# Treatment of atrophic vaginitis

*Camil Castelo-Branco*[†] *& Fabiola Rostro*

[†]*Author for correspondence*
*Institut Clínic de Ginecologia, Obstetrícia i Neonatologia, Hospital Clínic, Facultad de Medicina, Universidad de Barcelona, C/ Villarroel 170 08036 Barcelona, Spain*
*E-mail: castelobranco@ub.edu*

Up to 40%of postmenopausal women have symptoms of atrophic vaginitis. Since the condition is attributable to estrogen deficiency, it may also occur in premenopausal women who take antiestrogenic medications or who have medical or surgical conditions that result in decreased levels of estrogen. The thinned vaginal epithelium and increased vaginal pH level induced by estrogen deficiency predispose the vagina and urinary tract to infection and mechanical weakness. The earliest symptoms are decreased vaginal lubrication, followed by other vaginal and urinary symptoms, such as dryness, burning, itching and dyspareunia, which may be exacerbated by superimposed infection. These symptoms can contribute to sexual dysfunction, loss of sexual intimacy and may have a negative impact on overall quality of life. Once other causes of symptoms have been eliminated, treatment usually depends on estrogen replacement. Estrogen-replacement therapy decreases vaginal pH, thickens and revascularizes the vaginal epithelium, increases the number of superficial cells and reverses vaginal atrophy, and may be provided systemically, if symptoms are severe or affect quality of life, or locally; however, the dosage and delivery method must be individualized. Vaginal moisturizers and lubricants, and participation in coitus, may also be beneficial in the treatment of women with atrophic vaginitis.

Menopause is related to histological and functional changes owing to a decline in both follicular development and ovarian function. The resulting estrogen deprivation causes menopausal symptoms that include hot flushes, menstrual irregularities, night sweats, insomnia, headache, anxiety, dizziness, nervousness, depression, irritability, diminished libido, fatigue, gastrointestinal upset and urinary difficulties [1–6].

Atrophic vaginitis (AV) occurs as a result of a significant decrease in estrogens levels. When levels of estradiol are decreased, vaginal tissue becomes thinned, and this situation can be observed in menopause and some other conditions with low estrogen levels, including breastfeeding, ooforectomy before the age of natural menopause and use of gonadotropin-releasing hormone (GnRH) analogues.

Unlike vasomotor symptoms that resolve with time, urogenital symptoms do not improve and may actually worsen after the menopause [7].

Treatment for these symptoms has been based on systemic and local hormonal therapy (HT), and proved to be successful. However, this therapy is contraindicated in some women and is not accepted by others.

Despite the prevalence of symptoms, only 20–25% of symptomatic women seek medical attention [8]. Therefore, physicians have an opportunity to improve the urogenital health and quality of life (QoL) of a large patient population through identification of and intervention in this often overlooked and underdiagnosed condition.

The vagina, vulva, urethra and trigone of the bladder all contain estrogen receptors and undergo atrophy when estrogen levels decrease. This results in decreased vaginal secretion and susceptibility to trauma and pain. The vaginal epithelium becomes dry, atrophic and loses elasticity [9,10], which may cause inflammation, itching, burning, dryness, bleeding, spotting, dysuria, dyspareunia [3], urinary incontinence and recurrent urinary tract infections [10,11]. The vulvar skin becomes thinner, the labia flattens and shrinks and the clitoris, uterus and ovaries decrease in size [1]. Vaginal dryness is not limited to postmenopausal women; 15% of premenopausal women and 10–25% of women receiving systemic HT experience it [9].

More than 50% of postmenopausal women experience moderate or severe symptoms related to atrophic modifications in the genitourinary tract [9]. These symptoms can contribute to sexual dysfunction and loss of sexual intimacy [12,13] and may have a negative impact on overall QoL [14]. Dyspareunia leads to decreased interest in coitus and, as the frequency of coitus diminishes,

**Keywords:** hormonal therapy, local therapy, menopause, vaginitis

future medicine part of fsg

vaginal lubrication declines further [15]. Although cultural differences affect the frequency of, and distress caused by, menopausal symptoms [16], a decrease in sexual desire was reported in 90% of Chinese and 67% of North American women, corresponding to ranks of one and four out of 25 symptoms, respectively.

Cigarette smoking is strongly associated with worsened vaginal atrophy – smokers also have an earlier age of natural menopause and a greater proportion of them experience atrophy right from the beginning of menopause. Smoking has a direct effect on the vaginal squamous epithelium, [17] reduces estrogen bioavailability [18] and diminish blood perfusion [19].

More attention must be focused on the problems faced by women post menopause since an increasing number of women will spend approximately a third to a half of their life in the postmenopausal period. This is due to the fact that the age of spontaneous menopause in European countries is between 46.9 and 50.1 years [20] and women's life expectancy has increased significantly.

## Diagnosis

Increased clinical suspicion is the first step in the diagnosis of vaginal atrophy, which will prompt the initiation of safe therapies with proven efficacy. The diagnosis is based on physical examination and laboratory findings. During the examination, atrophic epithelium appears pale, smooth and shiny. Often, inflammation with patchy erythema, petechiae and increased friability may be present. External genitalia show diminished elasticity, ther is less turgor in the skin, a sparsity of pubic hair, dryness of the labia, vulvar dermatoses, vulvar lesions and fusion of the labia minora [8], and this friable and poorly rugated vaginal epithelium is more prone to traumatic damage. Ecchymoses and minor peri-introital lacerations may also occur after coitus or during a speculum examination, resulting in vaginal bleeding spotting.

Laboratory findings include follicle-stimulating hormone (FSH) and luteinizing hormone (LH) increased serum levels and decreased estradiol levels. Papanicolaou smear can confirm the presence of urogenital atrophy. Cytologic examination of the smears shows an increased proportion of parabasal cells and a decreased percentage of superficial cells (a high maturation index [MI] value). An elevated pH level (exceeding 4.5) [21] monitored by a pH strip in the vaginal vault may also be a sign of vaginal atrophy. On microscopic evaluation, loss of superficial cells is obvious with atrophy.

## Treatment

A number of strategies have been proposed in relation to AV; however, an agreement exists regarding the management and therapy of this condition (**Box 1**). The common treatment until the 1990s was systemic HT if symptoms are severe or affect QoL, but this treatment has been consequently reconsidered due to its adverse effects. Topical estrogenic products have subsequently been developed to minimize the systemic adverse effects of the oral HTs. Estrogen therapy decreases vaginal pH, thickens and revascularizes the vaginal epithelium, increases the number of superficial cells and reverses vaginal atrophy [3].

Estrogen or combined HT (estrogen–progestin) is highly efficacious for managing the signs and symptoms of urogenital atrophy [9]. All routes are effective, including systemic and local estrogen replacement. Various forms of estrogen-based therapies have been shown to effectively manage menopausal signs and symptoms, including those associated with vaginal atrophy [1–6].

Lower-dose estrogen therapy provides therapeutic efficacy while minimizing adverse effects. Literature supports the use of low doses of estrogen therapy for effectively relieving symptoms and restoring healthy vaginal cytology in postmenopausal women with vaginal atrophy, but even these low-dose therapies should be opposed by occasional progestogen to prevent endometrial carcinoma. Currently, the tendency is to use the effective minimum dose that combines the largest therapeutic effect with the minimum adverse effects. In a Cochrane revision, it was found that there is strong and consistent evidence that unopposed estrogen therapy, at moderate and high doses, is associated with increased rates of endometrial hyperplasia, irregular bleeding and consequent nonadherence to therapy. The addition of oral progestogens, administered either sequentially or continuously, is associated with reduced rates of hyperplasia and improved adherence to therapy. Irregular bleeding is less likely under sequential than continuous therapy during the first year of treatment, but there is a suggestion that continuous therapy over a long duration is more protective than sequential therapy in the prevention of endometrial hyperplasia. Hyperplasia is more likely when progestogen

**Box 1. Recommendations in the detection, management and treatment of atrophic vaginitis.**

- Lifestyle: increase sexual activity
- Homeopathic remedies, such as byronia, lycopodium and belladonna, administered as supplements may play a minor role
- Astroglide and other lubricants may be used (take into account whether they are compatible with latex condoms if safe sex is a consideration)
- Complementary and alternative treatments may also play a minor role, such as Chinese herbs and acupuncture
- Polycarbophilic gels
- Vitamin E, D oil, cream or capsules
- Drugs: vaginal estrogen or systemic hormone therapy

is administered every 3 months in a sequential regimen compared with a monthly progestogen sequential regimen [22].

Transdermal estradiol therapy, whether by patch or gel, also results in vaginal symptom improvement; it has been shown to relieve vasomotor symptoms and cause a significant shift in the vaginal MI compared with placebo [23,24].

Vaginal estrogen preparations are safe and effective treatments in patients with vaginal atrophy who are not candidates for systemic HT; alternatives include creams, pessaries, tablets and the estradiol-releasing vaginal ring that appeared to be equally effective in treating the symptoms of vaginal atrophy with significant differences compared with placebo and nonhormonal gel according to a Cochrane review including 19 trials of 4162 women [25]. One trial found significant side effects following cream (conjugated equine estrogen) administration when compared with tablets causing uterine bleeding, breast pain and perineal pain. Another trial found significant endometrial overstimulation following use of the cream (conjugated equine estrogen) when compared with the ring. As a treatment choice, women appeared to favor the estradiol-releasing vaginal ring for ease of use, comfort and overall satisfaction.

Rioux and colleagues found that treatment regimens with 25-µg 17β-estradiol vaginal tablets and with 1.25-mg conjugated equine estrogen vaginal cream were equivalent in relieving symptoms of AV [26]. The vaginal tablets demonstrated a localized effect without appreciable systemic estradiol increases or estrogenic side effects.

In another study, the vaginal estradiol tablet, Vagifem®, significantly raised systemic estradiol levels, at least in the short term [27]. This reverses the estradiol suppression achieved by aromatase inhibitors in women with breast cancer and is contraindicated in those cases.

Vaginal tablet therapy resulted in greater patient acceptance and lower withdrawal rates compared with vaginal cream therapy.

Mainini and colleagues observed that low-dose 17β-estradiol vaginal tablets in the treatment of postmenopausal AV constitutes an extremely valid approach in terms of effectiveness and safety [28].

Speroff observed that a ring containing an estradiol acetate core improves the vaginal MI in 97.5 compared with 70% of patients with a placebo ring. Self-reported symptoms of vaginal dryness and dyspareunia improved, as did the sexual dysfunction subscale of the Greene Climacteric questionnaire [29]. Marketed rings in the USA include a ring for systemic and vaginal menopausal therapy that provides average serum estradiol levels of 40.6 pg/ml for the 0.05-mg and 76 pg/ml for the 0.1-mg dose, and a ring for urogenital menopausal symptoms only that minimally elevates serum estradiol, usually within the menopausal range, treating AV and urethritis. Vaginal rings offer a novel approach to menopausal HT producing consistent serum levels sustained for up to 3 months per unit dose with lower adverse effects than other vaginal products and high acceptability among users [30].

In some cases, topical estrogenic products are still considered at risk in case of prolonged use and some women cannot or do not want to use them, therefore, they may use water-soluble vaginal lubricants and vaginal moisturizers applied on a regular basis that have an efficacy equivalent to local HT in relieving vaginal dryness [31].

As an alternative, two clinical trials were performed to investigate the effects of a medical device in the form of a gel, containing hyaluronic acid, liposomes, phytestrogens from *Humulus lupulus* extract and vitamin E. This device could be considered an effective and safe alternative treatment for genital atrophy in postmenopausal women, especially when HT is not recommended [32]. However, alone, these products are not a solution for AV.

## Sexual activity

Sexual activity is a healthy prescription for postmenopausal women. It has been shown to encourage vaginal elasticity and pliability, and initiate a lubricative response. Women who participate in sexual activity report fewer symptoms of AV and, on vaginal examination, have less evidence of stenosis and shrinkage in comparison with sexually inactive women. A

negative relationship exists between coital activity, including masturbation, and symptoms of vaginal atrophy [8]. Coitus is not hypothesized to restore or maintain estrogen in postmenopausal women because no positive relationship has been shown to exist between estrogen levels and sexual activity. The existence of a positive relationship between coital activities and both gonadotropins and androgens demonstrates the importance of these compounds to healthy vaginal epithelium when estrogen levels are decreased.

**Executive summary**

- Up to 40%of postmenopausal women have symptoms of atrophic vaginitis.
- Atrophic vaginitis is linked to estrogen deficiency and is not only related to postmenopausal status.
- The atrophy of the epithelium and an increase in vaginal pH predispose the vagina and urinary tract to infection and mechanical injury.
- Decreased vaginal lubrication, dryness, burning, itching and dyspareunia, the most common symptoms, can contribute to sexual dysfunction, loss of sexual intimacy and may have a negative impact on quality of life.
- Estrogen-replacement therapy decreases vaginal pH, thickens and revascularizes the vaginal epithelium, increases the number of superficial cells and reverses vaginal atrophy
- Vaginal moisturizers and lubricants and participation in coitus may also be beneficial in the treatment of women with atrophic vaginitis.

Johnston and colleagues recommended that healthcare providers routinely assess postmenopausal women for the symptoms and signs of vaginal atrophy, a common condition that exerts significant negative effects on QoL. Regular sexual activity should be encouraged to maintain vaginal health and should be offered to women wishing to avoid use of hormone-replacement therapy [31].

## Conclusion

AV is the result of a significant decrease in estrogens levels. When levels of estradiol are decreased, vaginal tissue becomes atrophic and common vaginal symptoms appear and tend to worsen with age, having a significant impact on sexuality and QoL. The use of HT in both local and systemic administration has been shown to effectively manage menopausal signs and symptoms, including those associated with vaginal atrophy and, if this therapy cannot be used or is refused, water-soluble vaginal lubricants and vaginal moisturizers can be an option.

## Future perspective

Since vaginal atrophy typically develops so slowly that a woman may not notice any symptoms until 5–10 years after menopause begins, prevention policies will be mandatory in the next few years. Vaginal lubricants, topical estrogens and regular sexual activity should be encouraged to patients.

## Bibliography


1. Beers MH, Berkow R: Gynecology and obstetrics. In: *The Merck Manual of Diagnosis and Therapy (17th Edition).* Merck Research Laboratories, Whitehouse Station, NJ, USA 1942–1944 (1999).
2. Bachmann GA: Urogenital aging: an old problem newly recognized. *Maturitas* (Suppl. 22), S1–S5 (1995).
3. Bachmann GA, Nevadunsky NS: Diagnosis and treatment of atrophic vaginitis. *Am. Fam. Physician* 61, 3090–3096 (2000).
4. Greendale GA, Judd HL: The menopause: health implications and clinical management. *J. Am. Geriatr. Soc.* 41, 426–436 (1993).
5. Nilsson K, Risberg B, Heimer G: The vaginal epithelium in the postmenopause-cytology, histology, and pH as methods of assessment. *Maturitas* 21, 51–56 (1995).
6. Semmens JP, Wagner G: Estrogen deprivation and vaginal function in postmenopausal women. *J. Am. Med. Assoc.* 248, 445–448 (1982).
7. Rymer J, Morris EP: Extracts from "clinical evidence": menopausal symptoms. *BMJ* 321, 1516–1519 (2000).
8. Bachmann G, Nevadunsky N: Diagnosis and treatment of atrophic vaginitis. *Am. Fam. Physician* 61(10), 3090–3096 (2000).
9. Willhite LA, O'Connell MB: Urogenital atrophy: prevention and treatment. *Pharmacotherapy* 21, 464–480 (2001).
10. Forsberg JG: A morphologist's approach to the vagina – age-related changes and estrogen sensitivity. *Maturitas* 22, S7–15 (1995).
11. Maloney C: Estrogen and recurrent UTI in postmenopausal women. *Am. J. Nurs.* 102, 44–53 (2002).
12. Sarrel PM: Effects of hormone replacement therapy on sexual psychophysiology and behavior in postmenopause. *J. Womens Health Gend. Based Med.* 9, S25–S32 (2000).
13. Berman JR, Goldstein I: Female sexual dysfunction. *Urol. Clin. N. Am.* 28, 405–416 (2001).
14. Freedman MA: Quality of life and menopause: the role of estrogen. *J. Womens Health (Larchmt.)* 11, 703–718 (2002).
15. Bachmann GA, Leiblum SR, Grill J: Brief sexual inquiry in gynecological practice. *Obstet. Gynecol.* 73, 425–427 (1989).
16. Avis NE, Stellato R, Crawford S *et al.*: Is there a menopausal syndrome? Menopausal status and symptoms across racial/ethnic groups. *Soc. Sci. Med.* 52, 345–356 (2001).
17. Kalogeraki A, Tamiolakis D: Cigarette smoking and vaginal atrophy in postmenopausal women. *In Vivo* 10(6), 597–600 (1996).

18. Baron JA, La Vecchia C, Levi F: The antiestrogenic effect of cigarette smoking in women. *Am. J. Obstet. Gynecol.* 162, 502–514 (1990).
19. Monfrecola G, Riccio G, Savarese C, Posteraro G, Procaccini EM: The acute effect of smoking on cutaneous microcirculation blood flow in habitual smokers and nonsmokers. *Dermatology* 197(2), 115–118 (1998).
20. Cuadros JL, Llaneza P, Mateu S: Demografía y epidemiologia del climaterio en España. In: *AEEM. Libro Blanco del Climaterio en España.* Bernard-Krieg (Ed.). Madrid, Spain 15–33 (2000).
21. Pandit L, Ouslander JG: Postmenopausal vaginal atrophy and atrophic vaginitis. *Am. J. Med. Sci.* 314, 228–231 (1997).
22. Lethaby A, Suckling J, Barlow D *et al.*: Hormone replacement therapy in postmenopausal women: endometrial hyperplasia and irregular bleeding. *Cochrane Database Syst. Rev.* (3), CD000402 (2004).
23. Henzl MR, Loomba PK: Transdermal delivery of sex steroids for hormone replacement therapy and contraception. A review of principles and practice. *J. Reprod. Med.* 48, 525–540 (2003).
24. Archer DF: Percutaneous 17β-estradiol gel for the treatment of vasomotos symptoms in postmenopausal women. *Menopause* 10, 516–522 (2003).
25. Suckling J, Lethaby A, Kennedy R: Local oestrogen for vaginal atrophy in postmenopausal women. *Cochrane Database Syst. Rev.*(4), CD001500 (2006).
26. Rioux JE, Devlin C, Gelfand MM, Steimberg WM, Hepburn DS. 17 β-estradiol versus conjugated equine estrogen vaginal cream to relieve menopausal atrophic vaginitis. *Menopause* 7(3), 140–142 (2000).
27. Kendall A, Dowsett M, Folkerd E, Smith I: Caution: vaginal estradiol appears to be contraindicated in postmenopausal women on adjuvant aromatase inhibitors. *Ann. Oncol.* 17(4), 584–587 (2006).
28. Mainini G, Scaffa C, Rotondi M, Messalli EM, Quirino L, Ragucci A: Local estrogen replacement therapy in postmenopausal atrophic vaginitis: efficacy and safety of low dose17 β-estradiol vaginal tablets. *Clin. Exp. Obstet. Gynecol.* 32(2), 111–113 (2005).
29. Speroff L: Efficacy and tolerability of a novel estradiol vaginal ring for relief of menopausal symptoms. *Obstet. Gynecol.* 102, 823–834 (2003).
30. Ballagh SA: Vaginal rings for menopausal symptom relief. *Drugs Aging* 21(12), 757–766 (2004).
31. Johnston SL, Farrell SA, Bouchard C *et al.*: Detection and management of vaginal atrophy. *J. Obstet. Gynaecol. Can.* 26(5), 503–515 (2004).
32. Morali G, Polatti F, Metelitsa EN, Mascarucci P, Magnani P, Marre GB: Open, non-controlled clinical studies to asses the efficacy and safety of a medical device in form of gel topically and intravaginally used in postmenopausal women with genital atrophy. *Arzneimittelforschung* 56(3), 230–238 (2006).