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ORIGINAL STUDY

Where does postmenopausal dyspareunia hurt? A cross-sectional report

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Abstract

Objective: A common symptom of genitourinary syndrome of menopause (GSM) is dyspareunia, attributed to vulvovaginal atrophy. Our objective was to systematically describe the pain characteristics and anatomic locations of tenderness in a cohort with moderate/severe dyspareunia likely due to GSM.

Methods: This cross-sectional study reports the baseline data of postmenopausal women with dyspareunia screened for an intervention trial of topical estrogen. Postmenopausal women not using hormone therapy who had moderate or severe dyspareunia were eligible if estrogen was not contraindicated. Biopsychosocial assessments were performed using the Vulvar Pain Assessment Questionnaire, and participants underwent a systematic vulvovaginal examination that included a visual assessment and cotton swab testing for tenderness rated using the Numerical Rating Scale (0-10). Vaginal pH and mucosal sensitivity were assessed; pelvic floor muscles and pelvic viscera were palpated for tenderness.

Results: Fifty-five eligible women were examined between July 2017 and August 2019. Mean age was 59.5 ± 6.8 years, and duration of dyspareunia was 6.2 ± 4.3 years. The mean intercourse pain score was 7.3 ± 1.8, most often described as ''burning'' and ''raw.'' Ninety-eight percent had physical findings of vulvovaginal atrophy. Median pain scores from swab touch at the vulvar vestibule (just outside the hymen) were 4 to 5/10, and topical lidocaine extinguished pain. Median vaginal mucosal pain was zero.

Conclusions: Participants described their pain as ''burning'' and ''dry.'' Tenderness was most severe and most consistently located at the vulvar vestibule. Correlating the symptom of dyspareunia with genital examination findings may further our understanding of treatment outcomes for GSM.

Key Words: Dyspareunia – Genitourinary syndrome of menopause – Gynecological exam – Pain measurement – Postmenopause.

Video Summary: http://links.lww.com/MENO/A916.

Postmenopausal dyspareunia is a common complaint, affecting 50% of women within a few years of losing estrogen.[1] It is generally attributed to vulvovaginal atrophy (VVA), and the term served as the identifying name for years. The term genitourinary syndrome of menopause (GSM) encompasses more symptoms and systems, and invites a more nuanced exploration of the dysfunctions accompanying loss of estrogen.[2] Although estrogen deficiency affects the entire lower genitourinary (GU) tract, women may report symptoms affecting one or multiple regions of the GU tract. Symptoms of GSM include several urinary conditions—overactive bladder, incontinence, recurrent urinary tract infections, and interstitial cystitis/bladder pain syndrome. Interstitial cystitis/bladder pain syndrome is commonly associated with dyspareunia[3,4] and peak prevalence, with estimates of 3.4% to 7.5%, occurs in the age range of 40 to 59.[5] The FDA-approved patient instructions for local estrogen therapy direct women to insert the product into the upper vagina,[6,7] and in one case the lower vagina,[8] and it is unclear how well intravaginal application provides treatment for the labia, introitus, urethra, and bladder.

Dyspareunia is specifically defined as pain during sexual intercourse. Dyspareunia includes the manifestation of ''tenderness,'' medically defined as ''sensitivity, discomfort, or

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pain associated with touch or pressure.'' ''Tenderness'' is a specific subset of ''pain,'' a symptom that may be evoked or elicited by a variety of triggers or no trigger at all. In this paper, we will use the term ''tenderness'' to mean a woman's report of pain elicited by touch or pressure during examination of GU structures.

Postmenopausal dyspareunia is often attributed to vulvovaginal dryness, thinning of the mucosa, and loss of tissue elasticity without specific measurements of the tenderness of the various GU structures.[2,9,10] Often there is insufficient consideration of the other diagnoses that can contribute to dyspareunia, such as tenderness of pelvic floor muscles, bladder, uterus, or adnexa. A study that assessed tenderness of GU structures in estrogen-deficient breast cancer survivors found that tenderness was localized and most prominent at the vulvar vestibule, the vulvar mucosa adjacent to and just outside the hymeneal ring (Fig. 1). In those women, tenderness was infrequently noted with touch to the vaginal walls or palpation of the muscles or pelvic viscera.[11] Therapies for dyspareunia that specifically target only the vulvar vestibule have demonstrated success.[12,13]

Vaginal estrogen for GSM aims to reverse atrophy, and can readily change maturation of the vaginal epithelium, but the successful reversal of vaginal atrophy as judged by mucosal maturation and pH does not fully alleviate symptoms in many women.[14,15] Understanding these treatment failures may require more precise delineation of the subsets of GSM symptoms and physical changes along with a better understanding of the pathophysiologic mechanisms that underlie the variability of symptoms. Our objective is to systematically describe detailed GSM symptoms and physical examination findings of the GU tract in a cohort of postmenopausal women with moderate/severe dyspareunia who underwent screening examinations for a clinical trial of two strengths of estradiol cream applied to the vulvar vestibule.

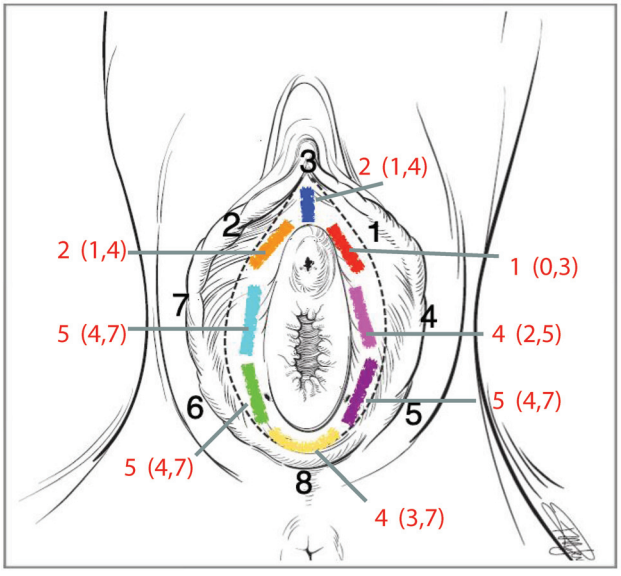

FIG. 1. An illustration of the vulva denotes the outer demarcation of the vestibule with a dotted line (Hart's line). Colored swaths indicate locations of cotton-swab touch testing. Black numbers indicate the order of examination. Red numbers indicate the median pain scores and interquartile ranges (NRS 0-10). Artist: Robin M. Jensen. ©2014 Robin M. Jensen. Used with permission.

METHODS

Setting and participants

This study reports baseline findings of a convenience sample of women recruited for participation in a blinded randomized pilot trial for moderate/severe dyspareunia associated with GSM. This study, (''Treating Where it Hurts''), was conducted at the Women's Health Research Unit of the Department of Obstetrics and Gynecology at Oregon Health & Science University (OHSU) in Portland, Oregon. We recruited women initially by flyers distributed to Obstetrics and Gynecology and primary care clinics at OHSU and in local healthcare systems. The flyer asked, ''Are you postmenopausal and experiencing pain with intercourse?'' Later in recruitment, we posted advertisements on social media. Potential enrollees were screened initially by telephone, and eligible women were invited to the research unit for full evaluation. The institutional review board of OHSU approved the protocol (#16770) and written materials.

Inclusion criteria for affected women were: 1) postmenopausal status as defined by: amenorrhea >1 year if age >50, or absence of ovaries, or, for women with prior hysterectomy or endometrial ablation, age >51 and peak climacteric symptoms >2 years prior; 2) being in a stable heterosexual partnership of >2 years; 3) postmenopausal onset of dyspareunia for at least 6 months with consistent severity; 4) no systemic estrogen use for at least 6 months, and no topical estrogen use for at least 4 weeks. The severity of dyspareunia was defined according to its effect on sexual activity—severe enough to reduce frequency (moderate dyspareunia) or resulting in periods of abstinence (severe dyspareunia). Exclusion criteria were: 1) non-GSM causes of dyspareunia (chronic pelvic pain, generalized vulvodynia, acute or chronic vulvovaginitis), and 2) a sensitivity to topical estrogen products or topical lidocaine. To reduce variability of penetrative sex, study participation was limited to heterosexual women in long-term relationships.

Symptom measures

The primary assessment tool for pain and psychosocial parameters was the screening Vulvar Pain Assessment Questionnaire (VPAQscreen),[16] modified in consultation with its authors for this intervention study. The tool was developed and validated specifically for vulvodynia, a chronic vulvar pain condition, to assess pain characteristics, sexual function, and distress parameters within one tool as guided by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials framework.[17,18] The VPAQscreen begins with descriptive questions about vulvar pain guided by a color-coded illustration of the external genitalia to help

respondents to identify locations of pain. We modified the diagram to focus on the labia and the vestibule, and added a qualitative question asking for three words describing penetrative pain. The remainder of the VPAQ was not modified, and consisted of 40 items to assess the domains of pain severity, cognitive/emotional difficulties, interference with sexual function, life functions, and self-stimulation/penetration. The subscale, VPAQdesc, asks respondents to assess 10 descriptors of pain in three categories, scoring qualities of Burning Pain, Incisive Pain, and Sensitivity. Because the descriptor ''dry'' is in common usage to describe the primary complaint in GSM/VVA, we added ''dry'' as a descriptor using the VPAQ format. Scoring for VPAQ subscales (range 0-4) was not modified; there is not a total VPAQ score.

Because there is no single validated instrument that includes all urinary symptoms of GSM, lower urinary tract symptoms were assessed using a 13-item questionnaire that was created from questions from several validated instruments. We used the Urinary Distress Inventory -6, which assesses urinary frequency, urgency, urge incontinence, stress incontinence, amount of leakage, difficulty voiding, lower abdomen, or genital discomfort or pain.[19] An additional question about urgency was added from the Urinary Distress Inventory long form.[20] The Sandvik Severity Index provides a measure of incontinence severity.[21] Selected questions from the O'Leary/Sant Interstitial Cystitis Symptom Index and Urinary Tract Infection Symptom Assessment questionnaire assess nocturia, dysuria, and number per year of doctor-confirmed UTIs.[22,23]

Participants also completed an intake questionnaire that asked about demographics, medical and gynecologic histories, histories of estrogen use, and pain parameters including genital symptoms in the absence of sexual touch.

Physical examination measures

First, a standardized tampon insertion/removal, the Tampon Test, was conducted, using an unlubricated medium Tampax (Cincinnati, OH) and scoring the sensation using the Numerical Rating Scale (NRS) with anchors of 0 (no pain) and 10 (''the worst possible pain'').[24] A standardized pelvic examination was performed by one of three clinician-investigators who were not blinded to participant symptoms. We conducted a visual examination of the external genitalia to evaluate atrophy, as evidenced by thinning, shrinkage of contours, or color changes (pallor, redness, or focal redness). Then an examination of the vulvar vestibule was conducted using the standardized cotton swab test at eight designated locations[25] (Fig. 1). Briefly, a dry cotton-tipped swab was lightly rolled back and forth at designated surfaces of the vestibule in the following systematic order referencing a clock face: the anterior mucosa cephalad to the urethra at 1:00, 11:00, and 12:00; the mucosa adjacent to the hymen at 2:00, 4:00, 8:00, 10:00, and 6:00. This examination was ordered so that locations least likely to be tender were touched before those expected to be most tender to reduce the phenomenon of sensitization. At each location participants scored pain elicited by touch using the NRS.

Next, a standardized lidocaine test was conducted for those with swab-provoked pain. Aqueous lidocaine 4% was applied to all surfaces of the vestibule using three large, saturated cotton swabs held against the surfaces for 3 minutes by the examiner. The cotton swab test was then repeated and scored with the NRS. The baseline score and the score after lidocaine application at each vestibule site was analyzed as an outcome. Any remaining tenderness was to be further treated with lidocaine until nontender to allow painless insertion of the speculum for the next portion of the examination.

Vaginal inspection followed, using a modestly lubricated Pederson speculum. The vaginal mucosa was evaluated for color, loss of rugae, and presence of adherent or pooled discharge. To test vaginal sensitivity, a cotton swab was used to lightly stroke the lateral vaginal wall at the mid-vault on the left and right, and participants were asked to rate any pain using the NRS. Vaginal discharge from the swab was tested for pH using a colorimetric indicator strip. After speculum removal, the pelvic floor muscles were examined digitally using a single gloved finger, starting with the superficial perineal muscles, and then progressing upward along the lower portion of the levator ani muscles (puborectalis and pubococcygeus), followed by the upper portion (iliococcygeus).[26] The muscles were assessed for tenderness and tonicity. Tenderness to palpation of the pelvic viscera (bladder, uterus, adnexa) was assessed along with any pain provoked by cervical motion.

Statistical analyses

Data were summarized using descriptive statistics. Continuous data are presented as mean ± standard deviation or median (interquartile range) after checking for normality; and categorical data are presented as frequency (percentage). Enrollment data were managed using the REDCap electronic database,[27] and statistical analyses were performed using Stata (version 15; Stat Corp, College Station, TX).

RESULTS

Participant characteristics

From July 2017 to August 2019, 60 women underwent screening evaluation, and 5 women were excluded due to mild dyspareunia (2), premenopausal onset of dyspareunia (1), vaginal lichen planus (1), and a partner recently unable to have intercourse (1). Table 1 describes demographics, menopause history, sexual history, and prior hormone use of the 55 women in this cross-sectional analysis. The mean age of women was 59.5 ± 6.8 years, the mean BMI was 25.3 ± 4.7, and by self-identification, 96% were White. On average they reported quite long relationships with their present partner (mean 28.1 ± 13.9 y) but had experienced dyspareunia for a mean of 6.2 ± 4.3 years. The mean pain score experienced with intercourse was 7.3 ± 1.8 by NRS, and

TABLE 1. *Characteristics of participants*

Characteristic mean ± SD; *n* (%)	*n* = 55
Age (y)	59.5 ± 6.8
Body mass index (kg/m^2)	25.3 ± 4.7
Education >12th grade	53 (96%)
Obstetric history	
Nullipara	21 (38%)
History of vaginal birth(s)	23 (42%)
Cesarean births only	11 (20%)
Current tobacco user	1 (2%)
Menopause	
Age at last period	48.2 ± 6.4
Vasomotor symptoms	
Significant in the past	36 (65%)
In past month	18 (33%)
Estrogen use since menopause	
Any	40 (73%)
In past year (all used only local products)	19 (34%)
Sexual history	
History of sexual abuse	7 (13%)
Duration of intimate relationship (y)	28.1 ± 13.9
Duration of dyspareunia (y)	6.2 ± 4.3
Mean dyspareunia score (NRS, 0-10)	7.3 ± 1.8
Use of nonhormone therapy	
Lubricants during sexual activity	49 (89%)
Vaginal moisturizer	6 (11%)
Use of estrogen therapy (vaginal or systemic)	
Past	23 (42%)
Intermittent use in past	16 (29%)
Current	1 (2%)
Never	15 (27%)
Beliefs regarding dyspareunia (may select > one)	
It is a normal feature of aging	37 (67%)
It is correctable with lubricants	12 (22%)
It is likely to be temporary	0 (0%)
It is caused by low estrogen	45 (82%)
It is likely to slowly worsen	25 (45%)
None of the above	1 (2%)

NRS, numerical rating scale.

TABLE 2. *Vulvovaginal symptoms (n = 55)*

Supplementary Questionnaire, Vulvovaginal Symptoms	
Uncomfortable feelings you have in the vulva without specific sexual touch[a]	
I have no vulvar symptoms without touch	23 (42%)
Dry	22 (40%)
Feeling thinned	14 (25%)
Burning	11 (20%)
Raw	9 (16%)
Tight or smaller	9 (16%)
Itchy	8 (15%)
Sharp	5 (9%)
Hot	1 (2%)
Modified VPAQ, Outer Vulva	
Pain location on diagram	
Outer vulva	27 (49%)
Outer vulvar symptoms [a]	
Itching	9 (16%)
Fissures, splits or tears	11 (20%)
Dryness	32 (58%)
Duration of outer vulvar symptoms (*n* = 54)	
<6 mo	0
7 mo-2 y	8 (15%)
3-5 y	11 (20%)
6-10 y	7 (13%)
10+ y	3 (6%)
No outer vulvar discomfort/pain	25 (46%)
Discharge contributing to pain?	
Maybe	2 (4%)
Modified VPAQ, Qualitative Pain Descriptors	
Qualitative terms offered for intercourse pain[a]	
''Burning''	54%
''Raw''	30%
''Dry''	28%
''Sharp''	26%
''Tender''	20%
Other	< 20%

VPAQ—descriptor subscales for penetrative pain (0-4)[b]	Mean ± SD	Range
Burning pain subscale (''burning,'' ''stinging'')	2.8 ± 1.1	0-4
Incisive pain subscale (''sharp,'' ''stabbing'')	2.3 ± 1.4	0-4
Sensitivity subscale (''aching,'' ''irritating,'' ''raw,'' ''sensitive,'' ''tender,'' ''sore'')	2.6 ± 0.9	0.5-4
Supplemental pain descriptor using VPAQ format (0-4)[b] ''Dry''	3.2 ± 1.0	0-4
VPAQ subscales (0-4)		
Pain severity subscale[c]	2.6 ± 0.5	1-4
Cognitive/emotional responses subscale[b]	1.1 ± 0.6	0-3.3
Life interference subscale[b]	0.3 ± 0.5	0-1.8
Sexual function interference subscale[b]	2.8 ± 0.9	0.2-4
Self-stimulation/penetration subscale[d]	1.5 ± 1.4	0-4

Mean ± standard deviation or *n* (%) reported.
VPAQ, Vulvar Pain Assessment Questionnaire.
[a]Respondents could mark >1 category or offer >1 term.
[b]0 = Not at all, 1 = A Little, 2 = Somewhat, 3 = A Lot, 4 = Very Much.
[c]0 = None, 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Worst Possible.
[d]0 = Never, 1 = Rarely, 2 = Sometimes, 3 = Often, 4 = Always.

30 of 55 women (54.6%) had stopped intercourse for ''lengthy periods'' (self-defined) due to pain.

Most participants, 40 of 55 (73%), had used estrogen after menopause, and 68% of users (27 of 40) identified dyspareunia as a reason for use. Seventy percent of users of vaginal estrogen (27 of 38) cited failure to obtain relief as a reason that they discontinued hormone therapy. Two participants noted progression of dyspareunia from irritation to pain over several years despite continuing to use the low-dose vaginal estradiol ring. Other reasons for hormone discontinuation included expense, difficulty cleaning applicators, messiness/inconvenience, and fear of cancer. Fifteen percent of those supplementing (6 of 40) had used compounded products.

Symptoms

Twenty-seven of 55 women (49%) reported symptoms affecting the outer vulva when referring to the diagram. The most common symptom described as occurring in the outer vulva was dryness in 32 of 55 (58%); 9 of 55 (16%) noted itching, and 11 of 55 (20%) had noted fissures, splits, or tears (Table 2). Of the half of participants reporting having looked at their vulva with a mirror, 17 of 27 (63%) had noted a change in appearance.

In the supplemental question about spontaneously having vulvar discomfort in the absence of sexual touch, the most common symptoms were dryness in 22 of 55 (40%), feeling thinned 14 of 55 (25%), and burning 11 of 55 (20%). Twenty-three women of 55 (42%) reported having no symptoms in the absence of sexual touch. Sixteen percent of women (9 of 55) noted that their condition affected their choice of clothing.

When asked to suggest three words to describe the quality of their penetration pain, the most commonly volunteered

TABLE 3. *Lower urinary tract symptoms*

	$n = 55$	
	Symptom present	Bother score[a]
Urinary distress inventory (UDI)-6, short form		
Frequent urination	24 (44%)	1.4 ± 0.7
Urinary urgency leakage	20 (36%)	1.8 ± 0.9
Stress leakage	30 (55%)	1.5 ± 0.8
Small amounts of leakage	26 (47%)	1.2 ± 0.9
Difficulty emptying bladder	10 (18%)	1.9 ± 0.6
Pain in abdomen/genital area	6 (11%)	1.8 ± 0.8
Urinary Distress Inventory, long form		
Strong feeling of urgency	24 (44%)	1.3 ± 0.9
Sandvik Incontinence Severity Index (0-12)		
Score (Mean ± SD)		4.1 ± 2.9
O'Leary/Sant Interstitial Cystitis Symptom Index (ICSI)		
Nocturia- voiding episodes at night		
Never		5 (9%)
Once		31 (57%)
More than once		18 (33%)
Episodes of non-urinary tract infection (UTI) bladder pain in past month		
Not at all		48 (87%)
Once		3 (5%)
More than once		4 (7%)
Urinary Tract Infection Symptom Assessment (UTISA)		
Episodes of non-UTI dysuria in past month		
Not at all		46 (84%)
Once		2 (4%)
More than once		7 (13%)
Episodes of clinically-diagnosed bladder infections or UTIs		
UTI in past year		
None		53 (96%)
One		1 (2%)
Two		0
Three or more		1 (2%)

Mean ± standard deviation or n (%) reported.
[a]0 = Not at all, 1 = Somewhat, 2 = Moderately, 3 = Greatly.

TABLE 4. *Physical examination findings*

	$n = 55$
Assessment of atrophy	
Vaginal pH (mean ± SD)	5.6 ± 0.7
Shrinkage, pallor of introitus or labia, *n* (%)	47 (85%)
Urethral caruncle present, *n* (%)	5 (9%)
Vestibule friable with rolling of a dry swab, *n* (%)	6 (11%)
Vaginal mucosal changes, *n* (%)	
None	1 (2%)
Mild (pale)	11 (20%)
Moderate (pale, diminished rugae)	19 (34%)
Severe (pale, no rugae)	24 (44%)
Vaginal discharge, *n* (%)	
None	38 (69%)
Clings to walls	14 (25%)
Pooled, usually yellow discharge	3 (5%)
Assessment of tenderness (elicited pain)	
Tampon Test scores (NRS 0-10) (median, IQR)	4 (3,6)
Severity of vestibular tenderness by swab roll before lidocaine application (NRS 0-10) (Median (IQR)	
Site 1 1 o'clock	1 (0,3)
Site 2 11 o'clock	2 (1,4)
Site 3 12 o'clock	2 (1,4)
Site 4 3 o'clock	4 (2,5)
Site 5 5 o'clock	5 (4,7)
Site 6 7 o'clock	5 (4,7)
Site 7 9 o'clock	5 (4,7)
Site 8 6 o'clock	4 (3,7)
Severity of vaginal tenderness by rolled swab (NRS 0-10) (median, IQR)	
Left vaginal side wall	0 (0,3)
Right vaginal side wall	0 (0,2)
Presence of tenderness, pain elicited by palpation, *n* (%)	
Labia minora or majora	1 (2%)
Vestibule ≥ 1 site > 3 (NRS)	50 (91%)
Lateral vaginal wall (NRS >3)	1 (2%)
Superficial perineal muscles	8 (15%)
Puborectalis and pubococcygeus	17 (31%)
Iliococcygeus	7 (13%)
Bladder	4 (7%)
Uterus	2 (4%)
Adnexa	0 (0%)
Pain elicited by cervical motion	2 (4%)

IQR, interquartile range; NSR, numerical rating scale.

words were ''burning'' in 29 of 54 (54%), ''raw'' in 16 of 54 (30%), ''dry'' in 15 of 54 (28%), ''sharp'' in14 of 54 (26%), and ''tender'' in 11 of 54 (20%). Less common descriptors were ''stinging,'' ''knives,'' ''raspy'' ''scary,'' ''ripping,'' ''unbearable,'' ''sandpaper,'' ''searing,'' ''stabbing,'' and ''tearing,'' among others.

The subscales of the VPAQ screen are shown in Table 2. Burning pain was the typical descriptor, rated between ''somewhat'' and ''a lot.'' Incisive pain and Sensitivity were rated almost as high. The added descriptor of ''dry'' was rated higher than the pain terms. Interference with sexual function was scored high, related to desire, pleasure, responsiveness to partner advances, orgasm frequency, and nonpenetrative and penetrative activities. Pain Severity was moderate to severe. Self-stimulation was sometimes disturbed, and Cognitive/Emotional wellbeing was ''a little'' affected. Dyspareunia interfered least with daily activities.

Lower urinary tract symptoms were reported by 45 (82%) of 55 respondents (Table 3). Stress incontinence in 55% (30 of 55), urgency in 44% (24 of 55), and frequency in 44% (24 of 55) were the most commonly reported symptoms. Difficulty voiding, a symptom usually not listed as a component of GSM, was reported by 10 (11%) of 55 women and was associated with the most bother. Dysuria was reported by 7 (12%) of 55 women, and bladder pain not associated with UTI was reported by 9 (17%).

Physical findings

The majority of affected women had GU structural and skin changes consistent with vulvovaginal atrophy (Table 4). One participant with no evidence of atrophy upon examination had discontinued her low-dose estradiol ring 6 weeks before entry. Not all participants had pain with insertion and removal of a tampon, but the median score was 4 (3.6) by NRS. Examination tenderness was most often localized to the vulvar vestibule, and Figure 1 depicts the locations and median severities at specific sites. Fifty of 55 women (91%) reported pain >3 at some location adjacent to the hymen. This vestibule tenderness was fully extinguishable in every participant and at every site by a 3-minute application of 4% lidocaine topical solution. The mean pH of the vaginal discharge was 5.6 ± 0.7, consistent with atrophy. Vaginal wall tenderness elicited by cotton swab stroking occurred in only one participant, who reported pain with scores of 7, 8 (left, right) by NRS. The second most common location of tenderness was in the pelvic floor muscles, present in 35% of women (19 of 55). The pelvic viscera were rarely tender.

DISCUSSION

Using the validated scoring portion of an instrument designed for chronic vulvar pain, we found that the term ''burning'' was the most frequently elicited descriptor volunteered by postmenopausal women with moderate/severe dyspareunia. The VPAQ, a broadly designed, validated tool guided by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials framework uses pain descriptors that are specific to vulvar pain and drawn from the McGill Pain Questionnaire, which has been foundational for pain research in many fields.[28] Of note, ''dry'' is not a listed descriptor in the VPAQ, nor is it in the list of 78 terms in the McGill Pain Questionnaire. Because the term ''dry'' is the most common symptom attributed to VVA/GSM, we asked participants to score ''dry'' as a descriptor of intercourse. Along with ''burning,'' ''dry'' was a similarly frequent descriptor endorsed by this cohort of women for both spontaneous pain and insertional pain. The impact of postmenopausal dyspareunia as measured in the VPAQ subscales is similar in magnitude to the VPAQ subscale scores for women with chronic vulvar pain.[29]

On physical examination, we found generalized changes consistent with vulvovaginal atrophy affecting the vulva and vagina, but tenderness to touch/pressure was localized, primarily occurring at the vulvar vestibule. Tenderness of the pelvic floor muscles was present in 35% of women, and a few had tender pelvic viscera. Recent pivotal randomized controlled trials of GSM dyspareunia all assessed the symptom of dyspareunia, but none assessed physical examination findings specific to dyspareunia.[30-35] Instead, physical examination measures were those required by FDA guidelines, typically limited to measures of vulvovaginal atrophy (vaginal pH and the vaginal maturation index).[36] These studies demonstrate a reduction in dyspareunia and improvement in physical assessments of vaginal atrophy. However, a full resolution of this symptom of dyspareunia is not indicated by the absolute value of dyspareunia symptom severity after treatment, suggesting that atrophy is not the only etiologic factor underlying postmenopausal dyspareunia.

Research implications

One of the dilemmas of GSM is the interpretation of dryness, the most common symptom of GSM, and its relation to discomfort and pain. The persistence of dyspareunia and a ''sensation of dryness'' after adequate lubrication argue for a more expansive explanation of the etiology of dyspareunia. Previous studies have noted that measures of atrophy and dryness do not necessarily mirror sexual function in studies of GSM.[14,15,37] Our data show that dryness and burning are both frequent descriptors, and burning pain may be the salient sensation.

The ability of topical lidocaine to extinguish vestibular tenderness in all women suggests that their dyspareunia is mediated by superficial nerves of the vulvar vestibule. Neural hyperplasia has been documented in vestibule samples from postmenopausal women with significant dyspareunia and vestibule tenderness extinguishable by lidocaine.[38] Provoked vestibulodynia (PVD), previously called vulvar vestibulitis, is a similar pain condition with neural hyperplasia that occurs in premenopausal women. The physiologic process of PVD specifically involves sensory axon sprouting driven by angiotensin II receptor 2 from a local inflammatory renin-angiotensin system.[39] Similarly detailed studies of postmenopausal vestibular tissues have not been reported.

While many studies have addressed the gross and histologic structural changes associated with estrogen deficiency—thinning of the mucosa, decreased blood supply, shrinkage of the genital tract—very few have assessed the effects of estrogen deficiency on the nerves of the human genital tract. Studies in animals show that genital tract innervation has a plasticity that varies dynamically with estrogen exposure, proliferating with low estrogen, and undergoing pruning when estrogen increases.[40,41] The epithelium of the human vulvar vestibule is richly innervated,[42] and these nerves have been documented to be increased in postmenopausal dyspareunia,[38] and confirmed to be sensory nerves in PVD.[39,43] In contrast, the innervation of the human vagina consists of submucosal autonomic nerves and only rare pain nerves.[44] This vestibular intraepithelial innervation with sensory nerves provides a plausible explanation for the tender vestibule's responsiveness to topical lidocaine.

Two clinical case series assessed vestibular pain scores after GSM treatment. A 12-week regimen of 0.005% estriol gel to the vestibule was associated with a significant reduction in cotton swab test scores.[12] A similar reduction in vestibular cotton swab test scores was measured after 60 days of ospemifene therapy, along with a reduction in the current (electrical) perception threshold for touch nerves (A-beta), myelinated pain fibers (A-delta), and especially non-myelinated pain fibers (C).[45] Further similar research aimed at understanding the mechanism of increased localized pain sensitivity after estrogen loss will be important.

In clinical research of GSM therapies, localizing the affected structures will allow more precise assessment of the benefits of potential treatments, whether therapies are systemic or local. For example, rather than assessing the most bothersome of a variable group of symptoms and treating the vagina with estrogen, an approach assessing and targeting specific symptoms and specific signs may be more instructive. Dyspareunia associated with vestibular tenderness may be most effectively treated locally by using introital estrogen. External vulvar symptoms could perhaps best be treated by estrogen cream and/or moisturizers applied to the vulva instead of ''vaginal moisturizers.'' Many urinary symptoms are improved by use of vaginal estrogen,[46] but the mechanism by which vaginal estrogen influences urinary symptoms is unknown. In this cohort, 13% of women reported dysuria and 17% reported bladder pain, and we do not know whether these symptoms contributed to their dyspareunia, or whether current GSM regimens address specific bladder symptoms. Our findings highlight that standardized and methodical physical pain assessments are needed for future studies, in addition to use of standardized definitions of symptoms and symptom severity. The recent publication of a core outcome set for GSM is an important first step.[47] Currently available population and pharmaceutical studies that allow participants to choose their own severity without guidelines or definitions

preclude making accurate comparisons across study outcomes. While resolution of the most bothersome symptom is ultimately of most importance to women, parsing of specific symptoms, and signs will be most helpful in discerning underlying mechanisms of dysfunction.

Clinical implications

When dyspareunia is a prominent symptom of VVA/GSM, a thorough, systematic examination should be performed, identifying all GU structures that may exhibit tenderness and specifically focusing on the vulvar vestibule. We recommend use of the rolling cotton swab test, a tool assessed for vulvar pain research.[25] The affected tissue is a narrow ring just outside the hymeneal remnant, approximately 1 cm in width, and is often somewhat retracted into a fold around the vaginal opening. After gently retracting the tissue for visualization, tenderness should be assessed by lightly rolling a small cotton swab over a small area of tissue, approximately 1 to 2 cm of mucosa at each site, as shown in Figure 1. Probing is to be avoided to ensure that assessment is of the mucosa only, not deeper structures. The tender mucosal areas are often narrow, and the swab test can be misleading if done even a centimeter away.[25] Use of topical lidocaine to extinguish the pain gives further evidence of the mucosal origin of the pain. While large cotton swabs are useful for administering the lidocaine, they are too large to identify the discrete areas of vestibular pain. These discrete variations in genital sensitivity may arise because of the different embryologic derivations of GU tract structures.[4] The labia, (ectodermal derivation) are distinct in origin from the vestibule and lower bladder/urethra (endodermal derivation)[48] and distinct as well from vagina structural tissues (mesodermal derivation).[10]

For postmenopausal women, lidocaine could be an alternative to or an adjunct to estrogen therapy. Its use was demonstrated in a randomized, controlled trial of topical lidocaine applied to the vaginal introitus, which was found to be an effective preventive therapy for dyspareunia in breast cancer survivors.[13] In that study, the primary location of tenderness was the vestibule. Application of aqueous lidocaine to the introitus before intercourse, along with use of a silicone-based lubricant, led to a reduction in median dyspareunia NRS pain scores from 8 to 1 (scale 0-10). After open-label lidocaine use, 37 of 41 women (90%) reported consistently comfortable penetration when the vestibule, rather than the vagina, was targeted. No partners reported penile numbness. That study demonstrated that treatment based on a neural concept can be successful without addressing atrophy.

Symptoms in other anatomic areas emerged during thorough evaluation. In addition to insertional pain, half of our cohort reported outer vulvar symptoms that had been present for less time than their dyspareunia. Estrogen therapies placed in the upper vagina will correct the vaginal pH and mucosal maturation indices, but this treatment location is distant from the outer vulva. Also, similar to premenopausal women with PVD, postmenopausal women with dyspareunia can exhibit tenderness in the pelvic floor muscles. When muscle tenderness or hypertonicity is found, referral for pelvic floor physical therapy should be a part of comprehensive care of dyspareunia associated with GSM.

Strengths and limitations

The strength of this study includes its focus on a precisely defined subset of dyspareunia symptoms within GSM and use of multiple validated instruments for assessment of symptoms and physical examination findings. The modifications of the VPAQ may limit comparisons to vulvodynia populations, but validity is maintained for the unchanged subscales. More data from GSM populations will be illuminating. In a further limitation, pelvic examinations were performed by three unblinded clinicians. Additionally, this was not a population-based study. Our results are generalizable only to heterosexually active, White women from a single geographic location with similarly defined moderate/severe dyspareunia, and not to all women with GSM. Larger, similarly detailed studies will need to establish what proportion of the GSM population shares these physical examination findings.

CONCLUSION

In this study of postmenopausal women with moderate/severe dyspareunia, the primary location of genital tract tenderness was the vulvar vestibule. This finding suggests consideration of targeted therapy to the introitus as a treatment for postmenopausal dyspareunia. The evidence that topical lidocaine extinguishes vestibular tenderness suggests that the study of superficial nociceptor function in the GU tract may lead to an improved understanding of the underlying mechanisms of dyspareunia. More attention in GSM research to specific GU structures may help assign common complaints to locations and lead to recognition that symptoms vary and relate to the duration and degree of estrogen deficiency. More precise therapy regimens may thereby emerge.

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