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NAMS COMMENTARY

Workshop on normal reference ranges for estradiol in postmenopausal women: commentary from The North American Menopause Society on low-dose vaginal estrogen therapy labeling

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A workshop on the measurement of estradiol levels in postmenopausal women was held from September 23 to 24, 2019, in Chicago, Illinois. The workshop was organized by The North American Menopause Society (NAMS) to provide a roadmap for the establishment of estradiol reference ranges in postmenopausal women. This workshop was part of NAMS' ongoing efforts to educate women, providers, and insurers about the safety of vaginal estrogen when systemic absorption and circulating levels do not exceed the postmenopausal normal reference range and is part of the efforts of NAMS and the Working Group on Women's Health and Well-Being in Menopause to address the need for more appropriate and evidence-based labeling of low-dose vaginal estrogen.[1]

A detailed review of the literature by workshop participants indicated that there were no established and universally agreed on reference ranges for postmenopausal estradiol levels and found considerable variance in the upper limit cited, ranging from 5 to 30 pg/mL across various studies presented during the workshop. Furthermore, it was clear that the reported results depended on the sensitivity and specificity of the different assays used. State-of-the-art liquid chromatography with tandem mass spectrometry assays provide improved technology to allow determination of potentially very low postmenopausal estradiol and estrone reference ranges. During the workshop discussion, the term *normal range* was thought to be an inaccurate descriptor because some normal persons would fall out of this range; instead, the term *reference range* was preferred.

POSTMENOPAUSAL REFERENCE RANGE FOR ESTRADIOL

Databases reviewed during the workshop, detailed in the workshop report, and speaker summaries appearing in this issue,[2] suggest that the normal postmenopausal estradiol range is much lower than the currently used normal postmenopausal estradiol levels. Using more accurate measurements, the normal postmenopausal estradiol concentration is likely to be less than 10 pg/mL, leading to a postmenopausal reference range for estradiol from below the limit of detection for liquid chromatography with tandem mass spectrometry assays up to 10 pg/mL. Use of harmonized sensitive assays of systemic concentrations of estradiol and estrone will allow researchers to understand and evaluate the associations of exogenous and endogenous estrogen with important health outcomes in postmenopausal women, including effects on bone, breast, cardiovascular system, brain, and genitourinary system.

SAFETY OF LOW-DOSE VAGINAL THERAPIES

The genitourinary syndrome of menopause (GSM) is chronic and progressive. It affects relationships, quality of life, and enjoyment of sexual activities and confers medical risks, including higher rates of urinary tract and vaginal infections.[3]

NAMS considers the issue of the safety of low-dose vaginal hormone therapies (HTs) to be critically important because these therapies are highly effective for GSM.[4] NAMS members indicate that many women have reported being frightened to use safe-and-effective methods to treat GSM because of fear that vaginal estradiol is unsafe, based on the ''black box'' warning required by the Food and Drug Administration (FDA). They are often confused about the difference between

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systemic HT risks and the distinctly different risks associated with low-dose vaginal therapies.

In NAMS 2017 Position Statement on HT,[5] NAMS stressed the differences in health risks seen between systemic HT (estrogen alone, estrogen with progestogens) and local low-dose vaginal therapies. In addition to the lower risks with the latter, some forms of systemic HT may pose less risk than others. For example, lower risks have been shown with systemic HT characterized by lower doses, estrogen-alone regimens, estrogen combined with progesterone compared with synthetic progestins or bazedoxifene, and with transdermal versus oral routes of delivery (especially concerning risks of venous thromboembolism and stroke).[5-10] Low-dose vaginal HT is felt to have minimal risks because of limited systemic absorption.[11-13]

Observational studies, including the Women's Health Initiative (WHI) prospective observational cohort study with median follow-up of 7.2 years, found no increase in cardiovascular disease, pulmonary embolism, venous thrombosis or stroke, or cancer.[14] Similarly, the Nurses' Health Study, with more than 18 years of follow-up for women using low-dose vaginal estrogen therapy,[15] did not find significantly increased risks of breast cancer or endometrial neoplasia nor increased risks of cardiovascular disease, total cancer, or all-cause mortality. A comprehensive meta-analysis of prospective observational studies found no association of these vaginal treatments with breast cancer.[16] These studies support NAMS conclusion that low-dose vaginal estrogens have primarily local vaginal effects without significant systemic effects, setting them apart from systemic HT.[1,17,18]

Concern has been raised for postmenopausal women on aromatase inhibitors, in whom serum estrogen levels are markedly suppressed and even small amounts of systemic absorption could potentially counteract the beneficial effects of aromatase inhibitors on reducing breast cancer risk.[19] A 2019 meta-analysis of eight studies, however, found no increase in estradiol levels after 8 weeks of local hormone treatment in women on aromatase inhibitors and is reassuring that significant systemic absorption of estradiol does not occur.[20]

Additional data from clinical trials were presented during the workshop on systemic estradiol and estrone concentrations when low- and ultralow-dose vaginal HTs were tested. Dosed appropriately, these vaginal therapies could be used safely by postmenopausal women when serum estrogen concentrations are kept within the newly determined postmenopausal reference range.[12,13] During the workshop, data were reviewed on the first-pass effect of vaginal estradiol into the uterus via local circulatory pathways with the suggestion that estradiol present in the upper one-third of the vagina may pass directly via venous and lymphatic channels to the uterus.[21] This concept, if proven, may have practical implications regarding endometrial safety depending on the location of vaginal estradiol administration.

CLASS LABELING FOR ESTROGEN INCLUDES LOW-DOSE VAGINAL ESTROGEN

Class labeling for estrogen therapy was instituted after the initial results from the WHI estrogen plus progestin trial. In 2002, FDA first issued the boxed warning, which included the cardiovascular, breast cancer, and dementia risks associated with oral conjugated equine estrogens and medroxyprogesterone acetate use seen in the WHI. The expanded warning has since been applied to all estrogen-containing postmenopausal therapies, regardless of dose, route of administration, or whether given alone or in combination with progestogens or bazedoxifene. The boxed warning requires a listing of the risks seen with oral standard-dose combination conjugated equine estrogens plus medroxyprogesterone acetate in the WHI trials, including cardiovascular disease, breast cancer, venous thrombosis, stroke, and dementia.[22-24]

NAMS believes that the black box warning for low-dose vaginal estrogen, defined as dosed appropriately to maintain serum concentrations within the new postmenopausal reference range, may cause unnecessary fear and deters women from using much-needed treatment.[1]

MOVING FORWARD

As proposed in the workshop, if the postmenopause reference range for estradiol is determined to be less than 10 pg/mL and if estrogen levels from low-dose vaginal estrogen do not exceed this reference range, the risks listed in the boxed warning of breast cancer, coronary artery disease, stroke, deep venous thrombosis, pulmonary embolism, and probable dementia as seen in the systemic hormone WHI trials would be ''rare and unlikely.'' Thus, we suggest FDA reconsider their denial of the 2016 Citizen's Petition to modify the labeling and remove the boxed warning on low-dose vaginal estrogen.[25]

NAMS RECOMMENDATIONS AFTER THE WORKSHOP ON NORMAL REFERENCE RANGES FOR ESTRADIOL IN POSTMENOPAUSAL WOMEN

NAMS recognizes the need for FDA to provide timely safety information about therapies and to address potential safety concerns for vaginal HT. NAMS suggests that FDA consider changing the black box warning on low-dose vaginal estrogen formulations. These treatments have low systemic absorption, leading to circulating estradiol concentrations in the postmenopausal reference range (<10 pg/mL). Instead of a boxed warning, FDA could potentially retain the warnings in the text with additional cautions added regarding the need for evaluation if postmenopausal bleeding or spotting occurs and for women with estrogen-sensitive cancers, including breast, to consult with their oncologists before use of these therapies.

1. Remove the black box warning in the Warnings and Precautions section of the labeling but retain the text about the risks identified in the WHI trials of oral systemic (higher dose) HT.
2. Highlight in the Warnings and Precautions section of the labeling as it relates to the use of low-dose vaginal estrogen products for the treatment of GSM symptoms that
   a. Vaginal bleeding is a concern because bleeding may be a sign of endometrial cancer. Report any bleeding or spotting without delay.
   b. Women with estrogen-sensitive cancers, including breast cancer, should consult with their oncologists before use of the product.

DISCUSSING LOW-DOSE VAGINAL THERAPIES

Until changes occur in the boxed warning on low-dose HT, NAMS recommends that clinicians discuss evidence-based risks and benefits with each patient for the products, doses, and routes being recommended. Women should be informed that, although the boxed warning on all estrogen products remains because of class labeling, the data reviewed in this workshop indicate that the risks from standard-dose systemic estrogen and progestin seen in the WHI are different from low-dose vaginal estrogen products—those dosed to keep blood levels within the newly determined postmenopausal reference range of less than 10 pg/mL. Higher-dosed vaginal therapies may increase the risk of uterine neoplasia and lead to higher systemic levels associated with different risks.[26]

Low-dose vaginal hormone options that have shown minimal detectable systemic absorption and are FDA approved and available in the United States include vaginal 10-μg estradiol tablet, estradiol 7.5-mg ring, 4- and 10-mg vaginal soft gel inserts, vaginal creams (conjugated estrogen and estradiol) dosed at 0.5 g, and the intravaginal dehydroepiandrosterone 6.5 mg/d suppositories.[12,13]

CONCLUSIONS

NAMS continues to request FDA to enact modifications in the estrogen therapy black box warning for low-dose vaginal estrogen formulations dosed within the postmenopausal estradiol reference ranges. Such modifications would include removal of the black box warning and replacement with cautions regarding the need for medical evaluation if postmenopausal bleeding or spotting occurs and for women to engage their oncologists in decision making if they have a prior estrogen-sensitive cancer.

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