

CASE REPORT

Experience with ospemifene in patients with vulvar and vaginal atrophy and urinary incontinence: case studies

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Abstract

Pelvic floor muscle atrophy and collagen loss in connective tissue due to declining estrogen production in women as they age may underlie the increasing prevalence of urge and stress incontinence. Estrogen therapy can correct the deficiency of estrogen receptors in genitourinary structures after menopause, but estrogen is not suitable for all women. A series of retrospective studies showed that urinary symptoms improved in women with overactive bladder syndrome who were receiving ospemifene for vulvovaginal atrophy (VVA), a component of genitourinary syndrome of menopause. Two case studies presented in this article support the findings. The woman in case 1 was 76 years old, had a 4-year history of urinary incontinence (UI), and several risk factors for urinary symptoms. During 15 months' treatment with ospemifene for VVA, her urinary symptoms also improved as evidenced by a reduction

(from four/day to one/day) in sanitary pad requirements to manage leakage. The patient in case 2 had predominantly moderate-to-severe VVA and mild mixed UI. During 6 months' treatment with ospemifene, she experienced marked improvement in VVA symptoms, including normalization of vaginal pH and disappearance of dyspareunia, accompanied by a decrease in urinary symptoms, which allowed her to resume a normal exercise program.

Keywords: ospemifene, urinary tract symptoms, vulvar and vaginal atrophy.

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Introduction

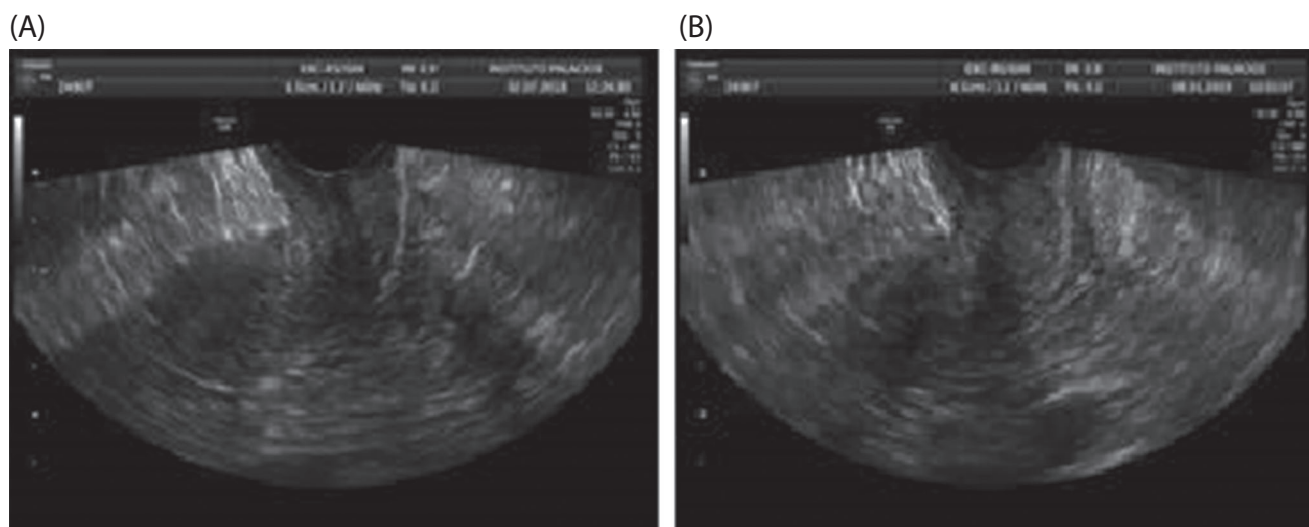
Genitourinary syndrome of menopause (GSM) is the term used to describe the signs and symptoms associated with a decline in ovarian estrogen secretion.¹ Estrogen receptors are present in the vagina, vulva, and pelvic floor muscles, urethra, bladder, and connective tissue surrounding the urethra.² GSM therefore encompasses, although is not limited to, genital symptoms (dryness, burning, irritation), sexual symptoms (lack of lubrication, dyspareunia, impaired function), and urinary symptoms (frequency, urgency, nocturia, incontinence, recurrent urinary tract infections).¹ Postmenopausal women may experience some or all of these symptoms to varying degrees of severity.

Pelvic floor muscle atrophy and the loss of collagen content in connective tissue due to estrogen deficiency are thought to underlie the increasing prevalence of urge and stress incontinence in women as they age.³ Additional risk factors for developing lower urinary tract symptoms in women include recurrent urinary tract infections, vaginal colonization by

Escherichia coli, diabetic peripheral neuropathy, hysterectomy or other interventions to the pelvic floor, obesity, chronic constipation, and other chronic diseases.⁴ Urinary symptoms can greatly impair quality of life, particularly by affecting sleep quality and general mental health.^{5,6}

Estrogen therapy can normalize the diminishing number of estrogen receptors in genitourinary structures after menopause,⁷ but not all women are candidates for estrogen therapy. Ospemifene is a selective estrogen receptor modulator with varying levels of activity in estrogen receptor-containing tissues.⁸ Ospemifene has an estrogen-like effect on the vaginal epithelium, an anti-estrogenic effect on breast tissue, and a neutral effect on endometrial tissue.⁹ The effectiveness and safety of ospemifene for treatment of vulvovaginal atrophy (VVA), a component of GSM, have been established in an extensive clinical trials program.^{10,11} The activity of ospemifene on urinary symptoms of GSM is also of interest. Two case studies examine outcomes in postmenopausal women with vaginal

Figure 1. Vaginal ultrasound (A) July 2018 and (B) January 2019. No change was observed in endometrial thickness during ospemifene treatment.



and urinary symptoms during treatment with ospemifene for VVA. As patient-specific information was deidentified to ensure anonymity, patient consent was not required.

Case 1

Case 1 describes a 76-year-old woman (weight 80 kg; body mass index [BMI] 32 kg/m²) with metabolic syndrome, hypertension, hypercholesterolemia, and hyperinsulinism. Current medications were atenolol, captopril, atorvastatin, and metformin. Five pregnancies had resulted in three terminations and two standard vaginal deliveries.

The patient entered menopause at 50 years and developed VVA symptoms at 54 years. Symptoms were managed with moisturizing creams and local estrogen, although irregularly as she found the products inconvenient to use. Two sessions of erbium vaginal laser treatment performed in November 2015 were unsuccessful.

The patient developed urinary symptoms in January 2015 and was diagnosed with mixed urinary incontinence (UI) by a urologist. In June 2015, she began treatment with mirabegron (a β_3 -adrenergic receptor agonist) but discontinued after a few months due to side effects (tachycardia, nausea, dry mouth). During this year, she experienced three separate urinary tract infections (UTIs) requiring antibiotic treatment. In October 2015, her incontinence severity index score was 6 (maximum 12).¹² She required four sanitary pads per day to manage urge incontinence and nocturia.

In September 2017, the patient presented vaginal dryness, dyspareunia, and vulvar itching. A physical examination revealed erythema of the vagina and introitus. Vaginal pH was 6. She continued to experience mixed UI with nocturia and

urgency. Urine culture was negative. As the patient refused local therapy, ospemifene was selected to treat her VVA.

In December 2017, after 3 months' treatment with ospemifene 60 mg/day the patient reported improvement in vaginal dryness, vulvar itching, and urinary control. Mammography performed at this time showed no sign of cancer (B1).

After 10 months' treatment with ospemifene, her vaginal pH was 4.5 (*versus* 6 at baseline). She reported further improvement in vaginal dryness and vulvar itching. Her requirement for sanitary pads was reduced to two per day.

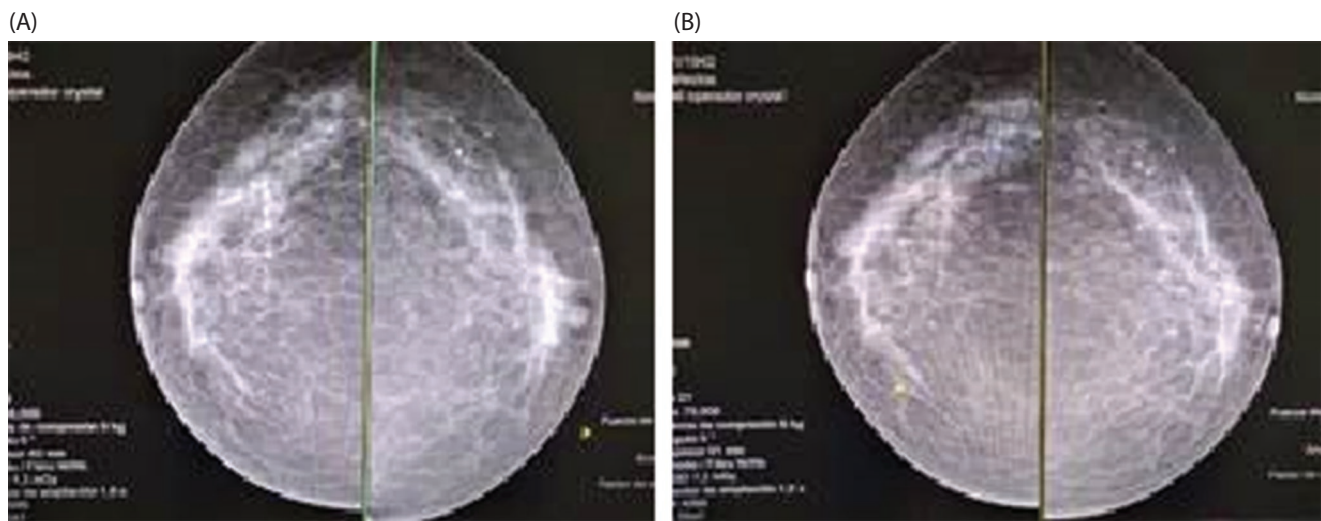
In January 2019, after 15 months' treatment with ospemifene, the patient's VVA was further improved and she expressed a desire to continue treatment. Vaginal ultrasounds performed in July 2018 and January 2019 indicated atrophy of the uterus and ovaries on both occasions and no change in endometrial thickness over this period (Figure 1). Her sanitary pad requirement to manage incontinence was one per day, and her incontinence severity index score was 2 (*versus* 6 at baseline). She experienced no UTIs during treatment with ospemifene. Mammography was normal (B1) with no changes since the previous assessment in December 2017 (Figure 2).

Case 2

Case 2 involves a 57-year-old Caucasian woman with a bodyweight of 65 kg and a BMI of 25.4 kg/m², with no history of gynecological surgery. Two pregnancies had resulted in one vaginal birth and one caesarian delivery. She entered menopause at 49 years. High blood pressure was controlled with diet and exercise and she was generally not constipated.

In September 2018, the patient presented to the Pelvic Floor Unit with complaints of urine leakage on exertion (coughing,

Figure 2. Mammography from (A) December 2017 and (B) January 2019. No change was observed in breast density during ospemifene treatment.



sneezing, laughing, and intense exercise), occasional difficulty in reaching the bathroom on time with a full bladder, and nocturia (3-4 times per night). She required up to three incontinence pads during the day and one at night to manage leakage.

During questioning, she complained of frequent severe vaginal burning and itching, and pain on sexual intercourse. She was using pharmacist-recommended lubricants for sexual activity. Antifungal creams and antihistamines (to be taken at night when symptoms were more severe) had been prescribed at her health center, although no vaginal swabs were taken. Vaginal cytology performed at the patient's primary care center a year prior to presentation showed an atrophic smear pattern.

The patient was examined on a full bladder in the lithotomy position. Physical examination revealed pale and atrophic external genitalia with loss of rugae, friable epithelium, atrophic labia minora, and lipodystrophy of the labia majora (Figure 3). She complained of a burning sensation and rated her dyspareunia a 6 on the pain 0-10 visual analogue scale (VAS). Her vaginal pH was 6.5. Speculoscopy indicated atrophy of the vaginal walls and cervix, with blood spotting after rubbing with the speculum. A Doppler-flow study of the vaginal and periurethral walls (as part of the protocol) showed decreased flow through the capillaries of the vaginal epithelium (lamina propria). The vaginal health index (VHI) score was 5 (maximum 25). Vaginal cytology showed a predominance of parabasal cells, consistent with VVA.

During the stress IU test, no leaks were observed following a Valsalva maneuver (intense fit of coughing). Urethral hypermotility (Q-tip test) indicated grade 1 rectocele. Muscle strength was Oxford scale 2/5. A UI test in the standing position (coughing fit) was ++. Ultrasound showed a total residual bladder volume of 200 mL (30 mL post-void), bladder wall thickness of 4 mm, and an anteverted uterus with a linear endometrium and atrophic-looking ovaries. Urine was negative

for leucocytes or red blood cells. She scored 10 (maximum 21) on the International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF).

Clinical evaluation suggested a diagnosis of GSM with predominance of moderate-to-severe VVA and a degree of (seemingly mild) mixed UI.

Based on this preliminary diagnosis, treatment was initiated with ospemifene 60 mg/day for 3 months, along with daily washing of the vulva using water and burdock gel, and continued use of lubricants for sexual intercourse. Incontinence pads were to be avoided but, if necessary, cotton pads were recommended.

After 1 month's treatment with ospemifene, the patient reported improvement in dyspareunia (VAS score of 2), itching/burning sensation, number of pads required (reduced to one during the day and none at night) and nocturia (reduced to one episode per night). On examination, clinical improvement was observed in the patient's vulvar and vaginal epithelium (Figure 4). Vaginal cytology indicated a decrease in parabasal cells.

After 60 days' treatment with ospemifene, there was improvement in vulvovaginal trophism and in the patient's self-assessed quality of life. Her vaginal pH was 4.0 (*versus* 6.5 at baseline). The VHI score had improved to 19 and the dyspareunia VAS score was ≤ 2 . The patient reported substantial improvement in vulvovaginal and UI symptoms and expressed satisfaction with treatment. Nocturia was absent and she no longer required sanitary pads. The ICIQ-SF score was 4 (*versus* 10 at baseline). The treatment plan was to continue with ospemifene 60 mg/day for 6 months, maintain hygienic and dietary measures (reduced fluid intake at night), and use vaginal moisturizers as required for sexual intercourse.

Six months later, vaginal cytology showed an increase in the number of superficial cells. Vaginal pH was 4.2, and her VHI

Figure 3. Pale epithelium with a cornered appearance in a postmenopausal woman with vulvovaginal atrophy.



Figure 4. Observable difference in epithelial color and hydration after 1 month's treatment with ospemifene.



score was 21 (*versus* 5 at baseline). The dyspareunia VAS score was 0. Doppler flow of vaginal and periurethral vessels showed relevant improvement (enhanced angiogenesis) and a decrease in the pulsatility index. The ICIQ-SF score was stable at 4 and incontinence pads were not required. The patient was able to undertake more exercise, although she avoided high-impact exercise. Overall, she expressed high satisfaction with treatment.

Clinical overview

Vaginal health is an integral part of a woman's social and sexual expression. As postmenopausal women may experience a wide range of genital, sexual, and urinary symptoms related to estrogen decline, effective management of genitourinary health can significantly enhance their quality of life.

Ospemifene is a selective modulator (agonist/antagonist) of estrogen receptors; it activates estrogenic pathways in

some tissues and blocks them in others.⁸ Improved trophism associated with stimulation of estrogen receptors along the urinary tract leads to improvement of urinary symptoms.

The efficacy of ospemifene in women with VVA and urinary symptoms has been assessed in a series of retrospective studies. In 46 postmenopausal women with VVA and overactive bladder syndrome (OAB), with or without UI, ospemifene 60 mg/day for 12 weeks significantly decreased the proportion of patients with detrusor overactivity (13 *versus* 39%; $p=0.04$); and significantly decreased the mean number of voids/24 hours (6.6 *versus* 9.6; $p<0.0001$), urgent micturition episodes/24 hours (1.4 *versus* 5.6; $p<0.0001$), nocturia episodes (1.1 *versus* 3.2; $p<0.0001$), and UI episodes/24 hours (0.33 *versus* 0.85; $p=0.003$) compared with baseline.¹³ In another study by this same group involving 39 postmenopausal women with GSM, 6 months' treatment with ospemifene 60 mg/day led to significant reductions from baseline in the mean number of positive urine cultures (0.25 *versus* 3.65; $p<0.0001$), mean number of urinary infection symptoms (dysuria, frequency, urgency; all $p<0.0001$), and total score on the pelvic pain and urinary/frequency patient symptom scale (12.14 *versus* 22.43; $p<0.0001$). Symptomatic relief was accompanied by a

significant improvement in quality of life using the Short Form (36) Health Survey (SF-36; 83.34 *versus* 52.86; $p < 0.0001$).¹⁴ A further retrospective analysis by these investigators involved 105 postmenopausal women with VVA and either OAB or urge UI who were treated with ospemifene 60 mg daily for 12 weeks. Along with significant improvement from baseline in the VHI score (19.76 *versus* 12.74; $p < 0.0001$), significant improvements were observed in urinary symptoms including mean number of voids (7.57 *versus* 9.12; $p < 0.0001$), urgent micturition events (1.09 *versus* 1.83; $p < 0.0001$), nocturia episodes (0.95 *versus* 1.47; $p < 0.0001$), and incontinence episodes (0.29 *versus* 0.45; $p = 0.015$), and in patients' subjective assessment of OAB symptoms (overactive bladder questionnaire scores) and quality of life using the SF-36 (both $p < 0.0001$). After treatment, the number of women reporting regular sexual activity increased from 57 patients (54.3%) at baseline to 90 patients (87.5%).¹⁵ These investigators also reported outcomes for 81 women with mixed UI (but no VVA) who underwent mid-urethral sling surgery (Trans-Obturator-Tape Sling Procedure), of whom 38 received ospemifene 60 mg/day for 12 weeks after surgery. Compared with surgery alone, ospemifene significantly improved urgency symptoms and quality of life.¹⁶

Consistent with the findings of these studies, the case reports demonstrate that ospemifene has a beneficial effect on urinary symptoms in postmenopausal women during treatment for VVA. The patient in case 1 had been experiencing VVA symptoms for more than 20 years and UI symptoms for 4 years. Her risk factors for the development of urinary symptoms included concomitant medical conditions and obesity.⁴ During 15 months' treatment with ospemifene, her incontinence improved and she had no UTIs despite a history of

recurrent infections. In case 2, the patient's mixed UI improved markedly during ospemifene treatment and she was able to resume a relatively normal exercise program. The extent of improvement in genitourinary health was reflected in her high level of satisfaction with ospemifene treatment. A unique feature of this case is the Doppler-flow study of the vaginal and periurethral tissues. This imaging procedure is part of the protocol at our clinic to validate the effect of treatments (e.g., photothermal, medicinal, regenerative) intended to improve vascularization and, therefore, regeneration and function in various parts of the body. In this patient, Doppler ultrasound was used to assess microvascularization of the lamina propria. Increased angiogenesis is indicative of improvement and adequate response to treatment.

Conclusion

Ospemifene is an effective treatment for VVA in postmenopausal women, and has the added benefit of improving urinary symptoms, if present. Several retrospective studies in women with VVA and urinary symptoms have documented symptomatic relief and an associated improvement in quality of life during ospemifene treatment. The featured case studies showed collateral improvement of urinary symptoms in women receiving ospemifene for VVA, markedly reducing their sanitary/incontinence pad requirements to manage leakage. Doppler ultrasound suggests that increased angiogenesis of the vaginal and periurethral tissues may underlie the benefits. Further research into the usefulness of local hormones or selective estrogen receptor modulators on urinary symptoms in menopausal women through randomized controlled trials is warranted.

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