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Audience: This activity was planned for obstetricians and gynecologists and women's health care providers.

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Learning Objectives

At the conclusion of this activity, the participant will be able to:

1. Understand the pathophysiology of dyspareunia due to vulvovaginal atrophy (VVA) of menopause.
2. Appreciate the underrecognition and undertreatment of dyspareunia due to VVA.
3. Discuss efficacy results of randomized placebo controlled trials of ospemifene.
4. Understand the adverse events associated with ospemifene.
5. Appreciate the safety data of ospemifine as well as other oral selective estrogen receptor modulators and estrogens.

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SUPPLEMENT TO
OBG MANAGEMENT
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Ospemifene, an oral SERM for dyspareunia of menopause: Is it being underutilized?

Vulvovaginal atrophy: an undertreated disorder

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Estrogen and androgen deficiency from menopause causes vulvovaginal and urogenital changes and a plethora of symptoms, most prominently dyspareunia. The nomenclature recently has been expanded to genitourinary syndrome of menopause (GSM).

Reproductive hormone deficiency leads to vulvar and vaginal thinning, loss of rugal folds, diminished elasticity, diminished vaginal glycogen, and decreased acidity (increased pH) of the vaginal secretions, thereby reducing the vagina's natural defenses.[1]

Few women with GSM report their symptoms to their health care professionals,[2] and conversely most health care professionals do not sufficiently query patients or inform them of their therapeutic options. Furthermore, class labelling of most available treatments has emphasized unsubstantiated risks[3] (ie, increased endometrial cancer, stroke, myocardial infarction [MI], deep vein thrombosis [DVT], pulmonary embolism [PE], probable dementia, and invasive breast cancer), thus resulting in only 7% of symptomatic women using any pharmacologic agent.[4]

CLINICAL DEVELOPMENT AND FDA APPROVAL

Until recently, all available vulvovaginal atrophy (VVA)/GSM treatments were systemic or local steroid hormones (estradiol, conjugated estrogens, dehydroepiandrosterone

Conflict of interest disclosure

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[DHEA]). Fear of estrogens from the "class labeling" and the nuisance of vaginal administration undermines utilization for some women.

Ospemifene, a third-generation selective estrogen receptor modulator (SERM) originally developed for osteoporosis, has estrogenic effects on bone, lipids, and vaginal tissue while remaining antiestrogenic or neutral in the breast and endometrium, respectively.[5] Multiple phase 3, placebo-controlled, clinical trials[6,7] resulted in US Food and Drug Administration (FDA) approval for moderate to severe dyspareunia from vulvovaginal atrophy of menopause. The American College of Obstetricians and Gynecologists (ACOG) endorsed ospemifene (Level A evidence) as first-line therapy for dyspareunia noting absent endometrial stimulation.[8] The most common adverse reactions in these ospemifene trials versus placebo were hot flashes and sweating (9.1% vs 3.2%), and muscle spasms (3.2% vs 0.9%), mostly leg cramps.[6,7] Only 1% of participants discontinued due to hot flashes, and there were no differences in rates of bleeding or breast tenderness.

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New important data on ospemifene

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ENDOMETRIAL SAFETY

There is a boxed warning in the ospemifene label that says, "in the uterus, ospemifene has estrogenic agonistic effects."[1] Despite the fact that ospemifene is not an estrogen (it's a SERM), it goes on to state, "there is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogen." This statement actually caused *The Medical Letter* to initially suggest that patients receiving ospemifene also should receive a progestational agent (something they later retracted).[2,3] In trying to understand why the labeling might possibly be worded in such a way, one has to review the actual data and understand the error the FDA made in response to that poorly named entity, "weakly proliferative endometrium." If one combines any proliferative endometrium (weakly + actively + disordered) in the clinical trial, 86.1 per 1000 in the ospemifene-treated patients (versus 13.3 per 1000 for those taking placebo) had any one of the proliferative types. The problem is that actively proliferating endometrial glands will have mitotic activity in virtually every nucleus of the gland as well as abundant glandular progression, whereas "weakly proliferative" is actually closer to inactive or atrophic endometrium with just an occasional mitotic figure in just a few of the nuclei of each gland.

Furthermore, at 1 year, the incidence of active proliferation with ospemifene was 1%.[4] Compare this finding with the Uterine Safety Study for raloxifene—both doses of that agent had an incidence of active proliferation at 1 year of 3%.[2] Furthermore, that study had an estrogen-only arm in which, at endpoint, the incidence of endometrial proliferation was 39% and hyperplasia, 23%![5] Thus, it is evident that, in the endometrium, ospemifene is much more like the SERM raloxifene than it is like estrogen.

OTHER EFFECTS OF OSPEMIFENE

Ospemifene was approved for use in the United States in 2013. Since that time a great deal of clinical and preclinical work has been brought to the attention of clinicians. As a SERM, based on class effects, one would expect it to be an estrogen antagonist in breast and estrogenic in bone. Additionally, improvement in overactive bladder (OAB) symptoms as well as prevention of recurrent lower urinary tract infections have been reported.

Previous data have demonstrated that ospemifene inhibits breast cancer cell growth in *in vitro* cultures as well as experimental animals[6] and inhibits proliferation of human breast tissue epithelial cells,[7] with such breast effects similar to tamoxifen and raloxifene. Thus, although one would not choose ospemifene as a primary treatment, or risk-reducing agent, for breast cancer, the *direction* of its activity in breast tissue is indisputable and is likely the reason that in the European Union, unlike in the United States, it is approved to treat dyspareunia from VVA of menopause in women *with* a prior history of breast cancer.

Furthermore, with increased aging, the morbidity and mortality associated with osteoporotic fractures becomes increasingly important. Ospemifene effectively reduced bone loss in ovariectomized rats, with activity comparable to estradiol and raloxifene.[8] Clinical data from three phase 1 or 2 clinical trials found ospemifene 60 mg/day to have a positive effect on biochemical markers for bone turnover in healthy postmenopausal women with significant improvements relative to placebo and effects comparable to raloxifene.[9] Actual fracture or bone mineral density (BMD) data in postmenopausal women are lacking but it is known that there is a good correlation between biochemical markers for bone turnover and occurrence of fracture.[10] Once again, women needing treatment for osteoporosis should not be treated with ospemifene but women using ospemifene for dyspareunia can expect positive activity on bone metabolism.

Shiavi et al[11] reported on 46 postmenopausal women with VVA and OAB syndrome who were evaluated at baseline and after 12 weeks of treatment with 60 mg/day of ospemifene. There was a statistically significant decrease in detrusor overactivity, mean number of voids, nocturia, and urinary incontinence episodes.

That same research group[12] studied 39 women (mean age, 59) with a history of recurrent urinary tract infections (UTIs). Twenty one of the 39 reported being sexually active. After treatment for 6 months with ospemifene 60 mg/day, only 2 of these women had a UTI confirmed by culture. Thus, the ospemifene behaved like estrogen, which has been shown to reduce recurrent UTIs.[13]

SUMMARY

Ospemifene is an oral SERM approved for treatment of moderate to severe dyspareunia from VVA due to menopause. The label currently states that, "[b]ecause ospemifene has not been tested in women with breast cancer, it should not be used in women with a history of breast cancer," although preclinical *in vitro*, experimental animal *in vivo*, and human *in vitro* testing all point to antagonistic activity in the breast, similar to other SERMs. The preclinical animal data and human markers of bone turnover all support the antiresorptive action of ospemifene on bones. In our opinion, one can safely surmise that the *direction* of activity of ospemifene in bone and breast is virtually indisputable. The *magnitude* of that activity is unstudied, however. Therefore, in trying to choose an agent to treat women with dyspareunia from VVA of menopause, determination of potential add-on benefit for that particular patient in either bone and/or breast is appropriate. There is also promising preliminary data that suggest a positive effect of ospemifene in patients with OAB or recurrent UTIs. Clearly, further study for both of these is necessary.

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