The Impact of Hormone Therapy on the Clinical Symptoms of Menopause

13

Claudio Hernández-Angeles and Camil Castelo-Branco

13.1 General Principles

Many women experience a range of symptoms during the menopause and perimenopause, and these symptoms are often short-lived and lessen or disappear over time. The most common include vasomotor symptoms (e.g., hot flushes and sweats), effects on mood (e.g., low mood), and urogenital symptoms (e.g., vaginal dryness). Postmenopausal women are at increased risk of a number of long-term conditions, such as osteoporosis, cardiovascular disease, and changes in the vagina and bladder. These occur because of natural aging as well as estrogen depletion [1].

During the latter part of the last century, hormone replacement therapy (HRT), also known as hormone therapy (HT) and menopausal hormone therapy (MHT), was advocated for both symptom relief and chronic disease prevention. Menopausal hormone therapy (MHT) is the broad term used to describe unopposed estrogen use for women who have undergone hysterectomy or combined estrogen–progestin therapy (EPT) for women with an intact uterus who need a progestin to prevent estrogen-associated endometrial hyperplasia. By convention, unopposed estrogen therapy is known as ET, combined estrogen–progestin therapy as EPT, and menopausal hormone therapy as MHT [2]. For menopausal women 60 years of age or 10 years past menopause with bothersome vasomotor symptoms (with or without additional climacteric symptoms) who do not have contraindications or excess cardiovascular or breast cancer risks and are willing to take MHT, we suggest initiating ET for those without a uterus and EPT for those with a uterus.

C. Hernández-Angeles
Hospital Ginecoobstetricia Número 4 “Luis Castelazo Ayala”, Instituto Mexicano del Seguro Social, CDMX, Mexico

C. Castelo-Branco (✉)
Obstetrics and Neonatology, Clinic Institute of Gynecology, Hospital Clinic-Institut d’Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Barcelona, Spain
e-mail: castelobranco@ub.edu

A. Cano (ed.), *Menopause*, DOI 10.1007/978-3-319-59318-0_13

Variations in consultation patterns for menopausal symptoms depend on many factors, including cultural, ethnic, educational, and psychosocial factors, as well as the impact of the symptoms on the women. However, it is thought that more than one-third of all women want more support for managing menopausal symptoms from their GP or practice nurse [1].

13.1.1 Goals of Therapy

The goal of MHT is to relieve menopausal symptoms, most importantly hot flashes (vasomotor symptoms). Other symptoms associated with perimenopause and menopause that respond to ET include mood lability/depression, vaginal atrophy, sleep disturbances (when related to hot flashes), and in some cases, joint aches and pains.

Women being treated for menopausal symptoms such as hot flashes require systemic estrogen; women being treated only for vulvovaginal atrophy (now referred to as "genitourinary syndrome of menopause" [GSM]) should be treated with low-dose vaginal estrogen rather than systemic estrogen.

In the past, MHT was also used by some clinicians to prevent coronary heart disease [CHD] and osteoporosis. However, we do not recommend MHT for prevention of disease given the results of the Women's Health Initiative (WHI), a set of two large randomized trials that demonstrated an unfavorable risk–benefit profile of MHT.

13.1.2 Importance of Patient Age

While the WHI clearly demonstrated adverse effects of MHT in older postmenopausal women (over age 60 years), this is not the age group that presents with new onset of menopausal symptoms. Almost all women who seek medical therapy for menopausal symptoms do so in their late 40s or 50s. Women in this age group should be reassured that the absolute risk of complications for healthy, young postmenopausal women taking MHT for 5 years is very low [2].

13.2 Benefits of Menopausal Hormone Therapy

13.2.1 Vasomotor Symptoms

Hot flashes are the classic symptom of the menopausal transition, experienced by more than 70% of women at some point during the menopausal transition. Hot flashes are associated with impairments in quality of life (QOL), depressed mood, reported sleep disturbance, and possibly even poorer memory function. Despite their prevalence and impact on women's lives, the understanding of the physiology of hot flashes remains incompletely understood. Leading models conceptualize hot flashes as originating in the central nervous system, yet there has been limited data

investigating relations between the brain and hot flashes. Some data support changes in the brain regions associated with awareness of bodily sensation, such as the insula and prefrontal cortex, acutely during hot flashes and the involvement of brainstem areas in the triggering of hot flashes [3, 4].

Hot flashes occur in the context of estrogen (E) withdrawal, and the effects of E on brain structure and function in humans remain controversial. Hot flashes often begin as the sudden sensation of heat centered on the upper chest and face. In some instances, this will become generalized, lasting for several minutes, and can be associated with profuse perspiration, palpitations, or anxiety which may be very distressing and limit activities of daily living, particularly when they occur repeatedly during the day and at night. At night, hot flushes and night sweats will often cause insomnia that leads to fatigue.

Treatment for VMS may include hormone replacement therapy (HRT), since symptoms occur at a time when estrogen levels are dropping and "replacement" leads to relief. HRT comprises synthetic hormones that may be identical to those produced from the ovaries during the reproductive years (estradiol and progesterone) although other similar compounds (such as conjugated equine estrogens, estradiol valerate, and several synthetic progestogens) are widely used. Although there are alternative therapies for vasomotor symptoms, none are as effective as estrogen which is the most effective treatment for vasomotor symptoms and improving QOL in symptomatic women. In a dose-dependent manner, MHT reduces hot flash frequency by approximately 75% and severity by 87%, compared with 50% with placebo [4].

13.2.2 Anxiety and Depressive Symptoms

Depression and mood change is common at times of hormonal change, such as during the menstrual cycle, after pregnancy, and in the perimenopausal period. There is a robust relationship between gonadal hormones such as estrogens and mood disorders in women. There are several known female-specific depressive disorders that are linked to changes in hormonal status. Premenstrual disorders, postpartum depression, and perimenopausal depression are all characterized by a sharp decrease in estradiol associated with symptom onset. This association reinforces the role for estrogens in the maintenance of mood. Studying these disorders both in humans and in animal models will provide opportunities for development of more successful treatment options and will clarify the relationship between estrogens and depression.

Anxiety symptoms increase during the menopause transition and are associated with an increased likelihood of a major depressive disorder. MHT, alone or in combination with an antidepressant such as a selective serotonin reuptake inhibitor (SSRI), is effective for women who experience mood lability or depression during the menopausal transition. ET may improve mild-to-moderate depressive symptoms during or shortly after the menopause transition, whereas antidepressant therapy remains appropriate treatment for major depression [5].

Mood disorders are common during the menopausal transition, often coexisting with vasomotor symptoms. Two small, short duration clinical trials assessed MHT in women with depression or depressive symptoms during the menopausal transition. After 3 weeks, depression scores improved significantly in depressed women treated with transdermal estradiol (0.05 mg/day) compared to placebo [6]. After 12 weeks, depressive disorders were significantly more likely to remit with transdermal estradiol (0.1 mg/day) compared to placebo [7].

The present approach is to choose initial therapy based upon the woman's predominant symptom. If her main concern is depression and hot flashes are not severe, we start with an SSRI. On the other hand, if vasomotor symptoms are the major symptom and depression or mood symptoms are mild, MHT should be recommended. For women in whom depression and vasomotor symptoms are both severe, both estrogen and an SSRI may be an option, but it is mandatory to refer them to a psychiatric unit for further consultation and monitoring [8].

13.2.3 Skin, Cartilage, Connective Tissues

Estrogen receptors have been detected in many skin elements including keratinocytes, melanocytes, fibroblasts, hair follicles, and sebaceous glands, so it is likely that the withdrawal of estrogen at menopause will have measurable effects on skin health. Skin surface texture, water-holding capacity, collagen content of the dermis, and viscoelasticity have shown improvement with the use of estrogen [9].

A spectrum of musculoskeletal symptoms follows estrogen deficiency in a large number of women, from arthralgia to osteoarthritis (OA). The effects of estrogen in bone are well characterized, but data on the impact of estrogen on cartilage, skin, and connective tissues have been slower to emerge. Estrogen is synthesized by aromatases in most connective tissues. Critically, estrogen receptors are present in all joint tissues including articular cartilage, subchondral bone, and synovium.

Although no clear association has been found between lifetime estrogen exposure and the risk of osteoarthritis, generalized muscle and joint aches are among the commonest symptoms experienced by women at menopause. Furthermore, arthritis in women is more likely to be progressive and symptomatic [9]. Estrogen receptors ERa and ERb have both been identified in chondrocytes, and recent studies have also demonstrated estrogen receptors in synoviocytes [10].

It is unclear if arthralgia is related to estrogen deficiency or is a rheumatologic disorder, but in the WHI, women with joint pain or stiffness at baseline were more likely to get relief with either combined EPT or unopposed ET than with placebo in 45% [9, 11]. Joint pain increased slightly after discontinuation of treatment [12]. In the absence of specific studies, three related mechanisms are proposed for possible effects of estrogen, or of MHT in the disease:

13.2.3.1 Inflammation

There is a large amount of data to suggest that estrogen is anti-inflammatory and mildly immunosuppressive.

13.2.3.2 Bone

The effects of MHT on bone are well known. Targeting bone turnover may be one mechanism by which MHT could interfere with osteoarthritis.

13.2.3.3 Pain

Estrogen receptors and aromatase are present in hypothalamus, limbic system, neurons, and joint. Estrogen therapy has been shown to decrease synovial nerve fiber substance P in a rat model of osteoarthritis. Estrogen is antinociceptive, activating inhibitory pain pathways in the spinal cord, while progestins are pronociceptive.

13.2.4 Genitourinary Symptoms of Menopause

The female genital and lower urinary tracts share a common embryological origin, arising from the urogenital sinus and both are sensitive to the effects of female sex steroid hormones throughout life. The epithelial linings of the vagina and urethra are very sensitive to estrogen, and estrogen deficiency leads to thinning of the vaginal epithelium. Estrogen is known to have an important role in the function of the lower urinary tract, and estrogen and progesterone receptors have been demonstrated in the vagina, urethra, bladder, and pelvic floor musculature [13].

Estrogen deficiency results in Genitourinary Syndrome of Menopause (also called vaginal atrophy or atrophic vaginitis), causing symptoms of vaginal dryness, itching, dyspareunia, and sometimes urinary symptoms. Both systemic and vaginal estrogen are effective for genitourinary atrophy symptoms, but we suggest vaginal rather than systemic estrogen for women who have only Genitourinary Syndrome of Menopause without other menopausal symptoms such as hot flashes [14].

Low-dose vaginal estrogen therapy is effective for the treatment of vaginal symptoms with some evidence of additive benefit against recurrent urinary tract infections and dysuria. Several vaginal preparations are available, including vaginal creams, tablets, and a silastic ring that releases E2 locally over a 3-month period. Of these, the 10 mg E2 tablet and the 7.5 mg vaginal ring result in the least amount of systemic estrogen absorption. When low-dose vaginal estrogen therapies are used according to labeling, it is unlikely that endometrial stimulation will occur, and progestogen therapy is therefore not routinely recommended for women using only vaginal estrogen therapy.

Systemic SERM therapy is also available for treating dyspareunia due to menopause. Oral ospemifene, 60 mg daily, improves dyspareunia, vaginal dryness, and female sexual function. Ospemifene seems well suited for women who prefer oral therapy rather than vaginal estrogens and who are without contraindications. Cost, accessibility, and individual preferences should dictate the choice of treatment formulation for managing GSM.

13.2.5 Urinary Incontinence

The role of systemic estrogens in the management of postmenopausal women with lower urinary tract symptoms has been investigated in three large epidemiological studies examining the use of combined estrogen/progestogen and estrogen-only systemic hormone replacement therapy [10–12]. In all of these trials, systemic estrogen replacement therapy was found to increase the risk of developing both stress and urgency urinary incontinence, and, in those women who complained of urinary incontinence at baseline, the symptoms were found to deteriorate. This was also reflected in deterioration in quality of life.

13.2.6 Cardiovascular Disease

Cardiovascular disease (CVD) is the major cause of death in women in all European countries; below 75 years, 42% of women die from CVD compared with 38% of men. The lower rates of CHD in women—but not of stroke—may be interpreted as a protective effect of endogenous estrogens. However, exploration of trends over time and between countries shows that the relationship varies, making this an implausible explanation. Sex differences in dietary fat intake (rather than excess smoking in men) may be responsible [15].

Major primary prevention measures are smoking cessation, weight loss, blood pressure reduction, regular aerobic exercise, and diabetes and lipid control [9]. There is strong and consistent evidence that estrogen therapy may be cardioprotective if started around the time of menopause (often referred to as the "window of opportunity" or "timing" hypothesis) and may be harmful if started more than 10 years after menopause.

The American Heart Association (AHA) [16] published an update of its guidelines for the prevention of CVD in women, which emphasizes that recommendations are the same for both men and women, with a few exceptions. Use of the Framingham score is recommended but now includes a category of "ideal cardiovascular health" comprising absence of raised risk factors, BMI <25 kg/m^2, regular moderate-to-vigorous physical activity, and a healthy diet.

The Endocrine Society guideline suggests calculating cardiovascular and breast cancer risks before initiating MHT [17]. They suggest nonhormonal therapies for symptomatic women who are at high risk (>10% 10-year risk) for CVD or moderate (1.67–5% 5-year risk) to high risk (>5%) for breast cancer. For women at moderate risk of CVD (5–10% 10-year risk), they suggest transdermal rather than oral estrogen, with micronized progesterone for those with a uterus. They note that a population-based CVD risk calculator should be used to estimate CVD risk.

Although this represents the ideal approach, a formal CVD calculation may not be necessary in a thin, healthy, nonhypertensive patient who is well known to the clinician. For women at increased risk of venous thromboembolism (VTE), they also suggest transdermal estrogen with a progestin that has a neutral effect on coagulation parameters (e.g., micronized progesterone) [17].

We suggest not using MHT for the prevention of cardiovascular disease, even in young postmenopausal women. Although the risk profile appears to be more favorable in young women taking unopposed estrogen, use for prevention is still not warranted [18]. The hormone regimen studied in the WHI was conjugated estrogens and medroxyprogesterone acetate (MPA). While it is possible that other estrogen or progestin formulations or doses might not have the same negative cardiovascular effects as conjugated estrogen and MPA, data to support their use for prevention are not available.

13.2.7 Osteoporosis

Osteoporosis is a systemic skeletal disease characterized by diminished bone strength with the risk of sustaining a fracture when falling from own body height (fragility fracture) [19]. Bone strength is determined by a combination of bone density and microarchitectural integrity. Postmenopausal osteoporosis results from a failure to attain peak bone density, accelerated bone loss after menopause, age-related bone loss, or a combination of factors. Accelerated postmenopausal bone loss is induced by estrogen deprivation [9].

Assessment of bone mineral density is not a cost-effective population screening tool but is best applied on a selective basis, based on age and other risk factors such as a personal or family history of fractures, history of amenorrhea, primary ovarian insufficiency, low body mass, diet, smoking, alcohol abuse, the use of bone toxic medication, and rheumatoid arthritis [9].

MHT is the only therapy available with proven efficacy of fracture reduction in patients with osteopenia. Although MHT prevents fractures at any age after menopause, age at the initiation of MHT is important [16]. In the age group 50–60 years or within 10 years after menopause, the benefits of MHT are most likely to outweigh any risk and can be considered as first-line therapy [18]. Initiation of MHT in the age group 60–70 years requires individually calculated benefit/risk, consideration of other available drugs, and the lowest effective dose [18]. MHT should not be initiated after age 70 years.

Non-estrogen-based treatments for osteoporosis include bisphosphonates, denosumab, selective estrogen receptor modulators (SERMs), parathyroid hormone (PTH), and strontium ranelate. Bisphosphonates (such as alendronate, risedronate, ibandronate, and zoledronic acid) inhibit bone resorption by inducing apoptosis of osteoclasts, thus preventing age-related bone loss and deterioration of bone microarchitecture. They are the most widely prescribed drugs, mainly due to their low cost and the generally favorable safety profile. Denosumab is a human monoclonal antibody to the receptor activator of nuclear factor-kappaB ligand (RANKL), a bone-resorbing cytokine. It is administered as a subcutaneous injection every 6 months. All antiresorptive agents are associated with an increased risk of osteonecrosis of the jaw and atypical femoral fracture. But both conditions are rare [20].

The two SERMS approved for the treatment of postmenopausal osteoporosis are raloxifene and bazedoxifene. Both reduce the risk of vertebral but not hip fracture

and increase the risk of venous thromboembolism and hot flushes. They are both associated with a decreased risk of breast cancer in postmenopausal women with osteoporosis. Future treatments for osteoporosis include cathepsin K inhibitors which appear to have mixed antiresorptive and anabolic actions as they inhibit one of the major osteoclast digestive enzymes without suppressing bone formation, thereby leading to anabolic effects on bone [21].

13.2.8 Cognitive Function and Dementia

Numerous studies have reported an effect of estradiol on memory ability. Central and peripheral administration of estradiol levels mimicking proestrus improves spatial memory in ovariectomized rats. It appears that estradiol improves hippocampal dependent memory performance through activation of Erβ. Despite current knowledge of the memory impairments associated with depression, little effort has been placed on exploring cognitive deficits and hippocampal changes related to postpartum depression and perimenopausal depression. Human research on memory impairments has produced conflicting results [22].

We currently do not suggest the routine use of MHT for peri- and postmenopausal women who are experiencing cognitive symptoms (memory loss and difficulty concentrating). Although substantial biologic evidence supports the importance of estrogen to cognitive function, clinical trial evidence has generally ruled out any global (but not domain-specific) cognitive benefits.

In addition, we suggest not using MHT to prevent dementia. Although some epidemiologic data suggest that estrogen may be beneficial, clinical trials of MHT administered to women over age 65 years showed harm. Strong evidence of cognitive benefits for women taking MHT at younger ages (e.g., near menopause) is also lacking, and thus MHT should not be prescribed for preservation of cognitive function in younger women [23].

13.2.9 Sexual Disorders

Sexuality in women is a relatively new field of biomedical research. Psychological, relational, and environmental factors are regarded as being of paramount importance in influencing sexual function and behavior. Indeed, a comprehensive approach to women's sexuality requires more than the mere understanding of a physiological process. The most relevant variables are age, general and mental health, achievement of reproductive goals, education, body image, self-esteem, norms, and experiences. Even duration and quality of partnership, and general and sexual health of the partner, are important.

The known decrease in ovarian androgen production rates and serum androgen concentrations has caused concern that menopause might be associated with a decline in libido. An age-associated decline in sexual desire has been observed in both men and women. However, it is unclear whether the decline in libido in women

is age or menopause related, since studies in women have not shown a significant correlation between libido and the serum estradiol or testosterone levels.

Clinical trials of exogenous testosterone replacement suggest modest benefits of testosterone therapy in some postmenopausal women. However, there are potential risks associated with androgen replacement, and the use of testosterone is limited by the lack of approved and commercially available products for women. Until the beneficial effects of androgen replacement are better established, it cannot be routinely recommended to postmenopausal women.

13.2.10 Extended Use of MHT

Both the North American Menopause Society [2] and the International Menopause Society [9] agree that the use of MHT should be individualized and not discontinued solely based upon patient age. They suggest that extended use of MHT (beyond age 60 or even 65 years) may be reasonable when the clinician and patient agree that the benefits of symptom relief outweigh the risks. As noted, over 40% of women ages 60–65 years have persistent hot flashes that can impair sleep and quality of life.

For women who choose extended use of MHT (more than 5 years or beyond age 60 years), we restart estrogen at the lowest dose possible and make plans for a future attempt to stop the estrogen.

13.3 Summary and Recommendations

- The goal of menopausal hormone therapy (MHT) is to relieve menopausal symptoms, most importantly hot flashes (vasomotor symptoms). Other symptoms associated with perimenopause and menopause that respond to estrogen therapy (ET) include mood lability/depression, genitourinary syndrome of menopause (GSM; vaginal atrophy), and sleep disturbances (when related to hot flashes).
- Healthy symptomatic women in their 50s should be reassured that the absolute risk of complications for healthy, postmenopausal women taking MHT for 5 years is very low.
- For healthy, peri/postmenopausal women within 10 years of menopause (or < age 60 years) with moderate-to-severe vasomotor symptoms, we suggest MHT as the treatment of choice (Grade 2B). Exceptions include women with a history of breast cancer, coronary heart disease (CHD), a previous venous thromboembolic event or stroke, active liver disease, or those at high risk for these complications.
- We suggest transdermal 17-beta estradiol for many women starting MHT (Grade 2C). The transdermal route is particularly important in women with hypertriglyceridemia or risk factors for thromboembolism. However, the baseline risk of both venous thromboembolism (VTE) and stroke is very low in otherwise healthy, young postmenopausal women. Therefore, if a patient prefers an oral preparation

over a transdermal one (cost or personal preference), we consider oral estrogen to be safe. All types and routes of estrogen are equally effective for hot flashes.
- For women who experience recurrent, bothersome hot flashes after stopping estrogen, we initially suggest nonhormonal options. However, if this approach is unsuccessful and symptoms persist, we resume MHT at the lowest dose possible in carefully selected women.
- For women with an intact uterus who choose ET, progestin therapy must be added to prevent endometrial hyperplasia and carcinoma.
- We suggest micronized progesterone as our first-line progestin because it is effective for endometrial hyperplasia, is metabolically neutral, and does not appear to increase the risk of either breast cancer or CHD, although data are limited (Grade 2C).
- Recommendations for women who choose not to take systemic estrogen, have contraindications to estrogen, or have stopped their MHT and are having recurrent symptoms are found elsewhere.
- We currently suggest not using MHT for the prevention of chronic disease (osteoporosis, CHD, or dementia) (Grade 2B). However, women who cannot tolerate other options for osteoporosis may be reasonable candidates.

References

1. National Collaborating Centre for Women's and Children's Health. Menopause Clinical Guideline. 2015;V1.5.
2. North American Menopause Society. The 2012 hormone therapy position statement of: The North American Menopause Society. Menopause. 2012;19:257.
3. Freedman RR. Menopausal hot flashes: mechanisms, endocrinology, treat- ment. J Steroid Biochem. 2014;142:115–20.
4. Thurston RC, Maki PM, Derby CA, Sejdic E, Aizenstein HJ. Menopausal hot flashes and the default mode network. Fertil Steril. 2015;103(6):1573–8.
5. Santen RJ, Allred DC, Ardoin SP, et al. Postmenopausal hormone therapy: an Endocrine Society scientific statement. J Clin Endocrinol Metab. 2010;95:s1–s66.
6. Schmidt PJ, Nieman L, Danaceau MA, et al. Estrogen replacement in perimenopause-related depression: a preliminary report. Am J Obstet Gynecol. 2000;183:414–20.
7. Soares CD, Almeida OP, Joffe H, Cohen LS. Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: a double-blind, randomized, placebo-controlled trial. Arch Gen Psychiatry. 2001;58:529–34.
8. Soares CN. Mood disorders in midlife women: understanding the critical window and its clinical implications. Menopause. 2014;21:198–206.
9. Baber RJ, Panay N, Fenton A, IMS Writing Group. 2016 IMS Recommendations on women's midlife health and menopause hormone therapy. Climacteric. 2016;19(2):109–50.
10. Karsdal MA, Bay-Jensen AC, Henriksen K, Christiansen C. The pathogenesis of osteoarthritis involves bone, cartilage and synovial inflammation: may estrogen be a magic bullet? Menopause Int. 2012;18:139–46.
11. Chlebowski RT, Cirillo DJ, Eaton CB, et al. Estrogen alone and joint symptoms in the Women's Health Initiative randomized trial. Menopause. 2013;20:600.
12. Marjoribanks J, Farquhar C, Roberts H, Lethaby A. Long term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database Syst Rev. 2012;7:CD004143.

13. Hendrix SL, Cochrane BR, Nygaard IE, et al. Effects of estrogen with and without progestin on urinary incontinence. JAMA. 2005;293:935–48.
14. Castelo-Branco C, Biglia N, Nappi RE, Schwenkhagen A, Palacios S. Characteristics of postmenopausal women with genitourinary syndrome of menopause: implications for vulvovaginal atrophy diagnosis and treatment selection. Maturitas. 2015;81(4):462–9.
15. Lawlor DA, Ebrahim S, Davey Smith G. Sex matters: secular, geographical trends in sex differences in coronary heart disease mortality. BMJ. 2001;323:541e5.
16. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in womend2011 update: a guideline from the American Heart Association. Circulation. 2011;123:1243e62.
17. Stuenkel CA, Davis SR, Gompel A, et al. Treatment of symptoms of the menopause: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015;100:3975.
18. Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA. 2013;310:1353–68.
19. Castelo-Branco C. Calcium-collagen chelate supplementation reduces bone loss in osteopenic postmenopausal women. Climacteric. 2015;18:105–6.
20. de Villiers TJ, Gass MLS, Haines CJ, et al. Global consensus statement on menopausal hormone therapy. Climacteric. 2013;16:203–4.
21. de Villiers TJ, Stevenson JC. The WHI: the effect of hormone replacement therapy on fracture prevention. Climacteric. 2012;15:263–6.
22. Mueller SC, Grissom EM, Dohanich GP. Assessing gonadal hormone contributions to affective psychopathologies across humans and animal models. Psychoneuroendocrinology. 2014;46:114–28.
23. Borrow AP, Cameron NM. Estrogenic mediation of serotonergic and neurotrophic systems: implications for female mood disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2014;54:13–25.