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CONSENSUS STATEMENT

Vulvodynia: still a dramatically neglected condition. A position statement on pathogenetic mechanisms from the Italian Society of Andrology and Sexual Medicine (SIAMS)

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Abstract

Purpose 8–10% of women experience vulvar pain. We aim to summarize the current literature on pathogenetic mechanisms of vulvodynia, and highlight its invisible nature, that often results in misdiagnosis, prolonged diagnostic process and/or inappropriate care.

Methods A comprehensive search was conducted on the main medical databases, including studies up to April 30, 2025. The statements were internally discussed, and levels of evidence were provided according to the Oxford 2011 LoE criteria.

Results The panel highlights the multifactorial and complex systems underlying vulvodynia, advocating for a more comprehensive and genuinely holistic evaluation of this condition. We discuss the role of vulvovaginal dysbiosis and vestibular inflammation, increased neuronal density, central sensitization, pelvic floor muscle dysfunction/hypertonicity, reduced plasma sex steroids levels, reduced expression/altered function of estrogen and androgen receptors, prolonged and early use of Combined Hormonal Contraceptives, and psychological distress, including symptoms of anxiety and depression.

Conclusion Vulvodynia is an often-unrecognized condition that significantly impacts a woman's quality of life. Our understanding of its underlying mechanisms is still limited, and more research is urgently needed. These gaps in knowledge pose major challenges for the diagnosis and effective treatment of the condition.

Keywords Vulvodynia · Neuroinflammation · Central sensitization · Hormones · Chronic pain

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Introduction

Genital pain is a common complaint affecting both pre- and postmenopausal women, typically emerging during reproductive age. Vulvar pain represents one of the more common forms of localized chronic pain with 8–10% of women experiencing this condition [1]. However, the exact prevalence is difficult to estimate, due to the stigma related to sexual dysfunctions in general, and to female sexual dysfunctions (FSD) in particular, but also to underreporting, misdiagnosis and changing definitions during recent years.

Vulvodynia is defined as a chronic pain syndrome affecting the vulva, characterized by persistent or recurring discomfort, burning, or pain, localized to specific areas or diffuse. These symptoms significantly impact on a woman's quality of life, affecting physical activities, sexual intercourse, and emotional well-being [1].

Unfortunately, the current edition of the Diagnostic and statistical manual of mental disorders (DSM-5) does not classify vulvodynia as a FSD itself, but recognizes it as a condition that can contribute to or cause genito-pelvic pain/penetration disorder (GPPPD), which is classified as a sexual dysfunction [2]. However, since "the pain is not sexual, the sex is painful" [3], this taxonomy appears as one of the more dramatic mistakes produced by the American Psychiatric Association when attempting to classify human sexual disfunctions. It has, in fact, been correctly argued that a significant number of vulvodynia patients which are included in the GPPPD are at risk of an inappropriate therapeutic approach [4].

For all these reasons, but also due to its complex nature and the lack of visible signs of infection or lesions which prevents a full medical attention, vulvodynia is often underdiagnosed. Another barrier is represented by the etiopathogenetic mechanisms underlying the disease, which are far from being fully understood, being believed to result from a combination of factors, including neural proliferation and irritation, hormonal changes, inflammation, and pelvic floor muscle dysfunction, amplified by the personality and the experience. In fact, psychological factors, such as stress, anxiety, and depression, are known sequelae and may also contribute to or exacerbate the condition. Due to the complex nature of vulvodynia, proper management usually requires a multidisciplinary approach, including medical treatments, physical therapy, and psychological support together with a dedicated sex therapy [1].

Despite the growing attention demonstrated by the medical community and the increasing awareness experienced by patients worldwide, vulvodynia remains also underresearched. This has led to a lack of standardized diagnostic criteria and effective treatment options. In the absence of clinical tests, the diagnosis relies on clinician judgement after exclusion of all other recognized explanations of pain.

In this Position statement, we aim to summarize the current literature on pathogenetic mechanisms of vulvodynia (see Table 1), and highlight the invisible nature of this disorder, that often results in misdiagnosis, prolonged diagnostic process and/or inappropriate care.

Table 1 Oxford Centre for Evidence-Based Medicine (CEBM) 2011 Levels of evidence and criteria [5]

Level of evidence	Criteria
1	Systematic review of randomized trials or n-of-1 trials
2	Randomized trial or observational study with dramatic effect
3	Non-randomized controlled cohort/follow-up study
4	Good quality retrospective "case–control" or "case series" studies
5	Expert opinion, mechanism-based reasoning

Methods

This position statement is based on a narrative literature review of relevant studies. The review was not systematic, but rather aimed to provide a comprehensive overview of the current understanding of the condition. To ensure a thorough and up-to-date analysis, we searched for articles published up to April 30, 2025 using the PubMed database.

The review focused on etiology, and the topics were selected to reflect the most pressing clinical questions. The retrieved studies were reviewed and grouped by topic, with a particular emphasis on the strength of the evidence. The statements were internally discussed and The Level of Evidence (LoE) for each statement was determined using the Oxford Centre for Evidence-Based Medicine (CEBM) 2011 criteria. This framework classifies evidence into 5 levels, from Level 1 (systematic reviews of randomized controlled trials, RCTs) to Level 5 (expert opinion without explicit critical appraisal) [5] (Table 1).

Definition and diagnosis

The definition of vulvodynia has undergone different modifications, based on the increased knowledge about this condition over the years. In 2015, the International Society for the Study of Vulvovaginal Disease (ISSVD), the International Society for the Study of Women Sexual Health (ISSWSH) and the International Pelvic Pain Society (IPPS) endorsed a Consensus Terminology and Classification of Persistent Pain and Vulvodynia, elaborating a more complete definition compared with those previously used [6]. In this document, vulvodynia was defined as *vulvar pain of at least 3 months' duration, without a clear identifiable*

Table 2 Summary of clinical factors potentially pathogenetic mechanisms of vulvodynia, including Oxford 2011 Levels of Evidence. Modified from [6]

Factors potentially associated with the pathogenesis of vulvodynia	Level of evidence
Dysbiosis, inflammation	2
Neurologic mechanisms	2
-Central (spine, brain)	2
-Peripheral: neuroproliferation	
Musculoskeletal (e.g., pelvic muscle overactivity)	3
Alterations in sex steroids levels or signaling	3
-Endogenous	3
-Pharmacologically induced	
Body Mass Index, metabolic and nutritional aspects	3
Psychopathological traits (e.g., depression, anticipatory anxiety, avoidant and anxious attachment) and cognitive aspects (e.g., catastrophizing, self-efficacy)	2

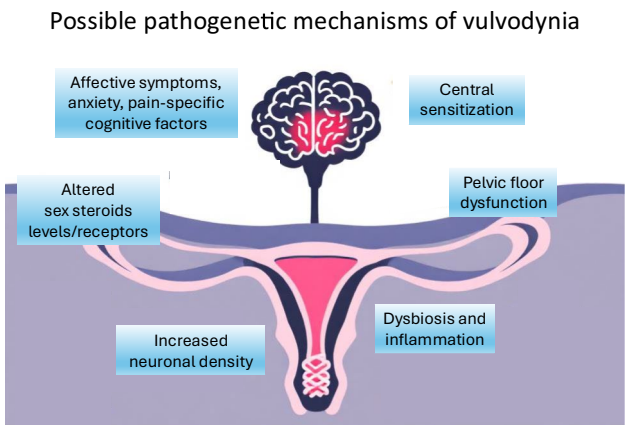

Fig 1 Possible pathogenetic mechanisms of vulvodynia

cause, with potential associated factors [6], and stressing the difference between vulvar pain and vulvodynia. Indeed, vulvar pain is described as a pain with a clear identifiable cause, that could be infectious (e.g. herpes), inflammatory (e.g. lichen), neoplastic (e.g. Paget disease), neurologic (e.g. post-herpetic neuralgia), traumatic (e.g. female genital cutting), iatrogenic (e.g. chemotherapy) or due to hormonal deficiencies (e.g. vulvovaginal atrophy, VVA). Furthermore, the Consensus emphasized the presence of factors potentially associated with vulvodynia, thus stressing its multimodal origin and the need of tailoring the therapeutic strategy to the single patient [6].

The same group identified several descriptors related to location, provocation, onset, and temporal pattern: localized (e.g. vestibulodynia, clitorodynia), generalized or mixed; provoked (e.g. contact), spontaneous or mixed; primary or secondary, in relation to initial onset; and intermittent, persistent, constant, immediate or delayed, according to the temporal pattern [7]. *Provoked vestibulodynia* (PVD), previously known as Vulvar vestibulitis syndrome, is the main subtype of vulvodynia, in which painful sensation is confined to the vestibule, an embryologically distinct band of tissue surrounding the vaginal opening, and provoked by mechanical stimulation, such as touch [6]. According to modified Friedrich's criteria, it has been suggested to diagnose PVD in the presence of moderate to severe pain during attempted penetration with pain limited to the vulvar vestibule, that is confirmed by a cotton-swab test [8].

In January 2022, vulvodynia was included, for the first time, in the category of "chronic primary visceral pain" in the 11th revision of the International Statistical Classification of Diseases and Related Health Problems, thus classifying this condition as a chronic pain syndrome [9, 10].

In the following sections we discuss each of the potential pathogenetic mechanisms of vulvodynia that are presented in Table 2. These discussions are not exhaustive, but meant only to provide an essential base necessary to understand the putative causal associations and mechanisms (see also Fig. 1).

Dysbiosis and the role of the inflammatory response

Statement #1 *The role of vaginal microbiota composition and vulvovaginal dysbiosis in vulvodynia remains unclear. (Expert Opinion).*

Statement #2 *Vestibular inflammation caused by an unregulated cytokines response consequent to a previously dysregulated vaginal microbiota has been proposed as one of the leading mechanisms in the etiology of provoked vestibulodynia (PVD). (Loe3).*

Evidence

The evidence regarding the role of infections and inflammation in the pathogenesis of vulvodynia, probably acting through the onset and maintaining of an abnormal immune response to a previously dysregulated microbiome, is still inconclusive [11–13]. These processes seem to play a role especially in cases of PVD. In fact, the vulvar vestibule, derived from the endoderm—as the bladder and anterior urethral wall-, displays unique immune properties, aimed at facilitating the rapid detection of pathogens at a critical anatomical gateway to the reproductive tract [14]. In fibroblast strains obtained from women affected by PVD, an enhanced pro-inflammatory response to yeast pathogens was detected compared with pain-free controls, suggesting their critical role in an early step of the pathogenesis and pain generation [15]. Similarly, a significant elevation of Dectin-1, a surface receptor that binds *Candida albicans* cell wall glucan, was found in cases versus controls, with a particular increase in cells derived from the vestibule compared with those from the external vulva [16]. Noteworthy, blocking Dectin-1 signaling significantly reduced production or

activities of pro-inflammatory mediators by fibroblasts [17]. More recently, the same group of research further demonstrated the link between inflammation and pain, by providing evidence that an imbalance in pro-resolving lipids and exaggerated responses to inflammatory stimuli in the vestibule lead to the activation of the transient receptor potential cation channel subfamily V member 4 (TRPV4), involved in conducting pain signals [18].

Consistent with these data, clinical studies indicate that approximately 70% of women with vulvodynia report a history of frequent or severe yeast infections [11–13]. A case–control study retrospectively assessed the correlation between recurrent vulvovaginal yeast infections prior and subsequent to vulvodynia diagnosis compared to controls from the general population [19]. A history of > 10 yeast infections was associated with currently diagnosed vulvodynia, after adjustment for age, age at first intercourse, and history of urinary tract infections (UTIs) (adjusted odds ratio 5.5) [19]. Similarly, vulvodynia was linked to a twofold increased chance of developing yeast infections in the future, even after controlling for the history of yeast infections before vulvodynia onset [19]. However, this study was based on self-reported data, carrying a relevant risk of misreported information and potential overestimation or underestimation of effect sizes. Moreover, given the cross-sectional nature of studies, it is not clear whether recurrent yeast infections play a role in the predisposition to vulvodynia, or if recurrent infections are a consequence of the development of vulvodynia itself. A recent retrospective analysis of data collected from 2017 to 2020, based on genital culture diagnostic tests, provided conflictual findings, showing no association between vulvodynia and vaginitis; on the other hand, factors correlated with vulvodynia were low Body mass index (BMI) and anxiety [20]. To explain these inconsistencies, it could be hypothesized that the individual risk of developing infection-related vulvodynia depends on many variables, including characteristics of the infectious agent, host susceptibility associated with specific genotypes, epigenetics and genetic expression/proteomics, the immune response, alterations of the vaginal microbiota and of the metabolites produced by the local flora (vaginal metabolome) [21].

Beyond yeast infections, there has been a growing interest in exploring the potential role of physiologic, paraphysiologic, and pathological variations in vaginal microbiota composition in the etiology of vulvodynia. A study of women with localized provoked vestibulodynia found that their vaginal microbiota had less bacterial diversity compared to a control group; the study specifically associated the Ochrobactrum genus and Pseudomonadaceae family with the condition [22]. Another case–control study revealed that *Lactobacillus gasseri* was more often dominant than other *Lactobacillus* species in the vagina and vestibule only in women with provoked vestibulodynia but not in healthy women, showing a significant correlation with pain severity [23]. It has been hypothesized that while this microorganism indicates a normal vaginal microflora, it may provide reduced defensive capacity and evolve toward an unstable microbiota, acting as an element of vulnerability for dysbiosis [23]. Overall, despite growing interest in this topic, the evidence remains inconsistent. Accordingly, a recent systematic review on 8 case–control studies concluded that no specific bacterial taxa were consistently associated with vulvodynia, and that the relationship between vaginal microbiota diversity and vulvodynia is still not fully understood [24].

Neurological involvement

Statement #3 *Acquired and congenital increased neuronal density in the vestibule may play a role in a specific subtype of vulvodynia, named neuroproliferative vestibulodynia (Loe2).*

Statement #4 *Central sensitization could act as the common etiology for vulvodynia and other overlapping chronic pain conditions such as fibromyalgia, endometriosis, interstitial cystitis/bladder pain syndrome (IC/BPS), and irritable bowel syndrome (IBS), which should be proactively investigated to provide a complete management strategy. (Loe2).*

Evidence

A neurological component has been proposed as one of the mechanisms contributing to the pathogenesis of vulvodynia at different levels, including alterations of nociceptor density, changes in synaptic function and response to non-noxious stimuli, reduction in threshold for neural activation, and an expansion of the receptive field beyond the initially affected tissue, involving both central and peripheral pathways.

Neuroproliferative vestibulodynia

Similar to inflammation, peripheral neurologic involvement seems to play a role especially in the vestibule. In fact, neuroproliferative vestibulodynia is considered a subcategory of vestibulodynia, in which up to a tenfold increase in the density of C-afferent nociceptors can be demonstrated in the vestibular tissue [25]. This increased neuronal density has been attributed to proliferation secondary to enhanced cytokine synthesis (acquired forms) or to congenital hyperplasia in tissues derived from the primitive urogenital sinus (congenital forms), and is consistent with the clinical presentation

characterized by mechanical allodynia and hyperalgesia in the vestibule with no apparent signs on physical examination [26]. Interestingly, inflammation-triggered neuroproliferation in the vulvar vestibule, in endometriosis epithelium/stroma and in the pelvic peritoneum has been claimed as the common denominator in cases of vulvodynia associated with endometriosis [27]. In patients with neuroproliferative vestibulodynia, immunohistochemistry studies performed on tissue samples derived from biopsy or therapeutical vestibulectomy show an increased in neuronal markers [such as protein gene product (PGP) 9.5] and mast cell markers (e.g. CD117) [28, 29]. The vanilloid receptor VR1 (TRPV1, an ion channel that is found both pre- and post-synaptically), triggered by capsaicin, noxious heat, protons, and chemicals produced during inflammation, has been reported to be overexpressed in vulvodynia tissues compared to controls [30].

Noteworthy, it has been demonstrated that yeast challenge to vulvar tissue leads to a long-term increase of gene expression of nerve growth factor (NGF) in the spinal cord, which is counteracted by the stabilization of mast cells activity [31]. Peripheral nerves and mast cells can establish a vicious cycle of mutual activation through the release of neuropeptides, tryptase, and histamine, thus maintaining an elevated inflammatory state and leading to peripheral sensitization and a transition from acute to chronic pain [32].

Central sensitization

Beyond allodynia, vulvodynia involves other neuropathic pain features, namely central sensitization, which originates from an alteration of pain processing pathways in the central nervous system [33, 34]. Central sensitization is a phenomenon of synaptic neuroplasticity based on altered sensory processing of the central nervous system, in which normal sensory inputs evoke exaggerated and painful responses, an expression of receptive field, and temporal dissociation of stimulus and pain. Recent evidence has led to hypothesize that central sensitization could act as the common etiology for vulvodynia and other overlapping chronic pain conditions such as fibromyalgia, endometriosis, chronic fatigue syndrome, chronic migraine, temporomandibular disorders, interstitial cystitis/bladder pain syndrome (IC/BPS), irritable bowel syndrome (IBS), and chronic low back pain [35]. In particular, bowel dysfunctions appear as the most commonly associated disorders in patients with chronic vulvar pain, with a 2-to fourfold increased likelihood of IBS diagnosis in those with vulvodynia [36], although a recent study found a similar association for endometriosis and a stronger association for fibromyalgia [37], both of which are also chronic pain conditions and likely involve central sensitization.

Accordingly, imaging studies revealed that PVD subjects had significantly higher gray matter densities in pain modulatory and stress-related areas, i.e. the parahippocampal gyrus/hippocampus and basal ganglia, compared with controls [38]. Additionally, in several of these regions, gray matter was related to lowered pain thresholds and increased pain catastrophizing scores [38]. These findings suggest the presence of morphological alterations in supra-spinal pain modulatory circuitry, which might contribute to the clinical symptoms of patients with chronic vulvar pain.

Central sensitization may also affect response to treatment. In a study conducted on 105 patients with vulvodynia, 33% had central sensitization according to the Convergence PP Criteria [39]. Central sensitization was associated with comorbidities, dyspareunia, pain with micturition, and pain with defecation, with dyspareunia and pain with defecation acting as independent prognostic factors for central sensitization [39]. Noteworthy, the subgroup of subjects with central sensitization responded worse to treatments (including pelvic floor physiotherapy and neuromodulation) and required a longer response time [39].

Pelvic floor muscle dysfunction

Statement #5 *Studies investigating pelvic floor muscle (PFM) dysfunction suggest the presence of hypertonicity in women with vulvodynia, especially provoked vestibulodynia; however, lack of consensus terminology and of validated methods of assessment complicate the interpretation of data. (LoE3).*

Evidence

A large clinical literature discusses the potential relevance of pelvic floor increased tone in the etiology and as a potential target of treatment for several pelvic pain conditions, including chronic vulvar pain. However, lack of consensus terminology and normative data on muscle properties, heterogeneous methods of assessment, and the use of tools not validated to measure tone, complicate the interpretation of data [40]. Overall, most available studies provide evidence of a hypertonic pelvic floor in women with PVD, the subtype of vulvodynia which has been more extensively investigated from this perspective. For example, Morin and colleagues, using a dynamometric speculum combined with surface electromyography, found greater PFM resting forces and stiffness in 56 women with PVD compared with controls, along with an increased active component, higher passive properties and decreased strength, speed of contraction, coordination, and endurance [41]. Another study using the same method (surface electromyography) and a digital intravaginal assessment revealed that women with PVD had

higher tonic activity in the pelvic muscles compared with the control group, but only in the superficial layer, with stronger contractile responses to painful pressure, decreased flexibility and lower relaxation capacity [42]. Another issue when exploring the relationship between PFM dysfunction and vulvodynia is that, given the cross-sectional nature of available data, it cannot be excluded that the observed hypertonicity represents a result of chronic pain instead of a cause related to the pathogenesis of the condition [10]. A bidirectional reciprocal-effects model may be most likely.

Vaginal delivery is well-recognized as one of the most common causes of pelvic floor dysfunction [43], and several studies have investigated the management and characteristics of parturition in women diagnosed with vulvodynia [44]. Specifically, operative delivery may cause imbalances and functional modifications in the pelvic floor myofascia and neural tissue, thus potentially contributing to the pathogenesis of vulvodynia [45, 46]. Moreover, surgical interventions such as episiotomy and subsequent episiorrhaphy can modify local innervation, causing chronic pain and dyspareunia [47]. However, the role of type of delivery as a risk factor for vulvodynia is still debated.

PFM dysfunction as a pathogenetic factor in vulvodynia is partly supported by descriptive data showing that physiotherapy can contribute to alleviating symptoms of genital pain. However, only one trial evaluated outcomes related to PFM function and morphometry using ultrasound measurements in 57 women with vulvodynia randomized to kinesiotherapy plus amitriptyline or amitriptyline alone for 8 weeks [48]. In the kinesiotherapy group only, 4D transperineal ultrasound suggested a greater excursion of the levator ani muscle plate and increased symphysis-levator distance after treatment, suggesting normalization of PFM tone [48]. Overall, outcome data on physiotherapy for treating PFM dysfunction are not sufficient to prove its efficacy.

Sexual hormones, response, and imbalance

Statement #6 *Reduced plasma estrogen and androgen levels are associated with anatomic modifications of genital tissues (e.g., vestibular mucosa), reduced pain threshold and an increased local and neurogenic inflammation that may potentially predispose to vestibulodynia in particular individuals. (Loe3).*

Statement #7 *Symptoms of vulvodynia may be associated with a reduced expression/altered function of estrogen receptor α (ERα) and androgen receptor (AR). (Loe3).*

Statement #8 *Prolonged and early use of Combined Hormonal Contraceptives (CHCs) has been associated with symptoms of vulvodynia, however results are conflicting and no RCT is available. (Loe3).*

Statement #9 *Women with suspected vulvodynia should be evaluated for the concurrent presence of hormonal conditions that may contribute to vulvar pain. (LoE2).*

Evidence

The role of sex hormones in the pathogenesis of vulvodynia is still debated. However, hormonal imbalance is recognized as one of the possible contributing factors, as part of a multifactorial pathogenesis.

Endogenous sex steroids and their receptors

Sexual hormones, namely estrogens, androgens and progestins, play an important role in maintaining the trophism and functionality of the genitals, and their role has been extensively studied in relation to the changes associated with the Genitourinary syndrome of menopause (GSM) [49]. In fact, androgen receptors (ARs) and estrogen receptors (ERs) have been detected throughout the female genitourinary system. The effects of androgens can be distinct from or complement those of estrogens. In particular, ARs and ERs are expressed throughout the vagina (mucosa, submucosa, stroma, smooth muscle, vascular endothelium), as well as in the urethra and bladder, at the level of labial and clitoral tissues [49]. Finally, ARs are widespread in the pelvic floor muscles, while the role of ERs in the pelvic musculature is less clear [49].

In addition, sex hormones are associated with sensation and pain, with both central and peripheral effects. It is hypothesized that decreased estrogen may increase sympathetic and sensory nerve density, contributing to vasoconstriction, dryness, and vaginal pain [50]. A preclinical study conducted in female rats showed a significant increase in nerve density in the ovariectomized rats, compared with those in estrus, and particularly an elevation in sympathetic nerves (+70%), that could be responsible for more pronounced vasoconstriction and consequently vaginal dryness in menopausal women [51]. Moreover, calcitonin gene-related peptide (CGRP)-immunoreactive sensory nociceptor nerves showed a significant increase in density (+84% in ovariectomized rats), which could account for typical menopausal symptoms such as pain and irritation, that are also associated with some types of vulvodynia [51].

In this context, progesterone could also play a role. Previous studies have already demonstrated that this hormone is able to mediate an increase in neurotrophic factors in the female reproductive tract, as well as to enhance axon sprouting and myelination [52, 53]. More recently, a preclinical study investigating the effect of sex steroids on the genital tract of female rats showed an overall increase in vaginal innervation after progesterone administration, both

prior to reproductive hormonal cycling and in the sexually mature rats, due to proliferation of peptidergic sensory and sympathetic axons [54].

On the whole, data suggest estrogens, androgens and progestins may modulate sensory nerve function and/or sensation. However, specific findings in genitourinary tissues are extremely limited, and we don't know whether effects of these hormones depends on circulating plasma concentrations, local hormone synthesis, expression of receptors in target tissues, and/or variability in receptor sensitivity.

Finally, few studies have been conducted to document modifications in these determinants in women with vulvodynia.

It should be noted that, in women with PVD, vulvar pain has been found to decrease during the periovulatory phase, which is characterized by a peak in estrogen levels, differently from the premenstrual phase, during which estrogen levels are lower [55]. This finding endorses a role of sex hormone levels, although this result could also be determined by a lowering of the pain threshold. There are no data comparing the circulating hormone levels of women with vulvodynia versus unaffected women.

Hormonal replacement therapy, hormonal contraception and other medications

Large observational studies have failed to find a significant difference in symptoms among perimenopausal patients (aged 40–65) between those using and not using Hormonal Replacement Therapy (HRT), suggesting that persistent pain symptoms were not primarily attributable to hormonal alteration in circulating estrogen levels. However, these findings may be attributable to the presence of two different combined factors – perimenopausal hormonal changes and HRT use [56]. In a second study [57], in which data from 371 postmenopausal women (56—68 years) from the Michigan site of the Study of Women's Health Across the Nation (SWAN) were analyzed, results regarding the association between chronic vulvar pain and HRT use were conflicting: indeed, some participants reported continued or first onset of pain while using hormones. Moreover, this study demonstrated that the relative odds of current pain inversely correlated with dehydroepiandrosterone-sulfate (DHEA-S) and T levels, also after adjustment for age, race, and BMI, thus supporting the hypothesis that chronic vulvar pain in postmenopausal women may also be associated with androgens deficiency, and not limited to estrogen deficiency-related atrophy [57].

Intriguingly, a retrospective analysis of vestibulectomy samples obtained from women with localized provoked vulvodynia compared with those collected from healthy controls, showed that patients had an increased expression of the ER β staining (both nuclear and cytoplasmic) compared with controls, whereas expression of ERα, ERγ, progesterone receptor (PR), and CD3 cells, was similar in the two groups [58]. The clinical implications of these findings are not clear, although these may involve dysregulation of estrogen signaling in localized PVD. In another study, examining vestibular biopsy specimens obtained from women with vulvar vestibulitis syndrome and controls, results showed a significant decrease in ERα expression in patients compared with controls, with 50% of patients not exhibiting ERα staining at all [59, 60].

Regarding medication-induced hormonal changes, the use of combined hormonal contraceptives (CHCs) represents one of the causes of iatrogenic decrease in circulating sex steroids. Several authors have found that women who used oral contraceptive (OCs) before the age of 16–17 were 9 to 11 times more likely to develop vulvodynia, and that early menarche was associated with increased odds of developing vulvodynia, leading to the hypothesis of a connection between vulvar pain and sex hormones through an effect on mucus secretion [61, 62]. This observation was confirmed by Berglund et al. who also found that long-time use of OCs was associated with vulvar pain [63]. Also, a recent study found that use of both estroprogestinic and progesterone only OCs were associated with diagnosis of vulvodynia [37]. Interestingly, this study also showed that self-reported genital-specific side effects of OC use (vaginal dryness and vulvar pain), but not affective or non-genital physical side effects of OC use, were associated with having a diagnosis of vulvodynia, suggesting a tissue-specific relevance of side effects [37].

Histopathological studies have also reported a decrease in the expression of the AR in women with vestibulodynia [64]. It could be hypothesized that the reduction in androgen levels, consequent to CHC use, may lead to down regulation in AR synthesis [59]. Noteworthy, women who were diagnosed with PVD while taking CHCs, had longer CAG (cytosine–adenine–guanine) repeats in their AR genes, and thus a decreased sensitivity to androgens as compared with controls [65]. It was suggested that the combination of lower free testosterone levels associated with CHC use, and the weaker androgen effects associated with the longer CAG repeats, resulted in compromised vulvar tissue health and vulnerability to the pathogenesis of vestibulodynia [65]. A preliminary case–control study with a different approach, comparing polygenic risk scores for vestibular mucosa thickness in vestibulodynia, also suggested a role for both ERs and androgen levels, although a small sample size limits its conclusion [66].

In addition, it has been demonstrated that CHC use can lead to morphologic alterations in female external genitalia, such as reduced clitoral volume, labial thickness and

vaginal diameter [67], as well as in the vestibular mucosa, that becomes more susceptible to mechanical stress [68]. Furthermore, taking CHCs has been related to a decrease in the mechanical pain threshold of vestibular mucosa [69] and to an increased risk of asymptomatic vaginal colonization of Candida and candidal vaginitis, factors often underlying vulvar vestibulitis syndrome [70].

Also, spironolactone has been anecdotally suggested to cause—or contribute to—vulvar pain and dyspareunia, in addition to decreased arousal, probably due to an anti-androgenic effect [71], but there is insufficient evidence to support this hypothesis.

Overall, to date no RCT has been performed to adequately measure the effect of early or prolonged use of CHCs or other sex-hormones affecting drugs on vulvodynia. Furthermore, evidence from a longitudinal study of adult women, could not confirm a significant association between OC therapy and vulvar pain, casting a shadow on a direct hormonal effect [72, 73].

In conclusion, although some data show a correlation between sex steroid hormone levels and the development of vulvodynia, studies on epidemiological association and pathophysiologic mechanism are scarce, precluding definite conclusions. An indirect indication of the complex relationship between vulvodynia and sex hormones is the current lack of evidence supporting the efficacy of sex hormone treatments (e.g., topical estradiol and testosterone) in affected women; however, this is beyond the scope of the present document.

Body Mass Index, metabolic and nutritional aspects related to vulvodynia

Statement #10 *Most women with vulvodynia present with a BMI within the normal range, and current evidence does not support an association between overweight/obesity and vulvodynia. (Loe3).*

Statement #11 *We suggest that low BMI may be considered a potential marker of poor therapeutic response in women with vulvodynia, although further research is needed to confirm this association. (Loe3).*

Evidence

Limited data are available in the literature concerning weight and BMI in women with vulvodynia or vulvar pain [74]. Given the low number of studies assessing BMI, most of which have relied on self-reported rather than clinically measured data, it appears that the majority of women with vulvodynia have a BMI within the normal range (18.5–24.9 kg/m^2) [75–78]. Most studies reported no significant difference compared to controls [75–77], while a few have found a slightly lower BMI in affected individuals [79, 80]. Regarding symptom remission, a community-based observational study of 138 women with vulvodynia, conducted by Nguyen et al., showed a significant difference in BMI between those who experienced a remission of vulvar pain and those who did not [78]. The authors reported that women with a BMI within the normal range were more likely to experience remission compared to those who were underweight or obese [78]. Moreover, a prospective observational study by Gerhardt et al. found that patients who did not respond to therapeutic local anesthesia for their vulvar pain demonstrated a significantly lower BMI than patients who achieved therapeutic success (BMI 20.6 vs. 23.1 kg/m^2), suggesting a potential predictive role of BMI in treatment outcomes [80]. The role of body composition in vulvodynia remains unclear and warrants additional investigation.

Regarding nutritional aspects, very few studies have assessed dietary factors in patients with vulvodynia [74]. Urinary oxalate excretion was reported to be similar between 130 patients with vulvodynia and 23 controls [82]. Moreover, a RCT including 242 women with vulvodynia and 242 controls found no association between high oxalate consumption and an increased risk of vulvodynia [83].

To date, the literature on the relationship between metabolic disorders, such as Diabetes Mellitus (DM) and insulin resistance, and vulvodynia remains limited. An Italian cross-sectional study investigating the epidemiological characteristics and comorbidities of chronic vulvar pain identified a positive association with a family history of DM [84]. Although diabetic neuropathy is a well-known complication of DM [85], no clinical trials have specifically examined the link between diabetes and vulvar pain. Additionally, the 2015 ISSVD, ISSWSH, and IPPS Consensus does not recognize DM or other metabolic disorders as direct causes of vulvar pain [6].

Given the lack of supporting evidence, specific diets, nutritional supplements, or BMI modifications should not be recommended for the unique purpose of symptom relief in women with vulvodynia.

Psychological aspects

Statement #12 *Evidence suggests that psychological distress, including symptoms of anxiety and depression, are common in those with vulvar pain, although measurement may inflate the estimated effects. (LoE2).*

Statement #13 *There is a multitude of psychological constructs and aspects of sexual function that are central to the experience of patients with vulvodynia and must be a focus of evaluation. (LoE2).*

Statement #14 *"Medical gaslighting" is a common experience among vulvodynia patients, involving*

symptom invalidation by health care professionals, resulting in psychological distress and a significant diagnostic delay. (LoE3).

Evidence

Enriching the Bio-Psycho-Social (BPS) model with a systems Sexology approach

Pain due to vulvodynia and vestibulodynia has been historically defined and treated as either a purely medical/pathophysiological condition or purely a psychosomatic condition. However, a more recent perspective in sexual medicine and psycho-sexology has begun to stress the importance of the mutual influences of biological, psychological, and social variables in the etiology of disease. Although this Bio-Psycho-Social (BPS) model is currently considered the most accredited integrated model for understanding and treating the complexity of the human illness [34], it is typically limited to a dichotomic mind/body perspective. Seeking to broaden this conceptualization of illness within the sexual sphere, Jannini has proposed a more comprehensive approach, named *Systems Sexology* (SS), which considers sexual dysfunction as the complex interaction between the systems of mind, the systems of experiences, the systems of the society, and the systems of the body [86]. SS, similar to the most popular model of Systems Medicine used for research and management of Non-communicable Chronic Disease (NCDs) [87], goes beyond the exclusive search for etiologies, and instead: i) highlights risk factors, mostly related to lifestyles and individual behaviors, ii) recognizes acute, subacute, and chronic inflammation as a common pathway to illness and sexual dysfunction, and iii) postulates that the developmental origin of sexual health and disease cannot be understood without considering the role of intrapsychic and relational factors along with previous experience and political and economic factors which may dramatically influence human sexuality. We propose that vulvodynia be considered not only within the context of the BPS model but also integrating the full range of systems addressed in the SS model.

Psychological and cognitive aspects related to chronic vulvar pain

Multiple studies have found a link between vulvodynia and affective symptoms such as depression [88]. Although these associations are often used to justify an attribution of symptoms to "psychosomatic" causes, there is evidence that the association between vulvodynia and depression is specific to a very limited set of symptoms, rather than a general state of depression. For example, studies by Aikens et. al. [89] and Nylanderlundqvist and Bergdahl [90] found that the association between vulvar pain and depression was attributable to the somatic symptoms and *not* cognitive-affective symptoms. Specifically, the relevant somatic symptoms were "loss of libido" and "concern for physical health problems". Thus, the association between vulvodynia and depression may be largely attributable to two symptoms that are specific to genital pain, rather than a general depressive state or depressive disorder.

Moreover, the increased risk of having vulvodynia associated with affective disorders should also be considered in the context of other risk factors. For example, Arnold et al. [91] found that, while a history of depression was associated with vulvodynia symptoms (OR = 1.93), a comparable effect was found for history of regular tampon use (OR = 2.29), and larger effects were found for chronic urinary tract infections (OR = 6.23) and chronic yeast infections (OR = 3.33). Moreover, in a recent paper considering a total of 2171 women of whom 582 (26.8%) had a diagnosis of vulvodynia, results again showed that while having a diagnosis of vulvodynia was associated with both depression (OR = 1.53) and anxiety disorder (OR = 1.62), these effect sizes were modest as compared to pathologies of chronic pain and inflammation, including, for example, fibromyalgia (OR = 7.74), IBS (4.16), and endometriosis (OR = 3.17) [37]. Thus, although significant, the relative importance of depression and anxiety does not warrant a strong focus on "psychosomatic" models to explain vulvodynia symptoms.

The association between vulvodynia and psychological distress and pathology, however, is not limited to mood disorders, and extends across diverse diagnostic conditions. For example, a recent case–control study, conducted in Sweden on medical registries concerning more than 7000 women diagnosed with vulvar pain, found that patients had adjusted odds ratios between 1.4 and 2.3 for a wide spectrum of psychiatric disorders, including depression, anxiety, attempted suicide, neurotic disorders, stress-related disorders, behavioral syndromes, personality disorders, psychotic disorders, and chemical dependencies [92]. These authors, however, acknowledge that the observed associations do not shed light on directionality of causal effects.

It is also important to remember that pain is a highly subjective psychological experience, and thus very personal, with a multitude of psychological variables contributing to each individual's experience of pain, and whether and how the chronic pain contributes to the development of negative psychological consequences, such as anticipatory anxiety. This complex developmental course is described in Spano and Lamont's model [93], which illustrates how initial negative experiences (in this case painful sexual intercourse) creates a fear of intercourse-related pain, which will reduce vaginal lubrication and compromise positive associations

with sexual intercourse. The final result is an avoidance of sexual intercourse, with the belief that it will be always painful. The fear of this supposed future negative experience (painful intercourse) exacerbates anticipatory anxiety. Following the fear-avoidance model, anxiety is not only present in anticipation of sexual intercourse, but before all situations involving the genitals, including gynecological visits, the insertion of tampons, mutual partnered masturbation, and use of sex toys [94].

In addition to mood disorders and psychiatric comorbidities, there are multiple aspects of psychological adjustment and sexual function that should be addressed when dealing with vulvodynia. Concurrent with anxious mood, it is common for these patients to exhibit cognitive factors associated with anxiety. Notably, these include catastrophizing, pain self-efficacy, and body-exposure anxiety during sexual intercourse [95]. Pain self-efficacy refers to the perceived ability to cope with difficult pain situations [96]. Importantly, this has been shown to longitudinally predict decreases in genital pain and increases in sexual function [96], thus providing insights and strategies for dealing with vulvar pain and its associated sexual difficulties. Moreover, research has also highlighted the complexity and multivariate contributions of other psychological aspects associated with chronic genital pain and challenges with sexual pleasure and intimacy, including a sense of inadequacy as a woman [97] and self-image/schemas [98].

Regarding attachment styles, it has been reported that, in couples where the woman has vulvodynia, both attachment anxiety and avoidance may contribute to increased perceptions of negative partner responses, as well as to negative interpretations of partner-reported behaviors [99]. Hence, it seems that the woman's interpretation of the partner's reactions may exacerbate her pain experience. A recent study integrated the concept of self-efficacy with attachment style [100], finding that higher levels of attachment anxiety and avoidance longitudinally predicted lower pain self-efficacy, highlighting the necessity to assess attachment style during sexual evaluation. Other psychological factors relevant to the experience of chronic pain include neuroticism, pessimism, and disgust propensity, although the latter appears to be particularly associated with vaginismus [101, 102].

"Medical gaslighting"

"Medical gaslighting" is when patient concerns are dismissed without adequate evaluation, for example being told that their symptoms are "all in their head" and that they "just need to relax". In a recent study by Moss et al., 447 patients with vulvovaginal disorders reported that 31.7% of their previous vulvovaginal health care practitioners belittled them and that 30.9% didn't believe their complaints [103]. Moreover, 41.6% of the sample were told they just needed to relax, 20.6% were told to drink alcohol to help with symptoms, and 39.4% were made to feel crazy [103].

A recent review of 151 qualitative reports on patients suffering from difficult-to-diagnose pain conditions, including vulvodynia, showed that clinical invalidation may result in: i) negative emotional states such as shame and suicidality, ii) health care-related anxiety and trauma, and iii) health care system avoidance and diagnostic delay [104]. The implications of this lack of care are increased suffering, prolonged diagnostic delay, increased cost of health care, and risk of more severe pathology. Such poor treatment is a direct consequence of inadequate training and awareness.

Final considerations

The "Biopsychosocial Model", proposed more than 50 years ago [105], is increasingly being recognized as a valid, if not essential, framework for addressing the chronic pain and many associated factors and sequalae of vulvodynia [106, 107]. The foundation of this model may today seem mundane to the informed reader – that disease must be addressed at the biological, psychological, and social levels – yet, in clinical practice it is not a simple matter. Health care professionals are highly specialized and assembling multidisciplinary groups to work with the same patients has both practical and professional challenges. Nonetheless, patients with vulvodynia need health care services from multiple disciplines, and this needs to be recognized across all levels of theory, research, and care.

The panel advocates for a more comprehensive and genuinely holistic, i.e. non-dichotomic, evaluation of different systems involved in the complex and multifactorial mechanisms underlying vulvodynia in the light of the SS model, discussed above. So far, research has concentrated on mind and/or body factors related to the invalidating symptoms of vulvodynia, but the role of society (for example, friends, partners, and peers), and of political (for example denying or supporting females with sexual dysfunctions, and the social role of females) and economic choices (for example, that use of endocrine disruptors in consumer products) are still obscure.

Conclusions

Vulvodynia remains a profoundly under-recognized and undertreated condition despite its significant impact on women's quality of life. This position statement highlights the multifactorial and complex systems underlying vulvodynia, involving interactions between immunological, neuromuscular, hormonal, metabolic, social, cultural, and

psychological factors. The current gaps in understanding these mechanisms contribute to the challenges in diagnosis and effective management.

There is an urgent need for increased research efforts, interdisciplinary collaboration, and awareness to develop evidence-based diagnostic criteria and targeted therapies. Addressing these unmet needs is essential to improve clinical outcomes and enhance the well-being of patients.

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