STANDARD AND LOW-DOSE HORMONE THERAPY FOR POSTMENOPAUSAL WOMEN—FOCUS ON THE BREAST

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SUMMARY

Menopause occurs naturally when the ovary ceases folliculogenesis, or artificially by surgical and/or medical ablation of the ovarian function. Menopause is a hypoestrogenic state, which may adversely affect estrogen target tissues, such as the brain, skeleton and skin, as well as the cardiovascular and genitourinary systems, with resultant frequency and severity of climacteric symptoms. The climacteric symptoms, however, vary significantly among women. For decades, hormone therapy (HT) has been the mainstay and is considered the most effective for managing menopausal symptoms. The prolonged use of either single estrogen therapy or a combination therapy of estrogen and progestogen (EPT) might be associated with a slightly increased risk of breast cancer and many resultant adverse events, such as coronary heart disease, stroke and venous thromboembolism. Perhaps because the clear benefits are limited to these end points of HT in treating menopausal women, the relatively significant adverse event profiles of these women may not be enough to trigger primary care physicians to be more aggressive than they have been to date in treating climacteric symptoms of postmenopausal women. However, severe climacteric symptoms really disturb the woman's life. Some epidemiologic studies have shown that the increased risk for breast cancer after 5 years of combined EPT is similar in magnitude to other lifestyle variables, such as 10-year delayed menopause, fewer pregnancies and reduced breastfeeding, postmenopausal obesity, excessive alcohol or cigarette use, and lack of regular exercise. Furthermore, elevated serum concentrations of either endogenous or exogenous (replaced by HT) sex hormone in either pre- or postmenopausal women are associated with an increased risk of breast cancer. Finally, the increased breast cancer risk diminishes soon after discontinuing hormones, and largely disappears by 5 years after cessation. Taken together, low-dose conventional HT can be used with symptomatic menopausal women, but is worthy of further evaluation because we found the following potential benefits, including (i) low-dose oral EPT appears to be effective for the alleviation of climacteric symptoms; (ii) it has a good tolerability profile with a low incidence of the most common and problematic side effects, such as breast tenderness and an increased mammographic density. Altogether, when compared with the standard dose HT, physicians may prefer to use low-dose HT initially in managing the climacteric symptoms of postmenopausal women. Time will prove. [*Taiwan J Obstet Gynecol* 2007;46(2):127–134]

Key Words: estrogen, hormone therapy, low-dose, menopause, postmenopausal women, progestins

Introduction

Menopause is a biologic process that occurs as part of aging in women. Aging is the natural progression of changes in structure and function in body systems that occurs as a function of the progress of time and in the absence of disease [1]. Therefore, menopause should not be considered as a disease, although menopause can be induced either by medical or surgical ablation of the ovarian function as a result of some diseases. However, menopause results in a hypoestrogenic state of the body, and subsequently may adversely affect estrogen target tissues, including the brain, skeleton and skin, as well as the cardiovascular and genitourinary systems [2]. The

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reaction of target tissues to estrogen deficiency, with the resultant frequency and severity of climacteric symptoms varies significantly among women [3]. These climacteric symptoms frequently bother perimenopausal (the menopausal transition) and/or postmenopausal women, resulting in severe interference in their quality of life [4,5]. There are two broad categories of menopausal hormone therapies (HTs): estrogen therapy (ET) alone and combined estrogen with progestin therapy (EPT) [2].

Although HT is the mainstay therapy for symptomatic postmenopausal women, concerns have arisen regarding the possible association of breast cancer and HT. An association between breast cancer and hormone use would be plausible because breast cancer incidence is increased by hormonal factors, such as early menarche and late menopause [6]. A summary of 51 epidemiologic studies, enrolling 161,116 women with breast cancer and hormone use, showed that breast cancer risk increased by 2.3% per year of hormone use (mostly estrogen use), compared with an increased risk of 2.8% per year of natural delay in the onset of menopause [7], suggesting that hormone use increases the risk of developing breast carcinoma and that this risk increases with the increasing duration of hormone use [2]. A review of 19 epidemiologic studies estimated the average breast cancer risks to be 1.18 (95% confidence interval [CI], 1.01–1.38) with current use of ET, and 1.70 (95% CI, 1.36–2.17) with current use of EPT [8]. Taken together, hormone, of either endogenous origin or from exogenous replacement, is correlated with an increased risk of breast cancer. However, some women suffer from persistent and intolerable vasomotor symptoms that are intractable to other alternative therapy and respond only to prescription therapy. How should we deal with these patients? The following will offer recent opinion and/or evidence addressing the use of HT in symptomatic postmenopausal women.

Estrogens and Progestins

The prescribed hormones are relatively complicated, and many products are available in the market. For example, estradiol is available in oral, transdermal, injectable and vaginal delivery systems [9]. To be absorbed orally, estradiol must be micronized. Once absorbed, estradiol is converted in the liver to estrone [10]. In contrast, transdermal application avoids hepatic "first pass" metabolism, resulting in sustained concentrations of estradiol [10]. Delivery systems for transdermal application include reservoir patches that have a pouch in which estradiol is dissolved in alcohol once or twice weekly, and a gel formulation that is applied to the skin daily. The matrix patches contain an adhesive matrix, in which the estradiol is dissolved and the gel is absorbed into the skin in 1 to 2 minutes and serum concentrations reach a steady state after the third daily administration [9].

One type of estrogen is known as conjugated estrogens (CEs), which are a blend of estrogens that can be chemically produced or derived from plant or animal sources [6]. Among the CEs, conjugated equine estrogens (CEEs) may be one of the best-known products. Other types of estrogens available in the market are ethinylestradiol (EE2) and estropipate [9]. The synthetic agonists EE2 and diethylstilbestrol were found to be considerably more potent than the natural CEE, estradiol (E2) and piperazine estrone sulfate [11]. However, potency by weight is not a significant factor in deciding the suitability of a drug for use in a clinical preparation. The situation is made more complex by the interconversion of different estrogenic compounds that are more or less potent. Estradiol valerate (E2V), for example, is rapidly hydrolyzed to E2 during first-pass hepatic metabolism. E2 is interconvertible with the less potent estrone (E1), and vice versa, by oxidation/reduction, and each can be irreversibly converted to estriol (E3) [11].

Similar to the abovementioned for estrogen, there are many progestin products available on the market, and they can be easily separated into two different classes: one is 17α-hydroxyprogesterone derivatives (including medroxyprogesterone acetate [MPA], megestrol, and progesterone), and the other is 19-nortestosterone derivatives (norethindrone, norgestimate [NGM], and norethindrone acetate [NETA]). A variety of progestins are used in EPT preparations. Besides the progestogenic effect which all progestins have in common, there is a wide range of biologic effects (anti-gonadotropic, anti-estrogenic, estrogenic, androgenic, anti-androgenic, glucocorticoid, anti-mineralocorticoid, sedative) which differ for the various progestins [12]. Amongst these various biologic activities, an issue of clinical significance is androgenicity. Whilst the androgenic properties of some progestogens could antagonize the beneficial effects of estrogen in HT [13], some androgenic effects may be welcome [14]. In general, the androgenic effects of progestogens used in HT are weak, but the differences between them may be clinically significant [15]. For example, deterioration in glucose tolerance, increases in low-density lipoprotein levels, and reductions in high-density lipoprotein levels all correlate with increasing androgenic potency (levonorgestrel [LNG] > NETA > MPA) [16].

Besides the above classification, one novel product, drospirenone [DRSP], which is unlike other currently available progestins, has a pharmacologic profile which

closely mimics that of endogenous progesterone, most notably its potent anti-aldosterone and anti-androgenic effects [17]. Consequently, DRSP, when combined with 17β-estradiol (17β-E2) as HT, offsets E2-related water and sodium retention by blocking the mineralocorticoid receptor [17]. The majority of progestins used in the market are oral form. Natural form progesterone can be used through either the oral or vaginal route.

Prescription HT for Relieving the Climacteric Symptoms of Postmenopausal Women

The most commonly prescribed hormone is estrogen, either alone ET or combined with a progestin EPT for women with a uterus [18]. The principal indication for the use of EPT is the presence of a uterus.

A meta-analysis of 21 randomized, double-blind, placebo-controlled trials found that systemic ET/EPT significantly reduced both hot flash frequency and severity compared with a placebo, with a reduction rate of up to 77% and 87%, respectively [19]. A recent report of the Women's Health Initiative (WHI) study lent further evidence to the above finding, which showed that 85.7% of subjects on EPT, compared with 57.7% of women on a placebo, had relief of hot flashes, and 77.6% of subjects on EPT, compared with 57.4% of women on a placebo, had relief of night sweats [20]. There are many ET/EPT preparations with different routes of administration, regimens, and doses available in our clinical practice. So far, there is an absence of evidence showing that one product or regimen is superior to another for symptom relief. Patch and gel formulations are equally effective in treating vasomotor symptoms (VMS) and the effects are comparable to those achieved by oral ET/EPT [21]. In addition, the dose–response relationship between EPT and symptomatic relief seems not to exist [18]. A large randomized, multi-center, placebo-controlled trial showed that the reduction in VMS was similar with a daily standard dose containing 0.625-mg CEE and 2.5-mg MPA, and all lower combination doses [22]. In contrast, a dose–response relationship seems to exist with ET alone, because the same study found that 0.625-mg CEE per day alleviated hot flashes more effectively than the lower doses of CE alone. Moreover, an ET/EPT trial of 4 weeks or longer may be required to obtain the full effect on VMS. However, a systemic progestin may be added to an ET regimen if a hysterectomized woman presents persistent vasomotor symptoms on standard or higher doses of estrogens (≥ CEE 0.625 mg/day or equivalent). The 2002 North American Menopause Society Advisory Panel Report recommended the use of lower-than-standard doses of HT for managing climacteric symptoms of postmenopausal women, and because hot flashes (climacteric symptoms) affect about three-quarters of Caucasian women [23], it seems preferable to use the lowest dose of oral or transdermal HT that adequately controls VMS [24].

Conventional HT and Risk of Breast Cancer in Postmenopausal Women

Data have accumulated in randomized clinical trials, to date, involving more than 30,000 women and in epidemiologic studies involving more than 1.8 million women [3,8]. With ET use, the average risk of invasive breast cancer was 0.81 (95% CI, 0.63–1.03) in four randomized trials involving 12,643 women [25–28]. With EPT use, the average breast cancer risk was 1.24 (95% CI, 1.03–1.50) in randomized trials involving 19,756 women [29–33]. The absolute effect of EPT in the WHI and heart and estrogen/progestin replacement study trials added 8 and 17 cases per 10,000 women per year, respectively, to natural risk [31,32]. Data from the Million Women Study (MWS) showed the increased risk to current users of ET, EPT, and tibolone as 1.30 (95% CI, 1.21–1.40; $p < 0.0001$), 2.00 (95% CI, 1.88–2.12; $p < 0.0001$), and 1.45 (95% CI, 1.25–1.68; $p < 0.0001$), respectively, but the magnitude of the associated risk was substantially greater for EP than for other types of HT ($p < 0.0001$) [34]. In six epidemiologic studies, including the MWS, the average relative risks with sequential and continuous progestin regimens were 1.85 (95% CI, 1.72–1.99) and 1.94 (95% CI, 1.78–2.11), respectively, a difference that was not significant [8].

Some epidemiologic studies showed that the increased risk for breast cancer after 5 years of combined EPT was similar in magnitude to other lifestyle variables, such as 10-year delayed menopause, fewer pregnancies and reduced breastfeeding, postmenopausal obesity, excessive alcohol or cigarette use, and lack of regular exercise [9]. Furthermore, elevated serum endogenous sex hormone concentrations in premenopausal women are associated with an increased risk of breast cancer [1]. Kaaks' studies showed that increased risks of breast cancer were associated with elevated serum concentrations of testosterone (odds ratio [OR] for highest *vs.* lowest quartile, 1.73; 95% CI, 1.16–2.57; $p = 0.01$), androstenedione (OR for highest *vs.* lowest quartile, 1.56; 95% CI, 1.05–2.32; $p = 0.01$), and dehydroepiandrosterone sulfate (DHEAS) (OR for highest *vs.* lowest quartile, 1.48; 95% CI, 1.02–2.14; $p = 0.10$), but not sex hormone-binding globulin (SHBG). Elevated serum progesterone concentrations were associated

with a statistically significant reduction in breast cancer risk (OR for highest *vs.* lowest quartile, 0.61; 95% CI, 0.38–0.98; $p = 0.06$). The absolute risk of breast cancer for women younger than 40 years followed up for 10 years was estimated at 2.6% for those in the highest quartile of serum testosterone *vs*. 1.5% for those in the lowest quartile; for the highest and lowest quartiles of progesterone, these estimates were 1.7% and 2.6%, respectively. Breast cancer risk was not statistically significantly associated with serum levels of the other hormones [35]. In addition, endogenous sex hormone concentrations were also associated with breast cancer risk among postmenopausal women not using postmenopausal hormones [36]. Missmer's group observed a statistically significant direct association between breast cancer risk and the levels of both estrogen and androgen, but did not find any (by year) statistically significant associations between this risk and the level of progesterone or SHBG. When they restricted the analysis to case subjects with ER+/PR+ tumors and compared the highest with the lowest fourths of plasma hormone concentration, they observed an increased risk of breast cancer associated with E2 (relative risk [RR], 3.3; 95% CI, 2.0–5.4), testosterone (RR, 2.0; 95% CI, 1.2–3.4), androstenedione (RR, 2.5; 95% CI, 1.4–4.3), and DHEAS (RR, 2.3; 95% CI, 1.3–4.1). In addition, all hormones tended to be associated most strongly with *in situ* disease. Therefore, they concluded that circulating levels of sex steroid hormones may be most strongly associated with risk of ER+/PR+ breast tumors [36]. Tworoger's group studied serum levels of sex hormones in postmenopausal hormone users and found that these women had statistically significantly higher estradiol, free estradiol, SHBG and testosterone, and lower free testosterone concentrations than non-postmenopausal hormone users [37]. After evaluating the relationship between hormone levels and breast cancer risk, they found modest associations with breast cancer risk when comparing the highest *vs.* lowest quartiles of free E2 (RR, 1.7; 95% CI, 1.1–2.7; $p = 0.06$), free testosterone (RR, 1.6; 95% CI, 1.1–2.4; $p = 0.03$), and SHBG (RR, 0.7; 95% CI, 0.5–1.1; $p = 0.04$), but not of E2 or of testosterone. However, E2 and free E2 were statistically, significantly, and positively associated with breast cancer risk among women older than 60 years (RR, 2.8; 95% CI, 1.5–5.0; $p = 0.002$; and RR, 2.6; 95% CI, 1.4–4.7; $p = 0.001$, respectively), and among women with a body mass index of less than 25 kg/m^2 (RR, 1.8; 95% CI, 1.1–3.1; $p = 0.01$; and RR, 2.4; 95% CI, 1.4–4.0; $p = 0.003$, respectively). Therefore, they concluded that although women using postmenopausal hormone have a different hormonal profile than those not using postmenopausal hormone, plasma sex hormone concentrations appear to be associated with breast cancer risk among postmenopausal hormone users [37], suggesting the possible benefits of using low-dose effective hormone in managing these symptomatic postmenopausal women because the low-dose HT may contribute to the low serum levels of hormone, which may contribute to lower breast cancer risk.

In addition, in the epidemiologic studies, the increased breast cancer risk diminished soon after discontinuing hormones, and it largely disappeared by 5 years after cessation [8]; the use of HT as a standard treatment applied to all menopausal women will not meet the needs of many individual women [1]. Health care providers should therefore consider the relative balance between the benefits and risks of treatment for each patient before drawing conclusions or recommending HT. Therefore, as with the abovementioned, alternative dosage and application methods, such as oral low-dose HT and ultra-low dose transdermal HT, which deliver the benefit but not the adverse side effects, would be clinically advantageous, although Collins' group found that breast cancer risk did not vary significantly with different types of estrogen or progestin preparations, with use of lower dosages or with different routes of administration [8]. Crandall [24] also announced that low-dose preparations should not yet be emphasized as being safer than traditional doses.

In order to understand the role of low-dose HT in the breast in postmenopausal women, it is appropriate to review the available data about the risk of breast cancer with low-dose HT in treating climacteric symptoms of postmenopausal women.

The Climacteric Symptoms in Postmenopausal Women

Some of the major climacteric symptoms of postmenopausal women may be related to VMS. The VMS associated with menopause are commonly termed hot flashes and night sweats [18]. Hot flashes are characterized by the sudden onset of intense warmth that begins in the chest and may progress to the neck and face [38]. They are often accompanied by anxiety, palpitations, and profuse sweating. VMS may interfere with a woman's ability to work, her social life, her sleep pattern, and her general perception of health. VMS are an early, readily apparent sign of menopause transition, and the maximal prevalence is during the first 2 years of postmenopause, after which the prevalence declines over time. Most women experience hot flashes for 6 months to 2 years, although some women have them for 10 years or longer [18]. The study of women's health across the

nation demonstrates the different prevalence rates of hot flashes among racial/ethnic groups. According to this multiethnic cross-sectional survey of more than 16,000 women aged 40–55, African-American women report hot flashes most frequently, followed by Hispanics, Caucasians, Chinese, and Japanese [39]. Multiple treatments have been used to relieve hot flashes, including lifestyle modifications, and non-prescription and prescription therapies [18]. Multiple placebo-controlled trials have shown about 25–30% reduction in hot flashes within 4 weeks of placebo treatment [38]. In addition, a Cochrane review of ET compared with a placebo for the treatment of hot flashes has shown that a placebo may cause a VMS reduction of up to 50% [40]. And finally, the menopausal state is a natural course, an aging process, and of most importance, it is not a disease. Therefore, we must take into account health status and personal choice when assisting postmenopausal women with mild to moderate VMS. We prefer the use of life modification as a first choice strategy for relieving mild-to-moderate VMS; life modification includes manipulating the environment and changing behaviors. After introducing non-medication therapy, many women with persistent VMS still respond only to HT. The following addresses the efficacy of low-dose HT in managing climacteric symptoms.

The Efficacy of Low-dose HT in Relieving Climacteric Symptoms in Postmenopausal Women

Before entering into the topic of the efficacy of low-dose HT in relieving climacteric symptoms, the definition of low-dose should be clarified. Based on the published data [11,24], a low-dose of estrogens was considered to be (at most) 0.3 mg CEE, 25–75 μg transdermal E2, 0.05–1 mg oral E2, 1 mg E2V, 0.3 mg esterified estrogens (EE), 5 μg EE2, and 0.3 mg synthetic CE. Dosages of progestogens used in low-dose cc-HT formulations are shown as follows: MPA 1.5–5 mg/day; LNG 5–20 μg/day; NETA 0.1–1.0 mg/day; dydrogesterone 5 mg/day; nomegestrol 2.5 mg/day; trimegestone 0.125 mg/day; DRSP 2 mg/day [11]. Likewise, in general, all low-dose regimens appear to be highly effective in the management of climacteric symptoms, with no consistently significant differences in the magnitude of the effect of conventional dose regimens [22,41–44]. However, some studies have reported a slight dose–response effect with EE2/NETA [45], both in terms of overall efficacy and time to onset of response. Although head-to-head comparisons are lacking, there is no evidence of any marked differences between different low-dose regimens. In a recent excellent review summarizing the results of low-dose estrogens for relieving VMS [24], there was a comparable efficacy of 25 μg and higher doses of transdermal E2 for VMS, and a dose-related trend in the proportion of severe hot flashes. However, there was a possible lag of a few weeks in the onset of effect, compared with higher doses. Synthetic CE may be efficacious by 4 weeks, but it is not clear how different doses compare with each other. E2/NGM 1 mg/90 μg is efficacious. Low doses of CEE/MPA (0.45/2.5, 0.45/1.5, 0.3/1.5 mg) are as effective as traditional doses, but with a week's lag. MPA adds to the efficacy of low-dose CEE, blunting the dose–response seen with low-dose CEE alone. CEE 0.3 mg/day is efficacious, although some older women may experience a flare-up in VMS when switching to CEE 0.3 mg/day plus cyclical MPA from 0.625 mg CEE. E2/NETA 1 mg/0.5 mg and 1 mg/0.25 mg have comparable efficacy, both to each other and to higher doses at 4 weeks. EE2/NETA 1 μg/5 mg is efficacious, but there is a lag of 1 week in therapeutic efficacy *vs*. higher doses, and a clear dose–response relationship. E2 alone 0.5 mg/day is efficacious for hot flashes, but response is dose-related in a range of 0.25–2 mg. An E2 dose of 0.25 mg/day is not adequate for suppression of hot flashes, and 0.5 mg may not be superior to a placebo.

In summary, evidence from well-conducted long-term oral EPT clinical trials has confirmed that low-dose EPT preparations are effective in alleviating climacteric symptoms, and that this effect was not influenced to a clinically relevant degree by the presence of progestins [11]. But for the estrogen-only group, the efficacy of lower doses of estrogen for the reduction of VMS may be less than a daily standard dose containing 0.625 mg CEE [28]. The effect on climacteric symptoms is sustained over long-term use.

Breast Tenderness of Women who are Treated with Low-dose HT

According to the above review [24], breast pain can occur with synthetic CE (about one third, but there is a lack of data by dose), with E2 in doses of > 0.5 mg (25% with 0.5 mg), and with E2/NETA (2% with 1 mg/0.5 mg). Breast tenderness is less frequent with oral E2 0.25 mg/day compared with higher doses. E2/NETA, 1 mg/0.5 mg is associated with less breast pain *vs*. higher doses. No matter which dose is used, about 20% of subjects experience breast tenderness with E2/NGM, and adding NGM to E2 raises the rate of breast tenderness. Breast tenderness with CEE/MPA is dose-related, with an incidence of about 10% with 0.3 mg/2.5 mg.

Breast tenderness with transdermal E2 is also dose-related, ranging from 20% to 65% with low doses in different trials. In summary, low-dose HT will result in a lower frequency of breast tenderness when compared with standard HT.

Mammography Changes in Women who are Treated with Low-dose HT

An increase in mammographic density should be regarded as an unwanted side effect of HT, because increased breast density can impair interpretation of mammograms, thus increasing the failure rate of breast cancer screening programs [2]. Greendale et al [46] studied mammographic density changes in 571 women aged 45–64 years, who were enrolled in the postmenopausal estrogen/progestin interventions trial and randomly assigned to receive a placebo, daily CEE at 0.625 mg/day, daily CEE and MPA at 10 mg/day on days 1–12 (CEE + MPA-cyclic), daily CEE and MPA at 2.5 mg/day (CEE + MPA-continuous), or daily CEE and micronized progesterone (MP) at 200 mg/day on days 1–12 (CEE + MP), using digitized mammograms to determine the percentage of the left breast that was composed of dense tissue (i.e. mammographic percent density). They found that the adjusted absolute mean changes in mammographic percent density over 12 months were 4.76% (95% CI, 3.29–6.23%), 4.58% (95% CI, 3.19–5.97%), and 3.08% (95% CI, 1.65–4.51%) for women in the CEE + MPA-cyclic, CEE + MPA-continuous, and CEE-MP groups, respectively. Each of those absolute mean changes was statistically significantly different from the adjusted absolute mean change in mammographic percent density for women in the placebo group, which was –0.07% (95% CI, –1.50–1.38%). Therefore, they concluded that greater mammographic density was associated with the use of estrogen/progestin combination therapy, regardless of how the progestin was given, but not with the use of estrogen only [46]. A follow-up WHI mammogram density study (using a standard dose of hormone) showed that mean mammographic percent density increased by 6.0% at year 1, compared with baseline, in the EPT group, but decreased by 0.9% in the placebo group (difference, 6.9%; 95% CI, 5.3–8.5%; $p < 0.001$) [47]. The mean changes in mammographic density persisted but were attenuated slightly after 2 years, with an absolute increase of 4.9% in the EPT group and a decrease of 0.8% in the placebo group (difference, 5.7%; 95% CI, 4.3–7.3%; $p < 0.001$). These effects were consistent across racial/ethnic groups but were higher among women aged 70–79 years in the EPT group (mean increase at year 1, 11.6%) than in the placebo group (mean decrease at year 1, 0.1%) (difference of the means, 11.7%; 95% CI, 8.2–15.4%; $p < 0.001$, compared across age groups). At year 1, women who were adherent to treatment in the EPT group had a mean increase in density of 7.7% (95% CI, 5.9–9.5%), and women in the placebo group had a mean decrease in density of 1.1% (95% CI, 0.3–1.9%). Use of EPT was associated with an increased risk of having an abnormal mammogram at year 1 (RR, 3.9; 95% CI, 1.5–10.2; $p = 0.003$), compared with a placebo, which was not explained by the increase in density [47]. Lundstrom et al [48] evaluated a total of 158 women who were treated with different regimens of HT and found that an increase in mammographic density was much more common among women taking continuous EPT (40%) than for those using oral low-dose estrogen (6%) and transdermal (2%) treatment, and the increase in density was already apparent at the first visit after starting HT. During long-term follow-up, there was very little change in mammographic status. Sendag et al [49] found that mammographic breast density changes related to postmenopausal HT are dependent on the selected hormone regimen, and the continuous administration of the progestin component of the EPT seems to effect the breast density most. Christodoulakos et al [50] found an increase in breast density in 13.2%, 31.8%, and 12.2% of women (5/38) treated with CE/MPA, E2/NETA, and low E2/NETA, respectively, and no woman exhibited an involution of fibroglandular tissue, suggesting that different HT regimens have a variable impact on breast density, probably depending on the steroid used, and low-dose HT is associated with significantly less of an increase in breast density. Conner's group further studied the effects of different regimens of EPT [51] and found an increase in mammographic density in approximately 50% of the women; there were no differences between the treatments. Increased density showed a positive correlation with estradiol, estrone, and SHBG and showed a negative association with free testosterone. Among hormonal factors, levels of free testosterone were the most important for predicting increased density. Therefore, the researchers concluded that continuous EPT with different progestogens has a marked impact on the breast [51]. Since progestins played a major role in the increased risk of mammographic density in the EPT group, some investigators have used a low-dose intrauterine system releasing 20 μg/24 hours of LNG in continuous combination with 2 mg of oral E2V to decrease the progestin stimulation on the breast without compromising uterine protection [52]. As expected, there was no increase in proliferation as expressed by the percentage of MIB-1-positive breast

cells in fine-needle aspiration biopsies. However, the increase in breast density displayed a positive correlation with patient age (r_s, 0.52) and an inverse relationship with levels of E2 (r_s, –0.50) and free testosterone (r_s, –0.50) [52]. Therefore, they concluded that low-dose intrauterine administration of progestogen may develop into an attractive alternative for HT in postmenopausal women, as endometrial protection may be achieved at very low systemic levels [51]. Junkermann's group compared continuous low-dose HT and standard-dose sequential HT and found that there were no marked differences between treatment groups, because approximately 20% of women in both groups had a slight increase in mammographic density [53]. Overall, there is a great deal of evidence showing that the estrogen-only group and the low-dose progestin in EPT group may have less of an increase in the mammographic density, although more strong evidence is required to support these findings.

Conclusion

Low-dose oral EPT appears to be effective for the alleviation of climacteric symptoms. It has a good tolerability profile with a low incidence of the most common and problematic side effects such as breast tenderness and increased mammographic density. However, regarding the long-term effects of different low-dose EPT on cardiovascular disease, and cerebrovascular events, and breast cancer incidence; more long-term data and direct head-to-head comparisons between the various low-dose preparations are needed. Taken together, physicians may prefer using low-dose HT initially, rather than standard dose HT, in managing the climacteric symptoms of postmenopausal women.

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