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Optimizing menopausal hormone therapy use: A review

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Abstract
Menopausal hormone therapy (MHT) has been used in clinical practice for postmenopausal women for decades. With further analysis and newer studies, the benefits, and risks of MHT have been repeatedly verified and discussed. MHT is essential to combat the vasomotor and genitourinary symptoms of menopause as well as to reduce the risk of fractures and manage osteoporosis in postmenopausal women. Before prescribing appropriate hormonal therapy to menopausal women it is important to navigate through the process of weighing risks against benefits effectively Identifying the window of opportunity to commence treatment, selecting the right estrogen and progestogen formulation, and administering the appropriate dose for optimal duration while maintaining the lowest risk profile has been a challenge for clinicians especially for two decades since the risks of hormone replacement therapy were strongly highlighted. To counter the risks and to optimize hormonal regulation, detailed recommendations are given including proposed dosages for the various available estrogens and estrogen/progestogens combinations. Determining how to make the best use of MHT to improve quality of life of postmenopausal women by optimizing the initiation time, regimen, and duration is crucial. This review discusses the guidelines and strategies for prescribing MHT in India for the management of estrogen deficiency symptoms, with focus on genitourinary and vasomotor symptoms, considering the long-term impact on prevention of osteoporosis and cardiovascular disease.

Keywords: Menopause, menopausal hormone therapy, MHT risks, MHT regimens

Introduction
Menopause is a physiological milestone in every woman's life. Women spend about one-third of their lifespan in the postmenopausal stage or longer if they experience premature menopause (Menopause before 40 years of age) [1]. By 2025, it is estimated that there will be over 1 billion women experiencing menopause in the world, which approximates to 12% of the entire world population [2]. Vasomotor symptoms (VMS), including hot flashes and night sweats, are experienced by approximately 75% of menopausal women [3]. These symptoms along with urogenital symptoms significantly impact health-related quality of life [4].
Menopause hormone therapy (MHT) is considered to be one of the most effective methods to improve quality of life especially in women experiencing major symptoms of menopause [5, 6]. It is the standard of care for moderate-to-severe vasomotor symptoms, vaginal atrophy symptoms [7], and osteoporosis [8].
The risks of hormone therapy are dependent on the dose and duration, route of administration, timing of initiation and use of a progestogen. The treatment must be designed appropriately using the best available evidence so that the risks are minimized and the aim of providing a better quality of life to menopausal women is achieved [9].
The estimated mean age of menopause in India is 46 years which is lower than that of Caucasians [10]. Indian data shows that the early age of menopause predisposes a woman to chronic health disorders like type 2 diabetes mellitus, osteoporosis, or risk of fractures. The incidence of vasomotor symptoms in an Indian study was reported to be 75%, which suggests the need to empower Indian clinicians for management of symptoms and long-term health consequences of menopause. However, there is dearth of Indian data on the use of menopausal hormone therapy (MHT) [11]. Therefore, there was a need to understand clinicians' opinions regarding the administration of MHT in different patient profiles and review the risk-benefit profile of MHT in the light of recent evidence to help improve quality of life of women experiencing vasomotor and genitourinary symptoms and to reduce risk of fractures and cardiovascular diseases.

Methodology

Independent focus group discussions were conducted by the authors along with 10 other experts in the field of gynecology and endocrinology to understand the clinicians' opinions on the administration of MHT. A literature search using the keywords "menopausal hormone therapy", "hormone replacement therapy", "tibolone in menopause", "combined oral contraceptives in menopause", "menopause", "window of opportunity", "risks of menopausal hormone therapy", "safety, and efficacy of MHT", and "MHT regimen" was conducted. This review proposes optimal methods for MHT use based on current literature evidence, expert consensus, and standard of care.

Patient profile for MHT use

Patient profiling helps in identifying symptoms that require intervention. MHT intervention should be initiated when menopausal symptoms affect quality of life [12]. Short term benefits of MHT help in relief of vasomotor and genitourinary symptoms, while its long-term benefits include protection from chronic diseases and pathological fractures [13].

In women with an intact uterus, addition of a progestogen helps in protecting the lining of the uterus [12]. Treatment with estrogen alone can cause abnormal cell growth in the lining of the uterus, which may develop into cancer [14]. Non-hysterectomized women require progestogen to minimize the risk of endometrial hyperplasia and endometrial cancer associated with unopposed estrogen exposure [15].

Most importantly, understanding the patient profile helps in identifying the window of opportunity for initiating MHT. Various menopause societies have reached a consensus that although MHT is the most effective treatment for vasomotor symptoms at any age, the ideal time frame to start therapy is within 10 years after menopause or before 60 years of age [9]. Greater absolute risks of coronary heart disease, stroke, venous thromboembolism (VTE), and dementia are seen if the therapy starts after 10 years of menopause or in older women (>60 years) [9].

Patient profiling is the first and the most crucial step in decision making regarding MHT. It is the patient profile that determines the risk-benefit ratio [16]. Most patients with menopause are middle aged, when there is presence of various other comorbidities. Age at natural menopause has also been related to all-cause mortality [17]. Moreover, women with comorbidities like hypothyroidism, pre-diabetes, diabetes, or family history of cardiovascular conditions may also experience early menopause [17, 18].

Comorbid conditions are often also associated with hypertension, dyslipidemia, and obesity, all of which are risk factors for heart diseases. The cardioprotective effect of estrogen is also lost after menopause, which already renders women at high risk of ischemic events and development of various heart conditions [16-18].

Expert Opinion

Family history of osteoporosis and osteopenia must also be considered as indications for starting treatment in menopausal women. Premature ovarian failure and surgical menopause can also be managed with MHT. Women more than 60 years of age may also receive MHT; however, the risk-benefit profile must be assessed thoroughly. In all women undergoing MHT, initial assessment of the endometrial lining must be made along with continual monitoring of lipid profile, liver function tests and breast examination.

Comparative landscape of menopausal therapy

Oral Estrogen

Estrogens exert their actions by binding to estrogen receptors, which are specific receptors that activate transcriptional processes and/or signaling events that result in the control of gene expression [19]. Out of the estrogens available for hormone therapy, 17-beta estradiol hemihydrate is chemically and biologically identical to endogenous estradiol; hence, it has better receptor binding affinity and is easily available after ingestion[20,21,]. Conjugated equine estrogens (CEE) have a prothrombotic effect, which is related to elevated levels of estrogen in the liver due to the 'first-pass' effect. This increases the risk of VTE and stroke [20, 21]. Ethinyl estradiol and estradiol valerate are synthetic compounds and they undergo a high rate of first-pass metabolism by the liver [20, 21].

Vaginal Estrogen

Vaginal dryness, dyspareunia, and burning in the genital area are the most bothersome symptoms in postmenopausal women. Vaginal estrogen cream causes symptomatic relief in women of menopausal age suffering from vaginal atrophy. The use of exogenous estrogen improves blood flow to vaginal mucosa, increases local secretions, and thickens vaginal epithelium in patients with vaginal atrophy. Local estrogen replenishes healthy microflora of the vagina and maintains the pH of vaginal tissue [22].

Transdermal Estrogen

Transdermal administration is preferred in case of intolerance to oral treatment, alteration of liver function, hypertriglyceridemia, diabetes mellitus, and increased risk of thromboembolic disease. This administration route bypasses the first-pass effect seen with the oral route, reduces the resulting load on liver cells, provides better bioavailability, and facilitates a long-term balance of estrogen levels and the physiological ratio of the estradiol and estrone levels [16].

Estrogen + Progestogen Combination

Estrogen–progestogen menopausal therapy involves the co-administration of an estrogen and a progestogen to perimenopausal or menopausal women. The timing of exposure to these hormones may be continuous (both estrogen and progestogen at set daily doses), sequential (Estrogen daily with progestogen for the last 10–14 days of the cycle) or cyclical (As with sequential, but including 7 days without hormonal exposure) [23].

Combined oral products that contain both estrogen and progestogen provide holistic treatment in women with intact uterus [14, 23]. The various preparations available differ in their estrogen component, their progestogen component, the doses of these components, regimen and mode of drug administration. Despite the potential for a plethora of combinations, a relatively small number are manufactured [23].

Most common options available for combined MHT are estradiol-dydrogesterone and conjugated equine estrogen (CEE)-medroxyprogesterone acetate (MPA). Both these combinations have different safety and efficacy profiles

based on their structure and derivation [24, 25,]. Estradiol has a better safety profile compared with CEE, and it is structurally closer to human natural estrogen. Dydrogesterone is a close stereoisomer of progesterone from a natural source [20, 26]. Hence, it has enhanced bioavailability and high selectivity for progesterone receptors [20].

Combined Oral Contraceptives (COC)

COCs contain ethinyl estradiol (EE), which is a synthetic compound [20]. COCs are standard of care for contraception and could be used in women undergoing menopausal transition who need contraception [24]. It is an option for perimenopausal (40–50 years) women who seek relief from menopausal symptoms, desire contraception, or may need control of heavy bleeding [24]. However, during pill-free interval of the COC regimen, the vasomotor symptoms might reappear due to relatively low levels of estrogen [27].

Although COCs may have benefits in menopause, they have not been tested nor approved for the treatment of estrogen deficiency symptoms of menopause and prevention of osteoporosis, neither can they be used in older women requiring estrogen replacement due to increased risks of thrombotic episodes or stroke [28]. The 17α-ethynyl group of EE prevents oxidation of the C17β position of EE by 17β-hydroxysteroid dehydrogenase (HSD), and for this reason, EE is not inactivated in these tissues and has stronger relative estrogenic activity in them. This is the mechanism of the disproportionately strong effects of EE on hepatic protein production, which results in a greatly increased magnitude of effect on VTE and cardiovascular risks relative to estradiol [20].

Tibolone

Tibolone is a synthetic steroid. Its mechanism of action is not well known but studies indicate that by undergoing different tissue selective metabolic transformations, the drug may exert weak estrogen, progestogen and/or androgen activities [29].

Some randomized controlled clinical trials (RCTs) have suggested that tibolone decreases vasomotor symptoms and ameliorates vaginal dryness and discomfort, but results are not consistent [30]. Moderate-quality evidence suggests that tibolone is more effective than placebo but less effective than hormonal therapy (HT) in reducing menopausal vasomotor symptoms and that tibolone is associated with a higher rate of unscheduled bleeding than placebo, but with a lower rate than HT [30]. Results of another RCT found that tibolone increases the recurrence of breast cancer [31].

A short course of tibolone can be given to women with sexual dysfunction or dyspareunia. It can be beneficial for menopausal symptoms in women who have undergone hysterectomy [32]. For longer duration of treatment, low-dose MHTs can be given. There is no literature evidence that tibolone increases the risk of other long-term adverse events or that it differs from HT with respect to long-term safety [30].

Effect of tibolone on the cardiovascular profile is, however, noteworthy as it increases total cholesterol levels apart from causing a significant reduction in high-density lipoprotein (HDL) cholesterol levels. Even 25%-30% reduction in HDL cholesterol is quite significant [30]. Oral estradiol, on the other hand, when sequentially combined with dydrogesterone, showed a beneficial influence on serum lipids and cardiovascular disease risk, which has not been seen with tibolone [33]. At 24 months, oral estrogen–dydrogesterone combination was found to increase mean HDL cholesterol by 7%, compared with a 26.8% reduction in HDL cholesterol with tibolone [33].

Although the drug is thought to have a possible role in preserving bone mineral density, control of osteoporosis is not a recommended indication [31].

Isoflavones

Isoflavones, phytoestrogens, or bioidentical molecules are considered to pose less harm as these are natural herbal products [34]. However, literature does not substantiate that these are better than pharmacological products for treating vasomotor symptoms in menopausal women and supporting evidence establishing the safety and efficacy of phytoestrogens is scarce [35].

Expert Opinion

When compared, CEE has a higher risk profile than estradiol hemihydrate. The risk of VTE is higher in patients with diabetes and hypertension; hence, post-menopausal women with comorbidities can opt for newer treatments like combined estrogen and dydrogesterone therapies, which have a relatively lower risk of VTE.

Patients with primary amenorrhea may have nausea and headaches with oral contraceptives, but they can tolerate low-dose MHT for years. Some women may attain psychological benefits with COCs as they bleed at the end of every cycle. However, the risk of breakthrough bleeding is a concern for most women; hence, continuous combined therapy is preferred over sequential therapy options. Women experiencing perimenopausal symptoms and seeking contraception may benefit from COCs while women who have attained menopause must be given appropriate MHT dosage.

A major side-effect observed with tibolone is weight gain [36]; hence, it not only leads to higher risk of cardiovascular diseases, but also affects patient compliance. Using tibolone for more than six months adversely affects cardiovascular profile. Tibolone was being used by various clinicians when it was the only available option. Estrogen-based MHT is now the preferred choice of treatment.

Maximum patient satisfaction is achieved with MHT, which has shown to reduce quality-of-life altering symptoms and to limit occurrences of breakthrough bleeding.

Role of lifestyle modification in menopause management

Lifestyle modifications are known to bring about positive changes and improve overall health and quality of life in all individuals. The Indian Menopause Society also advocates incorporating lifestyle modifications to manage menopause [24]. However, evidence for the effectiveness of lifestyle and behavior modifications for menopausal symptoms is mixed, limited, or non-existent.[37]. This may be due to limited number of studies conducted in this domain. There is absence of evidence that suggests that lifestyle modifications may work for genitourinary symptoms at all. Weight gain increases the severity of vasomotor symptoms; hence, maintaining healthy weight may help in managing symptoms of menopause. Exercise, controlling environmental temperature, or cognitive behavior therapy have not been shown to elicit changes other than general

well-being and help in decreasing the impact of menopausal symptoms [37].

Expert Opinion

In the view of clinicians, without lifestyle modification, any medication prescribed for managing menopausal symptoms will not show adequate benefits. Along with diet, exercise and quitting smoking, counselling may also bring about major benefits.

Decision making regarding MHT

Safety Profile and the Risk of Cancer

Results from the Women's Health Initiative (WHI) study published in 2002 indicated a significant increase in the incidence of breast cancer, cerebrovascular and cardiovascular disease associated with MHT, which led to a decrease in the overall use of MHT. This study provided estimates only for the specific treatments of conjugated equine estrogen (CEE) with and without medroxyprogesterone acetate (MPA). However, the results caused severe apprehension amongst women in seeking treatment for menopause and changed the attitudes of gynecologists and physicians who previously prescribed therapy for symptoms of menopause that alter quality of life [38]. Certain limitations of this study led to further research in the next two decades. The women included in the WHI study were older with an average age of 60 years, with 50% of them being smokers, 50% being overweight, and 30% having a history of myocardial infarction [38]. The combination therapy used included CEE and MPA; hence, the results could not be generalized to other available estrogens and progestogens [38].

While the WHI study concluded that the risks exceed the benefits of menopausal therapy, newer research suggests that this may only be true for women more than 60 years of age or who have not received treatment for >10 years after menopause [39]. Thus, there is a window of opportunity to improve the quality of life of women experiencing vasomotor and urogenital symptoms and to protect their bone health, thereby reducing the risk of fractures [9, 39].

In a long-term follow-up study similar to the WHI study, it was found that estrogen alone is not associated with increased risk of breast cancer.[40,41] In fact, it is the choice of progesterone that affects breast cancer outcomes. This was further confirmed in a French cohort study done involving 80,377 women, where it was demonstrated that the risk of invasive breast cancer was significantly lower with MHTs containing progesterone or dydrogesterone than with MHTs containing other progestogens [42, 43]. Another Finnish study from 2009, showed that risk of breast cancer with use of estrogen/dydrogesterone combination was not statistically significant compared to the nonusers [44]. A study using the two largest UK primary care databases, with 556,109 patients, found that there was no significant increased risk of breast cancer in women that initiated the therapy with estrogen/dydrogesterone combination between 50-59 years of age [45].

Administration of MHT

Clinical trial evidence on dose and duration of MHT is not uniform. Various guidelines published since 2016 agree that treatment must be decided according to the patient profile and clinical assessment [6, 15, 46]. The 2016 International Menopause Society recommendations advocate the use of lowest effective dose of MHT. However, the 2017 North American Menopause Society position statement and the 2020 British Menopause Society recommendations suggest using doses that meet treatment objectives based on symptom severity and response to therapy [6, 15, 46]. These guidelines also highlight that in symptomatic women benefits outweigh the risks [6].

Many studies have established the safety and efficacy of combination therapies at different doses. In a multicenter study, 446 healthy menopausal women received oral continuous combination therapy of 0.5/2.5 mg estrogen (E) /dydrogesterone (D) daily for a year. Amenorrhea rate was 68%, and 14% women had one of two bleeding/spotting episode; the rate of amenorrhea in months 10 to 12 was 88% [47]. Results from a similar study with continuous combination of 1/5 mg E/D also showed similar bleeding profile and endometrial safety[48]. In a multicenter double blind RCT involving 579 women receiving sequential therapy with 1/10 mg E/D or 2/10 mg E/D combination, cyclic bleeding rate was 79% with 1/10 mg E/D and 91% with 2/10 mg E/D. No cases of hyperplasia or malignancy were reported with either of the two dosing regiments [49].

It must be stressed that all types of estrogens whether oral/topical/transdermal have similar efficacy with no significant differences between oral and transdermal applications [50]. Because first-pass metabolism effect is avoided by using transdermal estradiol, all risks associated with hepatic pathophysiology can be reduced [50]. All estrogens or estrogenic products for topical vaginal use may not have enough systemic efficacy. They should only be used for local urogenital problems although they can also have sufficient efficacy for treating genitourinary syndrome of menopause [50].

Endometrial Protection

Endometrial hyperplasia and malignancy are key risks that lead to paradigm shifts in usage of hormone replacement therapy [38]. A recent systematic review of 28 studies found that different menopausal therapies pose risks differently [51, 52]. If estrogen was used unopposed, the risk of hyperplasia was higher. Dydrogesterone at 10 mg dose sequentially combined with 2 mg of estradiol for 14 days per month or 5 mg of dydrogesterone administered daily for a duration of up to 3 years is effective in protecting the endometrium from estrogenic effects [51, 52].

Furthermore, use of continuous combined therapy was found to pose lower risk compared with sequential therapy; however, if micronized progesterone was used in combination, the risk increased notably even in continuous combination therapy. Results from most studies evaluated in the review also indicated tibolone to have an increased risk against endometrium safety [51, 52].

In perimenopausal women, menstrual regulation can be optimized with sequential MHT by adding a progestogen to estrogen for at least 10 days to change the estrogen-induced endometrial proliferation to a secretory transformation caused by the progestogen component. After end of the progestogen phase, a progesterone-withdrawal bleed will occur in most patients. Regular withdrawal bleeding protects from endometrial hyperproliferation, and thus, reduces the risk of endometrial cancer. In postmenopausal women, continuous combined MHT should be administered to obtain and maintain endometrial atrophy without any bleeds. The addition of progestogen, sequentially or continuously is

important for the management of uterine bleeding disorders, including menstrual regulation during menopausal transition [50].

Cardiovascular Risk and Mortality

A 13-year follow up of the 27347 women aged 50–59 years who had been enrolled in the WHI study revealed that MHT was not associated with all-cause mortality or cardiovascular or total cancer mortality compared with placebo. Women receiving CEE alone were found to be at risk of developing deep vein thrombosis. These risks were identified based on difference in incidence of these events in placebo vs MHT groups over 5 years [53, 54].

Early initiation of MHT i.e., within 10 years of menopause or less than 60 years of age, has been found to not only reduce the risk of cardiovascular events but also to improve survival and cardiac outcomes [55]. A meta-analysis of 23 studies found that MHT reduced coronary heart disease events in women less than 60 years of age by 32%. However, if MHT was started after 60 years of age, no such benefits were observed [53, 55, 56].

A retrospective analysis of the Finland registrar between 1995 and 2009 showed that cardiovascular mortality improved in women who continued taking MHT for more than a year after menopause. Women younger than 60 years who discontinued treatment after the WHI study showed increased cardiovascular mortality [57, 58].

Results from the Estrogen and Thromboembolism Risk (ESTHER) case control study revealed that the thromboembolic risk profile was better with micronized progesterone and pregnane derivatives. Moreover, in a double blind RCT, the combination of estradiol/dydrogesterone was found to be superior to CEE/norgestrel in terms of lipid profile [59].

A comparison of odds ratios based on cases and controls matched by age and practice and adjusted for smoking status, body mass index, family history of VTE, chronic and recent medical events, other drugs, and past exposures to hormones revealed that transdermal MHT use was not associated with risk of venous thromboembolism compared with absence of MHT use, while conjugated equine estrogen with or without medroxyprogesterone acetate had the highest risk and estradiol with dydrogesterone had the lowest risk [60]. The use of tibolone, however, showed no difference versus placebo in the reduction of cardiovascular events and mortality from any cause [29].

Bone Health

Long-term, follow-up results from the WHI study have shown the efficacy of hormonal therapy on bone health [41, 42]. Results from another multicenter, double-blind, prospective, randomized, placebo-controlled study in 595 apparently healthy postmenopausal women who were given continuous oral estradiol 1 mg or 2 mg with sequential dydrogesterone for 2 years showed significant increase in bone mineral density of the lumbar spine and femoral neck – two most common fracture sites in osteoporosis [61].

Unlike common perception, Grade a evidence suggests that MHT use is safe and cost-effective in preventing all osteoporosis-related fractures, and trying all other available treatments for menopause-related osteoporosis may not be necessary if women are younger than 60 years of age [46]. Other treatment options can be explored for women more than 60 years of age, or MHT can be prescribed after a risk-benefit analysis.

Expert Opinion

As the average age for menopause in India is 46 years, it is easy to start menopausal therapy in the window of opportunity. Hence, to reduce coronary heart disease risk and overall mortality in women, the best strategy would be to initiate hormonal therapy within 10 years of menopause and/or before 60 years of age. MHT after 60 years has a risk, as with advancing age, the vascular lumen gets partially obliterated with atherosclerotic plaques, which may become unstable with the use of MHT.

The lowest effective dosage must be used. However, resolution of symptoms must also be obtained. The dose of 0.5/2.5 mg is most effective in women in whom cyclic bleeding is not required. Thus, this lowest dose can be used to attain better compliance and discourage apprehension amongst post-menopausal women. Higher doses have also proven to be safe and effective and must be used if required for optimal resolution of symptoms. In women with family history of osteoporosis, the risk of fractures can be minimized by dosage optimization to maintain bone health.

The apprehension about breast cancer often discourages clinicians from prescribing hormone replacement therapy or MHT, and it instills reluctance in women to undergo long-term treatment. The breast cancer risk connected to prolonged use of estrogen is significantly lower compared to the risks posed by factors such as consumption of alcohol, inactivity, and obesity. Family history of breast cancer must be considered before starting the treatment regimen. Choice of progesterone is important while prescribing MHT. A recent study from UK with a large sample size showed no significant increase in breast cancer risk on administration of combined MHT with estrogen/dydrogesterone in women aged 50-59 years of age [45].

Urogenital atrophy, vaginal dryness, and other urogenital symptoms are seldom addressed by women especially in India, where there is certain cultural barrier to opening up about these issues. At the same time, most women might be visiting clinicians for other age-related comorbidities who may not focus on menopausal symptoms. Urogenital atrophy may result in vaginal dryness, itching, burning, dyspareunia, urinary frequency, urgency, urge incontinence, and recurrent urinary tract infections, thereby affecting quality of life and lead to further severe infections.

Hormone therapy improves vaginal thickness and elasticity. Topical therapy may also improve lubrication and blood flow, favorably affect vaginal pH and microflora, and improve sexual response. It can alleviate vaginal dryness, soreness, irritation, pruritus, and dyspareunia, all of which are disturbing symptoms that are not usually addressed effectively. Therefore, all clinicians who treat postmenopausal women, especially the cardiologists and endocrinologists, must ensure that menopausal symptoms are not ignored, adequately assessed and treated.

Conclusion

There is enough evidence to use MHT in the treatment of vasomotor and genitourinary symptoms and management of osteoporosis in postmenopausal women. The treatment for these symptoms, which alter the quality of life of women, must be effectively designed after considering the risk-benefit profile. MHT must be started in the window of

opportunity, which lies within ten years of commencement of menopause or until 60 years of age. Considering that not all types of MHT are the same, the choice of hormone determines the safety and efficacy of treatment. A combination therapy of estradiol and dydrogesterone has a better safety and efficacy profile compared with CEE and MPA. Estradiol is superior to CEE and EE when estrogen only therapy needs to be prescribed. Dose and duration of the therapy must be determined after considering patient profile, and the effective dosage must be given to ensure resolution of symptoms.

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