REVIEW ARTICLE

Atrophic Vaginitis: Diagnosis and Treatment

Surveen Ghumman

ABSTRACT

Atrophic vaginitis is an inflammation of the vagina which develops when there is a significant decrease in estrogen levels after menopause. The initial and most common symptom is often lack of lubrication during intercourse. Eventually, persistent vaginal dryness may occur leading to dyspareunia. The onset of symptoms may not be immediate and may occur 3 to 4 years after menopause. Nonhormonal treatment includes vaginal moisturizers for atrophy symptoms, lubricants for dyspareunia, hyaluronic acid vaginal tablets and phtoestrogens. Estrogens are known to increase vascularity, secretions and thickness of vagina and decrease vaginal pH. They can be given both systemically or vaginally. Local therapy has been found to be more efficacious than systemic therapy and has the advantage of not having systemic adverse effects. They can be given as pessaries, creams or rings. Delivery system used should be convenient to patient so that therapy is consistent, as that is critical for effect. Improvement in vaginal atrophy symptoms starts within a few weeks of starting vaginal estrogen but, some may need to use it for 4 to 6 weeks before adequate improvement is observed. Selective estrogen receptor modulator bazedoxifene may be combined with estrogens. Postmenopausal vaginal atrophy is a common cause of easily treatable distressing symptoms which severely affect quality of life.

Keywords: Menopause, Vaginitis, Atrophy, Dyspareunia, Estrogens, Hyaluronic acid.

How to cite this article: Ghumman S. Atrophic Vaginitis: Diagnosis and Treatment. J South Asian Feder Menopause Soc 2013;1(1):4-12.

Source of support: Nil

Conflict of interest: None declared

INTRODUCTION

Atrophic vaginitis is an inflammation of the vagina which develops when there is a significant decrease in estrogen levels. The common known changes reported with menopause are hot flushes and bone changes. However, the lesser stressed changes like vaginal atrophy and urogenital changes, are major determinants of quality of life and sexual function after menopause. Vasomotor symptoms abate overtime regardless of therapy being instituted or not; however, vaginal atrophy is progressive and never resolves spontaneously. Up to nearly 10 to 40% of patients experience urogenital atrophy after menopause, although only 25% of these report with symptoms to the gynecologist.[1] Even 10 to 25% of women receiving systemic hormone replacement therapy (HRT) may experience some amount of vaginal atrophy.[2]

Vaginal Physiology and Estrogen Deficiency

The effects of endogenous estrogens on vulvovaginal tissues are mediated through estrogen receptors (ERs) α and β, found at sites throughout the urogenital area, including the vagina, vulva, labia, urethra and bladder trigone. Estrogen-receptor alpha is present in the vaginal tissues of both pre- and postmenopausal women, whereas estrogen-receptor beta appears to be present only in premenopausal vaginal tissues. The vagina is particularly sensitive to circulating levels of estrogen. Estrogen maintains the collagen content. It also maintains the skin and urogenital integrity by increasing acid mucopolysaccharides and hyaluronic acid and maintains epithelial barrier function. The term vaginal atrophy describes vaginal walls that are thin, pale, dry and sometimes inflamed. The collagen fibers tend to swell and hyalinise, while the elastic fibers and muscles tend to fragment. This leads to increased connective tissue and loss of elasticity resulting in decreased vaginal length, diameter and distensibility. There is disappearance of vaginal fornices and smoothening of rugae. The vaginal epithelium has a dry, glazed appearance with varying degrees of erythema or pallor and it can be easily traumatized and irritated.

As epithelial cells exfoliate and die, they release glycogen, which is hydrolyzed to glucose. Glucose, in turn, is broken down into lactic acid by the action of *Lactobacillus*, a normal vaginal commensal organism. After menopause, there is a decrease in superficial cells in response to decreased levels of estrogen. This results in decreased glycogen production and as the result a reduction in glucose. Lack of glucose leads to decreased lactic acid production by Lactobacilli resulting in rise of pH in the vagina. Rise in pH leads to a loss of Lactobacilli and an increased colonization of fecal flora, group B *Streptococcus*, Staphylococci and coliform organisms. Infiltration of submucosal layer of vagina by lymphocytes and plasma cells is seen.

In later stages, there may be a friable mucosa, with petechiae, ulcerations, tears and bleeding with increased chance of trauma, infection and pain.

As blood flow to the vagina and vaginal-cervical paracellular permeability is reduced, it results in decreased transudation during sexual arousal. Although, the sebaceous glands remain prominent, their secretions diminish and the onset of lubrication during sexual stimulation is delayed. Reduced tissue elasticity, in addition to shortening and narrowing of the vaginal vault and dryness of vagina, can lead to dysparunia. There is a reduced sexual desire, poor arousal and inadequate satisfaction. Diminished sensory response may reduce orgasmic intensity and, physiological

responses of sexual arousal like smooth muscle relaxation, vasocongestion and vaginal lubrication are blunted. Reduced androgen levels and aging of body systems may contribute to sexual dysfunction. However, sexual symptoms vary with women as they are dependent on the emotional well-being and interpersonal relationship of the women with her partner.

There are similar findings in the urethra and bladder with atrophy of smooth muscles. Urinary symptoms like urgency, incontinence, dysuria, nocturia reflect changes in urinary tract.

Etiology and Risk Factors

Since it is seen that the onset of vaginal atrophy is variable from the time of menopause in various women, besides decreased levels of estrogen, other factors may come into play and influence the onset of symptoms. Cigarette smoking has a direct effect on vaginal epithelium as it reduces bioavailability and decreases blood perfusion, thus accelerating changes in vaginal epithelium.

Postmenopausal levels of androgens, androsteinedione and testosterone may influence onset of symptoms. Women with higher levels have fewer atrophic changes and maintain sexual activity better.

Women who have a nulliparous vagina and have not given birth vaginally tend to have a greater chance of vaginal atrophy, while women who remain sexually active tend to have less atrophic changes and these changes are delayed in onset.

Patient Evaluation

Many women do not seek treatment for vaginal dryness as they consider it to be part of the aging process which has no treatment. Some are too embarrassed to talk about it and only one-third of affected women receive medical care. [3]

Symptoms

Most women have two types of manifestations, those pertaining to vaginal atrophy and those concerned with the lower urinary tract-like incontinence and recurrent urinary tract infection (UTI). The initial and most common symptom is often lack of lubrication during intercourse. Eventually, persistent vaginal dryness may occur leading to dyspareunia. Women present with symptoms of vaginal dryness, itching, discharge, pain and dyspareunia. Vaginal bleeding may occur due to small tears in the vaginal epithelium, if atrophy is severe. The overall prevalence of vaginal dryness, soreness and dyspareunia was 27% in a study. Almost half of the symptomatic women reported moderate to severe discomfort. Previous hysterectomy had no effect on the reported prevalence estimates.[3] Around 80% of women report a decrease in sexual desire, decline in sexual satisfaction and difficulty in having organism.[4] Some women present with recurrent UTI. Around 73% of the women had some degree of urinary incontinence.[5]

The onset of symptoms may not be immediate and may occur 3 to 4 years after menopause. This time period may vary from person to person. Many women may present only with symptoms without any classical signs of atrophy. It is important to workup sexual health problems by taking a comprehensive sexual, medical and psychosocial history. Information to be collected during the patient history includes her partner relationship, current sexual activity, history of interventions used, therapeutic goals for vaginal symptoms and level of perceived distress associated with the reported complaints. Physiological, psychological and behavioral responses to the symptoms should also be included.

A good history should rule out other causes of hypoestrogenic states (e.g. premature ovarian failure, hypothalamic amenorrhea, hyperprolactinemia and possibly prolonged lactation), some endocrine therapies (e.g. SERMs, aromatase inhibitors and gonadotropin-releasing hormone [GnRH] agonists or antagonists, long-term or potent progestogens) and medically-induced menopause (e.g. cancer chemotherapy and radiotherapy). Postmenopausal women suffering from infection (*Candida vulvovaginitis*, bacterial vaginosis and trichomoniasis), trauma, foreign body, allergic reaction, inflammatory conditions of the vulva, vulval dystrophy, lichen sclerosus, lichen planus and lichen simplex chronicus. Other medical disorders (e.g. diabetes, lupus erythematosus) and psychological causes can present in a similar way. Cancer and precancerous lesions, including vulvar intraepithelial neoplasm, vulvar cancer and extramammary Paget disease, may cause localized erythema.

Signs

There may be discrepancies in signs and symptoms in a woman. In early stages, the epithelium becomes thin and dry and vagina may be erythematous. Later, vaginal mucosa becomes flattened and pale due to loss of rugae. Epithelium becomes friable and inflamed with peticheal spots, ulcers and foul discharge. Fibrosis leads to shortening of vagina, smoothening of vaginal fornix, narrowing of enroitus and obliteration of vault. Urethral caruncle is often a sign of urogenital aging.

Vulval and labial loss of fat makes the labia majora pendulous and causes shrinkage of labia minora with shortening of prepuce. There is also loss of pubic hair.

Tissues of the vulva become pallid, thin and dry. Vestibule may become tender. Itching, dryness burning occur due to thinning of epithelium, dryness and decreased vascularity.

There may be other signs of urogenital atrophy like a prolapse, cystocele or rectocele.

Laboratory Findings

Diagnosis of vaginal atrophy is based on clinical findings. However, two tests may support the diagnosis. For objective assessment of the vagina, epithelium maturation index and pH are done, as in vaginal atrophy both are altered.

Vaginal pH is usually more than 5 in this condition. A piece of litmus paper placed on the lateral vaginal wall till moistened, showing a pH of 4.6 or greater indicates atrophy, assuming the patient does not have bacterial vaginosis.[6]

Vaginal cytology, expressed as mean maturation index (MI) shifted significantly from 94/6/0 to 0/65/35. Vaginal maturation index shows predominance of basal cells. Wet mount microscopy shows usually more than one white blood cell per epithelial cell, immature vaginal epithelial cells with relatively large nuclei (parabasal cells), and reduced or absent Lactobacilli. The wet mount of atrophy is identical to that of desquamative inflammatory vaginitis or vaginal lichen planus; therefore, a trial of adequate local estrogen is essential to differentiate these two conditions.

Vaginal culture may reveal growth of a pathogenic organism as diverse flora-like enteric organisms are commonly associated.

Treatment

Treatment would mean alleviation of symptoms which would happen once there is restoration of normal anatomy and physiology by reversing atrophic changes. Any condition caused due to decrease of a hormone can be reversed by supplementing the hormone. Although all urogenital changes cannot be reversed, most of the vaginal changes due to decreased estrogen levels can be reversed. The effects of estrogen on other urogenital symptoms, like urinary frequency, urgency, incontinence and UTIs, may respond differently because of multifactorial causes, not all related to estrogen deficiency. The principles of clinical management include measures to enhance overall health, lifestyle modification, supplementation with hormones like estrogens and/or androgen and adjustment of medication regimes to minimum effective doses in order to curtail side effects.

Lifestyle Modification

Certain lifestyle modifications may delay or decrease symptoms. Since symptoms are due to decreased estrogen, any habit which causes a depletion of estrogen like smoking should be discouraged. Smoking causes increased metabolization of estrogen and affects vaginal epithelium by increasing atrophic changes. It also causes an early menopause, on average 2.4 years sooner than nonsmokers, by mechanisms, some of which remain unclear. [7,8]

The second lifestyle change pertains to sexual activity. Less vaginal atrophy was apparent in the sexually active women as opposed to the sexually inactive women. Regular sexual coitus and masturbation are known to decrease the incidence of atrophy, probably by increasing blood flow. Further, women with high androgen levels (androstenedione and testosterone) and gonadotropins (particularly LH) have less atrophic changes and maintain sexual interest. [9]

Nonhormonal Therapies

It is indicated where patients have mild symptoms and do not want to use hormonal therapy or where hormones are contraindicated. Current over-the-counter treatments include, nonhormonal vaginal moisturizers for atrophy symptoms and lubricants for dyspareunia.

Lubricants

Lubricants are used to relieve the vaginal dryness and may help to alleviate dyspareunia. However, the effects are temporary and often require repeated application on the vaginal opening and/or to the penis during sexual activity to reduce dyspareunia. Lubricants can be either water or silicone based. The water-based products are most widely available. Silicone-based lubricants require application of only a very small amount and last longer, but have the disadvantage of interfering with the erectile function in male partners.

Moisturizer

The effect of a vaginal moisturizer lasts much more than a lubricant. Polycarbophil-based vaginal moisturiser is a bioadhesive polymer, it is water insoluble, but water swellable. Their hydrophilic property retains water and their bioadhesive property makes them bind to vaginal epithelial cells, releasing purified water to hydrate the underlying cells. The gel produces a moist film over the epithelial cell surface coating it and thus lubricates the vaginal wall and reduces the incidence of vaginal itching, irritation and dyspareunia. Their buffering properties lead to a lowering of vaginal pH to premenopausal values. They improved the maturation of the vaginal epithelium.[10] Vaginal moisturizers, which are water based, are available as liquids, gels or ovules inserted every few days. Gel is applied three times a week and provides complete therapy. Vaginal moisturizers can be

safely used long-term with no known serious adverse effects, but they need to be used regularly for optimal effect. It improves vaginal dryness in women taking HRT also.[11] On comparison of vaginal moisturizer to vaginal estrogen cream both, improved the vaginal dryness index but dienostrol cream was more effective. For symptoms like itching, irritation and discomfort during intercourse both were equally effective.[12,13] Hence, moisturizer forms not only an alternative treatment to local estrogen, but also a good complement to systemic HRT where vaginal symptoms are not responding adequately. However, a recent study showed only a transient beneficial effect with a polycarbophillic moisturizer, whereas estrogen in low doses was very effective in alleviating symptoms.[14]

Hyaluronic Acid Vaginal Tablets

Hyaluronic acid sodium salt given as a 5 mg vaginal tablet for 8 weeks showed beneficial effects. On comparison with vaginal tablets of 25 μg estradiol, both treatments provided relief of vaginal symptoms, improved epithelial atrophy, decreased vaginal pH and increased maturation of the vaginal epithelium, though improvements were greater with estradiol. Hyaluronic acid vaginal tablets are an alternative for patients who want nonhormonal treatment. [15]

Phytoestrogens

Soy and isoflavones have shown beneficial effects on vaginal atrophy and increased maturation index of the vaginal epithelium.[16] However, a randomized controlled trial evaluating dietary supplementation with 12 to 20 mg/d of soy showed no improvement in vaginal maturation index.[17]

Vitamins D and E

Vitamins D and E, both, have been found to be beneficial to vaginal atrophy symptoms. It is seen that vitamin D is involved in the regulation of growth and differentiation of many cells. Especially, stratified squamous epithelium, as present in the vagina, is under control of vitamin D. Postmenopausal women given vitamin D, had stratified epithelium with superficial: intermediate: basal in ratio of 35:45:20, whereas those untreated were in a ratio of 5:31:64.[18] Vitamin E is given in a dose of 100 to 600 IU/day orally. It can be applied locally also to increase lubrication.[19]

Pilocarpine

Oral pilocarpine has been shown to improve vaginal dryness.[20]

Topical Anesthetics

Topical anesthetics may have a role in women with painful atrophy.

Alternative Medicine Remedies

Homeopathic remedies include bryonia, lycopodium and belladonna. Other natural remedies are nettle to rehydrate dry vaginal tissues and comfrey root to keep vaginal tissues soft and lubricated. Black cohash, Dong quai, motherwort, chickweed tincture, wild yam and acidophilus capsules may have a beneficial effect. However, all these remedies have failed to show a significant effect in randomized controlled trials.[17,19]

Hormonal Therapy

Estrogens are known to increase vascularity, secretions and thickness of vagina, and decreases vaginal pH. This leads to decrease in both symptoms of the urinary tract and in genital tract-like atrophic vaginitis. Hormonal therapy in the form of estrogens can be given by both, systemic and local route. Systemic estrogen replacement therapy may be unacceptable for many women because of the concerns over possible risks and may not cure vaginal symptoms in up to 45% of users. Topical vaginal estrogen preparations reverse atrophic changes and relieve associated symptoms while avoiding systemic effects.[21] In a meta-analysis of 77 studies, it was found that all routes of administration appeared to be effective and maximum benefit was obtained between 1 and 3 months after the start of treatment.[22]

Systemic Estrogen Therapy

Systemic estrogen reverts changes in vaginal epithelium and thus relieves symptoms within 3 weeks. It is indicated specially if a women has other symptoms of menopause, like hot flushes which also need to be treated.

All preparations are effective but the ones with estriol are least effective. Treatment with low-dose slow release synthetic conjugated estrogen tablets, 0.3 mg for 16 weeks resulted in a highly significant mean increase in vaginal maturation index compared with placebo treatment in a recent study. A significant estrogenic improvement was detected as early as 4 weeks. Superficial cells were significantly increased from 2.1% at baseline to 15.9% at week 16, and parabasal cells were significantly reduced from 23% at baseline to 1.6%. These results confirm the relatively rapid estrogenic effect of a low-dose (0.3 mg/day) slow-release conjugated estrogen A in vaginal atrophy.[23]

Although, systemic administration of estrogen is effective in treating acute vasomotor symptoms typically associated with perimenopause and early menopause, standard doses may not be sufficient for the treatment of atrophic vaginitis-related symptoms that generally arise after long-term estrogen deficiency. It is to be noted that 25% of women may not be relieved of vaginal atrophy symptoms

and may need local estrogens.[24] Thus, vaginal estrogen preparations (e.g. creams, tablets, rings) are more often recommended for women with moderate to severe atrophic vaginitis. With any estrogen therapy, consideration of the potential adverse effects *vs* associated benefits is necessary.[25]

Local Estrogen Therapy

Local therapy has been found to be more efficacious than systemic therapy and has the advantage of not having systemic adverse effects. However, some amount of systemic absorption does take place more so in the initial stages of therapy when vaginal epithelium is atrophic. As epithelium thickens, less dose is required to maintain effect. With 0.3 mg vaginal conjugated estrogens, the response was similar to that exerted with 1.25 mg oral conjugated estrogen. Stepwise increases in circulating estrone and estradiol occurred with increasing dosages. The 2.5 mg dosage of vaginal conjugated estrogen raised estrone levels to values similar to those in premenopausal women in the late follicular phase, and estradiol concentrations were similar to early follicular phase concentrations. Small decreases in luteinizing hormone and follicle stimulating hormone levels were observed, but there was no significant effect on circulating levels of triglycerides or cholesterol levels. These data suggest that the vaginal administration of conjugated equine estrogens exerts mainly a local effect, with limited or no measurable changes in systemic markers of the action of estrogen.[26]

The various preparations are equine estrogens, estriol and estradiol. The advantage of using estriol is that since low doses of estrogen are required for relief of vaginal symptoms, low potency estriol has less systemic effects but alleviates vaginal symptoms. The least systemic absorption of estrogen was seen with estriol (administered orally or vaginally).[22] There are three modalities for local administration—pessaries, creams or rings.

Estrogen Vaginal Pessaries

Intravaginal estradiol tablets: Vaginal tablets of 17 β-estradiol hydrophilic slow release tablets are started in a dose of 1 tablet per day for 2 weeks and thereafter are inserted every 3 days high up in vagina for maintenance therapy. Upon contact with vaginal mucosa, a gel forms allowing rapid diffusion of the drug. (tablet contains 25.8 µg of estradiol hemihydrate equivalent to 25 µ of estradiol). There is an ease of use compared with creams and it has a higher compliance rate. However, in recent years a lower dose of estradiol tablet of 10 µg have been tried and showed that after 12 weeks, the change from baseline for 10 µg E2 compared with placebo demonstrated significant improvement in vaginal maturation index, maturation value, vaginal pH and the most bothersome symptoms. Effects became statistically different from placebo after 2 weeks of treatment.[27] On comparison of 10 µg vaginal tablets with 25 µg, both provided relief of vaginal symptoms, improved urogenital atrophy, decreased vaginal pH and increased maturation of the vaginal and urethral epithelium. However, these improvements were greater with 25 µg than with 10 µg E2.[28,29] The 25 µg estradiol tablet provides serum values of 5 to 10 pg/ml, while with 10 µg estradiol tablet the serum levels were found to be below 5 pg/ml.

Estriol vaginal suppository: In a 24-week trial of a vaginal suppository (tablet) containing 3.5 mg estriol, therapy significantly improved symptoms of urogenital complaints and relieved vasomotor symptoms as well, when compared with placebo.[30]

Estrogen Vaginal Cream

Conjugated equine estrogen cream: Vaginal cream has been in use longer than the other types of vaginal estrogen therapy. Each gram of conjugated equine estrogen cream contains 0.625 mg. Doses ranging from 0.5 to 2.0 g (delivering 0.3 mg to 1.25 mg CE) in schedules ranging from once daily to two or three times weekly have been tried. However, lowest effective dose is started, that is 0.3 mg of equine estrogen applied each day for 2 weeks. After the initial therapeutic response is attained, the frequency can be decreased to alternate day or twice weekly for maintenance, but it should be titrated to the lowest dose and frequency that provides the desired effect. Twice-weekly use of low-dose CE cream was as effective as daily administration in relieving symptoms of vulvovaginal atrophy. Both regimens showed endometrial safety and sustained efficacy of therapy at least over 1 year. Dosing is recommended at least 12 hours before coital activity.[31,32]

Vaginal estradiol cream: No randomized controlled trial data are available for a vaginal cream containing estradiol.

Sustained-Release Intravaginal Estradiol Ring

The sustained-release estradiol ring is a flexible silicon ring with an estradiol-loaded core containing 2 mg of micronized estradiol, and it releases 7.5 µg of estradiol every 24 hours over 3 months. It requires to be replaced every 3 months. More than 90% patients showed significant improvement in maturation value and restored vaginal pH to normal levels. About 90% did not remove the ring during any of the 3-month treatment periods, and 78% used this method continuously up to 1 year. There was a uniform, sustained local release unlike with the cream where irregular absorption caused erratic local levels. The ring was given a

strong preference by patients with previous experience of other administration forms as insertion was required only every 3 months. There were occasional reports of vaginal irritation and bleeding, none associated with malignancy or endometrial proliferation and serum estradiol levels remained unchanged. Rarely vaginal ulcers were reported.[33,34]

Patient Management for Local Estrogen Therapy

In starting estrogen therapy the aspects to be considered are choice of vaginal estrogen, patient selection with respect to risk factors, length of treatment with vaginal estrogen and on-going monitoring.

Choice of Vaginal Estrogen

When one has to decide which estrogen is to be used, the efficacy, side effects, ease and economics of administration have to be taken into consideration.

Efficacy: Efficacy would be assessed in terms of subjective vaginal symptoms (dryness, dyspareunia, burning), objective assessment by appearance of the vagina for signs of atrophy (e.g. pallor, dryness, friability, petechiae) and changes in pH and vaginal cytology. A Cochrane review conducted in 2006 with 19 trials and 4162 women showed creams, pessaries and the estradiol vaginal ring appeared to be equally effective for the symptoms of vaginal atrophy, and were more effective than nonhormonal gels and placebos.[35]

Adverse effects: The second aspect is adverse effects. The most commonly reported adverse effects associated with vaginal estrogen are vaginal bleeding, breast pain, nausea and perineal pain, all of which occur due to systemic absorption and have been seen with all preparations but more with creams because there is a greater potential for patients to apply higher-than-recommended dosing with cream. Systemic absorption occurs in all preparations of vaginal estrogens, but to a limited extent. It was seen that levels of estradiol increased on average from a baseline (pretreatment) level of 3 pg/ml to 17 pg/ml on day 7 of treatment for both estradiol vaginal tablets (25 μg) and conjugated estrogen cream (0.625 mg).[36] Although plasma estradiol concentration diminished by 2 weeks of daily treatment with 10 or 25 μg of vaginal estradiol, it was still statistically significantly higher than pretreatment levels.[37] Higher levels of estradiol are seen with cream compared with the estradiol tablet and in the estradiol tablet compared with the estradiol ring.

There is no increased incidence of endometrial hyperplasia, carcinoma or thromboembolic phenomenon with local estrogens. A few cases of hyperplasia are reported, on use of conjugated and estradiol preparations but none with estriol. However, the Cochrane review reported no significant differences among the delivery methods in terms of hyperplasia, endometrial thickness or the proportion of women with adverse events.[35] Subsequent studies also have shown no increase in endometrial hyperplasia.[38,39] The reported background incidence rate of endometrial hyperplasia and carcinoma in postmenopausal women is 0 to 1%. In a pooled analysis, there was an incidence of 0.52% of endometrial hyperplasia after 1 year of low dose (10 μg) local estrogens, thus showing no increase in incidence.[40] Hence, progestogens or yearly surveillance by biopsy is not recommended. However, if there is vaginal bleeding during the therapy complete evaluation is warranted.

There may be local symptoms of irritation with some preparations specially creams. There are no data to suggest that an allergic reaction occurs from the silastic plastic of the vaginal ring.[34] A review of 22 randomized controlled trials of vaginal estrogens used by postmenopausal women with signs or symptoms of vaginal atrophy showed that there were no serious adverse events reported. Long-term safety of the preparations is best established for estradiol tablets only up to 1 year but is lacking for all other preparations.[39,41]

Ease of administration: Other aspects which decide the preference for type of preparation are based on ease of administration, dosage and economics. Estrogen creams are most economical and widely used. Dosing vaginal creams can be confusing because the dose of active estrogen cream is specified in milligrams, the dose of base cream is in grams and applicator volume is in proportions. The estradiol tablet avoids the messiness of cream and is preferred by some. Vaginal creams and pessaries were more appropriate where there were coital problems as they provided better lubrication, although they had the disadvantage of vaginal discharge. There was less discharge with rings and tablets**.** The estradiol ring is long acting and does not need daily application. However, it requires skill to insert and remove and needs to be changed every 3 months. It had a disadvantage in women with very narrow entroitus and those with limited dexterity which accompany old age, as it was difficult to insert. In these cases, since the ring has to be changed every 3 months and need not be removed before that, it can be done by a healthcare professional. Cases of repeated expulsion in women with pelvic organ prolapse and those who have been hysterectomized are reported. It may change position or dislodge with bowel movements, Valsalva maneuvers, douching or vaginal sexual intercourse. The ring need not be removed during coitus but 2% complained of interference with coitus.[34] Hence, it

represents a safe, effective and very well-accepted administration form for long-term treatment of vaginal atrophy. As a treatment choice women appeared to favor the estradiol-releasing vaginal ring for ease of use, comfort of product and overall satisfaction. [35] If rings or pessaries cannot be inserted due to stenosis a cream may be given initially.

The choice of therapy should be guided by clinical experience and patient preference. All available low-dose local estrogen formulations are effective, but the optimal dose and preferred mode of estrogen administration to achieve symptom relief can vary from woman to woman. Individualization of therapy is the key to balancing the desired local effects of topical vaginal estrogens with potential systemic effects, which may or may not be desired.[42]

Patient selection: Local estrogens should be started in those where symptoms persist despite nonhormonal therapy. Women with undiagnosed vaginal/uterine bleeding should not be started on any form of estrogen.

Use of local estrogen treatment following breast and gynecological cancers: Most gynecological and breast cancers are hormone responsive and it may not be the ideal treatment for these women due to risk of cancer recurrence. Evidence for their safety in such situations is scant. These women should be recommended moisturizers and lubricants. Although, systemic absorption of estrogen from low-dose vaginal estrogen is minimal, but absorption may be variable according to state of vaginal epithelium and effects of small amount of absorption on women with hormone-dependent cancers have not been studied. A study on women with breast cancer and vaginal estrogen use showed no increase in recurrence after a mean follow-up of 5.5 years.[43] Vaginal vault is the most common site of recurrence after endometrial cancer, thus causing a possibility of increased risk with vaginal estrogen therapy. However, there are no data to support the same. A risk-benefit analysis is needed in women with severe symptoms and they should be counseled for the same, taking into account their individual risk factors. Those who want to take no risk can avoid therapy. With these patients cancer has already taken a psychological toll. Hence, the physical and psychological symptoms must be individualized. After counseling, their decision must be supported. If required, vaginal estrogens can be used at the lowest effective dose with appropriate patient counseling.

Those with nonhormone-dependent cancers, management of vaginal atrophy should not differ from women without a cancer history. With ovarian cancer, there are no data to support an increased risk of recurrence with either systemic or local estrogen therapy. Cancer therapies, including surgery, irradiation, chemotherapy and/or hormonal manipulation (especially aromatase inhibitors) can impact on sexual functioning. Aromatase inhibitors can cause severe vaginal atrophy. Squamous cell cervical cancers are not hormone responsive. However, local radiotherapy may reduce the number of estrogen receptors and the subsequent response to topical estrogen therapy. In these women, stimulation of epithelial regeneration and initiation of healing must be done before local therapy.

In women taking tamoxifen following breast cancer, efficacy of vaginal estrogen may be hampered by tamoxifen. However, in women on aromatase inhibitors, the binding with estradiol receptor is uncompromised.

Vaginal estrogens and thromboembolism: There is insufficient evidence on use of vaginal estrogen in women with prior history of thrombosis or those at a higher risk.

Therapy length and monitoring: Therapy length and monitoring depend on the response of the patient to the estrogen therapy started and whether they have any additional risk factors.

Response: Improvement in vaginal atrophy symptoms starts within a few weeks of starting vaginal estrogen, but some may need to use it for 4 to 6 weeks before adequate improvement is observed. However, it must be kept in mind that the lowest dose possible should be given. Creams may offer more immediate soothing relief, although some users consider them messy. There is an improvement in 80 to 90% of women treated with local vaginal estrogen. If unresponsive, an undiagnosed dermatitis/dermatosis or vulvodynia must be kept in mind and patient evaluated for the same.

Therapy length: For women with vaginal atrophy, low-dose, local vaginal estrogen should be continued as long as they have discomfort from symptoms. Safety of vaginal administration beyond 1 year has not been sufficiently studied. Hence, limits of therapy are still undefined. It must be kept in mind that certain estrogens have a more potent effect systemically.

Monitoring: As endometrial hyperplasia incidence is not increased, regular endometrial surveillance is not required. Closer surveillance in the form of transvaginal ultrasound or endometrial sampling is indicated in case a woman is at high risk for endometrial cancer, is using a greater dose of vaginal estrogen, or is having symptoms (spotting or breakthrough bleeding).

Combination of Bazedoxifene and Conjugated Estrogen

Selective estrogen receptor modulator bazedoxifene 20 mg/ conjugated estrogen 0.625 mg significantly increased

superficial cells and decreased parabasal cells, vaginal pH and most bothersome symptom improving vaginal dryness. It is effective in treating moderate to severe vaginal atrophy.[44-46]

Testosterone

It is well known that testosterone receptors are present in the fibrovascular layer of the vagina, and deficiency of this hormone may be responsible for changes of atrophy which occur postmenopausally. Studies have shown that local application of testosterone in combination with estrogen is as efficacious in relieving symptoms as estrogen alone and has the added advantage of improving sexual parameters to a higher degree. However, systemic levels of testosterone did rise beyond postmenopausal values.[47] Local therapy with 0.25 to 1% of dehydroepiandrosterone sulfate leads to significant improvement in clinical symptoms, maturation index and pH. It also improved sexual function.[48]

Postmenopausal vaginal atrophy is a common cause of easily treatable distressing symptoms which severely affect quality of life. Health care workers should initiate an open and sensitive discussion with postmenopausal women about their urogenital health to ensure that symptomatic atrophy is detected early and appropriately managed before irrevocable atrophic changes have occurred. Delivery system used should be convenient to patient so that therapy is consistent, as that is critical for effect. Moisturizers are an effective alternative to hormonal medication in alleviating symptoms and are indicated where patient does not wish to take hormonal medication, or in whom it is contraindicated. All local estrogen preparations are effective with no major side effects and all therapies must be started after considering patients preference.

REFERENCES

1. North American Menopause Society. The role of local vaginal estrogens for the treatment of vaginal atrophy in postmenopausal women: 2007 position statement of The North American Menopause Society. Menopause 2007;14(3):357-69.
2. Willhite LA, O'Conell MB. Urogenital atrophy—prevention and treatment. Pharmacotherapy 2001;21:464-80.
3. Van Geelen JM, van de Weijer PH, Arnolds HT. Urogenital symptoms and resulting discomfort in non-institutionalized Dutch women aged 50-75 years. Int Urogynecol J Pelvic Floor Dysfunct 2000;11:9-14.
4. Oskay UY, Beji NK, Yalcin O. A study on urogenital complaints of postmenopausal women aged 50 and over. Acta Obstet Gynecol Scand 2005;84(1):72-78.
5. Stenberg A, Heimer G, Ulmsten U, Cnattingius S. Prevalence of genitourinary and other climacteric symptoms in 61-year-old women. Maturitas 1996;24(1-2):31-36.
6. Nilsson K, Risberg B, Heimer G. The vaginal epithelium in the postmenopause—cytology, histology and pH as methods of assessment. Maturitas 1995;21(1):51-56.
7. Kalogeraki A, et al. Cigarette smoking and vaginal atrophy in postmenopausal women. In vivo. 1996;10(6):597-600.
8. Karamanidis D, Tamiolakis D, Koutsougeras G, Tripsanas CH, Retzos K, Karidis S, et al. Cigarette smoking and the degree of maturation of the vaginal squamous epithelium in postmenopausal women. Clin Exp Obstet Gynecol 2001; 28(4):274-76.
9. Leiblum S, Bachmann G, Kemmann E, Colburn D, Swartzman L. Vaginal atrophy in the postmenopausal woman. The importance of sexual activity and hormones. JAMA 1983; 249(16):2195-98.
10. van der Laak JA, de Bie LM, de Leeuw H, de Wilde PC, Hanselaar AG. The effect of Replens on vaginal cytology in the treatment of postmenopausal atrophy: Cytomorphology versus computerised cytometry. J Clin Pathol 2002;55(6):446-51.
11. Bachmann GA, et al. Vaginal dryness in menopausal women: Clinical characteristics and nonhormonal treatment. Clin Pract Sexuality 1991;7:25-32.
12. Bygdeman M, Swahn M. Replens versus dienoestrol cream in the symptomatic treatment of vaginal atrophy in postmenopausal women. Maturitas 1996;23:259-63.
13. Nachtigall LE. Comparative study: Replens versus local estrogen in menopausal women. Fertil Steril 1994;61:178-80.
14. Biglia N, Peano E, Sgandurra P, et al. Low-dose vaginal estrogens or vaginal moisturizer in breast cancer survivors with urogenital atrophy: A preliminary study. Gyneco Endocrinol 2010;26:404-12.
15. Ekin M, Yaar L, Savan K, Temur M, Uhri M, Gencer I, et al. The comparison of hyaluronic acid vaginal tablets with estradiol vaginal tablets in the treatment of atrophic vaginitis: A randomized controlled trial. Arch Gynecol Obstet 2011; 283(3):539-43.
16. Woods R, Colville N, Blazquez J, Cooper A, Whitehead M. Effects of red clover isoavones (Promensil) versus placebo on uterine endometrium, vaginal maturation index and the uterine artery in healthy postmenopausal women. Menopause Int 2004;10:17.
17. Reed SD, Newton KM, LaCroix AZ, Grothaus LC, Grieco VS, Ehrlich K. Vaginal, endometrial, and reproductive hormone findings: Randomized, placebo-controlled trial of black cohosh, multibotanical herbs, and dietary soy for vasomotor symptoms: The Herbal Alternatives for Menopause (HALT) Study. Menopause 2008;15(1):51-58.
18. Yildrim B, Kaleli B, Duzcan E, Topuz O. The effects of postmenopausal vitamin D treatment on vaginal atrophy. Maturitas 2004;49:334-37.
19. Weed S. Menopausal years: The wise woman way—alternative approaches for women vol 30-90. Woodstock, New York: Ash Tree 1992;ISBN 9614620-4-3.
20. Le Veque F, Hendrix S. Oral pilocarpine to treat vaginal xerosis associated with chemotherapy-induced amenorrhoea in premenopausal women. J Clin Oncol 2004;22(Suppl):14S, Abstr 8099.
21. Al-Baghdadi O, Ewies AA. Topical estrogen therapy in the management of postmenopausal vaginal atrophy: An up-to-date overview. Climacteric 2009;12:91-105.
22. Cardozo L, Bachmann G, McClish D, Fonda D, Birgerson. Meta-analysis of estrogen therapy in the management of urogenital atrophy in postmenopausal women: Second report of the hormones and urogenital therapy committee. Obstet Gynecol 1998;92(4 Pt 2):722-27.
23. Marx P, Schade G, Wilbourn S, Blank S, Moyer DL, Nett R. Low-dose (0.3 mg) synthetic conjugated estrogens. A is effective for managing atrophic vaginitis. Maturitas 2004;47(1):47-54.

24. Barnabei VM, Cochrane BB, Aragaki AK, et al. Menopausal symptoms and treatment-related effects of estrogen and progestin in the Women's Health Initiative. Obstet Gynecol 2005; 105:1063-73.
25. Lynch C. Vaginal estrogen therapy for the treatment of atrophic vaginitis. J Womens Health 2009;18(10):1595-606.
26. Mandel FP, Geola FL, Meldrum DR, Lu JH, Eggena P, Sambhi MP, et al. Biological effects of various doses of vaginally administered conjugated equine estrogens in postmenopausal women. J Clin Endocrinol Metab 1983;57(1):133-39.
27. Simon J, Nachtigall L, Gut R, Lang E, Archer DF, Utian W. Effective treatment of vaginal atrophy with an ultra-low-dose estradiol vaginal tablet. Obstet Gynecol 2008;112(5):1053-60.
28. Bachmann G, Lobo RA, Gut R, Nachtigall L, Notelovitz M. Efficacy of low-dose estradiol vaginal tablets in the treatment of atrophic vaginitis: A randomized controlled trial. Obstet Gynecol 2008;111(1):67-76.
29. Eugster-Hausmann M, Waitzinger J, Lehnick D. Minimized estradiol absorption with ultra-low-dose 10 mg 17b estradiol vaginal tablets. Climacteric 2010;13:219-27.
30. Foidart JM, Vervliet J, Buytaert P. Efficacy of sustained-release vaginal oestriol in alleviating urogenital and systemic climacteric complaints. Maturitas 1991;13:99-107.
31. Handa VL, Bachus KE, Johnston WW, Robboy SJ, Hammond CB. Vaginal administration of low-dose conjugated estrogens: Systemic absorption and effects on the endometrium. Obstet Gynecol 1994;84(2):215-18.
32. Bachmann G, Bouchard C, Hoppe D, et al. Efficacy and safety of low-dose regimens of conjugated estrogen cream administered vaginally. Menopause 2009;16:719-27.
33. Henriksson L, Stjernquist M, Boquist L, Cedergren I, Selinus I. A one-year multicenter study of efficacy and safety of a continuous, low-dose, estradiol-releasing vaginal ring (Estring) in postmenopausal women with symptoms and signs of urogenital aging. Am J Obstet Gynecol 1996;174(1 Pt 1): 85-92.
34. Smith P, Heimer G, Lindskog M, Ulmsten U. Oestradiol-releasing vaginal ring for treatment of postmenopausal urogenital atrophy. Maturitas 1993;16(2):145-54.
35. Suckling J, Kennedy R, Lethaby A, Roberts H. Local oestrogen therapy for vaginal atrophy in postmenopausal women. Cochrane Database Syst Rev 2006(4):CD 001500.
36. Labrie S , Cusan L, Gomez JL, et al. Effect of one-week treatment with vaginal estrogen preparations on serum estrogen levels in postmenopausal women. Menopause 2009;(16):30-36.
37. Nilsson K, Heimer G. Low-dose oestradiol in the treatment of urogenital oestrogen deficiency—a pharmacokinetic and pharmacodynamic study. Maturitas 1992;15(2):121-27.
38. Ulrich L, Naessen T, Elia D, et al. Endometrial safety of ultra-low-dose Vagifem 10 mg in postmenopausal women with vaginal atrophy. Climacteric 2010;13:228-37.
39. Weisberg E, Ayton R, Darling G, et al. Endometrial and vaginal effects of low-dose estradiol delivered by vaginal ring or vaginal tablet. Climacteric 2005;8:883-92.
40. Simon J, Nachtigall L, Ulrich LG, Eugster-Hausmann M, Gut R. Endometrial safety of ultra-low-dose estradiol vaginal tablets. Obstet Gynecol 2010;116(4):876-83.
41. Crandall C. Vaginal estrogen preparations: A review of safety and efficacy for vaginal atrophy. J Womens Health (Larchmt). 2002;11(10):857-77.
42. Archer DF. Efficacy and tolerability of local estrogen therapy for urogenital atrophy. Menopause 2010;17(1):194-203.
43. Drew JE, Wren BG, Eden JA. A cohort study of topical vaginal estrogen therapy in women previously treated for breast cancer. Climacteric 2003;6:45-52.
44. Kagan R, Williams RS, Pan K, Mirkin S, Pickar JH. A randomized, placebo- and active-controlled trial of bazedoxifene/conjugated estrogens for treatment of moderate to severe vulvar/vaginal atrophy in postmenopausal women. Menopause 2010;17(2):281-89.
45. Bachmann G, Bobula J, Mirkin S. Effects of bazedoxifene/conjugated estrogens on quality of life in postmenopausal women with symptoms of vulvar/vaginal atrophy. Climacteric 2010;13(2):132-40.
46. Stovall DW. Aprela, a single tablet formulation of bazedoxifene and conjugated equine estrogens (Premarin) for the potential treatment of menopausal symptoms. Curr Opin Investig Drugs 2010;11(4):464-71.
47. Raghunandan C, Agrawal S, Dubey P, Choudhury M, Jain A. A comparative study of the effects of local estrogen with or without local testosterone on vulvovaginal and sexual dysfunction in postmenopausal women. J Sex Med 2010;7: 1284-90.
48. Labrie F, Archer D, Bouchard C, et al. Intravaginal dehydroepiandrosterone (Prasterone), a physiological and highly efficient treatment of vaginal atrophy. Menopause 2009;16:907-22.

ABOUT THE AUTHOR

Surveen Ghumman

Senior Specialist, Department of Obstetrics and Gynecology Safdarjung Hospital; Assistant Professor, Vardhman Mahavir Medical College, New Delhi, India

Correspondence Address: B 517, New Friends Colony, New Delhi-110025, India, Phone: 91-9810475476, e-mail: surveen@hotmail.com