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The 2020 Menopausal Hormone Therapy Guidelines

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Based on the analysis conducted by the World Health Organization regarding the life expectancy in 35 Organisation for Economic Co-operation and Development (OECD) countries, South Korea's life expectancy is predicted to rank first in the world by 2030, with the life expectancy for women reaching 90.82 years. In other words, the importance of women's health and the quality of life (QoL) after menopause is increasing. The most effective treatment for vasomotor symptoms (VMS) and genitourinary syndrome of menopause (GSM) is menopausal hormone therapy (MHT), which is also effective in preventing osteoporosis. MHT is an effective therapy that offers more advantages than disadvantages for women aged less than 60 years or who have had menopause for less than 10 years. Therefore, the purpose of these guidelines is to provide help by sharing accurate knowledge and treatment methods regarding MHT based on recent research findings.

1. Examinations required prior to receiving MHT

Points to consider prior to initiating MHT include checking the indications and contraindications of MHT, which requires history recording, physical examinations, and other tests. Because the symptoms of menopause are varied, customized tests should be conducted for each risk factor based on the basic examination conducted according to the life cycle necessary for women [1-3].

The basic examination, which is a general examination conducted according to the life cycle, should identify lifestyles such as smoking and drinking habits; mental diseases such as depression; and with family history for diseases such as Alzheimer's disease, osteoporosis, diabetes, endometrial cancer, breast cancer, liver disease, thyroid disease, cardiovascular disease, and venous thromboembolism via history taking. In addition, the basic examination should include a physical examination for height, weight, and blood pressure as well as the pelvis, breast, and thyroid. Blood tests include tests for liver function, kidney function, anemia, and fasting blood sugar as well as lipid examination, followed by mammography, bone mineral density (BMD) test, and Pap smear screening [3]. Furthermore, it is reasonable to regard pelvic ultrasonography as part of the basic examination in Korea considering its cost-effectiveness. Elective examinations such as thyroid function test, breast ultrasonography, and endometrial biopsy are

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customized to fit individuals' risk factors. Depending on clinical manifestations and individual risk factors, the basic examinations and elective examinations are conducted at an interval of 1–2 years. MHT is used to prevent and treat symptoms and physical changes caused by estrogen deficiency, vasomotor symptoms, atrophy symptoms of the urogenital system, postmenopausal osteopenia, and osteoporosis. In the case of premature ovarian insufficiency (POI), MHT can be used at least until the mean age of menopause regardless of symptoms [1,2]. In case of undiagnosed vaginal bleeding, estrogen-dependent malignant tumors (such as endometrial cancer), breast cancer, active thromboembolism, active liver diseases, and gall bladder diseases, MHT should not be used [1,2]. Because the symptoms of menopause vary widely depending on an individual's physical, mental, social, cultural, and racial features, the physician is recommended to conduct an individualized menopause consultation and examination prior to MHT based on general principles of clinical examination as well as considering individual differences [3].

Key points: Examinations required prior to receiving MHT

1. The examinations required to be conducted prior to MHT are history taking, physical examination, and examinations for liver function, kidney function, anemia, fasting blood sugar, and blood tests of serum lipid profile, followed by mammography, BMD test, and Pap smear screening.
2. The elective examinations required to be conducted prior to MHT are thyroid function test, breast ultrasonography, and endometrial biopsy conducted as individualized tests according to individual risk factors. Depending on clinical manifestation and individual risk factors, the basic examinations and elective examinations are conducted at an interval of 1–2 years.

2. MHT for women in menopausal transition

Menopausal transition refers to the period from the moment of increased variation in menstrual cycle until the moment immediately prior to the last day of menstruation. It varies among individuals and is a period that often includes vasomotor symptoms such as hot flushes alongside frequent or excessive menstruation. Hot flushes vary among individuals but may appear from 1 year to 3 years prior to the last day of menstruation and are especially severe around the last day of menstruation. They may even last for several years. Approximately 75% of women aged between 45 years and 55 years suffer from symptoms of menopause, which may lead to low self-esteem, sleep disorder, and feelings of decreased energy. To evaluate the ovarian reserve during menopausal transition, measuring the serum level of anti-mullerian hormone (AMH), day 3 follicle-stimulating hormone (FSH), estradiol (E2), and ovarian antral follicle count (AFC) using pelvic ultrasonography is possible, but they are not used as indicators for predicting menopause. Additionally, because the function of the ovaries changes during this period, it is advised not to conduct a hormone test for menopause diagnosis [4].

Undergoing treatment for menopausal transition should be primarily decided according to the frequency and severity of the symptoms of menopause. Even in the case of menstruation, if a severe hot flush is experienced, a consultation is advised in order to discuss the necessary treatment to improve symptoms [4]. It is also possible to try alleviating the symptoms via improvement of lifestyles such as weight loss, stress reduction, hypnosis, and cognitive behavioral therapy. Medications such as omega-3, vitamin E, *Cimicifuga racemosa*, isoflavone, and soybean may be effective, but they are not more effective than placebo. In contrast, S-equol, a metabolite of soy isoflavone, seems to show slightly higher effectiveness than placebo [4].

Hormone therapies for treating the symptoms of menopause during menopausal transition are combination therapy of levonorgestrel releasing-intrauterine system (LNG-IUS) with oral or percutaneous estrogen, low-dose combined oral contraceptives (COCs), and estrogen–progestogen therapy (EPT) [4].

EPT is effective not only for treating women after menopause but also for controlling the symptoms of menopause in women in menopausal transition. However, the dose used in general MHT is very low compared with that used for treating women before menopause, and consequently, breakthrough bleedings could frequently occur. If contraception is simultaneously needed, the use of low-dose COCs is recommended. Low-dose COCs are effective for controlling irregular bleeding and alleviation of symptoms of hot flush [4].

In the case of using low-dose COCs, because the symptoms of menopause could worsen during the 7-day pill-free period, the use of continuous COCs or COCs such as Qlaira® with a shorter pill-free period

is recommended. With regard to the safety of low-dose COCs, if there are no risk factors involved such as obesity, smoking, high blood pressure, and other cardiovascular diseases, it may be used carefully from 40 to 55 years of age. However, careful screening of each individual's risk factors is important [5-7].

The use of oral or percutaneous estrogen therapy (ET) together with LNG-IUS is not only effective for alleviating the symptoms of menopause but also for preventing endometrial hyperplasia. Even in the case of a normal menstrual cycle, if the symptoms of menopause are severe, the use of a combination therapy of low-dose percutaneous estrogen and LNG-IUS could effectively control a hot flush [8]. In addition, some reports have shown that it could help improve symptoms that appear during menopausal transition such as depression, reduced quality of sleep, and increased anxiety [9,10].

However, as mentioned earlier, it remains unclear how ET initiated at this stage would affect cardiovascular diseases and breast cancer in the long term. Therefore, treatment during the menopausal transition period should be primarily based on the frequency and severity of the symptoms, and different treatment methods should be applied to improve symptoms according to the individual's risk factors [11].

Key points: MHT for women in menopausal transition

1. It is advised not to conduct a hormone test to diagnose menopause during menopausal transition.
2. Hormone therapy during menopausal transition should primarily be conducted based on the frequency and severity of symptoms, and lifestyle adjustments and use of adjuvant therapy could be partially effective.
3. EPT, low-dose COCs, and combination therapy of LNG-IUS with oral or percutaneous estrogen could be employed as individualized treatments depending on individual risk factors for the purpose of improving symptoms.

3. Vasomotor symptoms and quality of life

3-1. Vasomotor symptoms

Hot flush, a common VMS, suddenly appears in the face and the upper body and spreads to the rest of the body. It usually lasts for approximately 2–4 minutes. Anxiety, shivering, palpitation, or perspiration may occur alongside, and night sweat is linked to sleep disorder.

The prevalence rate of VMS differs according to region and race. A lower prevalence rate of VMS is observed among Asians than among Westerners. The prevalence rate in Europe is 74%, North America 36%–50%, Central and South America 45%–69%, and Asia 22%–63% [12]. VMS are known to be highly related to the reduction of physical activity, low socioeconomic status, symptoms of anxiety and depression, hysterectomy, and smoking and the symptoms increase as body fat increases [13,14].

Most severe VMS appear within 1–2 years from the last day of menstruation and usually continue for about 4–5 years. However, there are cases in which the symptoms last for more than 12 years, which is reported to be 10% of the total cases; therefore, the symptom duration greatly varies [13,15].

Similar to standard-dose MHT, low-dose MHT is reported to be effective for treating VMS [16].

In a research with a multistage stratified random sampling design conducted in 2010 that targeted 40–60-year-old South Korean women in menopause or menopausal transition, 41.6% of women in menopausal transition, 53.1% of women in early-phase menopause, and 36.5% of women in late-phase menopause were shown to have experienced VMS [17]. In case of experiencing VMS, many women aged less than 45 years (50%) were shown to experience only hot flush as a monosymptom, whereas for women aged 45–60 years, the cases in which both hot flush and sweating were experienced increased up to 70% [17]. The results of a survey conducted by Korean Gallup Epidemiology Research in 2001 that targeted women aged 50–59 years in menopause showed that the main reason for receiving MHT was experiencing menopause symptoms, and 62.7% women reported that it was helpful [18].

In terms of the degree of improvement of VMS according to dose, a placebo showed 20%–40% reduction of symptoms, and the effect of extreme low-dose therapy, low-dose therapy, and standard-dose therapy in alleviating symptoms was 55%, 60%–70%, and 80%–90%, respectively, in MHT [19-21].

In terms of the degree of improvement of VMS for non-hormonal therapies, selective serotonin receptor inhibitor (SSRI)/selective norepinephrine receptor inhibitor (SNRI) showed 40%–65%, gabapentin (900 mg/day) showed 50%, and pregabalin (150 mg/day)

showed 65% improvement of symptoms [22,23].

Progestogen (medroxyprogesterone acetate [MPA] 10 mg/day, oral megestrol acetate 20 mg/day, and MP 300 mg/day) is known to alleviate VMS with a minimal risk, and it is highly effective in the case of severe VMS. The symptoms are less likely to recur when progestogen therapy is discontinued compared with the discontinuation of estrogen therapy [23,24].

In the case of MHT discontinuation, a report showed that VMS recurred at 50% and at most 87%; nonetheless, the severity of VMS in the case of recurrence was not as bad as that before starting MHT [25]. There is no difference in the recurrence rate of symptoms whether MHT is suddenly or gradually discontinued by eventually reducing the dose [2].

3-2. Quality of life

Evaluation of the QoL may be divided into the following criteria: health-related QoL (HRQoL), menopause-specific QoL (MSQoL), and global QoL (GQoL).

MHT reportedly not only enhances MSQoL by improving menopause symptoms but also increases GQoL. In particular, MHT improves HRQoL and MSQoL of women experiencing severe menopause symptoms.

The Korean epidemiology research on the QoL and menopause symptoms of women in menopause also showed a similar correlation between the two, but women receiving MHT were shown to have a high QoL in aspects such as VMS, psychosociological changes, and physical changes [26]. In an evaluation of QoL using the SF-36 questionnaire, the group receiving MHT was shown to have a higher QoL score than the group not receiving MHT [27]. In another study, there was an increase in the score of Women's Health Questionnaire (WHQ) and an improvement of physical symptoms, depression symptoms, and sleep disorder in the treatment group receiving MHT [28].

Based on the analysis of WHQ scores, low-dose MHT (E2 1 mg/norethindrone acetate [NETA] 0.5 mg) and tibolone have been reported to improve QoL. Tibolone mostly improved sexual function while showing effectiveness in improving VMS. MHT enhances the quality of sleep and reduces VMS and thus helps improve sleep disorder. In a study using a low-dose oral or percutaneous MHT (0.5 mg 17β-estradiol and 0.1–0.25 mg NETA) for 24 weeks, sleep disorder was improved by 40%–50% [24]. When oral progestogen is used, there may be reduced waking up and increased sedation [2].

In addition, when a premenopausal woman reaches menopause while using SSRI to treat depression, compared with SSRI therapy alone, SSRI in combination with estrogen is more effective in improving depression and shows a faster rate of treatment [29].

In contrast to the prevalent views, MHT is not associated with an increase in weight, and in fact, it helps treat the accumulation of abdominal fat during menopausal transition. In animal experiments, lack of estrogen led to accumulation of central abdominal fat, which was improved via injection of estrogen [22]. In many randomized controlled studies, MHT has been shown to reduce abdominal obesity [22]. In a research by the Women's Health Initiative (WHI) on EPT, maintaining MHT for 3 years was shown to help maintain underweight status and prevent transformation into android fat distribution [22]. ET improves the accumulation of abdominal fat because it improves insulin sensitivity and reduces the occurrence of type 2 diabetes, thereby reducing overall body fat [22].

Key points: Vasomotor symptoms and quality of life

1. Because VMS appear in relation to the reduction of estrogen levels in the central nervous system, MHT is the most effective treatment.
2. VMS are the main indications of MHT.
3. Apart from VMS, MHT can treat other menopause symptoms such as sleep disorder, depression, and musculoskeletal pain and enhance the overall QoL of women in menopause.
4. MHT is not associated with increased weight; conversely, it helps improve the accumulation of abdominal fat.
5. There is a tendency for symptoms to recur when therapy is discontinued.

4. Urogenital atrophy and sexual dysfunction

4-1. Urogenital atrophy

Urogenital atrophy has been newly renamed as GSM. The term includes all the symptoms and signs caused by changes in the bladder, urethra, vagina, and genitalia due to the decreased estrogen level during menopause and vaginal atrophy. The main symptoms are vaginal dryness, burning sensation, and discomfort; sexual symptoms such as pain due to decreased lubrication; and urinary symptoms such as painful urination, re-

current urinary tract infections (UTIs), and urinary urgency [30].

GSM chronically progresses and requires long-term treatment because the symptoms recur if treatment is stopped. The principle of this treatment is to alleviate the symptoms by normalizing the physiological environment of the urogenital organs. For the treatment of moderate or severe vaginal atrophy, both systemic and topical estrogens are effective. They help recover normal vaginal flora, increase the quantity of vaginal discharge by improving the division of the vaginal epithelium, induce proliferation of capillaries, and improve the maturation index of the vaginal epithelium [31-33]. In particular, low-dose vaginal estrogen is effective and safe, although the quantity of absorption in the whole body is minimal. All types of topical estrogen medicine (cream, vaginal tablet, and vaginal ring) are effective in reducing the symptoms and signs of vaginal atrophy. However, because there is a potential risk of increasing the estrogen level in the blood even by the slightest degree, in women with breast cancer, especially those using an aromatase inhibitor to reduce the estrogen level, a breast cancer specialist must be consulted regarding the vaginal application of low-dose estrogen [34]. Because there is no clinical data to guarantee the safety of the endometrium for a long-term application of more than 1 year, the duration of using low-dose vaginal estrogen should be limited to less than 1 year, and afterward, it must be used along with the evaluation of the endometrium.

Ospemifene and dehydroepiandrosterone (DHEA) vaginal agents are non-estrogen medications that improve the symptoms of vaginal atrophy and dyspareunia. Ospemifene, which is a selective estrogen receptor modulator (SERM), is more effective than a lubricant in reducing dyspareunia by treating moderate or severe vaginal atrophy in menopausal women. Hence, it can be considered for women who are not suited to receive vaginal estrogen treatment [35].

Vaginal DHEA has received FDA approval as a medicine for the treatment of GSM because it reduces vaginal dryness and dyspareunia as well as vaginal acidity by recovering the thickness and safety of epithelial cells and increasing the quantity of vaginal discharge [36].

The North American Menopause Society (NAMS) recommends the use of a moisturizing cream or lubricant as the primary treatment for vaginal atrophy. If a lubricant and moisturizer are frequently used, they improve the symptoms of vaginal dryness, reduce discomfort, and maintain vaginal discharge during sex but do not transform the contracted internal environment of the vagina. The use of a vaginal moisturizer, lubricant, and regular sexual intercourse help in the treatment of vaginal atrophy. Some studies show that a vaginal moisturizer has a similar effect to topical estrogen; thus, it could be recommended to women who avoid using MHT [34].

Recently, carbon dioxide laser therapy has been shown to improve sexual function and alleviate symptoms such as dyspareunia, itchiness, burning sensation, and dryness by improving the quantity of glycogen inside the vaginal epithelial cells and encouraging remodeling of vaginal connective tissues for women suffering from vaginal atrophy. It is predicted to become a suitable treatment for patients who simultaneously suffer from symptoms of GSM, which leads to a huge concern about MHT [37]. However, because there have been reports of chronic pain, burning sensation, and dyspareunia after receiving laser therapy and the U.S. FDA warned against the safety and effectiveness of laser therapy in July 2018, attention should be paid toward future research findings [38,39].

Pelvic floor muscle training, vaginal ring insertion, and topical estrogen treatment improve the function of vaginal epithelial cells and accelerate the ingrowing of connective tissue. Vaginal estrogen reduces urinary urgency, urinary frequency, overactive bladder, and urinary incontinence by reducing the contraction of bladder muscles via increasing the blood flow around the bladder neck and urethra. In contrast, systemic ET increases the occurrence of urgency urinary incontinence and stress urinary incontinence [40-43]. In the case of women with existing symptoms of urinary incontinence, the therapy worsens the symptoms, which may lead to a reduced QoL [40-43]. To treat the symptoms of an overactive bladder, changes in lifestyles and bladder training are very important and are recommended as the primary treatment methods. The systemic ET shows a similar effect to a placebo with regard to the treatment of the symptoms of nocturia and urinary frequency, but it is more effective than a placebo for the treatment of symptoms. Combined administration of vaginal estrogen and antimuscarinic drug is more suitable, and topical estrogen is considered to play an important role in treating an overactive bladder. Hence, the combination therapy of an antimuscarinic drug and topical estrogen is the primary drug therapy for menopausal women with symptoms of an overactive bladder

[44-46]. Topical ET was shown to be effective in preventing recurrent UTIs by recovering microbiological changes that occurred within the vagina after beginning menopause and by reducing vaginal acidity, but systemic ET was not effective for preventing recurrent UTIs [47].

Key points: Urogenital atrophy

1. Urogenital atrophy has been newly renamed as GSM, which includes all the symptoms caused by changes in the contraction of the bladder, urethra, vagina, and genitalia due to the decreased estrogen level during menopause and vaginal atrophy.
2. The use of topical estrogen is recommended for the treatment of GSM and recurrent UTIs.
3. Lubricants, vaginal moisturizers, ospemifene, and vaginal DHEA are non-estrogen therapies available for treating urogenital atrophy, but laser therapy could be considered an additional therapy.
4. For menopausal women with symptoms of an overactive bladder, the primary drug therapy is the combination therapy of an antimuscarinic drug and topical estrogen.
5. Systemic ET is effective for treating vaginal atrophy but not effective for treating recurrent UTIs, overactive bladder, and urinary incontinence.

4-2. Sexual dysfunction

Increased age and decreased estrogen level lead to harmful effects on sexual function and reduce sexual desire and sexual response as well as cause vaginal dryness and dyspareunia. They also cause sexual dysfunction even more in the case of surgical menopause, and it is highly possible that hypoactive sexual desire disorder (HSDD) develops as a result of various endocrine changes [48-52].

Measuring the level of sexual hormones is not helpful. The serum androgen test has been used to diagnose androgen deficiency in healthy women, but it is also not recommended because there is mostly inconsistent correlation between the androgen level and particular symptoms and signs. Especially in the case of sexual dysfunction, the role of vaginal atrophy must always be considered because the most common symptoms of vaginal atrophy are vaginal dryness and dyspareunia, which significantly affect other aspects of sexual response (sexual desire, arousal, orgasm, and satisfaction) [53]. Because female sex possesses a variety of fundamental characteristics, the effect of MHT on women's sexual dysfunction cannot be clearly proven, and ET or EPT leads to improvement of sexual function and is especially effective in reducing dyspareunia in women in early menopause or with symptoms of menopause [31,54-57]. Tibolone is highly valuable for the treatment of women's sexual dysfunction because it is known to show a significant effect on improving vaginal dryness, sexual desire, sexual arousal, and frequency of sexual intercourse when compared with using estrogen or progestogen [58].

Systemic MHT and low-dose vaginal ET are effective in treating urogenital atrophy and improve sexual function by increasing vaginal lubrication, blood flow, and sensory function. Although ET is effective for the treatment of menopausal symptoms, it does not increase sexual desire, arousal, and orgasm. In the case of women who are in need of systemic MHT expressing decreased sexual desire, percutaneous therapy is preferred to oral therapy because oral intake of estrogen reduces free testosterone by increasing sex hormone-binding globulin (SHBG). An injection of testosterone for women suffering from sexual dysfunction due to decreased sexual desire improves sexual satisfaction, desire, arousal, and orgasm; thus, it is effective for both natural menopausal or surgical menopausal women and is effective regardless of whether the woman is receiving MHT. Testosterone is also effective for the treatment of sexual desire disorder and sexual arousal disorder, which are related to antidepressants [59-61]. Because the side effects of virilization due to testosterone therapy occur in proportion to the quantity administered, they may be reduced using the lowest quantity and medications suited for individual women [62,63]. Vaginal testosterone therapy, which is another treatment option for GSM, improves dyspareunia, sexual desire, lubrication, and satisfaction when administrated alone or simultaneously with vaginal estrogen three times a week compared with a placebo [64-66].

Combination therapy of conjugated equine estrogen (CEE)–bazedoxifene also improves certain sexual functions as well as genitourinary atrophy and dyspareunia in menopausal women [22,30,67].

Key points: Sexual dysfunction

1. Increase in age and decreased serum estrogen levels lead to harmful effects on sexual function and cause dyspareunia and reduction of sexual desire and sexual response.
2. Measuring the serum level of a sex hormone does not provide much help in diagnosing and treating sexual dysfunction, and conducting a blood test for testosterone to diagnose androgen deficiency in healthy women is not advised.
3. When considering sexual dysfunction, the role of vaginal atrophy should always be considered.
4. Systemic MHT and low-dose vaginal ET are effective for treating urogenital atrophy and improve sexual function by increasing vaginal lubrication, blood flow, and sensory function as well as improve dyspareunia in particular.
5. Regarding female MHT for women with HSDD, percutaneous therapy is preferred over oral therapy and tibolone is effective for treating female sexual dysfunction by increasing women's sexual desire and arousal.

5. Coronary artery disease

Based on a meta-analysis of existing observational studies, hormone therapy reduces the risk of coronary artery disease by 28% and the mortality risk by 38% for current users [68]. In the Heart and Estrogen–Progestin Replacement study (HERS) regarding the effect of hormone therapy on secondary prevention of coronary artery disease, CEE/MPA combination therapy showed no prevention effect and the risk increased by 50% in the first year of treatment but decreased thereafter [69,70]. Additionally, in a study by WHI about the effect on primary prevention of coronary artery disease, CEE/MPA combination therapy showed no primary prevention effect and the risk significantly increased by 80% in the first year of treatment but showed trends of decline thereafter [71]. Conversely, in another study by WHI, CEE alone showed no prevention effect, but no increase in the early-phase risk was observed [72].

Considering that hormonal therapy did not prevent coronary artery disease in large-scale randomized control studies, unlike in observational studies, it is important to note that the mean age of participants was older than 60 years old. It has been suggested that the results may not apply to women younger than 60 years who have recently experienced menopause.

Hence, their different characteristics compared with those of healthy, early menopausal women in observational studies are considered to be important aspects. Thus, women who are relatively older or for whom a long time has passed since menopause (average age, 63.2 years) in the WHI study may not have experienced any significant effect on cardiovascular protection from hormone therapy as women in early menopause who are in good cardiovascular health. In a subsequent WHI analysis, the risk of coronary artery disease actually showed differences according to the starting period of hormone therapy since menopause. For women who started the therapy within 10 years of reaching menopause, there was a trend toward reduced risk, whereas for women who started the therapy more than 20 years after reaching menopause, the risk significantly increased [73].

Based on the result of analyzing 23 other clinical tests, the risk of coronary artery disease reduced by 32% for early menopausal women who have been in menopause for less than 10 years or women who were younger than 60 years of age; however, for women aged 60 or more, such cardioprotective effect did not appear [74]. Based on the recent results of meta-analyzing 19 randomized controlled studies, starting hormone therapy within the first 10 years of menopause led to reduction of total mortality risk by 30% and cardiovascular mortality risk by 48% [75]. Additionally, women in their 50s who were previously enrolled in the ET arm of the WHI study showed significantly lower coronary artery calcification scores than those who received placebo [76].

In the Danish Osteoporosis Prevention Study, when hormone therapy was conducted for 10 years with 1,000 young menopausal women with the average age of 50 years, there was a 52% reduction of the indicator, which is a combination of mortality, heart failure, or myocardial infarction [77]. On the other hand, in the Kronos Early Estrogen Prevention Study (KEEPS), when hormone therapy was administered for approximately 4 years to young women with an average age of 52 years and all within 3 years of their final menstrual period, there was no significant difference in the rate of progression of carotid–intima-media thickness between the treatment and placebo groups. However, there was a nonsignificant trend for less accumulation of coronary calcium in the hormone therapy arms than in the placebo arms [76]. In the Early versus Late Intervention Trial with Estradiol study, the use of hormone therapy for about 5 years for younger postmenopausal women

who were less than 6 years past menopause showed that the carotid–intima media thickness significantly decreased compared with the use of a placebo but showed no difference compared with the use of a placebo for women who were 10 or more years past menopause at the time of randomization [78]. In summary, such research findings strongly imply ("timing hypothesis" or "window of opportunity") that the effect of hormone therapy on the cardiovascular system could differ depending on the timing of initiation.

On the other hand, considering there were differences in the effect of hormone therapy on coronary artery disease between CEE alone and CEE/MPA combination therapy, attention must be paid to the type of hormone used, particularly progestogen.

In contrast, the International Menopause Society (IMS) (2016) claimed that hormone therapy has shown to reduce the incidence of new-onset diabetes mellitus and has a beneficial effect on vascular function, lipid levels and glucose metabolism, which are risk factors for cardiovascular disorders [22]. There is strong evidence showing that the mortality rate and the incidence of coronary artery disease are reduced if started around the time of menopause or under the age of 60 or within 10 years of menopause. Progestin combination therapy also shows a similar tendency. Accordingly, hormone therapy does not increase the risk of coronary artery disease in young and healthy menopausal women, but it is not effective in case they already have the disease.

The mortality rate by ischemic heart diseases (myocardial infarction and angina) in South Korean women was 25.0 deaths per 100,000 individuals in 2017, but for women aged above 65 years, the mortality rate was very high, reaching 148.8 deaths per 100,000 individuals. A more significant factor is that the mortality rate by ischemic heart diseases in OECD countries was reduced by 52% in 2016 compared with that in 1990; it was increased in South Korea by 43%. Not only the mortality rate but also the economic burden of diseases are increasing as the number of patients who received treatments for ischemic heart diseases has almost doubled from 510,000 in 2004 to 860,000 in 2016, which led to the more than quadruple increase in health insurance fees from 2,900 billion won to 1 trillion 2,400 billion won; therefore, attention is required.

Key points: Coronary artery disease

1. In women aged less than 60 years and/or within 10 years of menopause with no evidence of cardiovascular disease, the initiation of hormone therapy could be expected to reduce the incidence of coronary heart disease and all-cause mortality.
2. The effect of hormone therapy on coronary heart disease may differ depending on the use of progestogen and the timing of initiation.
3. Currently, it is not recommended to initiate MHT solely for primary or secondary prevention of coronary heart disease.

6. Cerebral stroke

A meta-analysis including the WHI study found no increased risk of stroke in women aged less than 60 years or who were fewer than 10 years from menopausal onset [73,75,79,80].

In the WHI study, in case of EPT, the risk of stroke for women who initiated hormone therapy when aged younger than 60 years and/or who were within 10 years of menopause onset was rare (< 1/1,000) and statistically insignificant.

In case of ET, if the women initiated hormone therapy at the age of 50–59 years, the risk was reduced by 1/100,000 person-year, but for women fewer than 10 years from menopause onset, there was a trend of increase in the risk by 1/100,000 person-year. These results were inconsistent but were not statistically insignificant.

On the other hand, for women who initiate HT when aged above 60 years and/or who are more than 10 years from menopause onset, hormone therapy increases the risk of stroke. The risk differs depending on the age range; in case of EPT, the HR was 1.45 (95% CI, 1.00–2.11) for women in their 60s and 1.22 (95% CI, 0.84–1.79) for those in their 70s; hence, there was no statistical significance. In case of ET, HR was 1.55 (95% CI, 1.10–2.16) for women in their 60s and 1.29 (95% CI, 0.90–1.86) for those in their 70s.

In the results of a long-term follow-up observation up to 13 years after completing the WHI study, stroke risks did not differ significantly between women formerly assigned to hormones and women formerly assigned to placebo, and there was no statistical evidence that risks differed based on age or timing [81].

Based on the results of observational studies, lower-

dose oral hormone therapy and lower-dose transdermal therapy has less effect on the risk of stroke [82]. The increased risk of stroke due to hormone therapy may be limited to ischemic stroke and has no effect on hemorrhagic stroke.

Based on Korean epidemiology and the data from the National Statistical Office (2017), cerebrovascular disease is the third highest cause of death in both genders and the mortality rate by cerebrovascular diseases in women is 46.1 deaths every 100,000 people. In the national statistics released by the Korean Stroke Society in 2018, ischemic cerebral stroke constituted 76.3% and hemorrhagic cerebral stroke constituted 23.4% of the total cerebrovascular diseases (change order) [83]. The stroke incidence in 2013 was similar to that in 2004, but the stroke mortality is declining.

Key points: Cerebral stroke

1. The risk of stroke in younger postmenopausal women is rare, and a meta-analysis including a WHI study found no increased risk of stroke in women aged younger than 60 years or who were fewer than 10 years from menopausal onset.
2. The risk of cerebral stroke differs depending on the age range and MHT increases the risk of ischemic stroke in women aged above 60 years.
3. Lower-dose oral hormone therapy or transdermal hormone therapy could relatively reduce the risk of stroke.

7. Venous thromboembolism

Venous thromboembolism has an annual disease frequency of 5.4 diseases per 100,000 adult populations in Europe and the US regardless of gender. With an increase in age, some coagulation factors and activation increase, leading to an increase in the risk of thrombosis; however, this is rarely observed before the age of 60 years [84]. In case of women, it occurs in 1–2 women per 1,000 women annually. The risk factors of venous thromboembolism include age, obesity, personal history of thrombosis and genetic thrombophilia [85]. In general, a lower frequency of venous thromboembolism is observed in Asian women than in Western women [86].

In the U.S. Preventive Services Task Force (USPSTF) study, in which a meta-analysis was conducted with the WHI study, HERS study, and other references, the risk of venous thromboembolism due to hormone therapy approximately doubled and the risk was higher during the first year of oral estrogen use, with or without progestogen (Table 1) [87-89].

The absolute risk of VTE was significantly increased in women initiating hormone therapy more than 10 years from menopause onset [75]. In the WHI study, based on the analysis according to age, use of ET in women aged 50–59 years showed no significant increase in the risk. Because oral estrogen increases the activity of thrombin while reducing the activity of plasmin and has a higher thrombus tendency than that of transdermal estrogen, the use of transdermal estrogen could be better in case of women having a medical history or risk factors of venous thromboembolism [1,22,90]. Transdermal estrogen could be a better option for patients with diabetes, high blood pressure, and other risk factors of cardiovascular systems because it does not go through liver metabolism, thus leading to less stimulation of the synthesis of SHBG [87].

Regarding the risk of venous thromboembolism depending on the type of estrogen there is an opinion that CEE use was associated with a higher risk of incident VTE than estradiol use [75,90]. The risk of VTE may be affected by the type of progestogen, MPA may be associated with greater risk of venous thromboembolism. However, micronized progesterone may be safe with thrombotic risk.

The risk of VTE was higher in users of oral estrogen plus progestogen than oral estrogen therapy alone [70,85,89]. According to the WHI study, hormone therapy for women with factor V Leiden mutation increases the relative risk of venous thromboembolism to 6.69 compared with that for women without any mutations who do not receive any hormone therapy. For women with a body mass index of more than 25, EPT significantly increases the risk of venous thromboembolism [91].

Based on the review of domestic references, the incidence of VTE is lower in Asian population than in Western populations. There was no factor V Leiden mutation reported in Korean subjects at high risk for

Table 1. Relative risk of venous thromboembolism (VTE) in hormone therapy users (RR or HR with 95% CI)
Outcome USPSTF WHI HERS

Outcome	USPSTF	WHI	HERS
VTE overall	2.14 (1.64–2.81)	2.11 (1.26–3.55)	2.06 (1.26–3.36)
VTE first year	3.49 (2.33–5.59)	3.6 (no CI)	3.28 (1.07–10.1)

thrombophilia. There was one case of venous thromboembolism after using MHT in South Korea, but even in this case, there was no factor V Leiden mutation [92].

Key points: Venous thromboembolism

1. MHT increases the risk of venous thromboembolism. Particularly, the risk of VTE increases with age and increases in women initiating hormone therapy more than 10 years from menopausal onset.
2. The risk of venous thromboembolism increases in the first 1 to 2 years of MHT and decreases afterwards.
3. Estrogen therapy has a lower risk of venous thromboembolism than EPT, and if used in the early postmenopausal period, the risk of venous thromboembolism does not increase.
4. Oral estrogen therapy is banned for patients with anamnesis of venous thromboembolism, and they must use transdermal estrogen.
5. The occurrence of venous thromboembolism in Asian women is very low, and there has been no report of factor V Leiden mutation in South Korea.

8. Breast cancer

There have been controversies regarding the association between MHT and breast cancer. Different results are being reported according to the forms and types of hormones such as ET, EPT, and CEE–bazedoxifene, dose, starting date of medication, period, and individual characteristics [93-98]. According to a recent randomized controlled study on MHT and occurrence of breast cancer and the consultation instructions by British Menopause Society, ET did not increase breast cancer, whereas EPT showed a tendency of significant increase in breast cancer [93,99].

Based on a 5.6-year observation in the WHI study, the EPT group showed an increase in the risk of infiltrative breast cancer by approximately 1.24 times (absolute risk: annual increase of nine cases per 100,000 people), and the increase of the risk was observed from the third year of MHT [100]. However, the increase of breast cancer was limited to women with a history of having received MHT prior to participating in the WHI study, and in case of women with such histories, the increase did not occur until the seventh year and the increase of breast cancer was not observed even during the 11-year follow-up observation period [101,102]. In case of ET, based on the 7.2-year observation, there was a tendency of reduction of the risk of breast cancer (absolute risk: annual reduction of seven cases per 100,000 people), even though it was not statistically significant. In particular, in case of women without any history of receiving MHT or those who received it for more than 80% continuously, there was a statistically significant reduction (33%–35% reduction). In the 13.2-year cumulative follow-up observation after stopping ET, the occurrence of breast cancer was significantly reduced by 21% [81]. Moreover, in the extended study (on average, 5.9-year of use, 11.8-year of observation) conducted after the WHI study targeting women who wanted continuous single use of estrogen therapy, the risk of breast cancer significantly decreased [103,104]. According to the Nurse Health Study, there was no significant increase in the risk of breast cancer in the ET group until the 15th year [105].

There is no reliable research finding about whether low-dose estrogen–progestogen combination therapy increases the risk of breast cancer. In case of long-term use of progestogen, there has been a report about the possibility of increasing the frequency of breast cancer occurrence. However, according to the E3N-EPIC cohort study conducted in France, there is a report about how natural progesterone use would not increase the risk of breast cancer. Therefore, the risk of breast cancer is expected to differ depending on the progestogen medicine [106].

In a small number of observational studies, MHT did not increase the risk of breast cancer in women with a family history of breast cancer or who received ovariotomy and have *BRCA 1/2* [107-110]. Thus, because MHT could increase recurrence in breast cancer patients, it is not advised [111]. However, in case of low-dose vaginal ET, it could be considered as an effective therapy after trying non-hormonal therapy when suffering from urinogenital atrophy due to minimal systemic absorption [112].

However, difference of Korean epidemiology from western epidemiology must be considered when indicating the association between breast cancer and MHT after reaching menopause. The risk of occurrence of breast cancer in American women begins from the age of 15 years and increases from the age of 40–49 years, and the highest rate of occurrence is observed at the age of 70–74 years, which gradually decreases afterward. In case of South Korea, the middle age at the

point of diagnosis is 50 years and 40s is the age range in which the highest number of breast cancer cases occurred. The order of frequency of disease as per age is as follows: 40s, 50s, 60s, 30s, and 70s [113-115]. Compared with the past results, there is a general tendency of increase in the occurrence age, and from 2010, an increase in the number of patients in their 50s diagnosed with breast cancer was observed. Occurrence of breast cancer keeps increasing but is still relatively low as it is 1/2–1/3 of the occurrence in the west. In case of western women, the frequency of breast cancer increases as age increases, whereas in case of Korean women, the frequency increases until early 50s, then gradually decreases afterward [113-115]. The ratio of breast cancer before menopause is significantly higher than that in the west. There is a high occurrence rate in young patients in their 40s, and patients under 40s constitute about 13% of the cases, which is more than two times higher than that in the west [113]. The occurrence rate in American women is 126.4 cases per 100,000 people, whereas the mortality rate due to breast cancer is 20 cases per 100,000 people. The frequency in South Korea is 75.1 cases (2015), and the mortality rate is 9.6 cases (2016), which is a significantly low occurrence rate and mortality rate, therefore showing a very different aspect from an epidemiological perspective [113-115].

Key points: Breast cancer

1. After using EPT for an average period of 5.6 years, the risk of breast cancer increased but for women who were starting MHT for the first time, the risk of breast cancer did not increase until the 7th year.
2. In case of ET, the risk of breast cancer reduced after using it for 7.2 years and significantly reduced after 13.2 years of follow-up observation.
3. MHT is not advised for breast cancer patients.
4. As South Korean breast cancer epidemiology is very different from that of the US, it is impractical to apply the research findings of the US exactly to the cases in South Korea.

9. Ovarian cancer, endometrial cancer, colorectal cancer, and lung cancer

9–1. Ovarian cancer

Ovarian cancer, the 9th most common type of cancer in the west, occurs every 27 cases per 100,000 people among women aged above 50 years, and the average age at the point of diagnosis is approximately 64 years with more than 80% women aged above 50 years. Moreover, in South Korea, the number of ovarian cancer patients shows a trend of continuous increase (change of location) [116].

Until now, there is no reliable data that could confirm the association between MHT and the occurrence of ovarian cancer. According to the 5.6-year observation in the WHI study, which is the only randomized controlled study that could analyze the association between ovarian cancer and MHT, the risk of ovarian cancer did not significantly increase in both ET group and EP group (HR, 1.24; 95% CI, 0.83–1.87, HR 1.41; 95% CI, 0.75–2.66) [117]. However, several observational studies have reported an increased risk: Nurses' Health Study reported an increased relative risk of ovarian cancer by 1.41 times (95% CI, 1.07–1.86) when using estrogen for more than 5 years; NIH-AARP Diet and Health Study reported an increased relative risk of ovarian cancer by 2.15 times (95% CI, 1.30–3.57) when using ET for more than 10 years and by 1.68 times (95% CI, 1.13–2.49) when using EPT for more than 10 years. However, even if MHT increases the risk of ovarian cancer, the increase is about 0.8 cases per 10,000 people annually, which is considered very rare.

Based on the meta-analysis, in ovarian cancer patients, MHT does not increase the mortality rate or recurrence rate of ovarian cancer, but there is almost no data available yet on low-grade serous cancer as well as granulosa cell tumor or cancer, which involve positive estrogen receptors such as Sertoli–Leydig tumor [118].

Key points: Ovarian cancer

1. Estrogen–progestogen combination therapy does not increase the risk of ovarian cancer.
2. There are reports showing that long-term estrogen therapy increases the risk of epithelial ovarian cancer, but the absolute number is rare as it was about 0.7 cases per 1,000 people for 5 years.

9–2. Endometrial cancer

In women with the uterus, administration of estrogen alone increases the risk of endometrial cancer in proportion to its dose and duration. Therefore, in the presence of the uterus, estrogen and progestogen should be administered in combination. In the WHI study, the continuous EPT combination therapy showed a similar

result to the comparative group regarding endometrial cancer [117].

According to recent studies, among patients with endometrial cancer, if the patients that belong to endometrioid subtypes I and II had excision of the uterus and bilateral appendages and the estrogen receptors and progesterone receptors tested negative, the recurrence rate and mortality rate of endometrial cancer did not increase, even when MHT was applied [119]. However, even in case of early endometrial cancer, the therapy is recommended 5 years after complete recovery. For stages III and IV endometrial cancer, clear cell carcinoma, or serous papillary carcinoma patients, MHT is not recommended [120,121].

The incidence of endometrial cancer in Korea has rapidly increased, increasing more than 10 times from 132 cases in 1991 to 1,619 cases in 2009 and reaching 2,404 cases in women in 2015. According to age groups, women in their 50s showed the highest incidence at 38.4%, followed by those in their 40s at 25.2% and those in their 60s at 17.9%.

Key points: Endometrial cancer

1. For women with the uterus, estrogen–progestogen combination therapy should be administrated to protect the endometrium.
2. A sufficient dose of progestogen administered for a sufficient period of 12–14 days per month leads to little increase in risk of endometrial cancer, and continuous administration of combination therapy leads to a reduction in risk of endometrial cancer.
3. MHT may be considered if non-hormonal therapy is not effective in early endometrial cancer patients with an excised uterus and bilateral appendages when they show menopausal symptoms.
4. In case of patients with stages III and IV endometrial cancer or high-risk endometrial cancer, non-hormonal therapy should be used to control menopause symptoms.

9–3. Colorectal cancer

Observational studies including Nurses' Health Study showed that administration of hormone therapy during menopause significantly reduces the risk of colorectal cancer [121]. In the WHI study, which is a large-scale randomized controlled study, estrogen–progestogen combination therapy has been reported to reduce the risk of colorectal cancer by 38% when compared with a placebo (HR 0.62; 95% CI, 0.43–0.89) [122]. However, when the administration stops, the prevention effect of colorectal cancer disappears. Individual estrogen therapy does not have any effect on invasive colorectal cancer or on the mortality rate due to invasive colorectal cancer [123,124].

In Korean women, colorectal cancer is the third highest type of cancer in females (10.7%) and occurred among 10,846 women in 2015. It occurred most commonly among women aged above 65 years. The mortality rate of colorectal cancer is the second highest after that of lung cancer.

Key points: Colorectal cancer

1. Estrogen–progestogen combination therapy reduces the risk of colorectal cancer.
2. Estrogen therapy does not have any effect on colorectal cancer.
3. Executing MHT with the sole purpose of preventing colorectal cancer is not advised.

9–4. Lung cancer

In the WHI study, both individual estrogen therapy and estrogen–progestogen combination therapy did not increase the occurrence of lung cancer. However, in case of estrogen–progestogen combination therapy, the mortality rate due to lung cancer increased, which was limited to past or current smokers aged above 60 years. The absolute risk was also very low as the increased mortality was 4 cases per 10,000 people and individual estrogen therapy did not have any effect on the mortality rate of lung cancer [125].

The IMS claimed that based on the analysis of many observational research findings, MHT has a protective effect against occurrence of lung cancer in patients aged less than 60 years. In South Korea, lung cancer is the fifth highest type of female cancer (7.2%), which affected 7,298 women in 2015 and has the highest mortality rate among female cancers.

Key point: Lung cancer

1. MHT does not increase the occurrence of lung cancer.

10. Cognitive function and Alzheimer's

The WHI memory study (WHIMS), an ancillary study to WHI study, reported a significant increase in the risk (2.05) of probable dementia in the EPT group with women aged above 60 years every year, and the risk increased to 1.49 in the ET group, but no statistical significance was observed [126,127]. The WHI study of cognitive aging, another ancillary study about cognitive function, observed a slight improvement in nonverbal episodic memory in the EPT group but a reduction in verbal episodic memory, although no particular effect was observed in the ET group [128]. Another ancillary study, the WHIMS-Magnetic Resonance Imaging study showed a reduction in the volume of some brain areas, especially of the frontal lobe and hippocampus in MHT patients compared with the control group [129].

In contrast, according to the findings from the MIRAGE study, which compared 426 Alzheimer's patients with patients without Alzheimer's, the risk of Alzheimer's in the group that received MHT was 30% lower than that in the control group for all age groups [130]. Similarly in case of the Cache county study, which targeted 1,889 women, the risk of Alzheimer's in the MHT group was significantly lower by 0.41 times (95% CI, 0.17–0.86) when compared with the control group [131]. Such observational research findings showed different results from the WHIMS study; this could be owing to the effect of difference of age and the starting point of MHT (Table 2) [132]. WHIMS's research target was women aged above 65 years who had relatively increased risk of Alzheimer's. Thus, the patients diagnosed with Alzheimer's during the study could have already well manifested Alzheimer's symptoms, which were not clinically revealed at the starting point of the study.

In contrast to WHIMS, in the recently released KEEPS study, MHT did not have any effect on memory or cognitive function. This could also be because of the fact that the study targeted young women who had just reached menopause [133]. The "critical window hypothesis" refers to a concept that addresses that the effect of MHT on cognitive function could differ depending on the time of executing the MHT [134,135]. Although the highest improvement effect on cognitive function could be expected if MHT is started immediately at the point of decline in ovarian function due to natural menopause or ovariotomy, if MHT is started in old women in menopause, it could actually cause a harmful effect on cognitive function.

In the Study of Women's Health Across the Nation study, a better recall score was shown in case of starting MHT before the last menstruation, whereas in case of starting MHT after the last menstruation, a decline in cognitive function was observed [136]. Another observational study reported that although starting MHT at midlife helped prevent cognitive disorder, starting MHT during late life caused a negative effect on cognitive function [134]. In the MIRAGE research findings, although the risk of Alzheimer's was reduced by 65% for the age range of 50–63 years when using MHT, for the age range of 64–71 and 72–89 years such effects did not appear and the effect of MHT on Alzheimer's seemed better with younger age [130]. Based on research findings about women with the average age of 74 years, Zandi et al. [131] also suggested the possibility of a period during which MHT influences cognitive function and reported that in case of MHT administered for more than 10 years but currently stopped, the risk of Alzheimer's occurrence was reduced by 83%, and in case of MHT administered in the past, the risk of Al-

Table 2. Considerations for discrepant findings between most observational studies on MHT and the WHIMS randomized trials of MHT

Factors	Observational studies	WHIMS trials
Susceptibility to bias or confounding	Large	Small
Primary outcome	Alzheimer's disease	All-cause dementia
MHT formulation	Often CEE; sequential progestin	Only CEE; continuous progestin
Menopausal symptoms	Common	Uncommon
Age at the time of study	Variable; usually older	Older (65+ years)
Age at MHT exposure	Usually younger	Older (65+ years)
Timing of MHT initiation	Usually close to menopause	Remote from menopause
Overall outcomes	Generally beneficial	Generally detrimental

Adapted from Henderson (2006) [132].

zheimer's occurrence was reduced by 41% [6]. However, clinical evidence lacks such "critical window hypothesis" yet [90]. For example, in the WHIMS of Younger Women study, which targeted young menopausal women with the age range of 50–59 years and analyzed the effect of MHT on cognitive function, MHT using CEE did not result in improvement of general cognitive function regardless of combining with progestin [137].

Recently, the "healthy cell bias hypothesis" is often introduced instead of the existing "critical window hypothesis" about the difference in the effect of cognitive function regarding the execution time of MHT [138,139]. This means that in terms of the effect of MHT, the woman's health is a more important determinant than physiological age. Even an old woman could benefit from the use of MHT if her cognitive function is "healthy." However, both hypotheses share a limitation that they were not supported by large-scale random blind studies [90].

In case of surgical menopause, as the concentration of estrogen rapidly decreases, the effect on cognitive function could possibly differ from that in case of natural menopause [140,141]. The faster the surgical menopause is done, the higher is the risk of Alzheimer's or cognitive disorder [142]. Guidelines from both the North American Menopause Society and IMS recommend that estrogen therapy immediately after surgical menopause could help improve cognitive function [22,90].

In several small-scale studies that were conducted in 1980s–1990s on whether injection of female hormone could help improve cognitive function in women with Alzheimer's, improvement of cognitive function was reported when the female hormone was administered to the Alzheimer's patient [143-145]. However, the positive effect in the observational study could be because of the fact that the subjects were relatively young women and recall bias might have occurred. In the reported random double-blind study in 2000, no change in cognitive function was observed when administering individual female MHT for 1 year targeting 120 women with Alzheimer's who had undergone hysterectomy due to medical history [146].

Korean epidemiology reported that 4.2% of the elderly aged above 65 years has Alzheimer's. In the study that targeted South Korean Alzheimer's patients, MHT was administered for 1 year, and it was reported that the MMSE score did not decline, although it showed similar effects to the representative Alzheimer's medicine, tacrine, regarding cognitive function, and that the MHT improved the daily activity capacity. Thus, a positive effect of MHT was reported [147].

Key points: Cognitive function and Alzheimer's

1. If MHT is started in early menopausal women, a prevention effect against the reduction of cognitive function could be expected although the evidence from randomized controlled studies is lacking.
2. Executing MHT with the sole purpose of preventing worsening or treatment of current cognitive function is not advised.

11. Depression

The prevalence rate of major depressive disorder in women of age 50 and over is 4.0%–5.4% in South Korea, which is about three times higher than that in men (1.3%–2.4%) [148]. Most women (more than 85%) in menopausal transition do not experience a new onset of depression, and the risk of depression is similar to that before or after menopause. However, hormonal changes and vasomotor symptoms can lead to new depressive symptoms and the risk of developing depression could increase during menopausal transition or early menopause [149,150]. Although it has been shown that estrogen therapy has a positive effect on mood disorder in women who had surgical menopause, even without menopausal symptoms [151], it remains unclear whether MHT has a beneficial effect on mood disorder in women who are not diagnosed with depression [22,152].

Until now, there have been very few randomized controlled studies on MHT in middle-aged women with depression. Although some studies reported that short-term estrogen therapy could alleviate symptoms of depression during menopausal transition in women with depression [153,154], most studies failed to find a positive effect of MHT on depression in older menopausal women [155-157]. In women who experienced improvement in depressive symptoms with MHT, symptoms could get worse after stopping MHT [158].

Addition of progestogen could negatively affect mood in women with a past history of depression, premenstrual syndrome, or premenstrual dysphoric disorder [159]. The effect of progestogen on the central nervous system could differ depending on the ratio of estrogen and progestogen [160].

Key points: Depression

1. MHT could show a positive effect, although limited, on affective disorder during menopausal transition.
2. In women who experience improvement in depressive symptoms through MHT, symptoms could easily worsen when treatment is stopped.
3. There is lack of clinical evidence supporting the use of MHT for treatment of depression.

12. Osteoporosis

12-1. Bone density

The standard dose of MHT increases bone density by inhibiting bone resorption and reducing bone remodeling process. The response of bone density to estrogen is dose-dependent. In the Postmenopausal Estrogen/Progestin Interventions trial, bone density increased at the lumbar spine and femur in women who received ET or EPT (0.625 mg CEE/MPA or micronized progesterone) for 3 years compared with the control group [161]. In the WHI study, bone density at the lumbar spine and femur increased by 4.5% and 3.7%, respectively, with the standard-dose EPT (0.625 mg CEE + 2.5 mg MPA) compared with the control group [162].

In a meta-analysis, 2 years of oral MHT increased bone density at the lumbar spine (6.8%) and femur (4.1%) compared with the control group [163]. Bone density significantly increased at both the lumbar spine and femur with low-dose ET or EPT (oral CEE 0.3 mg, 17beta-estradiol 0.25 mg, 17beta-estradiol 0.014 mg patch) in young (average age: 51–52 years) and old (average age: 67–74 years) postmenopausal women [164,165].

12-2. Fracture

In the National Osteoporosis Risk Assessment (NORA) study, the risk of new fractures significantly decreased when evaluating 200,160 postmenopausal women using MHT with no history of osteoporosis. In current ET or EPT users, the risk of clinical fracture at the femur, spine, humerus, wrist, or rib was reduced, although this beneficial effect did not persist after stopping MHT for 5 years. In particular, the risk of fracture at the femur when women stopped MHT for 5 years was similar to that with no treatment [166].

In the WHI study, the risk of facture significantly decreased by 33% at the lumbar spine and 35% at the femur using EPT and by 38% at the lumbar spine and 39% at the femur using ET. This protective effect rapidly disappeared after stopping MHT, and the long-term follow-up study of WHI reported that the ET group showed a continued reduction effect of all fractures after stopping therapy, whereas the EPT group showed no reduction in all fractures [81].

Most (82%) menopausal women with fractures in the NORA study were reported to have osteopenia with a T score above −2.5, but even though the frequency of femur fracture was the highest in the study, only 6.4% of the patients had a T score below −2.5 [166]. Therefore, MHT is also necessary to prevent bone loss or fracture in women with osteopenia.

No difference was found between the continuous and cyclic use of progestogen, and no effect has been proven to reduce the risk of fractures using low- and ultra-low-dose estrogen therapy.

NAMS reported that MHT prevents menopause-related bone loss and reduces osteoporotic fractures including those of the spine and femur in the low-risk group. MHT is an appropriate first-line treatment in menopausal women aged less than 60 years with an increased risk of fracture, but MHT is not recommended solely for the prevention of fracture in women aged above 60 years. MHT also prevents bone loss in women with premature ovarian failure [90].

The prevalence rate of osteoporosis in individuals aged above 50 years was 7.5% in men and 35.5% in women from the Korean National Health and Nutrition Examination Survey in 2008–2009. The incidence rate of femur fracture increased from 99.6 cases per 100,000 in men and 209.9 cases per 100,000 in women in 2008 to 110.5 cases per 100,000 in men and 243.1 cases per 100,000 in women in 2012 from the data from National Health Insurance Service [167]. In the multi-center retrospective observational study conducted by the Korean Society of Menopause in 2012, patients whose bone density was reduced after the first year of MHT showed increased bone density in the second year of MHT. In contrast, patients whose bone density was remarkably increased after the first year of MHT demonstrated relatively lower or decreased bone density in the second year of MHT. This finding was similar across EPT, ET, and tibolone users. It was concluded that even if bone density is temporarily reduced after MHT, it should not be the only reason for changing therapy [168].

Key points: Osteoporosis

1. Because MHT prevents menopause-related bone loss and reduces the risk of fracture, it is an appropriate therapy for the prevention and treatment of osteoporosis in young menopausal women aged less than 60 years or those with less than 10 years since menopause.
2. Bone protective effect is rapidly lost after stopping MHT.
3. Standard dose of MHT reduces the femur, vertebral, and non-vertebral fractures in women without osteoporosis.
4. Efficacy of reducing the risk of fracture has not been proven in low- and ultra-low-dose estrogen therapy.
5. MHT is necessary for women with premature ovarian insufficiency (premature menopause) or osteopenia to prevent bone loss.

13. Sarcopenia

The prevalence rate of sarcopenia in community-dwelling older adults was 35.3% in women and 13.4% in men aged above 65 years from the Korean longitudinal study on health and aging. In another epidemiological study targeting the elderly in the Gangbuk district in Seoul, the prevalence rate of sarcopenia was 6.3% in men and 4.1% in women [169-171]. In addition, according to the cumulative data of more than 10 years from the Korean National Health and Nutrition Examination Study, 19.5% of women in their 50s, 16.6% of women in their 60s, 23.7% of women in their 70s, and 30.8% of women in their 80s were reported to have sarcopenia [172-174].

Several studies showed that MHT can preserve muscle strength and recover rapid loss of muscle strength. Muscle strength increased up to 24 months when using MHT, and the maximal voluntary force also increased in the MHT group in contrast to a decrease in the control group. Likewise, vertical jumping height and maximal walking speed were significantly higher with MHT in monozygotic twins. When combining MHT and exercise, the effect of improving the muscle tone, muscle mass, and muscle strength was enhanced. These results suggest that MHT can help increase muscle strength and prevent muscle contraction and movement limitation; furthermore, a meta-analysis showed that MHT helps improve muscle intensity. However, this beneficial effect was not found when MHT was used in older women aged above 60 years or when used for less than 6 months [175,176].

In contrast to the consistent effect being reported regarding muscle strength, the effect of MHT on muscle mass remains controversial. In the WHI study, a preservation effect of body mass except fat was observed during the first 3 years of MHT, but this effect was reduced and disappeared during the 3 years afterward. This implies that the effect of MHT can depend on age [177].

In summary, MHT alone or combined with exercise could increase muscle mass, alleviate its reduction, and improve muscle function and regeneration of skeletal muscle. However, as most studies are small with different age, health condition, and exercise program, the interpretation of results could be affected. Therefore, additional studies are needed to draw a clear conclusion. On the other hand, although there is a lack of studies, plant hormones such as isoflavone are considered to have no effect on sarcopenia [178].

Key points: Sarcopenia

1. MHT, particularly when combined with exercise, seems to be effective in increasing muscle mass, alleviating its reduction, and improving muscle function and muscle strength.
2. There is a lack of evidence regarding the use of MHT primarily for the purpose of treating and preventing sarcopenia.

14. Gallbladder disease and migraine

Gallstone (or gallbladder disease) occurs in 10%–15% cases in the US and increases by 1 million people annually. The occurrence of gallbladder disease has a close association with estrogen therapy. In South Korea, the frequency of gallstones is about 2%–4% and the number of patients with gallstones has increased by 49% from 129,226 people in 2014 to 192,551 in 2018, according to the data from the Health Insurance Review and Assessment Service. This is because of the westernization of eating habits. Gallstones are more common among women than among men. In South Korea, it is reported to occur 1.1 times more frequently in women than in men, and the frequency increases in both genders from 40 to 50 years of age [179].

Estrogen increases the risk of gallstone by accelerat-

ing the increase of secretion and saturation of cholesterol within the gallbladder, which leads to increased concentration of cholesterol and reduced activity of the gallbladder. Apart from MHT, factors such as use of combined oral contraceptive and pregnancy also increase the risk of cholesterol gallstones [180]. In the WHI study, the relative risk of cholecystitis and cholecystectomy was increased in case of both ET (79%) and EPT (61%) [181]. However, MHT was not associated with other bile duct surgeries. In a meta-analysis regarding the occurrence of cholecystitis, the relative risk increased to 1.8 in women who used MHT for less than 5 years, whereas it increased to 2.5 in women who used MHT for more than 5 years. The frequency of cholecystectomy was lower with non-oral MHT than with oral MHT [11,90].

There is a lack of data on the relationship between MHT and migraine, and evidence for banning the use of MHT merely due to migraines is very rare.

Key points: Gallbladder disease and migraine

1. ET or EPT increases the risk of gallbladder diseases.
2. Careful monitoring of gallbladder disease is required in women using oral MHT.
3. Non-oral MHT is recommended for women with gallbladder disease.
4. Because there is a lack of data on the relationship between MHT and migraine, it cannot be concluded that migraine is a contraindication for MHT.

15. Cautions for HT

15-1. Indication of progestogen

For women with the uterus intact, estrogen must be administered together with progestogen to reduce the risk of endometrial hyperplasia and cancer. For women with no uterus, progestogen may not be administered, but if there is a history of endometriosis or a partial uterus left when performing hysterectomy and in case of an endometrioid type of ovarian cancer, administration of progestogen is required. In case of receiving vaginal estrogen therapy due to vaginal atrophy or receiving minimum dose transdermal estrogen therapy to prevent bone disappearance, progestogen may not be administered, but the long-term safety of progestogen administration for more than 1 year remains unclear [90,159].

15-2. Route of administration

The route of administration can be oral and non-oral, and non-oral administration is known to have no first-pass effect on the liver and almost no effect on SHBG, blood pressure, neutral fat, and C-reactive protein level when compared with oral administration. In case of having only symptoms of vaginal atrophy and vaginal dryness, topical vaginal estrogen is recommended, whereas for women with a high risk of venous thromboembolism and high neutral fats as well as for obese women with metabolic syndrome, transdermal therapy should be selected first. For women with smoking habits and high blood pressure, transdermal therapy is also recommended [90,159].

15-3. Timing of initiation

It is better to start MHT immediately once symptoms appear before or after menopause. If premature hypoestrogenism or early menopause (menopause under 45 years of age) is diagnosed, it is recommended to start MHT regardless of whether symptoms of menopause are present [182].

15-4. Duration of MHT

Based on the results of previous research, it is not yet possible to provide clear instructions regarding the duration of MHT. However, there is no need to impose a limit on the duration of MHT as long as an effective minimum dose is used, if women are well aware of the potential benefits and risks, and a regular clinical follow-up observation is accompanied. Particularly for healthy women aged less than 60 years or those who have started MHT within 10 years of reaching menopause, if there is no occurrence of new diseases, it is safe to continue MHT. There is no need to discontinue daily MHT at 60–65 years of age, and evaluating comorbidity, trying to temporarily discontinue or reduce hormone therapy, or eventually switching to safer transdermal therapy could be considered instead [90,159].

When determining whether to continue MHT, the following factors should be considered: first, the positive effect of MHT for the treatment of continuous vasomotor symptoms, reduction of bone density, prevention of fracture, reduction of colorectal cancer, and prevention and treatment of symptoms of urinogenital diseases; second, consideration of the potential risk of

breast cancer, which could increase as the duration of MHT increases, as well as thrombotic events (VTE, PE, and stroke). Additionally, although starting MHT when almost reaching menopause could help reduce the mortality related to coronary artery disease and other diseases, in women starting MHT who have already passed 10 years of menopause, especially more than 20 years after menopause or are above 60 years of age, it must be noted that the absolute degree of risk of thrombotic events (VTE, PE, and stroke) and coronary artery disease is higher than that in women who have started MHT at the beginning of menopause [90,159].

Premature hypoestrogenism or early menopause does not have a high risk of breast cancer due to MHT, and in this case, diabetes and coronary artery disease could prematurely occur due to early menopause. Therefore, receiving MHT at least until the mean age of natural menopause (50–52 years) is advised [182].

15-5. Methods to stop MHT

There is no significant difference in the recurrence rate of vasomotor symptoms depending on whether MHT is gradually or abruptly discontinued. However, there is still no consensus on which is a better method to discontinue MHT [90,159].

15-6. Bioidentical MHT

Bioidentical MHT may be administered in excessive or very low doses, with no guidelines established for administration and routine tests, including blood tests. Moreover, there is a lack of evidence regarding its safety and effects [90,159].

15-7. Complementary therapy, non-pharmacological, lifestyle intervention

Reports claim that methods such as cognitive behavioral therapy, mindfulness training, hypnosis, and stellate ganglion blockade could help alleviate VMS, but there is a lack of evidence of the effects and safety of complementary therapy [90,159].

15-8. Other medication

Using DHEA topically everyday may be effective in treating GSM [90]. Ospemifene, an optional estrogen receptor agent, has been approved for use in treating GSM and severe dyspareunia in women who have difficulties using estrogen [90,159].

Key points: Cautions for HT

1. For women with the uterus intact, estrogen must be administered together with progestogen to reduce the risk of endometrial hyperplasia and cancer.
2. It is better to start MHT immediately once symptoms appear before or after menopause.
3. There is no need to impose a limit on the duration of MHT as long as an effective minimum dose is used, if women are well aware of the potential benefits and risks, and a regular clinical follow-up observation is accompanied.
4. Bioidentical MHT may be administered in excessive or very low doses, with no guidelines established for administration and routine tests, including blood tests.
5. There is a lack of evidence of the effects and safety of complementary therapy.
6. DHEA and ospemifene may be effective in treating GSM.

16. Tibolone therapy

Tibolone, a 19-nortestosterone derivative as well as a combined steroid, shows a biological effect and action via three metabolites. After intake, tibolone is transformed into Δ4-tibolone in the liver and stomach, which has the characteristics of androgen, progestogen, and estrogen metabolite (3α-,3β-hydroxytibolone). It plays a similar role as estrogen via the estrogen receptor and shows effects of alleviating menopausal symptoms and preventing bone loss while not irritating breast and endometrial tissue by showing tissue selectivity due to the changes in enzyme activation. Tibolone is considered safe against breast cancer by selectively reducing estrogen levels in breast tissue. Tibolone does not have biological activation in itself, but as its metabolites show particular medicinal effects according to human tissue, it is categorized as a selective tissue estrogen activity regulator.

16-1. Effects on menopausal symptoms

Tibolone shows an estrogen action effect, which is effective for treating menopausal symptoms. Tibolone is effective in alleviating symptoms such as fatigue, headache, insomnia, and perspiration.

1) VMS

The optimal daily dose of tibolone for treating VMS is 2.5 mg, and it shows a significant effect within 4 weeks

of administration and shows a maximum effect after 12 weeks of administration [183].

When taking more than 1.25 mg over a period of 12 weeks, 86% of participants experienced improvement of hot flush [183]. The results of the Tolerability Trial comparing Activelle with Livial study, which compared the effect on vaginal atrophy, VMS, and abnormal vaginal bleeding by randomly allocating 2.5 mg tibolone or low-dose MHT (E2/NETA, 1 mg/0.5 mg) to menopausal women with a mean age of 55 years, showed that VMS and vaginal atrophy were improved similarly in both groups when compared with the early phase of therapy [184]. In addition, the frequency of abnormal vaginal bleeding was significantly low in the group treated with tibolone during the first 3 months of therapy. In addition, the frequency of breast pain was significantly low in the group treated with tibolone when compared with the E2/NETA group.

2) QoL

In a randomized controlled trial (RCT) that compared a placebo, 17β estradiol (2 mg), and tibolone targeting women with surgical menopause, the group treated with tibolone presented a better effect in alleviating VMS as well as other symptoms such as mood disorder, insomnia, concentration disorder, fatigue or loss of energy, apathy, and migraine [185].

The International Tibolone Consensus Group in 2005 and Asia Pacific Tibolone Consensus Group in 2010 implied that tibolone is a treatment for menopausal women with mood changes as well as VMS because it shows a positive effect in treating mood disorder, sexual function, and sleep and causes less abnormal vaginal bleeding and less discomfort to the breast [185,186].

Based on the analysis of WHQ scores, low-dose MHT (E2/NETA, 1 mg/0.5 mg) and tibolone were reported to improve QoL, and tibolone mostly improved sexual function and showed good results in treating VMS [187]. Tibolone increased muscle mass and reduced the waist–hip ratio in menopausal women [188,189].

In an RCT that evaluated the effectiveness of medicine after administering tibolone (2.5 mg) or a placebo for 12 months to menopausal women with a mean age of 54 years, the muscle strength, which was evaluated by assessing the hand grip strength in the 12th month, in the group administered tibolone was improved compared with that in the control group [190].

3) GSM

Tibolone improves GSM, and women who received tibolone therapy experienced significant improvement of vaginal dryness, dyspareunia, and urinary symptoms [191].

4) Sexual function

Tibolone has the advantage of increasing libido by increasing the bioavailability of testosterone through the reduction of the direct androgen effect of Δ4-isomer and SHBG [192].

16-2. Osteoporosis

In the STEP RCT, which aimed to study the effect of tibolone on osteopenia and compared bone density after administering tibolone (1.25 mg) and raloxifene (60 mg) to menopausal women aged 60–79 years with osteopenia for 2 years, bone density in the tibolone group was significantly increased in both the lumbar spine and femur [193].

In the Long-Term Intervention on Fractures with Tibolone (LIFT) study, tibolone (1.25 mg) reduced vertebral fracture by 45% and the risk of non-vertebral fracture by 26% [194].

16-3. Cardiovascular disorders

When taking tibolone, high-density lipoprotein (HDL) cholesterol is reduced by 20%, total cholesterol by 10%, and triglycerides by 20%, and low-density lipoprotein (LDL) cholesterol is also reduced. Moreover, tibolone is effective considering the fact that it reduces anthogenesis and the acidity of LDL [195].

In the Livial Intervention following breast cancer: Efficacy, Recurrence, And Tolerability Endpoints (LIBERATE) study, which targeted patients with breast cancer, the tibolone group did not show an increase in the incidence of stroke, venous thromboembolism, and coronary artery disease compared with the placebo group [196].

In the LIFT study, which targeted women aged above 60 years with a risk of diabetes, the group administered tibolone experienced an increased incidence of cerebral stroke, but no significant difference was observed for venous thromboembolism and coronary artery disease [194]. The IMS also mentions that tibolone increases the risk of stroke in patients aged above 60 years but does not increase the incidence of venous thromboembolism [197]. However, there has been no large-scale prospective study with the purpose of examining the occurrence of cardiovascular disorder related to tibolone.

16-4. Cancer

1) Breast cancer

Tibolone does not increase the breast density in mammography and causes less breast pain than estrogen–progestogen combination therapy. In the LIFT study, tibolone (1.25 mg) reduced the risk of invasive breast cancer [194].

In the LIBERATE study, the risk of breast cancer recurrence was assessed in a clinical double-blind study of tibolone that compared the placebo group and patients who had undergone breast cancer surgery and had VMS [196].

Breast cancer was found to recur in 15.2% of patients in the tibolone treatment groups (237 of 1,556 patients) and in 10.7% of patients (165 out of 1,542 people) in the placebo group, and a 1.4-fold increase in the incidence of breast cancer was observed when taking tibolone. Therefore, tibolone should not be used in patients with breast cancer.

2) Endometrial cancer and colorectal cancer

Tibolone is associated with a lower incidence of irregular abnormal vaginal bleeding compared with estrogen–progestogen combination therapy [198]. Because it suppresses endometrial proliferation and estrogen activation, progestogen does not need to be added.

According to the results of the Tibolone Histology of the Endometrium and Breast Endpoints Study, tibolone does not cause endometrial proliferation or endometrial cancer [199]. In the LIFT study, tibolone (1.25 mg) reduced the risk of colorectal cancer by 69% [194].

In South Korea, no studies have assessed cardiovascular disease, breast cancer, and fractures, but some studies have assessed blood lipids and bone density. According to the results of a research on blood lipids, tibolone reduces neutral fats while reducing HDL cholesterol compared with MHT [200]. Tibolone generally showed a positive effect on bone density, and after comparing the effects of therapy for 1 year, an increased bone density of the lumbar, which is similar to that with MHT, was reported 42. Furthermore, tibolone users who had undergone surgical treatment for epithelial ovarian cancer and 33 tibolone non-users were retrospectively examined [201]. There was no evidence that tibolone negatively affects the overall survival rate as well as the survival-free rate of patients with epithelial ovarian cancer. Furthermore, in a study that compared 68 tibolone users who had received surgical treatment for endometrial cancer and the same number of non-users, tibolone did not show any harmful effects in the prognosis of the patients with endometrial cancer [202].

Key points: Tibolone therapy

1. Tibolone is effective in alleviating menopausal symptoms such as hot flush, VMS, and GSM.
2. Tibolone is associated with a lower incidence of abnormal vaginal bleeding as well as decreased breast density in mammography and reduced breast pain compared with estrogen–progestogen combination therapy.
3. Tibolone could be used relatively effectively for treating sexual dysfunction.
4. Tibolone could be effectively used for other symptoms such as mood disorder, sleep disorder, concentration disorder, and fatigue.
5. Tibolone increases bone density and reduces vertebral fracture and non-vertebral fracture.
6. Tibolone does not increase invasive breast cancer and endometrial cancer, but when used for patients with breast cancer, the recurrence of breast cancer increases.
7. Tibolone does not affect venous thromboembolism and coronary artery disease. In case of administering tibolone to patients aged above 60 years, there is an increased incidence of stroke.
8. Tibolone is effective in increasing muscle mass.

17. Instructions for tissue-selective estrogen complex (TSEC) treatment

TSEC is a newly developed treatment that involves a combination of bazedoxifene, a SERM, and conjugated estrogen to improve drug tolerance of the existing progestogen to reduce the risk of breast cancer, breast pain, and vaginal bleeding in addition to treating menopausal symptoms [203-206]. Combined estrogen/bazedoxifene (CE/BZA) is used to treat menopausal symptoms and osteoporosis through the unique pharmacological properties and mechanism of action of bazedoxifene, which acts as an agonist to estrogen receptors located in the bone and as an antagonist to those located in the uterus or breast. Moreover, while retaining the advantages of estrogen therapy, it secures stability against the endometrium. CE/BZA was approved by the Ministry of Food and Drug Safety in July 2014 for the treatment of VMS associated with menopause and the prevention of postmenopausal osteoporosis in women without an excised uterus.

17-1. Effects on menopausal symptoms

CE/BZA significantly improves QoL by improving sleep disorder, GSM, and hot flush while reducing irritation in the endometrium [207-209].

1) Vasomotor symptoms

The reduced incidence of hot flushes due to CE/BZA treatment starts to significantly appear ($P = 0.008$) from the third week of intake in a previous study. The daily average incidence of hot flush occurrence after 12 weeks of intake was reduced in the placebo group by 51%, whereas it was significantly reduced by 74% in the CE/BZA group ($P < 0.01$) [207].

2) GSM

Compared with placebo, CE/BZA significantly increased the number of vaginal epithelial cells and reduced the number of parabasal cells. According to clinical results, the effects of CE/BZA for improving sexual function and treating symptoms related to moderate-to-severe genital atrophy as well as for alleviating dyspareunia have been proven [208].

3) QoL depending on sleep disorder

Compared with placebo, CE/BZA has been shown to significantly improve QoL related to health and sleep. After 12 months, the CE/BZA group experienced significant improvement of sleep disorder and time taken to fall asleep. The vasomotor nerve function score as per The Menopause-Specific Quality of Life, which evaluates QoL related to menopause at 3–12 months, is also significantly improved [209].

17-2. Osteoporosis

CE/BZA increases bone density of the lumbar spine and femur and improves the markers of bone metabolism [204,210]. A study was conducted for 1 year to compare the effect of CE/BZA on bone density with that of placebo and estrogen/MPA (CE/MPA) in a target group of 1,061 healthy menopausal women with ovaries who were aged 40–65 years. According to the results, CE/BZA significantly increased the bone density of the lumbar and femur and improved the bone metabolism markers [204].

17-3. Safety

CE/BZA has been shown to be safe for the endometrium [206,211] while having a very low level of adverse reactions to MHT, such as breast pain, vaginal bleeding, and increased breast density, which are similar to those using a placebo [204,205]. Lipid metabolisms showed a similar change as other MHT and did not lead to negative effect on hemostasis [212].

1) Increased breast density and breast tenderness

In recent studies, CE/BZA did not increase in incidence of breast cancer, breast pressure, or breast density compared with placebo. On comparing the placebo group with the BZA 20 mg/CE 0.45 mg group and CE 0.45 mg/MPA 1.5 mg group in a study targeting 940 healthy menopausal women with ovaries who were aged 40–65 years, after 12 months, the CE/MPA group was observed to have a noticeably increased dense breast tissue ratio compared with that in the placebo group, whereas the CE/BZA group was confirmed to show no significant difference in breast density changes compared with the placebo group. Breast tenderness was similar to that in the placebo group. In the CE/MPA group, breast tenderness was significantly severe [205].

2) Vaginal bleeding and endometrial proliferation

For menopausal women receiving MHT, vaginal bleeding is a common adverse reaction and is a reason for many patients to either never start or stop MHT [213]. Until 1 year from the time of beginning CE/BZA therapy, hemorrhage and petechial hemorrhage were not reported in 85.3%–99.2% of patients; this result was similar to that in the placebo group but was less than that in the CE/MPA control group (48.9%–83.2%; $P < 0.001$) [204]. On checking the occurrence of endometrial proliferation 12 months after oral administration of placebo, raloxifene 60 mg, CE 0.625 or 0.45 mg, and BZA 10, 20, or 40 mg once a day to 1,843 healthy menopausal women to evaluate the safety of CE/BZA for the endometrium, less than 1% of patients showed endometrial proliferation after the 1-year treatment, and the minimum dose of BZA that could reduce the irritation of the endometrium due to CE was 20 mg [206,211].

3) Lipid and coagulation variables

Compared with placebo, CE/BZA reduced the levels of total cholesterol and LDL cholesterol while increasing the level of HDL cholesterol. In contrast to placebo, for hemostasis variables, CE/BZA reduced the activation of fibrinogen, PAI-1, and antithrombin and increased the activation of plasminogen. CE/BZA was demonstrated to not cause a negative effect on the balance of lipid metabolism and hemostasis [212].

17-4. Recommendations from abroad

1) NAMS [2]

NAMS recommends CE/BZA as an effective MHT

for treatment of VMS and prevention of osteoporosis and fracture in menopausal women without an excised uterus and states that progestogen is not required as bazedoxifene protects the endometrium.

2) American Endocrine Society [214]

According to the clinical guidelines by the American Endocrine Society, CE/BZA could be used to prevent bone loss and alleviate VMS in menopausal women without an excised uterus as well as to treat side effects such as mood changes, breast tenderness, and progestogen-related vaginal bleeding. Moreover, CE/BZA was shown to improve QoL in menopausal patients by improving sleep disorders and reducing dyspareunia by increasing the maturity level of the vagina.

Key points: Instructions for tissue-selective estrogen complex (TSEC) treatment

1. CE/BZA is effective in alleviating VMS such as hot flush and GSM including urogenital atrophy.
2. CE/BZA significantly increases the bone density of the lumbar spine and hip joint.
3. CE/BZA is associated with a low incidence of vaginal bleeding and breast pain and increased breast density.
4. The safety of CE/BZA for the endometrium has been proven.
5. No RCTs have been conducted with breast cancer, fracture, and cardiovascular disorder as the primary endpoints.
6. In South Korea, no studies on VMS, increased breast density, breast tenderness, endometrial proliferation, vaginal bleeding, and osteoporosis have been conducted yet, but CE/BZA is being selected as one of the MHT options.

REFERENCES

1. Cobin RH, Goodman NF; AACE Reproductive Endocrinology Scientific Committee. American Association of Clinical Endocrinologists and American College of Endocrinology Position Statement on menopause-2017 update. Endocr Pract 2017; 23: 869-80.
2. The 2017 hormone therapy position statement of the North American Menopause Society. Menopause 2018; 25: 1362-87.
3. Jane FM, Davis SR. A practitioner's toolkit for managing the menopause. Climacteric 2014; 17: 564-79.
4. The North American Menopause Society. Clinical Care Recommendations. Chapter 1-8. Cleveland (OH): The North American Menopause Society [cited 2020 Aug 21]. Available from: https://www.menopause.org/publications/clinical-care-recommendations.
5. Department of Reproductive Health, World Health Organization. Medical eligibility criteria for contraceptive use. 4th ed. Geneva: World Health Organization Press; 2010.
6. Blümel JE, Castelo-Branco C, Binfa L, Aparicio R, Mamani L. A scheme of combined oral contraceptives for women more than 40 years old. Menopause 2001; 8: 286-9.
7. Kaunitz AM. Clinical practice. Hormonal contraception in women of older reproductive age. N Engl J Med 2008; 358: 1262-70.
8. Santoro N, Teal S, Gavito C, Cano S, Chosich J, Sheeder J. Use of a levonorgestrel-containing intrauterine system with supplemental estrogen improves symptoms in perimenopausal women: a pilot study. Menopause 2015; 22: 1301-7.
9. Geiger PJ, Eisenlohr-Moul T, Gordon JL, Rubinow DR, Girdler SS. Effects of perimenopausal transdermal estradiol on self-reported sleep, independent of its effect on vasomotor symptom bother and depressive symptoms. Menopause 2019; 26: 1318-23.
10. Gordon JL, Rubinow DR, Eisenlohr-Moul TA, Xia K, Schmidt PJ, Girdler SS. Efficacy of transdermal estradiol and micronized progesterone in the prevention of depressive symptoms in the menopause transition: a randomized clinical trial. JAMA Psychiatry 2018; 75: 149-57.
11. Marjoribanks J, Farquhar C, Roberts H, Lethaby A. Long term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database Syst Rev 2012; (7): CD004143.
12. Huang KE. Menopause perspectives and treatment of Asian women. Semin Reprod Med 2010; 28: 396-403.
13. Hunter MS, Gentry-Maharaj A, Ryan A, Burnell M, Lanceley A, Fraser L, et al. Prevalence, frequency and problem rating of hot flushes persist in older postmenopausal women: impact of age, body mass index, hysterectomy, hormone therapy use, lifestyle and mood in a cross-sectional cohort study of 10,418 British women aged 54-65. BJOG 2012; 119: 40-50.
14. Mishra GD, Kuh D. Health symptoms during midlife in relation to menopausal transition: British prospective cohort study. BMJ 2012; 344: e402.
15. Hemminki E, Regushevskaya E, Luoto R, Veerus P. Variability of bothersome menopausal symptoms over time--a longitudinal analysis using the Estonian postmenopausal hormone therapy trial (EPHT). BMC Womens Health 2012; 12: 44.
16. Akhila V, Pratapkumar. A comparison of transdermal and oral HRT for menopausal symptom control. Int J Fertil Womens Med 2006; 51: 64-9.
17. Yum SK, Yoon BK, Lee BI, Park HM, Kim T. Epidemiologic survey of menopausal and vasomotor symptoms in Korean women. J Korean Soc Menopause 2012; 18: 147-54.
18. Park HM, Choi H, Lee HK. The HRT awareness and acceptance

in Korean postmenopausal women: results of Korean Gallup epidemiologic survey on menopause and HRT. J Korean Soc Menopause 2002; 8: 3-18.
19. Heikkinen JE, Vaheri RT, Ahomäki SM, Kainulainen PM, Viitanen AT, Timonen UM. Optimizing continuous-combined hormone replacement therapy for postmenopausal women: a comparison of six different treatment regimens. Am J Obstet Gynecol 2000; 182: 560-7.
20. Notelovitz M, Lenihan JP, McDermott M, Kerber IJ, Nanavati N, Arce J. Initial 17beta-estradiol dose for treating vasomotor symptoms. Obstet Gynecol 2000; 95: 726-31.
21. Panay N, Ylikorkala O, Archer DF, Gut R, Lang E. Ultra-low-dose estradiol and norethisterone acetate: effective menopausal symptom relief. Climacteric 2007; 10: 120-31.
22. Baber RJ, Panay N, Fenton A; IMS Writing Group. 2016 IMS Recommendations on women's midlife health and menopause hormone therapy. Climacteric 2016; 19: 109-50.
23. Birkhäuser MH, Panay N, Archer DF, Barlow D, Burger H, Gambacciani M, et al. Updated practical recommendations for hormone replacement therapy in the peri- and postmenopause. Climacteric 2008; 11: 108-23.
24. Ettinger B, Pressman A, Van Gessel A. Low-dosage esterified estrogens opposed by progestin at 6-month intervals. Obstet Gynecol 2001; 98: 205-11.
25. Lindh-Astrand L, Brynhildsen J, Hoffman M, Hammar M. Vasomotor symptoms usually reappear after cessation of postmenopausal hormone therapy: a Swedish population-based study. Menopause 2009; 16: 1213-7.
26. Kim OM, Lee YS. The climacteric symptoms and quality of life in climacteric women according to hormone replacement therapy. Korean J Women Health Nurs 2001; 7: 642-56.
27. Cho HH, Jung JE, Jung IC, Kim MJ, Kim SY, Hwang SJ. Influences of hormone therapy to tissue mineral concentration and quality of life in menopausal women. J Korean Soc Menopause 2007; 13: 209-16.
28. Kim JY, Cho JC, Lim SH, Jeong SM, Rhyu CH, Kim JD. Assessment about quality of life in menopausal women with hormone replacement therapy. Korean J Obstet Gynecol 1998; 41: 2429-35.
29. Westlund Tam L, Parry BL. Does estrogen enhance the antidepressant effects of fluoxetine? J Affect Disord 2003; 77: 87-92.
30. Palacios S, Castelo-Branco C, Currie H, Mijatovic V, Nappi RE, Simon J, et al. Update on management of genitourinary syndrome of menopause: a practical guide. Maturitas 2015; 82: 308-13.
31. Nappi RE, Davis SR. The use of hormone therapy for the maintenance of urogynecological and sexual health post WHI. Climacteric 2012; 15: 267-74.
32. Rahn DD, Carberry C, Sanses TV, Mamik MM, Ward RM, Meriwether KV, et al.; Society of Gynecologic Surgeons Systematic Review Group. Vaginal estrogen for genitourinary syndrome of menopause: a systematic review. Obstet Gynecol 2014; 124: 1147-56.
33. Lethaby A, Ayeleke RO, Roberts H. Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database Syst Rev 2016; 2016: CD001500.
34. Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society. Menopause 2013; 20: 888-902; quiz 903-4.
35. Constantine G, Graham S, Portman DJ, Rosen RC, Kingsberg SA. Female sexual function improved with ospemifene in postmenopausal women with vulvar and vaginal atrophy: results of a randomized, placebo-controlled trial. Climacteric 2015; 18: 226-32.
36. Labrie F, Archer DF, Koltun W, Vachon A, Young D, Frenette L, et al.; VVA Prasterone Research Group. Efficacy of intravaginal dehydroepiandrosterone (DHEA) on moderate to severe dyspareunia and vaginal dryness, symptoms of vulvovaginal atrophy, and of the genitourinary syndrome of menopause. Menopause 2016; 23: 243-56.
37. Sokol ER, Karram MM. An assessment of the safety and efficacy of a fractional CO_2 laser system for the treatment of vulvovaginal atrophy. Menopause 2016; 23: 1102-7.
38. U.S. Food and Drug Administration. FDA Warns against use of energy-based devices to perform vaginal 'rejuvenation' or vaginal cosmetic procedures: FDA safety communication. Silver Spring (MD): Food and Drug Administration, 2018 [cited 2020 Aug 21]. Available from: https://www.fda.gov/medical-devices/safety-communications/fda-warns-against-use-energy-based-devices-perform-vaginal-rejuvenation-or-vaginal-cosmetic.
39. Gordon C, Gonzales S, Krychman ML. Rethinking the techno vagina: a case series of patient complications following vaginal laser treatment for atrophy. Menopause 2019; 26: 423-7.
40. Long CY, Liu CM, Hsu SC, Chen YH, Wu CH, Tsai EM. A randomized comparative study of the effects of oral and topical estrogen therapy on the lower urinary tract of hysterectomized postmenopausal women. Fertil Steril 2006; 85: 155-60.
41. Robinson D, Cardozo L, Milsom I, Pons ME, Kirby M, Koelbl H, et al. Oestrogens and overactive bladder. Neurourol Urodyn 2014; 33: 1086-91.
42. Matsubara S, Okada H, Shirakawa T, Gotoh A, Kuno T, Kamidono S. Estrogen levels influence beta-3-adrenoceptor-mediated relaxation of the female rat detrusor muscle. Urology 2002; 59: 621-5.
43. Ismail SI, Bain C, Hagen S. Oestrogens for treatment or prevention of pelvic organ prolapse in postmenopausal women. Cochrane Database Syst Rev 2010; (9): CD007063.
44. Grady D, Brown JS, Vittinghoff E, Applegate W, Varner E, Snyder T; HERS Research Group. Postmenopausal hormones and incontinence: the Heart and Estrogen/Progestin Replacement Study.

Obstet Gynecol 2001; 97: 116-20.
45. Hendrix SL, Cochrane BB, Nygaard IE, Handa VL, Barnabei VM, Iglesia C, et al. Effects of estrogen with and without progestin on urinary incontinence. JAMA 2005; 293: 935-48.
46. Cody JD, Jacobs ML, Richardson K, Moehrer B, Hextall A. Oestrogen therapy for urinary incontinence in post-menopausal women. Cochrane Database Syst Rev 2012; 10: CD001405.
47. Dueñas-Garcia OF, Sullivan G, Hall CD, Flynn MK, O´Dell K. Pharmacological agents to decrease new episodes of recurrent lower urinary tract infections in postmenopausal women. A systematic review. Female Pelvic Med Reconstr Surg 2016; 22: 63-9.
48. Appa AA, Creasman J, Brown JS, Van Den Eeden SK, Thom DH, et al. The impact of multimorbidity on sexual function in middle-aged and older women: beyond the single disease perspective. J Sex Med 2014; 11: 2744-55.
49. Avis NE, Brockwell S, Randolph JF Jr, Shen S, Cain VS, Ory M, et al. Longitudinal changes in sexual functioning as women transition through menopause: results from the Study of Women's Health across the Nation. Menopause 2009; 16: 442-52.
50. Dennerstein L, Dudley E, Burger H. Are changes in sexual functioning during midlife due to aging or menopause? Fertil Steril 2001; 76: 456-60.
51. Lonnèe-Hoffmann RA, Dennerstein L, Lehert P, Szoeke C. Sexual function in the late postmenopause: a decade of follow-up in a population-based cohort of Australian women. J Sex Med 2014; 11: 2029-38.
52. Erekson EA, Martin DK, Ratner ES. Oophorectomy: the debate between ovarian conservation and elective oophorectomy. Menopause 2013; 20: 110-4.
53. Wierman ME, Arlt W, Basson R, Davis SR, Miller KK, Murad MH, et al. Androgen therapy in women: a reappraisal: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2014; 99: 3489-510.
54. Nappi RE, Domoney C. Pharmacogenomics and sexuality: a vision. Climacteric 2013; 16 Suppl 1: 25-30.
55. Nappi RE, Cucinella L. Advances in pharmacotherapy for treating female sexual dysfunction. Expert Opin Pharmacother 2015; 16: 875-87.
56. Pines A, Sturdee DW, MacLennan AH. Quality of life and the role of menopausal hormone therapy. Climacteric 2012; 15: 213-6.
57. Nastri CO, Lara LA, Ferriani RA, Rosa-E-Silva AC, Figueiredo JB, Martins WP. Hormone therapy for sexual function in perimenopausal and postmenopausal women. Cochrane Database Syst Rev 2013; (6): CD009672.
58. Biglia N, Maffei S, Lello S, Nappi RE. Tibolone in postmenopausal women: a review based on recent randomised controlled clinical trials. Gynecol Endocrinol 2010; 26: 804-14.
59. Davis S, Papalia MA, Norman RJ, O'Neill S, Redelman M, Williamson M, et al. Safety and efficacy of a testosterone metered-dose transdermal spray for treating decreased sexual satisfaction in premenopausal women: a randomized trial. Ann Intern Med 2008; 148: 569-77.
60. Goldstat R, Briganti E, Tran J, Wolfe R, Davis SR. Transdermal testosterone therapy improves well-being, mood, and sexual function in premenopausal women. Menopause 2003; 10: 390-8.
61. Fooladi E, Bell RJ, Jane F, Robinson PJ, Kulkarni J, Davis SR. Testosterone improves antidepressant-emergent loss of libido in women: findings from a randomized, double-blind, placebo-controlled trial. J Sex Med 2014; 11: 831-9.
62. Elraiyah T, Sonbol MB, Wang Z, Khairalseed T, Asi N, Undavalli C, et al. The benefits and harms of systemic dehydroepiandrosterone (DHEA) in postmenopausal women with normal adrenal function: a systematic review and meta-analysis. J Clin Endocrinol Metab 2014; 99: 3536-42.
63. Davis SR, Moreau M, Kroll R, Bouchard C, Panay N, Gass M, et al. Testosterone for low libido in postmenopausal women not taking estrogen. N Engl J Med 2008; 359: 2005-17.
64. Berman JR, Almeida FG, Jolin J, Raz S, Chaudhuri G, Gonzalez-Cadavid NF. Correlation of androgen receptors, aromatase, and 5-alpha reductase in the human vagina with menopausal status. Fertil Steril 2003; 79: 925-31.
65. Raghunandan C, Agrawal S, Dubey P, Choudhury M, Jain A. A comparative study of the effects of local estrogen with or without local testosterone on vulvovaginal and sexual dysfunction in postmenopausal women. J Sex Med 2010; 7: 1284-90.
66. Fernandes T, Costa-Paiva LH, Pinto-Neto AM. Efficacy of vaginally applied estrogen, testosterone, or polyacrylic acid on sexual function in postmenopausal women: a randomized controlled trial. J Sex Med 2014; 11: 1262-70.
67. US Preventive Services Task Force, Grossman DC, Curry SJ, Owens DK, Barry MJ, Davidson KW, et al. Hormone therapy for the primary prevention of chronic conditions in postmenopausal women: US Preventive Services Task Force recommendation statement. JAMA 2017; 318: 2224-33.
68. Humphrey LL, Chan BK, Sox HC. Postmenopausal hormone replacement therapy and the primary prevention of cardiovascular disease. Ann Intern Med 2002; 137: 273-84.
69. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1998; 280: 605-13.
70. Grady D, Herrington D, Bittner V, Blumenthal R, Davidson M, Hlatky M, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). JAMA 2002; 288: 49-57.
71. Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, et al. Estrogen plus progestin and the risk of coronary heart

disease. N Engl J Med 2003; 349: 523-34.
72. Hsia J, Langer RD, Manson JE, Kuller L, Johnson KC, Hendrix SL, et al. Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative. Arch Intern Med 2006; 166: 357-65.
73. Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA 2007; 297: 1465-77.
74. Salpeter SR, Walsh JM, Greyber E, Salpeter EE. Coronary heart disease events associated with hormone therapy in younger and older women. A meta-analysis. J Gen Intern Med 2006; 21: 363-6.
75. Boardman HM, Hartley L, Eisinga A, Main C, Roqué i Figuls M, Bonfill Cosp X, et al. Hormone therapy for preventing cardiovascular disease in post-menopausal women. Cochrane Database Syst Rev 2015; (3): CD002229.
76. Harman SM, Black DM, Naftolin F, Brinton EA, Budoff MJ, Cedars MI, et al. Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women: a randomized trial. Ann Intern Med 2014; 161: 249-60.
77. Schierbeck LL, Rejnmark L, Tofteng CL, Stilgren L, Eiken P, Mosekilde L, et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. BMJ 2012; 345: e6409.
78. Hodis HN, Mack WJ, Henderson VW, Shoupe D, Budoff MJ, Hwang-Levine J, et al. Vascular effects of early versus late postmenopausal treatment with estradiol. N Engl J Med 2016; 374: 1221-31.
79. Manson JE, Allison MA, Rossouw JE, Carr JJ, Langer RD, Hsia J, et al. Estrogen therapy and coronary-artery calcification. N Engl J Med 2007; 356: 2591-602.
80. Mikkola TS, Tuomikoski P, Lyytinen H, Korhonen P, Hoti F, Vattulainen P, et al. Estradiol-based postmenopausal hormone therapy and risk of cardiovascular and all-cause mortality. Menopause 2015; 22: 976-83.
81. Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, 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.
82. Renoux C, Dell'aniello S, Garbe E, Suissa S. Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study. BMJ 2010; 340: c2519.
83. Kim JY, Kang K, Kang J, Koo J, Kim DH, Kim BJ, et al. Executive summary of stroke statistics in Korea 2018: a report from the Epidemiology Research Council of the Korean Stroke Society. J Stroke 2019; 21: 42-59.
84. Archer DF, Oger E. Estrogen and progestogen effect on venous thromboembolism in menopausal women. Climacteric 2012; 15: 235-40.
85. Renoux C, Dell'Aniello S, Suissa S. Hormone replacement therapy and the risk of venous thromboembolism: a population-based study. J Thromb Haemost 2010; 8: 979-86.
86. Ridker PM, Miletich JP, Hennekens CH, Buring JE. Ethnic distribution of factor V Leiden in 4047 men and women. Implications for venous thromboembolism screening. JAMA 1997; 277: 1305-7.
87. Canonico M, Oger E, Plu-Bureau G, Conard J, Meyer G, Lévesque H, et al.; Estrogen and Thromboembolism Risk (ESTHER) Study Group. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. Circulation 2007; 115: 840-5.
88. Canonico M, Plu-Bureau G, Lowe GD, Scarabin PY. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. BMJ 2008; 336: 1227-31.
89. Cushman M, Kuller LH, Prentice R, Rodabough RJ, Psaty BM, Stafford RS, et al.; Women's Health Initiative Investigators. Estrogen plus progestin and risk of venous thrombosis. JAMA 2004; 292: 1573-80.
90. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. The 2017 hormone therapy position statement of The North American Menopause Society. Menopause 2017; 24: 728-53.
91. Miller J, Chan BK, Nelson HD. Postmenopausal estrogen replacement and risk for venous thromboembolism: a systematic review and meta-analysis for the U.S. Preventive Services Task Force. Ann Intern Med 2002; 136: 680-90.
92. Suh JH, Yoo EH, Yoo MY, Yoo HK, Yoo JH. A case of deep vein thromboembolism and Pulmonary embolism in postmenopausal hormone replacement therapy. J Korean Soc Menopause 2000; 6: 162-7.
93. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004; 291: 1701-12.
94. Beral V. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 2003; 362: 419-27.
95. Bush TL, Whiteman M, Flaws JA. Hormone replacement therapy and breast cancer: a qualitative review. Obstet Gynecol 2001; 98: 498-508.
96. Fournier A, Berrino F, Riboli E, Avenel V, Clavel-Chapelon F. Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. Int J Cancer 2005; 114: 448-54.
97. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus

progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002; 288: 321-33.
98. Stahlberg C, Pedersen AT, Andersen ZJ, Keiding N, Hundrup YA, Obel EB, et al. Breast cancer with different prognostic characteristics developing in Danish women using hormone replacement therapy. Br J Cancer 2004; 91: 644-50.
99. Marsden J; British Menopause Society. The risks and benefits of HRT before and after a breast cancer diagnosis. Post Reprod Health 2019; 25: 33-7.
100. Chlebowski RT, Hendrix SL, Langer RD, Stefanick ML, Gass M, Lane D, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. JAMA 2003; 289: 3243-53.
101. Anderson GL, Chlebowski RT, Rossouw JE, Rodabough RJ, McTiernan A, Margolis KL, et al. Prior hormone therapy and breast cancer risk in the Women's Health Initiative randomized trial of estrogen plus progestin. Maturitas 2006; 55: 103-15.
102. Chlebowski RT, Anderson GL, Gass M, Lane DS, Aragaki AK, Kuller LH, et al. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. JAMA 2010; 304: 1684-92.
103. Anderson GL, Chlebowski RT, Aragaki AK, Kuller LH, Manson JE, Gass M, et al. Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. Lancet Oncol 2012; 13: 476-86.
104. LaCroix AZ, Chlebowski RT, Manson JE, Aragaki AK, Johnson KC, Martin L, et al. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. JAMA 2011; 305: 1305-14.
105. Chen WY, Manson JE, Hankinson SE, Rosner B, Holmes MD, Willett WC, et al. Unopposed estrogen therapy and the risk of invasive breast cancer. Arch Intern Med 2006; 166: 1027-32.
106. Fournier A, Mesrine S, Dossus L, Boutron-Ruault MC, Clavel-Chapelon F, Chabbert-Buffet N. Risk of breast cancer after stopping menopausal hormone therapy in the E3N cohort. Breast Cancer Res Treat 2014; 145: 535-43.
107. Domchek SM, Mitchell G, Lindeman GJ, Tung NM, Balmaña J, Isakoff SJ, et al. Challenges to the development of new agents for molecularly defined patient subsets: lessons from BRCA1/2-associated breast cancer. J Clin Oncol 2011; 29: 4224-6.
108. Eisen A, Lubinski J, Gronwald J, Moller P, Lynch HT, Klijn J, et al. Hormone therapy and the risk of breast cancer in BRCA1 mutation carriers. J Natl Cancer Inst 2008; 100: 1361-7.
109. Gabriel CA, Tigges-Cardwell J, Stopfer J, Erlichman J, Nathanson K, Domchek SM. Use of total abdominal hysterectomy and hormone replacement therapy in BRCA1 and BRCA2 mutation carriers undergoing risk-reducing salpingo-oophorectomy. Fam Cancer 2009; 8: 23-8.
110. Rebbeck TR, Friebel T, Wagner T, Lynch HT, Garber JE, Daly MB, et al. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol 2005; 23: 7804-10.
111. Holmberg L, Anderson H. HABITS (hormonal replacement therapy after breast cancer--is it safe?), a randomised comparison: trial stopped. Lancet 2004; 363: 453-5.
112. Dixon JM, Renshaw L, Young O, Murray J, Macaskill EJ, McHugh M, et al. Letrozole suppresses plasma estradiol and estrone sulphate more completely than anastrozole in postmenopausal women with breast cancer. J Clin Oncol 2008; 26: 1671-6.
113. Korean Breast Cancer Society. Breast cancer facts & figures 2018. Seoul: Korean Breast Cancer Society, 2018 [cited 2020 Aug 21]. Available from: http://www.kbcs.or.kr/journal/file/181030.pdf.
114. Centers for Disease Control and Prevention; National Cancer Institute. United States cancer statistics: data visualizations. Atlanta (GA), Bethesda (MD): Centers for Disease Control and Prevention; National Cancer Institute, 2017 [cited 2020 Aug 21]. Available from: https://gis.cdc.gov/Cancer/USCS/DataViz.html.
115. National Cancer Institute. Cancer stat facts: female breast cancer. Bethesda (MD): National Cancer Institute, 2020 [cited 2020 Aug 21]. Available from: https://seer.cancer.gov/statfacts/html/breast.html.
116. National Cancer Information Center. Goyang: National Cancer Information Center, 2020 [cited 2020 Aug 21]. Available from: www.cancer.go.kr/
117. Anderson GL, Judd HL, Kaunitz AM, Barad DH, Beresford SA, Pettinger M, et al.; Women's Health Initiative Investigators. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. JAMA 2003; 290: 1739-48.
118. Li D, Ding CY, Qiu LH. Postoperative hormone replacement therapy for epithelial ovarian cancer patients: a systematic review and meta-analysis. Gynecol Oncol 2015; 139: 355-62.
119. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. JAMA 1996; 275: 370-5.
120. Biliatis I, Thomakos N, Rodolakis A, Akrivos N, Zacharakis D, Antsaklis A. Safety of hormone replacement therapy in gynaecological cancer survivors. J Obstet Gynaecol 2012; 32: 321-5.
121. Wei EK, Colditz GA, Giovannucci EL, Fuchs CS, Rosner BA. Cumulative risk of colon cancer up to age 70 years by risk factor status using data from the Nurses' Health Study. Am J Epidemiol

2009; 170: 863-72.
122. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, Hubbell FA, Ascensao J, Rodabough RJ, et al. Estrogen plus progestin and colorectal cancer in postmenopausal women. N Engl J Med 2004; 350: 991-1004.
123. Delellis Henderson K, Duan L, Sullivan-Halley J, Ma H, Clarke CA, Neuhausen SL, et al. Menopausal hormone therapy use and risk of invasive colon cancer: the California Teachers Study. Am J Epidemiol 2010; 171: 415-25.
124. Mørch LS, Lidegaard Ø, Keiding N, Løkkegaard E, Kjær SK. The influence of hormone therapies on colon and rectal cancer. Eur J Epidemiol 2016; 31: 481-9.
125. Chlebowski RT, Schwartz AG, Wakelee H, Anderson GL, Stefanick ML, Manson JE, et al. Oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): a post-hoc analysis of a randomised controlled trial. Lancet 2009; 374: 1243-51.
126. Shumaker SA, Legault C, Kuller L, Rapp SR, Thal L, Lane DS, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA 2004; 291: 2947-58.
127. Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 2003; 289: 2651-62.
128. Maki PM, Henderson VW. Hormone therapy, dementia, and cognition: the Women's Health Initiative 10 years on. Climacteric 2012; 15: 256-62.
129. Resnick SM, Espeland MA, Jaramillo SA, Hirsch C, Stefanick ML, Murray AM, et al. Postmenopausal hormone therapy and regional brain volumes: the WHIMS-MRI Study. Neurology 2009; 72: 135-42.
130. Henderson VW, Benke KS, Green RC, Cupples LA, Farrer LA; MIRAGE Study Group. Postmenopausal hormone therapy and Alzheimer's disease risk: interaction with age. J Neurol Neurosurg Psychiatry 2005; 76; 103-5.
131. Zandi PP, Carlson MC, Plassman BL, Welsh-Bohmer KA, Mayer LS, Steffens DC, et al. Hormone replacement therapy and incidence of Alzheimer disease in older women: the Cache County Study. JAMA 2002; 288: 2123-9.
132. Henderson VW. Estrogen-containing hormone therapy and Alzheimer's disease risk: understanding discrepant inferences from observational and experimental research. Neuroscience 2006; 138: 1031-9.
133. Gleason CE, Dowling NM, Wharton W, Manson JE, Miller VM, Atwood CS, et al. Effects of hormone therapy on cognition and mood in recently postmenopausal women: findings from the randomized, controlled KEEPS-Cognitive and Affective Study. PLoS Med 2015; 12: e1001833; discussion e1001833.
134. Whitmer RA, Quesenberry CP, Zhou J, Yaffe K. Timing of hormone therapy and dementia: the critical window theory revisited. Ann Neurol 2011; 69: 163-9.
135. Resnick SM, Henderson VW. Hormone therapy and risk of Alzheimer disease: a critical time. JAMA 2002; 288: 2170-2.
136. Greendale GA, Huang MH, Wight RG, Seeman T, Luetters C, Avis NE, et al. Effects of the menopause transition and hormone use on cognitive performance in midlife women. Neurology 2009; 72: 1850-7.
137. Espeland MA, Shumaker SA, Leng I, Manson JE, Brown CM, LeBlanc ES, et al. Long-term effects on cognitive function of postmenopausal hormone therapy prescribed to women aged 50 to 55 years. JAMA Intern Med 2013; 173: 1429-36.
138. Brinton RD. Investigative models for determining hormone therapy-induced outcomes in brain: evidence in support of a healthy cell bias of estrogen action. Ann N Y Acad Sci 2005; 1052: 57-74.
139. Maki PM. Critical window hypothesis of hormone therapy and cognition: a scientific update on clinical studies. Menopause 2013; 20: 695-709.
140. Henderson VW. Gonadal hormones and cognitive aging: a midlife perspective. Womens Health (Lond) 2011; 7: 81-93.
141. Rocca WA, Bower JH, Maraganore DM, Ahlskog JE, Grossardt BR, de Andrade M, et al. Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. Neurology 2007; 69: 1074-83.
142. Sherwin BB. Estrogen and/or androgen replacement therapy and cognitive functioning in surgically menopausal women. Psychoneuroendocrinology 1988; 13: 345-57.
143. Asthana S, Craft S, Baker LD, Raskind MA, Birnbaum RS, Lofgreen CP, et al. Cognitive and neuroendocrine response to transdermal estrogen in postmenopausal women with Alzheimer's disease: results of a placebo-controlled, double-blind, pilot study. Psychoneuroendocrinology 1999; 24: 657-77.
144. Ohkura T, Isse K, Akazawa K, Hamamoto M, Yaoi Y, Hagino N. Evaluation of estrogen treatment in female patients with dementia of the Alzheimer type. Endocr J 1994; 41: 361-71.
145. Fillit H, Weinreb H, Cholst I, Luine V, McEwen B, Amador R, et al. Observations in a preliminary open trial of estradiol therapy for senile dementia-Alzheimer's type. Psychoneuroendocrinology 1986; 11: 337-45.
146. Mulnard RA, Cotman CW, Kawas C, van Dyck CH, Sano M, Doody R, et al. Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. Alzheimer's Disease Cooperative Study. JAMA 2000; 283: 1007-15.
147. Yoon BK, Kim DK, Kang Y, Kim JW, Shin MH, Na DL. Hormone replacement therapy in postmenopausal women with Alzheimer's

disease: a randomized, prospective study. Fertil Steril 2003; 79: 274-80.
148. Seoul National University College of Medicine. The epidemiological survey of mental disorders in Korea 2011. Seoul: Korean Ministry of Health and Welfare; 2012.
149. Schmidt PJ, Haq N, Rubinow DR. A longitudinal evaluation of the relationship between reproductive status and mood in perimenopausal women. Am J Psychiatry 2004; 161: 2238-44.
150. Freeman EW, Sammel MD, Lin H, Nelson DB. Associations of hormones and menopausal status with depressed mood in women with no history of depression. Arch Gen Psychiatry 2006; 63: 375-82.
151. Sherwin BB. Affective changes with estrogen and androgen replacement therapy in surgically menopausal women. J Affect Disord 1988; 14: 177-87.
152. Ditkoff EC, Crary WG, Cristo M, Lobo RA. Estrogen improves psychological function in asymptomatic postmenopausal women. Obstet Gynecol 1991; 78: 991-5.
153. Schmidt PJ, Nieman L, Danaceau MA, Tobin MB, Roca CA, Murphy JH, et al. Estrogen replacement in perimenopause-related depression: a preliminary report. Am J Obstet Gynecol 2000; 183: 414-20.
154. Soares CN, 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.
155. Rubinow DR, Johnson SL, Schmidt PJ, Girdler S, Gaynes B. Efficacy of estradiol in perimenopausal depression: so much promise and so few answers. Depress Anxiety 2015; 32: 539-49.
156. Morrison MF, Kallan MJ, Ten Have T, Katz I, Tweedy K, Battistini M. Lack of efficacy of estradiol for depression in postmenopausal women: a randomized, controlled trial. Biol Psychiatry 2004; 55: 406-12.
157. Yalamanchili V, Gallagher JC. Treatment with hormone therapy and calcitriol did not affect depression in older postmenopausal women: no interaction with estrogen and vitamin D receptor genotype polymorphisms. Menopause 2012; 19: 697-703.
158. Schmidt PJ, Ben Dor R, Martinez PE, Guerrieri GM, Harsh VL, Thompson K, et al. Effects of estradiol withdrawal on mood in women with past perimenopausal depression: a randomized clinical trial. JAMA Psychiatry 2015; 72: 714-26.
159. North American Menopause Society. The 2012 hormone therapy position statement of: the North American Menopause Society. Menopause 2012; 19: 257-71.
160. Sherwin BB. The impact of different doses of estrogen and progestin on mood and sexual behavior in postmenopausal women. J Clin Endocrinol Metab 1991; 72: 336-43.
161. Effects of hormone therapy on bone mineral density: results from the postmenopausal estrogen/progestin interventions (PEPI) trial. The Writing Group for the PEPI. JAMA 1996; 276: 1389-96.
162. Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, LaCroix AZ, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA 2003; 290: 1729-38.
163. Wells G, Tugwell P, Shea B, Guyatt G, Peterson J, Zytaruk N, et al. Meta-analyses of therapies for postmenopausal osteoporosis. V. Meta-analysis of the efficacy of hormone replacement therapy in treating and preventing osteoporosis in postmenopausal women. Endocr Rev 2002; 23: 529-39.
164. Lindsay R, Gallagher JC, Kleerekoper M, Pickar JH. Effect of lower doses of conjugated equine estrogens with and without medroxyprogesterone acetate on bone in early postmenopausal women. JAMA 2002; 287: 2668-76.
165. Prestwood KM, Kenny AM, Kleppinger A, Kulldorff M. Ultralow-dose micronized 17beta-estradiol and bone density and bone metabolism in older women: a randomized controlled trial. JAMA 2003; 290: 1042-8.
166. Barrett-Connor E, Wehren LE, Siris ES, Miller P, Chen YT, Abbott TA 3rd, et al. Recency and duration of postmenopausal hormone therapy: effects on bone mineral density and fracture risk in the National Osteoporosis Risk Assessment (NORA) study. Menopause 2003; 10: 412-9.
167. Ha YC, Kim TY, Lee A, Lee YK, Kim HY, Kim JH, et al. Current trends and future projections of hip fracture in South Korea using nationwide claims data. Osteoporos Int 2016; 27: 2603-9.
168. Chun S, Kim MR, Lee BS, Yoon BK, Kang BM, Choi HH, et al. Bone response to hormone therapy according to basal bone mineral density and previous response to hormone therapy. J Korean Soc Menopause 2012; 18: 15-27.
169. Jang HC. How to diagnose sarcopenia in Korean older adults? Ann Geriatr Med Res 2018; 22: 73-9.
170. Kim JH, Hwang Bo Y, Hong ES, Ohn JH, Kim CH, Kim HW, et al. Investigation of sarcopenia and its association with cardiometabolic risk factors in elderly subjects. J Korean Geriatr Soc 2010; 14: 121-30.
171. Kim TN, Yang SJ, Yoo HJ, Lim KI, Kang HJ, Song W, et al. Prevalence of sarcopenia and sarcopenic obesity in Korean adults: the Korean sarcopenic obesity study. Int J Obes (Lond) 2009; 33: 885-92.
172. Kwon HJ, Ha YC, Park HM. Prevalence of sarcopenia in the Korean woman based on the Korean National Health and Nutritional Examination Surveys. J Bone Metab 2016; 23: 23-6.
173. Park HM. Current status of sarcopenia in Korea: a focus on Korean geripausal women. Ann Geriatr Med Res 2018; 22: 52-61.
174. Park HM, Ha YC, Yoo JI, Ryu HJ. Prevalence of sarcopenia adjusted body mass index in the Korean woman based on the Korean National Health and Nutritional Examination Surveys. J Bone Metab 2016; 23: 243-7.

175. Brooke-Wavell K, Prelevic GM, Bakridan C, Ginsburg J. Effects of physical activity and menopausal hormone replacement therapy on postural stability in postmenopausal women--a cross-sectional study. Maturitas 2001; 37: 167-72.
176. Chun SW. Female hormones. In: The Korean Society of Sarcopenia, editor. Sarcopenia. Paju: Koonja; 2017. pp 349-60.
177. Chen Z, Bassford T, Green SB, Cauley JA, Jackson RD, LaCroix AZ, et al. Postmenopausal hormone therapy and body composition--a substudy of the estrogen plus progestin trial of the Women's Health Initiative. Am J Clin Nutr 2005; 82: 651-6.
178. Choquette S, Dion T, Brochu M, Dionne IJ. Soy isoflavones and exercise to improve physical capacity in postmenopausal women. Climacteric 2013; 16: 70-7.
179. Health Insurance Review & Assessment Service. 2018 Health insurance statistical yearbook. Wonju: Health Insurance Review & Assessment Service, 2019 [cited 2020 Aug 21]. Available from: http://www.hira.or.kr/bbsDummy.do?pgmid=HIRAA020045020000&brdScnBltNo=4&brdBltNo=2311&pageIndex=1#none.
180. Cirillo DJ, Wallace RB, Rodabough RJ, Greenland P, LaCroix AZ, Limacher MC, et al. Effect of estrogen therapy on gallbladder disease. JAMA 2005; 293: 330-9.
181. Nelson HD, Humphrey LL, Nygren P, Teutsch SM, Allan JD. Postmenopausal hormone replacement therapy. JAMA 2002; 288: 872-81.
182. Panay N, Kalu E. Management of premature ovarian failure. Best Pract Res Clin Obstet Gynaecol 2009; 23: 129-40.
183. Landgren MB, Helmond FA, Engelen S. Tibolone relieves climacteric symptoms in highly symptomatic women with at least seven hot flushes and sweats per day. Maturitas 2005; 50: 222-30.
184. Hammar ML, van de Weijer P, Franke HR, Pornel B, von Mauw EM, Nijland EA. Tibolone and low-dose continuous combined hormone treatment: vaginal bleeding pattern, efficacy and tolerability. BJOG 2007; 114: 1522-9.
185. Somunkiran A, Erel CT, Demirci F, Senturk ML. The effect of tibolone versus 17beta-estradiol on climacteric symptoms in women with surgical menopause: a randomized, cross-over study. Maturitas 2007; 56: 61-8.
186. Kenemans P, Speroff L; International Tibolone Consensus Group. Tibolone: clinical recommendations and practical guidelines. A report of the International Tibolone Consensus Group. Maturitas 2005; 51: 21-8.
187. Sismondi P, Kimmig R, Kubista E, Biglia N, Egberts J, Mulder R, et al. Effects of tibolone on climacteric symptoms and quality of life in breast cancer patients--data from LIBERATE trial. Maturitas 2011; 70: 365-72.
188. Odabasi AR, Yuksel H, Kafkas S, Demircan S, Karul A, Kozaci D, et al. Effects of tibolone on abdominal subcutaneous fat, serum leptin levels, and anthropometric indices: a 6-month, prospective, randomized, placebo-controlled, double-blind study. Adv Ther 2006; 23: 926-37.
189. Dedeoğlu EN, Erenus M, Yörük P. Effects of hormone therapy and tibolone on body composition and serum leptin levels in postmenopausal women. Fertil Steril 2009; 91: 425-31.
190. Meeuwsen IB, Samson MM, Duursma SA, Verhaar HJ. Muscle strength and tibolone: a randomised, double-blind, placebo-controlled trial. BJOG 2002; 109: 77-84.
191. Rymer J, Chapman MG, Fogelman I, Wilson PO. A study of the effect of tibolone on the vagina in postmenopausal women. Maturitas 1994; 18: 127-33.
192. Nijland EA, Weijmar Schultz WC, Nathorst-Boös J, Helmond FA, Van Lunsen RH, Palacios S, et al.; LISA study investigators. Tibolone and transdermal E2/NETA for the treatment of female sexual dysfunction in naturally menopausal women: results of a randomized active-controlled trial. J Sex Med 2008; 5: 646-56.
193. Delmas PD, Davis SR, Hensen J, Adami S, van Os S, Nijland EA. Effects of tibolone and raloxifene on bone mineral density in osteopenic postmenopausal women. Osteoporos Int 2008; 19: 1153-60.
194. Cummings SR, Ettinger B, Delmas PD, Kenemans P, Stathopoulos V, Verweij P, et al.; LIFT Trial Investigators. The effects of tibolone in older postmenopausal women. N Engl J Med 2008; 359: 697-708.
195. von Eckardstein A, Crook D, Elbers J, Ragoobir J, Ezeh B, Helmond F, et al. Tibolone lowers high density lipoprotein cholesterol by increasing hepatic lipase activity but does not impair cholesterol efflux. Clin Endocrinol (Oxf) 2003; 58: 49-58.
196. Kenemans P, Bundred NJ, Foidart JM, Kubista E, von Schoultz B, Sismondi P, et al.; LIBERATE Study Group. Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. Lancet Oncol 2009; 10: 135-46.
197. de Villiers TJ, Pines A, Panay N, Gambacciani M, Archer DF, Baber RJ, et al; International Menopause Society. Updated 2013 International Menopause Society recommendations on menopausal hormone therapy and preventive strategies for midlife health. Climacteric 2013; 16: 316-37.
198. Archer DF, Hendrix S, Gallagher JC, Rymer J, Skouby S, Ferenczy A, et al. Endometrial effects of tibolone. J Clin Endocrinol Metab 2007; 92: 911-8.
199. Archer DF, Hendrix S, Ferenczy A, Felix J, Gallagher JC, Rymer J, et al.; THEBES Study Group. Tibolone histology of the endometrium and breast endpoints study: design of the trial and endometrial histology at baseline in postmenopausal women. Fertil Steril 2007; 88: 866-78.
200. Kim H, Ku SY, Kim SH, Choi YM, Kim JG, Moon SY. The effect of tibolone and estradiol-based hormone therapy on bone mineral density and serum lipid profiles. J Korean Soc Osteoporos 2012; 10: 12-9.

201. Lee KB, Lee JM, Yoon JH, Park CY. The safety of tibolone in epithelial ovarian cancer patients. Maturitas 2006; 55: 156-61.
202. Lee KB, Lee JM, Lee JK, Cho CH. Endometrial cancer patients and tibolone: a matched case-control study. Maturitas 2006; 20;55: 264-9.
203. Lobo RA, Pinkerton JV, Gass MLS, Dorin MH, Ronkin S, Pickar JH, 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: 1025-38.
204. Mirkin S, Komm BS, Pan K, Chines AA. Effects of bazedoxifene/conjugated estrogens on endometrial safety and bone in postmenopausal women. Climacteric 2013; 16: 338-46.
205. Pinkerton JV, Harvey JA, Pan K, Thompson JR, Ryan KA, Chines AA, et al. Breast effects of bazedoxifene-conjugated estrogens: a randomized controlled trial. Obstet Gynecol 2013; 121: 959-68.
206. Pickar JH, Yeh IT, Bachmann G, Speroff L. Endometrial effects of a tissue selective estrogen complex containing bazedoxifene/conjugated estrogens as a menopausal therapy. Fertil Steril 2009; 92: 1018-24.
207. Pinkerton JV, Utian WH, Constantine GD, Olivier S, Pickar JH. Relief of vasomotor symptoms with the tissue-selective estrogen complex containing bazedoxifene/conjugated estrogens: a randomized, controlled trial. Menopause 2009; 16: 1116-24.
208. Kagan R, Williams RS, Pan K, Mirkin S, Pickar JH. A randomized, placebo- and active-controlled trial of bazedoxifene/conjugated estrogens for treatment of moderate to severe vulvar/vaginal atrophy in postmenopausal women. Menopause 2010; 17: 281-9.
209. Pinkerton JV, Pan K, Abraham L, Racketa J, Ryan KA, Chines AA, et al. Sleep parameters and health-related quality of life with bazedoxifene/conjugated estrogens: a randomized trial. Menopause 2014; 21: 252-9.
210. Lindsay R, Gallagher JC, Kagan R, Pickar JH, Constantine G. Efficacy of tissue-selective estrogen complex of bazedoxifene/conjugated estrogens for osteoporosis prevention in at-risk postmenopausal women. Fertil Steril 2009; 92: 1045-52.
211. Thomas AM, Hickey M, Fraser IS. Disturbances of endometrial bleeding with hormone replacement therapy. Hum Reprod 2000; 15 Suppl 3: 7-17.
212. Pinkerton JV, Harvey JA, Lindsay R, Pan K, Chines AA, Mirkin S, et al. Effects of bazedoxifene/conjugated estrogens on the endometrium and bone: a randomized trial. J Clin Endocrinol Metab 2014; 99: E189-98.
213. Skouby SO, Pan K, Thompson JR, Komm BS, Mirkin S. Effects of conjugated estrogens/bazedoxifene on lipid and coagulation variables: a randomized placebo- and active-controlled trial. Menopause 2015; 22: 640-9.
214. Stuenkel CA, Davis SR, Gompel A, Lumsden MA, Murad MH, Pinkerton JV, et al. Treatment of symptoms of the menopause: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2015; 100: 3975-4011.