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Maturitas 52S (2005) S46–S52
MATURITAS
THE EUROPEAN MENOPAUSE JOURNAL
www.elsevier.com/locate/maturitas

Management of post-menopausal vaginal atrophy and atrophic vaginitis

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Received 21 February 2005; accepted 21 June 2005

Abstract

The involution of the female genital tract seems to reflect a built-in biological life expectancy, inter-related with the hypothalamic-hypophyseal-ovarian axis. Lower levels of oestradiol have a number of adverse effects, including on the lower urinary tract. The major universal change is vaginal atrophy. The vaginal mucosa becomes thinner and dry, which can produce vaginal discomfort, dryness, burning, itching, and dyspareunia. The vaginal epithelium may become inflamed, contributing to urinary symptoms such as frequency, urgency, dysuria, incontinence, and/or recurrent infections. Moreover, it has been suggested that reduced oestrogen levels may affect periurethral tissues and contribute to pelvic laxity and stress incontinence. In association with hypoestrogenemia, changes in vaginal pH and vaginal flora may predispose post-menopausal women to urinary tract infection.

Treatment to date has been based on local hormonal therapy, in the form of vaginal creams, tablets or suppositories. Other routes of hormone administration have also proved to be successful. Both local and systemic administration are both effective in maturation of the vaginal epithelium. However, despite the fact that the benefits of oestrogen replacement in preventing vaginal atrophy and reducing the incidence of related symptoms are well established, such therapy is contraindicated in some women and is not an acceptable option for others. Furthermore, the optimal HT administration route, the dosage regimen, and non-hormonal alternatives for improving symptoms and quality of life of the post-menopausal female population, have not been well studied. This review focuses on the changes involved in vaginal aging and efforts to present a synopsis of the pathophysiology and therapy of atrophic vaginitis and vaginal atrophy.
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Keywords: Vaginal atrophy; Vaginitis; Menopausal symptoms; Local therapy; Hormone therapy

1. Introduction

As the number of post-menopausal women grows, interest in the effects of oestrogen increase. The influence of oestrogen on certain body systems such as bone

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0378-5122/$ – see front matter © 2005 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.maturitas.2005.06.014

or cardiovascular has been well documented. However, one specific area that has not been emphasised is the effects on urogenital tract, and a major problem related to menopause is the development of urogenital atrophy [1]. Oestrogen may be related to urogenital aging in several ways: oestrogen prevents a decrease in collagen in post-menopausal women. Topical and systemic oestrogen therapy increases the skin collagen content and maintains skin thickness. In addition, oestrogen maintains skin and urogenital territory moisture by increasing acid mucopolysaccharides and hyaluronic acid and maintaining the epithelial barrier function. Vaginal integrity also may depend on oestrogen levels as a result of the effects of the hormone on the elastic fibres and collagen. The vagina, vulva, urethra, and trigone of the bladder all contain oestrogen receptors and undergo atrophy when oestrogen levels decrease. The vulva and the vaginal walls also become pale and thin and lose their elasticity. This results in decreased vaginal secretion and susceptibility to trauma and pain. In addition, the oestrogen-deficient vagina develops a less acid pH level, ranging from 5.5 to 6.8 [1], which increases the likelihood of urinary tract infections. Fifty to seventy percent of breast cancer survivors indicate in surveys that they experience one or more symptoms of urogenital atrophy [2]. Symptoms include vaginal dryness, dyspareunia, urinary frequency, repetitive urinary tract infections, or urinary incontinence. Dyspareunia leads to decreased interest in coitus. As the frequency of coitus diminishes, vaginal lubrication declines further [3]. However, urogenital aging occurs because of a combination of many factors, not only as a result of oestrogen deprivation.

The age of spontaneous menopause in European countries is between 46.9 and 50.1 years [4]. Women's life expectancy has increased significantly during the past century, and nowadays a female can easily expect to live until the eighth or ninth decade of her life. Most women will spend in the order of one-third of their life in the post-menopausal period, a hypoestrogenemic state. Fifteen percent of pre-menopausal women, 10–40% of post-menopausal women, and 10–25% of women receiving systemic hormone therapy experience urogenital atrophy [5]. Considering the proportions of this problem, more attention must be focused on the problems faced by women during the post-menopausal period.

The involution of the female genital tract seems to reflect a built-in biological life expectancy, inter-related with the hypothalamic-hypophyseal-ovarian axis. The major universal change is vaginal atrophy. Vaginal dryness, burning, itching, and dyspareunia are frequent complaints, along with dysuria, urinary frequency, and recurrent infections. Treatment to date has been based on local hormonal therapy, in the form of vaginal creams, tablets, or suppositories. Other routes of hormone administration have also proved to be successful. However, despite the fact that the benefits of oestrogen replacement in preventing vaginal atrophy and reducing the incidence of related symptoms are well established, such therapy is contraindicated in some women and is not an acceptable option for others. Approximately one-fifth of the 75–85% of post-menopausal women in whom symptoms of vaginal atrophy and atrophic vaginitis develop will actually go to a physician [6]. This review focuses on the changes involved in vaginal aging and attempts to present a synopsis of the pathophysiology and therapy for atrophic vaginitis, an inflammatory process, and vaginal atrophy, an involutive process.

2. What are we talking about?

Atrophic vaginitis is an inflammation of the vagina that develops when there is a significant decrease in levels of the female hormone oestrogen. Oestradiol, the main oestrogen, which is produced by the ovaries, plays a vital role in keeping vaginal tissues lubricated and healthy. When levels of oestradiol are decreased, vaginal tissue becomes atrophic—thin, dry, and shrunken. Common conditions from low oestrogen levels that result in atrophic vaginitis include menopause, breast-feeding, surgical removal of the ovaries before the age of natural menopause, which can be performed at the same time as a hysterectomy, and medication used to decrease oestrogen levels in women who have conditions such as uterine fibroids or endometriosis. It is clear that prolonged periods of transitional hypoestrogenism, such as during long-term breast-feeding or GnRH analogue therapy, may induce severe vaginal atrophy and atrophic vaginitis, and that therapy for these situations is essential.

In a recent review, double-blind randomised controlled studies of oestrogen and/or testosterone on sex-

ual function in menopausal women were evaluated [7], suggesting that oestrogen therapy was associated with increased frequency of sexual activity, enjoyment, desire, arousal, fantasies, satisfaction, vaginal lubrication and feeling physically attractive, and reduced dyspareunia, vaginal dryness, and sexual problems. Testosterone therapy was associated with higher frequency of sexual activity, satisfaction with that frequency of sexual activity, interest, enjoyment, desire, thoughts and fantasies, arousal, responsiveness, and pleasure. Whether specific serum hormone levels are related to sexual function, and how these group effects apply to individual women, are unclear.

3. Aetiology and risk factors of vaginal atrophy

Skin and mucosal surfaces atrophy with age. The cessation of oestrogen production operates in concert with these changes, concluding in the atrophic condition found in the urogenital tract after menopause [4–7]. The vaginal epithelium is influenced by oestrogen and is thick with abundant glycogen and well rugated. These cells, which are loaded with glycogen content, exfoliate constantly and, by the Doderlein's lactobacilli action present in the vagina, result in the production of lactic acid and other chemical substances, including H_2O_2, which control the other populations of microorganisms in the vaginal ecosystem. The interplay of hormones and bacteria help maintain the normal acidic vaginal pH of between 3.5 and 4.5 in healthy mature females, which protects them from recurrent vaginitis and urinary tract infections.

During the peri-menopause, oestradiol levels are about 120 ng/L. After menopause, these levels decrease to approximately 18 ng/L. Androstenedione becomes the most important androgen in post-menopausal women. Most of the testosterone secreted is transformed directly to oestradiol by the ovaries. As the oestrogen levels decrease at menopause, the vaginal epithelium loses it rugae and becomes thin and pale, or erythematous with fine petechial haemorrhages. There is a progressive loss of vascularity in the vaginal mucosa. Collagen fibres tend to swell, fuse, and undergo hyalinisation, elastic fibres experience fragmentation and the connective tissue increases. There is loss of elasticity and a secondary shortening and narrowing of the vagina, with a reduction in its distensibility. Vaginal secretions decrease, due to a reduced lubrication. These changes may cause dyspareunia, leading to coitus avoidance and can ultimately culminate in vaginal or introital contraction and rigidity.

In vaginal smears, superficial cells are scant and there is an increase in intermediate and parabasal cells in hypoestrogenemic conditions. This decrease in glycogen-rich cells improves the inhibition of lactobacilli and lactic acid production and increases vaginal pH [1,8]. The failure of this protective barrier facilitates vaginal discharge due to contamination by skin and rectal flora.

The effects of prolonged hypoestrogenism may include other symptoms such as urethral caruncle, kraurosis (a narrowed and contracted introitus), and a frail, unrugated vagina. However, factors other than low oestrogen levels may modulate vaginal atrophy since it is not a general phenomenon. In a number of women, atrophy progresses shortly after the onset of menopause, whereas in others, it does not become apparent, even in later years.

Among the factors that may enhance atrophy, cigarette smoking is one of the most widely studied. Smoking has a direct effect on the vaginal squamous epithelium [9], reduces oestrogen bio-availability [10], and diminishes blood perfusion [11]. Another factor to take into account are the levels of different androgens such as testosterone and androstenedione, since it has been suggested that post-menopausal women with higher levels of androgens who maintain sexual activity have fewer atrophic changes [7]. Finally, vaginal atrophy has been observed to be more manifest in women who have never given birth vaginally [6].

4. Clinical history and examination

4.1. Signs and symptoms

Clinical urogenital atrophy may include two types of manifestation: vaginal symptoms that predispose to sexual dysfunction and lower urinary tract symptoms, including urinary incontinence and recurrent lower urinary tract infection [6]. Frequent vaginal symptoms include dryness, itching, pruritus, leukorrhea, and finally, dyspareunia. Urinary urgency, polyuria, bladder instability, and urine incontinence may go along with vaginal complaints. All of these symptoms may dis-

play different degrees of severity in different samples of women.

One of the most accurate descriptions of urogenital aging was made by Robert Wilson, who stated in 1963 that 'a large percentage of women ... acquire a vapid cow-like feeling called the *negative state* .... The labia eventually almost disappear. The vagina loses its distensibility and becomes shorter and increasingly friable. The mucosa becomes thin, pink, and sometimes hemorrhagic due to the poor protective support of the blood vessels (senile vaginitis). Such a mucosa is susceptible to infections. There may be simple senile vaginitis with its adhesions or irritating discharge, or more troublesome concomitant infections with trichomonads or fungi' [12].

Interestingly, the firsts symptoms may occur before signs noted in pelvic examination and one of them is often reduced lubrication on sexual arousal. For these reasons, it is important to differentiate early sexual difficulties related to urogenital aging from interpersonal problems.

4.2. Examination procedures

In order to avoid further damage to the atrophic tissues or discomfort to the patient, women with urogenital atrophy should undergo gynaecological examination by means of a small-size speculum. Signs of irritation caused by urinary incontinence should be investigated in the vulvar skin close to the vagina. The vulva should be carefully inspected, pointing out signs of vulvar dystrophy or other lesions, including malignant diseases. The labia major and minora should be examined since both are oestrogen-sensitive. The labia major lose their subcutaneous fat and the labia minora may be irritated and friable. Furthermore, the vaginal epithelium should be examined attentively. Pale, smooth, shiny, and dry tissues are signs suggesting atrophy, whereas signs of inflammation suggestive of vaginitis include patch erythema, petechiae, increased vascularity, friability and bleeding and discharge.

Urethral caruncle is other common sign of urogenital aging, which comes into view as proliferative red tissue at the opening of the urethra. Urethral prolapse or polyps may also be observed.

Vaginal pH is easily assessable by a pH indicator strip inserted into the vagina. In contrast to the pH found during pre-menopause, vaginal pH after menopause is commonly higher than 5.0 up to 7.

A maturation index, which is available through vaginal cytology, may also inform on the oestrogen status. The total number of parabasal, intermediate and superficial cells in 100 cells from the smear are counted, and a mean index is calculated. In hypoestrogenemic menopausal states, the percentage of parabasal and intermediate cells shows an extreme increase in comparison with the pre-menopausal level. After hormone replacement, both systemic and topic, the percentage of superficial cells should increase significantly [13].

Last but not the least, in addition to examination for urogenital atrophy, prolapse (cystocele, rectocele, enterocele, and uterine prolapse), the cervix and pelvic masses should be examined.

4.3. Expected duration

Atrophic vaginitis characteristically develops gradually and women may not perceive any symptoms until 5–10 years after the onset of the menopause. This condition will persist until it is treated.

4.4. Prevention

If desired and acceptable, regular sexual activity is recommended, in general for all women and in particular for menopausal women. This is because sexual intercourse improves blood circulation to the vagina and seminal fluid also contains sexual steroids, prostaglandins and essential fatty acids, which serve to maintain vaginal tissue [14]. A water-soluble vaginal lubricant also can be used to moisten the tissues and to prevent painful sexual intercourse.

4.5. Prognosis

Oestrogen replacement promptly relieves symptoms of atrophic vaginitis. In most patients, the prognosis is excellent.

5. Diagnosis

In a middle-aged woman, the issues are whether the patient has started menopause or has been experiencing

Table 1
Vaginal health index[a]

Overall elasticity	Fluid secretion type and consistency	pH	Epithelial mucosa	Moisture
1. None	None	6.1	Petechiae noted before contact	None, mucosa inflammed
2. Poor	Scant, thin yellow	5.6–6.0	Bleeds with light contact	None, mucosa not inflammed
3. Fair	Superficial, thin white	5.1–5.5	Bleeds whit scraping	Minimal
4. Good	Moderate, thin white	4.7–5.0	Not friable, thin mucosa	Moderate
5. Excellent	Normal (white flocculent)	≤4.6	Not friable, normal mucosa	Normal

Lower score corresponds to greater urogenital atrophy.
[a] From Bachmann (reference [15]).

menopausal symptoms (absent or irregular menstrual periods, mood swings, hot flushes, difficulty sleeping at night, night sweats). Vaginal atrophy is also possible in other clinical situations, such as breast-feeding or irregular menstrual periods, which may be due to low oestrogen levels. Finally, medical and surgical history and current medications may be recorded.

The suspicion of atrophic vaginitis is based on age, symptoms and medical history. To confirm the diagnosis, a pelvic examination of the vulva and vagina for signs of dryness, redness, and thinning of tissue is essential. Menopausal women who experience bleeding after intercourse also may require an endometrial biopsy to rule out endometrial cancer, and a Pap smear to rule out a problem with the cervix.

An attempt to assess urogenital aging in post-menopausal women more accurately is the *vaginal health index* (Table 1) [15]. This index is a useful tool for monitoring urogenital health on a longitudinal basis and for sharing the findings with patients, so that they can use objective data in their decision-making on pharmacological or alternative therapy.

6. Treatment

If the other climacteric symptoms are severe or affect quality of life, hormone replacement is the choice for a time. Atrophic vaginitis can be treated with oestrogen therapy. All routes are equally effective: both systemic (oral, transdermal, implants, . . .) and local vaginal (tablets, suppositories, creams, rings, . . .). Oestrogen cream, tablets or suppositories are inserted into the vagina using an applicator, rings by manual placement. Women also may use combined local and systemic oestrogen therapy [13], and additionally, water-soluble lubricants for comfort. Women who cannot or do not want to use oestrogen may use a water-soluble vaginal lubricants as needed, to relieve vaginal dryness and moisten tissue. All these alternatives are discussed in this section.

The basic therapy for urogenital atrophy is oestrogen replacement. It is most commonly administered in the form of topical oestrogen. In carefully controlled trials, no specific treatment regimens have been shown to be superior to others [8,16–18]. Numerous studies have compared a diversity of treatment regimens including creams [19], tablets [20], suppositories [13], pessaries [18], and more recently, rings [1,18,21]. The degree of systemic absorption is low initially, probably because the vaginal epithelium is atrophic, but increases with the improvement in vascularity through ongoing treatment [22]. For these reasons, and also because low amounts of oestrogen are needed to maintain vaginal trofism, as confirmed by cytology [23], low doses are suggested [24,25].

Tibilone, a steroid with a tissue-specific mode of action, which displays weak oestrogenic, androgenic, and progestagenic action, also significantly improved vaginal atrophy and cytology in comparison with placebos [26].

A non-hormonal moisturizing vaginal gel containing purified water, glycerine, mineral oil, polycarbophil, carbopol 974P, hydrogenated palm oil glyceride, and sorbic acid (Replens®) used three times a week has also proved to be more effective for symptoms of vaginal atrophy in post-menopausal women than an oestrogen cream [27]. Various regimens and compounds in the forms of local douches, creams, and gels have been suggested as substitutes for the acidity of the normal pre-menopausal vagina and to provide protection against infection. Vaseline use is

not a good suggestion for the atrophic vaginitis. It is especially unsuitable if condoms are used for safe sex, as it breaks down the latex. Another unsuitable option is vaginal administration of yoghurt, if vaginal dryness is due to a lack of natural moisture or lubrication.

The homeopathic remedies and phytomedicines include bryonia (inflamed and dry vagina, dry stools, constipation), lycopodium (very dry vagina, low self-confidence, dry skin), and belladonna (vagina painfully dry and too sensitive to tolerate touch). Other 'natural' remedies are nettle (250 mL infusion/daily) to rehydrate dry vaginal tissues [28] and comfrey root (bath and massage twice/day) to keep vaginal tissues flexible, strong, and soft and to use as lubricant for sex [28]. Dong quai root is said to increase vaginal lubrication. Motherwort (tincture, safflower oil or flaxseed oil) may increase vaginal lubrication and vaginal wall thickness within a month of use [28]. Other alternative and complementary therapies are chickweed tincture, wild yam, and acidophilus capsules [28]. However, all these 'natural and safe' products have failed to show efficacy and safety in randomised blind trials in comparison with placebos.

Several vitamins, including E [28,29], D [30] and alpha-tocopherol [31], have been used to treat some menopausal disorders and atrophy of the vaginal mucosa. Vitamin E, either in daily oral doses of 100–600 IU or administered locally, has been found to increase vaginal lubrication [28] and to relieve the dryness and irritation that accompany atrophic and other forms of vaginitis [29]. Vitamin D and analogs have been used in the prevention and treatment of post-menopausal osteoporosis. However, it has been shown that Vitamin D is also involved in the regulation of growth and differentiation of stratified squamous epithelium present in the vagina [30].

7. Recommendations

Several guidelines have been proposed in relation to atrophic vaginitis. An agreement has been reached regarding the detection and management of urogenital atrophy (Table 2). The Joint Committee-Clinical Practice Gynaecology and Urogynaecology of the Canadian Obstetrics and Gynecology Society recorded the procedures for the detection and management of urogenital atrophy according the criteria of evidence-based medicine [32]. In conclusion, their recommendations are described here:

Table 2
Recommendations on the detection and management of urogenital atrophy

Lifestyle: sexual exercise
Supplements: homeopathic remedies such as byronia, lycopodium, and belladonna
Lubricants: astroglide or others (be sure that these are compatible with latex condoms if safe sex is a consideration)
Treatments: polycarbophilic gels, Chinese herbs, acupuncture
Vitamin E and D oil, cream or capsules
Drugs: vaginal oestrogen or systemic hormone therapy

1. Health-care providers should routinely assess postmenopausal women for the symptoms and signs of vaginal atrophy, a common condition that exerts significant negative effects on quality of life (III-C).
2. Regular sexual activity should be encouraged to maintain vaginal health (II-2B).
3. Women experiencing recurrent urinary tract infections should be instructed that consumption of pure cranberry–lingonberry juice, rather than cranberry drink, will decrease their risk of urinary tract infections (I-A).
4. Vaginal moisturizers applied on a regular basis have an efficacy equivalent to local hormone replacement for the treatment of local urogenital symptoms such as vaginal itching, irritation, and dyspareunia, and should be offered to women wishing to avoid use of hormone replacement therapy (I-A).
5. Women experiencing vaginal atrophy can be offered any of the following effective vaginal oestrogen replacement therapies: conjugated equine oestrogen cream (I-A), a sustained-release intravaginal oestradiol ring (I-A), or a low-dose oestradiol tablet (I-A).
6. Although systemic absorption of oestrogen can occur with local preparations, there is insufficient data to recommend annual endometrial surveillance in a-symptomatic women using local oestrogens (III-C).
7. For menopausal women experiencing recurrent urinary tract infections and who have no contraindication to local hormone replacement, vaginal oestrogen therapy should be offered (I-A).

References

[1] Smith P. Oestrogens and the urogenital tract: studies on steroid hormone receptors and a clinical study on a new oestradiol-releasing vaginal ring. Acta Obstet Gynecol Scand Suppl 1993;157:1–26.

[2] Ganz PA, Rowland JH, Desmond K, Meyerowitz BE, Wyatt GE. Life after breast cancer: understanding women's health-related quality of life and sexual functioning. J Clin Oncol 1998;16:501–14.

[3] Bachmann GA, Leiblum SR, Grill J. Brief sexual inquiry in gynecological practice. Obstet Gynecol 1989;73: 425–7.

[4] Cuadros JL, Llaneza P, Mateu S. Demografía y epidemiologia del climaterio en España. In: Bernard-Krieg (editor). AEEM. Libro blanco del climaterio en España. Madrid: España; 2000. p. 15–33.

[5] Willhite LA, O'Connell MB. Urogenital atrophy: prevention and treatment. Pharmacotherapy 2001;21(4):464–80.

[6] Pandit L, Ouslander JG. Post-menopausal vaginal atrophy and atrophic vaginitis. Am J Med Sci 1997;314(October (4)):228–31.

[7] Alexander JL, Kotz K, Dennerstein L, Kutner SJ, Wallen K, Notelovitz M. The effects of post-menopausal hormone therapies on female sexual functioning: a review of double-blind, randomised controlled trials. Menopause 2004;11(November–December (6 Pt 2)):749–65.

[8] Suckling J, Lethaby A, Kennedy R. Local oestrogen for vaginal atrophy in post-menopausal women. Cochrane Database Syst Rev 2003;(4):CD001500.

[9] Kalogeraki A, Tamiolakis D. Cigarette smoking and vaginal atrophy in post-menopausal women. In Vivo 1996;10(6):597–600.

[10] Baron JA, La Vecchia C, Levi F. The antiestrogenic effect of cigarette smoking in women. Am J Obstet Gynecol 1990;162:502–14.

[11] Monfrecola G, Riccio G, Savarese C, Posteraro G, Procaccini EM. The acute effect of smoking on cutaneous microcirculation blood flow in habitual smokers and non-smokers. Dermatology 1998;197(2):115–8.

[12] Wilson RA. Feminine forever. New York: M. Evans & Co., Inc.; 1996.

[13] Palacios S, Castelo-Branco C, Cancelo MJ, Vazquez F. Low-dose, vaginally administered oestrogens may enhance local benefits of systemic therapy in the treatment of urogenital atrophy in post-menopausal women on hormone therapy. Maturitas 2005;50:98–104.

[14] Ito H. Study of male sterility (Pt. 4) on the relationship of prostaglandin and male infertility. Nippon Funin Gakkai Zasshi 1968;13(1):33–41.

[15] Bachmann GA. Vulvo-vaginal complaints. In: Lobo R, editor. Treatment of the post-menopausal woman. New York: Raven Press; 1994.

[16] Cardozo L, Bachmann G, McClish D, Fonda D, Birgerson L. Meta-analysis of oestrogen therapy in the management of urogenital atrophy in post-menopausal women. Second report of the Hormones and Urogenital Therapy Committee. Obstet Gynecol 1998;92:722–7.

[17] Crandall C. Vaginal oestrogen preparations: a review of safety and efficacy for vaginal atrophy. J Women's Health (Larchmt) 2002;11(December (10)):857–77.

[18] Henricksson L, Stjernquist M, Boquist L, Alander U, Selinus I. A comparative multicenter study of the effects of continuous low dose oestradiol released from a new vaginal ring versus estriol vaginal pessaries in post-menopausal women with symptoms and signs of urogenital atrophy. Am J Obstet Gynecol 1994;171:624–32.

[19] Keenan NL, Franks AL, Croft JB, Scholes D, Murray ET. Vaginal oestrogen creams: use patterns among a cohort of women. J Am Geriatr Soc 1999;47(January (1)):65–70.

[20] Akrivis Ch, Varras M, Thodos A, Hadjopoulos G, Bellou A, Antoniou N. Action of 25 microg 17beta-oestradiol vaginal tablets in the treatment of vaginal atrophy in Greek post-menopausal women: clinical study. Clin Exp Obstet Gynecol 2003;30(4):229–34.

[21] Cothran MM, Engberg S. Vaginal ring: an HT alternative. Nurse Pract 2004;29(July (7)):54–5.

[22] Heimer G, Englund DE. Effect of vaginally administered estriol on post-menopausal urogenital disorders: a cytohormonal study. Maturitas 1992;14:171–9.

[23] Fraser IS, Ayton R, Farrell E, Weisberg E, Darling G, Murkies A. A multicenter Australian trial of low dose oestradiol therapy for symptoms of vaginal atrophy using a vaginal ring as delivery system. Maturitas 1995;22(Suppl):S41.

[24] Santen RJ, Pinkerton JV, Conaway M, et al. Treatment of urogenital atrophy with low-dose oestradiol: preliminary results. Menopause 2002;9(May–June (3)):179–87.

[25] Eriksen PS, Rasmussen H. Low dose 17[beta] oestradiol vaginal tablets in the treatment of atrophic vaginitis: a double blind placebo controlled study. Eur J Obstet Gynecol Reprod Biol 1992;44:137–44.

[26] Rymer J, Chapman MG, Fogelman I. A study of the effect of tibolone on the vagina in post-menopausal women. Maturitas 1994;18:127–33.

[27] Bygdeman M, Swahn ML. Replens versus dienoestriol cream in the symptomatic treatment of vaginal atrophy in post-menopausal women. Maturitas 1996;23(3):259–63.

[28] 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.

[29] Ronningen H, Langeland N. Indomethacin treatment in osteoarthritis of the hip joint. Acta Orthop Scand 1979;50:169–74.

[30] Yildirim B, Kaleli B, Duzcan E, Topuz O. The effects of post-menopausal Vitamin D treatment on vaginal atrophy. Maturitas 2004;49(December (4)):334–7.

[31] Giardinelli M. Effect of alpha-tocopherol in some disorders of the menopause and in atrophy of the vaginal mucosa. Minerva Ginecol 1952;4(November (15)):579–87.

[32] Johnston SL, Farrell SA, Bouchard C, et al., SOGC Joint Committee-Clinical Practice Gynaecology and Urogynaecology. Detection and management of urogenital atrophy. J Obstet Gynaecol Can 2004;26(May (5)):503–15.