VULVODYNIA:
OVERVIEW AND ASSESSMENT OF PAIN OUTCOMES and IMPLICATIONS FOR INCLUSION CRITERIA

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Vulvodynia

- Most recent nomenclature was developed by the Consensus Vulvar Pain terminology Committee sponsored by ISSVD, IPPS, and ISSWSH
- “2015 Classification”

“2015 Classification”

- Pain-based classification system
- 2 main categories of chronic vulvar pain

Vulvar pain: caused by a specific disorder

Vulvodynia: idiopathic vulvar pain of 3 months duration

Bornstein, J et al. Obset. Gynecol.2016;127:195-203

Pain-based system characterized on basis of **location, triggers, temporal pattern, onset**

Descriptors:

- Location : Localized (Vestibulodynia), Generalized or Mixed
- Triggers: Provoked (insertional/contact), Spontaneous or Mixed
- Temporal pattern: intermittent or constant
- Onset: life long or Primary (PVD1)
  acquired or Secondary (PVD2)

Classification includes potential factors associated with vulvodynia

- Musculoskeletal (pelvic muscle over-activity, myofascial, biomechanical)
- Neurologic mechanisms (CNS, peripheral neuroproliferation)
- Psychosocial (mood, coping, role, sexual function)
- Structural (perineal descent)

Vulvodynia is likely not one disease but a constellation of symptoms of several overlapping disease processes.

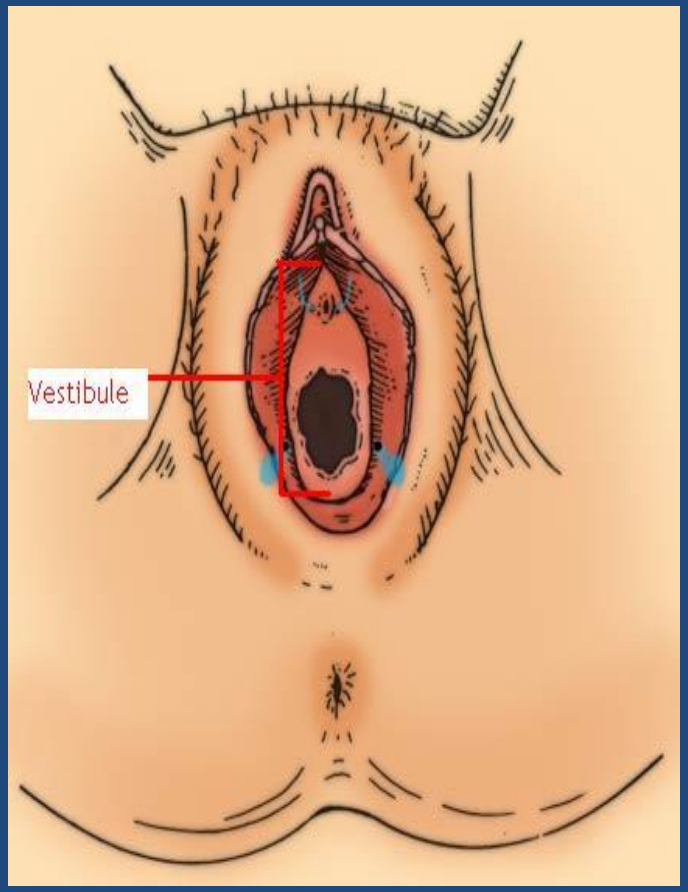
Pathophysiology

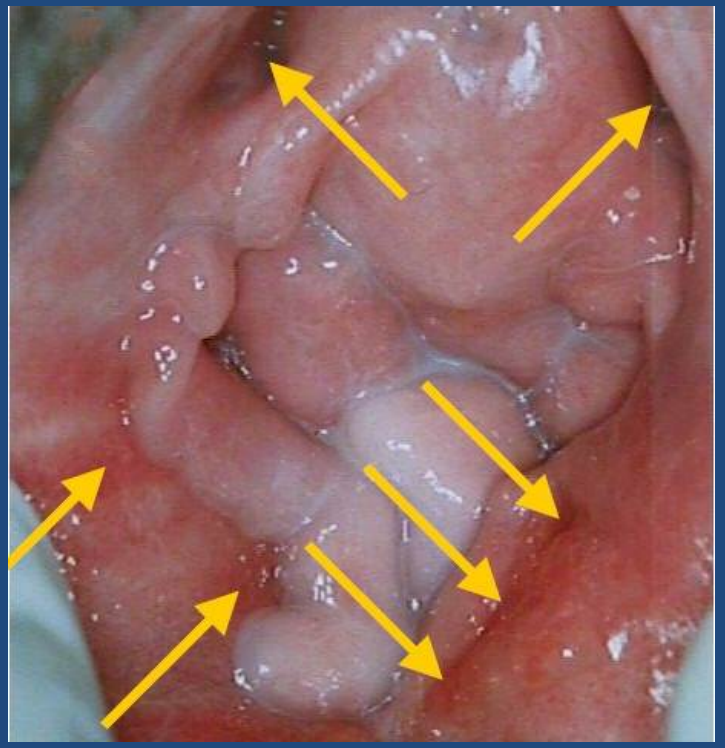
- Vestibular neuroproliferation
- CNS (augmented neural activity, altered intrinsic connectivity, increased grey matter density)
- Myofascial/muscular (over-activity, viscero-somatic reflexes, biomechanical)
- Hormonal (early use of low dose OCPs)
- Inflammatory (neurokines, cytokines)
- Co-morbidities (in 50%: IBS, fibromyalgia, IC/BPS, oro-facial)
- Congenital (urogenital sinus tissue)
- Genetic (polymorphisms affecting response to infection, inflammation and susceptibility to hormonal changes)

Psychological factors

- Mood: higher state and trait anxiety and possibly depression than controls
- Trauma: higher childhood sexual physical trauma
- Sexuality: lower desire, arousal, satisfaction, orgasm, more negative attitudes
- Partner and relationship: solicitous and negative responses are detrimental

Vestibulodynia





Prevalence of Vulvodynia

- 10-28 % of women under 40[1-3]
- 8% have localized pain in the vulvar vestibule (provoked vestibulodynia) impacting sexual intercourse[4]

1. Reed B et al 2008
2. Arnold L et al 2007
3. Harlow B and Stewart E 2003
4. Harlow B et al 2014

Recommendations for outcome measures for clinical trials

- Provide consistent measures across trials
- Facilitate comparisons between studies and multicenter trials
- Improve outcome measurements of multiple general and specific dimensions of vulvodynia pain experience and functional impact

Pukall C, Bergeron S, Brown C, Bachmann G, Wesselmann U. Clin J Pain 2016 /7

Recommendations for outcome measures for clinical trials

*Used IMMPACT framework + sexuality measures

*Focused on provoked vestibulodynia (PVD)

-most common subtype

-main focus of clinical trials

Pukall C, Bergeron S, Brown C, Bachmann G, Wesselmann U. Clin J Pain 2016 /7

Recommendations for outcome measures should account for

- Psychometric properties (ie validity and reliability)
- Issues related to practical application
- Prior use in clinical trials
- Vulvodynia- specific measures are preferable or include generic and specific

Core measures to consider in PVD trials

Inclusion criteria: PVD diagnosis based on 2015 criteria:

Descriptors: Pain based on clinical history:

- Location : Localized (Vestibulodynia), Generalized or Mixed
- Triggers: Provoked (insertional/contact), Spontaneous or Mixed
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  acquired or Secondary (PVD2)

NOTE:
1.History is adequate for dx . Exam not part of 2015 criteria
2. Level of pain to fulfill diagnostic criteria not described: Moderate to severe pain? Pain at least 3/10 on VRS? Pain precluding insertion of tampon or intercourse?

Inclusion criteria: Vulvodynia investigators still consider sensitivity testing to be essential

Recent publications continue to use Friedrich's criteria for diagnosis of PVD:

Pain with gentle contact of vestibule with cotton swab

- Pain level with cotton swab required for dx is not standardized. How to rate pain w swab? What is the threshold for inclusion in study?

3/10 or greater on VRS or 2-3/10 on 4 point Likert scale (none, mild, mod severe)

Vulvar sensitivity testing

- Vulvar sensitivity on exam and patient's reports of clinical improvement with pain with intercourse do not correlate well (Bohm-Starke N. et al 2007; Heddini U. et al 2012)
- Self report and objective pain ratings were not associated with sexual function parameters or satisfaction (Aerts L et al 2016)
- Cotton swab test: false positives and negatives (Vieria-Baptista P 2017 and Reed B et al 2016)

Vulvar sensitivity w cotton swab

- Associated with younger age at first vulvar pain, provoked pain and pain after intercourse
- Not associated with co-morbidities, primary vs. secondary PVD, or presence of spontaneous pain
- Correlates well with algometer findings

Reed B . et al J pain 2016

Exclusion criteria: exclude vestibular pain of different etiology: Vulvar Pain caused by specific disorder

- Infectious (e.g., recurrent candidiasis, herpes)
- Inflammatory (e.g., lichen sclerosus, lichen planus, immunobullous disorders)
- Neoplastic (e.g., Paget disease, squamous cell carcinoma)
- Neurologic (e.g., postherpetic neuralgia, nerve compression or injury, or neuroma)
- Trauma (e.g., female genital cutting, obstetrical)
- Iatrogenic (e.g., postoperative chemotherapy, radiation)
- Hormonal deficiencies (e.g., genitourinary syndrome of menopause [vulvovaginal atrophy], lactational amenorrhea)

Frequently studied parameters

- Pain intensity and vestibular sensitivity
- PVD1 vs PVD2
- Presence of more than 1 co-morbid pain condition
- Anxiety
- Depression

Clinical history and physical examination

- PVD 1 vs PVD2
- Exclude subjects with significant co-morbid pain and mood disorders?

- Vestibular allodynia
- Pressure pain threshold: algometer or cotton swab?
- Pelvic floor : algometer?
- Tampon test?

Tampon test

- Thought to refelct real life experience
- Reliable when retested week to week x 3
- Good construct validity: correlated with daily pain, intercourse pain, cotton swab pain, BPI
- 2 fold higher adherence than intercourse pain measurement
- Can consider for use as the primary efficacy endpoint in clinical trials

Foster D et al . Obstet Gynecol 2009

Pain Intensity

-11-point NRS (0-10)

- ❑ Most commonly used pain rating scale in vulvodynia literature
- ❑ Detects significant treatment effects and positive correlation with other measures of pain intensity

**Replace "pain in last 24 hours" with "pain last time you attempted vulvovaginal penetration" and "pain during non-sexual activities involving vulvovaginal pressure (e.g. tight clothes, sitting)"

**Report "in preceding month or last 4 penetration attempts"

-VRS (none, mild, moderate, severe and worst)

- ❑ Vulvar Pain Assessment Questionnaire[1] (VPAQ) has 2 pain intensity VRSs
- ❑ Demonstrates convergent and divergent validity

1. Dargie E. Holden R. Pukall C. Pain 2017

Pain quality (sensory descriptors) and affect (emotional responses to pain)

- Short- Form McGill Pain Questionnaire (SF-MPQ) or MPQ

  -demonstrated responsiveness in PVD trials

- VPAQ[1] Pain Descriptors subscale and 4 VRSs related to pain affect from the VPAQ Pain Severity subscale

  -recommended to include with SF-MPQ

1. Dargie E. Holden R. Pukall C. Pain 2017

Temporal pattern of pain (intermittent vs constant) and onset (PVD1/PVD2)

- Temporality assessment: recommended as a secondary outcome measurement by IMMPACT
- Relevant for spontaneous pain: less relevant to PVD
- Take into account pain onset? primary or secondary

  -women with primary PVD may benefit less from treatment

PVD1 vs. PVD2: Data is inconsistent

- PVD1 (vs PVD2): higher pain sensitivity, anxiety, catastrophizing , greater decreases GM density; similar fMRI to other chronic pain findings (Sutton K. et al 2015)

- Not all studies find PVD 1 to have higher pain sensitivity, more genetic influence, more inflammation, poorer treatment outcome, different neural activation and structural findings on MRI (Pukall C. et al 2015)

Physical function and HRQOL

- IMMPACT recommends SF-36 Health Survey

  -has not been used in many PVD trials as pain is provoked

  - consider including as PVD is associated with co-morbidities that can affect HRQOL

  -e.g. PROMIS Global health or Physical Function Scales

- Assess effect of PVD pain on physical functioning

  -Interference Scale of Multidimensional Pain Inventory(MPI) or pain interference items of Brief Pain Inventory (BPI) or PROMIS Pain Interference Scale

  -specific to PVD: Life Interference subscale of VPAQ or VQOLS[1]

  -for unprovoked dimension of pain and co-morbidities

1.Rosen N et al. Arch of Sexual Behav 2016

Sexual function

Many aspects of sexuality are negatively impacted by PVD

- Female Sexual Function Inventory (FSFI)

  -recommended as a core outcome measurement

  -domains: desire, arousal, lubrication, orgasm, pain, satisfaction

  -most commonly used sexuality scale, designed for clinical trials, included in several PVD trials

*artificially low score if not engaged in sexual activity in last 4 week recorded- Recommended missing responses be coded as missing (not 0) and total score not be calculated

*does not measure interference w solitary sexual activities w penetration-

Self –Penetration Interference Subscale of VPAQ as core outcome measure

- PROMIS Sexual Function and Satisfaction Scale (SexFS)

  -consider as secondary measure minus erectile fn question

Sexual satisfaction, distress, and interference

- Include as secondary outcome measures
- Various validated measures:

Global Measure of Sexual Satisfaction (GMSS), PROMIS Sex FS, Female Sexual Distress Scale (FSDS), Vulvar Pain Assessment Questionnaire (VPAQ)

Emotional function

- Vulvodynia is associated with psychological distress and depression and anxiety

  ----Clinically relevant levels of depression and anxiety are uncommon in PVD. ----Fear of pain contributes to sexual impairment.

- Self report measures of anxiety, depression and catastrophizing, and pain anxiety considered as core measures

Emotional function

- Most commonly used in PVD literature:

-BDI-II, CES-D for depression: core outcome measure

-State/Trait Anxiety Inventory (STAI): core

-Short- form PROMIS Anxiety Scale : secondary

-Pain Catastrophizing Scale (PCS): core

- Emotional responses specific to vulvovaginal pain in PVD

-Emotional Response subscale of VPAQ: core

-Pain Anxiety Symptom Scale (PASS-20): secondary

Global Improvement and treatment satisfaction

- Required in pain clinical trials
- Show statistically significant results are clinically meaningful
- Monitor post- treatment and at follow up visits

Patient Global Impression Change Scale (PGIC) has been adapted to women with vulvodynia

Symptoms and adverse events and disposition

- PVD trials: weekly calls or on-line measures
- Individual and SAE
- Follow Consolidated Standards of Reporting Trials (CONSORT) guidelines

Supplemental measures recommended for PVD trials

- Domains relevant to PVD

-Social role function: PVD leads to feelings of inadequacy as women/partner: PROMIS social role satisfaction scale; VPAQ Cognitive Response sub-scale

-Relationship adjustment: chronic pain affects partners and partners impact treatment outcome: Couples satisfaction index (CSI), VPAQ Partners Satisfaction Scale

- Document Co-morbidities: influence PVD pain, mood, sleep and pain interference

IMMPACT's core and supplemental domains

Core domains

- Pain
- Physical functioning
- Emotional functioning
- Participant ratings of improvement and satisfaction with treatment
- Symptoms and adverse events
- Participant disposition

Supplemental domains

- *Role functioning*
- *Interpersonal functioning*
- Pharmacoeconomic measure and health care utilization
- Biological markers
- *Coping*
- Clinician or surrogate ratings of global improvement
- Neuropsychological assessment of cognitive and motor function
- Suffering

There is no single validated PVD questionnaire for all measures

- VPAQ captures most core and supplementary domains identified by IMMPACT

pain intensity, quality, affect, physical functioning (interference with life, self penetration, sexual function), emotional responses, coping and effect of pain on social role function and interpersonal functioning

- Add some PROMIS measures as secondary