For the citation of the present AEPCC-Guide it will be stated:
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1. JUSTIFICATION AND OBJECTIVES

The main purpose of the Spanish Association of Cervix Pathologies and Colposcopy (Asociación Española de Patología Cervical y Colposcopia – AEPCC) is to “promote knowledge and investigation of the lower genital tract in women”. Therefore, the AEPCC has developed the “AEPCC-Guidelines” (AEPCC-guías) in order to guide decision making and to provide criteria for the diagnosis, management and treatment of lower genital lower genital tract pathologies. These scientific evidence-based guidelines are systematically developed and cover specific areas of knowledge of lower genital tract diseases, being characterized by their relevance and important impact on clinical practice.

The specific objectives of the AEPCC-guidelines are to:

- Promote standardized lines of action based on the current scientific evidence and on reliable information and scientific consensus.
- Ensure the equality of patients receiving health care, regardless of their location, thus promoting good practice.
- Improve the effectiveness of interventions and the quality of health care.
- Favor the implementation of quality control or clinical efficacy indicators.
- Facilitate decision-making among administrative managers and planners of health resources.

Lastly, the methodological rigor established for the preparation of the AEPCC-guidelines is aimed at the development of documents of outstanding scientific quality which will allow better clinical practice and greater knowledge of lower genital tract diseases.

2. METHODOLOGY

The specific methodology followed for the preparation of AEPCC-guidelines includes the following aspects:

- The AEPCC Steering Committee appoints a coordinator responsible for the preparation of the AEPCC-guidelines. In accordance with the Steering Committee, the Coordinator appoints the Writing Committee consisting of him/herself, a Secretary and the participants. The members are professional experts who are members of the AEPCC or other scientific societies with recognized prestige in this topic.
- Consensual development of the index.
- Critical review of the available literature and assignment of levels of evidence.
- Discussion and consensus among the committee members for assigning the grade of recommendation.
- Writing the document.
- Final analysis of the document by a Review and Editing Committee.
- Printed and online format of the final version.
- Dissemination of the AEPCC-guidelines in congresses, courses and seminars organized by the AEPCC.
- Development of online courses on the content of the AEPCC-guidelines to provide detailed knowledge of these guidelines and facilitate their implementation in daily clinical practice. (training credits).
- Update of the AEPCC-guidelines.
Assessment of the scientific evidence and extent and strength of the recommendations. The GRADE System.

“Clinical practice guidelines” consist of recommendations addressed to health care professionals to help them care for patients with a particular clinical condition. They are based on the most important literature on a certain topic (systematic reviews of the medical literature and identification of studies with greater scientific evidence) and on clinical experience. In general, prospective randomized studies are granted the highest level of consideration, whereas data obtained from the opinion of experts receive the lowest level. In this way it is possible to assess the quality of the evidence associated with the outcomes of a particular strategy. All the recommendations of the AEPCC-guidelines take into account the quality of the current scientific literature. The strength of each recommendation is agreed upon by the Writing Committee of the AEPCC-guidelines depending on the quality of the studies available.

The GRADE (Grading of Recommendations Assessment, Development and Evaluation Working Group) system (http://www.gradeworkinggroup.org) is used for the classification of scientific evidence and to determine the extent and strength of the recommendations.

To do this the following steps are followed:

1. The PICO (patient, intervention, comparison, outcomes) questions are established and outcome variables (in terms of benefit and risk) for each of the intervention questions asked are defined.

2. Outcome variables are scored from 1 to 9. Outcome variables considered key for decision making are scored from 7 to 9; important variables (but not key) from 4 to 6, and less important variables are scored from 1 to 3. The Working Group identifies, assesses and agrees upon the importance of the outcome variables.

3. Evaluation of the quality of the evidence for each of the key outcome variables. Search strategies have been designed to identify systematic reviews and randomized clinical trials and other studies published. The GRADE system assesses the quality of the evidence for each variable as high, moderate, low and very low. Randomized clinical trials and systematic reviews of randomized clinical trials have a high quality of evidence while observational studies and systematic reviews of observational studies have a low quality of evidence. Table 1 shows the different aspects which decrease or increase the quality of evidence.

4. Assessment of the overall quality of evidence. The overall quality of evidence was based across outcomes based on the lowest quality of evidence achieved for key outcome variables. In cases in which evidence for all the key variables favors the same alternative and there is evidence of high quality for some but not for all variables, the overall quality is considered as high. Low quality evidence on unimportant benefits and risks does not decrease the overall grade of evidence.

5. Designating strength to the recommendation. The GRADE system differentiates between strong and weak recommendations and makes explicit judgments about the factors that may affect the strength of the recommendation: balance between benefits and risks, overall quality of evidence, values and preferences of the population and costs. Both categories, strong and weak, may be for or against a particular intervention. Table II describes the meaning of the strong and weak categories.
QUALITY OF THE EVIDENCE

Table 1.- GRADE system for assigning the quality of evidence

<table>
<thead>
<tr>
<th>Study design</th>
<th>Initial quality of evidence</th>
<th>In clinical trials, decrease if *</th>
<th>In observational studies increase if</th>
<th>Final quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized clinical trials</td>
<td>High</td>
<td>Critical (-1) or very important (-2) limitation to study quality</td>
<td>Consistent and direct strong association** without confusing factors</td>
<td>High</td>
</tr>
<tr>
<td>Observational study</td>
<td>Low</td>
<td>Important inconsistency (-1) Some (-1) or major (-2) uncertainty about directness of evidence</td>
<td>Very strong evidence** without major threats to validity (no biases) and direct evidence (+2).</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Imprecise or sparse data</td>
<td>Dose response gradient (+1)</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High probability of reporting bias (-1)</td>
<td>All plausible confounders could have reduced the observed effect (+1)</td>
<td>Very low</td>
</tr>
</tbody>
</table>

* Increase (+1) or decrease (-1) a level (e.g. from high to moderate); 2, increase (+2) or decrease (-2) two levels (e.g. from high to low)
** A statistically significant relative risk > 2 (< 0.5) based on evidences consisting in two or more observational studies without plausible confounders.
*** a statistically significant relative risk > 5 (< 0.2) based on direct evidence and without major threats to validity.


STRENGTH OF RECOMMENDATIONS

Table 2.- GRADE system for designating strength to recommendations

<table>
<thead>
<tr>
<th></th>
<th>Strong</th>
<th>Weak</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>Most people would agree on the recommended course of action and only a small number would not.</td>
<td>Most informed people would choose the recommended course of action, but a substantial number would not.</td>
</tr>
<tr>
<td><strong>Clinicians</strong></td>
<td>Most patients should receive the intervention recommended</td>
<td>Recognizes that there are different options for different patients and health care professionals must help each patient to make the decision which is most consistent with their values and preferences.</td>
</tr>
<tr>
<td><strong>Managers/policy makers</strong></td>
<td>the recommendation can be adopted as a policy in most situations</td>
<td>Policy making will require substantial debate and involvement of many stakeholders</td>
</tr>
</tbody>
</table>

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VULVAR INTRAEPITHELIAL NEOPLASIA (VIN)

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# VULVAR INTRAEPITHELIAL NEOPLASIA (VIN)

## TABLE OF CONTENTS

1. **INTRODUCTION** .......................................................... 09

2. **TERMINOLOGY AND CLASSIFICATION** ................... 10
   2.1. 2004 ISSVD Classification .................................. 10
   2.2. 2004 WHO Classification and 2015 ISSVD Classification ................................................. 11

3. **EPIDEMIOLOGY** ...................................................... 12

4. **ETIOPATHOGENESIS** .............................................. 14
   4.1 HSIL (usual-type VIN) ............................................ 14
   4.2 Differentiated-type VIN ......................................... 14

5. **NATURAL HISTORY OF VIN** ...................................... 15

6. **HISTOLOGY** .......................................................... 16
   6.1 HSIL (usual-type VIN) ............................................ 16
   6.2 Differentiated-type VIN ......................................... 16

7. **CLINICAL CHARACTERISTICS** ................................. 18

8. **DIAGNOSIS** .......................................................... 19
   8.1 Clinical Examination and Vulvoscopy ..................... 19
   8.2 Biopsy (Indications and Methodology) .................... 19
   8.3 Suspected Occult Invasion .................................... 20
   8.4 Differential Diagnosis .......................................... 20

9. **TREATMENT** .......................................................... 21
   9.1 General Principles ................................................ 21
   9.2 Excision .......................................................... 21
   9.2.1 Simple local excision ...................................... 21
   9.2.2 Partial or Total Skinning Vulvectomy ................... 21
   9.2.3 Simple Vulvectomy ......................................... 22
   9.3 Ablation .......................................................... 22
   9.3.1 CO2 Laser Vaporization .................................... 22
   9.3.2 Other destructive therapies under investigation .... 23
   9.4 Topical Treatment ................................................. 23
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.4.1</td>
<td>5- Fluorouracil (5-FU)</td>
<td>23</td>
</tr>
<tr>
<td>9.4.2</td>
<td>Imiquimod</td>
<td>24</td>
</tr>
<tr>
<td>9.4.3</td>
<td>Cidofovir</td>
<td>24</td>
</tr>
<tr>
<td>9.5</td>
<td>Combined Treatments</td>
<td>25</td>
</tr>
<tr>
<td>9.6</td>
<td>Observation without treatment</td>
<td>25</td>
</tr>
<tr>
<td>9.7</td>
<td>Treatment under special circumstances</td>
<td>26</td>
</tr>
<tr>
<td>9.7.1</td>
<td>Pregnancy</td>
<td>26</td>
</tr>
<tr>
<td>9.7.2</td>
<td>Immunosuppression</td>
<td>26</td>
</tr>
<tr>
<td>9.8</td>
<td>Investigational Therapies: Therapeutic vaccines</td>
<td>27</td>
</tr>
<tr>
<td>9.9</td>
<td>Impact of VIN and its treatment in patients’ quality of life</td>
<td>27</td>
</tr>
<tr>
<td>9.10</td>
<td>Therapeutic Algorithm</td>
<td>28</td>
</tr>
<tr>
<td>10.0</td>
<td>FOLLOW-UP</td>
<td>29</td>
</tr>
<tr>
<td>10.1</td>
<td>Recurrences after treatment</td>
<td>29</td>
</tr>
<tr>
<td>10.2</td>
<td>Risk of Progression</td>
<td>29</td>
</tr>
<tr>
<td>10.3</td>
<td>Follow-up guidelines</td>
<td>30</td>
</tr>
<tr>
<td>10.4</td>
<td>Follow-up Algorithm</td>
<td>31</td>
</tr>
<tr>
<td>11.0</td>
<td>PRIMARY PREVENTION OF VIN. ROLE OF PROPHILACTIC VACCINES AGAINST HPV</td>
<td>32</td>
</tr>
<tr>
<td>12.0</td>
<td>RECOMENDATIONS</td>
<td>33</td>
</tr>
<tr>
<td>13.0</td>
<td>REFERENCES</td>
<td>34</td>
</tr>
</tbody>
</table>
1. Introduction

Vulvar intraepithelial neoplasia (VIN) is considered the precursor lesion for vulvar squamous cell carcinoma. Early diagnosis and adequate treatment of VIN is the only method of secondary prevention currently available to prevent the development of this neoplasia. However, in terms of efficiency, the low incidence of vulvar cancer does not justify the establishment of population screening programs.

Vulvar squamous cell carcinoma encompasses two different etiopathogenic entities. Infection by the human papillomavirus (HPV) is causally associated with a proportion of carcinomas of the vulva, while the remaining carcinomas develop from precursor lesions secondary to chronic skin diseases. Knowledge of this dual etiopathogenic pattern for vulvar cancer and its precursor lesions is based on the recently approved classification of the 2015 International Society for the Study of Vulvovaginal Disease (ISSVD) which establishes two VIN lesion patterns: HSIL (usual-type VIN) and differential VIN, with clearly differentiated epidemiologic factors, histological characteristics, clinical behavior and potential to progress to cancer.

Determination of the course of action to be followed in patients diagnosed with VIN is an important challenge in health care practice. The great variability in the clinical presentation, the high risk of occult invasion at the time of diagnosis, the multiple therapeutic options available without a defined optimal treatment, and the high percentage of relapse after treatment, establishes the complexity of this pathology. Therefore, it is essential that all specialists involved in the diagnosis and treatment of these lesions have thorough and detailed knowledge of all aspects related to VIN.

The aim of the AEPCC-guidelines is to provide a detailed updated review of each of the most relevant aspects of VIN to support and aid in the decision making process and allow standardized management of this disease based on the scientific evidence available and state-of-the-art knowledge.
2. Terminology and classification

The term VIN (from the Anglo-Saxon acronym, Vulvar Intraepithelial Neoplasia) was first introduced in the literature by Richart and was subsequently extended by Crum. This terminology was an adaptation of the much more frequent and better known terminology used for uterine cervical intraepithelial neoplasm (CIN). This parallelism was established on the basis of the clinical, etiologic, pathogenic and histological similarities between the two lesions.

The term VIN has been widely accepted by the leading societies and international organizations, including the World Health Organization (WHO), the International Society of Gynaecological Pathologists (ISGYP), the International Federation of Gynaecology and Obstetrics (FIGO) and the ISSVD. In 1986, the ISSVD, established 3 degrees of VIN based on their severity: VIN 1, 2 and 3, depending on the alteration of epithelial maturation, in analogy to the criteria used for cervical injuries. In this first classification, a distinct form of VIN called differentiated-type VIN was determined, making clear the clinical and histological differences between the two types of VIN.

2.1. 2004 ISSVD CLASSIFICATION

Since 1986, knowledge of the natural history of precursor lesions of lower genital tract cancers has significantly advanced. Indeed, in recent years there have been important modifications in the classification of VIN. First, several studies have described the presence of two types of VIN with clearly differentiated etiopathogenic and clinical-pathological features: usual-type VIN, related to HPV, which generally presents a basaloid, warty or mixed (basaloid/warty) morphology, and differentiated-type VIN, related to inflammatory dermatoses such as lichen sclerosus and lichen simplex chronicus.

Secondly, it was agreed to limit the classification of VIN to squamous intraepithelial neoplasia, thereby discarding in situ melanoma and vulvar Paget's disease. Finally, VIN1 was excluded as a precancerous lesion of the vulva since it represents a process without oncogenic potential secondary to HPV infection. The VIN 2 and VIN 3 categories, which are difficult to pathologically differentiate and have doubtful clinical difference, were grouped into a single category designated as VIN. Thus, VIN was considered the only precursor lesion of squamous vulvar cancer.

It is difficult to include some very rare histological forms of VIN such as pagetoid VIN within the aforementioned categories, and therefore, these lesions are included in a new category of "unclassifiable VIN". The 2004 ISSVD classification is shown in Table 3.

| Table 3.- 2004 ISSVD Classification of Vulvar Intraepithelial Neoplasia |
| VIN | Characteristics |
| Usual-type VIN | HPV-related |
| Basaloid type |
| Warty type |
| Mixed type |
| Differentiated-type VIN | Non HPV-related |
| Unclassifiable VIN | It cannot be included in the prior categories. It may include rare types such as Pagetoid VIN |
2.2. 2004 WHO CLASSIFICATION AND 2015 ISSVD CLASSIFICATION

In 2012, the American College of Pathologists and the American Society of Cervical Pathology and Colposcopy published the conclusions reached by the Consensus Committee of “Lower Anogenital Squamous Terminology (LAST) Standardization Project for HPV-Associated Lesions”. This aim of this classification was to standardize the nomenclature of the lesions associated with HPV infection. The LAST classification does not refer to differentiated or unclassifiable VIN but rather recognizes the existence of two basic forms of HPV infection: 1) productive infection, with minimal risk of oncogenic transformation and a high capacity of regression, and 2) infection with the capacity to induce cell transformation able to generate precursor lesions with a high risk of progression to cancer. Finally, the LAST classification combines all intraepithelial lesions associated with HPV infection into a single terminology regardless of their location in the anogenital tract (cervix, vagina, vulva, anus, perianal area or penis)6.

The LAST terminology recommends using the same terms as those in cervical cytology (Bethesda system) for histological diagnosis. Lesions previously called -IN 1 (CIN 1, vaginal intraepithelial neoplasia [VaIN]1, etc.) are now called low-grade squamous intraepithelial lesions (LSIL), and lesions previously called -IN2 or -IN3 (CIN 2-3, VaIN 2-3, etc.) are now known as high-grade squamous intraepithelial lesions (HSIL). In addition, this terminology recommends specifying in parentheses the anatomic location where the intraepithelial lesion is located (vulvar VIN, vaginal VaIN, anal AIN, etc.).

In the 2014 classification of gynecologic tumors7 the World Health Organization (WHO) incorporated the LAST terminology to include HPV-associated vulvar squamous intraepithelial lesions and recommended the use of LSIL and HSIL specifying the term “usual-type VIN” in parentheses. This terminology is not suitable for non-HPV-related lesions, and thus, the term “differentiated-type VIN” remains the same following the criteria established in the 2004 classification.

In July 2015, the ISSVD Terminology Committee proposed some changes to the 2014 WHO classification. Accordingly, LSIL (VIN1) should not be strictly considered as a precursor lesion, but a skin reaction secondary to HPV infection without oncogenic potential. The effect of HPV infection on the vulva is not biologically equivalent to that produced in the cervix or anus since the vulva consists of keratinized epithelium and lacks a transformation zone, and therefore, LSIL (VIN1) should not be considered or treated as a potential neoplastic lesion.

Ultimately, the latest edition of the ISSVD classification recommends not to use the term VIN in parentheses with LSIL, but the term “condyloma” or “HPV-related changes”. Therefore, only HSIL (usual-type VIN) and differentiated-type VIN are considered true precursor lesions6-9 (Table 4). This new classification has implications in the clinical course of action since the treatment for LSIL is not justified as prophylaxis for vulvar cancer but as a symptomatic treatment of HPV-related lesions.

<table>
<thead>
<tr>
<th>Table 4.- 2015 ISSVD Classification of Vulvar Intraepithelial Neoplasia (VIN)6</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-grade squamous intraepithelial lesion: HSIL (usual-type VIN)</td>
</tr>
<tr>
<td>Differentiated vulvar intraepithelial neoplasia: differentiated-type VIN</td>
</tr>
</tbody>
</table>
3. Epidemiology

VIN is a clearly under-diagnosed and under-reported entity. Population-based epidemiological data on VIN are virtually non-existent and most of the information available is based on studies in patients attended for medical evaluation. A standard population-based recommendation for the detection of VIN has not been established.

It is difficult to determine the actual incidence of VIN since the lesions are often asymptomatic and go unnoticed if a thorough and systematic exploration of the vulva is not made during gynecological examination. In addition, population-based cancer registries do not usually include the incidence of these lesions.

The incidence of VIN registered in Nordic countries is between 2.5 and 3.1 cases per 100,000 women/year, increasing after the age of 40. In an international series of 587 consecutive cases of VIN, the mean age at the time of diagnosis was 50 years.

Figure 1 shows the incidence rates of the precursor lesions of cervical, vulvar and vaginal cancer by country and age group. The reported incidence of VIN is below that of CIN (A) and above vagina intraepithelial lesions (C).

In a pooled analysis of three clinical trials on HPV vaccines, the incidence of HPV16/18-related VIN was 0.04 per 100 people/year in the placebo group (7785 women). However, it is difficult to extrapolate the data related to the incidence of VIN in these clinical trials to the general population due to the bias induced by the population included (young age, HPV infection related to vaccine types, among others).

In recent years, the incidence of VIN has increased, especially at younger ages. In addition to the increase in the number of lesions, detection is also greater due to greater awareness of HPV infection and better knowledge about the virus, precursor lesions and lower genital tract neoplasias. Data from the United States seem to confirm this increase in diagnosis.

Figure 2 shows the incidence rates of vulvar carcinoma in situ (equivalent to the current concept of VIN) between 1973 and 2000, demonstrating a clear rise in the incidence in the last period with a peak at age 40.

In Spain, a multicenter study including 5,665 women attended by 385 gynaecologists, found that VIN was diagnosed in 2% of all HPV-associated lower genital tract pathologies. Another study reported no differences in the frequency of VIN among the various age groups.

In addition, epidemiological features differentiate HSIL (usual-type VIN) and differentiated-type VIN. HSIL lesions (usual-type VIN) tend to affect women aged around 40-45, with a second peak after the age of 55. In contrast, differentiated-type VIN is most frequently found in older women usually over the age of 60.

The incidence of VIN is clearly higher in HIV-positive patients compared to the general population. The results of a study evaluating a cohort of 2,791 women over 13 years reported an incidence of VIN of 0.42 vs. 0.07 per 100 women/year, respectively.
Figure 1 - Comparison of the incidence rates of VIN, CIN and VAIN by age in Nordic countries during 2004-6.

Obtained from SanJosé S et al. Eur J Cancer 2013; 49(16):3450-61

Figure 2 - Trends of vulvar carcinoma in situ by age and diagnostic period.

Obtained from SanJosé S et al. Eur J Cancer 2013; 49(16):3450-61
Vulvar Intraepithelial Neoplasia (VIN)

4. Etiopathogenesis

The genesis of VIN involves two types of etiopathogenesis, which are the basis for the development of two distinct entities: HSIL (usual-type VIN) and differentiated-type VIN.

4.1 HSIL (USUAL-TYPE VIN)

The causative agents of this entity are oncogenic HPV genotypes. In most cases, HPV-16 is involved. Data from a multicenter study carried out by the HPV-VVAP working group which included 587 cases of VIN and 1,709 cases of vulvar squamous cell carcinoma highlighted that HPV is present in 86.7% of VIN cases compared with 25.1% of invasive vulvar lesions. The most common genotypes in HSIL (usual-type VIN) were HPV-16 (77.3%) followed by HPV-33 (10.6%) and HPV-18 (2.5%).

Similar to what occurs with precursor lesions related to HPV in other anatomical locations, infections are transitory in 90% of cases and resolve by immune response within 2 years after presentation. Therefore, immunosuppression is frequently associated with viral persistence and the development of intraepithelial lesions.

Persistent infection and the oncogenic activity of the E6 and E7 proteins are crucial for the development of HSIL (usual-type VIN). Most HSIL cases (usual-type VIN) are positive for p16 and p14 (reflecting the interaction of the E6 and E7 oncoproteins in the cell cycle) and negative for p53.

Smoking is frequently associated with HSIL (usual-type VIN).

4.2 DIFFERENTIATED-TYPE VIN

Differentiated-type VIN is not causally related to HPV and is much less frequent than HSIL (usual-type VIN). This entity is associated with chronic inflammatory dermatoses such as lichen sclerosus and lichen simplex chronicus. The exact pathogenic mechanism of the development of differentiated-type VIN is unknown. Chronic inflammatory processes constitute the main factors involved in the development of this disease. From a molecular point of view, more than 80% of the cases show overexpression of p53 and negativity to p16.
5. Natural History of Vin

The natural history of VIN is largely unknown. The risk of progression of these lesions is not uniform and is mainly determined by the type of VIN. In general, the risk of progression of VIN to vulvar squamous cell carcinoma is 7-10%\(^{36}\).

One of the main difficulties in assessing the true potential of progression to vulvar cancer is that most studies assess the risk of progression after VIN treatment. On the other hand, the presence of occult invasion at the time of VIN diagnosis is relatively frequent. A systematic review of 3,322 patients with VIN found that 6.5% of patients developed vulvar squamous cell carcinoma, half of which were occult carcinomas detected during the diagnostic study and treatment and the other half were discovered during follow-up\(^{27}\). Other studies have reported that in 3% of differentiated-type VIN there is an underlying occult carcinoma at the time of diagnosis\(^{8}\) (Table 5).

If no treatment is administered, VIN lesions may persist, progress or return to normal epithelium. In non-treated patients, VIN progression is estimated to be around 10% over a period of 1 to 8 years\(^{27}\). Nonetheless, in spite of treatment, up to 8% of patients with VIN can develop vulvar squamous cell carcinoma\(^{27,28}\).

Differentiated-type VIN has a higher risk of progression to vulvar squamous cell carcinoma than HSIL (usual-type VIN) (33% versus 6%, respectively) and within a shorter period of time. Immunosuppression, advanced age, or extensive or ulcerated lesions are associated with an increased risk of progression\(^{26}\). Immunosuppression facilitates maintenance, recurrence and progression of these lesions, especially in HSIL (usual-type VIN)\(^{29,30}\).

Spontaneous complete remission has been described in around 1% of patients. In a review of cases, Van Seters et al. found that remissions were seen especially in women under 35 years of age (mean age, 20 years) and were related to pregnancy in 17 out of 41 cases (Table 5). Along 10 months of follow-up, Jones et al. observed that spontaneous regression is possible in young people in 12% of cases\(^{31}\).

### Table 5 - Natural history of VIN

<table>
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<tr>
<th></th>
<th>n</th>
<th>%</th>
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<tbody>
<tr>
<td>Progression to cancer</td>
<td>215</td>
<td>6.5</td>
</tr>
<tr>
<td>Occult cancer</td>
<td>107</td>
<td>3.2</td>
</tr>
<tr>
<td>Progression during follow-up</td>
<td>108</td>
<td>3.3</td>
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<tr>
<td>Spontaneous regression</td>
<td>41</td>
<td>1.2</td>
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<tr>
<td>Pregnant women (from the remission group)</td>
<td>17</td>
<td>41.5</td>
</tr>
<tr>
<td>Systemic review of 97 series, 3,322 patients</td>
<td></td>
<td>27</td>
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</tbody>
</table>

\(^{27}\) Systemic review of 97 series, 3,322 patients.
6. Histology

6.1. HSIL (USUAL-TYPE VIN)

Histologically, the epidermis in HSIL (usual-type VIN) shows acanthosis (dermal thickening) hyperkeratosis (hypertrophy of the stratum corneum of the epidermis) and parakeratosis (a cell maturation disorder on the stratum corneum of the epidermis). Loss of cell maturation, chromatin, increased mitotic figures, pleomorphism and increased nuclear-cytoplasmic relationship are present.

HSIL (usual-type VIN) lesions are divided into two subtypes: basaloid (undifferentiated) and condylomatose or Bowenoid or so-called “warty” lesions. Basaloid lesions are typically flat and composed of small, uniform cells similar to basal cells, with an increased nuclear-cytoplasmic ratio and little or no evident koilocytic changes which replace the whole thickness of the epidermis. Warty lesions are characterized by acanthosis, with marked papilomatosis with thickened interpapillary ridges, marked cellular pleomorphism and prominent koilocytic changes. Basaloid and warty patterns are frequently combined in the same lesion. In one third of cases, the atypical cells extend to cutaneous annexes (pilosebaceous follicles and excretory ducts of the sweat glands). This may cause problems in the differential diagnosis with incipient invasion.

Immunohistochemically, HSIL (usual-type VIN) lesions are characterized by a continuous basal and parabasal band of positive cells showing intense nuclear and cytoplasmic staining for p16. Positivity for p16 is often extended to high strata of the epidermis. The Ki67 marker shows a notable increase in proliferative activity with positive cells spreading into the upper two-thirds of the epithelium. LSIL (HPV lesions) lesions secondary to transitory HPV infections may present staining patterns ranging from completely negative cases to others showing diffuse positivity similar to HSIL (usual-type VIN).

6.2. DIFFERENTIATED-TYPE VIN

Many HPV-negative keratinizing vulvar squamous cell carcinomas develop in intraepithelial lesions called differentiated-type VIN. Although these lesions may occur in young patients, they are generally diagnosed in women over 60 years of age. Differentiated-type VIN is often developed in chronic dermatological lesions such as lichen sclerosus and lichen simplex chronicus. Mutations of the p53 gene, a frequent phenomenon in HPV-negative vulvar squamous cell carcinomas, seem to be an early event in the development of lesions in this type of VIN.

Histological findings of differentiated-type VIN are subtle and difficult to recognize making diagnosis extremely difficult leading to little agreement among pathologists on the diagnosis of this entity. Consequently, up to 40% of these lesions are erroneously diagnosed as benign dermatoses.

Differentiated-type VIN lesions are characterized by thickening of the epithelium, elongated and anastomosed interpapillary ridges and parakeratosis. Cellular atypia, which is often important, is confined to the basal and parabasal layers of the epidermis. Atypical mitosis is frequently identified in these layers. Basal layer keratinocytes characteristically show abundant and eosinophilic cytoplasm, very prominent intercellular bridges and prominent eosinophilic nucleoli.

Dyskeratotic cells with premature maturation, cytoplasmic eosinophilia and premature keratinization in all epidermic layers are frequently observed. The epithelial cells of the upper layers have correct differentiation and marked maturation. These keratinocytes in the middle and upper layers do not show signs of atypia or show only focal atypia. Changes in lichen simplex chronicus or lichen sclerosus adjacent to lesions of differentiated-type VIN or other areas of the vulva are frequently identified.

Five histological criteria have proven to be particularly useful in the diagnosis of this lesion: atypical mitosis in the stratum basale, atypia of basal cells, dyskeratosis, prominent nucleoli, and elongation and anastomosis of interpapillary ridges. The differential diagnosis of differentiated-type VIN includes reactive lesions such as pseudo-epitheliomatosus hyperplasia, and some inflammatory skin lesions such as...
The clinical presentation of VIN is very heterogeneous and can manifest with different symptoms in each patient. Only 50% of VIN lesions are symptomatic. Pruritus is the most common symptom followed by pain, stinging, dyspareunia or dysuria. In asymptomatic patients, the lesions are usually diagnosed unexpectedly during a gynecologic examination. This fact reinforces the importance of conducting systematic and thorough vulvar examinations.

There is no characteristic lesion pattern of VIN, and clinical findings are very heterogeneous regarding color, surface, and topography. Lesions may be single or multiple, white, red or pigmented, and the surface can be completely flat or raised.

HSIL (usual-type VIN) and differentiated-type VIN differ in not only their epidemiologic characteristics but also in their clinical presentation.

- **HSIL (usual-type VIN):** lesions tend to be polymorphic (often elevated or papillomatous and pigmented), and multifocal, located in the mucous areas devoid of hair, preferably in the lower third of the vulva. They frequently compromise several areas (vulvar and perineal). Association with intraepithelial lesions in other anatomical regions of the anogenital tract is frequent (either synchronously or metachronically). HSIL (usual-type VIN) is frequently associated with multifocal and multicentric lesions in the cervix and vagina. Between 30-70% of women with HSIL (usual-type VIN) have a synchronous HSIL (CIN2-3). The frequent presence of a multicentric pattern in women diagnosed with HSIL (usual-type VIN) justifies the need for thorough examination of the whole anogenital tract.

- **Differentiated-type VIN:** clinical and macroscopic manifestations of these lesions are nonspecific. The most outstanding feature of these lesions is often the association with other vulvar skin lesions such as lichen sclerosus and lichen simplex chronicus. Differentiated-type VIN lesions tend to be single, small, white (due to hyperkeratosis) or reddish, ill-defined and frequently located in hairy areas. Patients frequently report long-term vulvar itching.

The clinical features that characterize HSIL (usual-type VIN) and differentiated-type VIN are shown in Table 6.

### Table 6 - Clinical-pathological types of Vulvar Intraepithelial Neoplasia (VIN)

<table>
<thead>
<tr>
<th>VIN histological type</th>
<th>HPV</th>
<th>Non HPV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HSIL (usual-type VIN)</td>
<td>Differentiated-type VIN</td>
</tr>
<tr>
<td>Age</td>
<td>20-40 years</td>
<td>&gt; 40 years</td>
</tr>
<tr>
<td>Presence of HPV</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Warts</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Abnormal cytology</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Smokers</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Immunosuppression, HIV</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Lesional foci</td>
<td>Multiple</td>
<td>Single</td>
</tr>
<tr>
<td>TGI-related neoplasms</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Related with inflammatory dermatosis</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Favourable</td>
<td>Unfavourable</td>
</tr>
<tr>
<td>Molecular markers</td>
<td>Integrates HPV p16 and p16</td>
<td>p53 mutation</td>
</tr>
</tbody>
</table>
8. Diagnosis

8.1. CLINICAL EXAMINATION AND VULVOSCOPY

Vulvar examination should be systematically performed in all women who visit the gynecologist, and especially in those with HPV-related lesions in other locations of the anogenital tract, vulvar skin diseases, or reporting any symptoms.

Vulvar examination should include general and perianal inspection. The examination should be meticulous and with the help of adequate lighting to facilitate the identification of various macroscopic aspects of the lesions.

Examination with a colposcope and acetic acid (vulvoscopy) allows magnified examination and more in depth inspection, and it is useful for the identification of suspicious lesions and for directing the biopsy.

An acetic acid 5% solution should be applied for several minutes to be effective in the areas of keratinized epithelium. Bleaching of certain areas after applying the acetic acid allows the diagnosis of specific lesions that otherwise would not be identified. However, this procedure has a low specificity, since the vulvar epithelium, mainly at the introitus level, often reacts to the acetic acid in a diffuse manner in the absence of pathology. A low-power magnified inspection is used for general vulvar tracking and a high-power magnified inspection is carried out for in depth examination of small lesions.

In addition to the acetowhite areas, abnormal mosaic and dotted vascular patterns may also occasionally be seen, although there is no analogy between the colposcopic changes described in the cervix and those found in the vulva.

After the examination, all clinical findings (color, surface and vascularisation) as well as the topography and exact location should be described in detail using descriptive schemas or ideally photographs, vulvophotographs, or videos can be taken.

8.2. BIOPSY (INDICATIONS AND METHODOLOGY)

Vulvar examination or vulvoscopy can identify suspicious lesions but is not useful for diagnostic purposes. Since VIN has no pathognomonic macroscopic characteristics, confirmation of the diagnosis requires histological study of a sample obtained by biopsy.

Table 7 describes the Indications for performing a vulvar biopsy.

| Pigmented lesions | Condylomas / verrucous lesions in menopausal women | Clinically non-filiated and doubtful vulvar lesion | Suspected invasion | Prior to destructive/medical treatment |

Biopsy is performed after infiltration of a local anesthetic forming a small wheal below the lesion. A punch clamp or Keyes dermal punch, a scalpel or scissors may be used. The sample should include subcutaneous tissue or stroma and allow proper orientation of the sample. Scant bleeding caused by the biopsy procedure can be easily controlled with perchloride of iron or Monsel's solution (ferric sulphate), silver nitrate, electrocoagulation, and exceptionally, stitches. When lesions are multifocal or diffuse it is recommended to take biopsies in different locations.

8.3. SUSPECTED OCCULT INVASION

Occult stromal invasion in patients with VIN is described in a high percentage of cases (2-22%, although the results in the literature are highly variable) and it is a primary target of the diagnosis. Clinical factors associated with a high risk of occult invasion are shown in Table 8.

The capacity of vulvoscopy to detect occult invasion has been questioned. However, some authors argue that a careful and comprehensive colposcopic examination of the vulva along with liberal practice of a directed biopsy, greatly reduces the possibility of an invasive lesion going unnoticed.
8.4. DIFFERENTIAL DIAGNOSIS

Given the great heterogeneity in the clinical presentation of VIN, many vulvar disorders can be confused with this entity. In clinically borderline cases, the histological study will allow differentiating this lesion from condyloma acuminata seborrheic keratosis, psoriasis, lichen simplex chronicus and lichen sclerosus.

<table>
<thead>
<tr>
<th>Lesional factors</th>
<th>Clinical factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcerated, nodular or extent lesions</td>
<td>Advanced age (&gt; 50 years)</td>
</tr>
<tr>
<td>Lesions with necrosis</td>
<td>Immunosuppression</td>
</tr>
<tr>
<td>Lesions with indurated base</td>
<td>Smoking</td>
</tr>
<tr>
<td>Hyperkeratotic areas</td>
<td></td>
</tr>
<tr>
<td>Multifocal lesions</td>
<td></td>
</tr>
<tr>
<td>Atypical vascularisation</td>
<td></td>
</tr>
<tr>
<td>Rapid growth of the lesion</td>
<td></td>
</tr>
</tbody>
</table>
9. Treatment

9.1.- GENERAL PRINCIPLES

There is no ideal treatment for patients with VIN, although there are specific recommendations to guide the most appropriate therapeutic course of action depending on specific clinical features\(^{37}\).

The main objectives of treatment are:

1. To prevent progression to invasive carcinoma
2. Cure or alleviate symptoms
3. Avoid relapses, and
4. To preserve vulvar anatomy and functionality.

The increased incidence of VIN in young women described in recent years has contributed to the search for more conservative treatments.

Before selecting a particular therapeutic option, it is essential to assess the risk of progression to cancer. This is conditioned by the characteristics of the patient (age, immunological status, associated pathology) and the lesion (location, extension, involvement of hairy/non-hairy uni/multifocality areas, and multicentricity)\(^{47,48}\). There are multiple treatment options (excision, ablation, medical) that can be administered alone or in combination.

In general, treatment is recommended in all patients with VIN. Excision is necessary in differentiated-type VIN and HSIL (usual-type VIN) with a high risk of occult invasion.

Ablation and/or combined therapies may be used in cases in which invasion is ruled out\(^{37}\). Expectant behavior by observation can be an alternative in very selected cases with a low risk of progression\(^{37}\). \textit{Quality of evidence: moderate; Grade of recommendation: strongly in favor.}

9.2.- EXCISION

Excision is the treatment of choice for differential VIN and HSIL (usual-type VIN) with no secondary lesions from ablation or topical treatments\(^{37}\). \textit{Quality of evidence: moderate; Grade of recommendation: strongly in favor.}

9.2.1. Simple local excision

**Procedure**

Excision of the whole lesion with a safety margin of 0.5 cm around the visible lesion (or less for lesions in which other anatomical structures such as the anus, urethra, or clitoris may be compromised) and a minimum depth of 3 mm in hairy areas and 1 mm in non-hairy areas.

**Indication**

Isolated unifocal or multifocal VIN lesions. \textit{Quality of evidence: moderate; Grade of recommendation: strongly in favor.}

**Justification**

Treatment with simple local excision can confirm the diagnosis of VIN, exclude the existence of invasion, and assess the status of the margins of the treated lesion\(^{37,48}\).

Compromised margins have shown to be an independent factor of lesion recurrence\(^{37}\), but they are not associated with an increase in the risk of progression to invasive lesions\(^{48,50}\). The analysis of a series of 405 VIN patients treated with excision or CO2 laser vaporization followed for 14 years showed, that half of the patients with positive margins and only 15% of patients with negative margins required a second treatment. Relapses occurred especially within the first 5 years after treatment\(^{26}\). Another study in 73 cases of VIN treated with excision showed a clear relationship between recurrence and the presence of positive margins (46% and 17% for positive and negative margins respectively; \(p < 0.005\))\(^{49}\). In a review of 12 series including 296 patients, 23.9% of the cases undergoing local excision presented recurrence\(^{51}\).

9.2.2. Partial or Total Skinning Vulvectomy

**Procedure**

Excision of the whole thickness of the vulvar skin includes hairy skin and adjacent follicles, with preservation of the subcutaneous tissue. This method includes the preservation of the clitoris although lesions on the surface of the gland or cap can be removed. The closure of the defect is usually...
primary and a free graft is used only exceptionally. In the case of lesions located in the perineum or perianal area, plastic surgery techniques (such as plasty by displacement and Dufourmentel LLL plasty) are frequently used to close the defect\textsuperscript{52}.

**Indication**

Widespread VIN lesions involving most of the vulvar tissue.  
Quality of evidence: low; Grade of recommendation: strongly in favor.

**Justification**

Widespread VIN lesions involving most of the vulva require skinning vulvectomy. In a review of 9 series including 157 patients undergoing skinning vulvectomy, 22.3% presented recurrence\textsuperscript{51}.

**9.2.3. Simple Vulvectomy**

**Procedure**

Vulvectomy consists of the removal of all the vulvar skin including the labia majora, labia minora and clitoris, resulting in major deformity of the external genitalia.

**Indication**

This procedure is currently not indicated in any case of VIN. Quality of evidence: low; Grade of recommendation: strongly against.

**Justification**

Vulvectomy is considered an excessive and unacceptable treatment for an intraepithelial lesion. Despite the invasiveness of this procedure, it is not exempt from recurrence, which has been described in up to 15% in some series\textsuperscript{53}.

**9.3. Ablation**

Ablation consists of removing the entire lesion with various methods of tissue destruction without obtaining any surgical specimen for histological study. Before this treatment, it is mandatory to rule out the presence of invasive lesions by taking multiple biopsies.

The main advantage of this procedure is the lesser invasiveness and better anatomical and functional conservation of the vulva compared with excisional procedures. These advantages are very important taking into account that VIN is increasingly diagnosed in younger women, in whom the most frequent histological type is HSIL (usual-type VIN), with a lower risk of progression to invasive lesions\textsuperscript{52}.

**9.3.1. CO\textsubscript{2} Laser Vaporization**

**Procedure**

CO\textsubscript{2} laser vaporization involves the destruction of affected tissue. The laser beam may be directed using a manual or colposcope-connected device, which allows accuracy. The laser is applied in continuous mode at 10-20w. This procedure requires anesthesia (local for small lesions and general or regional for more extensive lesions). The depth of vaporization ablation depends on the area affected: 3-4 mm in hairy areas and 0.5-1 mm in non-hairy areas\textsuperscript{52}.

**Indication**

HSIL (usual-type VIN), preferably located at the introitus or non-hairy areas, after ruling out invasion. This procedure is especially recommended in multifocal and extensive lesions\textsuperscript{50,52,54}. Quality of evidence: moderate; Grade of recommendation: strongly in favor.

**Justification**

CO\textsubscript{2} laser vaporization is one of the main ablative treatments, and it is characterized by its high accuracy and low aggressiveness. The minimum residual damage to the tissue significantly reduces the formation of scar tissue. The cosmetic advantages of surface vaporization (1 mm deep) over other excisional procedures are lost in cases in which hairy areas are involved since these areas require deeper vaporization (more than 2-3 mm). It is better to use other methods for the treatment of these surfaces\textsuperscript{37,39}.

**9.3.2. Other destructive therapies under investigation**

**9.3.2.1 Photodynamic therapy**

**Procedure**

This treatment is based on the interaction between a photosensitizing substance which finds tumor cells (5-aminolevulinic acid) in combination with non-thermal light at wavelengths matched to the absorption characteristics of the photosensitizer. When the photosensitizer contacts
the light, the formation of toxic singlet oxygen is induced generating free radicals. Within a few hours this procedure induces coagulative necrosis, apoptosis and microthrombosis of new tumor vessels and severe inflammation of the area by releasing vasoactive and procoagulant factors and the destruction of malignant cells.

**Indication**

HSIL (usual-type VIN), only in research. **Quality of evidence:** low; **Grade of recommendation:** strongly against.

**Justification**

To date there is little scientific evidence for the clinical application of this treatment. The studies available only include small series with short follow-up periods, reporting response rates of around 55% with 48% of relapses. Taking into account the mechanism of action of this procedure, its role could be limited to pigmented hyperkeratotic lesions.

### 9.3.2.2 Cavitational Ultrasonic Surgical Aspiration

**Procedure**

This treatment is based on the use of ultrasound to produce tissue destruction (cavitation), followed by aspiration to remove cell debris and blood.

**Indication**

HSIL (usual-type VIN), only in research. **Quality of evidence:** low; **Grade of recommendation:** strongly against.

**Justification**

In general, there is little evidence in the literature on the use of this therapy in the treatment of these lesions. However, several studies have concluded that ultrasonic surgical aspiration is a useful and safe technique for tissue removal. The advantage of this treatment over others is based on rapid healing with good esthetic and functional results, and it allows material to be obtained for histological study.

Data from a prospective randomized trial including 110 patients showed a recurrence rate of 25%.

### 9.4 TOPICAL TREATMENT

Topical treatments have emerged as an alternative to surgery in VIN, although the majority of studies on this type of therapy describe isolated cases or short series. Although at present the FDA has not approved any topical treatment for VIN, its use is recommended and accepted by scientific societies in certain situations.

**Indication**

Topical therapy alone or in combination with destructive or excisional therapies is indicated in the treatment of HSIL (usual-type VIN) in unifocal or multifocal isolated lesions after having ruled out occult invasion. Topical therapy is not indicated under any circumstance for differentiated-type VIN.

**Quality of evidence:** low; **Grade of recommendation:** weakly in favor.

#### 9.4.1. 5-Fluorouracil (5-FU)

**Procedure**

The mechanism of action of 5-FU is based on producing a chemical peeling of VIN. The most commonly used dosage consists on the application of a thin layer of 5-FU 5% on the lesion (avoiding the rest of the vulva) 1-2 times a day for 6-10 weeks.

Intense inflammatory response is observed in 2 weeks. Monitoring every 4-6 weeks during treatment is recommended. Local tissue response such as erythema, edema, skin desquamation and significant pain may be presented. In case of important local effects, the application may be reduced to once a week. Following completion of the treatment, complete tissue healing occurs within 4-6 weeks.

**Indication**

HSIL (usual-type VIN) after ruling out occult invasion and in the absence of other excisional or ablative treatments. **Quality of evidence:** low; **Grade of recommendation:** weakly in favor.

**Justification**

The use of 5-FU has shown to be effective in 75% of cases. The main drawback limiting the use of this treatment is poor tolerance due to burns, pain, swelling, edema, and the development of vulvar ulcers. Given these disadvantages, the use of 5-FU is very limited.
9.4.2 Imiquimod

**Procedure**

Imiquimod is an immune response modulator with antitumor effects. Its activity is due to the stimulation of local cytokines and cellular immunity.

The dosage most commonly used consists of the application of a thin layer of imiquimod 5% cream on the lesion (avoiding the rest of the vulva) before bedtime 2-3 times a week for a maximum of 12-20 weeks, with follow-up every 4-6 weeks during treatment. This treatment may cause itching, redness and a severe inflammatory reaction. If important local effects develop, cream administration may be reduced to once a week. To treat a local reaction, non-steroidal antiinflammatory drugs (NSAIDs) may be used since it has been demonstrated that these antiinflammatories do not interfere with the immunomodulatory effect of imiquimod.

**Indication**

HSIL (usual-type VIN) for isolated unifocal or multifocal lesions alone or in combination after having ruled out occult invasion. **Quality of evidence:** high; **Grade of recommendation:** weakly in favor.

**Justification**

Imiquimod is considered an effective treatment for VIN. However, studies comparing imiquimod with other therapies are needed.

The first double-blind placebo-controlled studies showed imiquimod to be significantly more effective than placebo in the treatment of VIN. Data from a more recent observational study showed a complete response rate of 66.6% at 30 months of follow-up, being more effective in pigmented lesions. Similarly, a Cochrane meta-analysis found that imiquimod had an 11-fold higher efficacy compared to placebo in the treatment of these lesions (Table 9). The best results were obtained in patients aged <65 and when severe local reactions were present.

Surgical treatment may be required if residual lesions or lesional persistence develops following treatment with imiquimod.

9.4.3 Cidofovir

**Procedure**

Cidofovir is an acyclic nucleoside analog with antiviral activity. It acts by inducing apoptosis of HPV-infected cells and may thereby be effective for the treatment of HSIL? (usual-type VIN). A topical formulation of 1% or 3% (gel, cream or intralesional injection) applied once or twice a day, up to a maximum of 10 weeks is generally used, although this Indication is not included in the summary of product characteristics.

**Indication**

HSIL (usual-type VIN), only in research. **Quality of evidence:** low; **Grade of recommendation:** weakly against.

**Justification**

There are few studies on the use of cidofovir in VIN. A recent randomized multicenter study compared the efficacy of cidofovir 1% gel with imiquimod 5% in 180 patients diagnosed with VIN and reported a complete response rate of 46% in both groups after 6 weeks of treatment.

9.5 COMBINED TREATMENTS

**Procedure**

Combined treatment approaches involve the combination of more than one primary treatment for VIN. Excisional therapy combined with ablative or topical treatment in the residual lesion is the general approach. The most frequent combined procedure is excision + CO2 laser vaporization or excision + imiquimod.

**Indication**

Complex widespread or multifocal VIN lesions with: 1) excision of areas at risk of occult infiltration or hairy areas in which ablative treatment is more difficult, and 2) ablation or topical treatment in muco-cutaneous lesional areas. **Quality of evidence:** low; **Grade of recommendation:** strongly in favor.

**Justification**

In the treatment of complex widespread lesions or multifocal lesions possible occult invasion must be ruled out while preserving the anatomical and functionality of the vulva. There are very few studies on combined
treatments in VIN. One study showed that the combination of excisional treatment and CO2 laser vaporization induced lower disease-free interval rates and a higher number of recurrences. Nonetheless, the results of this study may have been significantly biased by the inclusion of patients with complex lesions69. In a comparative study by Gentile et al. on the treatment of 80 patients with VIN (40 women treated with surgery alone and 40 undergoing surgery + imiquimod), the 5-year follow-up showed a recurrence rate of 44.8% versus 48.4%, respectively70.

### 9.6 OBSERVATION WITHOUT TREATMENT

#### Procedure

This approach involves clinical observation without treatment at variable time intervals (every 6 months maximum). Observation without treatment is discontinued in cases presenting clear progression or suspicion of infiltration.

#### Indication

Observation without treatment is rarely carried out in HSIL (usual-type VIN), except in very limited lesions or pregnant women. **Quality of evidence: low; Grade of recommendation: weakly in favor.**

There is no indication for observation without treatment for differentiated-type VIN. **Quality of evidence: low; Grade of recommendation: strongly in favor.**

#### Justification

Observation without treatment is only justified in cases with a low risk of progression or a high probability of spontaneous regression. For this reason, treatment is mandatory in women with differentiated-type VIN lesions and in elderly patients due to the high rate of progression and the risk of occult invasive carcinoma.

In a very select group of HSIL (usual-type VIN), some authors advise an observational period without treatment of between 6 months and one year taking into account the possibility of spontaneous regression. Several studies have reported regression in: 1) patients under 35 years of age, 2) the presence of limited unifocal lesions, 3) the presence of isolated multifocal lesions, 4) pregnancy, and 5) cases with transitory immunosuppression. In all these cases, follow-up must be carried out27,53.
In this sense, a systematic review including 97 articles and 3,322 cases found that only 1.2% of the patients showed spontaneous and complete remission (most within 10 months after diagnosis, 41% were pregnant, and all were under 35 years of age). In the subgroup of 88 non-treated patients, 9 (10.2%) progressed to cancer within a variable period of between 12 and 96 months\(^2\). Another study reported regression at between 3 and 30 months (mean, 9.5 months) in 14 young women (4 of whom were pregnant) with multifocal and pigmented VIN lesions associated with condylomas\(^4\).

### 9.7 TREATMENT UNDER SPECIAL CIRCUMSTANCES

#### 9.7.1 Pregnancy

**Indication**

Observation without treatment is carried out in all cases provided an invasive lesion is previously ruled out\(^2,5\). Quality of evidence: low; Grade of recommendation: strongly in favor. In cases requiring treatment, \(\text{CO}_2\) laser vaporization is recommended\(^2,5\).

**Justification**

Small series have described the potential of lesion regression, especially in women under 30 years of age with pigmented lesions\(^7\).

There is currently little data on the use of medical therapies during pregnancy. Imiquimod is considered class C, and its safety in pregnancy has not been clearly established. Neither is there any evidence regarding its effectiveness during gestation\(^7\).

#### 9.7.2 Immunosuppression

**Indication**

The treatment of choice is lesion excision. In selected cases with widespread lesions or with specific compromised areas, ablative or combined treatments with \(\text{CO}_2\) laser vaporization may be used. Quality of evidence: low; Grade of recommendation: moderately in favor.

**Justification**

The treatment of VIN in immunosuppressed patients is justified by the increased severity of the lesions, less likelihood of regression, an increased risk of progression to invasive cancer and a higher recurrence rate.

A retrospective study in 224 patients who received immunosuppressive therapy for renal transplantation reported an increased risk of developing a malignant tumor in the lower genital tract (2- to 6-fold for CIN, 3-fold for cervical carcinoma and 50-fold for vulvar cancer)\(^23\).

There are few data about the use of topical therapies in immunosuppressed patients. These treatments are used in cases in which ablative or surgical treatment compromises vulvar anatomy or functionality as in cases in which the lesions include anatomical areas such as the urethra, clitoris and non-hairy areas.

### 9.8 INVESTIGATIONAL THERAPIES: THERAPEUTIC VACCINES

Therapeutic vaccines in patients with VIN are intended to stimulate cell immunity with the aim of achieving lesion regression. After the excellent results obtained in the prevention of VIN with prophylactic vaccines against HPV in recent years, phase II trials have been conducted to assess the role of therapeutic vaccines designed to stimulate response against cells expressing the viral E6 and E7 oncogenes and with a proliferative phenotype.

Along this line, a study assessing the efficacy of a specific vaccine against HPV-16 E6 and E7 oncoproteins in 20 patients with HSIL (usual-type VIN) and HPV-16 infection yielded a response of 60% at 3 months and 79% at 12 months\(^74\).

The role of vaccines developed against oncogenes of HPV-16 and HPV-18 has also been evaluated, obtaining response rates (assessed as a reduction in lesion size) of 40-42%\(^75,76\).

These promising preliminary results, as well as those obtained with therapeutic vaccines for the treatment of CIN, must be validated in phase III clinical trials.
9.9 IMPACT OF VIN AND ITS TREATMENT ON PATIENT QUALITY OF LIFE

In recent years the treatment of VIN has evolved to more conservative forms with the aim of decreasing the psychosexual impact on patients and increasing their quality of life.

A recent multicenter study in 842 women evaluated the impact of HPV-related lesions in the lower genital tract on sexual function, general health and psychosocial burden using questionnaires. The results obtained were compared with those from women attended for a routine gynecological check-up. Patients with HPV lesions showed an increasing negative impact, proportional to the severity of the diagnosis. VIN patients showed a significant negative impact on sexual function compared with the general population.

In general, the studies undertaken to date have shown a negative impact of the treatment on the quality of life of patients treated for VIN or vulvar cancer. A study of 58 patients with VIN and vulvar cancer treated with surgery or CO2 laser vaporization showed that sexual dysfunction was independent of the type of treatment and increased with age. However, another study in patients with vulvar excision for VIN found a greater incidence of sexual and psychosomatic problems in women with vulvectomy compared to women with partial excision of the vulva.

Data on the impact on sexual function and quality of life of patients with VIN are not very consistent. Indeed, the presence of genital lesions and symptoms associated with VIN represents aggression to the personal and sexual identity of the patient which goes beyond the treatment itself.

Despite this, from the information available in the literature, it can be concluded that: 1) the diagnosis and treatment of VIN has a significant psychosexual impact on women, 2) the older the patient the greater the degree of involvement, and 3) the impact on the quality of life of patients is directly proportional to the aggressiveness of the treatment and the mutilation incurred. Therefore, in order to choose the most appropriate therapy for each patient it is essential to find the most effective and conservative options to preserve vulvar anatomy and functionality as well as the psychosexual dimension of the patients.

Follow-up of treated VIN patients is imperative to detect possible recurrence and prevent progression to cancer.
9.10 THERAPEUTIC ALGORITHM

Differentiated-type VIN

Excisional therapy: simple local excision

Usual-type VIN

Attempt to preserve vulvar anatomy and functionality

Occult invasion ruled out

Excisional therapies

Simple local excision

Partial/total skinning vulvectomy

Isolated unifocal or multifocal lesions

Confluent widespread multifocal lesions

Ablative therapies

C02 laser vaporization

Topical therapies

Imiquimod

Isolated unifocal or multifocal lesions

Combined therapies

Excision + C02 laser

Topical + Excision/C02 laser

Confluent widespread multifocal lesions

C02 laser – lesions in introitum, clitoris, periurethral, non-hairy areas
10. Follow-Up

10.1 RECURRENCE AFTER TREATMENT

According to the literature, the recurrence rate of VIN patients varies greatly from 20-50%, regardless of the therapeutic modality used\textsuperscript{69,27,80}. Risk factors for recurrence are: 1) widespread lesions, 2) positive margins at the excision site, 3) multifocal lesion, 4) immunosuppression, and 5) smoking.

Similar to what occurs in other pre-malignant lesions of the lower genital tract, widespread lesions are associated with an increased risk of recurrence. In addition, these lesions are more difficult to treat, with incomplete or suboptimal treatments frequently being administered.

Another factor clearly related to the risk of recurrence is the state of the surgical margins. Jones et al. described a recurrence rate of 50% in cases with affected margins compared with 15% in patients with disease-free margins\textsuperscript{26}. Other authors have reported similar findings\textsuperscript{27}. However, there are scarce studies including the state of the margins, and this may significantly bias the results. Some studies have questioned the association between affected margins and recurrence in HSIL (usual-type VIN)\textsuperscript{27} and concluded that only multifocality is related to the risk of recurrence, postulating that the affected margin, considered as minimal residual disease, is able to trigger an activation of the immune system that may be effective in the resolution of the lesion.

Evaluation of recurrence based on treatment is very complicated since the type of treatment is not an independent factor, being conditioned by multiple factors including lesion extension or multifocality. The few studies assessing treatment-related recurrence concluded that most of the therapeutic interventions for VIN have a similar efficacy with comparable recurrence rates. After a mean follow-up of 39 months, Van Seters et al. observed a recurrence rate of 19% after vulvectomy, 18% after partial vulvectomy, 22% after local excision and 23% after CO2 laser vaporization\textsuperscript{27}. A review including 16 non-randomized cohorts series including 504 VIN cases treated with CO2 laser vaporization reported a mean recurrence rate of 12.8% (0 - 33%)\textsuperscript{80}.

A retrospective study analyzing 93 VIN cases treated with different methods, with a mean follow-up of 54 months, showed a significantly higher risk of recurrence in cases with multifocal VIN (p=0.012) and positive HPV (p<0.001). In a multivariate analysis, the only risk factor was the presence of HPV (p=0.012) and multifocality in negative HPV cases (p=0.03)\textsuperscript{80}.

Finally, a recently published multivariate study showed that smoking plays a key role in the risk of recurrence and progression of VIN. Compared to non-smokers smokers have a 1.6-fold and 3-fold greater risk of recurrence and progression, respectively\textsuperscript{83}. Wallbillich et al. also found a significant association between smoking and relapse (p<0.001), extension of the lesion (p=0.016), and involvement of the margins (p=0.005)\textsuperscript{69}.

10.2 RISK OF PROGRESSION

VIN is considered a precursor lesion for vulvar squamous cell carcinoma based on the histological and clinical association between these two entities. In addition, the presence of foci of invasion in surgical specimens of patients previously diagnosed with VIN (occult invasion) is confirmed in 3-20% of cases\textsuperscript{21}. A systematic review of 3,322 VIN patients showed that 6.5% of cases developed vulvar squamous cell carcinoma, half of which were occult carcinomas detected during diagnostic studies\textsuperscript{27}. This same review also found that over a follow-up of 1-8 years, untreated patients had a 9% rate of progression to invasive cancer.

Several studies have shown that the risk of progression differs depending on the type of VIN. However, there is no specific test to determine the behavior of VIN in each case. The limited data available in the literature do not allow the risk of malignancy in patients with differentiated-type VIN to be clearly established, but it is recognized to be considerably greater than that of HSIL (usual-type VIN). This increased
risk may be explained by histological changes and the older age of the patients with differentiated-type VIN. Indeed, an analysis including 67 patients with differentiated-type VIN reported a rate of progression of 33% in non-treated patients.

The mean time to progression to vulvar squamous cell cancer in VIN patients varies (3.9 years in non-treated women, 2.4 years in cases with incomplete treatment and 13.5 years in patients adequately treated).

Quantitatively, the risk of developing vulvar cancer after treatment for VIN is at least 10-fold higher than the risk of cervical cancer after treatment for HSIL/CIN3. Among cases with progression, two different situations are of note: cases with early progression (mean 2.4 years) in which the lesion is located at the same site as the previous lesion, probably related to incomplete excision, and late invasive lesions (average 13.8 years) located at a site different from previous lesions that have been completely resected.

Advances in the knowledge of the role of the immune status of patients in the evolution of HSIL (usual-type VIN) will help to better understand the conditions favoring the persistence of HPV infection and the progression of VIN to invasive lesions. These advances could also help to determine immunological markers capable of predicting response to immunotherapy.

Finally, the limited knowledge of recurrence and progression of VIN should be taken into account since most of the studies published to date are retrospective, with a small number of cases and with different follow-up periods, leading to non-significant results. Therefore, prospective, multicenter, randomized studies with a sufficient number of cases are needed.

### 10.3 FOLLOW-UP GUIDELINES

The high risk of recurrence and progression of VIN lesions makes long-term follow-up after treatment necessary (up to 35% of relapses occur within the first 5 years post-treatment). However, follow-up data of VIN patients are very limited and prospective studies have not shown the value of self-examination and regular visits after treatment. Despite this, it is logical to think that follow-up will allow early diagnosis of recurrence.

Currently, there are no clinical guidelines defining the most adequate follow-up period of women treated for VIN. In 2011, the recommendations on VIN of the American College of Obstetricians and Gynecologists and the American Society of Cervical Pathology and Colposcopy stated that women with complete response to treatment should be monitored at six months and then at 12 months post-treatment. Subsequently, monitoring should be done annually for a minimum of 10 years (see follow-up algorithm). In the review conducted in Up-to-date biannual follow-up was recommended during the first five years followed by annual controls. Quality of evidence: low; Grade of recommendation: weakly in favor.

Closer monitoring is required in immunocompromised women in whom the risk of recurrence or progression is high, with quarterly follow-up being advisable during the first two years followed by biannually thereafter. Quality of evidence: low; Grade of recommendation: weakly in favor.

The coexistence of HSIL (usual-type VIN) with other HPV-related diseases has been clearly described. Therefore, follow-up of patients with VIN should include careful examination of the entire anogenital tract.

Finally, it is important to underline the need for these patients to be treated and followed by teams specialized in lower genital tract pathology. This criterion has been reinforced by the results of a study published in Northern Ireland which reported a rate of progression of VIN to cancer of greater than 20% in women treated by general gynecologists not following established protocols.
10.4 FOLLOW-UP ALGORITHM

VIN post-treatment follow-up

- Detailed inspection of vulva +/- vulvoscopy
- In depth examination of the lower genital tract

- First follow-up at 6 months*
- Second follow-up at 12 months
- Annual follow-up for 10 years

*Immunocompromised patients: quarterly follow-ups for the first two years followed by biannually thereafter
11. Primary prevention of VIN. Role of prophylactic vaccines against HPV.

For years, the primary prevention of HSIL (usual-type VIN) has been based on the prevention of HPV infection and the avoidance of factors involved in its persistence, such as smoking\textsuperscript{26}. Currently, prophylactic vaccination against HPV is the mainstay in the prevention of these lesions. Although the role of vaccines in the prevention of invasive vulvar cancer has not been directly demonstrated, the decrease in the incidence of pre-malignant HSIL lesions (usual-type VIN) as a surrogate marker suggests that a reduction in the rates of HPV-related invasive vulvar cancer can be foreseen\textsuperscript{4}.

There are currently two prophylactic vaccines against HPV. The results of phase II and III clinical trials have shown that both the bivalent and quadrivalent vaccines are effective in the prevention of VIN lesions, with figures ranging between 90-100\% depending on the population group analyzed. Based on these data one of the indications of both vaccines is the prevention VIN, as stated in the summary of the product characteristics of these vaccines\textsuperscript{85,86}.

The marketing of HPV vaccines has evolved around clinical trials designed to determine the impact of these vaccines on the development of cervical lesions, leading to the recruitment of a small number of VIN lesions and thereby impeding the analysis of other types of data such as cost-effectiveness.

The low incidence of VIN requires large multicenter studies to reliably determine both the future effectiveness (effectiveness in real life) and the cost-benefit ratio of prophylactic vaccines in all HPV-related lesions\textsuperscript{86}. However, although post-hoc studies do not exclusively address VIN lesions, the results of these studies indicate the need to consider the overall benefit that vaccination may have in high grade vulvar lesions with a positive impact.

Several pharmacoeconomic studies have analyzed the economic impact of prophylactic vaccines on the prevention of VIN and have shown that vaccines against HPV are cost-effective in cohorts of pre-adolescent girls\textsuperscript{87}.

Prophylactic vaccines against HPV are the only method of primary prevention of HSIL (usual-type VIN) available. In the near future, primary and secondary prevention based on early diagnosis and adequate treatment of these lesions will likely significantly reduce the incidence of vulvar cancer which, albeit rare, causes great patient morbidity and mortality.
12. Recommendations

1. The diagnosis and treatment of VIN aims to prevent vulvar squamous cell carcinoma.

2. Given the heterogeneity of the clinical presentation of VIN, histological study of all suspicious and non-fibilated vulvar lesions is essential.

3. Treatment is recommended in all cases of VIN.

4. The treatment of choice for differentiated-type VIN is excision. Ablative or topical therapies may be used in HSIL (usual-type VIN) after ruling out occult invasion.

5. Therapeutic strategies as conservative as possible are needed in order to preserve vulvar anatomy and functionality, while always ensuring satisfactory results in terms of efficacy.

6. The high percentage of recurrence, regardless of the therapeutic approach, as well as the risk of progression to invasive lesions despite treatment, makes close monitoring of these patients necessary, especially in immunocompromised subjects. Follow-up is recommended at 6 and 12 months post-treatment and annually thereafter.
13. References


Vulvar Intraepithelial Neoplasia (VIN)


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