World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 4.223

MENOPAUSE AND SEX

Dr. Vijayalakshmi Chandrasekhar (MD, DGO)

Assistant Professor, Gitam Institute of Medical Sciences and Research, Rushikonda, Visakhapatanam.

Article Received on 06/12/2016 Article Revised on 26/12/2016 Article Accepted on 15/01/2017

***Corresponding Author**
Dr. Vijayalakshmi Chandrasekhar (MD, DGO)
Assistant Professor, Gitam Institute of Medical Sciences and Research, Rushikonda, Visakhapatanam.

INTRODUCTION

Sexual health is an important, but often neglected component of health care in menopausal women. The female sexual response is a complicated and dynamic process. Apart from involving multiple areas of the brain, from the brain stem, cerebral cortex, hypothalamus and amygdale it is influenced by physiologic, psychological, sociocultural, and interpersonal factors. The six domains of female sexual functions are desire, arousal, lubrication, orgasm, satisfaction and pain during sexual intercourse.

As women age, they experience a decrease in sexual activity, interest in sex, and distress about sex. This may be associated with the loss of intimate relationships as part of separation, divorce or bereavement. Decreased sexual activity with aging may be interpreted as a biological phenomenon (part of the aging process) or as sexual dysfunction, or it may be the result of adapting to changed circumstances.[1]

Sexual dysfunction is a common problem among postmenopausal women and it impairs their quality of life. During the perimenopausal period, women (and also their spouses) undergo changes that negatively impact their sexual function. Most men (82%) and women (76%) agree with the statement that "a satisfactory sex life is essential to maintain a relationship." Most men (65%) and women (57%) disagreed with the statement that "older people no longer want sex." An increase in desire and interest is consistently reported with a new relationship even years after menopause.[2]

Prevalence of female sexual dysfunction increases with age, with nearly three quarters of women older than 60 years reporting sexual inactivity, difficulty with intercourse, or dyspareunia. 98% of perimenopausal women presenting for annual gynecologic examination, report one or more sexual concerns. Although more than 50% of these women want to discuss their sexual concerns, the subject is initiated by the physician only 19% of the time.[3]

In sexually active postmenopausal women, genital arousal may be reduced and sexual pain disorders (dyspareunia and vulvodynia) may frequently occur as a consequence of the hypoestrogenic state. Serum estradiol levels in the reproductive-aged woman range from 30 to 300 pg/mL, depending on the phase of the menstrual cycle. In postmenopausal women, this level decreases by more than 90% to a mean of 6.5 pg/mL. The principle estrogen in postmenopausal women is estrone, which also decreases by approximately 70% after menopause. Estrone is derived from peripheral aromatization of androstenedione.[4]

It is very common to observe a lack of mental arousal and a decline of sexual desire after a history of sexual pain, which can lead to the reduction of orgasmic capacity and sexual satisfaction. These factors may negatively influence sexual motivation, activity, and the couple's relationship. Therefore, it is crucial to avoid such a cascade of negative events by treating sexual problems during menopause.

Factors influencing sexual function

In general, it is known that:

- The reproductive hormones estrogen, testosterone, and even progesterone, l increase sexual desire.1
- Oxytocin has a beneficial effect on orgasm.
- The neurotransmitter serotonin has a negative effect on sexual desire and downstream arousal and orgasm
- Dopamine increases desire and subjective excitement.
- Norepinephrine increases sexual excitement and orgasm.[5]

Genital Changes at Menopause

Estrogen receptors α and β are expressed throughout the squamous epithelium, connective tissue, and smooth muscle of the vulva, vagina, urethra, and bladder trigone. These receptors are critical for mediating numerous biochemical and physiologic functions during a woman's reproductive years.[6, 7]

With the loss of estrogen stimulation, profound changes occur within the vulvovaginal and urogenital mucosa. The vagina loses its rugae and this decreases its distensibility. There is a shortening and narrowing of the vagina. The normally thick vaginal lining transforms into a pale, thin, smooth and friable layer prone to inflammation. The collagen fibers fuse and undergo hyalinization, whereas the elastin fibers fragment, resulting in significant loss of mucosal elasticity.

Vaginal secretions are primarily a transudate from the surrounding blood vessels. With loss of vascular support at menopause, the volume of vaginal and cervical secretions decreases. These changes contribute to dyspareunia in postmenopausal women.

Decreased levels of estrogens also result in urogenital atrophy and weakening of the urogenital diaphragm, resulting in dysuria, urethral discomfort, and stress incontinence.[8, 9]

Female Sexual Dysfunction (FSD) In Menopausal Diabetic Women

The prevalence of sexual dysfunction (SD) in diabetic women is estimated to be 20-80%.[10,11] The incidence of sexual dysfunction in women with DM is generally linked less to organic factors and more to psychological factors, especially coexisting depression. Depression is an independent predictor of female SD and even minor episodes of depression can affect woman's sexual desire. Poor diabetic control or diabetic complications may cause depressive episodes and thus sexual dysfunction in diabetic women. 65.3% of menopausal diabetic women have depression and 95.8% had anxiety, based on the Hospital Anxiety and Depression Scale (HADS) questionnaire. There is significant correlation between depression and female SD and this should be diagnosed and treated.[12, 13]

35% of the menopausal women with type 1 DM met the criteria for female SD. 57% reported loss of libido, 51% orgasmic dysfunction 47% problems in lubrication 38%, arousal dysfunction and 21% pain during intercourse. Decreased libido was reported in 50% of menopausal Type 2 diabetic women, arousal problems in 50%, problems in lubrication in 58%, problems with satisfaction in 42.5%, pain during intercourse in 47.3% and finally 32.7% had orgasmic problems.[14, 15]

On the other hand 35% of the menopausal women with type 1 DM met the criteria for female SD. Of these 57% reported loss of libido, 51% orgasmic dysfunction, 47% problems in lubrication, 38% arousal dysfunction and 21% pain during intercourse.[16, 17]

The somatic sensory system is affected by DM. The introitus vagina, labia minor and clitoris reflect the most deterioration in diabetic women. Although sexual complications are not present in all patients with DM, medications can improve blood flow in clitoris. Neuropathies, vascular impairments and psychological discomforts are the most recognized factors among the etiologies of SD in diabetic women.[18]

Diagnosis of FSD

1. The Female Sexual Function Index (FSFI) is a 19-item questionnaire, developed as a brief, multidimensional self-reported instrument for assessing the key dimensions of sexual function in women. It assesses domains of sexual functioning (e.g. sexual arousal, orgasm, satisfaction, pain) and useful in diagnosing female sexual arousal disorder (FSAD), female orgasmic disorder (FOD), and hypoactive sexual desire disorder (HSDD). A score ≤ 26.55 is classified as FSD.[19] FSFI total score and score for arousal, lubrication, and orgasm domains were lower in menopausal DM women than in controls ($P < 0.05$).[20, 21]
2. A comprehensive history taking and general and gynecologic examination is essential. Certain medical conditions associated with sexual dysfunction, such as diabetes mellitus, cardiovascular disease, hypercholesterolemia, hypertension, neurologic disease, genitourinary disease, psychiatric disorders, and use of medications must be evaluated before the treatment of sexual dysfunction.
3. The external genitalia should be examined for signs of vulvar atrophy and vulvar lesions. A speculum examination can reveal any vaginal, cervical lesion, vaginal discharge and vaginal atrophy. The classical changes in post menopausal women is an atrophic vulva include loss of labial and vulvar fullness with narrowing of the introitus, inflamed mucosal surfaces, loss of vaginal rugations, and occasional vaginal stenosis. Dyspareunia and vaginal bleeding from fragile atrophic skin are common problems that can occur in up to 30% of postmenopausal women not receiving hormone therapy. The prepuce of the clitoris may also become atrophic.[22]
4. A vaginal scraping can be used to measure the *vaginal maturation index*. This index consists of the percentages of the parabasal, intermediate, and superficial squamous cells noted on a cytologic smear of cells from the upper one third of the vagina. This is useful in evaluating chronic hormonal influence on the vaginal vault. An atrophic pattern shows the predominance of parabasal cells, whereas estrogen stimulates the development of superficial squamous cells.[23]

5. Hormonal influence can also be effectively measured by moistening a pH test strip to measure vaginal pH.[24]
6. Contact dermatitis, squamous hyperplasia, and lichen sclerosis can give symptoms similar to atrophic vaginitis and thus need to be ruled out before a hormonal etiology is diagnosed. Definitive diagnoses of nonneoplastic and neoplastic disorders can be made through tissue biopsies.

TREATMENT MODALITIES OF FSD

Hormonal Treatment

Treatment aims at relieving symptoms and reversing atrophic changes that are secondary to decreased estrogen levels. Estrogen therapy, either systemic or locally administered, unless contraindicated, is prescribed. Systemic estrogen therapy is preferred if hot flashes are also present, in addition to vulvovaginal atrophy-related symptoms. Estrogen therapy has been shown to alleviate subjective symptoms of atrophy, including dryness, irritation, pruritis, urinary urgency, and dyspareunia by restoring normal vaginal pH levels and thickening and revascularizing the epithelium.[25]

Local estrogens given intravaginally as short-term therapy in postmenopausal women are effective in relieving symptoms of urogenital atrophy and in improving sexual functions and urinary incontinence symptoms. Local estrogen treatments can improve sexual desire, arousal, and orgasmic function by increasing blood flow to the urogenital region and by increasing vaginal lubrication and oxygen levels.[26, 27, 28] Two different estrogen formulations (estradiol and conjugated estrogens as creams, tablets, and hormone-releasing rings may be selected. Low doses of vaginal cream and conjugated estrogens can be used cyclically (0.5-2 g daily for 21 days/mo) or continuously (0.5 g vaginally twice weekly). Estradiol vaginal cream can be used (2 to 4g vaginally daily for 1 to 2 weeks then 1g per day afterward). Vaginal estradiol tablets 25-µg doses can be used (one tablet vaginally daily for 2 weeks and then one tablet twice weekly). Estradiol vaginal rings delivering 7.5 µg/day, estradiol 50 µg/day or estradiol 100 µg/day are available; Women may also opt for the 3-month vaginal ring for ease of use, comfort, and overall satisfaction.[29,30,31,32,33] Long term therapy for atrophic vaginitis requires the use of the smallest effective dose. Once urogenital function improves, the dose of local estrogen can be tapered for long-term maintenance therapy. Treatment can be continued indefinitely.[34] Although vaginal estrogen preparations yield low levels of circulating estrogen, there is concern about the potential to induce endometrial

hyperplasia in users who have not had a hysterectomy. Systemic absorption occurs in a dose-response manner but low-dose estrogen formulations do not cause endometrial hyperplasia, so that endometrial surveillance is not recommended in asymptomatic, low-risk women, unless there is postmenopausal bleeding.[35,36,37]

Systemic estrogen therapies can, sometimes, combine estrogen plus progestogens.[38]

Selective Estrogen Receptor Modulators (SERMs)

Several studies have investigated the role of SERMs in treating vaginal atrophy. Raloxifene and tamoxifen are two estrogen agonists/antagonists that are commonly used in the treatment of osteoporosis and chemoprophylaxis/treatment of breast cancer, respectively. Neither of them seems to have a beneficial or detrimental effect on vaginal tissue and on symptoms of vulvovaginal atrophy.

Lasofoxifene is a SERM that shows a positive impact on vaginal tissue in postmenopausal women. The Postmenopausal Evaluation and Risk-Reduction with Lasofoxifene Trial has shown that lasofoxifene decreases vaginal pH in postmenopausal women and has a positive effect on the vaginal maturation index, with an increase in superficial cells of the vaginal epithelium. Other studies have also shown that lasofoxifene can significantly reduce vaginal pH, improve the vaginal maturation index, and improve dyspareunia in postmenopausal women. Lasofoxifene also seems to exert its positive effects on vaginal tissue without causing proliferation of the endometrium in animal studies.[39,40,41,42]

Ospemifene in a dose of 30 or 60 mg/day or placebo orally for 12 weeks is effective and well tolerated for the treatment of symptoms of vaginal dryness and dyspareunia associated with vulvovaginal atrophy. In addition, ospemifene has been shown to have no proliferative effect on endometrial tissue.[43,44]

Tissue-Selective Estrogen Complexes

Tissue-selective estrogen complexes (TSECs) are the pairing of estrogen(s) with a SERM. The goal of developing a TSEC is to provide the clinical benefits of each of its components with improved tolerability. This goal can potentially be achieved through the result of different molecular and cellular activities of the treatment's estrogen and SERM components.[45]

The therapeutic profile of a TSEC would optimally include relief of hot flashes, treatment of vulvovaginal atrophy and its symptoms, and prevention of bone loss while providing safety for the endometrium and breast. Bazedoxifene, a SERM in a dose of 20 mg) with conjuhated estrogen (CE) in a dose of 0.625 or 0.45 mg also improves vaginal atrophy and significantly reduced the incidence of dyspareunia relative to placebo. The bazedoxifene-CE combinations are well tolerated.[46,47]

Dehydroepiandrosterone

Levels of dehydroepiandrosterone (DHEA) and DHEA sulfate decline with age. It has been proposed that restoring the circulating levels of these steroids to those found in young women may have antiaging effects and improve sexual function and well-being in postmenopausal women. DHEA is an androgen and is classified as a prohormone because it can be converted into a variety of biologically active steroids. Treatment with oral DHEA 50 mg/day produces a significant improvement in frequency of sexual thoughts, sexual interest, and satisfaction, especially if associated with adrenal insufficiency. Intravaginal DHEA has been shown to increase the vaginal maturation index and decrease the pH in the vagina without increasing the circulating levels of estrogen above the postmenopausal range. It can improve vaginal atrophy with concomitant improvements in sexual function in women who are estrogen deficient because of menopause. Daily local intravaginal application of Prasterone for 12 weeks exerts beneficial effects on all four aspects (desire/interest, arousal, orgasm, and pain at sexual activity) of sexual dysfunction.[48,49,50,51,52]

Nonhormonal Treatment

Over-the-counter vaginal lubricant and moisturizers are commonly used for the treatment of vaginal atrophy-related dyspareunia. They can be safely used by women who do not want to use hormonal options.

Lubricants are specifically designed to reduce friction associated with sexual activity. There are two basic lubricant formulations, water- or silicone-based, with water-based products being the more common. The most commonly used water-based lubricants include K-Y Jelly, Astroglide and Slippery Stuff. They can be applied before intercourse to the vaginal introitus.

Vaginal moisturizers exert their effects by replacing normal vaginal secretions. They are used on a chronic maintenance basis to replace normal vaginal secretions. The most commonly used vaginal moisturizers are Replens, RepHresh and Emerita. They may not be able to

reverse severe vulvovaginal mucosal atrophy, but act as a viable alternative for the relief of vaginal dryness, especially in women with a contraindication to estrogen use. Moisturizers improve vaginal moisture, vaginal fluid volume and pH, and vaginal elasticity and reduce symptoms of itching, irritation, and dyspareunia.

Treatment of Vulvovaginal Atrophy-Related Sexual Dysfunction in Breast Cancer Patients

Sexual dysfunction after breast cancer diagnosis and treatment is common, Surgical treatment of breast cancer in the form of oophorectomy, premature ovarian failure as a consequence of chemotherapy, or endocrine therapy results in estrogen deprivation and the onset of menopausal symptoms, which can impair well-being and negatively affect sexual function. Breast cancer survivors have a high prevalence of severe symptoms because of the induction of a premature menopause with chemotherapy[and the increased use of aromatase inhibitors (AIs) over tamoxifene leading to profound estrogen deprivation. AIs have previously been shown to disrupt sexual function. In the Arimidex, Tamoxifen, Alone or in Combination Trial, anastrozole (AI) users experienced significantly more vaginal dryness, diminished libido, and dyspareunia compared with tamoxifen users. A safe and effective nonestrogen therapy is necessary.[53,54,55]

Vaginal testosterone cream can be used to treat vaginal atrophy in women with history of breast cancer on AIs. A dose of 150 to 300 μg over 4-weeks is associated with improvement of dyspareunia, vaginal dryness, and vaginal maturation index without increasing estradiol or testosterone levels.[56]

Although systemic estrogens are avoided after estrogen receptor–positive breast cancer, vaginal estrogens are commonly used via an estradiol-releasing vaginal ring, estrogen-based vaginal creams, pessaries containing estriol, and a slow-release 17β-estradiol tablet. 12.5 μg estradiol tablets twice a week for 12 weeks or 0.25estriol cream is not associated with an increased risk of recurrence.[57]

Alternative Therapies

Alternative therapies such as acupuncture, plant estrogens, herbal supplements, soy, chasteberry, and ginseng are popular among postmenopausal women. They cannot be recommended as treatment of vulvovaginal atrophy-related symptoms. Vitamin D may provide benefit in preventing vulvar symptoms but dietary supplementation with a soy-based

product, a well-known source of phytoestrogens, has not been shown to improve vaginal maturation index.[58]

CONCLUSIONS

The World Health Organization defines sexual health as a "state of physical, emotional, mental and social well-being in relation to sexuality; it is not merely the absence of disease, dysfunction or infirmity. Normal sexual response and function is about as individualistic as anything can be. Every woman has her own standard of what sexual health or satisfaction, based on her individual culture, background, personal sexual experiences, and biological makeup. Dr. Hope Ricciotti, gynecologist at Harvard Medical school feels that there is nothing as "shriveling" after menopause. The sex drive suffers if one is unhealthy physically or emotionally. Having energy from a healthy diet and regular exercise, along with good sleep and mental health, are key ingredients in a healthy sex drive. The act of having intercourse post menopause stimulates blood flow to the vagina and keeps it healthy and for a healthy, comfortable sex life. Vaginal dryness, thinning and loss of elasticity makes the vaginal mucosa fragile and sensitive. The resulting itching, dryness, burning, irritation, soreness or pain during sexual intercourse is distressing. Much can be done to alleviate these symptom. Sex remains a taboo subject in our country and gynecologists must address this issue, especially among perimenopausal women and offer appropriate therapy.

REFERENCES

1. Howard JR, O'Neill S, Travers C. Factors affecting sexuality in older Australian women: sexual interest, sexual arousal, relationships and sexual distress in older Australian women. Climacteric, 2006; 9(5): 355-67.
2. Tan O, Bradshaw K and Bruce R. Management of Vulvovaginal Atrophy-related Sexual Dysfunction in Postmenopausal Women. Menopause, 2012; 19(1): 109-117.
3. Kao A, Binik YM, Kapuscinski A, Khalife S. Dyspareunia in postmenopausal women: A critical review. Pain Res Manag, 2008; 13(3): 243–254.
4. Meston CM. Aging and sexuality. West J Med, 1997; 167: 285–290.
5. Dennerstein L, Randolph J, Taffe J et al. Hormones, mood, sexuality, and the menopausal transition. Fertil Steril, 2002; 77:
6. Onnis A, Nardelli GB, Lamaina V, Mozzanega B, Becagli L, Fais GF. Hormonal receptors in vulvar tissues. Eur J Gynaecol Oncol, 1985; 6: 125–128.

7. Pettersson K, Gustafsson JA. Role of estrogen receptor β in estrogen action. Annu Rev Physiol, 2001; 63: 165–192.
8. Okeke TC, Ezenyeaku CCT, Ikeako LC et al. An Overview of Vulvovaginal Atrophy-Related Sexual Dysfunction in Postmenopausal Women. Journal of Basic and Clinical Reproductive Sciences, 2012; 1(1): 2-8
9. Calleja-Agius J, Brincat MP. Urogenital atrophy. Climacteric, 2009; 12: 279–285.
10. Fatemi SS, Taghavi SM. Evaluation of sexual function in women with type 2 diabetes mellitus. Diab Vasc Dis Res., 2009; 6: 38–9.
11. Abu Ali RM, Al Hajeri RM, Khader YS, Shegem NS, Ajlouni KM. Sexual dysfunction in Jordanian diabetic women. Diabetes Care., 2008; 31: 1580–1.
12. Giraldi A, Kristensen E. Sexual dysfunction in women with diabetes mellitus. J Sex Res, 2010; 47: 199–211.
13. Enzlin P, Mathieu C, den Bruel AV et al. Prevalence and Predictors of Sexual Dysfunction in Patients With Type 1 Diabetes. Diabetes Care, 2003; 26(2): 409-414.
14. Rutherford D, Collier A. Sexual dysfunction in women with diabetes mellitus. Gynecol Endocrinol, 2005; 21: 189–92.
15. Elyasi F, Kashi Z, Tasfieh B et al. Sexual Dysfunction in Women with Type 2 Diabetes Mellitus. Iran J Med Sci, 2015; 40(3): 206-213
16. Enzlin P, Rosen R, Wiegel M, Brown J, Wessells H, Gatcomb P, et al. Sexual dysfunction in women with type 1 diabetes: long-term findings from the DCCT/ EDIC study cohort. Diabetes care, 2009; 32: 780–5.
17. Esposito K, Maiorino MI, Bellastella G et al. Determinants of female sexual dysfunction in type 2 diabetes. Int J Impot Res., 2010; 22: 179–84.
18. Amaral S, Oliveira PJ, Ramalho-Santos J. Diabetes and the impairment of reproductive function: possible role of mitochondria and reactive oxygen species. Curr Diabetes Rev., 2008; 4: 46–54.
19. Rosen R et al. The Female Sexual Function Index (FSFI): A Multidimensional Self-Report Instrument for the Assessment of Female Sexual Function. Journal of Sex and Marital Therapy, 2000; 26(2): 191-208.
20. Giraldi A, Kristensen E. Sexual dysfunction in women with diabetes mellitus. J Sex Res, 2010; 47: 199–211.
21. Cortelazzi D, Marconi A, Guazzi M et al. Sexual dysfunction in pre-menopausal diabetic women: clinical, metabolic, psychological, cardiovascular, and neurophysiologic correlates. Acta Diabetologica, 2013; 50(6): 911–917.

22. Panay N. Menopause and the postmenopausal woman. Edmonds DK, ed. Dewhurst's Textbook of Obstetrics and Gynaecology. Oxford, UK: Blackwell Publishing, 2008: 479–495.
23. McEndree B. Clinical application of the vaginal maturation index. Nurse Pract, 1999; 24(9): 48, 51-2
24. Carranza-Lira S, Fragoso-Diaz N, MacGregor-Gooch AL, Garduno-Hernandez MP, Rios-Calderon K, Aparicio H. Vaginal dryness assessment in postmenopausal women using pH test strip. Maturitas, 2003; 45: 55–58.
25. Bachmann GCR, Rovner E. Treatment of the Postmenopausal Woman. New York, NY: Elsevier, 2007: 263–269.
26. 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: 1053–1060.
27. Cayan F, Dilek U, Pata O, Dilek S. Comparison of the effects of hormone therapy regimens, oral and vaginal estradiol, estradiol + drospirenone and tibolone, on sexual function in healthy postmenopausal women. J Sex Med, 2008; 5: 132–138.
28. 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.
29. Bachmann G, Bouchard C, Hoppe D, et al. Efficacy and safety of low-dose regimens of conjugated estrogens cream administered vaginally. Menopause, 2009; 16: 719–727.
30. Speroff L. Efficacy and tolerability of a novel estradiol vaginal ring for relief of menopausal symptoms. Obstet Gynecol, 2003; 102: 823–834.
31. Nachtigall LE. Clinical trial of the estradiol vaginal ring in the U.S. Maturitas, 1995; 22: S43–S47.
32. Lose G, Englev E. Oestradiol-releasing vaginal ring versus oestriol vaginal pessaries in the treatment of bothersome lower urinary tract symptoms. BJOG, 2000; 107: 1029–1034.
33. Goldstein I, Alexander JL. Practical aspects in the management of vaginal atrophy and sexual dysfunction in perimenopausal and postmenopausal women. J Sex Med, 2005; 2: 154–165.
34. Bachmann G, Bouchard C, Hoppe D, et al. Efficacy and safety of low-dose regimens of conjugated estrogens cream administered vaginally. Menopause, 2009; 16: 719–727.
35. Bachmann G, Bouchard C, Hoppe D, et al. Efficacy and safety of low-dose regimens of conjugated estrogens cream administered vaginally. Menopause, 2009; 16: 719–727.

36. Suckling J, Lethaby A, Kennedy R. Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database Syst Rev, 2006; 18(4) CD001500.
37. The North American Menopause Society. Estrogen and progestogen use in postmenopausal women: 2010 position statement of The North American Menopause Society. Menopause, 2010; 17: 242–255.
38. Bachmann G, Gass M, Kagan R, Moffett A, Barcomb L, Symons J. Lasofoxifene (laso), a next generation selective estrogen response modulator (SERM) improves dyspareunia in postmenopausal women with vaginal atrophy (VA). Menopause, 2005; 12: 238.
39. Bachmann G, Gass M, Moffett A, Portman D, Symons J. Lasofoxifene improves symptoms associated with vaginal atrophy. Menopause, 2004; 11: P63.
40. Goldstein SR, Cummings SR, Eastell R, Ensrud K, et al. Vaginal effects of lasofoxifene: 3-year results from the PEARL Trial. Menopause, 2008; 15: 1228.
41. Portman D, Moffett A, Kerber I, Drosman S, Somayaji V, Lee A. Lasofoxifene, a selective estrogen receptor modulator, improves objective measures of vaginal atrophy. Menopause, 2004; 11: 675.
42. Simon JA, Komi J. Ospemifene, a new SERM, improves the symptoms of vaginal dryness and dyspareunia in postmenopausal women: results from a pivotal Phase 3 study. Paper presented at: 12th World Congress on the Menopause International Menopause Society; May 19–23, 2008; Madrid, Spain.
43. Bachmann GA, Komi JO. Ospemifene effectively treats vulvovaginal atrophy in postmenopausal women: results from a pivotal phase 3 study. Menopause, 2010; 17: 480–486.
44. Archer DF. Tissue-selective estrogen complexes: a promising option for the comprehensive management of menopausal symptoms. Drugs Aging, 2010; 27: 533–544.
45. Miller PD, Chines AA, Christiansen C, et al. Effects of bazedoxifene on BMD and bone turnover in postmenopausal women: 2-yr results of a randomized, double-blind, placebo-, and active-controlled study. J Bone Miner Res, 2008; 23: 525–535.
46. Lobo RA, Pinkerton JV, Gass ML, et al. Evaluation of bazedoxifene/conjugated estrogens for the treatment of menopausal symptoms and effects on metabolic parameters and overall safety profile. Fertil Steril, 2009; 92: 1025–1038.
47. Panjari M, Davis SR. DHEA for postmenopausal women: a review of the evidence. Maturitas, 2010; 66: 172–179.

48. Panjari M, Bell RJ, Jane F, et al. A randomized trial of oral DHEA treatment for sexual function, well-being, and menopausal symptoms in postmenopausal women with low libido. J Sex Med, 2009; 6: 2579–2590.
49. Labrie F, Cusan L, Gomez JL, et al. Effect of intravaginal DHEA on serum DHEA and eleven of its metabolites in postmenopausal women. J Steroid Biochem Mol Biol, 2008; 111: 178–194.
50. Labrie F, Archer D, Bouchard C, et al. High internal consistency and efficacy of intravaginal DHEA for vaginal atrophy. Gynecol Endocrinol, 2010; 26: 524–532.
51. Labrie F, Archer D, Bouchard C, et al. Effect of intravaginal dehydroepiandrosterone (Prasterone) on libido and sexual dysfunction in postmenopausal women. Menopause, 2009; 16: 923–931.
52. Kwan KW, Chlebowski RT. Sexual dysfunction and aromatase inhibitor use in survivors of breast cancer. Clin Breast Cancer, 2009; 9: 219–224.
53. Wilmoth MC, Botchway P. Psychosexual implications of breast and gynecologic cancer. Cancer Invest, 1999; 17: 631–636.
54. Ganz PA, Greendale GA, Petersen L, Zibecchi L, Kahn B, Belin TR. Managing menopausal symptoms in breast cancer survivors: results of a randomized controlled trial. J Natl Cancer Inst, 2000; 92: 1054–1064.
55. Witherby S, Johnson J, Demers L, et al. Topical testosterone for breast cancer patients with vaginal atrophy related to aromatase inhibitors: a phase I/II study. Oncologist, 2011; 16: 424–431.
56. Ponzone R, Biglia N, Jacomuzzi ME, Maggiorotto F, Mariani L, Sismondi P. Vaginal oestrogen therapy after breast cancer: is it safe? Eur J Cancer, 2005; 41: 2673–2681.
57. 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: 51–58.
58. Yildirim B, Kaleli B, Duzcan E, Topuz O. The effects of postmenopausal Vitamin D treatment on vaginal atrophy. Maturitas, 2004; 49: 334–337.