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NAMS
The North American Menopause Society

Not Time to Abandon Use of Local Vaginal Hormone Therapies
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Clinicians caring for menopausal women are familiar with the genitourinary syndrome of menopause (GSM), previously referred to as vulvovaginal atrophy, a progressive condition that impairs sexual function and quality of life. Although GSM affects up to 45% of midlife and older women, most with the condition go undiagnosed and untreated.[1]

Estrogen represents a key regulator of vaginal physiology. Declines in estrogen associated with menopause play a central role in the pathophysiology of GSM. The occurrence of symptomatic GSM in premenopausal women with hypoestrogenemic states, including lactation and use of GnRH agonists, underscores the central role estrogen plays in maintaining normal vaginal function.

Over-the-counter (OTC) vaginal lubricants used with sexual activity and vaginal moisturizers used on a routine basis several times per week can provide some relief from symptoms of GSM.[1]

In March 2018, a report published in *JAMA Internal Medicine* described results of an NIH-funded, short-term (3 mo), double-blind trial that randomized women with symptoms suggestive of GSM to these three groups: 1) Currently marketed 10 µg estradiol tablets plus placebo vaginal gel, 2) Placebo vaginal tablets plus a currently marketed vaginal moisturizer gel, or 3) Placebo tablets plus placebo gel.[2] The trial's primary outcome related to reported severity of participants' most bothersome symptom (MBS), which was defined at enrollment.

In the 302 women randomized, pain with penetration represented the most common MBS (reported by 69% of participants), followed by dryness (21%). A small reduction in MBS was observed with all treatments. Neither vaginal estradiol tablets nor the commercially marketed moisturizer reduced the MBS more than placebo gel. Likewise, participants reported an improvement in sexual function that was similar in those randomized to estradiol versus placebo gel as well as those randomized to moisturizer versus placebo gel.

As the authors noted, their trial differs from others in that they employed gel placebo rather than placebo cream or tablets. They speculate that use of gel placebo may help explain the substantial placebo response noted with this trial. The trial was underpowered for the subjective endpoints described, whereas the objective endpoints and patient satisfaction with the treatment for which the trial was powered all favored estradiol vaginal tablets.

One takeaway message from this study, which is consistent with current guidance from The North American Menopause Society (NAMS),[1] is that use of OTC lubricants and moisturizers represents appropriate first-line therapy for women with symptomatic GSM. Editorialists, however, concluded that rather than use vaginal estrogen, "Postmenopausal women experiencing vulvovaginal symptoms should choose the cheapest moisturizer or lubricant available over-the-counter."[3]

As soon as the report of this trial came off embargo, misleading messaging appeared on the web. For example, on March 19, 2018, a report on this trial posted on the website *MedPage Today* headlined "Vaginal estradiol offers little help for menopausal symptoms."[4] Based on the findings of this short-term trial, some clinicians and women will conclude that use of vaginal estrogen, which after all is often expensive and mired in the controversies surrounding systemic hormone therapy, should be abandoned. However, our interpretation of the trial and clinical perspectives are different.

An understanding of this common condition's etiology underscores the key role played by estrogen. Numerous longer-term (12 mo) published trials of women with symptomatic GSM have consistently demonstrated vaginal estrogen's superiority to placebo in managing symptoms, as well as its safety.[5]

A single short-term and underpowered clinical trial does not override a large body of previous evidence, and use of low-dose vaginal estrogen or the newer intravaginal dehydroepiandrosterone (DHEA) should not be abandoned for GSM management.

Genitourinary syndrome of menopause is a progressive condition. Early-on response may be found with lubricants and moisturizers, and NAMS recommends trying these agents first. But, if these OTC products are unsuccessful, either initially or over time, robust evidence from longer (1-y duration) randomized, placebo-controlled clinical trial data support the efficacy and safety of both low-dose vaginal estrogen and intravaginal DHEA, including improvement in the MBS of dyspareunia and vaginal dryness. Over the long term, outcomes for our patients with symptomatic GSM not adequately responsive to OTC products will be enhanced if treatment includes local low-dose vaginal estrogen or intravaginal DHEA or oral ospemifene when appropriate.

Because of the importance of this topic to NAMS members and others, this summary is provided through a collaborative effort among Dr. Andrew Kaunitz, Dr. JoAnn Manson, and me. We also have plans to publish an editorial in *Menopause* on this important topic.

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References

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