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EDITORIAL

Why the product labeling for low-dose vaginal estrogen should be changed

This commentary summarizes the activities of several clinicians and researchers to encourage modifications to the labeling of low-dose vaginal estrogen. Motivated by concerns of practicing clinicians that the boxed warning on the labels and package inserts for these products overstate potential risks and thus adversely affect patient care, leaders in the field are spearheading an effort to encourage consideration of alternative labeling, as discussed below. The members of the Working Group on Women's Health and Well-Being in Menopause have affiliations with a number of medical societies, including The North American Menopause Society, the American College of Obstetricians and Gynecologists, the Endocrine Society, the American Society for Reproductive Medicine, the International Society for the Study of Women's Sexual Health, and other professional organizations. We appreciated the opportunity to share our concerns, literature review, and proposal for alternative labeling with members of the US Food and Drug Administration (FDA) Division of Bone, Reproductive, and Urologic Products via a teleconference earlier this year. We encourage further consideration of our rationale and proposal by both the FDA and the pharmaceutical companies that own these products.

Overview of the proposal for label change

Vulvovaginal atrophy (VVA; also known as genitourinary syndrome of menopause) is a common and progressive condition that adversely affects the health and quality of life of many postmenopausal women.[1] Symptomatic VVA is a growing problem because of the confluence of several factors, including the burgeoning population of older postmenopausal women and the declining use of systemic menopausal hormone therapy since the initial report of the Women's Health Initiative (WHI).[2,3] Our view is that an additional factor—the boxed warning on the package label for low-dose vaginal estrogen—discourages clinicians from prescribing the product and women from taking it even after purchase. The boxed warning, which reflects estrogen class labeling, states "WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER, and PROBABLE DEMENTIA" and is based on extrapolations of data from clinical trials of systemic hormone therapy such as the WHI, which involved substantially higher levels of exposure. We believe that the boxed warning is not evidence-based and harms women by discouraging the use of a highly effective local treatment of a common condition with medical risks and adverse effects on quality of life. We contend that the boxed warning for low-dose vaginal estrogen products is unjustified based on several lines of reasoning described below, including the following: (a) the dramatic differences in blood hormone levels achieved by low-dose vaginal estrogen (eg, Vagifem tablets [estradiol 10 μg], Estring [releasing estradiol 7.5 μg/d], or comparable low-dose vaginal estrogen cream formulations) versus conventional systemic estrogen therapy; (b) absence of randomized trial evidence or consistent observational evidence linking low-dose vaginal estrogen to cancer, cardiovascular disease, dementia, or any of the other conditions highlighted in the boxed warning; and (c) absence of evidence that changes in blood hormone levels—of the small magnitude achieved with these products—increase risk of these conditions. As a result of the boxed warning, a large number of older women with symptomatic VVA and genitourinary symptoms are being undertreated and do not receive the substantial benefits that these medications could provide.

We believe that women would be better served by a modified label that more closely reflects the safety profile of low-dose vaginal estrogen and would actually enhance safety by emphasizing the key information that women and clinicians need to know about the products. Our proposal is to state in the package labeling, in regular text and font, that estrogen and estrogen-progestin given systemically, in higher doses, have been linked to the health conditions currently noted in the boxed warning, but that the relevance to low-dose vaginal estrogen remains unknown, given minimal increase in serum estrogen levels with low-dose vaginal estrogen products. We recommend bolding the phrase "**report any vaginal bleeding or spotting right away while using _____.**" We also recommend adding in bold "**Women with a history of cancer of the breast or uterus (womb), or other hormone-sensitive cancers, are encouraged to consult their oncologist before using this product.**" We believe that these label changes will, paradoxically, enhance patient safety because the relevant information and cautions will stand out and be highly visible, rather than being obscured by extraneous and alarming bolded and boxed statements that lack proven relevance to the product. Thus, the proposed label change would serve the purpose of informing women of previous research and addressing safety issues while stating that the relevance of past research findings on

systemic hormone therapy to low-dose vaginal estrogen is unknown. The specific suggested wording of our proposed label change is provided at the end of this commentary.

Prevalence of VVA (Genitourinary Syndrome of Menopause) and the impact on women's health and quality of life

VVA symptoms, such as vaginal dryness, lack of lubrication, pain or spotting with intercourse, and burning with urination, affect 20% to 45% of midlife and older women.[4,5] In contrast to vasomotor symptoms, which tend to improve across time irrespective of treatment, VVA is usually progressive and unlikely to resolve without intervention. VVA symptoms can have a significantly adverse effect on a woman's sexual health and quality of life. In an online survey conducted in six countries, an estimated 45% of postmenopausal women reported experiencing vaginal symptoms.[6] The largest survey of US women, REVIVE (Real Women's Views of Treatment Options for Menopausal Vaginal Changes), included 3,046 women with VVA symptoms.[7] In this study, 85% of women with partners reported "some loss of intimacy," 59% indicated that VVA symptoms detracted from enjoyment of sex, 47% of women with partners reported that VVA interfered with their relationship, and 27% reported that VVA had a negative effect on their general enjoyment of life. Similar results were found in the VIVA (Vaginal Health: Insights, Views & Attitudes) survey.[6] Aging and diminished estrogen levels are major contributors to VVA, atrophic vaginitis, and recurrent urinary tract infections.[1,8]

Efficacy of treatment and impact of product labeling/boxed warning

As emphasized in the 2013 North American Menopause Society VVA position statement,[1] the primary goal of treating symptomatic VVA is to alleviate symptoms. First-line therapies include nonhormonal lubricants and long-acting vaginal moisturizers, as well as low-dose vaginal estrogen in those remaining symptomatic, assuming no contraindications.[1] For women with moderate to severe dyspareunia related to VVA who prefer nonvaginal therapy, transdermal or oral systemic hormone therapy and the oral estrogen agonist/antagonist ospemifene are options. Women with significant vasomotor symptoms may choose systemic (oral or transdermal) hormone therapy, which will also treat VVA if present. Low-dose vaginal estrogen, however, is the preferred mode of treatment when vaginal symptoms are the only complaint.[1] Low-dose vaginal estrogen products can provide sufficient local estrogen effect to relieve symptoms, decrease vaginal pH, and increase maturation of the vaginal and urethral epithelia, with minimal systemic absorption.[1,9-11] These products have been shown to be at least as effective as systemic oral estrogen therapy in relieving VVA symptoms, with 80% to 90% of women reporting a favorable response compared with 75% of women using oral estrogen.[9,10] A 2006 Cochrane review of 19 efficacy trials reported that all local estrogen products tested had similar efficacy in alleviating symptoms.[11] Therapeutic benefit of vaginal estrogen has also been observed with conditions other than VVA, such as recurrent urinary tract infections[12,13] and overactive bladder.[14,15] Although systemic hormone therapy has been associated with an increase in stress incontinence,[8,16] the low-dose estradiol ring has been approved for the treatment of dysuria and urinary urgency. VVA has been linked to considerable impairment of quality of life; nonetheless, clinical studies demonstrate that a substantial proportion of women are undertreated.[1]

Moreover, in our collective clinical experience and in those of the professional colleagues we represent, among women who seek treatment and/or receive prescriptions for low-dose vaginal estrogen, a substantial proportion ultimately choose not to use the product or discontinue use because of concerns and alarm about the boxed warning in the package insert. Testimonials by working group members during the teleconference with the FDA highlighted the adverse impact of VVA on women's lives, including their physical, sexual, and emotional health; clinical experience with the marked efficacy of treatment; and the deleterious effect of the boxed warning on women's health by discouraging clinician colleagues from prescribing, and women from using, these highly effective low-dose vaginal estrogen products. Specifically, several clinicians reported that many women who have purchased the low-dose vaginal estrogen products, often at significant financial cost, ended up not using them after reading the boxed warning.

Comparative blood concentrations of estrogens associated with low-dose vaginal estrogen versus systemic estrogens versus no treatment

"Low-dose" vaginal estrogen refers to products such as Estring (vaginal ring releasing estradiol 7.5 μg/d), Vagifem (10-μg tablets two times a week), and comparable low doses of vaginal creams (eg, Estrace [estradiol]) or Premarin [conjugated estrogens]).[17] These products are considered to have a more favorable risk profile than commonly used doses of systemic estrogen therapy because they lead to small, if any, increases in serum estrogen concentrations.[1,18-23] When low-dose vaginal estrogen is used as directed, reported serum estrogen levels fall generally within the average postmenopausal range (below 20 pg/mL).[1,18] Reported estradiol levels ranged from 5 to 10 pg/mL with use of the vaginal ring (releasing estradiol approximately 7.5 μg/d)[19-21] and from 3 to 11 pg/mL with use of the 10-μg vaginal tablet.[22,23] In contrast, use of 0.2 mg (200 μg) of estradiol cream led to serum levels of 80 pg/mL.[24] However, a small pilot study showed that using one twentieth of the dose of estradiol cream (a 10-μg dose) was associated with full efficacy in genitourinary tissues, whereas circulating estradiol levels measured using a highly sensitive assay remained within the postmenopausal range of 3 to 10 pg/mL.[22] Conjugated estrogens cream at a dose of 0.3 mg produced no change in serum estradiol levels,[25] but conjugated estrogens products contain multiple estrogenic compounds, and plasma estradiol levels may not fully reflect estrogenic activity. Among women treated with 0.3 mg of vaginal conjugated equine estrogens three times a week for 6 months, the serum estrone levels were 61.6 pg/mL compared with 55.6 pg/mL at baseline.[25]

It is instructive to compare the serum estrogen concentrations of women on low-dose vaginal estrogen with the endogenous estrogen levels in untreated premenopausal and postmenopausal women, as well as with the hormone concentrations of postmenopausal women treated with systemic estrogen. Among untreated women in the Melbourne Women's Midlife Health Project, the average serum estradiol levels were 78 pg/mL (range, 39-158 pg/mL) 4 years before the final menstrual period, 31 pg/mL (range, 23-42 pg/mL) at the time of the final menstrual period, and 10 pg/mL (range, 8-11 pg/mL) 2 years after menopause.[26] Among postmenopausal women treated with systemic estrogen, serum estrogen concentrations increase markedly. For example, in a 12-week trial of oral estradiol 1 mg/day, the average estradiol level on treatment was 164 pg/mL (range, 86-243 pg/mL), representing a 9.5-fold increase from baseline menopausal levels.[27] Among women in the Kronos Early Estrogen Prevention Study (average age, 53 y; all within 3 y of their final menstrual period), estradiol levels after treatment with a transdermal patch containing estradiol 50 μg/day were more than three times higher than baseline levels; among women treated with oral conjugated estrogens 0.45 mg/day, estrone levels were more than twice as high as baseline levels.[28] Thus, treatment with systemic estrogen leads to substantial increases in blood hormone levels compared with baseline, whereas serum hormone levels among women treated with low-dose vaginal estrogen remain within the reference postmenopausal range.

Low-dose vaginal estrogen and the endometrium

Endometrial tissue response is an extremely sensitive bioassay for estrogenic action and reflects the integration of serum estrogen levels with duration of estrogenic exposure. Three different low-dose vaginal estrogen therapies have been evaluated, and their endometrial effects have been assessed via either transvaginal ultrasound–measured endometrial thickness or endometrial biopsy. The largest trial to date is a randomized double-blind controlled study of 1,612 postmenopausal women in which vaginal estradiol tablets were administered at a dose of 25 μg/day for 2 weeks, followed by a dose of 25 μg two times a week for 12 months. This study demonstrated no increases in serum estradiol levels at 4 and 12 months compared with baseline levels: (mean [SD], 15.7 [2.3] pg/mL {baseline} vs 15.5 [2.5] pg/mL {12 mo}).[29] Vaginal ultrasound–determined endometrial thickness remained essentially unchanged after 12 months of therapy (mean [SD], 3.1 [0.4] mm {baseline} vs 2.9 [0.5] mm {12 mo}).[29] There was no change in uterine volume or enlargement of preexisting myomas across 12 months. In a separate study of a vaginal estradiol tablet 10 μg/day, endometrial biopsies were performed in 297 women after 12 months of treatment; 183 women had endometrial tissue that was atrophic or inactive, whereas 111 women had no tissue or had insufficient tissue for diagnosis. There was one case of complex hyperplasia without atypia.[30] Similar findings have been reported in a trial of estradiol vaginal cream given at a dose of 10 μg/day for 3 weeks then 10 μg two times a week. Endometrial thickness remained stable at less than 5 mm during the 12-week treatment.[22] Moreover, in a randomized study of a low-dose vaginal estradiol ring delivering estradiol 7.5 μg/day, estradiol levels increased less than 1 pg/mL above baseline ($P = 0.59$) and endometrial lining thickness at 12 months was similar to baseline, with a mean (SD) change of −0.14 (0.53) mm ($P = 0.54$).[21]

If low-dose vaginal estrogens have either regional or systemic effects beyond their local action, one would expect to observe endometrial proliferation, as determined by either transvaginal ultrasound–measured endometrial thickness or endometrial biopsy. Collectively, these studies demonstrate that low-dose vaginal estrogen therapy, including assessments of three different estradiol preparations at 12 months of evaluation, does not seem to have significant endometrial impact beyond the local vaginal estrogenic effects. Higher dosing, long-term use, and use by women with comorbidities may carry higher risks.

Low-dose vaginal estrogen and breast-related outcomes

Assessment of the potential biologic effects of low-dose vaginal estrogen on breast tissue can be approached by considering three separate endpoints: mammographic breast density, breast cancer, and breast pain. Although we could find no studies examining the endpoint of breast density in relation to low-dose vaginal estrogens, a 2-year placebo-controlled randomized trial examining a transdermal preparation delivering estradiol 14 μg/day showed no difference in breast density at 2 years compared with placebo.[31] Regarding breast cancer, a large-scale observational study of Finnish women, including 18,314 users of vaginal estrogen, indicated no increase in the risk of breast cancer associated with vaginal estrogen use.[32] Moreover, no increased risk would be expected based on the results of the unopposed estrogen arm of the WHI.[33,34] With 7.2 years of oral conjugated equine estrogens (0.625 mg/d), the hazard ratios (95% CIs) were 0.79 (0.61-1.02) for the intervention phase and 0.79 (0.65-0.97) for the 13-year cumulative follow-up phase,[34] suggesting no increased risk of breast cancer with unopposed conjugated equine estrogens across this time frame. Evidence that this finding applies to other formulations of estrogen remains inconclusive. However, one would not expect that an even lower dose of unopposed estrogen given vaginally, and with minimal systemic absorption, would have an adverse effect on breast cancer risk. Regarding breast pain, this symptom has been reported with intermediate doses of vaginal estrogen. However, in a study of low-dose vaginal estrogen (Estring), only 1 of 108 women complained of breast pain while the ring was in place.[13] Reports on the use of 10 μg of low-dose vaginal estrogen make no mention of breast pain.[35] Based on these collective findings, it is improbable that these products exert important biologic effects on the breast.

Special considerations for women with a history of breast cancer

Despite the reassuring evidence mentioned previously, women with a history of breast cancer warrant special consideration. The clinical relevance of even very small increases in circulating estrogen levels with low-dose vaginal estrogen products in women with breast cancer remains unclear. Aromatase inhibitors (AIs), which block 95% of estrogen synthesis,

are typically associated with circulating estradiol levels lower than 1 pg/mL.[36] Thus, as would be expected, vaginal administration of low-dose estrogen will lead to higher-than-baseline serum estradiol levels in women receiving AI therapy.[37] As any rise above baseline serum estradiol levels may affect AI efficacy, the use of any hormone therapy product in women with breast cancer warrants special caution, especially in view of sparse research on the safety of these products in breast cancer patients. In one case-control study, women receiving endocrine treatment (such as tamoxifen or AIs) for breast cancer did not have higher rates of recurrence with local estrogen use compared with nonuse,[38] but vaginal estrogen treatment by ring or tablet did increase circulating estrogen levels, at least initially.[39] For systemic hormone therapy, inconsistent results for breast cancer recurrence have been found in randomized trials and observational studies.[40] Patients with breast cancer who have symptomatic VVA and do not respond to nonhormonal therapies are encouraged to discuss the risks and benefits of low-dose vaginal estrogen therapy with their oncologist. Oral ospemifene has not been tested in women at high risk for breast cancer or with a history of breast cancer; thus, no recommendations can be given for its use in this population.

Low-dose vaginal estrogen and cardiovascular, cerebrovascular, cognitive, and other outcomes

Compared with oral systemic estrogen and estrogen-progestin, as studied in the WHI and forming the basis for the boxed warning, low-dose vaginal estrogen has lower systemic absorption and, similar to transdermal estradiol formulations, avoids "first-pass" liver metabolism and effects on hepatic enzymes.[1,41,42] Lower-dose transdermal estradiol has been shown to have less risk of venous thromboembolism (VTE)[42] and possibly stroke[43]; thus, the significantly lower systemic absorption of low-dose vaginal estrogen makes it even less likely to increase risk of VTE and other cardiovascular events than oral systemic estrogen.[42,43] The increased risks of coronary heart disease, stroke, and VTE, which have been reported with oral systemic hormone therapy,[1,42,43] have not been reported with low-dose vaginal estrogen therapy.[1] Moreover, long-term follow-up of women in the WHI trial of unopposed estrogen[44] showed no increased risk of coronary events or all-cause mortality, indicating that low-dose vaginal estrogen is unlikely to affect these outcomes. The 2006 Cochrane review of VVA did not find evidence of an increased risk of VTE with low-dose estrogen,[11] but data for women at high risk for these events are lacking. An increase in probable dementia was observed in the WHI among women aged 65 years or older who were treated with oral systemic estrogen-progestin therapy (equivocal results for systemic oral estrogen alone); there is no evidence that the minimal absorption of low-dose vaginal estrogen preparations would have the potential to affect dementia risk among women in any age group or would have biologic plausibility to do so.

Effects of endogenous estrogen concentrations within the reference postmenopausal range

The main source of endogenous estrogen in postmenopausal women is the peripheral conversion of steroid precursors via the aromatase enzyme located primarily in peripheral adipose and muscle tissues.[45] Obesity itself is a risk factor for breast and endometrial cancers and cardiometabolic disorders.[45,46] Pathways implicated in the association of obesity with these disorders include insulin resistance, hyperinsulinemia, growth factors, and inflammation,[45,46] in addition to elevation of sex steroid hormones. Central adiposity is further associated with dyslipidemia, type 2 diabetes, and higher levels of inflammatory cytokines, which likely also contribute to cardiovascular disease. Thus, observational studies linking endogenous estrogen concentrations within the postmenopausal range to cardiometabolic disorders or cancer have potential for confounding by the abovementioned factors and are not viewed as a concern for the use of low-dose vaginal estrogen products.

Conclusions and proposed label changes

Based on these data, we submit that revisiting the labeling of low-dose vaginal estrogen to include the changes below would enhance women's safety and improve their health and well-being. As discussed previously, the boxed warning on these products is based on extrapolations of data from trials of systemic estrogen or combination estrogen-progestin hormone therapy, which involve substantially higher levels of exposure. It is noteworthy that there are dramatic differences in estrogen blood levels achieved with low-dose vaginal estrogen therapies compared with systemic estrogen administration. Our view is that the highly visible boxed warning on low-dose vaginal estrogen is unsubstantiated and not evidence-based and is harming women by discouraging the use of effective treatments that would provide substantial benefits to postmenopausal women with symptomatic VVA. We believe that women would be better served by a modified label that more closely reflects the safety profile of low-dose vaginal estrogen and could ultimately enhance safety by emphasizing the key information that women and clinicians need to know about the products.

Our proposal, as noted above, is to mention in the product labeling, in regular text and font, that estrogen and estrogen-progestin given systemically, in higher doses, have been linked to the health conditions currently included in the boxed warning, but that the relevance to low-dose vaginal estrogen remains unknown, given minimal increase in serum estrogen levels with low-dose vaginal estrogen products. We recommend bolding the phrase "**report any vaginal bleeding or spotting right away while using _____**." We also recommend adding in bold "**Women with a history of cancer of the breast or uterus (womb), or other hormone-sensitive cancers, are encouraged to consult their oncologist before using this product**." This label change would serve the purpose of informing women of previous research and addressing safety issues while stating that the relevance of past research

findings on systemic hormone therapy to the current vaginal products is unknown.

Regarding other statements in the boxed warning, we propose the following (all would be listed in regular and unbolded font, except as noted; none of the text would be boxed):

What is the most important information I should know about _____?

- Instead of: Using estrogen alone may increase your chance of getting cancer of the uterus (womb). Report any unusual vaginal bleeding right away while you are using _____. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find the cause.

  Change to: Using higher doses of estrogen alone is associated with an increased chance of getting cancer of the uterus (womb), but the relevance of these findings to low-dose vaginal estrogen is unknown. Nonetheless, **report any vaginal bleeding or spotting right away while you are using _____**. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any vaginal bleeding or spotting to find the cause.

- Include: Do not use estrogen alone to prevent heart disease, heart attacks, strokes, or dementia (decline of brain function).

  Comment: Include this in regular unbolded font, not boxed.

- Instead of: Using estrogen alone may increase your chances of getting strokes or blood clots.

  Change to: Using higher doses of estrogen may increase your chances of getting strokes or blood clots, but the relevance of these findings to low-dose vaginal estrogen, which leads to minimal increase in blood estrogen levels, is unknown.

- Instead of: Using estrogen alone may increase your chance of getting dementia, based on a study of women aged 65 years or older.

  Change to: Using higher doses of estrogen may increase your chance of getting dementia, based on a study of women aged 65 years or older, but the relevance of these findings to low-dose vaginal estrogen, which leads to minimal increase in blood estrogen levels, is unknown.

- Instead of: Using estrogens with progestins may increase your chance of getting breast cancer.

  Change to: Using estrogens with progestins may increase your chance of getting breast cancer, but the relevance of these findings to low-dose vaginal estrogen without progestins is unknown.

Add in bold: **Women with a history of cancer of the breast or uterus (womb), or other hormone-sensitive cancers, are encouraged to consult their oncologist before using this product.**

Include the statement below in regular unbolded font:

- You and your healthcare provider should talk regularly about whether you still need treatment with _____.

We believe that these label modifications will improve women's health.

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