Menopausal hormone therapy (MHT) is surrounded by controversies after the revolutionary reports from Women’s Health Initiative (WHI) trial in 2002. The universal hormone therapy (HT) policy used before WHI became obsolete after 2002. Majority of women who were already taking MHT discontinued the therapy worldwide. Even practitioners stopped prescribing MHT. Several studies have suggested a “timing hypothesis” or a “window-of-opportunity” for the initiation of MHT, which is early after menopause. This means that MHT is best given immediately postmenopause for a short duration of time. MHT started many years is best given immediately postmenopause for a short duration of time. MHT started many years after menopause and given for long duration following menopause has more side effects. The use of MHT decreased drastically after the results of these two studies were published. However, due to Danish Osteoporosis Prevention Study and the Kronos Early Estrogen Prevention Study, interest has been generated in MHT due to beneficial results of MHT. Excellent symptom relief can be provided by MHT for healthy women who experience menopausal symptoms. MHT poses a low risk in these healthy women with no comorbidities. With regard to cardiovascular diseases and osteoporosis, not giving MHT in symptomatic women may pose a risk. When MHT is initiated in elderly women and in those with comorbidities, it may be associated with increased risk. Prior discussion with patient about HT is a must before starting MHT. Personalized discussion with patient about symptoms, treatment goals, analysis of age, time since menopause, and consideration of comorbidities influences decision-making about starting MHT. We recommend further studies on MHT for better understanding of risk versus benefit of MHT.

**Key words:** Menopausal hormone therapy, hormone replacement therapy, menopause

**INTRODUCTION**

Menopausal hormone therapy (MHT) is surrounded by controversies after the revolutionary reports from Women’s Health Initiative (WHI) trial in 2002. The universal hormone therapy (HT) policy used before WHI became obsolete after 2002. Majority of women who were already taking MHT discontinued the therapy worldwide. Even practitioners stopped prescribing MHT.

Average age of menopause is around 51 years, but in Indian women, it occurs much earlier, that is, at around 48 years of age. If average life expectancy of women is considered 80 years, they have to face the estrogen deficiency for almost 30–35 years. Postmenopausal women who seek help for perimenopausal symptoms will need HT. Hence, it is important to understand the pros and cons of MHT.

**EFFECT OF ENDOGENOUS ESTROGEN**

Due to decline in levels of endogenous estrogen, the risk of vasomotor symptoms (VMSs), osteoporosis, cardiovascular diseases (CVDs), and dementia increases. Endogenous estrogen has anti-atherosclerotic and anti-inflammatory properties. Apart from its role in reproductive functions, estrogen decreases the process of plaque formation and modifies lipid profile (high HDL and low LDL) preventing cardiovascular events. Estrogen has beneficial effects on the vascular endothelium and smooth muscle cells which cause vasodilatation preventing cardiovascular risks.

**WHAT IS THE EFFECT OF EXOGENOUS MHT?**

Logically, the effect of exogenous estrogens should be the same, but evidence does not support this logic. According to the Nurses’ Health Study which was conducted in 1976, it was concluded that cardiac risk increased after surgical menopause whereas natural menopause did not increase cardiac risk.

Because the risk of heart disease in women increased after menopause, it was hypothesized that exogenous hormones
MHT started many years after menopause and given for long duration following menopause has more side effects. The use of MHT decreased drastically after the results of these two studies were published.

However, due to Danish Osteoporosis Prevention Study (DOPS) and the Kronos Early Estrogen Prevention Study (KEEPS), interest has been generated in MHT due to beneficial results of MHT.[3]

The DOPS was started in 1990 and continued for a duration of 20 years. It was a partly randomized study conducted on 2016 normal, healthy postmenopausal women. This study demonstrated a beneficial effect of MHT on the reduction of coronary artery disease. The study concluded that hormonal therapy initiated early after menopause (on an average, 7 months postmenopause) significantly reduced heart failure, myocardial infarction, and mortality. No increased risk of thromboembolic events, stroke, or cancer was noted.

The KEEPS was a year multicentric, double-blinded, randomized, placebo-controlled trial. A total of 728 women with a mean age of 50 years were enrolled within 6–36 months of menopause. The progression of carotid intima media thickness and atherosclerosis was assessed using the coronary artery calcium score. They concluded that the use of MHT did not lead to progression of carotid intima media thickness or progression of atherosclerosis. The study proves that when the initiation of MHT is done in the early postmenopause, there is a window of time which has a net beneficial effect. Therefore, duration and timing of hormonal therapy determine the cardiovascular risk-lowering effects of menopause HT. To maximize the beneficial effects of hormonal therapy, it has been postulated that considering the “window of opportunity” for reducing CHD and overall mortality in women, it is advisable to initiate hormonal therapy within 6 months of menopause and/or before 60 years of age and for a short duration of time.

CURRENT RECOMMENDATIONS

MHT is beneficial for VMS, osteoporosis, colonic cancer, and probably new onset of diabetes.

Comorbidities such as CVD, stroke, dementia, breast cancer, and venous thromboembolism increase the risks of MHT.

The benefit–risk profile of MHT is determined by variables such as age and years since menopause at which MHT is started. The benefits of MHT generally outweigh the risks for symptomatic menopausal women who are under 60 years of age or within 10 years of menopause. The progression of atherosclerotic disease can be reduced by initiating systemic MHT early after menopause, thereby reducing the mortality and morbidity risk of CVDs. MHT provides protection against cognitive decline during this window of opportunity. The benefit–risk balance of MHT is less favorable in older women and women more than 10 years past menopause, particularly with regard to cardiovascular risk and cognitive impairment. MHT ameliorates the risk of CVD, osteoporosis, and cognitive decline during this window of opportunity.
decline, especially for women entering menopause prematurely (<40 years). Due to the lack of first-pass hepatic metabolism, non-oral administration of estrogen offers advantages, which, in turn, avoids the increased hepatic synthesis of clotting proteins, triglycerides, C-reactive protein, and sex hormone-binding globulin. As the risk of breast cancer increases after 3–5 years of use of hormonal therapy, it is advisable to limit the period of use of combined MHT to <5 years. As estrogen alone does not appear to increase the risk of breast cancer, there is no clarity to limit its use in these women. When non-hormonal management approaches fail, MHT for the treatment of bothersome menopausal symptoms poses low risk and is an acceptable option for women under the age of 60 years, or within 10 years of onset of natural menopause.

Approximately 75% of perimenopausal or early postmenopausal women are affected by vasomotor menopausal symptoms. The US Food and Drug Administration (FDA) has approved HT for the primary indication of treating moderately severe-to-severe menopausal symptoms. In the past, osteoporosis was one of the main indications for the use of MHT. However due to the risks as documented by the WHI and other clinical trials, MHT is currently a second line of treatment for osteoporosis. Another FDA-approved indication for MHT is treatment of vulvovaginal atrophy which is reported in 50% of menopausal women. Localized estrogen therapy (topical application) is preferred for this indication. Substantial proportion of women during the menopausal transition is affected by non-vasomotor menopausal symptoms such as mood instability, sleep disturbance, sexual function changes, and difficulty with concentration. These effects have not been extensively studied in clinical trials and are not considered primary indications for starting MHT. MHT may be offered when non-hormonal approaches fail to relieve non VMS, and women report a poor quality of life.

General guidelines for use of MHT are not applicable to women with premature menopause (<40 years) who constitute a unique group. In these women, MHT uses until the average age of natural menopause appears to be important for reducing the deleterious health consequences of early estrogen deprivation (in the absence of contraindications). The deleterious effects of estrogen deprivation include an increased risk of CHD, cognitive decline, osteoporosis, and premature death.

For women with a history of pre-existing illness such as coronary artery disease, deep venous thromboembolism, stroke, or breast cancer, the benefit–risk ratio is less favorable. MHT is ideally avoided in these women.

The 2012 Cochrane Collaboration systematic review assessed the clinical effects of using MHT for 1 year or more.[4] Twenty-three randomized double-blind studies were included involving 42,830 women aged 26–91 years. It concluded that there was no indication to use HT for primary or secondary prevention of CVD or dementia or for the protection of cognitive function.

The American College of Obstetricians and Gynecologists (ACOG) recommends that clinicians should encourage heart-healthy lifestyles and other strategies to reduce cardiovascular risk in menopausal women. Persistent VMS in some women aged 65 years and above may require continuation MHT. Hence, it is not recommended to discontinue MHT routinely at 65 years of age by ACOG.

Natural progesterone is known to have vasorelaxation effects and has been shown to have a neutral slightly salutary effect on blood pressure unlike synthetic medroxyprogesterone acetate which is vasoconstrictive.

The USPSTF recommends against the use of estrogen alone (in women who have undergone hysterectomy) and combined estrogen and progesterin (in women with uterus in situ) for the primary prevention of chronic conditions in postmenopausal women (D recommendation).[5]

Like most clinical guidelines, the ACOG and the American Heart Association recommend against the use of HT for the primary or secondary prevention of CHD. It is not recommend to use HT for primary prevention of any chronic diseases as per guidelines of the Canadian Task Force on Preventive Health Care and the American Academy of Family Physicians.

The American Association of Clinical Endocrinologists recommends that age, time from menopause, and cardiovascular risk be considered when using HT. HT is approved by FDA in women at increased risk of osteoporosis and fractures.

The ACOG mentions that early versus late initiation of HT with respect to onset of menopause determines the effect of HT on risk of CVD.

The North American Menopause Society states that symptomatic women should receive MHT. They further state that MHT prevents fractures and that treatment should be individualized after balancing the potential health risk ratio. The Endocrine Society focuses primarily on the use of HT for the treatment of symptoms of menopause.[6]

Revised Global Consensus Statement on MHT 2016 gives detailed update on benefit–risk analysis and general principles guiding prescription of MHT given in menopause.[7]

If used judiciously for menopausal women in their perimenopausal transition years and postmenopause, MHT is an effective therapy.

Treatment goals, patient preference, and safety issues determine the type and route of administration of MHT. MHT should be individualized after considering patient factors and preferences. The dosage of MHT should be titrated to the lowest appropriate and most effective dose. Treatment goals of the individual determine the duration of treatment. The benefit/risk profile of the patient needs to be individually reassessed annually. Some women may require longer duration of MHT for treatment of VMS as per new data.

A personalized discussion between the patient and the physician determines the decision of whether or not to initiate or continue MHT. Important factors in the decision-making are the age of the woman, the age at the onset of menopause,
and an assessment of overall cardiovascular health and other preexistent comorbidities. Hormonal therapy is not advised in the setting of pre-existing coronary disease, cerebrovascular disease, or a history of thromboembolic disease as it may be harmful. Decision-making process is influenced by several factors such as the presence of menopausal symptoms, quality of life as desired by patient, and the patient preferences. Women need to be aware of the non-hormonal therapies available for both management of VMS associated with perimenopause and early menopause, and for reducing cardiovascular risk, including maintaining a healthy lifestyle.

In the current scenario, it is proven that MHT should not be used for the primary or secondary prevention of CHD. MHT has several cardiovascular benefits when it is started during the opportunity window (immediately or within 10 years of menopause). Further research is recommended to study the superiority of natural progesterone versus synthetic progestins in MHT. Women should adopt a healthy lifestyle to decrease cardiovascular complications in postmenopausal period. Alternative strategies can also be tried to treat postmenopausal symptoms. The most important result of prescribing MHT is the improvement of quality of life in these women.

CONCLUSION

Before starting MHT, the two important factors that we need to consider are age of the patient and time since menopause. One must calculate the benefit–risk ratio of MHT after careful consideration of these factors. In cases of premature or early menopause, estrogen therapy may be administered until the average age of natural menopause is reached. Excellent symptom relief can be provided by MHT for healthy women who experience menopausal symptoms. MHT poses a low risk in these healthy women with no comorbidities. With regard to CVDs and osteoporosis, not giving MHT in symptomatic women may pose a risk. When MHT is initiated in elderly women and in those with comorbidities, it may be associated with increased risk. Prior discussion with patient about HT is a must before starting MHT. Personalized discussion with patient about symptoms, treatment goals, analysis of age, time since menopause, and consideration of comorbidities influences decision-making about starting MHT. We recommend further studies on MHT for better understanding of risk versus benefit of MHT.

REFERENCES

1. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1998;280:605-13.
2. Writing Group for the Women's Health Initiative. Investigators risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the women's health initiative randomized controlled trial. JAMA 2002;288:321-33.
3. Mosekilde L, Hermann AP, Beck-Nielsen H, Charles P, Nielsen SP, Sørensen OH. The Danish Osteoporosis Prevention Study (DOPS): Project design and inclusion of 2000 normal perimenopausal women. Maturitas 1999;31:207-19.
4. Farquhar C, Marjoribanks J, Lethaby A, Roberts H. Long term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database Syst Rev 2009;15:CD004143.
5. Final USPSTF Recommendations on Prevention by MHT. Available from: https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/menopausal-hormone-therapy-preventive-medication. [Last accessed on 2020 Jul 07].
6. Pinkerton JA, Aguirre FS, Blake J, Cosman F, Hodis H, Hofstetter S, et al. The 2017 hormone therapy position statement of the North American Menopause Society. Menopause 2017;24:728-53.
7. de Villiers TJ, Hall JE, Pinkerton JV, Pérez SC, Rees M, Yang C, et al. Revised global consensus statement on menopausal hormone therapy. Climacteric 2016;19:313-5.
8. Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA 2007;297:1465-77.