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Menopausal Hormone Therapy: Current Trends

ABSTRACT

Menopausal hormone therapy (MHT) is surrounded by controversies after the path breaking reports from Women's Health Initiative (WHI) trial were published in 2002. The universal hormone therapy policy used before WHI became obsolete after 2002. Majority of women who were already taking MHT discontinued the therapy all over the world. Even practitioners stopped prescribing MHT. After a few years, a "timing hypothesis" emerged and a "window-of-opportunity" was conceptualized supported by newer safety data for the initiation of menopausal hormone therapy. This means that MHT is best given immediate postmenopausal stage for a short duration of time. MHT started many years after the onset of menopause and continued for long duration following menopause reported more side effects hence use of MHT decreased drastically. However due to beneficial results, Danish Osteoporosis Prevention Study (DOPS) and the Kronos Early Estrogen Prevention Study (KEEPS), interest has been regenerated in 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. When MHT is initiated in elderly women and in those with comorbidities, it may be associated with increased risk. Prior discussion with patient about hormone therapy 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 menopausal hormone therapy for better understanding of risk versus benefit of MHT.

Key words: Hormone replacement therapy, Menopausal hormone therapy, Menopause

INTRODUCTION

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. It was being prescribed universally to all women irrespective of their symptoms, to replenish the deficient state.

Menopausal hormone therapy (MHT) became surrounded by controversies after the revolutionary reports from Women's Health Initiative (WHI) trial which were published in 2002. The universal hormone therapy policy used before WHI became obsolete after 2002. Majority of women who were already taking MHT discontinued the therapy worldwide. Because of the global wave of fear of increased associated risks, many practitioners stopped prescribing MHT.

Postmenopausal women who seek help for perimenopausal symptoms, however, will need hormone therapy for symptom relief. Hence, it is important to understand the pros and cons of MHT to offer them a choice to help them make a balanced decision regarding use of MHT.

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EFFECT OF ENDOGENOUS ESTROGEN

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 causes vasodilatation preventing cardiovascular risks. Due to decline in levels of endogenous estrogen after menopause, the risk of vasomotor symptoms, osteoporosis, cardiovascular diseases, and dementia increases.

WHAT IS THE EFFECT OF EXOGENOUS MHT?

Logically, the effect of exogenous estrogens should help prevent or treat the disease states caused by estrogen deficiency, but evidence does not support this logic.

In 1998, the HERS study (Heart and Estrogen/Progestin Replacement Study) reported their results of randomized, blinded, placebo-controlled secondary prevention trial which was done in 2763 postmenopausal women (average age 66.7 years old) with established coronary heart disease. There was no reduction in overall risk of myocardial infarction, coronary heart disease (CHD), other cardiovascular outcomes, or death during follow-up (average follow-up of 4.1 years). Thus, it was proved that MHT should not be given for the sole purpose of secondary prevention of CHD.

Because the risk of heart disease in women increased after menopause, it was hypothesized that exogenous hormones (estrogen with or without progesterone) would have a protective role and would reduce the risk of heart disease. Similar to HERS study, Women's Health Initiative (WHI) trial also did not demonstrate beneficial effects of the use of menopausal hormone therapy for primary or secondary prevention of coronary heart disease.[1,2] A total of 27,347 postmenopausal women, aged between 50 and 79 years, were included in the Women's Health Initiative (WHI) trial. It was a prospective, randomized controlled clinical trial. Women were subdivided in two arms estrogen plus progesterone (E+P arm) (5.6 years) and estrogen alone arm (E arm) (7.2 years). Women were followed up for an extended period of 13 years (with no treatment).

The risk of CHD increased by 18% in the E+P arm. The risk of CHD did not increase in the estrogen alone arm. The risk of breast cancer increased to 24% in the E+P arm. Estrogen alone decreased breast cancer risk. The risk of stroke and thromboembolism increased in both arms. The risk of hip fracture decreased in both arms by 33%. The risk of colorectal cancer decreased in E+P arm. No effect on colorectal cancer was observed in estrogen alone arm. The global index of combined illness and death increased by 12% in the E+P arm, no effect was observed in estrogen alone arm. The risk of gallbladder disease and urinary incontinence increased in both arms. Thus, the trial concluded that MHT cannot be recommended for long-term prevention of chronic diseases. MHT is certainly useful to treat symptoms of menopause such as hot flushes and night sweats but is not useful for primary prevention of comorbidities.

IS MHT HARMFUL? TIMING HYPOTHESIS

Several studies have reported that MHT when given immediately postmenopause for a short duration of time, the beneficial effects can be observed. MHT started many years after menopause and given for long duration following menopause has shown more adverse effects. This is the "timing hypothesis" or a "window-of-opportunity" for the initiation of menopausal hormone therapy.

Danish Osteoporosis Prevention Study (DOPS)[3] and the Kronos Early Estrogen Prevention Study (KEEPS)[4] results have regenerated interest in MHT due to documentation of beneficial results of MHT.

The Danish Osteoporosis Prevention Study (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 menopausal hormone therapy 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 Kronos Early Estrogen Prevention Study (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 menopausal hormone therapy 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 hormone therapy. To maximize the beneficial effects of hormonal therapy, it has been postulated that considering the "window-of-opportunity" for reducing coronary heart disease and overall mortality in women, it is advisable to initiate hormonal therapy within 6 years of menopause and/or before 60 years of age, and for a short duration of time. ELITE study[5] has also supported the timing hypothesis.

CURRENT RECOMMENDATIONS

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

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 cardiovascular diseases. 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 cardiovascular disease, osteoporosis, and cognitive decline, especially for women entering menopause prematurely (<40 years).

Comorbidities such as cardiovascular disease, stroke, dementia, breast cancer, and venous thromboembolism increase the risks of MHT.[6] Hence, the benefit-risk ratio is

less favorable in these women, therefore, MHT is ideally avoided. 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. Hence, the use of non-oral preparations in high-risk women with comorbidities may be preferred to oral MHT.

Approximately 75% of perimenopausal or early postmenopausal women are affected by vasomotor menopausal symptoms. The US Food and Drug Administration (FDA) has approved hormone therapy for treating moderately severe-to-severe menopausal symptoms as a primary indication.

MHT for the treatment of bothersome menopausal symptoms is an acceptable option for women under the age of 60 years or within 10 years of onset of natural menopause. In case, MHT is contraindicated or non-desirable, other non-hormonal options may be considered. 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. Medroxyprogesterone acetate in combined MHT has been implicated for higher incidence of breast cancer and higher cardiovascular risks. Dydrogestrone and natural progesterone have better safety profiles. Natural progesterone is known to have vasorelaxation effects and has been shown to have a neutral or slightly salutary effect on blood pressure unlike synthetic medroxyprogesterone acetate which is vasoconstrictive.

As estrogen alone does not appear to increase the risk of breast cancer, there is no clarity to limit its use in these women.

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. For symptomatic menopausal women in window of opportunity, MHT seems the preferred choice as it will serve dual purpose. MHT has a proven positive effect on bone mineral density. Another FDA-approved indication for MHT is the treatment of vulvovaginal atrophy which is reported in 50% of menopausal women. Localized estrogen therapy (topical application) is preferred for this indication and is considered safe. 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 MHT may be offered when non-hormonal approaches fail to relieve non-vasomotor symptoms, and women report a poor quality of life.

General guidelines for the 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. MHT is offered only when there are no contraindications for its use.

IS MHT USEFUL TO PREVENT COMORBIDITIES?

The 2012 Cochrane Collaboration systematic review assessed the clinical effects of using MHT for 1 year or more.[7] 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.

A brief review of various guidelines and position statements is presented here.

ACOG recommends that clinicians should encourage heart-healthy lifestyles and other strategies to reduce cardiovascular risk in menopausal women.[8] Persistent vasomotor symptoms in some women aged 65 years and above may require continuation menopausal hormone therapy. It should be done with great caution after due calculation of individual risks against benefits. One must not initiate the MHT in women beyond 60 years of age.

The *USPSTF* recommends against the use of estrogen alone (in women who have undergone hysterectomy) and combined estrogen and progestin (in women with uterus *in situ*) for the primary prevention of chronic conditions in postmenopausal women (Grade D recommendation).[9]

Like most clinical guidelines, the American College of Obstetricians and Gynecologists[8] and the American Heart Association[10] recommend against the use of hormone therapy for the primary or secondary prevention of coronary heart disease. It is not recommended to use hormone therapy for primary prevention of any chronic diseases as per guidelines of the *Canadian Task Force on Preventive Health Care*[11] and the American Academy of Family Physicians.[12]

The American Association of Clinical Endocrinologists recommends that age, time from menopause, and cardiovascular risk be considered when using hormone therapy. Hormone therapy is approved by FDA in women at increased risk of osteoporosis and fractures.[13]

The American College of Obstetricians and Gynecologists mentions that early versus late initiation of hormone therapy with respect to onset of menopause determines the effect of hormone therapy on risk of cardiovascular disease.

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 hormone therapy for the treatment of symptoms of menopause.[14]

Revised Global Consensus Statement on Menopausal Hormone Therapy 2016 gives detailed update on benefit-risk analysis and general principles guiding prescription of MHT given in menopause.[15]

MHT is an effective therapy when used in smallest possible dose and for shortest possible period, if used judiciously for menopausal women in their perimenopausal transition years and postmenopause, in widow of opportunity.

COUNSELING AND MAKING DECISIONS FOR INITIATION OF MHT

A personalized discussion between the patient and the physician determines the decision of whether or not to initiate or continue menopausal hormone therapy. 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 vasomotor symptoms associated with perimenopause and early menopause, and for reducing cardiovascular risk, including maintaining a healthy lifestyle.

Treatment goals, patient preference, and safety issues determine the type and route of administration of MHT. MHT should be individualized after counseling and taking patient factors and preferences into consideration. The dosage of MHT should be titrated to the lowest appropriate and most effective dose. The benefit/risk profile of the patient needs to be individually reassessed annually. Some women may require longer duration of MHT for the treatment of vasomotor symptoms and they should be offered after individual risk calculation.

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).[8] 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. In cancer survivors, it is best avoided and alternative therapies may be undertaken in case of hormone-dependent cancer.[16] The most important result of prescribing MHT is the improvement of quality of life in these women. A close supervision by menopause experts is recommended for best outcomes.

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. When MHT is initiated in elderly women and in those with comorbidities, it may be associated with increased risk. Prior discussion with patient about hormone therapy is a must before starting MHT. Personalized discussion with patient about symptoms, treatment goals, analysis of age, time since menopause, and consideration of comorbidities influence decision-making about starting MHT. Close supervision by menopause experts will be desirable for best outcome.

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