Review

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Update on hormone therapy for the management of postmenopausal women

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SUMMARY Hormone therapy (HT) has been used in postmenopausal women for decades in clinical practice. With further analysis and newer studies, the benefits and risks of HT have been repeatedly verified and discussed. HT is recommended for the treatment of vasomotor symptoms (VMS), genitourinary syndrome of menopause (GSM) and the prevention of osteoporosis. However, the precise association between HT and the risks of cardiovascular diseases, venous thromboembolism, neurodegenerative diseases, breast cancer, and endometrial cancer remains controversial. Therefore, determining how to take advantage of and control the risks of HT by adjusting the initiation time, regimen, and duration is crucial. Recent studies have indicated that HT is not related to the risk of all-cause, cardiovascular, or breast cancer mortality although it might increase the incidence of some chronic diseases. For symptomatic postmenopausal women under the age of 60 without contraindications, early initiation of HT is safe and probably has a mortality benefit over the long term. Initiating HT close to menopause at the lowest effective dose is more likely to have maximal benefits and the lowest risks. Transdermal and vaginal HT may have a lower risk, but recent evidence suggests additional clinical benefits of oral HT formulations in relieving VMS and preventing osteoporosis. The pooled cohort risk equation for atherosclerotic cardiovascular disease (ASCVD) and the free app named Menopro can be used to perform individual risk assessments. In addition, Chinese herbal medicines have benefits in alleviating hot flashes, depression, and menopausal symptoms, although further data are needed to strongly support their efficacy. Acupuncture and electroacupuncture have definite efficacy in the treatment of postmenopausal symptoms with few adverse effects, so they are a reasonable option as an alternative therapy for high-risk women. This review discusses the history of, guidelines on, and strategies for HT in order to make suggestions based on the most up-to-date evidence for the management of postmenopausal women.

Keywords hormone therapy, post-menopause, menopausal management, gynecology

1. Introduction

Menopause is by definition amenorrhea for 12 consecutive months after the final menstrual period (FMP) (*1*). It is a permanent end to the menstrual cycle following the loss of ovarian follicular activity. The prominent decrease in estrogen production of the ovaries often leads to menopausal symptoms such as systemic vasomotor symptoms (VMS), vulvovaginal atrophy (VVA), and genitourinary syndrome of menopause (GSM). Menopause is also related to an increased prevalence and incidence of cardiovascular disease, stroke, Alzheimer's disease, dementia, and breast cancer (*2,3*). Post-menopause refers to the stage after the final menstrual period in a woman's life (*4*). As life expectancy increases, women will have a longer postmenopausal period. Menopausal symptoms and the risk of various related diseases are markedly higher in postmenopausal women compared to premenopausal women (*5*).

Hormone therapy (HT) is considered to be the most effective way to relieve menopausal symptoms. It has been used in clinical practice for over 60 years since the 1960s; however, the benefits and risks of HT have been controversial. In 2002, the Women's Health Initiative (WHI) found that HT increased the incidence of coronary heart disease and breast cancer, which led to a precipitous decline in the use of HT (*6*). Upon further analysis of the WHI data and with support from newer

studies (*7-9*), international societies and organizations such as the International Menopause Society (IMS), the North American Menopause Society (NAMS), the European Menopause and Andropause Society (EMAS) have formulated guidelines and announced consensus opinions on the use of HT. As understanding of HT improves, studies have found that HT is highly beneficial to symptomatic women who are younger than 60 years of age, within 10 years of menopause, and without contraindications such as active liver disease or thromboembolic disease (*10-12*).

This article reviews HT for the management of postmenopausal women by discussing various guidelines, strategies, and evidence. The purpose of this review is to organize the information on postmenopausal HT and to make suggestions according to the most up-to-date evidence for the management of postmenopausal women.

2. History of HT

In 1942, an estrogen product named Premarin was approved by the FDA for treatment of postmenopausal symptoms. With the feminist movement and the desire to be "feminine forever" in the 1960s, estrogen therapy (ET) was widely used to treat menopausal women (*13*). In the 1970s, a study found that estrogen supplements were related to an increased risk of endometrial cancer (*14*). Nevertheless, studies over the following years found that combining estrogen with progesterone could reduce the risk of endometrial cancer, so ET was switched to hormone replacement therapy (HRT) or HT (*15*). In the 1980s and 1990s, numerous clinical studies such as the Postmenopausal Estrogen/Progestin Intervention (PEPI) trial suggested that HT was safe for the treatment of menopausal symptoms and beneficial at preventing chronic diseases including cardiovascular disease (CVD) (*16,17*). The use of HT increased rapidly, reaching the second peak in its history. The first guideline on HRT management was published by the American College of Physicians in 1992, and it suggested the use of HT to prevent related chronic diseases (*18*). The FDA also approved HRT for the treatment of menopause and prevention of postmenopausal osteoporosis in 1995 (*19*).

To confirm the clinical benefits of HT, many organizations and scholars started large randomized trials to evaluate the effect of HT on related chronic diseases. In 1998, the Heart and Estrogen/progestin Replacement Study (HERS) found that HT did not reduce the overall rate of coronary heart disease (CHD) events but it did increase thromboembolic events and gallbladder disease in postmenopausal women with established coronary disease (*20*). The Women's Health Initiative (WHI) trial started in 1998 and preliminary results were published in 2002; the trial found that HT increased the incidence of CHD and breast cancer, with a reduction in colorectal cancer and osteoporotic fractures (*6*). The Oral Conjugated Equine Estrogens (o-CEE) plus Medroxyprogesterone Acetate (MPA) trial by the WHI was prematurely discontinued in 2002 and a trial of o-CEE alone was also stopped in 2004 because of the high risks of breast cancer and CVD. The unexpected results of the WHI trials increased panic and confusion among HRT recipients and doctors, which led to a precipitous decline in the use of HT.

After the results of the WHI trials were published, the safety and effectiveness of HT have been disputed. Many of the results of those trials have also been extensively debated. Professor Thomas Clarkson, DVM was a pioneer who demonstrated that the initiation time of HT may determine whether the benefits exceed the risks involved in coronary artery atherosclerosis (*21*). The timing hypothesis or "window of opportunity" theory attracted great attention in helping to explain the different results of various observational studies and the WHI trials (*7*). Subsequent clinical trials including the 2017 Kronos Early Estrogen Prevention Study (KEEPS) and the 2016 Early Versus Late Intervention Trial with Estradiol (ELITE) substantiated the safety of HT when initiated early in post-menopause (*8,9*).

In 2007, a secondary analysis of the WHI trials reported that women who began HT within 10 years of menopause tended to have a reduced risk of CHD and a favorable total mortality (*22*). Cumulative follow-up data from the WHI trials published in 2017 indicated that HT was not related to cause-specific mortality or all-cause mortality (*23*). Further follow-up data from the WHI trials focusing on the long-term risk of breast cancer were published in 2020 and led to the conclusion that CEE combined with MPA or CEE alone would not increase breast cancer mortality (*24,25*).

The history of HT development is complex and tortuous (Figure 1). As understanding of HT has improved, guidelines and consensus opinions have been published and updated to regulate its use.

3. Guidelines and consensus opinions

Based on the secondary analysis of the WHI trials and further studies, how HT can benefit postmenopausal women has become clearer. Several guidelines and consensus opinions have been updated in order to guide clinicians to make clinical decisions more appropriately and accurately (*1,10,11,26-31*). Nevertheless, there are similarities and differences among the guidelines that warrant attention (Table 1-2).

Guidelines and consensus opinions recommend HT in the treatment of postmenopausal symptoms including VMS and GSM, but none of them recommend its use to prevent CHD or breast cancer. Before making a clinical decision, risk factors such as CVD, breast cancer, obesity, age, and time from the onset of menopause should be taken into consideration. Most statements generally agree in recommending the use of HT in

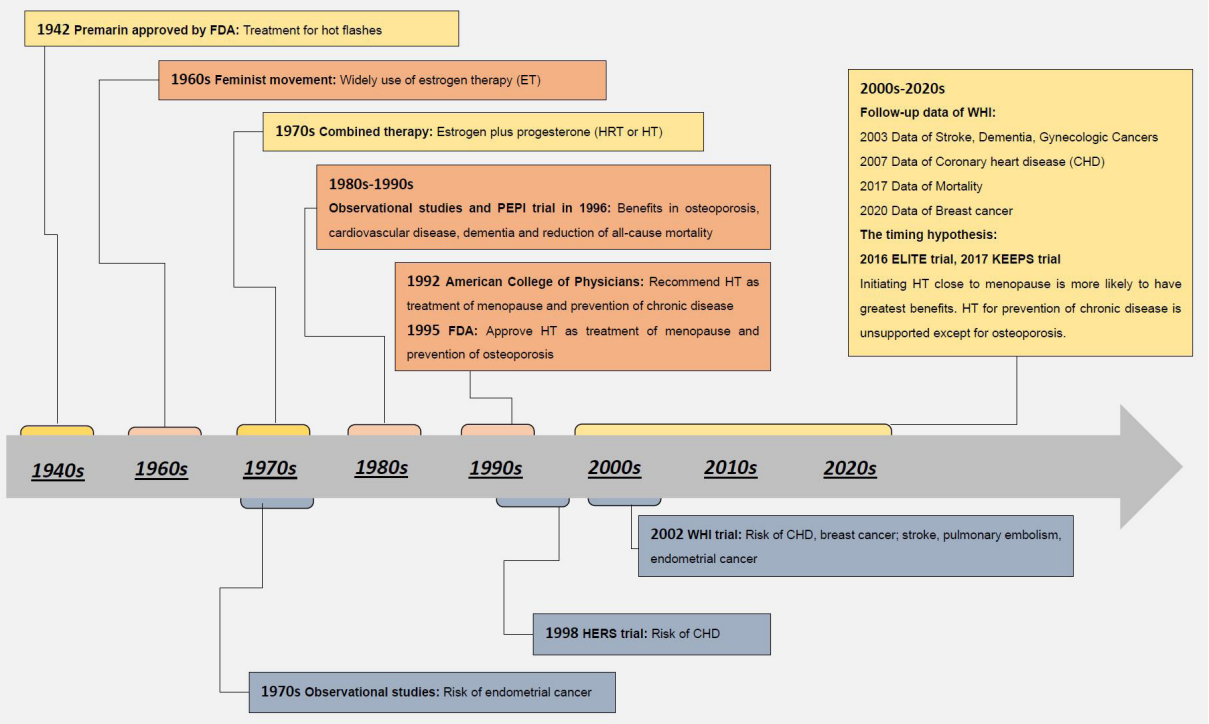

Figure 1. Timeline of development of hormone therapy for postmenopausal women. CHD: Coronary heart disease; ELITE: the Early versus Late Intervention Trial with Estradiol; FDA: the United States Food and Drug Administration; HERS: the Heart and Estrogen/progestin Replacement Study; HT: Hormone Therapy; HRT: Hormone Replacement Therapy; KEEPS: the Kronos Early Estrogen Replacement Study; PEPI: the Postmenopausal Estrogen/Progestin Intervention trial; WHI: the Women's Health Initiative trial.

symptomatic postmenopausal women younger than the age of 60 within 10 years of the onset of menopause. Use of HT is also encouraged in women with hypogonadism, early menopause, or primary ovarian insufficiency (POI) without discontinuation until they reach the mean age for the onset of menopause. Initiating HT close to menopause at the lowest effective dose is more likely to have the greatest benefits and the lowest risks, including short-term symptomatic relief and long-term prevention of chronic disease. Most guidelines also mention different routes and formulations. Compared to oral HT, transdermal therapy is recommended as a safer approach in women with an elevated risk of VTE because it is less likely to cause thrombotic risks such as stroke and coronary artery disease. Low-dose vaginal HT is recommended for genitourinary syndrome, and involvement of an oncologist is recommended for women who at risk of breast cancer. Compounded HT is not recommended due to the lack of evidence of its safety and effectiveness.

Most of the differing recommendations in the updated guidelines involve the duration of HT and opinions on related chronic diseases such as postmenopausal osteoporosis, CHD, dementia, obesity, and breast cancer. Some guidelines advocate individualized decisions regarding the duration based on consideration of the risk-benefit ratio without mandatory limits; some suggest that clinicians attempt to reduce or stop administration after symptoms have been relieved and then adjust the dose depending on the patient's quality of life. The NICE, AACE, and ACE advise a duration of 5 years or less. Although none of these latest guidelines support HT for the primary or secondary prevention of CHD, some still feature data supporting its potential cardiovascular benefits if given close to menopause. Recommendations for the use of HT to prevent osteoporosis and diabetes also vary in different guidelines. Individualized formulations are proposed in new recommendations, and the NAMS offers a mobile app called Menopro to help women and clinicians ascertain possible treatment options to make an appropriate decision together.

4. Indications for HT

4.1. Vasomotor symptoms (VMS)

VMS affects over 80% of postmenopausal women, with overwhelming symptoms including hot flashes, fatigue, muscle and joint aches, sleep disturbances, obesity, and depression (*32*). In postmenopausal women without contraindications, HT containing estrogen alone or together with progesterone in cyclic or continuous administration remains the recommended treatment for VMS. Combined progesterone with estrogen is used in women with an intact uterus to protect the endometrium while estrogen alone can be used in women without a uterus. Over 32 randomized, placebo-controlled trials currently recommend HT as a treatment for VMS (*31*).

Table 1. General agreement in guidelines on hormone therapy

Aspect of hormone therapy	General agreement
Indications	• **Menopausal symptoms** • **Primary ovarian insufficiency (POI) or early menopause** (ACOG, BMS, Endocrine Society, Global Consensus, IMS, NAMS, NICE)
Risk considerations	• **Age, time from onset of menopause** (AACE and ACE, BMS, Global Consensus, IMS, NAMS) • **CVD, breast cancer** (AACE and ACE, Endocrine Society) • **Lipid profile, Smoking history** (AACE and ACE) • **Individualized decisions based on the risk-benefit ratio** (ACOG) • Not evaluated (USPSTF)
Initiation	• **Age < 60 yr, within 10 years of the onset of menopause** (AACE and ACE, BMS, Global Consensus, IMS, NAMS) • **Possible benefit at preventing CVD when initiated close to menopause** (AACE and ACE, ACOG, BMS, Global Consensus, NAMS)
Duration	• **Individualized decisions** based on consideration of the risk-benefit ratio without mandatory limits (ACOG, BMS, Endocrine Society, Global Consensus, IMS, NICE,) • **Shortest total duration** for treatment goals and risk assessment (AACE and ACE, Endocrine Society, NAMS) • **5 years or less** (AACE and ACE, NICE) • Not evaluated (USPSTF)
Dosage	• **Lowest effective dose** needed to relieve symptoms and minimize risks of therapy (AACE and ACE, ACOG, Global Consensus, NAMS) or • **individualized dose to minimize risks** (BMS, IMS, NICE,)
Transdermal therapy	• **Recommend for women with an elevated risk of VTE** (AACE and ACE, ACOG, BMS, Endocrine Society, Global Consensus, IMS, NICE, NAMS,) • **obesity** (Endocrine Society, IMS, NICE) • **hypertension** (AACE and ACE; Endocrine Society) • **hypertriglyceridemia, or cholelithiasis** (AACE and ACE) • Not recommended (USPSTF)
Vaginal therapy	• **Recommend for genitourinary syndrome of menopause** (AACE and ACE, ACOG, Endocrine Society, Global Consensus, IMS, NICE, NAMS) • **An oncologist needs to be involved in treating woman at risk of breast cancer** (ACOG, Endocrine Society, IMS, NAMS) • Not addressed (USPSTF)
Compound hormone therapy	• **Recommend against** non-FDA approved compounded hormone therapy

Included Guidelines: AACE and ACE (*27*) 2017; ACOG (*28*) 2014; BMS (*31*) 2020; Endocrine Society (*29*) 2015; Global Consensus (*30*) 2016; IMS (*10*) 2016; NICE (*26*) 2016; NAMS (*11*) 2017; USPSTF (*1*) 2017.
AACE and ACE: American Association of Clinical Endocrinologists and American College of Endocrinology; ACOG: American College of Obstetricians and Gynecologists; BMS: British Menopause Society; IMS: International Menopause Society; NAMS: the North American Menopause Society; NICE: National Institute for Health and Care Excellence; USPSTF: United States Preventive Services Task Force.

Table 2. Different opinions on hormone therapy to prevent chronic disease

Items	Osteoporosis	CVD/CHD	Diabetes	Dementia
AACE and ACE (*27*) 2017	A	B	D	E
ACOG (*28*) 2016	D	B	E	E
BMS (*31*) 2020	A (First-line)	B	E	C
Endocrine Society (*29*) 2015	B	D	B	D
Global Consensus (*30*) 2016	A (Second-line)	B	E	B
IMS (*10*) 2016	A	D	A	B
NAMS (*11*) 2017	A	B	B	D
NICE (*26*) 2016	B	C	C	D
USPSTF (*1*) 2017	B	D	B	D

A Supported
B Not recommended but data suggest potential benefits
C Not recommended but safe
D Not recommended
E Not mentioned

AACE and ACE: American Association of Clinical Endocrinologists and American College of Endocrinology; ACOG: American College of Obstetricians and Gynecologists; BMS: British Menopause Society; CVD: Cardiovascular disease; CHD: Coronary heart disease; IMS: International Menopause Society; NAMS: North American Menopause Society; NICE: National Institute for Health and Care Excellence; USPSTF: United States Preventive Services Task Force.

Estrogen or combined estrogen/progestogen therapy can relieve the weekly frequency and severity of hot flashes by 75% and 87%, respectively (*33*).

Both oral and transdermal estrogens have been found to be clinically effective in relieving VMS, but opinions are divided in different studies regarding the optimal choice. The KEEPS trial suggested parallel and definite alleviation of hot flashes, night sweats, and poor sleep by oral or transdermal estrogen with a dosage lower than that commonly recommended (*34,35*). Transdermal estradiol (t-E2) plus intermittent micronized progesterone (IMP) has proven to be effective in prevention of depressive symptoms (*31*). Although oral and transdermal HT were both effective and did not differ significantly in efficacy, transdermal HT was thought to be more cost-effective and likely to cause fewer adverse events or result in a lower rate of discontinuation (*36*). However, a recent systematic review noted a cumulative amenorrhea rate ranging from 18% to 61% with oral HT and from 9% to 27% with transdermal HT. Oral HT formulations have a higher rate of amenorrhea and a lower rate of discontinuation than most transdermal HT formulations. A combination of oral 17 β-estradiol (E2) plus progesterone (P4) resulted in the lowest rate of bleeding and is probably an appropriate option for relieving moderate to severe VMS (*37*).

4.2. Genitourinary syndrome of menopause (GSM)/ vulvovaginal atrophy (VVA)

The concept of GSM was defined and formally endorsed by NAMS and the International Society for the Study of Women's Sexual Health (ISSWSH) in 2014 as more accurate and inclusive than the term VVA. GSM is defined as a collection of symptoms caused by estrogen deficiency, comprising changes in the genital area or the urinary tract such as a burning sensation or dryness of the vagina, dyspareunia, dysuria, and urinary tract infections (*38*).

Lubricants and moisturizers are considered the first-line treatment for the symptoms of vaginal dryness and painful sex, and especially for women whose symptoms primarily occur with coitus. Lubricants and moisturizers can be used alone or in combination with estrogen depending on the severity of GSM symptoms or the patient's preference (*26*). If vaginal lubricants or moisturizers are not effective at alleviating pain, systemic and local estrogen HTs are recommended to treat GSM in postmenopausal women without contraindications. Low-dose vaginal estrogen, the "gold standard" of therapy, remains the most effective way to treat postmenopausal women with only vulvovaginal symptoms. Systemic estrogen therapy is effective at treating concurrent symptoms of GSM, and it is approved or recommended for women with GSM as well as vasomotor symptoms (*26,39*).

Low-dose vaginal estrogen therapies include various preparations used vaginally such as tablets, creams, rings, and capsules with different compounds and doses, and studies have demonstrated that those therapies are an effective and safe treatment for GSM. Vaginal estrogen therapies can prevent recurring atrophy caused by estrogen deficiency, resulting in an enhancement of blood flow, vaginal wall thickness, and elasticity (*40-42*). The various forms of vaginal estrogen products are all effective and safe for the treatment of GSM; trials of these forms of topical estrogen products do not differ significantly in terms of objective endpoints, subjective endpoints, or adverse reactions (*41,42*). Estradiol vaginal cream in a very low-dose of 0.003% used twice a week is effective and well-tolerated (*43*). Conjugated estrogen tablets (0.625 mg) used vaginally have been found to adjust the vaginal pH and the vaginal maturation value (VMV) (*44*). Since clinical effects on objective signs and subjective symptoms will respectively wear off about 3 months and 1 month after the cessation of vaginal estrogen, long-term therapy rather than a short-term intervention with topical estrogen should be considered (*45*). Given that low-dose vaginal estrogens may restrict but not eliminate the systemic absorption of estrogen (*40*), discussing vaginal HTs with an oncologist is an appropriate approach for postmenopausal women with breast cancer or endometrial cancer that is refractory to non-hormonal therapies.

4.3. Osteoporosis prevention

Postmenopausal osteoporosis is a skeletal disorder characterized by low bone mass and micro architectural deterioration of bone tissue mainly resulting from a conspicuous deficiency of reproductive hormones in postmenopausal women (*46*). FDA-approved estrogen is used to prevent instead of treat postmenopausal osteoporosis. The Endocrine Society updated one of its guidelines in 2020 in order to provide professional advice for the pharmacological management of osteoporosis. The guideline recommends HT to prevent all categories of fractures in postmenopausal women with symptoms and a high risk of fracture, and especially in those who are not eligible for specific bone active medications/ bone-specific treatment (bisphosphonates, denosumab, *etc*.). In addition, estrogen-only therapy is appropriate for women who have undergone a hysterectomy. HT is not recommended as a treatment for postmenopausal osteoporosis while some osteoporosis drug treatments (ODT) such as bisphosphonates, denosumab, teriparatide, abaloparatide, romosozumab, and SERMs are recommended (*47*).

Studies have elucidated the mechanism by which estrogen protects bone (*48*). Estrogen is the major hormonal regulator in bone resorption and formation. It has a protective effect on bone by regulating osteocytes, osteoclasts, and osteoblasts. Receptors include ERα, osteoclast progenitors, and T-lymphocytes (*49*). OPG/

RANKL and the Sost/Dkk1/Wnt are important signaling pathways in bone metabolism (*48,50*).

Clinical trials have demonstrated the clear role of HT in the prevention of postmenopausal osteoporosis. The large WHI trials first indicated that a fixed composition of CEE and MPA may lead to a decreased risk of fractures. However, the WHI trials also reported an increased risk of breast cancer and cardiovascular and cerebrovascular events, which led to a sharp decline in the use of HT. After the decline in its use, parallel increased incidence of fractures was also reported (*6,51*). More recently, HT has proven to be effective in reducing the risk of hip, vertebral, and total fractures. However, this protection is attenuated when HT is discontinued or begun after the age of 60 (*52*). Individualized treatment should be used while considering different formulations, doses, and regimens of HT. Studies have indicated that low-dose and standard-dose sequential therapy with estrogen and progesterone are both safe and effective in increasing or maintaining bone mineral density (BMD) (*53,54*). Use of low-dose estrogens alone is not suggested for women with an intact uterus and ultra-low-dose transdermal estradiol is not recommended for women under the age of 60 (*55*). Moreover, low-dose HT and transdermal HT are considered to be safer than standard-dose oral HT because adverse events such as breast cancer or VTE are less likely while standard-dose HT displays more clinical efficacy in increasing the density of vertebrae and the femoral neck (*54,55*). Recent studies have also explored choosing HT, bone-specific treatment, or a combination of both. Estrogen therapy is a preferred choice compared to bone-specific treatment for women with premature menopause, which is related to increased fracture risk (*56*). However, significant differences in BMD were not found in postmenopausal women receiving HT alone or a combination of bone-specific treatment and HT (*57*).

Overall, HT has proven to have additional benefits of preventing fractures in postmenopausal women with VMS or GSM, and the combined use of HT and calcium plus vitamin D supplements has a synergistic effect on reducing hip fractures (*58*). Bone-specific treatment is needed for treatment of osteoporosis, and individual formulations should be used in light of the benefit-risk balance (*59*). Some of the main ingredients in medicinal plants, such as dioscin, have proven to be effective in animal models, but more clinical trials need to be conducted (*60*).

5. Controversies of HT

5.1. Cardiovascular disease (CVD) and coronary heart disease (CHD)

HT was found to prevent CVD and CHD in postmenopausal women in several observational trials and epidemiological studies such as the Nurses' Health Study (NHS) and PEPI trials (*61,62*). However, an increased risk of CVD was noted in a group receiving o-CEE+MPA in the HERS trial and the subsequent WHI trial (*63,64*). HT was not recommended for long-term prevention of cardiovascular disease, and a post hoc analysis of the WHI trial data as well as several clinical studies were initiated.

Postmenopausal women 10 years after menopause began and women ages 50-59 receiving HT have a lower risk of CHD, although these trends are not significant (*22*). The risks of CHD may possibly persist during CEE+MPA intervention and post-intervention, but cardiovascular disease mortality is not related to HT with CEE+MPA or CEE alone (*23,65*). Studies have also demonstrated that there is little increase in possible cardiovascular risks when initiating HT early during post-menopause, *i.e.*, within 10 years of onset (*8,66,67*).

Published guidelines emphasize that use HT for primary or secondary prevention of CVD is not evidence-based, and initiation before the age of 60 or within 10 years of the onset of menopause appears to reduce the risk of CVD (*68-70*). According to recent guidelines, HT is not recommended for prevention of CVD, and the risk of CVD should be assessed prior to initiation (*71*). The pooled cohort risk equation for atherosclerotic cardiovascular disease (ASCVD) from the ACC/AHA is recommended for individual risk assessment (*72,73*).

Recent studies have also assessed the effect of different formulations and routes of HT on CVD. Evidence shows that o-CEE appears to slow down accumulation of epicardial adipose tissue while transdermal 17 β-estradiol may increase the progression of coronary artery calcification related to epicardial and paracardial adipose tissue (PAT) (*74*). Moreover, o-CEE may also help reduce an increase in PAT as gauged by carotid intima-media thickness (CIMT) compared to transdermal 17 β-estradiol (*75*). o-CEE may be safer than transdermal 17 β-estradiol in women with cardiovascular risks. Nevertheless, further studies need to be conducted to explore the definite role of different forms, routes, and durations of HT in terms of cardiometabolic health.

5.2. Venous thromboembolism (VTE)

Observational and clinical studies including the WHI trials have noted increased VTE and stroke events in postmenopausal women receiving oral HT containing estrogen (*76*). Oral estrogen is associated with an increased risk of VTE whereas transdermal estrogen, micronized progesterone, and pregnane derivatives appear to be safe (*77*). Recent studies have indicated that transdermal estrogen alone or combined with micronized progesterone may possibly be the safest formulations for women at high risk of VTE, while oral HT is not recommended because of the relevant risk (*78,79*). Thus, the personal risk of VTE needs to be evaluated before making a decision, and transdermal

HT should be considered beforehand in postmenopausal women with a high risk of VTE. Additional trials need to be conducted to determine the effect of various routes and formulations of progestin and estrogen on the risk of VTE.

5.3. Alzheimer's disease (AD), Parkinson's disease (PD), and dementia

The WHI trials also mentioned that the use of o-CEE+MPA increased the risk of neurodegenerative diseases such as AD, PD, and dementia (*6,80*). The timing hypothesis and healthy cell bias hypotheses were proposed by scholars to explain those negative effects (*81,82*). The potential relationship between neurodegenerative diseases and HT is still hotly debated due to the incompatible results of different observational studies and randomized controlled trials (RCTs) (*83*).

A recent nationwide case-control study of 84,739 postmenopausal women in Finland indicated that systemic HT increased the risk of AD but vaginal estradiol did not affect that risk (*84*). However, the latest systematic reviews of various clinical studies have yielded disparate results. A meta-analysis of 25 case-control studies and cross-sectional studies suggested that estrogen replacement therapy reduced the incidence of AD and PD and that it had positive clinical effects, such as slowing their progression (*85*). Another meta-analysis of 14 observational and 11 controlled clinical trials indicated the HT and AD are not significantly related (*86*). A large systematic review of 28 case-controlled, cohort, and randomized-controlled studies found that HT was significantly associated with AD and all-cause dementia, but the review found no significant association between HT and PD. A non-linear time-response relationship between HT and AD has also been noted. In a subgroup analysis, estrogen-progestogen was related to a higher risk of AD compared to other formulations while progestogen and estrogen-progestogen may contribute to the development of PD. However, the relationship between HT and AD is restricted to the first 5 years of treatment and the association appears to reverse after that (*87*).

In summary, growing evidence supports the timing hypothesis in neurodegenerative diseases and suggests that HT be initiated early (*83,87*). The controversial results of different clinical studies and systematic reviews are possibly due to a small sample size or different HT formulations used in the studies analyzed. Therefore, studies with large sample sizes need to be conducted and formulations used in HT need to be clearly identified.

5.4. Breast cancer and endometrial cancer

The association between HT and breast cancer remains controversial. Based on the 5.2-year follow-up data from the WHI trial, an increased risk of breast cancer was noted in women with an intact uterus receiving o-CEE plus MPA, but a similar trend was not noted in women who underwent a hysterectomy and who received CEE alone (*6,80*). Moreover, the 10.7-year follow-up data from the WHI trial indicated a possible reduction in the group of taking CEE alone, in contrast to several observational studies suggesting CEE may increase the incidence of breast cancer, and especially in women with a lower BMI and receiving treatment for a longer duration (*88*). The latest follow-up data suggests that women who have undergone a hysterectomy and who are receiving CEE alone have a lower incidence of breast cancer and breast cancer-specific mortality, whereas women receiving CEE plus MPA have a higher incidence of breast cancer. Women who underwent a hysterectomy before the age of 60 and who received CEE seem to have a mortality benefit over the long term *(89*). Although taking CEE alone will not increase the incidence of breast cancer and HT will not increase the breast cancer mortality over time, HT should not be used for the sole purpose of reducing the risk of breast cancer risk because of complicated factors related to it (*24,25*). Estrogen-progestogen combinations are related to a higher risk of breast cancer compared to estrogen-only preparations, which indicates that the progestogen component is possibly the reason for the increased risk (*90,91*). The risk also increased with a longer duration of HT. HT for longer than 5 years was significantly related to an increased incidence of breast cancer in patients ages 50-69 (*91*). Recent data also indicated that HT containing micronized progesterone appears to be safe for the breasts with a markedly lower risk of breast cancer in comparison to HT with progestins (*92*). Although current thinking suggests that estrogen-progestogen combinations have a potential risk of promoting breast cancer, some scholars have contended that the practical risk is not as high as that for other endogenous factors or lifestyle factors (*93*). In addition, avoid use of HT in all patients is irrational because the all-cause mortality was not significantly affected and benefits may outweigh risks when initiated early (*24,25*).

The risk of endometrial cancer is also a concern for postmenopausal women receiving HT. An increased risk of endometrial cancer was reported in postmenopausal women receiving estrogen alone, tibolone, or sequential combined therapy (*94*). Since the balance between progestogen and estrogen is a key factor influencing the endometrium, the dose or duration of progestogen needs to be adjusted depending on the estrogen treatment. Continuous combined therapy at the right dose is safer than sequential administration in protecting the endometrium (*95*). Although studies have indicated that HT containing micronized progesterone is related to a lower risk of breast cancer, it may not be as efficient as therapies with synthetic progestins in terms of reducing the risk of endometrial cancer (*25,96*).

6. Complementary and alternative therapies

HT is recommended as the treatment of choice for relieving moderate-to-severe postmenopausal symptoms. However, many women still prioritize complementary and alternative therapies, and especially those worried about potential risks or with contraindications for HT. Alternative therapies such as herbal remedies, acupuncture, and mind-body therapies are also definite clinical options for postmenopausal women.

Herbal derivatives are commonly used for relief of mild-to-moderate postmenopausal symptoms. Black cohosh, Hypericum perforatum (St John's wort), and Dan quai have been found to be effective in relieving VMS (hot flashes, insomnia, and irritability). Schisandra chinensis is useful at relieving sweating and heart palpitations. Ginkgo is effective at treating attention disorders and ginseng can improve sexual function (*97*). Epimedium brevicornum Maxim can significantly increase BMD (*98*). In addition, individual RCTs have found that Chinese herbal medicines including compound capsules, granules, and oral herbal decoctions have benefits in alleviating hot flashes, depression, and menopausal symptoms (*99,100*). However, there is still insufficient data from large systematic reviews to conclude that Chinese herbal medicines are more effective than a placebo or HT (*101,102*).

Acupuncture has become more popular as a traditional Chinese therapy with few adverse reactions. Acupuncture and electroacupuncture have definite effects in treating postmenopausal symptoms such as insomnia but are ineffective in relieving hot flashes (*103-105*). Current evidence shows that manual acupuncture is safer than HT (106). For menopausal women with breast cancer, additional acupuncture significantly relieves relevant symptoms for at least 3 months. Acupuncture is an appropriate alternative to HT for women with breast cancer (*105*).

To date, although there is insufficient evidence to strongly support the effectiveness and safety of alternative therapies, but these therapies warrant exploration. Strictly regulated herbal supplements need to be used and standardized clinical studies need to be conducted to provide strong evidence.

7. Conclusion

HT has a tortuous and complex history with controversial risks and benefits. With further studies and analysis, the use of HT has gradually been standardized based on updated guidelines, and more preparations are available for patients to choose. Although many potential therapies are being developed, HT continues to be the most effective treatment available for postmenopausal women with VMS or GSM. It is not related to the risk of all-cause, cardiovascular, or breast cancer mortality although some formulations might increase the incidence of chronic diseases. For symptomatic postmenopausal women under the age of 60 without contradictions, early initiation of HT is safe and probably has a mortality benefit over the long term. Considering the long-term risks of HT, different types, doses, and durations of HT need to be devised for different individuals. The free app named Menopro and the pooled cohort risk equation for atherosclerotic cardiovascular disease (ASCVD) can be used to perform individual risk assessments. Depending on the willingness of patients and assessment of risks, non-hormone therapy and alternative therapy can also be choices. Chinese herbal medicine has benefits in alleviating hot flashes, depression, and menopausal symptoms. Acupuncture and electroacupuncture have definite efficacy in the treatment of postmenopausal symptoms with few adverse effects.

Current discussions of and issues with HT focus on the duration, the assessment of risks, and the optimal choice of regimens. Although there is insufficient data on how long HT can be safely used, clinicians are advised to reduce or stop therapy after menopausal symptoms have been relieved. The risks of HT mainly involve CVD, VTE, neurodegenerative diseases, breast cancer, and endometrial cancer. The relationship between HT and these chronic diseases remains controversial, and HT is not recommended to prevent them. Initiating HT within 10 years of menopause at the lowest effective dose is more likely to have maximal benefits and the lowest risks. Transdermal and vaginal HT may also have lower risks, but recent evidence suggests additional clinical benefits of oral HT formulations in relieving VMS and preventing osteoporosis. In terms of different formulations, o-CEE appears to help reduce the risk of CVD. Transdermal estrogen with or without micronized progesterone has a lower risk of VTE. HT containing micronized progesterone appears to be safe for the breasts while those containing synthetic progestin have stronger protective effects on the endometrium and a lower risk of endometrial cancer.

Therefore, more studies need to be conducted in the future to clarify the precise association between HT and related chronic diseases. The safety of specific durations and various preparations of HT needs to be examined in trials with a large sample size and specific formulations. Stronger evidence is needed to prove that Chinese herbal medicine and acupuncture have synergistic effects with HT.

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