Vaginal Hormone Therapy for Urogenital and Menopausal Symptoms

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ABSTRACT

Reduction of ovarian steroids at menopause leads to significant changes in the urogenital tract. These changes often worsen with time, particularly in nonsmokers, affecting up to 38% of menopausal women. Urogenital symptoms that clearly respond to estrogen therapy include atrophic vaginitis, dryness, and accompanying dyspareunia. Estrogen reduces urinary tract infections in women plagued by frequent recurrence. The sensation of urgency improves with estrogen but urge incontinence improvement is similar to that with placebo. Stress incontinence does not improve with estrogen. Until recently, vaginal therapy was reserved for local symptoms. Rings make systemic vaginal therapy acceptable and even preferred by some users. Vaginal delivery, like other parenteral therapies, bypasses the gastrointestinal tract, with less anticipated impact on lipids, globulins, clotting, and fibrinolytic factors. Evidence of a lowered risk of venous thromboembolism is reviewed. Options for estrogen therapy include native, synthetic, or biologically derived estrogens delivered by cream, gel, insert (pessary), ring, or tablet. Even the lowest dose estradiol (7.5 μg daily or 25 μg twice per week) shows evidence of systemic absorption. In long-term placebo-controlled studies, bone density was better preserved and lipid profiles were more favorable. Therefore, even these low dose therapies should be opposed by occasional progestogen to prevent endometrial carcinoma. Intermittent therapy is best given for a minimum of 12 days based on laboratory data. Less frequent dosing, although preferred by patients, likely confers a slightly increased risk of hyperplasia. No combination estrogen/progestogen vaginal product is currently available. The best dose to reduce risk of endometrial pathology adequately in the lower dose therapies will be defined not only by the dose and potency of the exogenous estrogen but by the individual is body habitus and lifestyle choices.

KEYWORDS: Urogenital, vaginal, menopause, therapy, progestogen

Until recently, urogenital menopausal therapy was confined to therapy for local symptoms. Systemic absorption was acknowledged as an added—even desired—side effect but the vaginal route was chosen and intended primarily for local symptom relief. This review discusses the physiology of menopause in the urogenital tract and the local effect of sex steroids on urogenital tissue, and reviews the available therapies that are administered vaginally, providing evidence of the parenteral effects of vaginal drug delivery.

VAGINAL SYMPTOMS IN MENOPAUSE

The reduction of ovarian steroid production at menopause leads to significant changes in the vulva, vagina, cervix, urethra, and bladder. Unlike vasomotor

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symptoms that resolve with time, urogenital symptoms do not improve and may actually worsen with time since menopause,[1] particularly in nonsmokers.[2] Overall, a survey of 1200 Swedish menopausal women randomly selected from a birth cohort indicated that half reported some type of vaginal or urogenital symptom, the most common being dryness and associated dyspareunia[3] followed by itching and burning or pain. Barlow et al[4] surveyed and found itching and burning to be the predominant urogenital symptom, affecting 30 to 38% of a European cohort. Vaginal dryness is not limited to postmenopausal women; up to 15% of women who are still menstruating also report dyspareunia and dryness.[5] As early as 1888, Kellogg reported that postmenopausal women often had a "distressing leucorrhoeal discharge, accompanied by violent itching. . .,"[6] a syndrome now called atrophic vaginitis. A survey of hormone users found that only 55% of women using a patch and 73% of women taking oral therapy or percutaneous gel reported urogenital relief.[4] Hargrove et al[7] similarly found that two of eight hormone users reported persistent vaginal dryness or dyspareunia after 12 months of therapy. Unmedicated vaginal lubricants offer moderate relief of vaginal dryness and itching but have not proved better than placebo[8] or estrogen.[9] Vaginal symptoms are relieved consistently in 80 to 95% of women using local estrogen therapy.[10] A meta-analysis of 10 randomized, placebo-controlled studies found that estrogen therapy consistently relieved vaginal symptoms but local vaginal therapy was more efficacious than oral therapy.[10]

UROLOGIC SYMPTOMS IN MENOPAUSE

Urinary symptoms in postmenopausal women include dysuria, frequency, urgency, incontinence, and an increased risk of recurrent urinary tract infections (UTIs).[11] At least one urogenital symptom is reported by 23 to 40% of menopausal women.[4]

Bacteriuria is present in 20% of noninstitutionalized elderly women, postulated to be due to fecal bacterial colonization of the vagina.[12] Overt recurrent UTI in noted by 12 to 17% of menopausal women.[3,12,13] Risk factors for UTI include sexual activity and prior history of UTI.[13]

Urinary incontinence prevalence increases with age, affecting 15 to 30% of women older than 60 years living in the community.[14] Seventy percent of women with urinary incontinence relate the onset of symptoms to menopause.[3] Incontinence is associated with frailty among the elderly and may be the final caregiver burden resulting in a nursing home admission.[15] Significant incontinence occurs in 8 to 55% of female nursing home residents and increases with age.[16] Mixed incontinence is most prevalent (55%) in women older than 60 years, with pure stress incontinence noted in only one fourth and pure urge incontinence noted in only 9%. Other voiding difficulties account for the rest (9%).[17] Most urgency and irritative symptoms are due to atrophic urethritis, defined as symptoms of a UTI despite a sterile urine culture.[18] Incontinence leads to lifestyle changes including altered clothing selection, use of sanitary protection, altered fluid intake, and restricted activity outside the home.[19] The direct cost of incontinence in the United States is estimated at $12.5 billion annually, including 70% for absorbent products, extra laundry, etc.[20] Yet despite the cost and prevalence of incontinence, only 54% of women who reported incontinence to be moderately or extremely bothersome sought medical therapy for this condition.[21] Incontinence was identified as a medical problem in the patient diagnosis list in only 15% of incontinent nursing home residents,[16] suggesting that incontinence is often inadequately managed.

Which Urologic Symptoms Are Relieved with Hormone Therapy?

Similar products may be given for urologic symptoms as those used for vaginal symptoms. The evidence for efficacy of urologic symptoms must be drawn from placebo-controlled studies because, as with vasomotor symptoms, many women improve in response to counseling and attention to the urologic problem.[22,23] The placebo effect is as high as 56% in some studies.[23]

INCREASED URINARY TRACT INFECTIONS (UTIs)

Urinary tract infections, particularly recurrent ones, are hypothesized to be due to colonization of fecal-type bacteria in the vagina. Vaginal flora includes more lactobacilli and fewer enteric organisms after estrogen compared with placebo therapy,[24] consistent with the finding of fewer recurrent UTIs with local, low-dose estrogen therapy.[25,26] Brandenberg et al[27] also found more than 90% reduction in UTIs among institutionalized women in their 80s when given oral estriol daily. This hypothesis is further supported by a study of estriol inserts (pessaries) that were less effective than estriol cream (in a prior study). The inserts caused less of a shift in the vaginal flora.[28] A systematic review of evidence on UTIs suggests significant benefit in reducing recurrent UTIs with estrogen—especially when applied vaginally—compared with placebo.[29]

INCONTINENCE

One randomized, placebo-controlled clinical trial of 64 incontinent menopausal women showed an increased maximal bladder capacity with estrogen therapy and larger volumes for sensing the first urge to void.[22] A cross-sectional comparison of menopausal women with and without estrogen therapy[30] reinforced this finding for urge incontinence. Urethral closing pressure was increased in six of the 11 menopausal women using

vaginal estrogen cream at evaluation who reported subjective improvement of their incontinence with treatment,[31] and in 95% of women ingesting 2 mg of estriol daily for at least 2 months.[32] Women with relief demonstrated concurrent squamous metaplasia of the lower urethral transitional epithelium.[31] Uninhibited bladder contractions were noted to decrease in estrogen users compared with the placebo users.[11] Conversely, oral estrogen replacement did not improve incontinence due to anatomy or detrusor instability in two small placebo-controlled trials,[33,34] fitting with the theory that estrogen reduces irritation and thickens the urethral epithelium but does little to increase anatomic support of the bladder neck or urethra.[23] Although a placebo-controlled, randomized, multicenter trial failed to show improvement with 3 mg of oral estriol beyond that of placebo,[22] it was underpowered because of an unexpectedly large placebo response. A study with the 25-μg estradiol vaginal tablet suggested subjective relief of urgency but no objective sign of improvement.[35] Finally, another randomized placebo-controlled trial of 2 mg oral estradiol valerate daily[34] supported a consensus report[23] and other data[33] that documented no impact of estrogen on stress incontinence beyond that of the placebo effect.

The 1500 participants in the Heart and Estrogen/Progestin Replacement Study actually noted a worsening of very mild incontinence (one episode or more per week) over the 4-year follow-up with 38% of hormone users reporting worsened symptoms compared with only 28% of the placebo users.[36] This seeming paradox could be explained if the main effect of estrogen was to increase the thickness of the urethral epithelium, reducing irritative symptoms. Thickened epithelium would provide better urethral function or seal without affecting the anatomic support structures to any significant degree.[37] Hence the urethral syndrome, urge incontinence, urgency and frequency, could improve without a significant impact on stress incontinence. Studies with sufficient numbers and duration have lacked detailed urologic evaluation to distinguish how hormones affect each specific etiology of incontinence.

LIFESTYLE IMPACT ON MENOPAUSAL SYMPTOMS

Lifestyle and culture impact women's experience of the menopausal change in hormone milieu. Sufficient exercise during the early menopausal transition can reduce bone loss and lower cholesterol and triglyceride levels compared with controls.[38] Dietary phytoestrogens reduce vasomotor symptoms to some degree,[39] minimally better than placebo.[1] The vaginal maturation index was improved with soy phytoestrogens but not linseed.[39] Yet, other trials fail to demonstrate improved cytology compared with controls at 6 months.[40,41] Clinical trials have not demonstrated urogenital symptom relief from phytoestrogens.[42] The processing of soy and other products is important to consider because extraction with lipid solvents may result in a loss of phytoestrogen activity in the final consumer product.

Kalogeraki et al[2] showed that cigarette smoking is strongly associated with worsened vaginal atrophy, as demonstrated by atrophic cytology in 90% of smears. Smokers also have an earlier age of natural menopause. Changes with smoking are associated with elevated androgens, particularly androstenedione.[43] Estrogen levels do not differ significantly between smokers and nonsmokers.[44] Atrophy is more common in nonsmokers who have been menopausal for more than 10 years (75% atrophic smears) compared with nonsmokers more recently menopausal (66% atrophic smears).[2] Given that atrophy is at least that common in smokers, no worsened atrophy is noted. A greater proportion of smokers experience atrophy right from the start of menopause.

MENOPAUSAL UROGENITAL PHYSIOLOGY

Vulva

With menopause, the collagen content declines[45] and the vulva lose adipose tissue.[46] The prepuce (clitoral glans cover) shrinks.[45] Pubic hair becomes sparse and gray as the labia become drier.[47] A fusion of a portion of the labia minora has been reported.[48] Few studies actually examine vulvar skin. Most information is extrapolated from nongenital biopsies. Skin tone and elasticity are reduced with age but the reduction is minimized in postmenopausal women receiving hormone therapy.[49] Six months of topical estrogen therapy to the face and neck reduced wrinkle depth and pore size and increased elasticity, firmness, and type III collagen content measured by immunohistochemistry.[50]

Vagina

A gradual decline in vaginal epithelial thickness and character is measured grossly in biopsies (Fig. 1). Cytologic markers include the maturation index (MI), a sum of the percentage of superficial cells plus half the percent of parabasal cells, or the karyopyknotic index, the percentage of superficial cells with karyopyknotic nuclei. The MI has been used successfully as a bioassay for estrogen for nearly three decades[51] but it is not a perfect reflection of estrogen status because infection, medication, and other steroid hormones can alter the result.[52] The MI was documented to change within just 1 week of high-dose estrogen replacement (4000 to 10,000 RU of estradiol benzoate or 1 to 5 mg of estradiol dipropionate given intramuscularly one to three times per week) in menopausal women.[53,54] Other authors have noted changes in 1 to 3 months with the lower doses

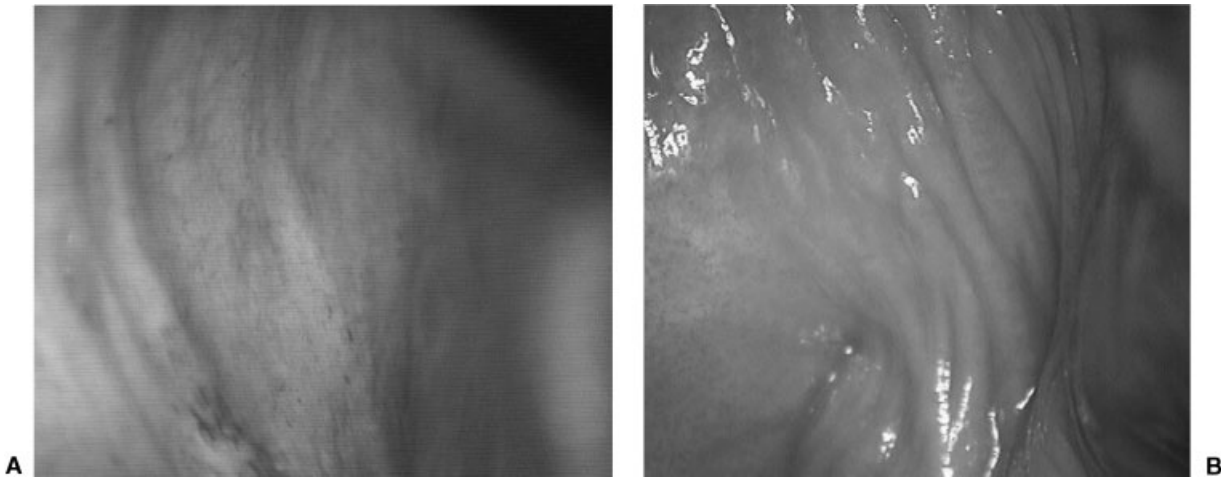

Figure 1 Vaginal colposcopy. (A) Menopausal vagina with decreased ruggae, pallor, and petechiae. (B) Premenopausal vagina; ruggae with normal pink color and sheen reflecting normal moisture.

commonly used today,[10,55] even at 300 μg of synthetic[54] or equine[55] conjugated estrogen. The MI did not correlate well with menopausal symptoms in untreated postmenopausal women,[56] but did reflect the use of exogenous oral estrogen.[57] Women with atrophic vaginitis had the highest percentage of parabasal cells and few superficial cells. However, the estrogen deficiency in the vagina did not mirror vasomotor or other menopausal symptoms,[57] consistent with the clinical observation that between 10 and 25% of women with vasomotor symptom relief from oral hormone therapy still show evidence of urogenital atrophy.[58]

Another measure, which can be used in women without pathogenic vaginitis, is vaginal pH.[59] A vaginal pH of 5 or more in untreated menopausal women reflects menopause with a sensitivity of 64 to 67%, equivalent to the sensitivity of serum follicle-stimulating hormone levels in one study.[60] Vaginal pH correlates significantly with cytologic MI in a healthy menopausal cohort.[61] Women with pH values equal to or below 4.5 have higher serum estradiol levels than their counterparts.[59] Sexually active women have lower vaginal pH and better MIs.[62] Associated with higher pH is a reduction in epithelial glycogen content that can be restored with estrogen administration.[63]

A loss of vaginal epithelial rugae, erythema, and petechia are often seen with examination in many women (Fig. 1). Histologic specimens show increased macrophages and neutrophils in postmenopausal vaginal mucosa (Fig. 2).[64] Subjective complaints of vaginal

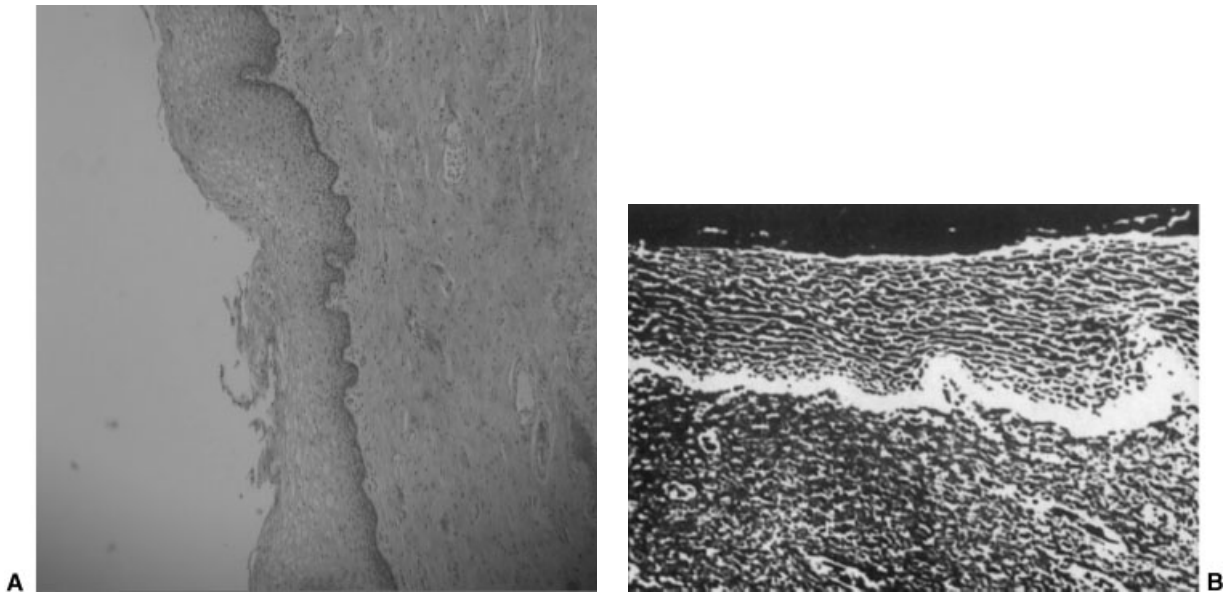

Figure 2 Histology of the vagina. (A) Normal vaginal muscosa. (B) Postmenopausal vaginal mucosa. Images courtesy of Dr. Lila Nachtigal.

dryness accompany this physiologic change. Vaginal fluid is a combination of vaginal transudate that varies with vaginal blood flow and the cervical mucus secretions. There are no true glands within the vagina itself. Both types of secretions are reduced in menopausal women, with dryness noted by physicians on examination.[45,65] Dennerstein et al[65] showed a rapid increase in vaginal dryness with menopause—up from 3% in premenopausal women to 21% within 1 year of menopause to 47% at 3 years after menopause. Vaginal atrophy is noted in more than 60% of women by 4 or more years postmenopause. The vaginal cell proliferation is 50% slower in the untreated menopausal subjects compared with estrogen-replete women, but because the epithelium is thinner, no difference in overall cellular transit time from the parabasal epithelium to exfoliation is actually noted in hypoestrogenic women.[65,66] Thinned atrophic epithelium absorbs estrogen more quickly[67] with less duration[68] than well-estrogenized tissues. Regular sexual activity moderates these menopausal changes.[69]

CERVIX

Little systematic description of cervical change is found in the literature. Clinically, the cervix loses ectropion and shrinks, often to the point of becoming flush with the vaginal vault.[52] Pallor and petechial changes noted in the vagina are also seen in the cervix itself. Less mucus is detected on clinical visual inspection.

URETHRA AND TRIGONE

Derived from the urogenital sinus, these structures share the same embryologic origin with the distal vagina. Notelowitz[70] documented that the pH of the urethra mimics that of the vagina and is lowered following estrogen therapy. Portions of the lower urogenital tract that are covered with squamous epithelium, even urogenital epithelium that has undergone metaplasia, consistently express estrogen receptors.[71] Some women may be prone to recurrent bladder infections with elevated pH because enteric pathogens colonize the vagina more easily (as a result of reduced glycogen content of the epithelial effluent that would otherwise serve as an energy source for lactobacilli).[24] Cytologic specimens from menopausal women receiving estrogen therapy demonstrate more mature/superficial epithelial components in urethral swabs compared with untreated menopausal women.[31] Similar to atrophic vaginitis, atrophic urethritis (previously termed senile urethritis) results in urgency, frequency, and dysuria despite a sterile urine.[18] Even urethral stricture appears to be prevented with estrogen therapy.[72]

VOIDING FUNCTION

Several mechanisms ultimately control voiding that may involve estrogen. Estrogen receptors are expressed throughout the lower urogenital tract, including the trigone and urethra.[14] A significant portion of the intrinsic urethral sphincter function relates to the thickness of the urethral epithelium,[37] and the collagen content and connective tissue of the muscularis layer. Other factors include the integrity of the support structures that transmit abdominal pressure to the urethral sphincter, which may relate to the type and amount of collagen that is produced. Versi et al[73] demonstrated that thigh skin collagen correlated with urethral sphincter function, and Bergman[74] demonstrated altered ratios of type III to type I collagen in the perineum of women with stress incontinence that was independent of prolapse. Collagen is produced by fibroblasts that are rich in estrogen receptors.[75] Fibroblasts from incontinent women secrete 30% less collagen when cultured.[76] The round ligament[77] and fascial anatomic support tissues that contribute to continence mechanisms also contain estrogen receptors.

Animal studies suggest that estrogen alters sensation, increasing bladder sensitivity to α adrenergic stimulation.[78] In rabbits, these changes are partially due to increased density of adrenergic receptors in the lower urinary tract.[79] Estrogen also increases urethral smooth muscle sensitivity and increases the sensory threshold in the bladder.[80] Estrogen decreases rat detrusor muscarinic receptors[81] and inhibits rat and human in vitro detrusor contractility.[82]

Women with detrusor instability taking estrogen ($n = 6$) showed a lower volume for first sensation to void and a higher maximal bladder capacity than untreated menopausal women ($n = 12$).[30] The bulbocavernosus reflex is more prevalent in estrogen users.[30] A small placebo-controlled study of menopausal women with detrusor instability or stress incontinence did not show any benefit of estrogen therapy,[33] but subjects with detrusor instability were not analyzed separately from women with both stress and detrusor factors or stress incontinence alone.

THERAPEUTIC OPTIONS FOR RELIEF OF VAGINAL AND UROGENITAL SYMPTOMS

It is just as important to account for the significant placebo effect seen in controlled clinical trials when evaluating therapeutic options for urogenital relief as with vasomotor symptoms. Both vaginal and urinary symptoms are documented to improve without active therapy.[10,23] Hence placebo-controlled trials with objective endpoints are important to delineate the true effects of medication. To date, no herbal therapy has demonstrated any significant urogenital symptom relief[83] and lubricants are less effective than estrogen cream,[9] leaving vaginal and urogenital symptoms as a clear indication for hormonal therapy.

Systemic Therapy

Relief of vasomotor symptoms often relieves urogenital symptoms simultaneously.

ORAL

Oral estrogen therapy options include (1) native estrogens such as micronized estradiol, estrone sulfate, or estriol; (2) conjugated estrogens, whether isolated from urine or plants; and (3) synthetic estrogens such as ethinyl estradiol or quinestrol. At sufficient doses, all of these oral compounds improve vaginal symptoms. Even lower doses of oral therapy resulted in improvement in the vaginal MI by the sixth cycle of use.[55] Marxet al[54] showed that low-dose oral conjugated estrogens (300 μg) increased the vaginal MI by 18 points compared with 4 points with placebo. Superficial cells increased (2 to 16%) and basal cells decreased (23 to 2%) within the first 4 weeks. Although oral estrogen therapies differ widely in the estrone serum levels attained, effective therapy seems to correlate to the attainment of estradiol levels of at least 35 to 55 pg/mL.[84] Oral therapy is the preferred method of hormone delivery worldwide, but a variable percentage of women will still suffer from vaginal and urogenital symptoms despite a dose of oral estrogen that fully alleviates vasomotor symptoms.

TRANSDERMAL

Transdermal estradiol therapy, whether by patch or gel, also results in vaginal symptom improvement. The transdermal route bypasses the gastrointestinal conversion of estradiol to estrone with less elevation of triglycerides, clotting factors,[85] and globulins, including angiotensinogen, thyroxine, cortisol, or sex hormone binding globulin.[86] A systematic review found that higher oral or transdermal doses provide vaginal symptom relief.[10] Estradiol is the only estrogenic steroid available in transdermal products to date. One patch system delivers estradiol in combination with norethindrone. A combination patch with estradiol and levonorgestrel also relieved vaginal symptoms better than placebo (80% reduction compared with 65% reduction).[87] Mean serum estradiol levels vary between patches marketed as delivering 50 μg of estradiol daily from 39 to 103 pg/mL.[88] Patches are marketed by several companies to deliver an estradiol dose from 25 to 100 μg daily. Most are reservoir patches changed twice weekly with the exception of the matrix patch that lasts for 1 week. An estrogen lotion/emulsion (Estrasorb; Novavax, Inc., Columbia, MD) that is white in color was approved by the U.S. Food and Drug Administration (FDA) in 2003. The soy-based product is provided in premeasured foil pouches containing 4.2 mg of estradiol hemihydrate. One pouch rubbed on each leg daily produces serum estradiol levels of 60 to 70 pg/mL (Estrasorb package label). A clear, alcohol-based gel marketed as EstroGel (Oestrogel in Europe) (Laboratoires Besins International, Montrouge, France) resulted in an average serum estradiol concentration of 65 pg/mL when 2.5 g of product was rubbed over each arm daily.[89] The skin products relieved vasomotor symptoms and caused a significant shift in the vaginal MI compared with placebo[88,89]

VAGINAL

Vaginal estrogen delivery, like transdermal therapy, is not subject to gastrointestinal conversion of estradiol to estrone: serum estradiol levels increase rapidly with limited increase in estrone.[90] Of note is that the estrogen effect on blood flow varies by the vaginal application site. Doppler flow studies show increased flow in the uterine arteries when estradiol is applied near the cervix and posterior fornix.[91] Little change in uterine flow is noted when the estrogen is applied to the distal vagina, but instead increased flow is seen around the urethra and bladder. Patients have not reported a clear difference in symptom relief based on the vaginal placement of the estrogen dose in the literature.

An estradiol ring for simultaneous relief of both systemic vasomotor symptoms and vaginal symptoms (Menoring in Europe; Femring in the United States [Galen Holdings PLC, Craigovan, UK]) is made in two strengths: 50-μg release achieving a mean serum estradiol level of 41 pg/mL, and 100-μg release with a mean serum estradiol level of 76 pg/mL (product label). The silicone ring contains an estradiol acetate core that is rapidly hydrolyzed to estradiol once released providing "90% vasomotor symptom relief" for 58% of women using the 50 μg dose and 79% with the 100-μg dose users at 13 weeks.[92] Based on vaginal cytology in a subgroup with cytology-defined atrophy, the vaginal MI improved with active treatment in 97.5% (39 of 40) compared with 70% (14 of 20) with a placebo ring.[92] Physician assessment of the vagina showed significantly reduced atrophy and pallor. Self-reported symptoms of vaginal dryness and dyspareunia improved, as did the sexual dysfunction subscale of the Greene Climacteric questionnaire.[92] Symptoms of frequency and leakage noted initially by 51 and 41% of subjects, respectively, but rated as mild, improved similarly for placebo and active ring users.[92] The urogenital effects of the systemic vaginal ring have not been studied in women with recurrent bladder infections, urgency, or frequency as a presenting complaint.

Estrogen creams can also be given in sufficient dose to relieve vasomotor symptoms[93] but they are rarely used for that purpose because of low acceptability and continuation rates.

METABOLIC FEATURES OF PARENTERAL DELIVERY

Parenteral estrogen delivery, whether through the skin or vagina, reduces the first-pass effect of oral delivery

whereby large amounts of estradiol are converted to less active compounds. The equivalent doses, therefore, are 10 times less when estradiol is delivered parenterally (1 mg micronized estradiol versus 0.1 mg via vaginal or transdermal delivery).

Acute phase reactants produced by the liver are increased in oral estrogen users compared with women using transdermal estrogen. These include hormone-binding proteins[86] and C-reactive protein.[94,95] Of note, the elevation of C-reactive protein with oral estrogen is accompanied by a reduction, not increase, in insulin-like growth factor-1. This suggests that the change may not represent activation of the inflammatory cascade, which is the probable modulator of cardiovascular risk.[95] Transdermal therapy has less effect on lipids compared with oral dosing, with less prominent elevation of high-density lipoprotein (HDL), little change in triglyceride,[94,96] and no reduction in lipoprotein(a) that is seen with oral therapy.[96,97]

Transdermal estrogen did not reduce fibrinolytic activity, as did oral therapy. Neither plasminogen activator inhibitor nor tissue plasminogen activator antigen were reduced.[85] Unlike oral contraceptives, oral estrogen does not consistently stimulate hepatic globulin synthesis of coagulation factors such as factor VII,[98,99] but reduction in the coagulation inhibitors antithrombin III[99,100] and protein C was observed with oral but not transdermal therapy.[100] In one study, oral and not transdermal estradiol increased prothrombin activation peptide F1 + 2 significantly.[100] Antithrombin III activity decreased with oral estrogen use.[98,101] The theoretic advantage of parenteral delivery suggested by the limited effect on procoagulant milieu was not initially verified by epidemiologic work.[102] However, these studies were inadequately powered to reach definitive conclusions. A recent case-control study with a large proportion of transdermal estrogen gel exposure in France has demonstrated reduced risk of venous thromboembolism (VTE) with transdermal versus oral therapy.[103] Women using transdermal estrogen had a relative risk of 0.9 (95% confidence interval [CI], 0.5 to 1.6) of VTE compared with never-users, whereas the relative risk was 3.5 (95% CI, 1.8 to 6.8) for current users of oral estrogen. Given the significant impact of oral hormone therapy on thromboembolism,[104,105] parenteral estrogen would be considered first-line therapy were these preliminary findings supported by additional studies.

Local Therapy

Urogenital symptom relief requires much lower doses of estrogen when applied directly to the vagina. Absorption is faster through thin atrophic vaginal tissue than through well-estrogenized epithelium.[68] The lower estrogen dose is associated with fewer days of bleeding or spotting compared with systemic therapy[85] yet rates of vaginal symptom relief are higher.[4] Use of the oral selective estrogen receptor modulator, raloxifene, does not hamper the urogenital efficacy of local estrogen therapy.[106,107] Little change in serum estradiol level is noted with these therapies, but evidence is accumulating to suggest significant accompanying systemic absorption with beneficial side effects on bone and lipids.

BONE DENSITY EFFECT

The low-dose estradiol (7.5 μg) vaginal ring, intended for urogenital relief only, improved forearm bone density by 2.1% in 20 users compared with a 2.7% loss of bone density in the 10 women older than age 59 who were randomly assigned to no therapy.[108] Prestwood et al[109] confirmed the positive effect of low dose estradiol on bone in a study of 167 women older than age 65, but used a larger dose (250 μg) of estradiol orally as a tablet daily vs. placebo. As expected, the serum estradiol was significantly increased but was within menopausal range, with estradiol from 23 to 29 pg/mL and estrone from 70 to 90 pg/mL. Bone mineral density increased significantly: 2% for the femoral neck, 3% for the total hip, and 3% for the lumbosacral spine 3 years later in estradiol users compared with nonusers.

LIPID EFFECT

In an elderly cohort of 70 Scandinavian women older than age 59, Naessen et al[110] also showed a 7.6% reduction in serum low-density lipoprotein (LDL) cholesterol with a 7.3% change in LDL/HDL ratio using the low-dose estradiol (7.5 μg) vaginal ring for 1 year. A 4% reduction in total cholesterol and apolipoprotein B was also noted. Serum HDL triglyceride increased by 25% without any change in total triglyceride. All of these lipid changes reached statistical significance. Serum estradiol and estrone sulfate were elevated 13 and 16%, respectively, in ring users, but remained within the menopausal range.[110]

OPTIONS FOR LOW-DOSE VAGINAL THERAPY

Vaginal Ring. A vaginal ring of core design, made from Silastic, measuring 9 by 55 mm, is currently marketed as Estring (Q_Pharma AB, Malmö, Sweden) in the United Kingdom, Europe, and North America. It is indicated for urogenital symptoms and does not relieve vasomotor symptoms. The ring contains 2 mg of micronized 17β-estradiol releasing 6.5 to 9.5 μg of estradiol daily. Serum estradiol is slightly elevated above pretreatment levels but usually remains less than 20 pg/mL, which is within the menopausal range.[111] Eighty-five percent of subjects using a silastic vaginal ring reported improved vaginal symptoms by 3 weeks. Vaginal pH decreased from 6.3 to 5.1, with complete normalization of pH (< 5.0) in 39%.[112,113]

Visual appearance improved in 70 to 80% of the women with baseline menopausal changes such as pallor and petechiae. One third of the 136 women enrolled with vaginal dryness were cured (95%) or improved (2%) at the end of 1 year of use in the Scandinavian trial. Three fourths of the sexually active subset reported dyspareunia at the start. The ring eliminated (92%) or reduced (7%) pain with intercourse for nearly all of them. Half (51%) of women reported urinary urgency at the outset and 81% were subsequently cured and 13% improved with treatment. Only one woman felt that her urgency worsened and three asymptomatic women developed mild urgency during the year-long therapy. Results from a multicenter trial in North America were similar.[113] Compared with estradiol inserts (pessaries), the ring was equally efficacious in alleviating dysuria (76%), urge incontinence (58%), and stress incontinence (53%), but was much more acceptable (60% *v* 14%).[114] Patients preferred the vaginal ring to conjugated estrogen[115] or estriol cream[116] as well. Recurrent UTIs were less frequent in women using the ring compared with nonusers.[117] Urogenital symptom relief was unaffected by simultaneous use of oral raloxifene, a selective estrogen receptor modulator.[106]

Vaginal Tablet. A vaginal tablet formulation marketed as Vagifem is made with a hydrophilic cellulose-derived adhesive matrix designed to release 25 μg of micronized estradiol into the vaginal milieu. It is usually applied with an applicator daily for 2 weeks and then chronically 2 times per week.[118] It resolved vaginal symptoms well, with 86% showing objective signs of improvement on examination by a physician, statistically more than with placebo ($p < .001$); 79% reporting relief of annoying vaginal dryness ($p < .002$ compared with placebo users).[26] No greater improvement of vaginal symptoms of dryness, soreness, or irritation was noted with 1.25 mg of conjugated estrogen cream compared with the 25-μg vaginal tablet.[119] The 25-μg estradiol tablet, although not specifically studied for urologic symptoms, did provide symptom relief for half of the volunteers who complained of frequency, dysuria, urge, or stress incontinence beyond their qualifying vaginal complaints. After 12 weeks, 63% of these initially symptomatic women reported improvement, compared with only 32% of those symptomatic women assigned to placebo.[26] Most subjects experienced relief within 2 weeks. In a recent assessment of Thai women, the percent of women reporting urinary frequency decreased from 79% to 13% by 12 weeks and nocturia was reduced from 83 to 46%, which was similar to the response seen with conjugated estrogen cream.[120] The small improvement in stress incontinence symptoms (71 to 54%) is consistent with the aforementioned placebo effect and was seen with the tablet and the cream.

Estriol Inserts. Estriol inserts, also called pessaries in the United Kingdom, provide 500 μg of estriol. More than 90% of women attained vaginal symptom relief with the inserts in one trial[121] whereas only a 39% rate of response was noted in a trial sponsored by a competing manufacturer.[112] In a clinical trial by Lose et al,[114] the estriol inserts and the low-dose vaginal ring were equally efficacious in alleviating urgency, urge incontinence, and nocturia. The estriol inserts may be somewhat less effective than estriol cream in restoring vaginal flora and reducing the incidence of UTIs compared with cream.[28]

Estrogen Creams. Compounds formulated into vaginal creams include native estrogens such as estrone sulfate, estradiol, and estriol; conjugated estrogens from equine or plant sources; and synthetic estrogens such as dienestrol. Conjugated equine estrogen vaginal cream produces vaginal maturation at one fourth the dose of oral therapy but given in sufficient dose it is also adequate to relieve vasomotor therapy.[93] Product formulation alters the rate of estrogen absorption from the vagina.[122] All estrogens studied have been shown to be absorbed well through the vaginal epithelium. Simultaneous administration of the selective estrogen receptor modulator, raloxifene, did not diminish the effect of concurrent application of conjugated equine estrogen cream (300 μg daily).[107] An estriol cream marketed in Europe as Synapause improved vaginal symptoms in 83% of treated women with more than half reporting complete symptom relief.[116] Of note, two of 165 subjects using 500 μg of estradiol daily for 2 weeks followed by 500 μg three times a week developed hyperplasia within 6 months of therapy. The estriol is affected by food intake because of enterohepatic circulation of the drug, which prolongs its duration of action.[123]

Progestins

The effect of progestins alone on urogenital tissues has not been well studied. Early work on vaginal maturation suggested that progestins accentuate the number of intermediate cells found on vaginal cytology, similar to the effect of corticosteroids.[52] Progesterone receptors have been noted in the trigone[124,125] and dome of the bladder.[71] The expression of progesterone receptors in the urethra and squamous epithelium was increased in estrogen-replete women. Progestin (1 g of hydroxyprogesterone caproate) did not alter maximum urethral pressure or resting urethral length.[126] Progestins may increase detrusor overactivity. Case reports of urgency with high-dose progestin-only contraceptives in premenopausal women[127] may relate to secondary hypoestrogenism rather than a progestin effect itself. Unlike vasomotor symptoms that respond to progestin therapy,

there is no clear data to suggest that progestins relieve urogenital symptoms.[1]

ENDOMETRIAL PROTECTION

Most progestins are prescribed to protect the endometrium from unopposed estrogen that can result in proliferation, hyperplasia, or ultimately adenocarcinoma.[128] Greenblatt[129] proposed adding progestin for 5 to 10 days per month as early as 1965 to prevent hyperplasia. The concept was verified by a 10-year prospective study[130] showing reduced endometrial hyperplasia and adenocarcinoma in women receiving combination therapy. Given in a pulsed fashion, for a duration of at least 10 days,[134] progestin therapy effectively opposed the estrogenic biochemical effects,[131] preventing endometrial hyperplasia.[128] Data from Studd et al[132] suggested that 13 days of progestin might be more optimal to oppose estrogen therapy. Bleeding during the progestin therapy may signal inadequate dosing or endometrial pathology.[134] Lack of withdrawal bleeding suggests minimal endometrial buildup provided the outflow tract is patent and the cervix is not stenotic. Light or minimal bleeding would support an increased progestin dosing interval. In one study, 21% of women bled after a progestin challenge after using 2 g of conjugated equine estrogen cream three times per week for 12 weeks and 12% showed a sonographic endometrial thickness more than 5 mm.[135]

DOSING FOR SYSTEMIC HORMONE THERAPY

The Postmenopausal Estrogen/Progestin Interventions study[136] showed less impact on lipids with progesterone and generated increased interest in both vaginal and oral progesterone administration. The exact dose of progesterone to oppose estrogen therapy has not been clearly delineated. Nightly vaginal dosing with 100 to 200 mg of micronized progesterone in a suppository 25 days of each month to oppose 150 μg of transdermal estradiol resulted in poor bleeding control but may have been related to poor absorption from the formulation.[137,138] Eight of 14 subjects completing 1 year in the trial had proliferative endometrium on biopsy.[137] One study using 100 mg of progesterone nightly for 21 of 28 days of a cycle or 25 days per month in women receiving 1.5 mg of daily estradiol by transdermal gel noted inactive or quiescent endometrium in 69%.[139] Another study of 31 women using 625 μg of conjugated equine estrogen were given 45 or 90 mg of progesterone in a vaginal bioadhesive gel; only one proliferative sample and no hyperplasia was observed in 41 evaluable endometrial biopsies. The mean plasma progesterone was 4.6 and 6.8 ng/mL, respectively for the two doses.[140] The delivery of progesterone is affected by the formulation and defined doses for continuous or cyclic dosing have not yet been standardized.

With new vaginal ring therapies, a 3-month dosing interval would be particularly appealing because many women who choose ring therapy wish to avoid frequent pill use. The ring refill would prompt use of the progestin. Preliminary data with quarterly norethindrone acetate, 2.5 mg for 12 days, showed that 61% experienced a withdrawal bleeding that lasted a mean of 4.8 ± 1.6 days in women using 50-μg estradiol patches.[141] Withdrawal bleeding averaged one half day less when the progestin was given every other month. Hirvonen et al[142] gave more than 200 women an average of 1 mg of estradiol transdermal gel daily opposed by 10 mg of oral medroxyprogesterone acetate (MPA) for 12 days every 28- or 84-day cycle. Ninety-five percent of women with the quarterly progestin experienced withdrawal bleeding lasting an average of 6.1 days. The reduced frequency of bleeding was acceptable but one of 163 subjects receiving quarterly progestin demonstrated hyperplasia and another subject had an endocervical adenocarcinoma detected by study safety screening at the end of 1 year, compared with no hyperplasia in the group obtaining cyclic therapy. In another study of cyclic oral MPA,[144] endometrial hyperplasia was found in 1.5% of 199 women completing follow-up, a rate similar to the 0.9% prevalence found at baseline. Compared with monthly medroxyprogesterone, quarterly medroxyprogesterone resulted in longer menses (7.7 ± 2.9 days vs. 5.4 ± 2.0 days), more reports of heavy menses (31.1 vs. 8.0%), and more unscheduled bleeding (15.5 vs. 6.8%). A Cochrane review confirms that hyperplasia was slightly more common with the quarterly progestogen dosing studied to date.[143] Despite this problem, women preferred the quarterly regimen nearly four to one.[144]

Other potential options for progestin delivery include the levonorgestrel intrauterine system (Mirena; Schering Oy, Turku, Finland), labeled for use as a contraceptive, which delivers 20 μg of levonorgestrel into the uterine cavity daily. It creates an atrophic or secretory endometrium in menopausal women using 50 μg estradiol skin patches for 1 year.[137] A smaller device releasing only 10 μg of levonorgestrel is in development that would target postmenopausal women.[145] A progesterone skin cream, Pro-Feme, popularized in the lay literature and the Internet, is insufficient to transform proliferative endometrium even at doses up to 64 mg/day for 14 days per month.[146] Two other studies also showed inadequate endometrial transformation with transdermal progesterone.[147,148] The only transdermal progestin that is FDA approved is norethindrone acetate in a combination estradiol/progestin patch.

Can Low Dose Estrogen Be Used Alone?

Despite concerns about unopposed estrogen therapy and several professional organization position statements advocating use of progestins,[149,150] White et al[151] found

that 6% of women who receive unopposed estrogen therapy have an intact uterus. In particular, women using vaginal creams often do not receive progestins, including women with long-term therapy. Sixty percent of the 733 women with a uterus with average prescription claims equivalent to 22 tubes of vaginal cream did not receive any progestin therapy through their insurance program.[152] With new data about the modulation of estrogen effect by progestin therapy, use of estrogen alone may be on the rise.[153] Unopposed lower dose therapies such as 25 μg of transdermal estradiol[154] or 300 μg of conjugated equine estrogen[155] showed up to 7% proliferation by 12 weeks and 3.2% endometrial hyperplasia by the end of 2 years of therapy, respectively.

Some have proposed that very low dose vaginal therapies do not need to be accompanied by progestin,[156] but the 70-fold increase in endometrial estradiol content following vaginal compared with oral dosing[157] suggests a more cautious approach. Endometrial proliferation has been reported within 12 weeks when 2 weeks of daily use of the 25-μg estradiol tablet or 1 g of vaginal conjugated estrogen cream followed by twice weekly doses were evaluated. Two of the 48 women had proliferative endometrial biopsies; one cream user had an endometrial thickness of 7.5 mm on ultrasound and the other had a normal ultrasound but experienced bleeding using the tablets. On average, the plasma estradiol remained in the menopausal range, increasing from 7.6 pg/mL at baseline to 8.9 pg/mL with the tablet (25 μg) or 12.6 pg/mL with conjugated estrogen cream.[120] Felding et al[158] documented proliferative endometrial changes in two of 12 women using the 25-μg tablet for only 3 weeks. Ayton et al[115] reported that two of 194 women using the 8-μg estradiol ring for 12 weeks had bleeding and showed proliferative endometrium on biopsy. Five percent of the urogenital ring users had proliferation in the North American safety trial, with one hyperplasia detected in an endometrial polyp compared with 10% of conjugated equine estrogen cream users who showed proliferative changes but no hyperplasia at 12 weeks.[130] Several studies verify an endometrial response even to the lowest dose of local estrogen treatment. No clear threshold effect appears from review of these studies.

A more extensive experience is found with use of low-dose estriol, once thought to be of such low potency as to preclude need for progestin.[159] Weiderpass et al[160] found a 3-fold increase in endometrial cancer and an 8.3-fold increase in atypical hyperplasia among women exposed to 5 years of oral estriol therapy. Low dose vaginal estrogen therapy was used alone by 6.9% of cases compared to 6.8% of controls with an adjusted odds ratio for every use of 1.4 (95% confidence interval: 1.0–2.0). It is likely that other unopposed low-dose vaginal estrogen therapies will also increase the risk of endometrial cancer unless opposed periodically by progestins. In particular, women with chronic alcohol use[161] or altered liver metabolism may experience augmented serum estradiol levels, leading to endometrial proliferation. As a clinician, I find it difficult to identify women with heavy alcohol use at increased risk of endometrial hyperplasia. The systemic benefits of low-dose therapy noted above also suggest that women are exposed to sufficient doses locally to obligate periodic progestin for endometrial protection. Patients receiving very low dose vaginal therapy may only need a yearly progestin challenge test to provide an adequate margin of safety. Those with little bleeding in response to the progestin are unlikely to have significant proliferation.[134] Those with marked bleeding would be candidates for more frequent progestin dosing or diagnostic procedures, as indicated by the clinical scenario. In my practice, I schedule a return visit within 3 months of therapy initiation to assess blood pressure and overall response to therapy. I provide a progestin challenge at that point. If no significant vaginal bleeding is noted, switching to a yearly progestin challenge seems appropriate.

CONCLUSIONS

Urogenital menopausal symptoms are common and tend to worsen rather than remit with age. These symptoms have a significant impact on sexuality and quality of life. The use of hormone products, particularly estrogen, provides proven relief not obtained from herbal therapies. Several low dose options allow clinicians to individualize long-term therapy while minimizing estrogen dose. The limited systemic actions of these products may prove beneficial but suggest that intermittent progestin withdrawal is prudent for women with an intact uterus. Systemic therapy may also be given through the vagina, providing better relief of urogenital symptoms than other dosing forms.

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