Revitalizing research in genitourinary syndrome of menopause

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THE PROBLEM: There are barriers to the treatment of genitourinary syndrome of menopause.

A SOLUTION: Clinical research, assistance to patients without insurance coverage of treatment, and patient education are needed to make genitourinary syndrome of menopause treatment more accessible.

Viagra was launched in 1998 as a treatment for erectile dysfunction, although one of the first epidemiologic studies on female sexual dysfunction was published only in 1999.[1] Women are less likely to discuss sex with a physician after the age of 50 years and less likely to be taking medications to improve sexual function.[2] Female sexual dysfunction, particularly for menopausal women, rarely has captured public attention as much as its counterpart, male sexual dysfunction. In June of 2018, however, a *New York Times* article revealed that the prices of vaginal estrogen therapy have doubled over 5 years, despite the availability of generic options.[3] In July of 2018, the Food and Drug Administration (FDA) released a statement cautioning women against vaginal rejuvenation devices. The FDA stated that these products have serious risks and do not have adequate evidence to support their use for "vaginal rejuvenation."[4] Vaginal rejuvenation has been adopted as an umbrella term and marketing tool with promises to reverse the expected changes seen in menopause, including vaginal laxity, dryness, dyspareunia, and improve sexual experiences. Plastic surgeons, dermatologists, and gynecologists offer "vaginal rejuvenation" procedures across the United States at a wide variety of sites that range from medical spas to academic tertiary-referral centers; some providers were not trained to recognize and manage symptoms of menopause. Although energy-based procedures are often performed for cosmetic indications, this therapy can be an effective treatment for women with genitourinary syndrome of menopause (GSM). These recent events should be a call to action to urge physicians to address the barriers that exist in the treatment of GSM because of limited clinical research, cost of treatment, and fear.

GSM is defined as the collection of signs and symptoms of the genitourinary tract from menopause; it is a term previously known as vulvovaginal atrophy.[5] During menopause, a hypoestrogenic state causes thinning of the vaginal epithelium. The atrophic vaginal tissue may cause vaginal burning, itching, bleeding, and dyspareunia caused by decreased lubrication, epithelial thickness, and elasticity. An estimated 10−40% of postmenopausal women experience ≥1 of the symptoms of GSM and the associated sexual dysfunction; however, the actual number of women who are symptomatic is likely higher due to under-reporting.[2,6]

The FDA has approved select hormonal and nonhormonal treatment for GSM that includes systemic estrogen, vaginal estrogen, estrogen receptor modulators ,and dehydroepiandrosterone. Systemic hormone therapy is an effective treatment for symptoms of vaginal atrophy. Studies have shown that estrogen can enhance sexual function by maintaining vaginal elasticity, lubrication, and tone while reducing the rates of dyspareunia.[7] A randomized controlled trial of 550 participants showed that a lower-dose estradiol vaginal cream reduced dyspareunia severity and vaginal pH when compared with placebo.[8] The American College of Obstetricians and Gynecologists recommends individualized treatment for women who experience GSM with the lowest effective dose of hormonal therapy for the shortest duration of time (level A evidence).[6] The challenge lies in determining the duration of treatment. Providers must evaluate the risk-benefit ratio. Systemic estrogen plus progesterone increases the risk of thromboembolic disease and breast and endometrial cancer. Alternatives to systemic estrogen therapy include vaginal estrogen.

Patients with a history of hormone-sensitive breast cancer are not candidates for estrogen products, such as systemic estrogen and vaginal estrogen creams, that increase serum estrogen levels. FDA-approved nonestrogenic treatment options are ospemifene and dehydroepiandrosterone. Ospemifene is a selective estrogen receptor modulator that acts as an estrogen agonist in the vagina and thus improves vaginal atrophy. It has a theoretic risk of endometrial hyperplasia and thromboembolic events, although more long-term data is needed. Vaginal prasterone, or dehydroepiandrosterone, increases baseline estrone through aromatization and thus relieves dyspareunia caused by vaginal atrophy for menopause. Prasterone has been studied in women with gynecologic cancers in a randomized controlled trial. The severity of the most bothersome symptom, either vaginal dryness or dyspareunia, was not significantly different from plain moisturizers after 12 weeks of treatment.[9]

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Energy-based therapy has emerged as an option for women with GSM who are not candidates for hormonal therapy. Colloquially, this treatment has been referred to as "vaginal laser." There are 2 types of energy-based devices: laser and radiofrequency. Laser therapy uses fractional CO2 laser energy or nonablative photothermal Erbium:YAG-laser to thicken the vaginal epithelium by improving vascularization, angiogenesis, and stimulating the production of collagen and elastic fiber production.[10] Radiofrequency-based therapy uses electromagnetic waves to stimulate collagen formation. Metaanalysis of available data shows that women who receive laser therapy seemed to have improved quality of life, sexual function, and satisfaction.[11,12] Although there were few adverse events, the studies were limited by the small sample size, general lack of control groups, and short-term follow up. Of all the published studies, the longest duration of follow up was 18 months (range, 11−18 months; median, 1 month). For radiofrequency devices, 1 multicountry randomized controlled trial demonstrated favorable improvements in vaginal laxity, sexual function, and sexual distress in patients who receive radiofrequency-based therapy.[13] There were only a few mild and moderate adverse events, although the study was not powered to detect a difference in adverse outcomes, and no follow-up evaluation was conducted past 6 months. The limitations on the published literature underscores the need to have well-designed, adequately powered studies with long-term follow up. Ideally, these studies are conducted in geographically and racially diverse populations to demonstrate that energy-based technology is both safe and effective in all women.

Energy-based therapy remains a fee-for-service procedure. The price for each treatment is at least $500 with the most conservative estimations. Treatment often consists of 3 sessions every 6 weeks. Vaginal estrogen is also cost-prohibitive. For example, Premarin, a conjugated estrogen cream, is not covered by the original Medicare plan. For a patient living in Ohio, the estimated monthly cost of 1 tube of conjugated estrogen cream is $426.92.[14] According to a website that tracks drug prices, the price of a tube of estradiol cream has doubled in price from $183.98 to $372.17 in the past 5 years.[15] Many private insurance companies categorize vaginal estrogen as tier-3 or -4 medications with high copays. Socioeconomically disadvantaged patients are not able to access these treatment options. The end result is a marginalized group of women without access to treatment for GSM. Numerous variables factor into the complicated algorithm in calculating the price of a drug. It is challenging to make vaginal estrogen drastically more affordable or energy-based therapy more accessible for patients with GSM. However, physicians should feel empowered to assist their patients with finding vouchers or determining which type of medication will yield the lowest copay. Physicians can help make the public aware of the financial barriers to obtaining treatment for GSM and that these barriers are affecting certain patients disproportionately in the United States. This public awareness can generate momentum to urge leaders in healthcare to address the high costs of the treatment for GSM at the policy and administrative level.

In addition to limited clinical research and high cost of treatment, the final barrier to seeking care for GSM is fear. On one hand, patients may hesitate to seek care for GSM for fear or misunderstandings. One recent example is the FDA communication on the concern for complications that are associated with transvaginal placement of surgical mesh for the repair for pelvic organ prolapse. Four years after the FDA statement was released, a survey of women in need of urogynecologic care demonstrated significant misunderstanding about vaginal mesh and a high level of aversion to prolapse surgery.[16] On the other hand, providers may not offer energy-based laser therapies for fear of litigation, as observed with the decrease in transvaginal mesh procedures after the FDA communication on transvaginal mesh.[17] The late-night law office commercials can continue to foster a fearmongering discourse on energy-based therapy, which perpetuates fear for patients and physicians alike. To overcome this barrier, physicians must be proactive in screening and educating women on GSM. For vaginal laser therapy, until the results of more research studies are available, energy-based therapy providers must be prepared to discuss treatment alternatives and possible adverse outcomes of energy-based therapies. For all treatment options for GSM, providers should understand and communicate the available research data and its limitations and report serious adverse events if they occur.

GSM can disrupt a woman's relationship with her partner and her psychosocial well-being and negatively affect her quality of life. There are barriers to the treatment of GSM. Clinical research, assistance to patients without insurance coverage of GSM treatment, and patient education are needed. Research should be prioritized to ensure that treatment options are safe and beneficial. The FDA statement should be the spark to revitalize scientifically sound research to alleviate the genitourinary symptoms of menopause safely. ■

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ABSTRACT

Revitalizing research in genitourinary syndrome of menopause

Genitourinary syndrome of menopause is defined as the collection of signs and symptoms of the genitourinary tract from menopause, previously known as vulvovaginal atrophy. The Food and Drug Administration has approved select hormonal and nonhormonal treatment for vaginal atrophy, including systemic estrogen, vaginal estrogen, estrogen receptor modulators, and dehydroepiandrosterone. These medications can increase the risk of thromboembolic disease and malignancy; furthermore, the cost of the medications have been increasing. Energy-based therapy such as the fractional CO2 laser energy or nonablative photothermal Erbium:YAG-laser has emerged as an alternative treatment option for genitourinary syndrome of menopause. However, in July of 2018, the Food and Drug Administration released a statement cautioning women against vaginal rejuvenation devices and highlighted the paucity of long-term clinical research in this field. This statement may result in patients' hesitation to seek care for genitourinary syndrome of menopause. These recent events should be a call to action to urge physicians to address the barriers that exist in the treatment of genitourinary syndrome of menopause because of limited clinical research, cost of treatment, and fear.

Key words: energy-based therapy, estrogen, genitourinary syndrome of menopause, genitourinary tract, hormonal therapy, menopause, vulvovaginal atrophy