10.5005/jp-journals-10032-1105

REVIEW ARTICLE

Management of Postmenopausal Vaginal Atrophy: Review of Literature

[1]Preeti Yadav, [2]Meena Dayal

ABSTRACT

Aim: As there is dilemma for treatment of postmenopausal vaginal atrophy, effort has been made to review the literature for the same.

Background: About half of all postmenopausal women will experience symptoms related to urogenital atrophy. Vaginal atrophy becomes clinically apparent 4 to 5 years after menopause, and subjective complaints as well as objective changes are present in 25 to 50% of all postmenopausal women.

Review results: Measures could be taken for not only treatment but also prevention of atrophy before symptoms become troublesome, but establishment of this prevention principle globally would require a formal cost-effective analysis and further research.

Conclusion: Treatment with local estrogen is simple, safe, and can transform a woman's quality of life.

Clinical significance: Women experiencing sexual and urinary symptoms as a consequence of vaginal atrophy should be diagnosed and treated without delay in order to avoid a cascade of events which do not resolve spontaneously.

Keywords: Local estrogen, Postmenopausal, Vaginal atrophy.

How to cite this article: Yadav P, Dayal M. Management of Postmenopausal Vaginal Atrophy: Review of Literature. J South Asian Feder Menopause Soc 2017;5(1):51-57.

Source of support: Nil

Conflict of interest: None

Date of submission: 15 February 2017

Date of acceptance: 28 March 2017

Date of publication: June 2017

INTRODUCTION

Menopause is an inevitable natural stage in a woman's life which is associated with several physical and psychological changes that can be significant enough to disrupt the normal life of woman experiencing it. While hot flushes and night sweats are universally recognized as the most common features in the Western world, other symptoms may be more prevalent elsewhere. In Indian women, urogenital symptoms have been shown to increase progressively in the perimenopausal period reaching an incidence of more than 40% after menopause.[1] About half of all postmenopausal women will experience symptoms related to urogenital atrophy, affecting sexual function and quality of life as the urogenital tract is particularly sensitive to the decline in estrogen levels. Vaginal atrophy becomes clinically apparent 4 to 5 years after the menopause and subjective complaints as well as objective changes are present in 25 to 50% of all postmenopausal women. As the number of women has increased in the menopausal age group because of advances in health care and public initiatives toward healthy living, this exposure to age-related diseases presents not only a distinctive challenge for patients, but for health care providers too and are called on to offer alternatives that are preventive and improve quality of life.

INDIAN SCENARIO

In India, psychological issues and a negative attitude toward vaginal atrophy are quite prevalent. Problems associated with vaginal atrophy, especially sexual dysfunction, are underreported by women with a low level of education and ignorance with regard to menopausal symptoms. Even the educated urban women are culturally inhibited. They do not admit to these issues and fail to seek help with their sexual problems. However, these women are hesitant in discussing their sexual problems but are relieved if their doctor initiates a discussion. As vaginal atrophy is not an inevitable consequence of menopause, early diagnosis and intervention can prevent atrophic vaginitis. In India, estrogen replacement therapy is offered as appropriate to the individual, in addition to alternative strategies. Women are encouraged to improve their personal hygiene for better vaginal health and are advised to remain sexually active as an important non-pharmacological option for preventing vaginal atrophy and shrinkage. Additionally, this helps to improve psychological and physical well-being, both in rural and urban groups, leading toward a positive attitude. Indian women need greater awareness of the implications of vaginal atrophy and the benefits of early treatment.

[1]Senior Resident, [2]Professor

[1,2]Department of Obstetrics and Gynecology, Moti Lal Nehru Medical College, Allahabad, Uttar Pradesh, India

Corresponding Author: Preeti Yadav, Senior Resident Department of Obstetrics and Gynecology, Moti Lal Nehru Medical College, Allahabad, Uttar Pradesh, India, Phone: +919918310149, e-mail: preeti_yadav3@yahoo.com

PHYSIOLOGICAL CHANGES IN VAGINA DUE TO ESTROGEN DEFICIENCY

Serum estradiol ($S.E_2$) levels in the premenopausal women range from 147 to 1,468 pmol/L (40–400 pg/mL) and fall to less than 73 pmol/L (20 pg/mL) in postmenopausal women.[2] This change in circulating estrogen levels is reflected in vaginal physiology and symptoms. Since vagina is an accessible and sensitive biological indicator of the declining and low circulating estrogen levels in postmenopausal women, the loss of ovarian estrogen production is associated with vaginal atrophy. Sexually active postmenopausal women are reported to have fewer symptoms and less physical evidence of vaginal atrophy and slightly higher serum levels of androgens.[3] The loss of vaginal rugal folds and thinning of epithelium become apparent 2 to 3 years postmenopause, but the onset is variable. The cause of loss of rugosity is breakdown of the collagen support of the vaginal epithelium. Collagen turnover is decreased in ageing women without hormone therapy, and these changes may be of importance in vaginal prolapsed.[4-6]

Dryness of the vagina occurs early in the postmenopausal period and is most apparent in sexually active women in whom it is associated with pain with intercourse or dyspareunia.[2,7] The majority of vaginal fluid in postmenopausal women appears to be secreted from the vaginal epithelium.[8] The vaginal pH in premenopausal women is less than 4.5, due to production of lactic acid by lactobacillus organisms which increases to over 6 in postmenopausal women, due to a reduction in the colonization of the vagina by lactobacillus, secondary to a decrease in superficial cells and hence, decreased glycogen, and the vaginal epithelium is thinner.[2,9] All these lead to increased risk of infections and inflammation, though the evidence for an increased incidence of vaginal infections is limited.[9-11] The female urethra and urinary bladder are associated with the developing vaginal anlage in the embryo. The urethra has high levels of estrogen receptors because it is derived from the same embryonic origin as the distal vagina.[2] Atrophy of the urethra with a relative increase in urethral epithelial transitional cells and a corresponding decrease in intermediate and superficial squamous cells occurs after menopause.[12] The abrupt change with the onset of menopause affects the superficial muscle layers of the trigone, the proximal and distal urethra and vagina, and the lamina propria of the trigone and proximal urethra.[13]

Symptoms

Although symptoms of estrogen deficiency, urogenital atrophy, and symptoms of ageing are not clearly defined till date, effort has been done to enumerate vulvar, vaginal, and urinary tract symptoms (Table 1). The most common symptoms of vaginal atrophy include dryness (75%), dyspareunia (38%), and vaginal itching, discharge, and pain (15%). Vaginal dryness is not necessarily associated with sexual activity, it is a symptom into itself. Despite having symptoms, only about 25% of women suffering from them actually seek medical advice. Instead, patients attribute the symptoms to a natural and unavoidable part of the ageing process.

Table 1: Urogenital symptoms due to estrogen deficiency

Vulva
• Susceptibility to chemical and physical irritants, mechanical injuries, and infections
Vagina
• Dryness and insufficient moistness
• Dyspareunia
• Itching
• Burning sensation
• Soreness
• Susceptibility to mechanical injuries
• Adverse impact on healing of mechanical and postoperative wounds
• Leukorrhea and/or foul secretion
Urinary bladder and urethra
• Increased urinary bladder retention after micturition
• Decreased urethral flow of urine
• Symptoms of dysuria, nocturia and urgency
• Urinary incontinence
• Recurrent urinary tract infections

Signs

With declining estrogen, the mucosa of cervix, epithelium of vagina, and vulva get thinned out and become susceptible to injury. The vaginal rugae are also diminished, leading to a smoother appearing vaginal wall, which is accompanied by diminished blood flow. Together, these changes result in a pale appearance, which may contain small petechiae and/or other signs of inflammation. While the normal acidity of an estrogenized vagina is usually in the moderately acidic range (normal range of pH 3.5–5.0, favoring lactobacilli), this normal pH increases with falling estrogen concentrations (range of pH 6.0–8.0, favoring pathogenic organisms, including yeast and bacteria, i.e., coliforms). This more alkaline pH leads to a shift in the vaginal flora toward more coliforms and, together with the other atrophic changes, is responsible for increased susceptibility to and frequency of infections and odor,[14] as well as traumatic bleeding associated with sexual intercourse or secondary to speculum insertion during routine gynecologic examinations. Both microscopic and macroscopic ulcerations can appear in the vaginal epithelium spontaneously or with minor trauma. In patients who are not sexually active or those who engage in penetrative

vaginal intercourse only rarely, severe atrophy can result in vaginal narrowing, shortening, and even obliteration of the vaginal vault.[15] Although the physical signs of atrophy in the vulva and vagina are more clearly apparent upon gynecologic examination, estrogen deficiency-related anatomic and physiologic changes within the urinary tract may cause or accentuate dysfunction during micturition, including increased frequency, dysuria, nocturia, as well as urge, stress, and mixed forms of urinary incontinence.[15] Estrogen deficiency causes atrophic changes in the bladder trigon, decreased tension of muscular and connective structures of the urogenital diaphragm, disorders of collagen metabolism, and decreased activity of the adrenergic system innervating both the bladder neck and urethral sphincter.[16] The urethral mucosa becomes thinner along with its submucosal vascular plexus. Taken together, these changes contribute to a decrease in intraurethral pressure, an important mechanism facilitating urinary continence, thereby allowing urine loss. The same pH and bacterial changes in the vagina can impact on the lower urinary tract, increasing the risk for acute and recurrent urethritis and cystitis.

Diagnosis

Although diagnosis of vulvovaginal atrophy is made after combining the patient's symptoms, clinical situation, and visual inspection, more objective and reproducible measures, including patient-reported outcomes like the severity of the patients' most bothersome symptom, are required for diagnosis.[17,18] Historically, vaginal pH, obtained using litmus paper and the vaginal maturation index (VMI), is used for both the diagnosis and the assessment of treatment efficacy. The VMI is a calculation of the relative percentages of superficial cells compared with intermediate and parabasal cells.

REVIEW RESULTS

Considering the fact that most low-dose vaginal preparations are virtually free of risks and side effects (although long-term data are lacking), a step could be taken for not only intervention, when symptoms are established, but also for the prevention of atrophy before symptoms become troublesome, but establishment of this prevention principle globally would require a formal cost-effective analysis and further research.

DISCUSSION

Treatment of Vaginal Atrophy

Rationale for Treatment

The positive impact of treatment of vaginal atrophy on a woman's general and sexual quality of life cannot be underestimated.[19] The incidence of urogenital atrophy is probably underreported and therefore, underestimated.[20,21] The principles of treatment in women with established vaginal atrophy are (1) restoration of urogenital physiology and (2) alleviation of symptoms.

Treatment Options

Nonhormonal treatment: Nonhormonal options are primarily indicated in women wishing to avoid hormonal therapy or in high-risk individuals with a history of hormone-sensitive malignancy, such as breast or endometrial cancer. Most of these products are available without prescription over the counter and can be expensive.

Lubricants: Lubricants for vaginal atrophy mainly consist of a combination of protectants and thickening agents in a water-soluble base and nonhormonal substances that have a maturation effect on the urogenital epithelium. Lubricants are primarily used to relieve vaginal dryness during intercourse and therefore, do not provide a long-term solution. Lubricants are nonphysiological, giving only a very temporary relief of symptoms, often followed by vaginal irritation. Vaseline can break down the latex of condoms.

Moisturizers: Moisturizers are hydrophilic, insoluble, cross-linked polymers. They are bio-adhesive in that they attach to mucin and epithelial cells on the vaginal wall, thus retaining water. They are eliminated by epithelial cell turnover. The beneficial effects on symptoms related to vaginal atrophy are mainly through buffering properties which lead to a reduction in vaginal pH. The efficacy on vaginal symptoms is lower than that of topical estrogen therapy in trials published thus far. One of the few randomized controlled trials comparing the efficacy of a vaginal moisturizer with vaginal estrogen, Bygdeman and Swahn[22] studied a vaginal moisturizer *vs* dienoestrol cream in the symptomatic treatment of vaginal atrophy in postmenopausal women over 12 weeks. Both treatments led to a significant improvement in the vaginal dryness index in the first week of treatment, but the dienoestrol was more effective than the nonhormonal preparation.

Biglia et al[23] in a recent trial compared vaginal moisturizer with low-dose vaginal estrogen, 18 patients received estriol cream (n = 10) or estradiol tablets (n = 8) and 8 received a polycarbophilic moisturizer. Both low-dose vaginal preparations were found to be effective on vaginal symptoms and health, whereas the nonhormonal moisturizer provided only transient benefit.

Phytoestrogenic Preparations: There are some data demonstrating beneficial urogenital activity of phytoestrogenic preparations, such as soy and red clover isoflavones,[24] but these preparations are not really "nonhormonal" as they have estrogen-type effects. In a study by Woods et al,[24] 8 weeks of oral 40 mg red clover

isoflavones reduced parabasal cells and increased superficial cells, thus increasing the VMI with no significant effect on endometrial thickness. As there are no data regarding the safety of these preparations in women with hormone-sensitive tumors, caution should be exercised in recommending them in these situations.

Vitamins: Vitamin E has been shown to increase vaginal lubrication in trial conducted by Weed.[25] Yildrim et al[26] found that vitamin D also appears to be involved in the regulation of vaginal stratified squamous epithelium, but there are no clinical data relating to vaginal atrophy.

Oral Pilocarpine: This has been shown to stimulate vaginal lubrication. Le Veque and Hendrix[27] noted a significant improvement in vaginal dryness in women with atrophic symptoms following chemotherapy.

Topical Anesthetics: Topical anesthetics have been studied in women with vulvar vestibulitis (overnight 5% lidocaine ointment) and in women with vulvodynia (topical gabapentin 6%). These products could theoretically be useful in women with painful atrophy, but there are no data.

Tibolone: Tibolone 2.5 mg/day for 6 months in postmenopausal women with vaginal atrophy has significantly shown to improve vaginal dryness, dyspareunia, and signs of atrophic vaginitis without causing endometrial proliferation.[28]

Herbal Products: Further data are required before any recommendations can be made regarding the use of herbal products (nettle, comfrey root, dong quai root, motherwort, wild yam, bryonia, and acidophilus capsules, etc.) for vaginal atrophy.[29]

Systemic Hormone Therapy

Administration of exogenous estrogen restores normal vaginal pH levels, thickens and revascularizes the epithelium, and increases vaginal lubrication. As a result, hormone replacement therapy (HRT) alleviates the vaginal atrophy-related symptoms and may also lower the incidence of lower urinary tract infections. Most of the data are old, as was summarized in 1998 by a meta-analysis of 58 studies (both systemic and local administration) done by Cardozo et al,[20] 10 of which were placebo controlled. Of the various HRT preparations, only those containing estriol seem to be less effective. It is noteworthy that very few studies assessed treatment efficacy beyond 6 months, the Women's Health Initiative being one of these: About 10% of women participating in the estrogen and progestin arm (mean age 63 years) complained of vaginal dryness, of whom 74% reported relief at year 1, as compared with 54% in the placebo arm.[30] Thus, 10 to 25% of women using systemic hormonal therapy will still experience the symptoms of urogenital atrophy. This finding plus the safety concerns about oral/transdermal HRT are the reasons why systemic therapy is usually not recommended in women with vaginal symptoms only,[31] and in many women, a combination of systemic and vaginal estrogen may be necessary initially.

Local Estrogen Therapy

Local vaginal estrogen therapy is preferable, when systemic treatment is not needed for other reasons, because local therapy avoids most systemic adverse events and is probably also more efficacious for vaginal problems.

Local estrogen therapy can be given as tablets, pessaries, cream, or a vaginal ring. Therapy is available as conjugated equine estrogens (CEE), estradiol, estriol, or estrone. Estrogen is readily absorbed through the vaginal wall and effects will not only be local unless pharmaceutical formulations are used to prevent absorption. Even so, there is some absorption especially during the beginning of treatment, when the vaginal epithelium is still atrophic. When the epithelium matures as a result of therapy, absorption decreases and, in addition, smaller dosages of estrogen are necessary to prevent recurring atrophy. Only small dosages are normally needed to treat vaginal compared with systemic symptoms, and also low-potency estrogens like estriol can be used, which provides sufficient effect in the vagina with only limited systemic effects in spite of absorption. Cochrane review by Suckling et al[32] identified 37 trials, including 19 with randomized comparisons of estrogenic preparations administered intravaginally to 4,162 postmenopausal women for at least 3 months. Creams, pessaries, tablets, and the estradiol vaginal ring appeared to be equally effective in relieving the symptoms of vaginal atrophy and significantly better than placebo and nonhormonal gels.

Contraindications for local estrogen therapy are women, such as those with undiagnosed vaginal/uterine bleeding or known or suspected endometrial cancer, and are not an acceptable option for others. Additionally, almost all preparations are effective in decreasing signs and symptoms of vaginal atrophy but they differ slightly in their adverse event profiles. The vaginal ring and tablets cause less discharge compared with pessaries and creams, which may be preferable to some women; however, when therapy is needed for sexual dysfunction, the added lubrication from pessaries and creams may be advantageous. Individual patient preference will determine the choice of product. The need for concurrent progestin use by women using vaginal estrogen preparations has been evaluated in numerous clinical trials and in a Cochrane review. Preparations studied include estriol cream and pessaries, estradiol vaginal tablets in two doses, 25 and 10 mg, CEE cream in two doses, and estradiol-impregnated vaginal rings. While topical estriol preparations do not appear to stimulate the endometrium,

both conjugated estrogens and estradiol preparations may do so in a dose-related manner. In the Cochrane review of Suckling et al,[32] endometrial hyperplasia was reported in two studies using conjugated estrogen creams and none in another using estriol pessaries. Two recent studies of 25 mg estradiol vaginal tablets and low-dose CEE cream for 1 to 2 years found no incidence of hyperplasia, while a study of low-dose (10 mg) estradiol vaginal tablets for 1 year also found no incidence of endometrial hyperplasia among 284 biopsies or any change in endometrial thickness throughout the study.[33] A 48-week study by Weisberg et al[34] compared an estradiol-releasing vaginal ring and 25 mg estradiol vaginal tablets found no change in endometrial thickness for either group, but less bleeding among the ring users compared with those using vaginal tablets. In a recent study of Bachmann et al,[35] low-dose CEE cream (0.3 mg), proliferative endometrium was reported in 6 of 423 women over 52 weeks of follow-up, with no cases of endometrial hyperplasia or carcinoma. The incidence of hyperplasia seen in these studies is very low and similar to that seen in an untreated postmenopausal population. Al-Baghdadi and Ewies[36] concluded that no studies show evidence of endometrial proliferation after 6 to 24 months of use of topical estrogen, so the literature thus provides reassurance regarding the safety of low-dose vaginal estrogen preparations and does not support the concomitant use of systemic progestins for endometrial protection. This evidence has been endorsed in recent clinical practice guidelines issued by The International Menopause Society[37] and The North American Menopause Society,[38] with neither body advocating the use of progestins by women who are using topical estrogen preparations appropriately.

Androgens and Dehydroepiandrosterone

The vulva and vagina are endowed with both estrogen and androgen receptors. In the vagina, estrogen receptor regulates the levels of androgen receptor in the fibrovascular layer and these levels correlate well with the cellular proliferation index within the vagina, also these levels are low in atrophic vaginitis.[39] Therefore, androgen therapy might play an important role for women with atrophic vaginal symptoms. Most data on testosterone in postmenopausal women come from studies using transdermal testosterone for hypoactive sexual desire; in addition, most studies also included the use of estrogen. A recent study by Raghunandan et al[40] has compared the effects of estrogen cream 1 gm of CEE (0.625 mg) with the same dose of estrogen and testosterone cream (0.5 gm of 2% testosterone) and placebo. Over 12 weeks of therapy, compared with placebo, both hormonal groups showed similar and significant improvements in vaginal health parameters. It also appeared that the combination group with testosterone had a greater improvement in sexual function. However, the group receiving testosterone exhibited a significantly higher serum-free testosterone, which increased by 154%, suggesting that this is a form of systemic therapy. A fair amount of data, however, has been generated using intravaginal dehydroepiandrosterone (DHEA). Dehydroepiandrosterone has been delivered to the vagina in ovules in a lipophilic base in doses of 0.25% (3.25 mg) to 1% (13 mg DHEA). Phase 3 randomized trials in postmenopausal women have shown that DHEA, estrogen, and several metabolites are not increased above the normal postmenopausal range with this vaginal therapy for 12 weeks. Efficacy data have shown significant improvements with all doses compared with placebo in all parameters of vaginal maturation, a reduction in pH, an improvement in clinical symptoms of atrophy, as well as a reduction in pain with sexual activity.[41] Despite not having any systemic steroid effects, intravaginal DHEA improved various parameters of sexual function, including domains, such as sexual desire.[42] However, longer-term studies are needed to confirm these data.

Therapy Duration, Monitoring, and Adverse Events

At present, there are no guidelines pertaining to the duration of therapy. The only recommendation is that, if long-term therapy is going to be implemented, then low-dose therapy must be used. Invariably, women will obtain substantial relief from their symptoms after about 3 weeks of treatment, although in some women it may require 4 to 6 weeks before adequate improvement is observed. About 80 to 90% of women will obtain subjective improvement, and treatment failure should mandate further evaluation with the view to exclude other underlying conditions, such as dermatitis/dermatoses or vulvodynia. But, there is a paucity of data for the use of local estrogen preparations beyond 6 months, even though it is well known that symptoms commonly return when treatment is discontinued. This is because most of the preparations used are licensed for only 3 to 6 months of continuous use, in addition to the unproven concern that use beyond this may lead to endometrial pathology.

Adverse Effects of Local Estrogen Therapy

Serious adverse events are particularly uncommon. All preparations may, however cause vaginal irritation or itchiness, vaginal discharge, vaginal bleeding, pelvic pain, breast tenderness, and paresthesias. It appears that the creams may be associated with more of these events than the tablets and the ring. This may be due to the preparation itself, to greater absorption or to higher doses than those recommended being inadvertently inserted

into the vagina.[43] The potential effects of local estrogen therapy in causing endometrial hyperplasia have already been discussed. From all studies, there is no evidence of any increase in thromboembolic events or increase in metastases in breast cancer survivors who were using the vaginal tablets for symptom relief. At present, there is no reason why women with symptomatic vaginal atrophy cannot use low-dose, local vaginal estrogen therapy for as long as they have symptoms. However, it is necessary to investigate fully all patients who present with any vaginal bleeding to exclude endometrial pathology.[44] It is likely that vaginal absorption may vary from one woman to another and increasing administration to one application/day (instead of twice a week, the usual recommended schedule) can be associated with breast tenderness. There is no valuable study to recommend any evidence-based policy. An important question is whether vaginal estrogens can be used safely in women with hormone-responsive cancers, namely breast, ovarian, and endometrial cancers and adenocarcinoma of the cervix. For women with breast cancer, nonhormonal therapies are preferred but, where these are ineffective, vaginal estrogens can be used at the lowest effective dose with appropriate patient counseling. Following endometrial cancer, the most frequent recurrence occurs at the vaginal vault, thus raising concern of a possible increased risk with vaginal estrogen therapy. There are no data. Following ovarian cancer, although some concerns have been expressed about systemic treatment, there are no data to suggest an increased risk of recurrence with either systemic or local estrogen therapy. Following any gynecological cancer, it may be appropriate to discuss the relative risk of using estrogen with the oncology team as well as the patient.

CONCLUSION

Postmenopausal vaginal atrophy is a common cause of distressing symptoms caused by estrogen deficiency, but it remains poorly recognized by health-care attendants and women are often reluctant to consult or complain about it. Treatment with local estrogen is simple, safe, and can transform a woman's quality of life. It is important for practitioners to initiate discussion with postmenopausal women about their urogenital health to ensure that symptomatic atrophy is detected early and appropriately managed. Treatment should be started early and before irrevocable atrophic changes have occurred. All local estrogen preparations are effective and patient preference will usually determine the treatment used. Additional progestogen is not indicated when appropriate low-dose, local estrogen is used, although long-term data (more than 1 year) are lacking. If estrogen is ineffective or undesired, vaginal lubricants and moisturizers can relieve symptoms due to dryness.

CLINICAL SIGNIFICANCE

Vaginal atrophy is one of the most important determinants of sexual function and urogenital health, with a significant impact on the quality of life. Women experiencing sexual and urinary symptoms as a consequence of vaginal atrophy should be diagnosed and treated without delay in order to avoid a cascade of events which do not resolve spontaneously.

REFERENCES

1. Kakkar V, Kaur D, Chopra K, Kaur A, Kaur IP. Assessment of the variation in menopausal symptoms with age, education and working/non-working status in north-Indian sub population using menopause rating scale (MRS). Maturitas 2007 Jul;57(3):306-314.
2. Archer DF. Efficacy and tolerability of local estrogen therapy for urogenital atrophy. Menopause 2010 Jan-Feb;17(1): 194-203.
3. 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 Apr;249(16):2195-2198.
4. Moalli PA, Talarico LC, Sung VW, Klingensmith WL, Shand SH, Meyn LA, Watkins SC. Impact of menopause on collagen subtypes in the arcus tendineous fasciae pelvis. Am J Obstet Gynecol 2004 Mar;190(3):620-627.
5. Phillips CH, Anthony F, Benyon C, Monga AK. Collagen metabolism in the uterosacral ligaments and vaginal skin of women with uterine prolapse. BJOG 2006 Jan;113(1):39-46.
6. Tinelli A, Malvasi A, Rahimi S, Negro R, Vergara D, Martignago R, Pellegrino M, Cavallotti C. Age-related pelvic floor modifications and prolapse risk factors in postmeno-pausal women. Menopause 2010 Jan-Feb;17(1):204-212.
7. Bachmann GA, Nevadunsky NS. Diagnosis and treatment of atrophic vaginitis. Am Fam Phys 2000 May;61(10):3090-3096.
8. Semmens JP, Wagner G. Estrogen deprivation and vaginal function in postmenopausal women. JAMA 1982 Jul;248(4): 445-448.
9. Heinemann C, Reid G. Vaginal microbial diversity among postmenopausal women with and without hormone replacement therapy. Can J Microbiol 2005 Sep;51(9):777-781.
10. Pabich WL, Fihn SD, Stamm WE, Scholes D, Boyko EJ, Gupta K. Prevalence and determinants of vaginal flora alterations in postmenopausal women. J Infect Dis 2003 Oct;188(7): 1054-1058.
11. Smith EM, Ritchie JM, Levy BT, Zhang W, Wang D, Haugen TH, Turek LP. Prevalence and persistence of human papillomavirus in postmenopausal age women. Cancer Detect Prev 2003;27(6):472-480.
12. Bergman A, Karram MM, Bhatia NN. Changes in urethral cytology following estrogen administration. Gynecol Obstet Invest 1990;29(3):211-213.
13. Semmelink HJF, de Wilde PCM, van Houwelingen JC, Vooijs GP. Histomorphometric study of the lower urogenital tract in pre- and post-menopausal women. Cytometry 1990;11(6): 700-707.

14. Caillouette JC, Sharp CF Jr, Zimmerman GJ, Roy S. Vaginal pH as a marker for bacterial pathogens and menopausal status. Am J Obstet Gynecol 1997 Jun;176(6):1270-1275.
15. Robinson D, Cardozo L. The menopause and HRT. Urogenital effects of hormone therapy. Best Pract Res Clin Endocrinol Metab 2003 Mar;17(1):91-104.
16. Jackson S, James M, Abrams P. The effect of oestradiol on vaginal collagen metabolism in postmenopausal women with genuine stress incontinence. BJOG 2002 Mar;109(3):339-344.
17. Greendale GA, Zibecchi L, Petersen L, Ouslander JG, Kahn B, Ganz PA. Development and validation of a physical examination scale to assess vaginal atrophy and inflammation. Climacteric 1999 Sep;2(3):197-204.
18. US Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Guidance for industry. Estrogen and estrogen/progestin drug products to treat vasomotor symp-toms and vulvar and vaginal atrophy symptoms – recom-mendations for clinical evaluation (Draft Guidance). Rockville (MD): US Department of Health and Human Services, Food and Drug Administration; 1997. Available from: http :// www. fda.gov /cder/guidance /5412dft.pdf.
19. Graziottin A, Leiblum S. Biological and psychosocial pathophysiology of female sexual dysfunction during the menopause transition. J Sex Med 2005 Sep;2(Suppl 3):133-145.
20. Cardozo L, Bachmann G, McClish D, Fonda D, Birgerson L. 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 Oct;92(4 Pt 2):722-727.
21. Calleja-Agius J, Brincat M. Urogenital atrophy. Climacteric 2009 Aug;12(4):279-285.
22. Bygdeman M, Swahn ML. Replens versus dienoestrol cream in the symptomatic treatment of vaginal atrophy in postmenopausal women. Maturitas 1996 Apr;23(3):259-263.
23. Biglia N, Peano E, Sgandurra P, Moggio G, Panuccio E, Migliardi M, Ravarino N, Ponzone R, Sismondi P. Low-dose vaginal estrogens or vaginal moistuizer in breast cancer survivors with urogenital atrophy: a preliminary study. Gynecol Endocrinol 2010 Jun;26(6):404-412.
24. Woods R, Colville N, Blazquez J, Cooper A, Whitehead MI. Effects of red clover isoflavones (Promensil) versus placebo on uterine endometrium, vaginal maturation index and the uterine artery in healthy post-menopausal women. J Br Menopause Soc 2004 Jun;10:17.
25. Weed, S. Menopausal years: the wise woman way – alternative approaches for women. Woodstock (NY): Ash Tree; 1992.
26. Yildrim B, Kaleli B, Duzcan E, Topuz O. The effects of postmenopausal Vitamin D treatment on vaginal atrophy. Maturitas 2004 Dec;49(4):334-337.
27. Le Veque FG, Hendrix S. Oral pilocarpine to treat vaginal xerosis associated with chemotherapy-induced amenorrhoea in premenopausal women. J Clin Oncol 2004 Jul;22(14 Suppl):8099.
28. Swanson SG, Drosman S, Helmond FA, Stathopoulos VM. Tibolone for the treatment of moderate to severe vasomotor symptoms and genital atrophy in postmenopausal women: a multicenter, randomized, double-blind, placebo-controlled study. Menopause 2006 Nov-Dec;13(6):917-925.
29. Panay N, Fenton A. Complementary therapies for managing the menopause: has there been any progress? Climacteric 2010 Jun;13(3):201-202.
30. Barnabei VM, Cochrane BB, Aragaki AK, Nygaard I, Williams RS, McGovern PG, Young RL, Wells EC, O'Sullivan MJ, Chen B, et al. Meno-pausal symptoms and treatment-related effects of estrogen and progestin in the Women's Health Initiative. Obstet Gynecol 2005 May;105(5 Pt 1):1063-1073.
31. Goldstein I. Recognizing and treating urogenital atrophy in postmenopausal women. J Womens Health (Larchmt) 2010 Mar;19(3):425-432.
32. Suckling J, Lethaby A, Kennedy R. Local oestrogen therapy for vaginal atrophy in postmenopausal women. Cochrane Database Syst Rev 2006 Oct;4:CD001500.
33. Ulrich L, Naessen T, Elia D, Goldstein JA, Eugster-Hausmann M, VAG-1748 trial investigators. Endometrial safety of ultra-low-dose Vagifem 10 microg in postmenopausal women with vaginal atrophy. Climacteric 2010 Jun;13(3):228-237.
34. Weisberg E, Ayton R, Darling G, Farrell E, Murkies A, O'Neill S, Kirkegard Y, Fraser IS. Endometrial and vaginal effects of low-dose estradiol delivered by vaginal ring or vaginal tablet. Climacteric 2005 Mar;8(1):883-892.
35. Bachmann G, Bouchard C, Hoppe D, Ranganath R, Altomare C, Vieweg A, Graepel J, Helzner E. Efficacy and safety of low dose regimens of conjugated estrogen cream administered vaginally. Menopause 2009 Jul-Aug;16(4):719-727.
36. Al-Baghdadi O, Ewies AA. Topical estrogen therapy in the management of postmenopausal vaginal atrophy: an up-to-date overview. Climacteric 2009 Apr;12(2):91-105.
37. Board of the International Menopause Society, Pines A, Sturdee DW, Birkhäuser MH, Schneider HP, Gambacciani M, Panay N. IMS Updated Recommendations on postmenopausal hormone therapy. Climacteric 2007 Jun;10(3):181-194.
38. North American Menopause Society. Estrogen and progestogen use in postmenopausal women; 2010 statement of the North American Menopause Society. Menopause 2010 Mar;17(2):242-255.
39. Taylor AH, Guzail M, Al-Azzawi F. Differential expression of oestrogen receptor isoforms and androgen receptor in the normal vulva and vagina compared with vulval lichen sclerosus and chronic vaginitis. Br J Dermatol 2008 Feb;158(2): 319-328.
40. 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 Mar;7(3):1284-1290.
41. Labrie F, Archer D, Bouchard C, Fortier M, Cusan L, Gomez JL, Girard G, Baron M, Ayotte N, Moreau M, et al. Intravaginal dehydroepiandrosterone (Prasterone), a physiological and highly efficient treatment of vaginal atrophy. Menopause 2009 Sep-Oct;16(5):907-922.
42. Labrie F, Archer D, Bouchard P, Fortier M, Cusan L, Gomez JL, Girard G, Baron M, Ayotte N, Moreau M, et al. Effect of intravaginal dehydroepiandrosterone (Prasterone) on libido and sexual dysfunction in postmenopausal women. Menopause 2009 Sep-Oct;16(5):923-931.
43. North American Menopause Society. The role of local vaginal estrogen for treatment of vaginal atrophy in postmenopausal women: 2007 position statement of The North American Menopause Society. Menopause 2007 May-Jun;14(3 Pt 1): 357-369.
44. Kalentzi T, Panay N. Safety of vaginal oestrogen in postmenopausal women. Obstet Gynaecol 2005 Oct;7(4):241-244.