPV.
3. Discuss the clinical manifestations of genital HPV infection.
4. Identify methods used to diagnose genital warts and cervical cellular abnormalities.
5. Discuss CDC-recommended treatment regimens for genital warts.
6. Summarize appropriate prevention counseling messages for genital HPV infection.
7. Describe public health measures for the prevention of genital HPV infection.

Lessons

I. Epidemiology of genital HPV infection in the U.S.
II. Pathogenesis
III. Clinical manifestations and sequelae
IV. Diagnosis of genital warts and cervical cellular abnormalities
V. Patient management
VI. Patient counseling and education
VII. Partner management and public health measures

Lesson I: Epidemiology of Genital HPV Infection in the U.S.

Introduction

- Genital HPV is one of the most common STDs.
- More than 30 HPV types can infect the genital tract.

Introduction

- HPV types are divided into 2 groups based on their association with cervical cancer:
  - Low-risk types associated with genital warts and mild Pap test abnormalities
  - High-risk types associated with mild to severe Pap test abnormalities and cervical cancer
- Most genital HPV infections are transient, asymptomatic, and have no clinical consequences.

Incidence in the U.S.

- Estimated annual incidence of sexually transmitted HPV infection is 6.2 million
- Estimated $1.6 billion spent annually in direct medical costs to treat symptoms of genital HPV infection
- Estimated 20 million people currently have a detectable genital HPV infection

Prevalence in the U.S.

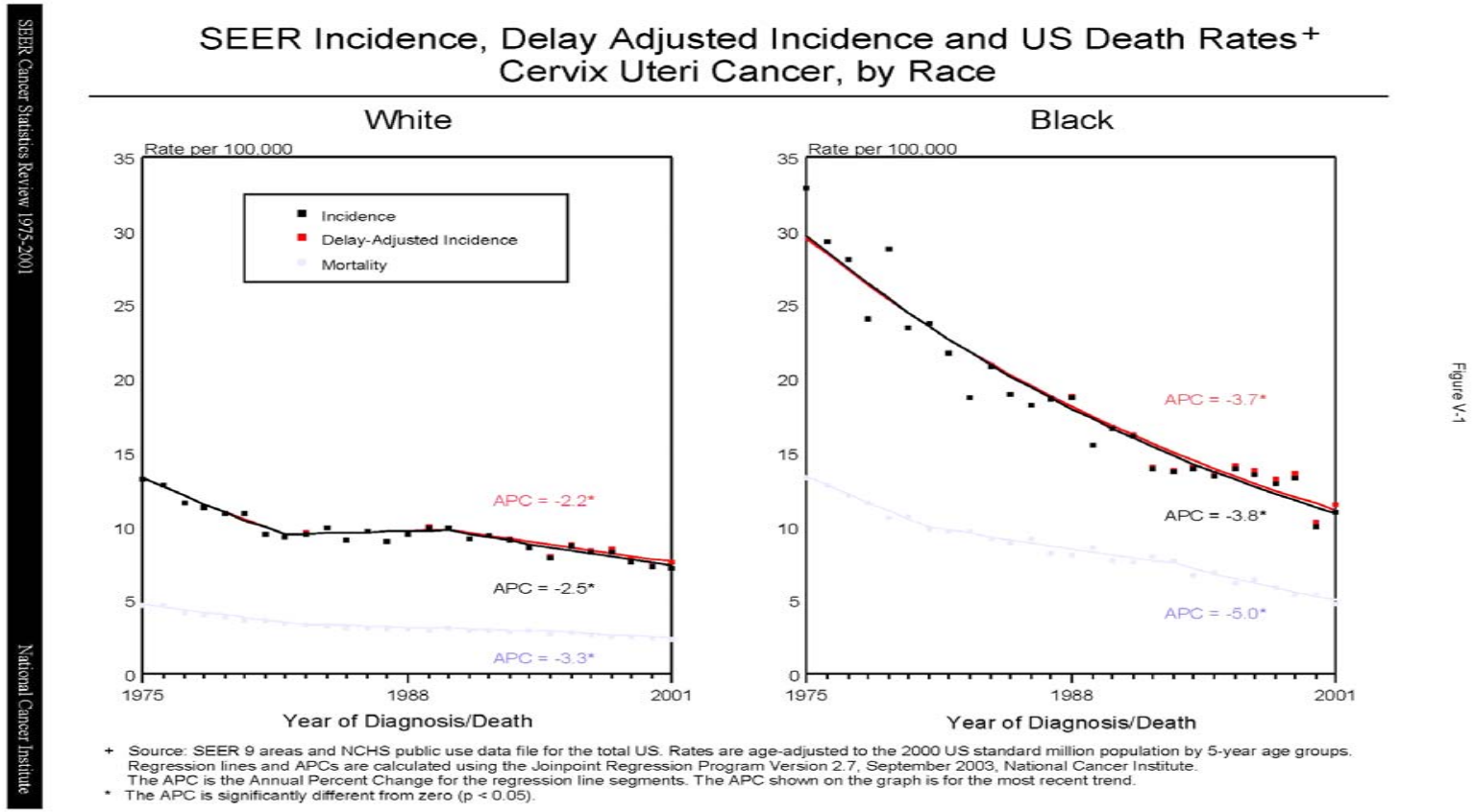
- It is estimated that at least 50% of sexually active men and women acquire genital HPV at some point in their lives.

- A recent estimate suggests 80% of women will have acquired genital HPV by the age of 50.

Incidence and Prevalence of HPV-associated Diseases

- Genital warts
  - Incidence may be as high as 100/100,000.
  - An estimated 1.4 million are affected at any one time.
- Cervical cancer
  - Rates of cervical cancer have fallen by approximately 75% since the introduction of Pap screening programs.
  - Incidence is estimated at 8.3/100,000.

Delay Adjusted Incidence and U.S. Death Rates of Cervical Cancer by Year of Diagnosis and Race: 1973-2001



CDC STD Prevention

Transmission of Genital HPV

- Predominantly associated with sexual activity
- Can occur from asymptomatic and subclinical patients
- Infectivity after treatment of genital warts or cervical cell abnormalities is unknown

Risk Factors for Women

- Young age
- Sexual behavior
  - Risk increases with increasing lifetime number of male sex partners
  - Early age of first sexual intercourse
- Sexual behavior of male sex partners–risk increases for women whose sex partners had multiple sex partners
- Immune status–HPV more likely to be detected in immune-suppressed women

Risk Factors for Men

- Greater lifetime number of sex partners
- Greater number of recent sex partners
- Being uncircumcised

Lesson II: Pathogenesis

Virology

- Double-stranded DNA virus that belongs to the Papovaviridae family
- Genital types have specific tropism (affinity) for genital skin and mucosa
- Infection generally indicated by the detection of HPV DNA or capsid protein

HPV Genotyping System

- Low-risk types
  - Most visible warts caused by HPV types 6 and 11
  - Recurrent respiratory papillomatosis associated with HPV types 6 and 11
- High-risk types
  - HPV types 16 and 18 found in more than half of anogenital cancers
  - Most women with high-risk HPV infection have normal Pap test results and never develop precancerous cell changes or cervical cancer

Pathology

- HPV infects stratified squamous epithelium and stimulates cellular proliferation.
- Affected cells display a broad spectrum of changes ranging from benign hyperplasia to dysplasia to invasive carcinoma.

Natural History of HPV

- Most genital HPV infections are transient, asymptomatic, or subclinical, and have no clinical consequences in immunocompetent individuals.
- The incubation period is unclear.
- The median duration of new cervical infections is 8 months but varies by type.
- Gradual development of an effective immune response is the likely mechanism for HPV DNA clearance.

Natural History of HPV (continued)

- **Persistent infection** is infection that is not cleared by the immune system and is characterized by persistently detectable HPV DNA.
  - HPV infection that persists is the most important factor for precancerous cervical cell changes and cervical cancer.
  - Most women with persistent HPV infection do not develop cervical cancer precursors or cervical cancer.

Lesson III: Clinical Manifestations and Sequelae

Clinical Manifestations and Sequelae

- In most cases, genital HPV infection is transient and has no clinical manifestations or sequelae.
- Clinical manifestations of genital HPV infection include:
  - Genital warts
  - Cervical cell abnormalities
  - Anogenital squamous cell cancers
  - Recurrent respiratory papillomatosis
- Most common clinically significant HPV infection manifestations:
  - Genital warts
  - Cervical cell abnormalities

Genital Warts: Appearance

- Condylomata acuminata
  - Cauliflower-like appearance
  - Skin-colored, pink, or hyperpigmented
  - May be keratotic on skin; generally non-keratinized on mucosal surfaces
- Smooth papules
  - Usually dome-shaped and skin-colored
- Flat papules
  - Macular to slightly raised
  - Flesh-colored, with smooth surface
  - More commonly found on internal structures (i.e., cervix), but also occur on external genitalia
- Keratotic warts
  - Thick horny layer that can resemble common warts or seborrheic keratosis

Genital Warts: Location

- Warts commonly occur in areas of coital friction.
- Perianal warts do not necessarily imply anal intercourse.
  - May be secondary to autoinoculation, sexual activity other than intercourse, or spread from nearby genital wart site.
- Intra-anal warts are seen predominantly in patients who have had receptive anal intercourse.
- Patients with visible warts can be simultaneously infected with multiple HPV types.

Genital Warts: Symptoms

- Genital warts usually cause no symptoms other than the warts themselves.
- Vulvar warts--dyspareunia, pruritis, burning discomfort
- Penile warts--occasional itching
- Urethral meatal warts--occasional hematuria or impairment of urinary stream
- Vaginal warts--usually asymptomatic; occasional discharge/bleeding, obstruction of birth canal (secondary to increased wart growth during pregnancy)
- Perianal warts--usually asymptomatic; pain, bleeding on defecation, itching
- Most patients have fewer than 10 genital warts, with total wart area of 0.5-1.0 $cm^{2.}$

Genital Warts: Duration

- May regress spontaneously or persist with or without proliferation.
  - Frequency of spontaneous regression is unclear.
  - Persistence of infection occurs, but frequency and duration are unknown.
  - Recurrences after treatment are common.

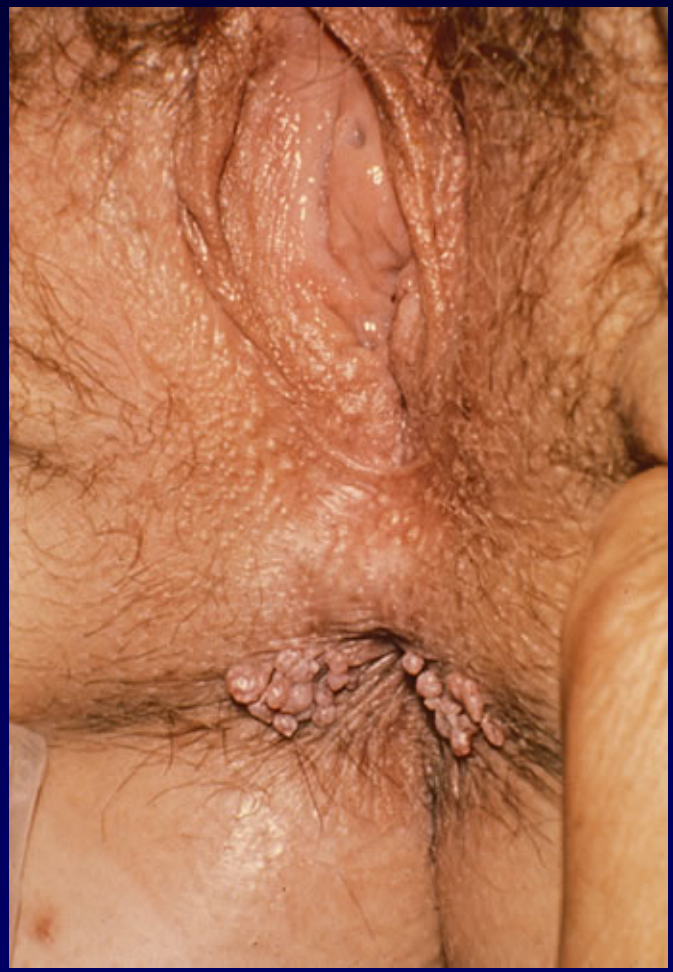
Genital Warts and High-Risk HPV

- High-risk HPV types occasionally found in visible genital warts
- Associated with external genital (i.e., vulvar, penile, and anal) squamous intraepithelial lesions

Genital Warts in Preadolescent Children

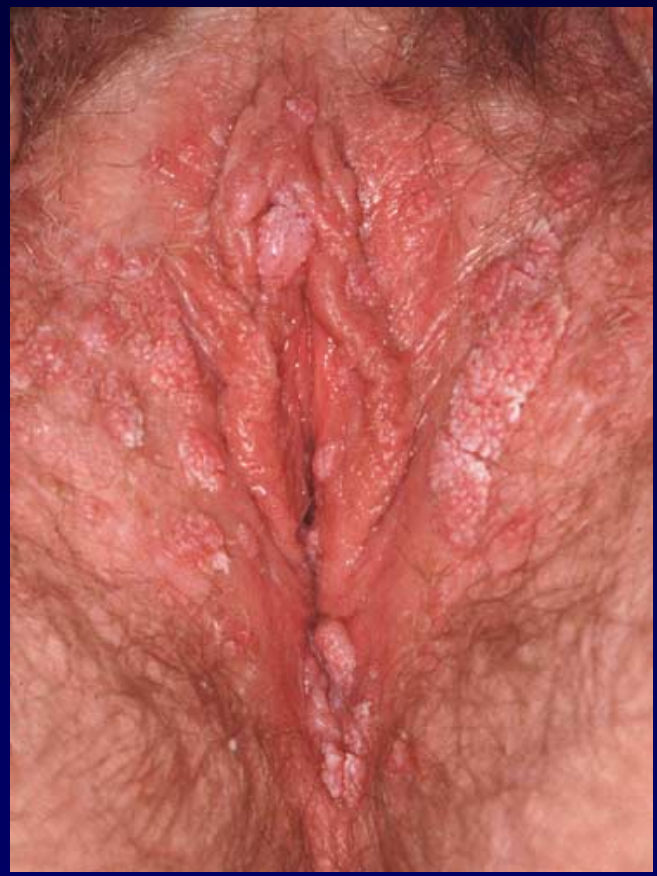
- May be due to sexual abuse and should prompt an evaluation for such
- May also result from vertical transmission, and transmission of non-genital HPV types to genital surface, and possibly fomite transmission (although fomite transmission has never been documented)

Perianal Warts



Source: Seattle STD/HIV Prevention Training Center at the University of Washington/ UW HSCER Slide Bank

Vulvar Warts



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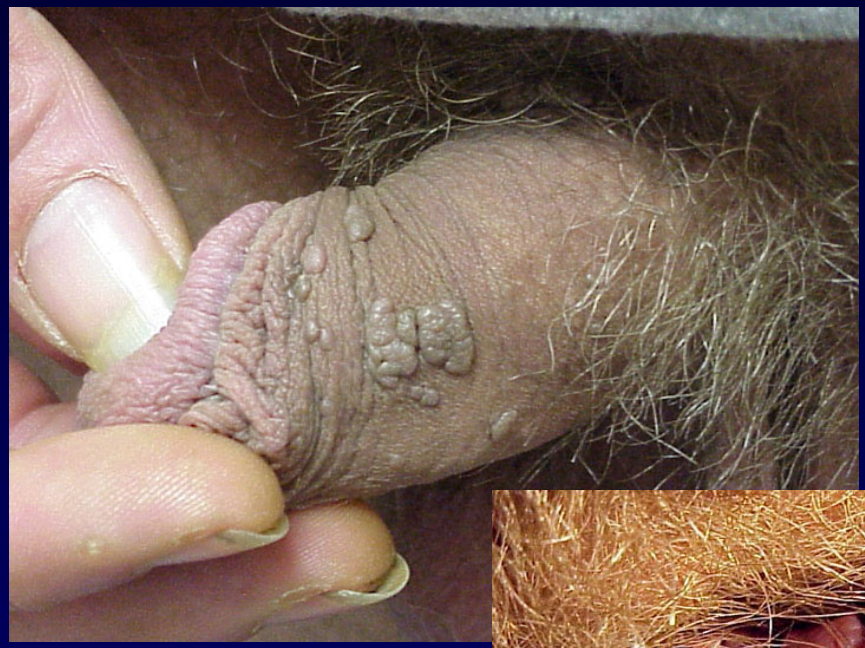
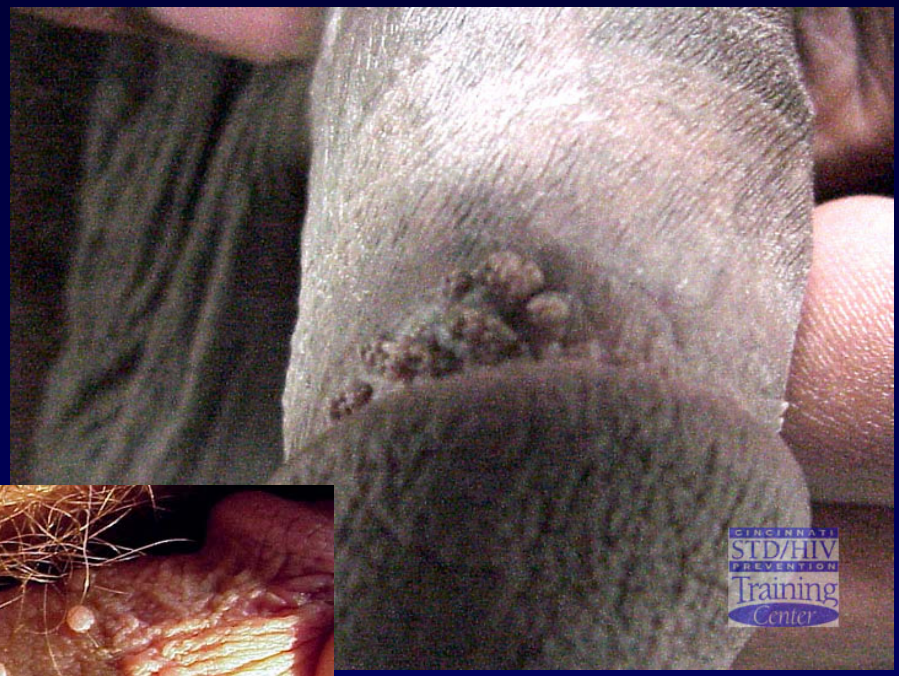
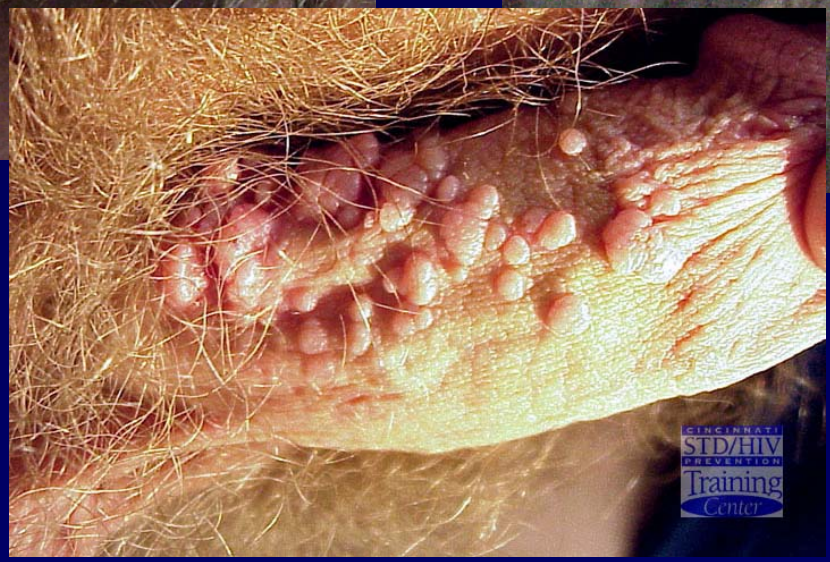
Penile Warts

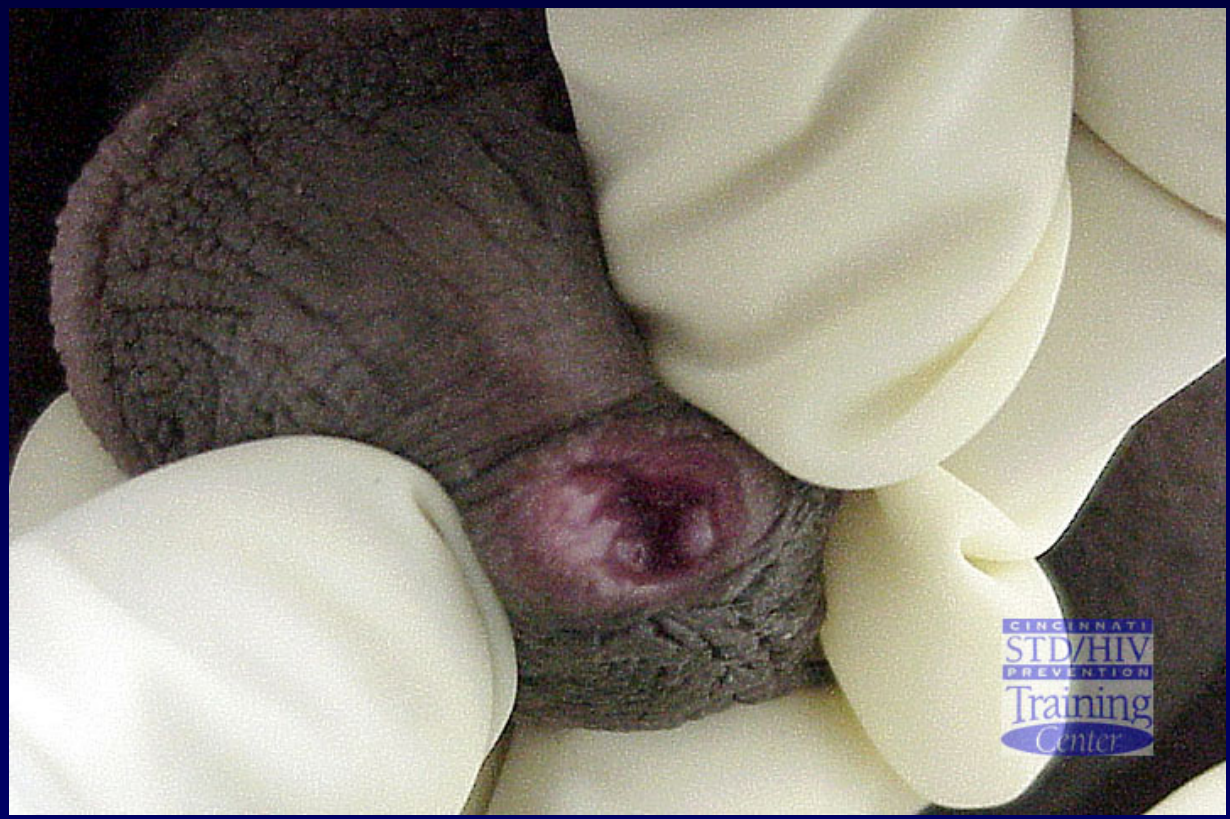






Source: Cincinnati STD/HIV Prevention Training Center

Intrameatal Wart



Source: Cincinnati STD/HIV Prevention Training Center

CDC STD Prevention

Cervical Cell Abnormalities

- Usually subclinical
- Detected by Pap test, colposcopy, or biopsy
- Usually caused by high-risk HPV types
  - Most of the time high-risk HPV types do not cause any abnormalities.
  - Most women infected with high-risk HPV types have normal Pap test results.
- Often regress spontaneously without treatment

Classification of Cervical Cell Abnormalities

2001 Bethesda System

- Atypical squamous cells (ASC) are cells that do not appear to be completely normal.
- ASC–US—atypical squamous cells of undetermined significance. Sometimes the changes are related to HPV infection. ASC–US changes are usually mild abnormalities.
- ASC–H—atypical squamous cells cannot exclude a high-grade squamous intraepithelial lesion. ASC–H changes are more likely to be precancerous abnormalities.

Classification of Cervical Cell Abnormalities (continued)

- Low-grade squamous intraepithelial lesion (LSIL)--generally a transient infection with a high-risk HPV type
- High-grade squamous intraepithelial lesion (HSIL)--generally a persistent infection with a high-risk HPV type with a higher risk for progression to cervical cancer

Anogenital Squamous Cell Cancers

- HPV infection is causally associated with cervical cancer and probably other anogenital squamous cell cancers (e.g., anal, penile, vulvar, vaginal).
- Over 99% of cervical cancers have HPV DNA detected within the tumor.
- Persistent infection with a high-risk HPV type is necessary but not sufficient for the development of cervical cancer.

Recurrent Respiratory Papillomatosis

- HPV infections in infants and children may present as laryngeal papillomatosis, also known as juvenile onset recurrent respiratory papillomatosis (JORRP).
- Respiratory papillomatosis is a rare condition, usually associated with HPV types 6 and 11.

Lesson IV: Diagnosis of Genital Warts and Cervical Cellular Abnormalities

Diagnosis of Genital Warts

- Diagnosis is usually made by visual inspection with bright light.
- Diagnosis can be confirmed by biopsy when:
  - Diagnosis is uncertain
  - Patient is immunocompromised
  - Warts are pigmented, indurated, or fixed
  - Lesions do not respond or worsen with standard treatment
  - There is persistent ulceration or bleeding

Diagnosis of Genital Warts (continued)

- Use of type-specific HPV DNA tests for routine diagnosis and management of genital warts is not recommended.
- Acetic acid evaluation (acetowhitening) of external genitalia is not recommended.
- External genital warts are not an indication for cervical colposcopy or increased frequency of Pap test screening (assuming patient is receiving screening at intervals recommended by her health care provider).

Differential Diagnosis of Genital Warts

- Other infections
  - Condylomata lata--tend to be smoother, moist, more rounded, and darkfield-positive for *Treponema pallidum*
  - Molluscum contagiosum--papules with central dimple, caused by a pox virus; rarely involves mucosal surfaces

Differential Diagnosis of Genital Warts (continued)

- Acquired dermatologic conditions
  - Seborrheic keratosis
  - Lichen planus
  - Fibroepithelial polyp, adenoma
  - Melanocytic nevus
  - Neoplastic lesions
- Normal anatomic variants
  - “Pink pearly penile papules”
  - Vestibular papillae (micropapillomatosis labialis)
  - Skin tags (acrochordons)

Diagnosis of Cervical Cell Abnormalities

- Cytology (Pap test)
  - Useful screening test to detect cervical dysplasia (not HPV per se)
  - Provides indirect evidence of HPV because it detects squamous epithelial cell changes that are almost always due to HPV

Diagnosis of Cervical Cell Abnormalities (continued)

- Nucleic acid testing
  - FDA-approved for two optional uses:
    - To triage women with atypical cells of undetermined significance (ASC-US) Pap test results
    - As an adjunct to the Pap test to screen for cervical cancer in women 30 years or older.
  - Use of HPV DNA testing for women with SIL Pap test results is unnecessary because the vast majority of women with SIL are infected with HPV.

Diagnosis of Cervical Cell Abnormalities (continued)

- Indication for colposcopy is guided by physical exam or Pap test findings with or without HPV DNA test findings.
- Indications for cervical biopsy include:
  - Visible exophytic lesions on the cervix
  - Pap test with HSIL
  - Pap test with ASC-H or LSIL with colposcopic abnormalities

Lesson V: Patient Management

General Treatment of Genital Warts

- Primary goal is removal of symptomatic warts.
- If left untreated, genital warts may regress spontaneously or persist with or without proliferation.
- In most patients, treatment can induce wart-free periods.
- Currently available therapies may reduce, but probably do not eradicate infectivity.
- Effect of current treatment on future transmission is unclear.

General Treatment of Genital Warts (continued)

- No evidence that presence of genital warts or their treatment is associated with development of cervical cancer.
- Some patients may choose to forgo treatment and await spontaneous resolution.
- Consider screening persons with newly diagnosed genital warts for other STD (e.g., chlamydia, gonorrhea, HIV, syphilis).

Treatment Regimens

- Patient-applied and provider-administered therapies are available.
- Providers should be knowledgeable about and have available at least 1 patient-applied and 1 provider-administered treatment.
- Choice of treatment should be guided by:
  - The preference of the patient
  - The available resources
  - The experience of the healthcare provider

Treatment Regimens (continued)

- Factors influencing treatment selection:
  - Wart size
  - Number of warts
  - Anatomic site of wart
  - Wart morphology
  - Patient preference
  - Cost of treatment
  - Convenience
  - Adverse effects

Treatment Response

- Affected by:
  - Number, size, duration, and location of warts, and immune status
  - In general, warts located on moist surfaces and in intertriginous areas respond better to topical treatment than do warts on drier surfaces.
- Many patients require a course of therapy rather than a single treatment.
  - Evaluate the risk-benefit ratio of treatment throughout the course of therapy to avoid over-treatment.
- No evidence that any specific treatment is superior to any of the others.
  - The use of locally developed and monitored treatment algorithms has been associated with improved clinical outcomes.

Recurrence

- Up to 2/3 of patients will experience recurrences of warts within 6-12 weeks of therapy; after 6 months most patients have clearance.
  - If persistent after 3 months, or if there is poor response to treatment, consider biopsy to exclude a premalignant or neoplastic condition, especially in an immunocompromised person.
- Treatment modality should be changed if patient has not improved substantially after 3 provider-administered treatments or if warts do not completely clear after 6 treatments.

Complications

- Complications rarely occur if treatments for warts are employed properly.
  - Depressed or hypertrophic scars are uncommon but can occur, especially if the patient has had insufficient time to heal between treatments.
  - Rarely, treatment can result in disabling chronic pain syndromes (e.g., vulvodynia or hyperesthesia of the treatment site).
- Patients should be warned that persistent hypopigmentation or hyperpigmentation are common with ablative modalities.

CDC-Recommended Regimens For External Genital Warts (Patient-Applied)

- Podofilox 0.5% solution or gel (Condylox™)
  - Patients should apply solution with cotton swab or gel with a finger to visible warts twice a day for 3 days, followed by 4 days of no therapy.
  - Cycle may be repeated as needed up to 4 cycles.

OR

- Imiquimod 5% cream (Aldara™)
  - Patients should apply cream once daily at bedtime, 3 times a week for up to 16 weeks.
  - Treatment area should be washed with soap and water 6-10 hours after application.

CDC-Recommended Regimens For External Genital Warts (Provider-Administered)

- Cryotherapy with liquid nitrogen or cryoprobe
  - Repeat applications every 1-2 weeks, OR
- Podophyllin resin 10%-25% in compound tincture of benzoin
  - Apply a small amount to each wart and allow to air dry
  - Treatment may be repeated weekly if needed, OR
- Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80%-90%
  - Apply small amount only to warts and allow to dry
  - Treatment may be repeated weekly if needed, OR
- Surgical removal--tangential scissor excision, tangential shave excision, curettage, or electrosurgery

CDC-Recommended Alternative Regimens

- Intralesional interferon

OR

- Laser surgery

Treatment of Exophytic Cervical Warts

- High-grade squamous intraepithelial lesions (SIL) must be excluded before treatment is initiated.
- Management should include consultation with a specialist.

CDC-Recommended Regimens for Vaginal Warts

- Cryotherapy with liquid nitrogen
  - The use of a cryoprobe in the vagina is not recommended because of risk for vaginal perforation and fistula formation.

OR

- TCA or BCA 80%-90% applied to warts
  - Apply small amount only to warts and allow to dry (white “frosting” develops).
  - Treatment may be repeated weekly if needed.

CDC-Recommended Regimens for Urethral Meatus Warts

- Cryotherapy with liquid nitrogen

OR

- Podophyllin 10%-25% in compound tincture of benzoin
  - Treatment area must be dry before contact with normal mucosa.
  - Treatment may be repeated weekly, if needed.

CDC-Recommended Regimens for Anal Warts

- Cryotherapy with liquid nitrogen

OR

- TCA or BCA 80%-90% applied to warts
  - Apply small amount only to warts and allow to dry (white “frosting” develops)
  - Treatment may be repeated weekly if needed

OR

- Surgical removal

CDC-Recommended Regimens for Oral Warts

- Cryotherapy with liquid nitrogen

OR

- Surgical removal

Management of Genital Warts in Pregnancy

- Genital warts can proliferate and become more friable during pregnancy.
- Cytotoxic agents (podophyllin, podofilox, imiquimod) should not be used.
- Cryotherapy, TCA, BCA, and surgical removal may be used.
- Prevention value of cesarean delivery is unknown, thus C-section should not be performed solely to prevent transmission to neonate.

Management of Genital Warts in Immunodeficient Patients

- More frequent, more pronounced clinical manifestations and occurrence of atypical lesions
- More resistant to conventional therapy
- More common recurrence of lesions after treatment
- Role of warts (or irritated treatment sites) in HIV transmission is unknown.
- Treatment unlikely to be effective due to high recurrence rate; therefore, treat only if the patient is symptomatic.
- Because HSIL and invasive cancer can occur in wart-like lesions, especially in the perianal area, lesions which are hyperpigmented or which persist despite treatment should be evaluated by biopsy.

Pap Test Screening in Immunodeficient Patients

- Immunodeficiency appears to accelerate intraepithelial neoplasia and invasive cancer.
  - Provide cervical Pap test screening every 6 months for 1 year, then annually for all HIV-infected women with or without genital warts.
  - Anal pap tests and anoscopy: value in absence of symptoms not established, but is under investigation

Genital Wart Follow-Up

- Counsel patients to:
  - Watch for recurrences
  - Get regular Pap screening at intervals as recommended for women WITHOUT genital warts
- After visible warts have cleared, follow-up evaluation not mandatory, but provides opportunity to:
  - Monitor or treat complications of therapy
  - Document the absence of warts
  - Reinforce patient education and counseling messages
- Offer patients concerned about recurrences a follow-up evaluation 3 months after treatment.

Treatment of Cervical Cellular Abnormalities

- For more information on managing women with cervical cell abnormalities, refer to:
  - CDC National Breast and Cervical Cancer Early Detection Program http://www.cdc.gov/cancer/nbccedp/index.htm
  - 2001 Consensus Guidelines for the Management of Women with Cervical Cytologic Abnormalities http://www.asccp.org/consensus/cytological.shtml

Lesson VI: Patient Counseling and Education

The Nature of HPV Infection

- Genital HPV infection is common in sexually active adults.
- Incubation period is variable, and it is often difficult to determine the source of infection.
- Natural history of HPV infection is usually benign:
  - Low-risk genital HPV types are associated with mild Pap test abnormalities and genital warts.
  - High-risk types are associated with mild to severe Pap test abnormalities and, rarely, cancers of the cervix, vulva, anus, and penis.
  - Most women infected with high-risk HPV types have no Pap test abnormalities and do not develop cervical cancer.
- Genital warts have a high recurrence rate after treatment.

Transmission Issues

- Determining source of infection is usually difficult.
- Recurrences usually are not re-infection.
- Transmission risk to current and future partners is unclear.
- Abstinence and long-term mutual monogamy with an uninfected partner are the most effective options to prevent transmission.
- Likelihood of transmission and duration of infectivity with or without treatment are unknown.
- Value of disclosing a past diagnosis of genital HPV infection to future partners is unclear, although candid discussions about past STD should be encouraged.

Risk Reduction

- Assess patient's behavior-change potential.
- Develop individualized risk-reduction plans with the patient for lasting results.
- Discuss prevention strategies such as abstinence, mutual monogamy with an uninfected partner, condoms, limiting number of sex partners, etc.
- While the effect of condoms in preventing HPV infection is unknown, condom use has been associated with lower rates of genital warts and cervical cancer, both HPV-associated diseases.
- HPV infections can occur in male and female genital areas that are not covered by a latex condom, as well as in areas that are covered.

Resources

- National HPV and Cervical Cancer Prevention Resource Center, created by the American Social Health Association
  http://www.ashastd.org/hpvccrc/
- CDC Cervical Cancer Screening Fact Sheet
  http://www.cdc.gov/cancer/nbccedp/cc_basic.htm
- National Cancer Institute Cervical Cancer Screening Information For Patients
  http://www.nci.nih.gov/cancerinfo/pdq/screening/cervical/patient/
- American Society of Colposcopy and Cervical Cancer Pathology
  http://www.asccp.org/pdfs/patient_edu/women_should_know.pdf

Partner Management and Public Health Measures

Partner Management for Patients with Genital Warts

- Sex partner examination is not necessary for management of genital warts because no data indicate that reinfection plays a role in recurrences.
- Providing treatment solely for the purpose of preventing future transmission cannot be recommended because the value of treatment in reducing infectivity is not known.
- The counseling of sex partners provides an opportunity for these partners to:
  - Learn about the implications of having a partner who has genital warts and about the potential for future disease transmission.
  - Receive STD and Pap screening if necessary.

Cervical Cancer Screening

- The key strategy to prevent cervical cancer is regular cervical cancer screening (Pap test screening) for all sexually active women.
- New technologies, including liquid-based cytology and testing for high-risk HPV types, may offer potential advantages over conventional Pap testing.
- Several organizations provide guidelines for cervical cancer screening, including:
  - The American Cancer Society
  - The American College of Obstetricians and Gynecologists
  - The U.S. Preventive Services Task Force

Reporting Requirements

- Genital HPV infection is not a reportable infection in any state.
- Genital warts are reportable in some states.
- Check with state or local health department for reporting requirements in your area.

HPV Vaccines

- Several potential approaches are under investigation.
- The most promising is the use of virus-like particles (VLPs), which preserve native conformations of viral proteins without presence of viral DNA.

Case Study

History

- **Anne Drew:** 34-year-old woman who wants to get "checked out" because Jonathan, her sex partner, has small solid "bumps" on the skin on the shaft of his penis
- Jonathan told her that he was diagnosed and treated for genital warts about a year ago, and his health care provider told him they could recur.
- No history of abnormal Pap smears and no history of STDs
- Last Pap smear performed 4 months ago
- Sexually active with men only since age 16; has had a total of 7 sex partners over her lifetime
- Currently sexually active with 1 partner for the last 8 months
- Uses oral contraceptives for birth control

Question

1. What should be included in Ms. Drew's evaluation?

Physical Examination

- Vital signs: blood pressure 96/74, pulse 78, respiration 13, temperature 37.1° C
- Cooperative, good historian
- Chest, heart, musculoskeletal, and abdominal exams within normal limits
- Pelvic exam is normal
- Visual inspection of the genitalia reveals multiple small (<0.5 cm), flesh-colored, papular lesions in the perineal area

Questions

2. What is the differential diagnosis for the papular genital lesions?
3. What is the **most likely** diagnosis based on history and physical examination?
4. Which laboratory tests should be ordered or performed?

Patient Management

The following genital warts management options are discussed with Ms. Drew:

- Patient-applied therapy
  - Podofilox 0.5% solution or gel (Condylox™)
  - Imiquimod 5% cream (Aldara™)
- Provider-administered therapy
  - Cryotherapy with liquid nitrogen or cryoprobe
  - Podophyllin resin 10%-25% in compound tincture of benzoin
  - Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80%-90%
- Surgical removal
- No intervention

Questions

5. What is the effect of treatment on future transmission? What is the possibility of recurrence after treatment?
6. What are appropriate counseling messages for Ms. Drew about genital warts and HPV infection?
7. What condition could cause a substantial increase in the number and size of Ms. Drew's genital warts?