



The American College of Obstetricians and Gynecologists

Women's Health Care Physicians

COMMITTEE OPINION

Number 509 • November 2011

Committee on Gynecologic Practice

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Management of Vulvar Intraepithelial Neoplasia

ABSTRACT: Vulvar intraepithelial neoplasia (VIN) is an increasingly common problem, particularly among women in their 40s. The term VIN is used to denote high-grade squamous lesions and is subdivided into usual-type VIN (including warty, basaloid, and mixed VIN) and differentiated VIN. Usual-type VIN is commonly associated with carcinogenic genotypes of human papillomavirus (HPV) and other HPV persistence risk factors, such as cigarette smoking and immunocompromised status, whereas differentiated VIN usually is not associated with HPV and is more often associated with vulvar dermatologic conditions, such as lichen sclerosus. Biopsy is indicated for any pigmented vulvar lesion. Treatment is indicated for all cases of VIN. When occult invasion is not a concern, VIN can be treated with surgical therapy, laser ablation, or medical therapy. After resolution, women should be monitored at 6 and 12 months and annually thereafter.

Scope of the Problem

Vulvar intraepithelial neoplasia (VIN) is an increasingly common problem, particularly among women in their 40s. Data from the U.S. Surveillance, Epidemiology, and End Results program show that VIN incidence increased more than fourfold between 1973 and 2000 (1). Although spontaneous regression has been reported, VIN should be considered a premalignant condition, as shown by a case series of 405 New Zealand women with VIN (2). Sixty-three (16%) women received no treatment of whom 10 women experienced invasive cancer progression before treatment (2). Although cancer regression has been reported, especially among women in whom cancer was diagnosed during pregnancy (3), the risk of cancer progression appears to outweigh the risks of treatment, and prognostic factors are not sufficiently reliable to select women for treatment. Occult invasive cancer has been reported in 3% of women undergoing surgery for VIN, although two thirds of cases of invasive cancer in women receiving surgical treatment for VIN are superficial (3). The focus of this Committee Opinion will be on the management of high-grade squamous lesions recognized as VIN under the International Society for the Study of Vulvovaginal Disease (ISSVD) system.

Classification

Traditionally, squamous VIN was classified into three grades, analogous to the three-grade cervical intraepi-

thelial neoplasia classification. Subsequent studies determined that VIN 1 reflects a usually self-limited infection caused by human papillomavirus (HPV). In 2004, the ISSVD replaced the previous three-grade classification system with the current single-grade system, in which only high-grade disease is classified as VIN (4). In the current system, VIN is subdivided into usual-type VIN (including warty, basaloid, and mixed VIN) and differentiated VIN. Usual-type VIN is commonly associated with carcinogenic genotypes of HPV and other HPV persistence risk factors, such as cigarette smoking and immunocompromised status, whereas differentiated VIN usually is not associated with HPV and is more often associated with vulvar dermatologic conditions, such as lichen sclerosus. However, differentiated VIN associated with lichen sclerosus is more likely to be associated with a squamous cell carcinoma of the vulva than usual-type VIN.

Flat lesions associated with basal atypia and koilocytic changes (formerly termed VIN 1) are considered condylomas in the current ISSVD classification system and can be treated as such (4). Other intraepithelial vulvar neoplasms, such as Paget disease and melanoma in situ, are rare.

Prevention

Immunization with the quadrivalent HPV vaccine, which is effective against HPV genotypes 6, 11, 16, and 18, has

been shown to decrease the risk of VIN and should be recommended for women in target populations (5). The bivalent HPV vaccine is not approved for this indication, because this endpoint was not assessed in clinical trials. Cigarette smoking is strongly associated with usual-type VIN, and cessation should be encouraged, although no studies have shown a reduction in VIN incidence or posttreatment recurrence after smoking-cessation efforts. Differentiated VIN may be associated with vulvar dermatoses, and treatment of vulvar dermatologic disorders may reduce VIN and cancer risk.

Diagnosis

No screening strategies have been developed for the prevention of vulvar cancer through early detection of VIN. Vulvar cytologic testing is complicated by the keratinization of vulvar skin, making performance and interpretation of test results problematic. Diagnosis is limited to visual assessment. The appearance of VIN can vary. Most women have visible lesions that are elevated, but flat lesions occur. Color can vary from white to gray or from red to brown to black. Biopsy is indicated for any pigmented vulvar lesion. Expert opinion is divided regarding the need for biopsy of all warty lesions, but biopsy should be performed in postmenopausal women with apparent genital warts and in women in whom topical therapies have failed. Colposcopy, or other forms of magnification of the vulva, can be useful in determining the extent of disease and should be performed after applying 3–5% acetic acid to the vulva for several minutes using soaked gauze pads. Keratinization requires longer acetic acid application for effect and often renders typical colposcopic grading criteria useless. Although toluidine blue testing is often cited for use in the assessment of VIN, this method is infrequently used and rarely beneficial in the diagnosis of VIN.

Treatment

Treatment is recommended for all women with VIN. Wide local excision is recommended when cancer is suspected. When occult invasion is not a concern, VIN can be treated with surgical therapy, laser ablation, or medical therapy.

Surgical Therapy

Wide local excision is the preferred initial intervention for women in whom clinical or pathologic findings suggest invasive cancer, despite a biopsy diagnosis of only VIN, to obtain a specimen for pathologic analysis. The excision should be tailored to the lesion. Wide local excision is also acceptable for women in whom cancer is not suspected. Skinning vulvectomy, which removes all vulvar skin, is rarely needed, although it may be useful for cases of confluent multifocal lesions, which can occur in women who are immunocompromised. Women with pathologic clear margins have a lower, although still significant, risk of recurrence compared with women with

involved margins (6); gross margins of 0.5–1 cm around tissue with visible disease appear optimal but may be altered to avoid injury to the clitoris, urethra, anus, or other critical structures.

Laser Ablation

Laser ablation is acceptable for the treatment of VIN when cancer is not suspected. It can be used for single, multifocal, or confluent lesions, although the risk of recurrence may be higher than with excision (7, 8). Appropriate power density (750–1,250 W/cm²) is critical to avoid deep coagulation injury. Colposcopy after application of 3–5% acetic acid facilitates delineation of lesion margins, and use of a micromanipulator or a hand piece with a depth gauge allows application of high-power density without inadvertent defocusing. As with excision, a margin of normal-appearing skin should be treated. In contrast to its application to genital warts, when superficial ablation is acceptable, laser treatment of VIN requires destruction of cells through the entire thickness of the epithelium. In hair-bearing areas, laser procedures must ablate hair follicles, which can contain VIN and extend into the subcutaneous fat for 3 mm or more. Consequently, large VIN lesions over hair-bearing areas may be preferentially treated with other modalities. Ablation over skin that does not bear hair should extend through the dermis (up to 2 mm).

Medical Therapy

Randomized controlled trials have shown that the application of topical imiquimod 5% is effective for the treatment of VIN (9), although it is not approved by the U.S. Food and Drug Administration for this purpose. Published regimens include three times weekly application to affected areas for 12–20 weeks, with colposcopic assessment at 4–6-week intervals during treatment. Residual lesions require surgical treatment. Erythema and vulvar pain may limit adverse effects. Experience with imiquimod in immunosuppressed patients is limited, and because it is believed to act through local immunomodulators, it may have decreased effectiveness in women who are immunocompromised. Sinecatechins are effective for the treatment of genital warts but have not been tested as a therapy for VIN and so should not be used for management of VIN outside of clinical trials. Photodynamic therapy has been effective in some trials but requires specialized equipment and training. Topical cidofovir cream and 5-fluorouracil creams have been tested in clinical trials with varying degrees of efficacy but have more pronounced adverse effects on skin and have fallen out of favor.

Surveillance

Posttreatment recurrence rates exceed 30–50% with all treatment regimens and are higher with positive excision margins. Follow-up has been limited in most studies, and women with VIN should be considered to be at risk of recurrent VIN and vulvar cancer throughout their

lifetimes. The value of vulvar self-examination and serial office visits in the detection of recurrence has not been proved prospectively, but both appear prudent. Given the relatively slow rate of progression, women with a complete response to therapy and no new lesions at follow-up visits scheduled 6 and 12 months after initial treatment should be monitored annually thereafter.

Conclusions and Recommendations

The Committee on Gynecologic Practice of the American College of Obstetricians and Gynecologists and the American Society for Colposcopy and Cervical Pathology make the following conclusions and recommendations:

- Immunization with the quadrivalent HPV vaccine has been shown to decrease the risk of VIN and should be recommended for women in target populations.
- No screening strategies have been developed for the prevention of vulvar cancer through early detection of VIN.
- Diagnosis is limited to visual assessment. Biopsy is indicated for most pigmented vulvar lesions.
- Presumed genital warts should be biopsied in postmenopausal women and in women in whom topical treatments have failed.
- Treatment is indicated for all cases of VIN. Wide local excision is recommended when cancer is suspected, despite a biopsy diagnosis of only VIN, to identify occult invasion.
- When occult invasion is not a concern, VIN can be treated with excision, laser ablation, or topical imiquimod (off-label use).
- Women with VIN should be considered at risk of recurrent VIN and vulvar cancer throughout their lifetimes. After resolution, women should be monitored at 6 and 12 months and annually thereafter.

References

1. Judson PL, Habermann EB, Baxter NN, Durham SB, Virnig BA. Trends in the incidence of invasive and in situ vulvar carcinoma. *Obstet Gynecol* 2006;107:1018–22.

2. Jones RW, Rowan DM, Stewart AW. Vulvar intraepithelial neoplasia: aspects of the natural history and outcome in 405 women. *Obstet Gynecol* 2005;106:1319–26.
3. van Seters M, van Beurden M, de Craen AJ. Is the assumed natural history of vulvar intraepithelial neoplasia III based on enough evidence? A systematic review of 3322 published patients. *Gynecol Oncol* 2005;97:645–51.
4. Sideri M, Jones RW, Wilkinson EJ, Preti M, Heller DS, Scurry J, et al. Squamous vulvar intraepithelial neoplasia: 2004 modified terminology, ISSVD Vulvar Oncology Subcommittee. *J Reprod Med* 2005;50:807–10.
5. Munoz N, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, et al. Impact of human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV-associated genital diseases in young women. *J Natl Cancer Inst* 2010;102:325–39.
6. Modesitt SC, Waters AB, Walton L, Fowler WC Jr, Van Le L. Vulvar intraepithelial neoplasia III: occult cancer and the impact of margin status on recurrence. *Obstet Gynecol* 1998;92:962–6.
7. Sideri M, Spinaci L, Spolti N, Schettino F. Evaluation of CO(2) laser excision or vaporization for the treatment of vulvar intraepithelial neoplasia. *Gynecol Oncol* 1999;75:277–81.
8. Reid R. Superficial laser vulvectomy. III. A new surgical technique for appendage-conserving ablation of refractory condylomas and vulvar intraepithelial neoplasia. *Am J Obstet Gynecol* 1985;152:504–9.
9. van Seters M, van Beurden M, ten Kate FJ, Beckmann I, Ewing PC, Eijkemans MJ, et al. Treatment of vulvar intraepithelial neoplasia with topical imiquimod. *N Engl J Med* 2008;358:1465–73.

Copyright November 2011 by the American College of Obstetricians and Gynecologists, 409 12th Street, SW, PO Box 96920, Washington, DC 20090-6920. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, posted on the Internet, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without prior written permission from the publisher. Requests for authorization to make photocopies should be directed to: Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923, (978) 750-8400.

ISSN 1074-861X

Management of vulvar intraepithelial neoplasia. Committee Opinion No. 509. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2011;118:1192–4.