Update in Female Hormonal Therapy: What the Urologist Should Know

NYU Case of the Month, December 2020

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A 64-year-old woman was referred for recurrent urinary tract infections (UTIs). She presented with progressive complaints of vaginal dryness, sensitivity, and pain at the introitus with associated dyspareunia despite the use of over-the-counter vaginal lubricants. She reported having 3 or 4 UTIs per year since entering menopause, often occurring postcoitally. She was finding wearing tight pants and bike riding increasingly difficult because of her introital discomfort. She was avoiding sexual activity with her husband because of pain and fear of UTIs.

The patient entered menopause at age 52 years and was never offered hormone replacement therapy (HRT). At the time of presentation, her hot flashes were minimal, and she denied any other bothersome menopausal symptoms. She reported some mild frequency during the day, which she perceived as urethral discomfort, but she denied significant urgency, urge incontinence, or stress incontinence. She denied vaginal bulge symptoms.

The patient was gravida 3 para 2 with two prior uncomplicated vaginal deliveries and no gynecological surgery. Her past medical history was notable for hyperlipidemia. She had no past surgical history. Her current medications were a statin, vitamin D3, and calcium. Her family history was notable for a sister with breast cancer in her 50s.

Evaluation

The patient's pelvic examination was notable for pale pink and dry introital tissues with normal labia majora. She had a normal-appearing urethral meatus with significant sensitivity to palpation of the introitus and urethra as well as diffuse sensitivity throughout the vaginal canal. There was loss of rugae vaginally with moderate to severe atrophy. There was no significant anterior, middle, or posterior compartment prolapse during Valsalva maneuvers.

Management

The patient was offered treatment with vaginal estrogen therapy for her genitourinary syndrome of menopause (GSM). She was initiated on a 2-week course of nightly estradiol cream followed by maintenance therapy twice weekly. She was educated on the potential benefits of vaginal hormone treatment, including improvements in dryness and vaginal epithelial elasticity, and lowering of vaginal pH to premenopausal levels. The clinical benefits of improved lubrication, reduced or eliminated dyspareunia, and restoration of the vaginal microbiome to reduce UTI risk were also explained. Most important, the difference between systemic HRT and vaginal estrogen therapy was discussed, including the risks and benefits.

The patient returned for a 3-month follow-up and reported significant improvements in her vaginal dryness, with resolution of her introital irritation and dyspareunia. She had not had a UTI in this time frame. She reported significant improvements in her quality of life and sexual function.

Comment

Effective care of female urology patients requires knowledge of hormonal effects on genitourinary anatomy and symptomatology and current recommendations for treating both menopausal symptoms in general and GSM. GSM often occurs 10 years after the onset of menopause. Both the lower urinary tract in women and the vaginal and introital tissues are rich in estrogen receptors. Estrogen depletion associated with natural menopause, contraceptive use (causes estrogen suppression through negative feedback on gonadal axis), and various estrogen receptor–modulating medications have direct implications on the female lower urinary tract and the vagina. It is not uncommon for women with a range of symptoms such as vaginal dryness, dyspareunia, recurrent UTIs, and lower urinary tract symptoms to present to a urologist for evaluation and management. It is imperative that urologists gain knowledge and offer treatment for this range of conditions associated with GSM.

Menopause

As life expectancy continues to increase, it is estimated that women may spend up to 40% of their lifespan in the postmenopausal years.[1] In addition, many women may enter premature menopause, which can be idiopathic, surgically induced, radiation therapy–induced, or medically induced, often related to a diagnosis of breast cancer with its resultant hormone-modulating therapies.[2] An astute history is necessary to uncover factors other than age and last menstrual period that may play a role in GSM and menopause symptoms. GSM can occur in younger women because of estrogen depletion associated with certain medications such as systemic contraceptives and selective estrogen receptor modulators (SERMs). Given the prevalence of UTIs in women of all ages, further studies of the effects of such medications on UTI risk are needed.

The indications for systemic HRT in postmenopausal women should be familiar to urologists treating women. These include bothersome vasomotor symptoms and osteoporosis risk reduction. Vasomotor symptoms include hot flashes, night sweats, myalgias, depression, irritability, and sleep disruptions. Systemic HRT is FDA approved for the treatment of vasomotor symptoms and has well-established efficacy.[2] In addition, women with osteoporosis at risk for fractures are also candidates for systemic HRT. Ideally, HRT should be initiated within the first 10 years following the onset of menopause as it has been shown to reduce cardiovascular risk during this time. In patients treated with systemic HRT, often GSM remains problematic and requires local vaginal estrogen therapy.

Estrogen depletion alters the vaginal epithelium, with distinct impairments in lubrication, elasticity, pH, and blood flow.[3] Pubic hair becomes scant, the vaginal epithelium becomes pale and dry, and the labia minora recede or fuse. Furthermore, the vaginal microbiome changes, with increasing pH following menopause and loss of lactobacillus predominance. These alterations allow a more hospitable environment for bacterial growth and increase the risk of UTI.[4] Estrogen may also play a role in urothelial health as well as in the autonomic and sensory innervation of the vagina.[5,6]

Recurrent UTIs are very common in postmenopausal women. The use of vaginal estrogen therapy is both safe and efficacious in lowering UTI risk. Vaginal estrogen increases the presence of lactobacillus in the vagina in postmenopausal women. The 2019 American Urological Association guideline for recurrent uncomplicated UTIs in women recommends that clinicians offer vaginal estrogen therapy to peri- and post-menopausal women with recurrent UTIs to reduce their risk.[7] In addition, the guideline recommends vaginal estrogen therapy for women already on systemic HRT without an increased risk of adverse events with the added vaginal estrogen use. Systemic HRT has not been shown to improve risk of recurrent UTIs. Several randomized controlled trials of various applications of vaginal estrogen therapy have shown a decreased incidence and time to recurrence of UTIs in hypoestrogenic women.[8-11] These studies did not identify any form of vaginal estrogen as clearly superior in reducing UTI risk or treating GSM symptoms. Thus, the choice of vaginal estrogen formulation should be according to patient preference.

Formulations of Vaginal Estrogen

There are currently 7 FDA-approved vaginal estrogen products for the treatment of GSM: creams (Estrace® estradiol, Allergan, Madison, NJ; Premarin® conjugated estrogens, Pfizer, New York, NY; generic estradiol cream 0.01%), tablets (Vagifem® estradiol, Novo Nordisk Inc., Plainsboro, NJ; Yuvafem® generic estradiol, Amneal Pharmaceuticals, Bridgewater, NJ), inserts (Imvexxy®

TABLE 1

Vaginal Estrogen Formulations

Product	Brand	Dosing
Conjugated estrogen cream	Premarin®	0.5 g nightly for 2 weeks, then 1-3 times weekly
Estradiol cream	Estrace® and generic estradiol	1.0 g nightly for 2 weeks, then 1-3 times weekly
Estradiol tablets	Vagifem® and Yuvafem®	10 mcg nightly for 2 weeks, then twice weekly
Estradiol inserts	Imvexxy®	4 mcg or 10 mcg nightly for 2 weeks, then twice weekly
Estradiol ring (local)	Estring®	7.5 mcg daily, with ring removal and replacement every 3 months

Estrace® estradiol, Allergan, Madison, NJ; Estring®, Pfizer, New York, NY; Imvexxy® estradiol capsule, TherapeuticsMD, Inc., Boca Raton, FL; Premarin® conjugated estrogens, Pfizer; Vagifem® estradiol, Novo Nordisk Inc., Plainsboro, NJ; Yuvafem® generic estradiol, Amneal Pharmaceuticals, Bridgewater, NJ.

estradiol capsule, TherapeuticsMD, Inc., Boca Raton, FL), and a ring (Estring®, Pfizer) (see Table 1). Shared decision making with the patient for choice of vaginal estrogen product is important and can improve compliance with therapy. It is generally recommended to initiate therapy with nightly application/use of the creams, tablets, or inserts for 2 weeks followed by application between 1 and 3 times weekly. The Estring is placed in the upper vagina and replaced every 3 months, thus requiring less maintenance. The Estring can be a better choice for management of recurrent UTIs for women who may have difficulty adhering to a twice-weekly treatment regimen or difficulty self-administering vaginal medication.

Vaginal estrogen is safe and effective (minimal risk of vaginal bleeding) in treating GSM, including vaginal dryness, dyspareunia, and vaginal burning. A systematic review of the safety and efficacy of vaginal estrogen for the treatment of GSM revealed no significant difference in efficacy between vaginal creams, tablets, and the estradiol ring compared with placebo.[12] Menopausal women using vaginal estrogen score higher on sexual health questionnaires and quality-of-life scales. In addition, as discussed earlier, vaginal estrogen is safe and efficacious in the treatment of recurrent UTIs.

Vaginal Estrogen in the Breast Cancer Patient

In women with a history of breast cancer, GSM is highly prevalent and can be caused by premature menopause due to chemotherapy, surgical menopause following oophorectomy, or anti-hormone therapy such as aromatase inhibitors. GSM is a common cause of noncompliance with aromatase inhibitor therapy. The use of vaginal estrogen results in serum estrogen levels only slightly higher than the normal menopausal range.[13,14] The lowest rates of systemic absorption are associated with the Estring and the tablets (Vagifem and Yuvafem). Several studies have highlighted the safety of vaginal estrogen in breast cancer patients, with no increased risk of breast cancer recurrence compared with non-users.[15] The decision to use vaginal estrogen therapy in this population can be made together with the oncologist.

Systemic Treatment for GSM

An FDA-approved alternative to vaginal estrogen for the treatment of GSM is ospemifene (Osphena®, Duchesnay USA, Rosemont, PA), which is a SERM. This medication has estrogen agonist effects in the vagina but no significant clinical effects on the breast or endometrial tissues. It is a once-daily oral tablet (60 mg). There is one retrospective study that revealed a significant reduction in UTI risk in women taking ospemifene over a 6-month period.[16] Larger trials are needed to assess the efficacy of SERMs in reducing recurrent UTI risk in this population.

Conclusion

Knowledge of menopause, whether natural, medically induced, or surgically induced, is an important aspect of the care of the female urologic patient. Estrogen depletion at any age has direct implications on genitourinary health and lower urinary tract function. It is often in the perimenopausal age group that

GSM and recurrent UTIs become prevalent, driving women to the urologist for evaluation and treatment. Urinary tract evaluation with imaging and cystoscopy is often of low yield and can be frustrating for both the patient and the clinician. Vaginal estrogen therapy is safe and extremely efficacious in treating these symptoms and lowering the risk of UTIs. It can be used safely in most women, even in those already on systemic HRT. Systemic HRT is useful in treating the vasomotor symptoms of menopause as well as osteoporosis but has limited efficacy in treating GSM or reducing UTI risk. A collaborative approach between urologist, gynecologist, and primary care practitioner will enhance the care of the female menopausal patient. ■

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