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Vulvodynia: An often-overlooked cause of dyspareunia in the menopausal population

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Vulvovaginal pain may stem from various causes, affect women of all ages, and may or may not be associated with sexual activity (TABLE 1). Vulvodynia is defined

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as “vulvar discomfort, most often described as burning pain, occurring in the absence of relevant findings or a specific clinically identifiable neurologic disorder.”¹ It is most commonly diagnosed in young women and is seldom considered in the diagnostic workup of peri- and postmenopausal women. For that population, diagnosis often focuses on genital atrophy; scant attention is given to other etiologies. This review describes the importance of a complete workup for such women.

Vulvodynia definition and etiology

Vulvodynia is classified as generalized or localized, and provoked or unprovoked (TABLE 2).

Its exact etiology remains unknown. It has not been consistently linked to candidiasis, human papillomavirus, high urinary oxalates, sexual abuse, or any specific infectious, hormonal, allergic, or inflammatory processes.² Recent theories include abnormalities of embryologic development and genetic or immune factors.^{3,4} The pain ultimately results from a neuropathic process that may

TABLE 1 Causes of vulvovaginal pain

INFECTIOUS

- Vaginitis (yeast, bacterial vaginosis, Trichomonas)
- Herpes simplex
- Bartholinitis

NEOPLASTIC

- Vulvar intraepithelial neoplasia
- Paget's disease
- Vaginal/vulvar cancer

ALLERGIC

- Contact dermatitis

INFLAMMATORY

- Vulvar dystrophies
- Lichen planus
- Eczema

ANATOMIC

- Trauma
- Vaginismus

NEUROLOGIC

- Referred musculoskeletal pain (disc disease, hip, back)
- Multiple sclerosis
- Pudendal nerve entrapment or injury
- Postherpetic neuralgia

VULVODYNIA

- Unexplained

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FROM THE EDITOR



Everybody knows...

Maybe it's me, but whenever I hear a sentence that begins with the phrase, 'everybody knows,' I can't resist feeling deeply skeptical before the speaker has finished the statement! There are just so many things that 'everybody knows' that just aren't true.

This month, in *Menopausal Medicine*, our authors walk with us through some complicated clinical areas to help us truly figure out what 'everybody knows'—and doesn't know. What we learn from Drs Bachmann, Phillips, and Sternfeld is that when the answer seems obvious, it's time to reflect.

For example, everybody knows...that vaginal symptoms after menopause are due to estrogen deficiency—right? Drs Bachmann and Phillips provide a larger differential diagnosis that includes clinical entities that a busy doctor might well overlook. If our knee-jerk response to a menopausal woman with a vaginal complaint is to provide her with estrogen, and if that doesn't work, prescribe more estrogen—we are not likely to give optimal care to the few with more unusual problems.

Another thing 'everybody knows' is that exercise is good for you. Period. However adherent to a regular exercise routine we might be ourselves, we recommend it to our patients and tend to assume it makes everything better. But does it? Dr Sternfeld takes us on a tour of a complicated set of data to show us that it's not a straightforward issue when it comes to exercise and hot flashes.

It's always wise to check our assumptions. Our patients deserve nothing less.

Nanette F. Santoro, MD

be central, peripheral, or both.

Vulvodynia is a diagnosis of exclusion. Examination is essentially normal, although erythema may be present.

Patient evaluation

The medical history obtained from a menopausal patient with vulvovaginal pain should include targeted questions about the nature and timing of the pain. The presence of coexistent menopausal symptoms, vaginal discharge, vulvar lesions, and other sexual problems, as well as sexual contacts, should be determined. Systemic symptoms and current medical conditions and medications should be documented. In addition to complaining of dyspareunia with coital activity, women with vulvodynia often note constant or intermittent burning, itching, rawness or irritation, or pain with any touch. They may report a history of severe pain associated with gynecologic exams or with the use of vaginal preparations.

To rule out other causes of pain, a comprehensive physical and pelvic exam should include examination of the vulva and vagina, wet prep and cultures (as indicated), palpation to assess levator spasm and bladder or urethral tenderness, and bimanual exam to rule out pelvic pathology. Neurologic examination should be performed as indicated. Areas where pain is most intense should be mapped by exerting gentle pressure over the vulva, clitoris, and vestibule with a moist cotton swab. Posttreatment pain mapping will help ascertain whether management is successful, as evidenced by improved patient tolerance to areas that had been tender.

In the absence of visible genital pathology, and if not contraindicated, a trial of topical estrogen may be helpful if the patient reports dryness and

has diminished lubrication. If symptoms resolve, estrogen should be titrated to the minimal dose that provides desired results.

If no or inadequate response to treatment is observed, a diagnosis of vulvodynia is confirmed, regardless of patient age.

Women with vulvodynia often note constant or intermittent burning, itching, rawness or irritation, or pain with any touch.

Vulvodynia management: Therapeutic options

The best treatment for vulvodynia is as elusive as its etiology. Simple measures may help: wearing absorbent underwear, as well as loose clothing in the perineal area, and using mild, unscented soaps and detergents. Vulvar irritants (TABLE 3) should be avoided. Patient diaries may help uncover potential offensive triggers. Cold packs applied to the vulvar area may provide temporary relief.

The application of topical lidocaine (2% or 5% cream or ointment) may be used for symptomatic and therapeutic treatment. Application may initially result in an escalation of burning symptoms, which usually resolve when the anesthetic takes effect. Ointments are generally less irritative than creams. Diluting the lidocaine by mixing it with a tolerated substance, such as mineral oil or estrogen cream, may be helpful, especially at initiation of treatment. For localized vulvodynia, applying lidocaine to a cotton ball and placing it over the affected area overnight will assure a constant therapy and aid sleep.⁵

In small trials, physical therapy and biofeedback for pelvic floor retraining has been shown to provide

vulvovaginal pain relief and facilitate intercourse. Some experts feel that these modalities will only benefit patients with levator spasm on exam or evidence of vaginismus⁶; others maintain that all vulvodynia patients have a degree of pelvic muscle hypertonus, and these options should always be considered.⁷ Internal and external soft tissue mobilization, trigger point pressure, and exercises for posture, back, and pelvic floor are some examples of these interventions.

Pharmacologic agents

Oral tricyclics have been used for many years, although not all data confirm their superiority over other options.⁸ Therapy begins at 10 mg of nortriptyline or amitriptyline at bedtime, and increases in 10 mg increments to a maximum daily dose of 75 mg. Anticholinergic and cardiac side effects may occur even at low doses; the clinician should titrate upward over several weeks.

Gabapentin has shown promising results. This agent produces fewer anticholinergic side effects than the

TABLE 2 Classification of vulvodynia

GENERALIZED

- Involvement of the entire vulva

LOCALIZED

- Involvement of a portion of the vulva, such as the vestibule

SUBDIVIDED

(generalized or localized PLUS)

- Provoked (present only with contact, sexual or nonsexual)
- Unprovoked (present without contact)
- Mixed (provoked and unprovoked)

Adapted from: Moyal-Barracco M, Lynch PJ. 2003 ISSVD terminology and classification of vulvodynia: a historical perspective. *J Reprod Med.* 2004;49:772-777.

tricyclics but may be sedating or cause ataxia. Various dosing regimens have been evaluated, but a small initial dose of 100 mg at bedtime, increasing by 100 mg every 2 to 7 days to a maximum of 3600 mg/d in divided doses, is a reasonable approach in an older population.

Scant data suggest that pregabalin 250 mg to 450 mg may be beneficial. Pregabalin-induced remission in a 62-year-old woman with a 20-year history of vulvodynia has been reported.⁹ A clinical trial is being conducted at The Cleveland Clinic.

Any oral regimen that produces desired efficacy should be titrated to the lowest dose that results in acceptable symptomatic relief.

Topical formulations of both gabapentin (2%-6%, formulated by a compounding pharmacy) and amitriptyline 2%/baclofen 2% have shown moderate success in small numbers of patients.^{10,11} These are appealing as a potential means of decreasing systemic drug levels and subsequently decreasing unwanted side effects. More clinical experience and controlled trials are needed to establish efficacy.

TABLE 3 Common vulvar irritants

- Bubble baths
- Condoms
- Douches and vaginal sprays
- Excessive or chronic vaginal discharge
- Laundry detergents
- Lubricants
- OTC ointments, lotions, yeast treatments
- Sanitary pads or panty liners
- Soaps (scented, colored, antibacterial)
- Spermicides
- Thong or noncotton underwear

TABLE 4 Treatment options for vulvodynia

Gabapentin ^a	Initial dose: 100 mg at bedtime Increase by 100 mg every 2-7 days Maximum dose: 3600 mg/d in divided doses
Oral tricyclics ^a (amitriptyline, nortriptyline)	Initial dose: 10 mg at bedtime Increase by 10 mg every 1-4 weeks Maximum dose: 75 mg at bedtime
Physical therapy	Perineal massage, biofeedback with progressive muscle relaxation
Pregabalin ^a	Initial dose: 250 mg orally Maximum dose: 450 mg orally
Topical baclofen 2%/amitriptyline 2% ^a	Apply twice daily
Topical gabapentin (2%-6%) ^a	Apply sparingly twice daily
Topical lidocaine (2%-5%) ^a	Apply as needed as with intercourse, or Apply soaked cotton ball to affected area overnight
Nerve blocks (intralesional, pudendal, caudal-epidural)	Steroids (triamcinolone acetonide, methylprednisolone) Anesthetics (lidocaine, bupivacaine)
Surgery	For localized vestibulodynia

^aOff-label use; dosages represent commonly prescribed regimens.

Any oral regimen that produces desired efficacy should be titrated to the lowest dose that results in acceptable symptomatic relief.

Additional treatment options

Additional treatment options include nerve blocks, which may be intralesional, pudendal, or even caudal-epidural, using a combination of steroids (triamcinolone acetonide, methylprednisolone) and anesthetics (bupivacaine, lidocaine). Although intra-lesional injections are often done in a primary care setting, blocks that are more regional are usually referred to an anesthesiologist or pain center.

Surgical options, such as vestibulectomy, are reserved for localized disease, especially vestibulodynia, and should be considered for the most re-

sistant cases and after other options have failed. The woman must be fully informed about surgical risks and benefits. Limited data in postmenopausal patients are available. Presurgical topical estrogen therapy will help postoperative healing of vaginal tissue. After surgery, a period of pelvic rest will be required to ensure incision healing, followed by use of a vaginal dilator prior to attempted intercourse. Success rates as high as 80% have been reported postsurgically,⁷ but few data apply to the peri- and postmenopausal population.

Psychosocial factors

Psychosocial evaluation and therapy may be useful in therapeutic success. Women with vulvodynia, as with any chronic pain condition, are often depressed or anxious. Secondary sexual dysfunctions may develop, and intimate relationships become

TABLE 5 Treatment guidelines

- All medications should be started at the lowest dose and titrated upward at a slow rate, over at least 2-4 weeks per advancement in dose.
- Only one treatment should be introduced at a time.
- Pain and symptom diaries should be kept to help guide and monitor treatment.
- In the absence of direct adverse interactions, multiple therapies may be used simultaneously, although little to no data are available to support this strategy.
- Physical therapy is a helpful adjunct to medical treatment.
- Counseling should be offered as appropriate (longstanding disease, history of abuse, coexisting sexual dysfunctions, or relationship difficulties).
- Surgery should be reserved for localized vestibulodynia only after failure of medical therapy.

stressed. A multidisciplinary approach overseen by the gynecologist can be beneficial.

A summary of treatment options is shown in **TABLE 4**, and general guidelines for treatment are reviewed in **TABLE 5**.

Vulvodynia management: Special considerations

All treatment options discussed here are off-label for premenopausal patients. In aging women, additional factors must be considered.

Few randomized, controlled trials assess vulvodynia treatments; because the incidence of vulvodynia in the menopausal population is low, even less data are available.

Older patients are more likely to have chronic medical conditions, increasing the potential for drug interactions and the impact of side effects, such as sedation or constipation. Medical clearance or specialist consultation may be warranted.

Older patients are more likely to have chronic medical conditions, increasing the potential for drug interactions and the impact of side effects.

The coexistence of vulvodynia and atrophy may demand the use of estrogen or other nonhormonal

therapies for vulvovaginal atrophy, in addition to those aimed at treating vulvodynia. Use of topical estrogen may be alternated with other topical agents, whereas oral estrogen or vaginal inserts or rings may be used concomitantly.

Vulvodynia symptoms resolve slowly with any therapeutic option. Several weeks are often needed for appreciable relief. In an older population, therapies—especially systemic medications—may be increased slowly over time frames that are longer than usual, and expected intervals for symptom improvement should be adjusted.

Conclusion

This condition can occur in women across the life cycle.^{12,13} The diagnosis of vulvodynia should be considered the etiology for women who report vulvar burning and tenderness, especially when noted with sexual contact or any type of vulvar pressure. Although estrogen therapy may be used as a first-line therapy in older women, vulvodynia management strategies should be considered in women with no obvious pathology and an inadequate response to estrogen intervention. ■

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Is physical activity beneficial for hot flushes?

► BARBARA STERNFELD, PHD

Can physical activity help resolve menopausal vasomotor symptoms (VMS)? In this article, we summarize the reports regarding physical activity and VMS and discuss biological mechanisms by which physical activity might exert a beneficial effect. The potentially mediating role of mood, quality of sleep, and/or body weight on the relation between physical activity and VMS will be reviewed, as will the clinical and public health implications of our current state of knowledge.

Review of the literature

Approximately 27 published articles have explored the relation between physical activity and VMS (a complete reference list is available from the author). Generally, these studies have evaluated Caucasian populations in the United States, Australia, and Sweden; a few have included African Americans and other racial/ethnic groups.¹⁻³

Most studies feature observational, cross-sectional designs: one had a case-control design,⁴ and one cross-sectional study assessed physical activity prior to onset of VMS.⁶ Two observational studies followed cohorts prospectively,^{1,2} and 6 were randomized controlled trials. Assessment of physical activity ranged from response to a single global question to detailed recalls of activity duration, frequency, and mode.

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Exercise interventions in the randomized clinical trials usually featured moderate-intensity walking programs, 30 minutes a day, 3 to 5 days a week for 12 to 16 weeks. One intervention specifically evaluated increased intensity of exercise over time.⁶

Symptom assessment also varied: some studies considered frequency, severity, and/or bother as separate domains; others used a single measure or symptom frequency. No study has objectively measured VMS.

Although the etiology of the hot flush is not fully understood, experiments suggest a variety of potential mediators, many of which are associated with exercise.

Many observational studies had null findings, but 2 reported significantly increased risk of hot flushes in active women.^{5,7} One showed increased risk only in women who were highly active at a younger age.⁵ Other studies have reported protective associations: In one study, the prevalence of moderate to severe hot flushes in women in an exercise program was reported to be 21.5% compared with 43.8% in nonparticipants.⁸ A more recent study⁹ noted that highly active postmenopausal women had a lower prevalence of hot flushes compared with those who had little or no exercise (5% vs 14%-16%; $P < .05$); however, 35% of the sample used hormone therapy (HT). HT users were more likely to be active than nonusers.

Perhaps the strongest observational data indicating a protective association of exercise on VMS comes from the longitudinal Melbourne Women's Midlife Health Project, which followed 438 women for 8 years.² At baseline, physical activity was not associated with VMS in this cohort¹⁰; however, women who at study initiation reported exercising every day were 49% less likely to report bothersome hot flushes during follow-up (odds ratio [OR] = 0.51; 95% confidence interval [CI] = 0.27-0.96). Over follow-up, decreases in exercise level were associated with increased VMS.

The results from randomized trials are inconsistent. Two trials (only one was designed to test a specific hypothesis about VMS) reported no effect of exercise on VMS; one reported a significant increase in hot flush severity in exercisers vs controls. In contrast, 2 small, short-term trials reported statistically significant reductions in frequency and severity of VMS. A 4-month intervention enrolling 164 previously sedentary women randomized either to a walking group, yoga, or a control group⁶ showed decreased VMS in both arms relative to the control group; however, the differences were not statistically significant. Change in VMS appeared to be mediated by increases in physical fitness: participants who had the most pronounced improvement in fitness also had the most significant decrease in symptoms.

In summary, although the evidence for a protective effect of exercise on VMS is minimal, the literature is limited. Most studies had insufficient power to detect any potential effect.

Potential biological mechanisms of VMS

Although the etiology of the hot flush is not fully understood, experiments suggest a variety of potential mediators, many of which are associated with exercise.

Studies suggest that an increase in the body's core temperature precedes the onset of a hot flush.¹¹ Potentially, a narrowing of the thermoregulatory zone triggers the event. This may result from a decrease in the threshold for sweating and/or an increase in the threshold for shivering.¹²

Stress is a precipitating factor for hot flushes¹³; therefore, neuroendocrine substances—which play a role in the stress response and affect thermoregulation at the level of the hypothalamus—may be implicated in their etiology.

Prior to hot flush onset, increased levels of brain norepinephrine (NE) are observed and are further elevated during episodes,¹¹ suggesting that hot flushes may result from imbalances in the autonomic system. The “stress-buffering” role of the parasympathetic nervous system may be inadequate to counter the increased activation of the sympathetic nervous system.^{14,15} Heart rate variability—an indicator of reduced vagal control—appears to be reduced during the hot flush itself,¹⁶ providing some empirical support for this hypothesis.

Increased cortisol levels are observed during the later stages of the menopausal transition. Higher cortisol levels are associated with higher epinephrine and NE levels as well as with more severe VMS^{17,18} and may also indicate an imbalance in the autonomic nervous system.

Animal studies suggest that b-endorphins may play a role in the pathogenesis of the hot flush. Administration of naloxone, an opiate

antagonist, in morphine-dependent rats causes symptoms similar to those of the hot flush, as well as luteinizing hormone (LH) surge.¹⁹

However, in postmenopausal women, the infusion of naloxone has not consistently reduced the frequency of hot flushes or LH pulses.²⁰ Studies of plasma b-endorphin levels prior to hot flushes have also been contradictory,^{21,22} although plasma levels may not reflect the endorphin levels in the brain.

Physical activity and neuroendocrine responses

Physical activity might reduce the incidence of VMS because of associated neuroendocrine responses. In response to acute exercise, increases in brain NE and its metabolites occur. However, 24-hour urinary NE appears to decrease with training,²³ perhaps because of an increase in vagal tone.

Exercise training also results in decreased resting heart rate, typically ascribed to a shift of autonomic balance in favor of the parasympathetic nervous system. Several studies have shown that heart rate variability is greater in active women compared with sedentary women²⁴ and that variability improves in response to training.²⁵

Physical activity could favorably affect the frequency or bother of VMS because release of endogenous opioids, particularly b-endorphins, is increased, particularly in response to a single, sustained bout of vigorous exercise.²⁶ Although it is not known whether b-endorphins are responsible for the so-called runner's high,²⁷ the endogenous opioids are biochemically similar to exogenous opiates and have physiologic effects of temperature regulation, decreased sensitivity to pain, and decreased heart and respiratory rates.

Exercise does cause an acute rise in core temperature. If symptomatic

women have a narrowed thermoregulatory zone, exercise might actually induce hot flushes. However, it is unclear how bothersome an exercise-induced hot flush would be, given the sweating that occurs with exercise.

Physical activity and well-being in midlife

Studies of midlife women show that physical activity is directly related to positive mood, vigor, and general well-being.²⁸⁻³⁰ It is inversely related to negative symptoms, such as depression, anxiety, problems with memory and concentration, decreased sexual desire, difficulty sleeping, and perceived stress.^{29,31-33} Sleep, mood, and quality of life are often negatively impacted by the occurrence of VMS. Possibly, the beneficial effects of physical activity may affect the frequency, severity, or bother of VMS. The Harvard Study of Moods and Cycles demonstrated that a significantly lower risk of VMS was associated with higher levels of physical activity in women with a history of major depression,³⁴ suggesting the mediating effect of mood.³⁴

Sleep, mood, and quality of life are often negatively impacted by the occurrence of VMS.

Body weight may mediate the effect of physical activity on VMS: Heavier women report more VMS. Weight loss resulting from increased activity may be a crucial step in the relationship between increased activity and decreased VMS. However, no empirical evidence supports this hypothesis.

Future directions

Clearly, we face many unanswered questions about physical activity and VMS. Does participation in regular

physical activity affect frequency, severity, bother of hot flashes, or duration of VMS over time? If so, does exercise improve or worsen VMS?

Does the “dose” of physical activity matter: Is vigorous-intensity exercise more effective than moderate-intensity exercise? Is mode of exercise (eg, aerobic vs resistance exercise) a factor? If physical activity is effective, how does it work?

Well-designed and adequately powered randomized trials are required to answer these questions.

Within the next few years, the Menopause Strategies: Finding Lasting Answers for Symptoms and Health (MsFLASH) research network will be testing a series of innovative treatments for menopausal symptoms in randomized controlled trials, including one on the efficacy of aerobic exercise.

Meanwhile, the existing evidence of the health benefits of regular physical activity for midlife women suggests that all clinicians should prescribe regular physical activity to their patients, and that they be prepared to

discuss and problem-solve with their patients the barriers to becoming more physically active. One resource is “Exercise is Medicine” at www.exerciseismedicine.org. Public health professionals need to continue and enhance their ongoing efforts to promote physical activity among all midlife women. Even if regular physical activity does not prevent or treat VMS, the other health benefits that it confers will ensure both a healthy menopausal transition and healthy aging. ■

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