

## Menopausal Hormone Therapy (MHT): The Current Thinking, the Benefits, and the Risks

Wattegama M<sup>1</sup>, Siyambalapitiya S<sup>1</sup>

<sup>1</sup>Endocrine and Diabetes clinic, North Colombo Teaching Hospital, Ragama

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 <https://orcid.org/0000-0001-9894-2028>

**Correspondence email:** [siyambalapitiyasp@hotmail.com](mailto:siyambalapitiyasp@hotmail.com)

At some point in life, all women undergo a transition from a reproductive period to a menopausal period. This usually begins in the mid-to-late 40s and lasts for about 4 years. It is retrospectively defined as the absence of menstrual cycles for 12 or more months and in the majority, it occurs at a median age of about 51 years<sup>(1)</sup>.

Menopause is characterized by a variety of symptoms such as vasomotor symptoms (hot flashes and night sweats), vaginal symptoms, urinary incontinence, sexual dysfunction, sleep problems, and mood changes. This can also be associated with joint pains and progressive weight gain. The years and decades following menopause are also when the rates of chronic disease start rising among women. Much of these rising rates can be attributed to ageing alone, but there has been some uncertainty whether menopause also contributes to some of these risks.

The symptoms and the chronic complications of menopause are related to estrogen deficiency that occurs due to the

gradual reduction of gonadal function with age. It was argued that most of the symptoms and the associated complications can be prevented or at least delayed by menopausal hormone therapy (MHT). In the backdrop of these arguments, hormone replacement therapy (HRT) was prescribed for postmenopausal women for decades. However, with the publication of women's health initiative study (WHI) results, there was a major concern regarding the safety of this form of therapy and most of the health authorities discouraged the use of HRT for postmenopausal females. However, with the use of newer natural estrogen and progesterone preparations, the emerging new evidence is much more encouraging, and researchers have started re-evaluating the use of HRT for postmenopausal women.

### DEFINITE BENEFITS

#### Vasomotor instability: hot flashes

Hot flashes are common and experienced by 60 to 80% of menopausal women. For some, it may be mild and for a few, it may be severe enough to interfere with their daily activities



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and with quality of life<sup>(2)</sup>. The Cochrane review has demonstrated clear benefit where a 75% (CI, 64-82%) reduction in the frequency and 87% reduction in the severity (RR, 0.13; CI, 0.06-0.27) of hot flashes with MHT<sup>(3)</sup>. Most of the available data on MHT and hot flashes are based upon “standard dose” estrogen (conjugated estrogen, 0.625mg; oral micronized 17B-estradiol, 1mg; transdermal 17B-estradiol, 50ug/d) preparations<sup>(3,4)</sup>.

### Genitourinary symptoms

A recent meta-analysis has shown that estrogen therapies are associated with a statistically significant reduction in all genitourinary outcome variables related to menopause. These beneficial effects are mostly related to the reduction of diurnal frequency (P = 0.0011), nocturnal frequency (P = 0.0371), urgency (P = 0.0425), number of incontinence episodes (P = 0.0002), first sensation to void (P = 0.0001) and bladder capacity (P = 0.0018). It further concluded that local administration may probably be the most beneficial route of administration to achieve these benefits<sup>(5)</sup>.

### Vaginal Atrophy

Estrogen therapy promotes vaginal cell growth and cell maturation, fosters recolonization with lactobacilli, enhances vaginal blood flow, decreases vaginal PH to premenopausal levels, improves vaginal thickness, and elasticity and improves sexual response<sup>(6-8)</sup>. Hormone replacement with creams, pessaries, tablets, and oestradiol vaginal rings appeared to be equally effective in relieving the symptoms of vaginal atrophy<sup>(8)</sup>.

### Osteoporosis

The benefit of MHT on postmenopausal osteoporosis is well documented. A meta-analysis that compared MHT intervention

with placebo has demonstrated a 5.4%, 3.0% and 2.5% higher bone mineral density (BMD) after 1 year of treatment in the lumbar spine, forearm, and femoral neck, respectively. After 2 years of treatment, the percentage change in favour of HRT increased by about another 1.5% at all sites<sup>(9)</sup>. In addition to the BMD improvement, the data showed a non-significant trend toward a reduced incidence in vertebral, and non-vertebral fractures<sup>(9)</sup>. Women’s Health Initiative study (WHI) has shown that the conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA) therapy can achieve a significant reduction of fracture risk: hip, vertebral and other osteoporotic fractures except those of ribs, chest/sternum, skull/face, fingers, toes, and cervical vertebrae by 24% (RR, 0.76; CI 0.69-0.83) and hip fractures by 33% (CI, 0.47-0.96). CEE alone arm also demonstrated that all the fractures were reduced by 29% (RR, 0.71; CI, 0.45-0.94) and hip fractures by 29% (RR, 0.71; CI, 0.64-0.80) by MHT<sup>(10,11)</sup>. It has also shown that the effects of CEE plus MPA on hip fractures were only apparent in women older than age 70 years or more than 20 years after menopause.

HRT in combination with alendronate increase the bone mineral density than either agent alone<sup>(12)</sup>. However, an accelerated bone loss is seen after withdrawal of estrogen therapy, but not after the withdrawal of alendronate or combination therapy<sup>(13)</sup>.

### Diabetes Mellitus

The available evidence suggests a beneficial effect of MHT on pancreatic B cells, skeletal muscle, adipose tissue, and liver in postmenopausal women. This is associated with decreased abdominal fat, decreased fasting glucose and insulin, improved glucose effectiveness and insulin sensitivity, and reduced incidence of diabetes<sup>(14,15)</sup>.

The Heart and Estrogen/Progestin Interventions Study was the first large, randomized, placebo-controlled trial to study the effect of MHT on diabetes incidence in post-menopausal women. This study demonstrated a marked decrease in fasting glucose and insulin levels, suggesting improved insulin sensitivity after 3 years of MHT<sup>(16)</sup>. The heart and estrogen/progestin replacement study (HERS), which evaluated the incidence of diabetes among postmenopausal women with coronary artery disease assigned to MHT or placebo, showed a 35% reduction in the MHT group after four years<sup>(17)</sup>. The most recent WHI data concerning this topic showed a lower rate of self-reported, treated type 2 diabetes mellitus in women randomized to MHT (277 women; 0.61% annual incidence) in comparison with the placebo group (324 women; 0.75% annual incidence)<sup>(18)</sup>. However, the protective effect on diabetes incidence was slightly attenuated in women who used oestrogen without progestogen<sup>(19)</sup>.

However, diabetes prevention was not examined as a primary outcome in any of these RCTs, and therefore, MHT is not offered as an appropriate treatment option for the prevention of diabetes in women.

## DEFINITE RISKS

### Endometrial Cancer

It has been well established that unopposed oestrogen exposure can increase the risk of endometrial hyperplasia. A meta-analysis has demonstrated that the endometrial cancer risk can increase by 2-fold, which increases substantially with a longer duration of unopposed oestrogen use. It has also been suggested that the risk persisted after cessation of oestrogen, with a risk as high as 1.9 even after 12 years after cessation<sup>(20)</sup>.

The Postmenopausal Estrogen/Progestin Interventions Trial (PEPI), a 3-year multicenter, randomized, double-masked, placebo-controlled trial, showed that a daily administration of 0.625mg CEE enhance the development of endometrial hyperplasia and combining CEE with cyclic or continuous MPA or cyclic Medroxyprogesterone (MP) to be protective<sup>(21)</sup>.

### Venous Thromboembolism (VTE)

Data from the WHI study on the effect of combined CEE plus MPA on venous thromboembolism demonstrated a 2-fold higher rate of venous thromboembolism compared to placebo. (HR 2.06; CI, 1.57-2.70). In contrast, with the use of CEE alone, the risk was only increased by 1.3-fold (HR 1.32, CI, 0.99-1.75). According to these results, the estimated excess number of venous thromboembolism events in 10000 women taking CEE+MPA for 1 year is 18, whereas, in women taking CEE alone, it is 8<sup>(22)</sup>.

Oral MHT increases clotting protein production via a first-pass hepatic effect, which is circumvented by the transdermal route. Therefore, the route of administration of oestrogen should impact the thrombosis risk. Bases on case-control studies, the adjusted RRs for VTE with oral or transdermal oestrogen compared with non-users are 4.2 (CI, 1.5 -11.6) and 0.9 (CI, 0.4-2.1), respectively. However, these data need to be confirmed with RCTs<sup>(23)</sup>.

### Stroke

In the WHI trials with the community-dwelling women aged 50 -79 years, it was demonstrated that conjugated oestrogens with or without MPA increased the risk of ischemic strokes (RR, 1.31; CI, 1.02- 1.68

with MPA; RR, 1.37; CI, 1.09 – 1.73 without MPA) <sup>(24)</sup>. A meta-analysis of 28 trials suggested a 29% increase (RR, 1.29; CI 1.13-1.47) in ischaemic strokes due to hormone use. It also showed that the risk was not modified by hormone preparation (E alone or E+P) or type of estrogen (conjugated oestrogen vs estradiol) <sup>(25)</sup>.

## CARDIOVASCULAR DISEASE (CVD) CONUNDRUM

Oestrogen in females is thought to be cardioprotective and results in a lower incidence of cardiovascular disease compared to males. However, after menopause, with the reduction of estrogen levels, females tend to lose this cardioprotective effect and the cardiovascular disease incidence rises to levels equivalent to that seen among males.

Many studies have demonstrated that oestrogen therapy in postmenopausal women leads to favourable changes in cholesterol levels by lowering of serum total cholesterol and low-density lipoprotein (LDL) cholesterol, increases serum high-density lipoprotein (HDL) cholesterol and serum Lp(a) lipoproteins<sup>(26)</sup>. Moreover, continuous estrogen therapy can increase fibrinolysis by decreasing plasma fibrinogen concentrations and by lowering antifibrinolytic protein plasminogen-inhibitor type 1. Furthermore, it has the ability to regulate the vasomotor tone. Furthermore, it has the ability to regulate the vasomotor tone through various mechanisms <sup>(18)</sup>. However, oestrogen therapy may also have potentially detrimental effects on cardiovascular disease by increasing biomarkers such as triglyceride levels, coagulatory proteins like factor VII, prothrombin fragments 1, 2, and fibrinopeptide <sup>(27)</sup>. According to a large group of observational studies, it has been shown

that, in aggregate, a significant (35%) reduction in CVD events in postmenopausal women who chose to take menopausal hormone therapy <sup>(28)</sup>. In contrast, randomized controlled trials have demonstrated conflicting results. In Women's Health Initiative studies (WHI), the largest, randomized controlled primary prevention trial enrolled 27347 healthy postmenopausal women in order to assess the primary outcome of coronary artery disease. It comprised of two parallel trials of CEE + MPA (EPT trial) and CEE (E alone trial). In EPT 16 608 women were randomized to oral CEE (0.625mg/day) plus MPA (2.5mg/day) or placebo with a plan of 8-year follow-up. After a median of 5.6 years of follow-up, the EPT trial was prematurely terminated due to an increase in the rate of invasive breast cancer. After further evaluation, the overall cohort showed an increased risk of developing CHD by 18% during the first year of the trial <sup>(22)</sup>. However, the most recent secondary analysis done with WHI study data did not show a statistically significant association with CHD <sup>(20)</sup>.

Due to this discrepancy between the results of observational studies and clinical trials, the “timing hypothesis” was conceived. Accordingly, the postmenopausal women at a younger age and closer to menopause who started on menopausal hormone therapy (MHT) had a lower risk of coronary heart disease compared to the women who started taking MHT at an older age and/or more than 10 years after menopause. For example, in the subgroup analysis of the WHI study, it was shown that the estimated absolute risk for CHD for women who were started on MHT within 10 years of menopause was lower compared to placebo (-6 per 10 000 person-years), However, absolute CHD risk for women where the MHT was started 10 to

19 years after the menopause was higher compared to placebo (4 per 10 000 person-years) and even higher for women where MHT was started 20 or more years after the menopause (17 per 10 000 person-years) <sup>(29)</sup>.

Vascular Effects of Early Versus Late Postmenopausal Treatment with Estradiol (ELITE) study was one of the studies that were designed to further evaluate the above hypothesis. ELITE was a single-centre, randomized, double-blind, placebo-controlled trial stratifying 643 healthy postmenopausal women according to time since menopause less than 6 years (early postmenopause) or more than 10 years (late postmenopause). Recruited subjects were randomly assigned to receive either oral 17 $\beta$ -oestradiol with progesterone vaginal gel administered sequentially or placebo. After a median of 5 years, it was concluded that oral estradiol was associated with less progression of subclinical atherosclerosis (measured as carotid intima-medial thickness) than was placebo in the early postmenopausal group but not in the late postmenopausal group <sup>(30)</sup>. Preliminary results of Kronos Early Estrogen Prevention Study (KEEPS), which evaluated 2 different types of oestrogen (low dose oral conjugated oestrogen 0.45mg/day) and a 50ug transdermal oestradiol patch along with cyclic progesterone over placebo, also showed very little progression of atherosclerosis and coronary artery calcification when estrogen was started for young women in early menopause compared to placebo <sup>(31)</sup>. However, the secondary prevention trials such as Heart and Estrogen/Progestin Replacement Study (HERS), Estrogen Replacement and Atherosclerosis Trial, and Papworth Hormone- Replacement Therapy Atherosclerosis Study showed no cardiovascular benefit with hormone

Replacement therapy <sup>(32-34)</sup>.

All this evidence suggest that postmenopausal HRT does not increase cardiovascular disease risk and may be having a marginal cardiovascular benefit when it is initiated in early menopause. Although the menopausal hormone therapy is not recommended for CHD risk reduction in current guidelines, its use for other indications should not be hindered by fear of increasing CHD in younger, newly menopausal women.

## CANCERS

### Breast cancer

WHI was the first clinical trial to confirm that combined oestrogen and progestin do increase the risk of incident breast cancer. It reported a statistically significant (26%) increase in invasive breast cancer rates in the oestrogen plus progestin group compared to placebo. In contrast, it also showed no significant increase in the risk of breast cancer among women using oestrogen alone for an average of 7 years (RR, 0.80; CI, 0.62-1.04) compared to placebo <sup>(22)</sup>. Similarly, pooled data involving four RCTs, Women's Health Initiative (WHI), Estrogen in the Prevention of Atherosclerosis Trial (EPAT), Women's Estrogen for Stroke Trial (WEST), Estrogen for Prevention of Reinfarction Trial (ESPRIT) reported a RR of 0.79 (CI, 0.61 – 1.01) with estrogen therapy <sup>(26)</sup>. The risk of breast cancer was related to the duration of HRT and becomes more significant after 5 years of use <sup>(22, 35-38)</sup>. However, in a recently published meta-analysis, it was shown that 5 years of MHT, starting at the age of 50 years, would increase breast cancer incidence at the age of 50-69 years by about one in every 50 for oestrogen and daily progestogen; one in every 70 for oestrogen plus intermittent progestogen; and one in every 200 for

oestrogen-only users. The corresponding excess risk for 10 years of MHT usage would be about twice as great <sup>(39)</sup>.

It is well known that increased mammographic density is associated with an increased risk of breast cancer <sup>(40)</sup>. It is reported that the relative risk of increased density with oestradiol-only treatment is 1.5, and the relative risk for oestradiol combined with cyclical progestins, and continuous progestins is 3.6 and 12.4, respectively <sup>(41)</sup>. Furthermore, it has been shown that women taking testosterone-like progestins also have similar mammographic density changes. It increases by 52% for women using the combined/continuous progestin treatment, 13% in women using the cyclic regimen and 18% for oestrogen-only users <sup>(42)</sup>. There are few studies to suggest that Testosterone derived progestins could be positively associated with breast cancer <sup>(43-45)</sup>. However, these findings need further investigation.

### Ovarian cancer

Scientific evidence on MHT and the risk of ovarian cancer is very limited. However, the available observational studies have shown a positive association between ovarian cancer and menopausal hormone therapy. A Danish study conducted from 1995 to 2005 demonstrated that the current users of hormone therapy had a higher incidence rate for all ovarian cancers and epithelial ovarian cancer (1.38 and 1.44 respectively) <sup>(46)</sup>. The risk started to decline after cessation of therapy and the risk was no longer statistically significant by 2 years after discontinuation. There is a randomized clinical trial that has examined the effect of MHT on ovarian cancer. In this study, 16608 study participants were randomized to receive conjugated equine estrogen 625ug with medroxyprogesterone 2.5mg or placebo and

followed up for an average of 5.6 years. The incidence of 20 patients with invasive ovarian cancer was higher among individuals receiving HRT compared to placebo (20 vs 12 per 100000 person-years, HR, 1.58, 95% CI, 0.77-3.24). However, this difference showed no statistical significance <sup>(47)</sup>. Available evidence suggests that postmenopausal HRT has minimal effects on ovaries. However, further studies would be needed to supplement these findings.

### Colon cancer

WHI results showed a significant reduction in colorectal cancer in the combined CEE + MPA arm compared to placebo. The absolute risk reduction was 6 per 10000 person-years. The invasive colorectal cancers were comparable in histology and grade to those of the placebo group <sup>(48)</sup>. In oestrogen alone arm, there were no reductions in the risk of colonic cancer. Recent studies including a meta-analysis have further confirmed the beneficial effect of postmenopausal HRT on colon cancers at least during the first few years of treatment <sup>(49,51)</sup>.

### COGNITION AND DEMENTIA

Natural ageing is generally associated with significant memory loss. In the WHI memory study (WHIMS), the women, 65 to 79 years of age who were randomized to receive the active intervention with CEE were compared with placebo. Women with a uterus were randomized to CEE plus MPA versus placebo. Mean scores on a test of global cognitive ability were very slightly lower among the women in the hormone-treated groups than in the placebo, after an approximately 4–5-year follow-up <sup>(52)</sup>.

In the same study, dementia was identified in 108 women. In half of them, the diagnosis was Alzheimer's disease. Dementia incidence

was greater in hormone groups compared with placebo (RR 2.05; CI, 1.21 – 3.48, for women with a uterus; and RR, 1.49; CI, 0.83 – 2.60, for women without a uterus). However, another meta-analysis done with observational studies implies a reduction of Alzheimer's disease of about one-third with hormone replacement<sup>(53)</sup>.

### MHT AND TOTAL MORTALITY

In the WHI, the relative risk for all-cause mortality was 1.04(CI, 0.88-1.22) in the CEE-alone and it was 1.00(CI, 0.83 – 1.19) in the CEE plus MPA group. Pooled data analyses of both groups showed a significant reduction in mortality (RR, 0.70; CI, 0.51 – 0.96) among women aged 50 – 59 years (25). In another meta-analysis of 30 randomized trials, in which participants had a mean age below 60 years or within 10 years of menopause demonstrated that MHT was associated with a 40% reduction in mortality<sup>(54)</sup>.

### CLINICAL IMPLICATIONS

MHT is a safe and effective option for postmenopausal symptoms for women with a low risk for development of complications, < 60 years and within 10 years of menopause onset. Local vaginal preparations are preferred for genito-urinary symptoms and do not require progestogens.

MHT improves bone mineral density in early postmenopausal women and also has the ability to reduce the fracture risk among postmenopausal women. However, considering the risk and the benefit ratio, it is not recommended as a therapy for osteoporosis.

Combined MHT has a favourable effect on glucose homeostasis. However, MHT does not prevent CVD and it is not recommended

to be prescribed for this purpose. Alternative studies have not demonstrated mortality difference in women who do and do not take MHT for symptomatic purposes. Therefore, concerns regarding mortality risks should not withhold prescribing MHT to appropriately selected women with bothersome VMS.

The Standard dose of MHT may increase the risk of stroke by about one-third in health postmenopausal women and it increases the risk of VTE approximately 2-fold. Therefore, it is important to be cautious in prescribing for patients with a risk of thrombosis and strokes.

Combined oestrogen and progesterone therapy increases the risk of invasive breast cancer risk, which may occur 3 – 5 years after initiation and rises progressively beyond that time. However, the use of estrogen alone for less than 5 years may reduce the risk of breast cancer even in patients starting therapy many years after menopause.

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