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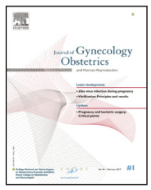

Review

Provoked vulvar vestibulodynia: Epidemiology in Europe, physio-pathology, consensus for first-line treatment and evaluation of second-line treatments☆

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Definitions

Vulvar pain located next to the vestibule, Provoked vulvar vestibulodynia (PVD) is essentially triggered by contact, sexual intercourses, gynecological examination, the introduction of a tampon, but without any vulvar lesions specific to the clinical

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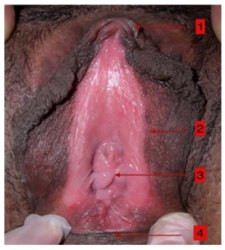
examination (Consensus on terminology and classification of vulvar pain ISSVD 2003, (1,2)).

The principal complaint is the dyspareunia of intromission, named orificial.

Differential diagnosis: Once sclero-atrophic lichen is discarded the main differential diagnosis is pudendal neuralgia, which is responsible for neuropathic vulvar pain, presenting the peculiarities that is spontaneous and essentially aggravated when seated.

The pain is triggered by the contact of the cotton tip (Q-tip test) of the vulvar vestibule during the clinical examination.



The vulvar vestibule is an anatomical entity whose limits are: the clitoris forward [1], the Hart line laterally and outwards [2], the vaginal opening and the hymen within [3], the fork back [4].

The vulvar vestibule is a specific entity, with its embryological particularity, resulting from the uro-genital and histological sinus, conferring on it a richness in nerve endings [3].

Prevalence and epidemiology in Europe

The analysis of the various European registers by the ICD 10 (code N 76.3, of the International Classification of Diseases), the national registers, the important epidemiological studies [4] and surveys of gynecologists of European countries, make it possible to draw up an epidemiological profile European PVD:

- The Italian registry Progetto Vu-net (reported by F Murina), confirms that PVD accounts for 72.6% of all vulvar pain. It affects women of all ages with a peak frequency between 20 and 29 years (29%)
- the prevalence can be estimated between 10 and 16% of women (4)
- Only 10–25% of patients get the correct diagnosis from their first gynecological visit.
- 45 to 65% of gynecologists have no diagnostic knowledge of PVD.
- Nearly 20% of gynecologists know PVD but feel that it is not up to them to start a treatment.
- Only 20% of gynecologists know the diagnosis of PVD and start a suitable treatment (investigation reported by E Bautrant)
- Despite a large disparity of diagnoses between countries and regions in each country, there is still a doubling of PVD diagnoses between 2006 and 2016 (Swedish register reported by H Mühlrad).

Pathophysiology

All experts agree to involve two physiopathological mechanisms:

- an anatomical entity, the vulvar vestibule particularly rich in nerve endings, unlike other vulvar tissues or the vagina.
- Hyperalgesia phenomena with central and peripheral sensitization.

This sensitization of the peripheral and central nociceptive system explains the existence of chronic pain in areas where no(or little) tissue damage can be found at clinical examination or diagnostics testings. There is therefore, as O. Porta points out, a paradigm shift from the classical anatomo-clinical model where the intensity of the pain is supposed to be proportional to the importance of the tissue lesions.

For F Murina, the phenomena of hyperalgesia are associated with significant neuro-inflammatory changes in the vulvar vestibule with mast cell activations adjacent to the nerve endings [5,6].

PVD is significantly associated with perineal dysfunction including a marked hypertonic tendency, a decrease in the flexibility of mechanisms of muscular relaxation capabilities and muscular power compared to control groups [7].

Genetic factors have been advanced. In front of, many situations of aggregation of family cases of PVD have been described. Several studies have shown that there is a genetic susceptibility to pain and inflammation in patients with PVD [8].

The frequent association of comorbidities, such as painful bladder syndrome, irritable bowel syndrome, dysmenorrhea, can be explained by the aggravation of pelvic hypersensitivity mechanisms [9].

PVD may be one of the symptoms of central pelvic hypersensitivity (CPH) ([10])

The causes which are triggering this hyperalgesia of the vulvar vestibule are many and encountered throughout life, since the repeated infections of the young woman (candidas, HPV), through the traumas of childbirth, the severe hormonal modifications of the menopause or the consequences of vulvar pathologies such as sclero-atrophic lichen after the menopause. To these causes of local hyperalgesia, changes in the thresholds of central sensitization are added that can be induced by affective disorders, relational or sexual trauma.

Consensus for first-line treatment

1 Treatment of local hyperalgesia of the vulvar vestibule by bi-daily application in the long term, of local anesthetics (Lidocaine 2–10%). Local treatment can also be used before sex. Alternatively a topical Amitriptyline or Gabapentin may be proposed. Possible combination with the use of a pelvic sensitization treatment: Amitriptyline first-line, then Pregabalin or Gabapentin in case of comorbidities.

2 **Perineal rehabilitation:** perineal and global external rehabilitation and progressive manual endo-cavitary muscle relaxation, negative biofeedback, recovery technique of the perineal function. Overall treatment of perineal hypertonia. Reappropriation of the body diagram and rehabilitation of vesical and recto-sphincter dysynergies.

3 **Cognitive-behavioral therapeutics:** cognitive psychotherapy, psychosexual and trauma therapies, central therapies such as EMDR or Hypnosis. The initial therapeutic protocol, here summarized, benefits, in addition to the expert consensus, from a high level of proof of effectiveness, as confirmed by the levels of scientific evidence found in the literature, with grade A and B levels, for each of the three items [3,11–14].

Second-line therapies

In the event of failure of the first-line therapeutic protocol, numerous therapeutic options have been described, without being able to confirm their true interest and their precise indication, in the light of the results reported in the literature.

Here we report these techniques, which are currently being validated when they are indicated and remain in the domain of centers of expertise:

- **Vaginal vestibular infiltrations:** local anesthetics, corticosteroids or hyaluronic acid. None of them has demonstrated any efficacy in the treatment of PVD [15]. The infiltrations on the other hand have the important disadvantage of being particularly painful on a hyperalgesic vestibular area.
- **Other topicals in the treatment of hyperalgesia of the vulvar vestibule:** Gabapentin, Amitriptyline, Ketamine, Botulinum toxin are under evaluation ([13,16]
- **Botulinum toxin injections:** several publications report a therapeutic efficacy of Botulinum Toxin injections in the vulvar vestibule [17] with a level of evidence of grade C. The results, however, appear inconstant and in limit of significance. On the other hand, the effectiveness of the Botulinum Toxin is very interesting in case of severe perineal hypertonia resistant to reeducation. This is a good indication in the therapeutic protocol for injection of hypertonic perineal muscles.
- **TENS systems:** electrical transcutaneous nerve stimulation (TENS) of the vulvar vestibule, appears effective in the treatment of PVD, with Grade B evidence levels [18,19]. It is widely used by F Murina within a multimodal protocol. Its interest has been confirmed by other teams [20], who place it in second-line therapy before vestibulectomy surgery;
- **The CO2 Laser:** a recent and promising technique for F Murina [21], especially in post-menopause, in combination with the treatment of the urogenital syndrome of the menopause. However recent studies do not confirm a significant efficacy in the treatment of PVD [22,23]
- **Therapies and phototherapies by LED lamps:** simple to use and enjoying a real craze, these techniques could be used in the treatment of PVD, but without significant effectiveness proven to date [24].
- **Lipofilling:** very recently the use of fat growth factors has been proposed in the treatment of painful perineal scars [25] The Lipofilling techniques, as a second-line treatment of PVD, appear to be very promising, particularly in cases of tissue lesions, fissures and are being evaluated in the E Bautrant's team.
- **Infiltration of the ganglion impar:** therapeutic option recently proposed by T Riant [26] in the treatment of rebel PVD. Being evaluated.
- **Vestibulectomy:** several types of vestibulectomy are possible. From the simple posterior vestibulectomy, which can be associated with the vestibulectomy of the lateral vestibules, up to the total vestibulectomy, including the periurethral vestibule, or even the inter-clitorideal-urethral vestibule. Vulvoplasty most often uses the vaginal wall, after the mobilization of a vaginal flap, to fill the loss of substance. This is the second-line technique most used in the team of E Bautrant. Vestibulectomy represents, among the therapeutic options that we have placed in the second line, the technique which benefits from the greatest number of publications in the literature and since the greatest number of years, with a grade B of levels of proof and incontestably a large number of healings [13,15]. As a result, vestibulectomy appears to be widely used by centers of expertise, particularly in North America [27]. However, we believe that this option, being of the surgical type, with a non-negligible postoperative complication rate, must be positioned in the second therapeutic line.

Conclusion

PVD is a very common condition that benefits from a simple diagnosis that can be put in place by any gynecologist consulted in first intention in any European country, after eliminating common vulvar pathologies.

The objective of this work is:

- Disseminate knowledge on the positive diagnosis of PVD to all European gynecologists;
- Encourage the initiation of a consensual multimodal first-line treatment as proposed here.
- Facilitate second-line treatment evaluation studies. In the current state of knowledge, the implementation of second-line treatment will have to be validated in a multi-disciplinary consultation meeting.

Convergences PP Network Consensus

Convergences PP Network Consensus document (*) with the participation of:

(*) Convergences PP is an international non-profit scientific society dedicated to scientific advances, research, knowledge, dissemination and teaching on the theme of chronic pelvic pain (CPP).

Concerning the Provoked Vestibulodynies (PVV), the goal of Convergences PP is:

1 **Define the disease and spread knowledge about positive diagnosis.**
2 **Present a first-line treatment**
3 **Make a list of existing and published second-line treatments for evaluation.**

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