Urogenital Health

The vagina, lower urinary tract, and pelvic floor have the same embryologic origin, and therefore all contain estrogen receptors and undergo atrophy in the estrogen-deficient state of menopause. The concept of urogenital aging encompasses the altered structure and function of the urogenital tissues under the combined influence of estrogen loss from menopause and tissue aging. Although tissue aging is both insidious and inevitable, the effect of estrogen loss on the urogenital tissues is relatively rapid and, at least to some extent, reversible with ET.

CONSEQUENCES OF ESTROGEN LOSS FOR UROGENITAL TISSUES

Significant physiologic changes occur to the female genital anatomy during menopause because of estrogen loss. The vulva loses most of its collagen and adipose tissue in response to estrogen loss. Oriba and Maibach[1] showed that when lipids in the stratum corneum are lost the barrier function they provide is lost, and the vulvar tissue loses its ability to retain water; it becomes flattened and thin. Glandular secretions also diminish. The prepuce of the clitoris atrophies, exposing the gland to irritation from clothing, prolonged sitting, and sexual contact. The vaginal surface becomes thinner, less elastic, and more friable. The production of secretions is reduced, and during sexual stimulation the production of fluid is delayed. Estrogen loss alters the urethral and vaginal flora, resulting in a less acidic (more basic) tissue pH. This allows enteric colonization of the urethra and vagina, predisposing both to infection. Because of the high number of estrogen receptors in the lower urinary tract, atrophy secondary to estrogen loss has been assumed (without clear evidence) to be a factor contributing to the development of urinary incontinence and irritative lower urinary tract symptoms, such as urgency, frequency, and dysuria.

The most common symptoms of vaginal atrophy include vaginal dryness, dyspareunia, vulvar pruritus, and vulvar burning or pain.[2] In the WHI trial cohorts, vaginal dryness was reported by 27.0% of participants, irritation or itching by 18.6%, vaginal discharge by 11.1%, and dysuria by 5.2%.[3] A population-based study has shown that these symptoms present early after the menopausal transition, not years later, as previously thought: although only 3% of premenopausal women reported vaginal dryness, Dennerstein et al.[4] noted vaginal dryness in 21% of women within 1 year of menopause and 47% by 3 years after the menopausal transition. Smokers have more vaginal dryness than non-smokers.[5] In a cohort of 76 postmenopausal survivors of breast cancer, 71% reported vaginal dryness.[6] Although no good prevalence data exist, vaginal dryness may be even more problematic for women with breast cancer who are receiving AIs because of the marked hypoestrogenic state induced by these agents.[7,8] In all groups, women with atrophic vaginal symptoms experience decreased quality of life; almost one third of women with vaginal dryness have concomitantly lost interest in sex.[9] In breast-cancer survivors, symptoms of vaginal atrophy have a negative effect on quality of life and may even affect adherence to cancer treatment.[10]

Despite the high prevalence of these symptoms and their negative effect on quality of life, women across all cultures remain reluctant to seek medical help. Although this may be due to sociocultural factors including patient embarrassment and complacency, a recent publication has highlighted that, in addition, postmenopausal women across the world have a remarkably poor understanding of vaginal atrophy. Nappi and Kokot-Kierepa [11] conducted an anonymous survey of 3520 women aged 55 to 65 years across the world. Almost half of the total survey population (45%) reported troublesome vaginal symptoms, though only 4% attributed their symptoms to vaginal atrophy. Shockingly, of the 500 Canadians participating in the survey, 52% were unaware of the effects of local ET, perhaps in part because 59% claimed that their health care provider had never raised the subject of vaginal health.

VAGINAL ATROPHY

Non-hormonal treatment

Locally applied lubricants can alleviate dryness and discomfort but do not reverse the histologic changes associated with urogenital aging.[12,13] A gel containing hyaluronic acid (Hyalfem; Triton Pharma, Concord,

Ontario) is now available as a vaginal moisturizer, although no scientifically robust data exist to support its efficacy. Dietary phytoestrogens have little trophic effect on the vaginal mucosa.[14] Sparse data exist to support the concept that the phytoestrogen genistein, vaginally adminstered in gel form, might lessen vaginal symptoms and provide cytomorphologic improvements in menopausal women.[15] Oral supplements with black cohosh[16] and dong quai[17] afford no measurable therapeutic benefit over placebo. Although oral vitamin D therapy (calcitriol, 0.5 μg/d) did not provide symptom benefit in a small cohort of 60 postmenopausal women, physical and cytologic examination showed less atrophy in users than in non-users, suggesting a possible objective benefit of vitamin supplementation.[18] Polycarbophil gel (Replens; Columbia Laboratories, Boston, Massachusetts, USA) may lessen vaginal dryness and even improve tissue elasticity, although it is not clear if the subjective benefit is only a lubricant placebo response that is not durable.[19] Importantly, neither lubricants nor polycarbophil gel would be expected to yield vaginal cytomorphologic or pH improvements or reduce the lower urinary tract symptoms associated with urogenital atrophy such as dysuria and urinary urgency.

Hormonal treatment

Because urogenital aging is at least in part related to estrogen deficiency, ET is the mainstay of effective therapy. Estrogen improves blood supply to the urogenital tissues, inducing normal mucosal proliferation and lubrication and restoring a lactobacilli-predominant flora and thus an acidic tissue pH. Estrogen administration can be either systemic (oral or transdermal) or vaginal (local), but the vaginal route is more efficacious both objectively and subjectively.[20] Up to 40% of women receiving systemic therapy do not get an adequate effect of estrogen on the vaginal mucosa.[21]

A comprehensive meta-analysis concluded that ET, particularly vaginal ET, is highly effective for alleviating the symptoms of vaginal atrophy and for reversing atrophic cytomorphologic changes.[22] Vaginal ET significantly reduces the risk of UTI in menopausal women[23,24] and prolongs the interval between infections.[25] Its effectiveness for managing other symptoms of urogenital aging, including urinary urge incontinence, frequency, and nocturia, is less clear, perhaps because the latter conditions have a complex, multifactorial etiology that is less clearly related to estrogen deficiency than is vaginal atrophy.

Currently multiple delivery vehicles for vaginal estrogen are available in Canada, including CEE cream (Premarin Vaginal Cream; Pfizer Canada, Kirkland, Quebec), a low-dose estradiol-releasing ring manufactured from silicone elastomer (Estring; Pfizer), and a micronized estradiol tablet (Vagifem 10; Novo Nordisk Canada, Mississauga, Ontario). Generic equivalents are not yet available. All are considered equally effective.[22] Patient preference may vary.[26]

Estrogen is readily absorbed from the vagina,[27] and systemic effects will be avoided only if the dose and formulation are controlled for this purpose. Very low doses are needed in the vagina to reverse atrophic change, so systemic absorption can be limited. That said, when the vaginal mucosa is most atrophic is also when it is most permeable, so minor absorption may occur at the beginning of treatment until the mucosa matures and becomes less permeable. This "spill-over effect" has been estimated to be transient over the first 7 to 14 days;[28] the serum estradiol concentration returns to pre-treatment levels thereafter and remains low on serial assay over 12 weeks, which suggests that there is no long-term accumulation of estradiol with vaginal therapy.[29] The "spill-over effect" is further limited to less than 24 hours (i.e., after a single initial dose) when an ultra-low-dose vaginal tablet containing only 10 μg of estradiol is used, which indicates that there is minute (and insignificant) systemic absorption with this dose and yet equal therapeutic effect.[29] Many studies of vaginal estrogen (all formulations) have shown no evidence of endometrial proliferation after 6 to 24 months of use; therefore, in general, concomitant progestogen therapy or endometrial surveillance is not recommended in asymptomatic (non-bleeding) women.[22,30,31] After conducting their population-based case–control study of 789 cases of endometrial cancer, Weiderpass et al.[32] concluded that vaginal low-potency ET did not increase the risk of endometrial hyperplasia over the population baseline.

Conclusions with respect to the use of vaginal ET in breast cancer patients are less clear. A recent trial recommended caution in daily use of Vagifem 25 (each tablet providing 25 μg of estradiol) in breast cancer survivors who are concomitantly receiving AIs in view of the authors' observation of a significant rise in serum estradiol levels after 14 days of treatment.[33] Their study, however, included only 7 women, there was high intersubject variability with the radioimmunoassays for estradiol, and measurements were conducted for only 2 weeks (during the "spill-over" interval), so it is impossible to draw broad conclusions from this work. Furthermore, the FSH and LH levels did not change in the study participants. The new dosing for this product is only 10 μg per tablet; hence, negligible absorption would be expected.

Two large cohort studies demonstrated no difference in the outcome of breast cancer for women choosing to receive vaginal ET. Dew et al.[34] followed 1472 women