Vulvodynia
Causes and Diagnosis

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Disclosures

• I have no financial relationships to disclose related to this topic
Learning Objectives
At the end of this presentation, the participant will:

• Understand the current classification system for vulvar pain (2015 Consensus Terminology and Classification of Persistent Vulvar Pain)

• Explore the various causes of vulvodynia

• Be familiar with the diagnosis of vulvodynia
Definition of Vulvodynia

International Society for the Study of Vulvovaginal Disease (ISSVD)

Chronic discomfort
Burning
Stinging
Irritation
Rawness
8.3% of women have vulvodynia

By age 40 years, 7-8% in Boston and Minneapolis/St. Paul reported vulvar pain consistent with vulvodynia.

Diagnosis of Vulvodynia

Define disease
  Cotton swab test
  Vulvoscopy?
Not tender; no area of vulva described as area of burning

Alternative diagnosis
Diagnosis of Vulvodynia

Define disease

Cotton swab test

Vulvoscopy?

Thorough history
Various Terms Utilized for Vulvar Pain Prior to 2003

- Essential vulvodynia
- Dysesthetic vulvodynia
- Vulvar vestibulitis syndrome
- Vulvar dysesthesia (generalized or localized)
- Provoked vulvar dysesthesia
- Spontaneous vulvar dysesthesia

CONTROVERSY!
Generalized
2015 Consensus terminology and classification of persistent vulvar pain

Jacob Bornstein MD, MPA, Andrew Goldstein MD, and Deborah Coady MD
for the consensus vulvar pain terminology committee

From the International Society for the Study of Vulvovaginal Disease (ISSVD),
the International Society for the Study of Women's Sexual Health (ISSWSH),
and the International Pelvic Pain Society (IPPS)

Support from the National Vulvodynia Association
2015 Consensus Terminology and Classification of Persistent Vulvar Pain and Vulvodynia

A. Vulvar pain caused by a specific disorder*
   • Infectious (eg, recurrent candidiasis, herpes)
   • Inflammatory (eg, lichen sclerosus, lichen planus, immunobullous disorders)
   • Neoplastic (eg, Paget disease, squamous cell carcinoma)
   • Neurologic (eg, postherpetic neuralgia, nerve compression or injury, neuroma)
   • Trauma (eg, female genital cutting, obstetric)
   • Iatrogenic (eg, postoperative, chemotherapy, radiation)
   • Hormonal deficiencies (eg, genitourinary syndrome of menopause [vulvovaginal atrophy], lactational amenorrhea)

B. Vulvodynia—Vulvar pain of at least 3 months’ duration, without clear identifiable cause, which may have potential associated factors

The following are the descriptors:
   • Localized (eg, vestibulodynia, clitorodynia) or Generalized or Mixed (Localized and Generalized)
   • Provoked (eg, insertional, contact) or Spontaneous or Mixed (Provoked and Spontaneous)
   • Onset (primary or secondary)
   • Temporal pattern (intermittent, persistent, constant, immediate, delayed)

* Women may have both
2015 Consensus Terminology and Classification of Persistent Vulvar Pain and Vulvodynia

Appendix:
Potential Factors Associated with Vulvodynia

- Comorbidities and other pain syndromes (e.g., painful bladder syndrome, fibromyalgia, irritable bowel syndrome, temporomandibular disorder; level of evidence 2)
- Genetics (level of evidence 2)
- Hormonal factors (e.g., pharmacologically induced; level of evidence 2)
- Inflammation (level of evidence 2)
- Musculoskeletal (e.g., pelvic muscle overactivity, myofascial, biomechanical; level of evidence 2)
- Neurologic mechanisms
  - Central (spine, brain; level of evidence 2)
  - Peripheral: neuroproliferation (level of evidence 2)
- Psychosocial factors (e.g., mood, interpersonal, coping, role, sexual function; level of evidence 2)
- Structural defects (e.g., perineal descent; level of evidence 3)

a The factors are ranked by alphabetical order.
Etiologies

Topical review

Vulvodynia: Current state of the biological science

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Painful Bladder Syndrome
Embryologic Derivation

Urogenital sinus
Similarities Between Interstitial Cystitis/Bladder Pain Syndrome and Vulvodynia: Implications for Patient Management

- Intertwined from the perspectives of embryology, pathology and epidemiology
- Similar responses to therapies

Fariello and Moldwin 2015
Oxalates and Vestibulodynia


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Genetics

- Inflammatory response
  - Candida
    - Mannose binding lectin
    - NALP3 expressed in macrophages
- Neurotransmitters
  - Guanosine triphosphate cyclohydrolase (GCH1)
- G protein coupled-receptors
  - Melanocortin-1 receptor
- Neuroinflammatory (cytokines)
  - Interleukins (IL)
- MicroRNA
- New thoughts
  - Dectin 1
  - Familiality
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Familiality Analysis of Provoked Vestibulodynia Treated by Vestibulectomy Supports Genetic Predisposition

- 183 potential vestibulectomy probands were identified using CPT codes.

- Relative risk of vestibulectomy was elevated in first-degree (20 [6.6-47], P < 0.00001), second-degree (4.5 [0.5-16], P = .07), and third-degree female relatives (3.4 [1.2-8.8], P = .03).

- Our data suggest that vestibulodynia treated by vestibulectomy has a genetic predisposition.

  Morgan et al. 2016
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Hormonal Changes Controversy!


Estrogen Receptor Expression

Study group showed a significant decrease in estrogen receptor expression, and 50% of the samples did not exhibit any receptor expression.

Eva LJ, MacLean AB, Reid WM, Rolfe KJ, Perrett CW
Steroid receptor expression and morphology in provoked vestibulodynia

Ulrika Johannesson Karolinska Institutet,
Danderyd Hospital, Sweden
Co-authors; Lena Sahlin, Britt Masironi, Bo Blomgren,
Marita Hilliges, Eva Rylander, Nina Bohm-Starke
Conclusion

- Increased expression of ERα in the vulvar vestibular mucosa in patients with provoked vestibulodynia in the absence of an altered epithelial morphology
For women aged <50 years of age, OC use did not increase the risk of subsequent vulvodynia.
Polymorphisms of the Androgen Receptor Gene and Hormonal Contraceptive Induced Provoked Vestibulodynia

Goldstein et al. 2014

• Risk of developing CHC-induced vestibulodynia may be due to lowered free testosterone combined with an inefficient androgen receptor that predisposes women to vestibular pain
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Vulvodynia: The Role of Inflammation in the Etiology of Localized Provoked Pain of the Vulvar Vestibule (Vestibulodynia)

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Semin Reprod Med 2015;33:239–245
Mast Cells

- Bornstein et al. (2004) found significant increase in inflammatory infiltrate, number of mast cells and degranulated mast cells in vestibulitis patients (N=40) compared to normal controls (N=7, ages 18-48)
- Regauer et al. (2015) evaluated 35 patients with vulvodynia
  - Median age was 24 years (ranged from 18 to 70 years).
  - Control tissues obtained from autopsies (? number)
  - Only 20/35 vulvodynia specimens showed a T-lymphocyte dominant inflammatory infiltrate on HE-stained sections, but all showed mast cells. 4/35 biopsies showed <10 mast cells/mm², 15/35 specimens 40–60 mast cells/mm² and 16/35 specimens >60 mast cells/mm² (average 80/mm²). Control tissue contained typically <10 mast cells.
Vestibular Mast Cell Density in Vulvodynia: A Case-Controlled Study

- No difference in mast cell density in biopsies of the vestibule found between white cases and racially matched controls
- Black control women have a lower mast cell density compared with white control women

Papoutsis D, Haefner HK, Crum CP, Opipari AW, Reed BD. J Lower Genit Tract Dis 2016;20: 275-9
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Pelvic Floor Muscle Function in Women with Provoked Vestibulodynia and Asymptomatic Controls

• Assess vaginal resting pressure (VRP), pelvic floor muscle (PFM) strength and endurance, and surface EMG activity in women with and without provoked vestibulodynia (PVD) (70 women)

• Young, nulliparous women with PVD had significantly higher vaginal resting pressure, however this finding was not confirmed by vaginal surface EMG

Naess and Bo, 2015
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Vulvodynia as Neuropathic Pain

Central

Peripheral
Vulvodynia and the Brain

Vulvodynia and the Brain

- On MRI, 24 vestibulodynia patients displayed greater levels of activation during thumb stimulation within the insula, dorsal mid-cingulate, posterior cingulate and thalamus compared to controls ($P<0.005$ corrected)
- The augmented brain activation in VVD patients in response to a stimulus remote from the vulva suggests central neural pathology in this disorder
Mechanisms of Pain

Stimulus

A-delta – 1st sharp

C fiber – 2nd burning, throbbing

Brain

Spinal cord

Willis 1985

from Robert Bennett, MD
Mechanisms of Pain

**Acute pain**
Peripheral nociceptive input from thermal, chemical or mechanical nociceptors

**Chronic pain**
Central factors typically predominate

Stimulus → Spinal cord → Brain

from Robert Bennett, MD
Pudendal Nerve

Originates from S2, S3, and S4 foramina
Proposed neuroimmunological mechanism of the allodynia/hyperpathia of vulvodynia

Potentially inciting factors:
- Infections
- Irritants
- Toxins
- Medications
- Other

Increased proinflammatory cytokines:
- IL-1, IL-6, IL-8
- IFN-α
- TNF-α

Nerve growth factor increased

Mast cell accumulation

Allodynia and hyperpathia

Distal nerve sprouting

Legend:
- = stimulatory
- = inhibitory
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A Prospective 2-Year Examination of Cognitive and Behavioral Correlates of Provoked Vestibulodynia Outcomes

• Changes in both cognitive and behavioral variables were significantly associated with improved pain and sexual satisfaction outcomes.

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New Concepts on Functional Chronic Pelvic and Perineal Pain: Pathophysiology and Multidisciplinary Management

- Dysregulation of nociceptive messages derived from the pelvis and perineum

The Human Dimension