Vulvar Cancer: Diagnosis and Prevention

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Dr. Mayeaux lives and practices in Columbia, South Carolina. He has received the American Society for Colposcopy and Cervical Pathology (ASCCP) Award of Merit three times and has also received numerous faculty teaching awards. He focuses on women’s health and skin diseases, noting that the most important trends in the field are the rise and fall of methicillin-resistant Staphylococcus aureus (MRSA), changes in Pap test recommendations and follow-up, and changes in human papillomavirus (HPV) testing recommendations. Dr. Mayeaux considers keeping up with the rapidly changing knowledge base in medicine to be family medicine’s most critical challenge. Other professional interests include health care quality, preventive medicine, and returning joy to medical practice.

Learning Objectives

1. Provide counseling and patient education resources for female patients to maximize HPV prevention, including HPV vaccination safety and efficacy.
2. Institute systems strategies that optimize the evaluation of suspicious lesions of the vulva for cancer.
3. Order appropriate laboratory and diagnostic tests to determine a diagnosis of vulvar cancer.
4. Develop collaborative care plans for treatment, as indicated by staging, coordinating care and follow-up as necessary.

Audience Engagement System

Step 1 Step 2 Step 3
HPV Causes Multiple Cancers in Men & Women

HPV Risk Factors

Reduce HPV Transmission

AES POLL QUESTION

Mrs. H states she heard there is a new HPV vaccine available. Which of the following would be correct information to give her?

A. HPVv9 may only be used if the series is started from the 1st dose
B. HPVv9 is only indicated in females 11 or 12 years of age
C. HPVv9 prevents about 70% of cervical cancers
D. 9vHPV is indicated for males 11 or 12 years and males through 21 years who have not been fully vaccinated

HPV Vaccination in Females

- Girls 11 or 12 years old should get HPV2, HPV4, or HPV9 vaccine to protect against cervical cancer
- Age ≤26 years who did not complete series should also get the HPV vaccine series
- 3-dose schedule with second dose 1 to 2 months after the first dose, and the third dose 6 months after first dose
- If the HPV vaccine schedule is interrupted, resume with next dose

HPV Vaccination in Males

- Boys 11 or 12 years old should get 3 doses of HPV4 or HPV9 vaccine to protect against genital warts and anal cancer
- Boys and young men 13-21 years, who did not complete three recommended doses, should also get the HPV vaccine series
- MSM and immunocompromised males should receive the vaccine through age 26 years, if they did not start or complete the vaccine series when they were younger

Distribution of HPV Types Cx Ca- International

HPV 45, 31, 52, 33 and 58 are responsible for an additional ≈19% of cervical cancer cases

Recommendations to Ensure Patients get Fully Vaccinated

- Strongly recommend. Studies consistently show that provider recommendation is the strongest predictor of vaccination.
- Use every opportunity to vaccinate your adolescent patients including sick visits and sports physicals.
- Use patient reminder and recall.
- Educate parents about the diseases that can be prevented. In the end, HPV vaccination is about cancer prevention. Who doesn’t want that?
- Implement standing orders and involve the whole office.

HPV-4 Prophylactic Efficacy EGWs
Par-Protocol Population (Protocols 007, 013, and 015)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Mean Follow-Up of 44 months</th>
<th>HPV-4 Cases (N = 9075)</th>
<th>Placebo Cases (N = 9075)</th>
<th>% Efficacy</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV 6/11/16/18-related Ext Gen Lesion</td>
<td>2</td>
<td>227</td>
<td>99</td>
<td>(97, 100)</td>
<td></td>
</tr>
<tr>
<td>By Type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV 6-related</td>
<td>2</td>
<td>179</td>
<td>99</td>
<td>(96, 100)</td>
<td></td>
</tr>
<tr>
<td>HPV 11-related</td>
<td>0</td>
<td>26</td>
<td>100</td>
<td>(99, 100)</td>
<td></td>
</tr>
<tr>
<td>HPV 16-related</td>
<td>0</td>
<td>46</td>
<td>100</td>
<td>(92, 100)</td>
<td></td>
</tr>
<tr>
<td>HPV 18-related</td>
<td>0</td>
<td>13</td>
<td>100</td>
<td>(68, 100)</td>
<td></td>
</tr>
<tr>
<td>By Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genital Warts</td>
<td>2</td>
<td>193</td>
<td>99</td>
<td>(96, 100)</td>
<td></td>
</tr>
<tr>
<td>VIN 1 or VaIN 1</td>
<td>0</td>
<td>28</td>
<td>100</td>
<td>(98, 100)</td>
<td></td>
</tr>
</tbody>
</table>

HPV Vaccine Works - Proportion of Australian-born Women with Genital Warts by Age Group, 2004-2011

Resources
- Adolescent Vaccination Call to Action: www.adolescentvaccination.org/doc/call_to_action.pdf
- Centers for Disease Control and Prevention, Vaccine Homepage: www.cdc.gov/vaccines
- Vaccine information statement (VIS) in many languages: www.cdc.gov/vaccines/pubs/vis/default.htm

LSIL / Condyloma
- Flat condylomas are vulvar LSIL

Diagnosis of LSIL / Condyloma
- Majority diagnosed by visual inspection in bright light – Magnifying glass helpful
Genital Warts Diagnosis

- Can be confirmed by biopsy
  - If diagnosis is uncertain
  - Lesions do not respond to standard tx
  - Worsens during therapy
  - Atypical lesion
  - Patient has compromised immunity
- GW pigmented, indurated, fixed, bleeding, or ulcerated


Genital Warts Treatment

- Primary reason is symptoms (including relieving cosmetic concerns)
  - Can usually induce wart-free periods
  - Visible GWs can resolve on their own
- Tx likely reduces but not eradicates HPV infectivity
  - Reduces future transmission unclear
- GW not associated with cervical Ca


AES POLL QUESTION

Which is the following are not CDC recommended treatments for genital warts?
A. 5 fluorouracil
B. Imiquimod cream
C. Podofilox gel/solution
D. Sinecatechins ointment

**2015 CDC STD Treatment Guidelines: Patient-Applied Therapies**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Application/Dose</th>
<th>Duration of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imiquimod cream</td>
<td>Apply at bedtime 3 nights/week, wash off after 6-10 hours</td>
<td>Up to 16 weeks (D/C when clear)</td>
</tr>
<tr>
<td>Podofilox gel/solution</td>
<td>Apply twice a day</td>
<td>3 days followed by 4-day rest; repeat for up to 4 cycles</td>
</tr>
<tr>
<td>Sinecatechins ointment</td>
<td>Apply thin layer to each wart three times a day</td>
<td>Up to 16 weeks (D/C when clear)</td>
</tr>
</tbody>
</table>

CDC. Sexually transmitted diseases treatment guidelines. MMWR; 2015; 64: 85-90.

**2015 CDC STD Treatment Guidelines: Provider-Administered Therapies**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Application/Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryotherapy</td>
<td>Applications may be repeated every 1-2 weeks</td>
</tr>
<tr>
<td>Podophyllin resin</td>
<td>0.5 mL applied to each wart and allowed to air dry</td>
</tr>
<tr>
<td>TCA or BCA</td>
<td>Can be applied weekly, if needed, and allowed to air dry</td>
</tr>
<tr>
<td>Surgical</td>
<td>Better for isolated lesions</td>
</tr>
</tbody>
</table>

CDC. Sexually transmitted diseases treatment guidelines. MMWR; 2015; 64: 85-90.

**Incidence of Vulva HSIL**
- Heightened awareness of neoplasia
- Increased tendency to perform biopsies
- Commonly associated with other lower genital tract neoplasias / carcinomas – Anus, vagina, cervix
- 75% of increase in younger women


**Risk Factors for Vulvar HSIL**
- HPV (vulva, vagina, cervix)
- Cigarette smoking
- Immunosuppression
  - Pregnancy
  - HIV
  - Autoimmune disorders
  - Diabetes
  - Transplant recipient
  - Chronic hepatitis
  - Chemotherapy


**Incidence Rate of Neoplasias in Women With and Without a History of CIN3**

Symptoms

- Most - completely asymptomatic
- Itching or burning
- Irritation
- Dyspareunia

Colposcopic Techniques

- 3% to 5% acetic acid
- Soak initially for 3-5 min.
- Use copious amounts
- Reapply often
- Avoid using in presence of breaks in epithelium or inflammation

Pitfalls of Vulvar Colposcopy

- Acetowhiteness is nonspecific
- Marked acetowhite changes in up to 65% of normal women
- Normal variants – like vestibular micropapillae – often confused with HPV

Gray-Brown HSIL

White HSIL

Red HSIL

Vin Differentiated
Acceptable treatment is surgical excision
AES POLL QUESTION
A 79 y.o. G2P2 complains of a vulvar sore and itching for 1 year. A biopsy is performed. Diagnosis?
A. Lichen planus
B. HSIL (squamous)
C. Lichen sclerosus
D. Paget’s disease

Paget Disease
- Occurs most commonly on the nipple and areola
- Also found on vulva and scrotum
- Apocrine origin

Paget Disease of the Vulva
- Pink eczematous lesion with islands of white hyperkeratosis & pruritus
- Most commonly diagnosed in Caucasian postmenopausal women
- At risk for a second synchronous or metachronous neoplasm
  - Colorectal adenocarcinoma
  - Cervical adenocarcinoma
  - Carcinoma of the transitional epithelium from the renal pelvis to urethra
  - Breast and/or vulvar carcinoma
- Routine screening with colonoscopy, Pap test, mammogram and cystoscopy is recommended

Melanomas of the Vulva and Vagina
- Malignant melanoma is most malignant type of skin cancer
- Average age at diagnosis ~77 years
  - Median overall survival time ~22 months
  - 5-year survival ~18%
- Nodular and superficial spreading melanomas found
- Symptoms: vaginal bleeding, stinging in the area, felt pain, itching

Punch Biopsy
- Adequate for dx of most skin tumors
  - OK for Melanoma dx
  - Select early lesion or well-advanced
  - Consider underlying structures
  - Include most clinically suspicious area
- There is no evidence that biopsy increases the risk of disease progression
**Punch Biopsy**
- **Anesthesia**
  - 1% lidocaine (sodium bicarb)
  - 27-30 gauge needle to inject 1-3 cc's of anesthetic agent
  - Inject subepidermally
- **3-5 mm Keyes punch**
- **Fine suture (3.0 or 4.0)**
  - Hemostasis & ↓ pain
  - Monsel's/Silver nitrate slows healing

**Vulvar Punch Biopsy**

**Cervical biopsy instruments that can also be used for vulvar biopsy**

**Management**

**AES POLL QUESTION**
Acceptable treatment modalities for Vulvar HSIL includes
A. Surgical excision
B. Laser ablation
C. Electrosurgical excision
D. All of the above

**Vulvar Excisional**
Margins and Depth
Vulvar HSIL

- Margins
- Depth
  - Hair bearing areas to 2.7 mm
  - Non-hair bearing = 0.1 to 1.9 mm (average = 0.5 +/- 0.2 mm)


Recurs After Treatment
(mean follow-up 39 months)

- No statistically significant differences between groups

Gynecologic Oncology. 2005; 97: 645-651

Imiquimod

- Systematic review of treatment of vulvar HSIL that included the two randomized trials and eight observational studies (total n = 162)
  - Complete response rate = 51%
  - Partial response rate = 25%
  - Recurrence rate = 16%
- Side effects mostly site inflammation
  - mild to moderate erythema or erosions.


HGSIL Progression to SCC
(from PALGA, the Nationwide Netherlands Database of Histo- and Cytopathology)

- Progression to SCC over 14 years, treated patients
  - 5.7% of 1826 patients with HPV-associated vulvar HSIL
  - 32.8% of 67 patients with VIN differentiated
- Median time from vulvar HSIL dx to SCC diagnosis
  - 41.4 mos for HPV-associated vulvar HSIL
  - 22.8 mos for VIN differentiated


Stop Smoking!

Paget Disease Workup

- History and PE
  - Symptoms include itching, burning (soreness)
  - Signs include velvety appearance and bleeding
- Pap testing
- Mammogram
- Cystoscopy
- Colonoscopy

Courtesy of the CDC/Debora Cartagena
Paget Disease Treatment

Wide local excision (usually), Imiquimod, 5-Fluorouracil, Laser ablation

- The majority of patients with Paget’s disease of the vulva develop multiple recurrences regardless of treatment modality or margin status


When Biopsy = Cancer

- Referral to oncology most common
- Staging tests include
  - Cystourethroscopy, Proctoscopy
  - Imaging modalities (CT, MRI, or PET)
- Lymph node metastasis most important prognostic factor
- Suspected distant metastases confirmed with biopsy or fine-needle aspiration


Vulvar Cancer Surgical Treatment

- Surgery is the standard treatment for stage IA, local regional SCC of the vulva.
  - Microinvasive carcinomas (<2 cm size and <1 mm stromal invasion) are treated with wide local excision with at least a 1 cm free margin.
  - Local recurrence and lymph node metastases rare, so lymphadenectomy not recommended as initially.
- Stages IB and II cancers are treated with radical vulvectomy with inguinofemoral lymphadenectomy


ICD-10 Codes

<table>
<thead>
<tr>
<th>Code</th>
<th>Descriptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>D07.1</td>
<td>Carcinoma in situ of vulva (VIN3/HSIL)</td>
</tr>
<tr>
<td>C51.0</td>
<td>Malignant neoplasm of labium minus</td>
</tr>
<tr>
<td>C51.1</td>
<td>Malignant neoplasm of labium minus, each separate additional lesion</td>
</tr>
<tr>
<td>C51.2</td>
<td>Malignant neoplasm of clitoris</td>
</tr>
<tr>
<td>C51.8</td>
<td>Malignant neoplasm of overlapping sites of vulva</td>
</tr>
<tr>
<td>D39.8</td>
<td>Neoplasm of uncertain behavior of other specified female genital organs</td>
</tr>
<tr>
<td>N90.0</td>
<td>Mild vulvar dysplasia (VIN1/LSIL)</td>
</tr>
<tr>
<td>N90.1</td>
<td>Moderate vulvar dysplasia (VIN2/HSIL)</td>
</tr>
<tr>
<td>N90.2</td>
<td>Mild vulvar dysplasia (VIN1/LSIL)</td>
</tr>
<tr>
<td>N90.3</td>
<td>Moderate vulvar dysplasia (VIN2/HSIL)</td>
</tr>
<tr>
<td>C51.9</td>
<td>Malignant neoplasm of vulva, unspecified</td>
</tr>
</tbody>
</table>

Practice Recommendations

- HPV vaccination should be used at indicated ages to prevent future HPV related diseases (SORT A)
- Vulvar dysplasia may present with multiple morphologies and colors (SORT V)
- Biopsy is diagnostic method of choice (SORT C)
Questions