

## Post-reproductive health. Opportunity window for the prevention of co-morbidities, a review

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### Abstract

Post-reproductive health is challenging, and menopausal hormone therapy (MHT) is surrounded by many controversies. It has witnessed a rise and fall lasting several years. Comorbidity increases its incidence beyond menopause and it is necessary to prevent it. When MHT was used universally, the risk-benefit ratio became unfavorable, its use fell dramatically; although more recent studies have introduced the concept of window of opportunity, where MHT has no ill effects and will in fact prevent comorbidities associated with menopause.

**Keywords:** post-reproductive health; menopause; hrt; mht window of opportunity

### Background

Millions of women [1,2] around the world face health challenges beyond menopause, and a significant proportion of them have a longer life expectancy at birth, while the average age of menopause is only 46 years, therefore it is important to maintain positive post-reproductive health, prevent disease, reduce mortality rates, and improve quality of life. Menopausal hormone therapy (MHT) has documented benefits, although it is also associated with [3] some risks such as breast cancer and thromboembolism, worsening the already increased risks related to morbidity, age and pregnancy and menopause. In the prevention of comorbidities beyond menopause, MHT is a window of opportunity to reduce the associated risks [1-5].

Worldwide, cardiovascular diseases [6-19] are the main causes of morbidity and mortality; the risk of cardiovascular diseases increases with age in men and women; however, in women due to the cardioprotective effect of estrogen, the risk is delayed until menopause. Osteoporosis-related fractures and cancer [20,21] are two other major morbidities. Cerebrovascular events, pulmonary embolism, dementia, breast cancer, and endometrial cancer (can occur as a side effect of MHT, Table 1; The highest incidence of heart disease in women occurs after menopause, estrogen / progesterone MHT, to reduce the risk of heart disease, was prescribed to menopausal women prior to the results of the Health Initiative study of Women (WHI) [1-6].

Morbidities related to age, menopause and MHT
Cardiovascular morbidities
Deep venous and pulmonary embolism
Dyslipidemia
Diabetes
Dementia
Breast cancer
Endometrial cancer
Ovarian cancer
Cervical cancer

Table 1

### Osteoporosis-related fractures

The study of the Women's Health Initiative (WHI) with Heart and Estrogen and Progestin Replacement (HERS) [6] concluded that MHT is not recommended for primary or secondary prevention of coronary heart disease; which decreased its universal use after menopause. Although the WHI trial [2, 11] was stopped after 7 years, 27,347 postmenopausal women between the ages of 50 and 79 were followed up for an extended period of 13 years without treatment.

Regardless of the use of the benefits and risks of MHT, postmenopausal women now seek help only if they have symptoms, to improve their

quality of life. Universal use of MHT is no longer recommended, so how do we select women to prescribe MHT, to control symptoms, ¿prevent comorbidities and give them a better quality of life? What strategies should we use to achieve the best balance between the risks and benefits of MHT? The answers to these questions are not very clear, but the recently introduced "window of opportunity" concept can be helpful in achieving the objectives.

The concept of "time hypothesis" or "window of opportunity" for the initiation of the MHT; indicates that MHT is best given immediately after menopause for a short period. MHT that starts many years after menopause for a long period of time has been associated with more side effects; WHI data showed that MHT was not associated with major complications in women (50-59 years of age) [6].

Other studies [7-9] have generated interest in MHT due to encouraging results with a beneficial effect on coronary artery disease; Hormone therapy started immediately after menopause (up to 7 months postmenopause) significantly reduces mortality from coronary artery disease.

It also showed a lower incidence [5, 10, 18] of heart failure and myocardial infarction; without increasing the risk of thromboembolic events, stroke, or cancer; in women with an average age of 50 years, within the first 3 years of menopause. The progression of the thickness of the carotid artery intima-media and atherosclerosis was evaluated by means of the calcium score in the coronary artery; not finding an increase in the carotid intima-media thickness or a higher incidence of atherosclerosis, which supports the concept of the window of opportunity, this is when the initiation of MHT in early postmenopause has a net benefit. [9]. MHT reduces risk of cardiovascular disease only if used in this "window of opportunity" period. Therefore, to reduce [22-24] the risk of coronary heart disease and general mortality in women, the best strategy would be to start hormone therapy within 10 years of menopause and / or before 60 years of age, for a short period of time. MHT after 60 years of age is at risk; due to advanced age, the vascular lumen is partially obliterated with atherosclerotic plaques; MHT will make the plaque unstable, reducing vasodilation, which will eventually increase the risk of cardiovascular disease [10]; the effects of using MHT [11] for the primary or secondary prevention of CVD or for the preservation of cognitive function was not indicated, it should be noted that only 30% of women were 50 to 59 years of age at the beginning of the study, the incidence of Venous thromboembolism increased, while no other risk was observed. Initiating MHT early, before atherosclerosis has established itself, helps slow its progression.

### Endogenous Estrogen and Comorbidities

Endogenous estrogen has many beneficial and protective effects, delaying the onset of age-related comorbidities. Due to hypoestrogenism in menopause, the risk of vasomotor symptoms (VMS), osteoporosis, cardiovascular disease, cancer and dementia increases. Estrogen prevents atherosclerosis, inflammatory changes and has a favorable effect on lipids with high and low density lipoproteins (HDL and LDL), thus avoiding cardiovascular events. Estrogen acts on the endothelial vessels and smooth muscles causing vasodilation, and preventing cardiovascular risks [18-24].

### Biomarkers of Vasomotor Symptoms of Cardiovascular Diseases and the Window of Opportunity

Evidence suggests that VMSs could be considered biomarkers of cardiovascular disease [12]. MHT is effective in controlling SVMS associated with menopause at any age. Comorbidities can be prevented if MHT is started for symptomatic women before age 60 or within 10 years after menopause. Non-hormonal options can be used only if MHT is

contraindicated or if the patient does not want it. SVMSs could be a biomarker of cardiovascular diseases and will help in the selection of patients for the longest duration of MHT [5, 6].

### THM on vasomotor symptoms, mood swings and osteoporosis

The most recent evidence suggests that all women with VMS are likely to have lower bone mineral density (BMD); women aged 50-79 years with moderate / severe VMS had lower BMD in the femoral neck and lumbar spine, increased rates of hip fractures during more than 8 years of follow-up compared to women who did not have VMS [13]. Focus on these symptomatic women for the prevention of osteoporosis-related morbidity and mortality, MHT decreases the risk of fractures. MHT can be started in postmenopausal women at risk of fracture or osteoporosis in the window of opportunity, starting after 60 years requires an individualized approach [1-6].

THM helps improve mood swings in early postmenopausal women. MHT may also be helpful for women transitioning to menopause (TM) with major depression. Some women with suicidal tendencies improve with MHT, but antidepressant therapy should be the first option in this context in consultation with a psychiatrist [6].

### Reduction of comorbidities related to the administration, routes and duration of MHT

There is a large body [22-24] of high-quality evidence showing that estrogen-only MHT decreases the incidence of myocardial infarction and also mortality from other causes when initiated in women younger than 60 years and / or within 10 years of menopause. But estrogen-only therapy is not recommended when the uterus is intact, so the addition of progesterone is mandatory to prevent the development of endometrial cancer (EC).

Evidence on estrogen plus progestogen therapy initiated in women younger than 60 years or within 10 years of menopause shows mixed results compared to the estrogen-alone group. To reduce progesterone-related morbidity, the strategy of using lipid-friendly molecules such as natural progesterone and dydrogesterone may be preferred; however, the risk of arterial and venous thromboembolism (VTE) has not been reduced with oral MHT.

The increased risk of breast cancer (MC) is associated with the use of a medroxyprogesterone. MHT started in early menopause has shown evidence that it can prevent Alzheimer's disease in later life [14]. Oral MHT started in older women has shown an increased risk of dementia.

The world consensus [2-4, 22-24] recommends that MHT be used in low doses for the shortest possible duration before the age of 60 years or within 10 years of menopause; women who have VMS beyond the age of 60 may require MHT; if it is needed beyond the age of 60, then an individual risk calculation must be performed to keep morbidities to a minimum; A recent study changed the belief that VMS are short-lived and disappear within 2 years. VMS can last for many years; therefore, they may not be adequately included in the "short-lived symptoms" in menopause.

The VMS lasted more than 7 years; in more than 50% of women, persisting for 4.5 years after the last menstrual period [15]. In women between 65 and 79 years, the prevalence of VMS was 39.2%, the highest prevalence of VMS was observed in women between 65 and 69 years 16 and it is not recommended to routinely discontinue systemic estrogen at the age of 65 years. The dose, type and route of administration of MHT should be selected according to the treatment objectives, the choice of patients and risk factors; therefore, it must be individualized [1-6].

Reassessment of individual risk annually or for a longer period is required; in making decisions about when to start and stop the MHT, in an informed consent of the patient about the risks and benefits under the supervision of the doctor. Hormone therapy can be harmful in women who have pre-existing coronary artery disease, cerebrovascular disease, or thromboembolic tendencies. In the presence of high risk factors if MHT is indicated, transdermal preparations are preferred. Women should be aware of the non-hormonal therapies available for the management of SVM associated with TM and early menopause. Premature menopause requires a standard MHT dose prescribed until the age of natural menopause and then discontinued with an informed decision.

## Discussion

MHT is used to alleviate menopausal symptoms and maintain BMD [1-5, 17], it can reduce cardiovascular risk, particularly if it is started early after menopause [18]. Estrogen with the addition of a progestin is required for women with a uterus [17]. Although the inclusion of progestogens in MHT regimens is associated with approximately one case of breast cancer per 1000 women per year for current users of MHT, micronized progesterone or dydrogesterone [19] may be associated with a lower risk [20,21].

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The type of progestogen is also important when considering the risk of VTE, micronized progesterone and dydrogesterone which appear to show the lowest risk [22]. CEE and CEE/MPA regimens have favorable effects on lipids, but progestogens have little effect on estrogen-induced reductions in total and LDL cholesterol [23, 24]. Dydrogesterone does not appear to oppose the potentially beneficial effects of estradiol on insulin [25].

There is no current guidance on the choice of progestogen for use in MHT in the UK; therefore, individual risk factors, patient preference, and clinical setting must be taken into account [26-28].

## Conclusion

THM should not be used routinely for the primary or secondary prevention of CVD; healthy lifestyles and alternative strategies reduce. The initiation, route and duration of MHT are individualized and its use at the early onset of menopause improves the balance of risks and benefits in the prevention of comorbidities.

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