

Update on Vaginal Atrophy

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Introduction

What is vaginal atrophy? Estrogen deficiency in women during perimenopause and after menopause has both systemic and urogenital consequences. The systematic consequences include bone loss and vasomotor symptoms such as hot flashes. Vaginal atrophy almost always occurs as a result of estrogen deficiency. While vasomotor symptoms usually improve with time and bone loss usually slows down within a few years after menopause—especially in women who remain active and get enough calcium and vitamin D—vaginal atrophy only gets worse with time. This is partially because atrophy, although mainly due to hormonal deficiency, is also caused by aging itself.

Symptoms of atrophy include vaginal dryness and pressure, vaginitis, dyspareunia, dysuria, genital pruritis and urinary urgency.¹ Declining levels of estrogen cause the supporting pelvic and urogenital diaphragms to become weakened, increasing the risk of prolapse.² Urogenital atrophy leads to decreases in the size of the uterus, ovaries, vaginal canal and vulva. Vaginal atrophy leads to the breakdown of collagen, smooth muscle and elastin in the vagina.³ Blood flow to the vagina is also reduced, leading to decreased transudation during sexual arousal as well as increased risk of trauma and pain.³ The rise in the vaginal pH, as well as thinning of the epithelium, increases the incidence of urinary tract and yeast infections in women during perimenopause and after menopause.¹

Consideration must be given to other reasons for vaginal dryness in general. Certain medications, such as antihista-

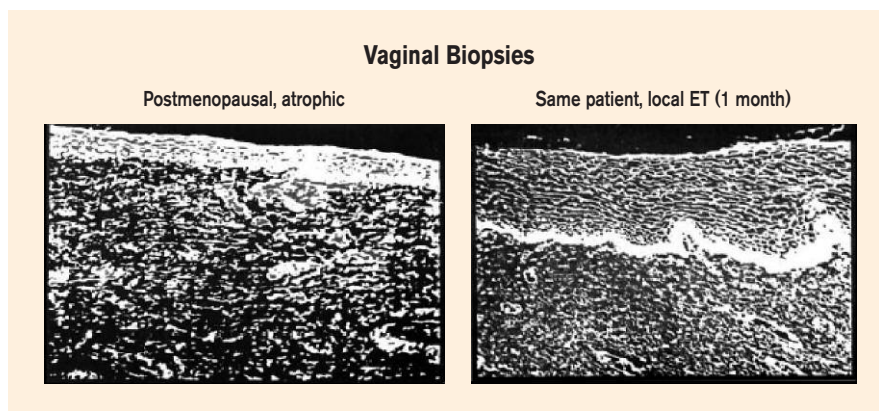


Figure. Biopsy of an estrogen-deficient woman after menopause, revealing thin and atrophic vaginal epithelium. After 1 month of local estrogen therapy, the epithelium shows almost complete regeneration. ET=estrogen therapy.

mines, parasympathomimetics and tricyclic antidepressants, can cause significant dryness that leads to atrophy. Patients with Sjögren's syndrome have insufficient moisture throughout their reproductive years that, despite adequate estrogen levels, can cause vaginal dryness.

Current Systemic Treatment

With the usual doses used in systemic estrogen-progestin therapy (EPT), it was rare not to have complete remission of vaginal atrophy symptoms, as evidenced by subjective improvement in symptoms and objective improvements, such as decreasing pH levels and a definitive change in the maturation index. This reversal of atrophy can occur even after many years of estrogen deprivation, and can be effected by both systemic and local therapy. This is demonstrated in the Figure, which shows the biopsy of an estrogen-deficient woman after menopause and almost complete regeneration of epithelium after 1 month of local estrogen therapy.

In the past 3 years there has been an effort to use lower systemic estrogen doses to meet therapeutic goals. A result of a recent study³ of a low-dose synthetic, conjugated oral estrogen tablet (0.3 mg) versus placebo randomly administered to 71 women with vaginal atrophy lends support to those efforts. After 16 weeks, all indices of atrophy reversal were shown to be significantly improved in patients receiving EPT: pH decreased from 6.2 to 5.2 compared with placebo, which did not decrease at all ($P = 0.0001$). Utian et al⁴ also showed that low-dose EPT and estrogen therapy were able to increase superficial cells and improve urogenital atrophy. However, when atrophic vaginitis and urethritis are the only significant symptoms, there has been increasing interest in treating these urogenital symptoms locally when systemic replacement therapy is no longer required for other menopause symptoms. In addition, the controversy over using systemic hormone therapy during perimenopause and after menopause has led many

women to seek alternative treatments for vaginal atrophy.

Local Estrogen Treatments

There are currently three FDA-approved formulations that provide estrogen locally, rather than systemically, to the vagina: creams, tablets, and rings. The vaginal estrogen creams contain either conjugated equine estrogens (Premarin Vaginal Cream, 0.625 mg/g conjugated estrogen) or estradiol (Estrace Vaginal Cream, 0.1 mg/g estradiol); the estrogen tablet is a slow-release estradiol tablet (Vagifem, 25 µg); and the ring is an estradiol-releasing ring (Estring, 2 mg over 3 months).

Use of the vaginal cream has been associated with a higher incidence of breast symptoms and occasional increases in endometrial thickness on pelvic sonogram, which has not been noted with use of either the ring or the tablet.⁵ However, these studies were done using a dose that is much higher than that which is used currently. The present recommended dose of estrogen cream is only 0.5 g to 1 g twice weekly. The 17β-estradiol tablet and ring also have been found to be equally effective as the hormonal cream, and women may choose these delivery systems due to their ease of use.⁵

The slow-release hydrophilic estrogen tablet contains 25 µg of 17β-estradiol.¹ It is inserted into the vagina via applicator every 3 days.

The vaginal ring releases a low-dose (8 µg/24 h) of 17β-estradiol to the vaginal mucosa continuously for 3 months.⁶ The active estrogen in both treatments is 17β-estradiol, which binds with a higher affinity to the estrogen receptors than estriol and conjugated estrogens. It is therefore possible to administer lower doses with the same efficacy.¹ The two estrogen receptors, α and β, are found in various places throughout the urogenital system. Estrogen receptor β is thought to be more important in reproductive functions, with the α receptor having a lesser effect.⁷ Specifically, these receptors are found in the proximal and distal

urethra, the vagina and the trigone of the bladder, as well as the pubococcygeus muscles of the pelvic diaphragm.⁸ Locally applied 17β-estradiol has been shown to be an excellent long-term treatment that improves the symptoms of vaginal dryness, superficial dyspareunia, vulval pruritus and urinary urgency and frequency, probably by activating and binding to estrogen receptors in these regions.⁹

There does not seem to be any significant difference in improvement levels between these two treatment options. With both ring and tablet delivery systems of 17β-estradiol, vaginal pH drops from 7.0 to 5.0 within 12 weeks of treatment, and vaginal smears also show improvement.¹ In addition, vaginal estrogen replacement has been demonstrated to help prevent urinary tract infections more than tenfold in women with urogenital atrophy.³ Simunic's comprehensive study of vaginally administered 25-µg tablets of 17β-estradiol or placebo to 1,612 symptomatic women showed a success rate in the active treatment group of 85.5% versus 41.4% in the placebo group.¹⁰ In addition, urinary symptoms, such as cystometric capacity and volume of bladder for urgency impulse, were increased ($P = 0.001$). Of course, vaginal lubricants and moisturizers are helpful in minimizing symptoms of vaginal atrophy, but they do not alleviate them, and they are totally ineffective for urinary symptoms.¹¹

All local estrogen treatments have been shown not only to decrease dyspareunia, but to improve sexual function as well. This includes improved orgasm, probably due to increased blood flow to the area.¹² Low-dose vaginal estrogen can also be used to treat symptoms of vaginal atrophy that are associated with other causes, such as chemotherapy, which has been demonstrated in some cases to cause vaginal irritation and mucositis.¹³ Raloxifene, used in the prevention and treatment of osteoporosis, has also been reported to increase vaginal dryness.¹⁴ However,

several studies have been done combining raloxifene with either a 17β-estradiol ring or conjugated estrogen cream,^{14,15} and there was both an improvement in vaginal dryness and reversal of dyspareunia.

Endometrial and Breast Effects

One of the major concerns with estrogen therapy without progesterone is endometrial proliferation, which can lead to hyperplasia and increased risk of endometrial cancer. Endometrial proliferation has been assessed in users of both the 17β-estradiol ring and the estrogen tablet in a number of ways, including progesterone challenge tests (PCTs). Withdrawal bleeding after the PCTs was rare with users of the estrogen tablet, but even though it occurred in only a few women, this response was greater than was seen for users of the estrogen ring, in whom there was no reported progesterone-induced bleeding.¹ These results suggest that neither treatment led to any significant estrogen-dependent thickening of the endometrium. Using vaginal ultrasound to assess endometrial thickness, Weisberg et al¹ reported that in both ring and tablet users, the pretreatment average endometrial thickness was 2.5 mm; after 48 weeks of treatment, the average endometrial thickness for both groups was only 2.6 mm. In the few cases in which there was any significant endometrial proliferation a biopsy was performed, and there was no evidence of malignancy in any case. Naessen and Rodriguez-Macias also confirmed that no significant change in endometrial thickness was observed with low-dose, local delivery of 17β-estradiol to the vagina.¹⁶ As far as systemic absorption, there seems to be some absorption of estrogen initially due to the atrophic nature of the vaginal epithelium; however, after 14 days of treatment, when the vaginal epithelium has been restored, absorption levels declined.¹⁷ More important, after 1 year of use, serum levels of estradiol did not show any significant increase in either group compared with placebo.¹⁸ Cicinelli et al¹⁹ have

suggested that where estradiol is placed in the vagina makes a difference in absorption into the endometrium. However, their studies were early in the treatment of atrophic vaginas and, as has been noted, there are few differences in absorption after the vaginal epithelium has been restored.

There is still much debate over whether women with either current or past breast cancer or women with a family history of breast cancer can take hormone therapy because of the role estrogen may play in tumor growth and development. However, even though the Women's Health Initiative (WHI) reported a 26% increase in diagnosed breast cancer in women taking progesterone and estrogen together after 5 years, there was no additional risk observed for women taking estrogen only.²⁰ Observational studies have demonstrated a 1.2- to 2-fold increased risk of breast cancer with 5 years' use of systematic hormone therapy that includes both estrogen and progesterone. The use of estrogen alone was not linked to an increased risk of breast cancer after a mean duration of 6.8 years.²¹ This may suggest that progesterone, and not estrogen, contributes to the increase in breast cancer that accompanies the use of systemic hormone therapy. In addition, in women who currently have breast cancer, a 5-year study by Dew et al²² demonstrated that local estrogen therapy does not appear to be associated with an increased risk for recurrence of breast cancer. Even though the study was too small to be conclusive (of 342 women using some hormone treatment in the study, 69 had only vaginal dryness and were treated with vaginal estrogens only), the results are very encouraging.

Because local treatment using low-dose, estrogen-containing vaginal creams, rings or tablets is not absorbed systematically to any significant degree, and is an estrogen-only treatment that has not been shown to pose any additional risk, it would follow that vaginal estrogen therapy would be acceptable

and appropriate for women diagnosed with breast cancer who require treatment for vaginal atrophy. However, although the blood levels and endometrial biopsies indicate almost no absorption from the vagina, it is impossible to know whether estrogen receptors are stimulated in other parts of the body, such as the breast, in some other unknown way. Currently, the FDA has not approved the use of vaginal estrogen therapy for women with diagnosed breast cancer because of this concern.

Conclusions

The biggest problem associated with vaginal atrophy is that it is often overlooked, both by the patient, who is embarrassed to bring up the subject, and by the healthcare professional, who may not think it is important or may misinterpret its importance to the patient. In the WHI, for example, diaries were used to inquire about many topics, but no woman was asked about either vaginal comfort or sexual activity. Certainly, with women and men living longer, healthier lives, both of these issues are a vital part of their quality of life and should be addressed for all women, especially after menopause. ■

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