AUA Update Series 2021
Lesson 13 Volume 40

Female Sexual Pain Disorder*

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to define, diagnose and treat female sexual pain disorder.

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***This AUA Update addresses the Core Curriculum topic of Sexual Medicine and the American Board of Urology Module on Neurogenic Bladder, Voiding Dysfunction, Female Urology, BPH and Urethral Stricture.**

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Release date: April 2021

Expiration date: April 2024

Key Words: female, pain

INTRODUCTION/EPIDEMIOLOGY

Female sexual pain disorder, or genito-pelvic pain/penetration disorder (previously known as dyspareunia), is defined as persistent or recurrent symptoms with one or more of the following for at least 6 months: marked vulvovaginal or pelvic pain during penetrative intercourse or penetration attempts, marked fear or anxiety about vulvovaginal or pelvic pain in anticipation of, during or as a result of penetration, and marked tensing or tightening of the pelvic floor muscles during attempted vaginal penetration.[1] In the last 2 decades, there has been increased interest in the management of female sexual dysfunction, including sexual pain disorders, in the field of urology. Due to their complexity, sexual pain disorders are still largely misunderstood and often undertreated. **The estimated prevalence in the United States varies between 3% and 25%, with causes differing by age group.**[2,3] Genito-pelvic pain/penetration disorder is frequently multifactorial and requires a multidisciplinary approach that includes biological, psychological, sociocultural and relational factors. Psychological factors that may contribute to dyspareunia include anxiety or guilt about intercourse, memories of distressing early sexual experiences, fear of penetration, unresolved anger, feelings of shame or guilt, and inadequate precoital stimulation.[4]

Common causes of GPPPD found in the urological setting include:

- Genitourinary syndrome of menopause
- Vestibulodynia
- Urinary tract infections
- Interstitial cystitis
- Erosion of implantable mesh
- Tissue damage from radiation
- Pelvic organ prolapse
- Urethral abscesses/vaginal cysts
- Pelvic floor dysfunction
- Sexually transmitted diseases

Nonurological causes of GPPPD include:

- Irritable bowel syndrome
- Fibromyalgia
- Endometriosis
- Vaginitis/vulvovaginitis
- Vulvar dermatoses
- Childbirth

ANATOMY

An understanding of female genital anatomy is essential in order to provide comprehensive evaluation and optimize treatment outcomes for women with sexual concerns. Female sexual organs include the clitoris (glans and crura), labia majora and minora, vulvar vestibule, vagina, cervix, vestibular bulbs and the pelvic floor muscles.

Vulva. The vulva is a complicated anatomical structure intricately involved in the female sexual response cycle. It is the homologue of the male genital anatomy. It includes the mons pubis, labia majora, labia minora, vestibule and clitoris.

Vestibule. The vulvar vestibule is located between the labia minora and the hymen. This tissue is embryologically endoderm and mediated by testosterone. The medial border is the hymen and the lateral border, called Hart's line, is located inside the labia minora. The vestibule contains the external urethral meatus and the openings of the 2 greater vestibular Bartholin's and perivestibular/Skene's glands, which are analogous to the Cowper's glands and glands of Littre in the male.[5] The vestibule is an area of significance in patients presenting with vulvar pain and GPPPD. The vulvar vestibule can become painful due to changes in hormones, inflammation or muscle hypertonicity (fig. 1).

Clitoris. The clitoris is composed of large dilated vascular spaces that engorge with blood during arousal. It is the female homologue of the male penis and includes a prepuce, glans, corona, bilateral corpora cavernosa and crura. The glans clitoris is the component of the clitoris that is visible but often covered by a "hood" of preputial skin, particularly in the unaroused state. This prepuce can develop phimosis and/or balanitis, which can contribute to clitoral pain (clitorodynia) and/or anorgasmia.[6]

Vagina. The vagina is an elastic, muscular canal that extends from the vulva to the cervix. It serves a multitude of functions in response to hormonal changes and plays a vital role in the female reproductive system and female sexual pleasure. The vaginal mucosa contains a high concentration of estrogen and androgen receptors.[7] Estrogen modulates blood flow and lubrication by causing nitrous oxide release, which increases the capillary blood flow. This increased blood flow creates vasocongestion within the vaginal submucosa, increasing oncotic pressure, which leads to production of a fluid transudate (lubrication) that passes into the vaginal lumen via aquaporins located in the vaginal mucosa.[8,9]

Pelvic floor. The female pelvic floor muscles support the bladder, uterus and colon and play a vital role in sexual function as well as bladder and bowel control. A clock face is used as a reference when describing the location of the pelvic structures. The 12 o'clock and 6 o'clock positions correspond

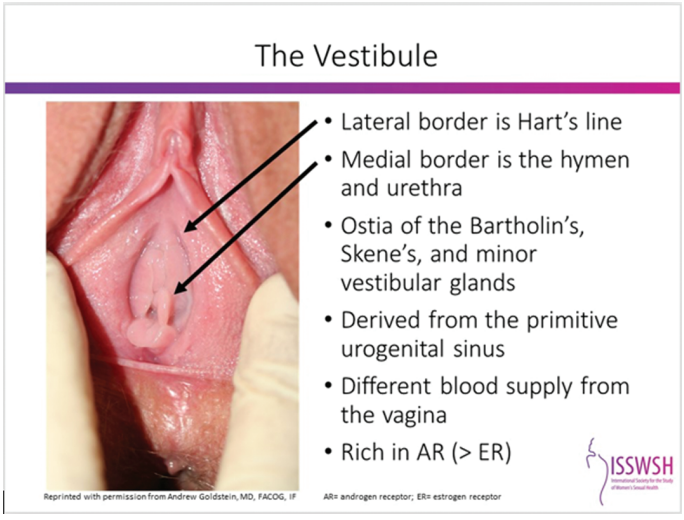

Figure 1. Anatomy of vulvar vestibule. *AR*, androgen receptors. *ER*, estrogen receptors.

ABBREVIATIONS: DHEA=dehydroepiandrosterone, GPPPD=genito-pelvic pain/penetration disorder, GSM=genitourinary syndrome of menopause, VD=vestibulodynia

to the anterior and posterior midline, or pubic symphysis and anus, respectively.[10] The obturator internus and externus can be palpated by sweeping from the pubic ramus downward along the muscle belly behind the pubic ramus at 1 and 11 o'clock. At 3 and 9 o'clock, the levator ani complex is present, and at 5 and 7 o'clock, the iliococcygeus muscle (distal) is palpable. Approximately a finger's length depth into the vagina, at around 4 and 8 o'clock, the ischial spines are palpated as bony prominences. The ischial spines serve as the anatomical marker for the pudendal nerve, which runs approximately 2 cm posteromedial to the ischial spine and innervates the clitoris, vulva and anus.[11]

Autonomic nervous system. The female sexual response is dependent on the coordinated activity of parasympathetic, sympathetic and somatic innervation. The parasympathetic nervous system promotes vasodilation, leading to increased vaginal lubrication and clitoral engorgement. The sympathetic nervous system causes rhythmic smooth muscle contractions of the vagina during orgasm. The somatic nervous system, via the pudendal nerve, controls sensation and contractions of the somatic pelvic muscles that accompany orgasm.[12]

Hormonal. Estradiol is the primary "female" sex steroid and acts by binding to the estrogen receptor.[13,14] Estrogens maintain female genital tissue integrity and thickness. Peak estradiol levels occur at the midpoint of the menstrual cycle and are associated with maximal vaginal mucosal thickness and glycogen content. Androgens (ie DHEA, androstenedione, testosterone) are necessary precursors for the biosynthesis of estrogens and have an important role in the physiology and homeostasis of the vagina.[15] Androgen receptors are widespread throughout the genitourinary tract and independently regulate vaginal health such as vaginal and vestibular lubrication, smooth muscle activity and blood flow. Their production is significantly greater than that of estrogens in premenopausal women.[16] Thus, decreased levels of androgens during menopause are also thought to be contributory to GSM.[16,17]

PATHOPHYSIOLOGY

Genitourinary syndrome of menopause. **GSM, previously vulvovaginal atrophy/atrophic vaginitis, is characterized by genital symptoms (eg dryness, burning, irritation), sexual symptoms (eg lack of lubrication, discomfort or pain, decreased libido, difficulty with arousal and orgasm) and urinary symptoms (eg urgency, dysuria, recurrent urinary tract infections).** GSM can also occur in hormone-depleted states, including breastfeeding, oral contraceptive use, adjuvant hormonal deprivation therapy for breast cancer treatment, gender-confirming hormone therapy, thyroid disorders and pituitary tumors.[18–20] As estrogen and androgens decline, blood flow to the vagina and vulva also decreases, which leads to impaired vaginal lubrication, vaginal burning, dryness, irritation and an increased pH.[21] Impaired lubrication can affect sexual function and cause pain with intercourse (fig. 2).

Vestibulodynia. **Vestibulodynia, previously known as vulvar vestibulitis syndrome, is defined as vestibule pain lasting more than 3 months, unrelated to infection, skin disorders or other identifiable factors.** It is characterized by burning, stinging, itching or rawness. The most common factors associated with VD are hormonal changes (hormonally mediated), hypertonic pelvic floor dysfunction and an increased number of nerve endings in the mucosa of the vestibule (neuroproliferative VD).[22]

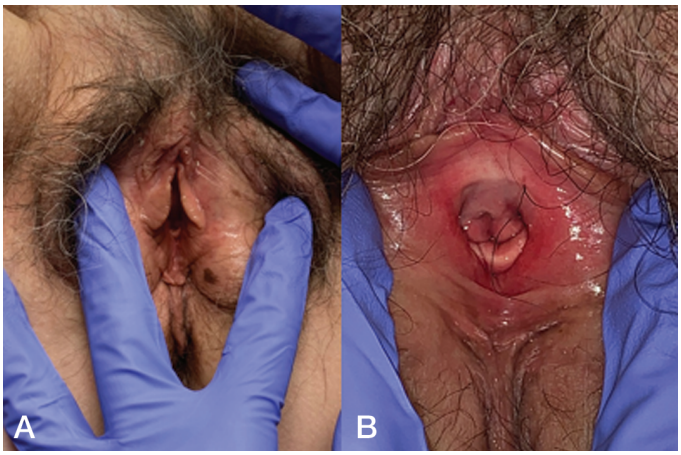

Figure 2. Patient with genitourinary syndrome of menopause. (A) Note 50% resorbed and thin labia minora. (B) Note protruding urethra, pallor and erythema of vestibule. Vaginal pH is 7.5, while goal should be 4.5. Photographs courtesy of Rachel S. Rubin.

Clitorodynia. Clitorodynia is a form of vulvodynia localized to the clitoris. It is characterized by frequent and intense pain episodes that can be provoked or unprovoked and can cause significant impairment in both daily and sexual function. It may be associated with other chronic pain disorders, lichen sclerosus, multiple sclerosis, pelvic surgery and vaginal delivery.[23] Physical examination may show clitoral adhesions, phimosis, balanitis or skin changes associated with lichen sclerosus.

Pelvic floor dysfunction. Pelvic floor dysfunction refers to the constellation of symptoms secondary to the non-relaxing pelvic floor musculature. Pelvic floor dysfunction presentation depends on the particular muscles in spasm. Manifestations include dyspareunia, voiding dysfunction, incontinence, urinary retention, constipation and dyschezia.

HISTORY AND PHYSICAL EXAMINATION

History. **Due to the sensitive nature of the topic, providers must be able to discuss the subject matter assuredly while making patients feel comfortable and safe.** The most important goal during the introductory discussion is to provide validation of the patient's pain, which will aid in establishing rapport and trust between the patient and provider. This is best done with the patient fully dressed and ideally not in an examination room. A comprehensive history should then be performed using open-ended questions, affirming statements and reflective listening. Using generalizing statements is a helpful tool to engage the patient, such as, "Many women with (a specified condition) experience (a specific or generalized issue with sex). Do you experience this?" The use of validated self-reported questionnaires, such as the Female Sexual Function Index, McGill Pain Questionnaire and the Patient Reported Outcomes Measurement Information System (PROMIS)® vulvar discomfort scale, can also provide objective information when quantifying pain and its impact on the patient's life.

A focused sexual history should review the following:

1) Pain characteristics (location, duration, exacerbating factors, alleviating factors)
2) Associated symptoms such as bowel, bladder or musculoskeletal symptoms

3) Sexual activity and behavior
4) Medical history
5) Surgical history
6) Medication history (use of hormonal birth control, selective serotonin reuptake inhibitors etc)
7) Mental health history
8) Obstetrical and gynecologic history, including onset of menstruation, characteristics of periods and onset of menopause
9) History of physical or sexual abuse
10) Previous interventions

Physical examination. Many objective findings on physical examination can be seen in a patient with sexual complaints, and a full vulvar and vaginal examination will aid in finding the proper treatment for the patient.

Important anatomy to assess includes:

- Labia majora and minora
- Clitoris, including glans and hood
- Urethra and periurethral glands
- Vestibule
- Vaginal vault
- Cervix
- Pelvic floor levator ani muscles

Important factors to evaluate in the focused genital examination include:

- Distribution of hair
- Symmetry and size of genital tissues
- Evidence of atrophy or stenosis
- Areas of provoked pain
- Color uniformity, erythema or other discoloration
- Visible lesions, excoriations or scars
- Pelvic organ prolapse
- Pelvic floor muscle tone and voluntary control
- Presence of vaginal discharge
- Presence or absence of vaginal rugae

It is advantageous for patients to visualize their anatomy with either a vulvoscope or a mirror as this empowers them to better understand and feel comfortable with their anatomy. Begin the physical examination by describing and explaining the specific actions during each step and discussing the examination findings with the patient. **The examination should include an external and internal musculoskeletal evaluation, external visual and sensory examination, and a bimanual examination if tolerated by the patient.** The external musculoskeletal examination should include evaluation of posture/gait, taking note of any asymmetry and/or pain, palpation of abdominal, gluteal, back and lower extremity muscles, identifying areas of tension and/or pain, and an assessment of muscle strength, range of motion, sensation and reflexes.

Next, a systematic examination of the vulva is performed by inspecting the external genitalia, perineum, perianal areas and the mons pubis. The clinician should evaluate signs of infection, trauma, atrophy, fissures and dermatological changes. A cotton swab can be used to assess for vulvar allodynia and/or hyperalgesia by light palpation, which is suggestive of neuropathy. Next the vestibule should be examined. Physical findings to note include hyperemia or erythema, and periurethral and perivaginal glands. A cotton swab test should be performed by palpating the vestibule in 7 anatomical sites (12 o'clock, 1 o'clock, 3 o'clock, 5 o'clock, 7 o'clock, 9 o'clock and 11 o'clock).

The internal muscle examination should start with light palpation for general tone, then deeper pressure to assess for trigger points, which are hallmark diagnostic indicators of pelvic floor dysfunction. Using the index finger, the examiner can palpate the lateral, anterior and posterior walls of the vagina, the urethra and pelvic floor muscles, assessing for tone, tenderness or involuntary contractions. Clinical criteria that indicate presence of a trigger point include 1) a palpable taut band, 2) an extremely tender nodule in the taut band, 3) the ability to reproduce the pain with palpation of the tender nodule and 4) painful limit to stretch or full range of motion.[24] If pain or hypertonic muscles are noted, consider pelvic floor physical therapy referral.

If the patient can tolerate the single digit examination, a bimanual examination should be performed to evaluate the uterus and adnexa for any masses or tenderness. Next, the provider should proceed to an internal examination using a warmed, small-sized Graves or Pederson speculum. Slow insertion of the speculum while avoiding the urethra or vestibule is important to ensure patient comfort as this can elicit pain. This portion of the examination should be performed by providers who are trained and skilled in a performing an internal vaginal examination. During the speculum examination, the internal vaginal tissue, cervix and vaginal secretions are evaluated. Cultures or biopsies can be collected at this time to rule out infections, dermatoses or abnormal cellular dysplasia that can cause dyspareunia or vulvodynia.

TREATMENT

Genitourinary syndrome of menopause. **The primary goal for treating GSM is alleviation of symptoms, restoring vaginal pH and preventing recurrent urinary tract infections.** For women with vulvovaginal symptoms related to sexual activity, multimodal treatment may be helpful. Lifelong low-dose vaginal hormone therapy is the mainstay of treatment (eg vaginal creams, intravaginal tablets, intravaginal rings). These have been shown to maintain tissue integrity, elasticity and pliability. Additional available treatment options include nonhormonal vaginal lubricants to be used during intercourse, long-acting vaginal moisturizers for symptom control, laser therapy and pelvic floor physical therapy with possible use of vaginal dilators.

Topical lubricants and moisturizers: Various over-the-counter vaginal lubricants (water, silicone or oil-based) and moisturizers are commonly used for the treatment of postmenopausal women with vulvovaginal symptoms. These serve as supplemental/symptomatic treatments but do not correct the hormonal imbalance. They are used as needed typically for sexual activity but can be used independently of sexual activity. It is recommended to choose a product that is physiologically most similar to natural vaginal secretions, and balanced in terms of both osmolality and pH.[25] Water-based lubricants are often preferred over oil-based lubricants as they are non-staining and associated with fewer genital symptoms. Caution should be used with oil-based lubricants as this can lead to condom breakage.[26]

Low dose vaginal estrogen and testosterone: Topical, low dose vaginal estrogen restores hormone levels within the tissue without significant systemic absorption. This typically results in rapid improvement in vaginal symptoms within 2 to 3 weeks but may take 2 months for maximal benefit. **Topical estrogen is recommended by the American Urological Association for**

the treatment of recurrent urinary tract infections in premenopausal and postmenopausal women as data show it prevents urinary tract infection by restoring vaginal flora and pH. Systemic estrogen therapy can be considered in addition to topical estrogen if there are concomitant vasomotor symptoms. Systemic estrogen has not been shown to treat symptoms of GSM when used on its own. The American College of Obstetricians and Gynecologists recommends use of nonhormonal options as the first choice for treatment of vaginal atrophy in women with current or a history of estrogen dependent breast cancer. However, they also consider vaginal estrogen therapy appropriate for patients with a history of estrogen dependent breast cancer who are unresponsive to non-hormonal remedies, but only after a thorough discussion of risks and benefits with their oncologist.[27]

Vaginal DHEA suppositories are approved for the treatment of moderate to severe GPPPD. DHEA is converted by enzymes in the vulva, vestibule and vagina into estrogen and testosterone. This results in significant improvements in vaginal epithelial cells and integrity, vaginal pH, parabasal cells and increased vaginal secretions, all without affecting serum levels of estradiol and testosterone or endometrial tissues.[28–31]

Oral selective estrogen receptor modulators: Selective estrogen receptor modulators are oral systemic nonhormonal therapy approved for the treatment of GPPPD due to GSM. Ospemifene is the only selective estrogen receptor modulator approved by the U.S. Food and Drug Administration for treatment of moderate to severe dyspareunia.[32] Several studies have shown that it increases vaginal maturation index and vaginal pH, causing improved lubrication. Common side effects include hot flashes, vaginal discharge and muscle spasm. Contraindications include estrogen dependent neoplasms, history of venous thromboembolism, previous stroke or myocardial infarction, and active heart disease (see table).[32, 33]

Vaginal dilators and lasers: Dilators have been shown to increase vaginal elasticity, which decreases pain with penetration. Women with GSM may see benefit from gentle stretching of the vagina with the use of lubricated gradual dilators in combination with correction of vaginal lubrication. Pelvic floor muscle therapy may also be useful in patients with non-relaxing or high tone pelvic floor muscle dysfunction triggered by painful sexual activity related to GSM.[34] Patients and providers can find pelvic floor physical therapists through various online resources, such as APTA Pelvic Health (https://aptapelvichealth.org/).

Laser therapy, with either a fractional CO_2 laser or erbium:YAG laser, can be used as a nonhormonal treatment option for GSM.[35] Although data are limited, several small studies have shown restoration of the vaginal epithelium, increase in premenopausal vaginal flora and subjective improvement in symptoms of GSM, including lower urinary tract symptoms.[36] At this time, laser therapy is not U.S. Food and Drug Administration approved and should be used in experimental treatment only.

Vestibulodynia. **The treatment of GPPPD associated with VD requires a multidisciplinary approach as a majority of cases are multifactorial.** Due to feedback loop of pain and anxiety associated with GPPPD, cognitive behavioral therapy and sex therapy have a role in treatment. **Pelvic floor physical therapy, biofeedback, onabotulinumtoxinA injection, pudendal nerve blocks and neuromodulation are other adjuvant therapies that have been shown to be beneficial in the treatment of VD. In terms of medical management, discontinuation of hormonal contraception should be considered, and patients should be counseled on alternative options for nonhormonal contraception.** Hormone therapy of both estrogen and testosterone is the mainstay of medical management for hormonally mediated VD, including DHEA vaginal inserts and compounded estrogen/testosterone.[37,38] **Other considerations include the addition of topical steroids if VD is associated with dermatological conditions (eg lichen sclerosus), onabotulinumtoxinA injection and vaginal valium.** In refractory cases or those with persistent pain despite correction with hormone therapy, surgical intervention consisting of vulvar vestibulectomy with vaginal flap advancement should be offered. Studies have shown a high success rate of cure when performed by an experienced surgeon (fig. 3).

Clitorodynia. **Treatment for clitorodynia is dependent on the underlying cause.** Topical treatment with potent steroids is used for management of phimosis and treatment/management

Table. Pharmacological treatments for GSM

	Product Name	Dose
Vaginal cream:		
17-beta-estradiol cream	Estrace®, generic	0.5–1 gm daily for 2 wks, then 0.5–1 gm 1–3 times weekly
Conjugated equine estrogens	Premarin®	0.5–1 gm daily for 2 wks, then 0.5–1 gm 1–3 times weekly
Vaginal insert:		
Estradiol vaginal tablets	Vagifem®, Yuvafem®	10 µg inserts daily for 2 wks, then twice weekly
Estradiol soft gel capsules	Imvexxy®	Four 10 µg inserts daily for 2 wks, then twice weekly
DHEA (prasterone) vaginal insert	Intrarosa®	6.5 mg capsule daily
17-beta-estradiol vaginal ring	Estring®	1 ring inserted every 3 mos
Ospemifene oral tablets (selective estrogen receptor modulator)	Osphena®	60 mg tablet daily

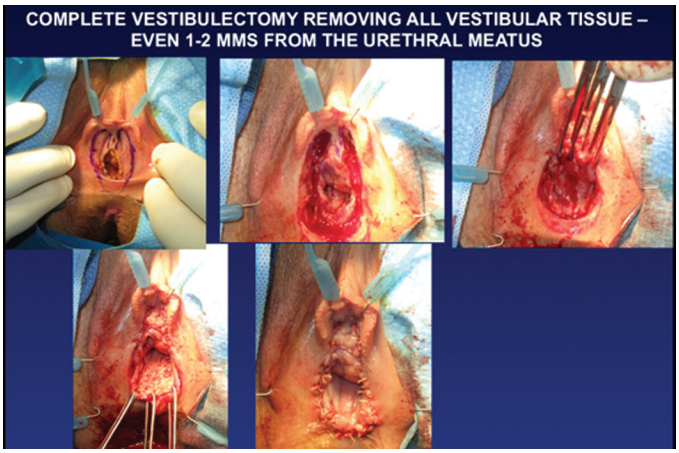

Figure 3. Complete vestibulectomy with left and right anterior vestibulectomy, and posterior vestibulectomy with vaginal advancement flap reconstruction. Photographs courtesy of Irwin Goldstein. Video of procedure is available at https://www.youtube.com/watch?v=ARvyvvu7Nfg.

of lichen sclerosus. If pain is associated with correctable physical examination findings (clitoral pearl, adhesions refractory to medication), surgical treatments should be considered, including office-based lysis of adhesions or surgical dorsal slit (fig. 4).

Pelvic floor dysfunction. **Pelvic floor rehabilitation is the foundation of management of pelvic floor dysfunction.** It requires a multimodal treatment plan that is developed with a licensed pelvic floor physical therapist. **The mainstay of pelvic floor rehabilitation is pelvic floor physical therapy, which includes manual techniques of massage, myofascial and trigger point release, and joint mobilization.** Adjunct therapies include trigger point injections with steroids or onabotulinumtoxinA for pelvic floor tightness or spasticity, intravaginal diazepam

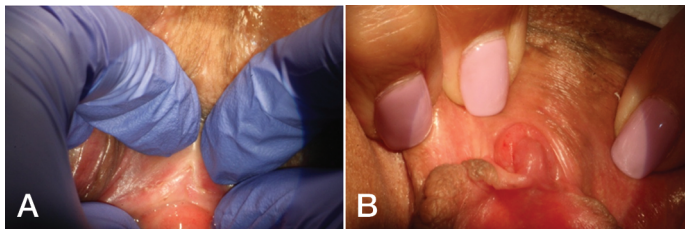

Figure 4. (A) Phimosis of clitoris. (B) Clitoral lysis of adhesions. Photographs courtesy of Rachel S. Rubin.

suppositories, transcutaneous electrical nerve stimulation and neuromodulation.[39,40]

CONCLUSION

Female sexual pain disorders are within the scope of urological practice, and comfort with their management should be encouraged. Sexual pain may be multifactorial, and treatments often require a multidisciplinary approach that can include medical, surgical, behavioral and musculoskeletal interventions.

DID YOU KNOW?

- Genito-pelvic pain/penetration disorder is a common yet poorly understood diagnosis in the world of urology.
- Understanding of female anatomy is imperative for diagnosis.
- Treatment of GPPPD requires a multimodal and integrative treatment plan.

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Study Questions Volume 40 Lesson 13

1. During orgasm, contractions of the pelvic muscles are mediated through the somatic nervous system via the
   a. hypogastric nerve
   b. pudendal nerve
   c. inferior hypogastric nerve
   d. vagus nerve

2. The primary goals of treatment for GSM are alleviation of symptoms, restoration of vaginal pH and
   a. increased frequency of intercourse
   b. maintenance of tissue integrity
   c. reduced vaginal infections
   d. reduced urinary tract infections

3. A 24-year-old woman has had dyspareunia for the last 2 years. She is unable to have penetrative intercourse due to pain. She has a painful bowel movement once per week. She was recently started on clean intermittent catheterization for urinary retention. She has generalized increased pelvic floor tone on rectal and vaginal examination, and there are at least 3 trigger points in the levator ani. The first step in treatment is
   a. cognitive behavioral therapy
   b. physical therapy
   c. trigger point onabotulinumtoxin A injection
   d. pudendal nerve blocks

4. A 21-year-old woman has been treated for presumed yeast vaginitis 3 times in the last 3 months. She has constant burning and itching of the vestibule and notes that the tissue feels raw. She has never had a positive culture for yeast and denies having vaginal discharge. She has been on hormonal contraception for the last year. On examination of the genitalia, the tissues of the vestibule are erythematous without lesions or discharge. Pelvic floor tone is normal. Vaginal cultures are negative, and biopsies are negative for cellular dysplasia or lichen sclerosus. The next step in management is
   a. stop oral contraceptives
   b. cognitive behavioral therapy
   c. vaginal valium
   d. vulvar vestibulectomy

5. The tissue of the vestibule is derived from
   a. mesoderm
   b. ectoderm
   c. endoderm
   d. neural crest