COMMITTEE OPINION

Management of Vulvar Intraepithelial Neoplasia

SCOPE OF THE PROBLEM

- Vulvar disease is an increasingly common problem
- From SEER, the rate of in situ vulvar disease has increased 4-fold since 1973
- But it remains relatively rare: 3/100,000 women/year (10 fold lower than CIN)
TERMINOLOGY FOR VIN

- The old terminology for vulvar disease matched that for cervical disease:
- Vulvar intraepithelial neoplasia (VIN) graded as 1, 2, 3 (corresponding to mild, moderate and severe dysplasia/carcinoma in situ respectively)

TERMINOLOGY

- In 2004 ISSVD* changed the VIN terminology to be used only for high grade disease
- Subdivided VIN into 2 categories:
  - Usual type VIN (associated with HPV, immunocompromise, smoking). There are 3 categories of usual type VIN: warty, basaloid or mixed
  - Differentiated type VIN (associated with vulvar dermatoses such as lichen sclerosus, and more likely to be associated with squamous cell cancer)

*N ISSVD = International Society for the Study of Vulvovaginal Disease

TERMINOLOGY

- In 2015 the ISSVD changed terminology to unify nomenclature with WHO, ACOG and ASCCP:
  - Vulvar LSIL (external genital warts, condyloma, HPV effect, VIN 1)
  - Vulvar HSIL (precancer, usual type VIN)
  - Differentiated VIN (remains the same)

NATURAL HISTORY

- Vulvar HSIL is considered a true cancer precursor
- 16% of women with untreated vulvar disease progressed to cancer
- Occult invasive cancer was present in 3% of excisions performed for VIN
- Women with a history of vulvar HSIL remain at increased risk of recurrent disease and vulvar cancer throughout their lifetime
RISK FACTORS

<table>
<thead>
<tr>
<th>Vulvar cancer</th>
<th>Vulvar HSIL</th>
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<tr>
<td>Infection with high risk genital HPV types</td>
<td>Infection with high risk genital HPV types</td>
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<td>Age &gt; 50</td>
<td>Age &lt; 50</td>
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<td>Smoking</td>
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<td>HIV infection</td>
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<td>Immune suppression</td>
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DIAGNOSIS

- There is no screening strategy for prevention of vulvar cancer
- Detection of vulvar LSIL and HSIL is based on visual inspection with biopsy as needed

DIAGNOSIS

- Biopsy is indicated for visible lesions in which:
  - A definitive diagnosis cannot be made clinically
  - Appearance suggests possible malignancy
  - There are atypical vascular patterns
  - The lesion was previously stable but changes rapidly in color, border or size

DIAGNOSIS

- Expert opinion is varied as to the need for biopsy of women with warty lesions, but is indicated if
  - Suspected condyloma do not respond to topical therapy
  - In postmenopausal women with apparent genital warts
**DIAGNOSIS**

• Colposcopy of the vulva can be useful
  – in women with no visible lesion but with focal symptoms (pain, itching)
  – in women who remain symptomatic after appropriate treatment for vulvovaginitis
  – To delineate the extent of disease during laser therapy

• Colposcopy of the vulva requires longer application of acetic acid (3-5%)
• Usual colposcopic features seen on the cervix (punctuation, mosaicism) are not usually present on vulva

**TREATMENT of VULVAR HSIL**

• Vulvar HSIL is considered a true cancer precursor
• 16% of women with untreated vulvar disease progressed to cancer
• Therefore treatment is recommended for vulvar HSIL
• Treatment can be with excision, laser ablation or topical imiquimod (off-label use)

**TREATMENT: Excision**

• Wide local excision is indicated in cases in which invasion is suspected from the clinical or pathological impression, even if a biopsy only shows vulvar HSIL
• Margins of 0.5-1.0 cm are recommended, although this may need to be modified to avoid injury to structures such as the urethra, clitoris, anus etc.
TREATMENT: Laser

- Laser is acceptable if cancer is not suspected
- Use of appropriate power density and micromanipulator or hand piece allow precise ablation without deep coagulation injury
- Ablation of vulvar LSIL can be more superficial confined to the lesions, whereas ablation of vulvar HSIL should extend through the full thickness of the epithelium and extend into hair follicles in hair-bearing areas

TREATMENT: 5% imiquimod

- Off-label use with well-documented efficacy in randomized trials
- Applied to lesions 3x weekly for 12-20 weeks
- Assessment at 4-6 week intervals
- Side effects can be severe erythema and pain, at which point therapy should be terminated
- Mechanism of action is to activate local immune response, therefore may have reduced efficacy in immunosuppressed women

TREATMENT: Other medical therapies

- 5% 5-fluorouracil (effudex) cream: used frequently in the 1970s and 80s, has fallen out of fashion and there are no recent studies about efficacy of VULVAR HSIL
- Topical cidofovir cream is under investigation. At this point it needs to be formulated into a cream base by the pharmacy and is expensive.

RECURRANCE AFTER TREATMENT

- Cure rates range from 50-90%
- Women with a history of vulvar HSIL remain at increased risk of recurrent disease and vulvar cancer throughout their lifetime
- Recurrence is higher in women with
  - Multifocal disease
  - Positive margins on surgical samples
  - Medical rather than surgical disease
  - Immune suppression
  - Smoking
SURVEILLANCE AFTER TREATMENT

- ACOG recommends follow-up visits at 6 and 12 months after treatment
- Annual visual inspection is recommended thereafter in women with no evidence of recurrence

PREVENTION

- Vaccination with the quadrivalent or 9-valent HPV vaccine has been shown to reduce the incidence of vulvar LSIL and HSIL
- CDC recommends vaccination of girls ages 11-12, with catch-up to the age of 26

PREVENTION

- Smoking cessation
- Treatment of vulvar dermatologic disorders (lichen sclerosus) that are associated with differentiated VIN and with squamous cancer

TREATMENT of VULVAR LSIL

- The goal of treatment is to destroy genital warts, when desired
- Preserve integrity of normal adjacent tissue
- Reduce potential for transmission
- Prevent high grade disease
- Minimize chance of disease recurrence
- Address psychological concerns
- Provide patient education
TREATMENT of VULVAR LSIL

- Provider administered
  - TCA, BCA
  - liquid nitrogen
  - podophyllin
- Patient administered
  - Podofilox 0.5% solution or gel (condylox)
  - Imiquimod 5% cream (Aldara)
  - Polyphenon E (Veregen)
- Providers should be comfortable with one treatment modality from each category
- Success rates are essentially equivalent with all modalities

Genital warts: patient administered

- eliminates need for multiple clinic visits, usually painless, convenient
- requires that patient be able to reach the affected area, is comfortable with self examination and self treatment
- Follow-up visit useful to determine efficacy of therapy

VAIN

- Prevalence 0.2-0.3/women/year
- Risk factors:
  - HPV infection
  - HPV-related disease elsewhere in the genital tract (eg CIN or VIN)
  - Smoking
  - DES exposure
  - Immune suppression

TERMINOLOGY FOR VAIN

- The old terminology for vaginal disease matched that for cervical disease:
- Vaginal intraepithelial neoplasia (VAIN) was graded as 1, 2, 3 (corresponding to mild, moderate and severe dysplasia/carcinoma in situ respectively)
**TERMINOLOGY FOR VAIN**

- In 2012 the Lower Anogenital Squamous Terminology (LAST) standardization project was sponsored by the American College of Pathologists and the American Society for Colposcopy and Cervical Pathology (ASCCP)
- Recommended a 2-tiered nomenclature for all squamous lesions: LSIL and HSIL
- Vaginal LSIL corresponds to VAIN 1
- Vaginal HSIL corresponds to VAIN 2 and 3

**NATURAL HISTORY**

- No large prospective studies
- 0-10% of women with vaginal HSIL developed vaginal cancer (retrospective studies and small prospective studies)
- The current standard of care is that vaginal HSIL is considered a true cancer precursor

**DIAGNOSIS**

- Vaginal HSIL is usually asymptomatic, but may be associated with abnormal bleeding, postcoital bleeding, vaginal discharge or pain
- Consider the presence of vaginal HSIL in a woman with HSIL cytology and no obvious source on cervical colposcopy

**DIAGNOSIS**

- There is some evidence that women s/p hysterectomy with a history of cervical HSIL remain at increased risk of development of vaginal HSIL with a mean interval of 10 years
- ACOG (2016) recommends cytology every 3 years for 20 years in women s/p hysterectomy with a history of CIN 2+
**DIAGNOSIS**

- Digital exam to assess for areas of uneven texture or masses
- Colposcopic exam to assess for acetowhiteness, vascular abnormalities, and Lugol's iodine or Schiller's non-staining
- Biopsy of abnormal areas for histological diagnosis

**TREATMENT**

- If the lesion is worrisome for cancer, excision is indicated (wide local excision, partial vaginectomy, vaginectomy)
- Disease in the hysterectomy cuff can be challenging to visualize and is optimally treated with excision
- CO2 laser ablation is appropriate for lesions in which no invasion is suspected colposcopically and on biopsy
- Multifocal disease can be best treated with laser ablation

**TREATMENT**

- Treatments can lead to vaginal shortening and stenosis, more common with excisional treatments
- Topical therapies eg 5% 5-fluorouracil are of unproven efficacy
- Imiquimod is not intended for internal use

**SURVEILLANCE AFTER TREATMENT**

- Recurrence rates are approximately 20-30%
- Vaginal cytology is appropriate for surveillance, with colposcopic exam if the cytology is abnormal
PREVENTION

• Vaccination with the quadrivalent or 9-valent HPV vaccine is recommended by CDC in girls ages 11-12, with catch-up to the age of 26
• Smoking cessation

CASES

• We will review clinical cases to highlight key points