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MENOPAUSAL HORMONE THERAPY AND SYMPTOM MANAGEMENT: A COMPREHENSIVE REVIEW

Obstetrics & Gynaecology

Dr Eman Khaled Medical Student, Dubai Medical College, Dubai

Dr Juhi Godara Specialist obstetrics and Gynaecology, Dubai Hospital, Dubai

Dr Ghaya Alrais Medical Student, Dubai Medical College, Dubai

Asra'a Alnakeb Medical Student, Dubai Medical College, Dubai

ABSTRACT

This comprehensive narrative review elucidates the complexities surrounding menopausal hormone therapy (MHT), encompassing diverse symptom management strategies and associated risks. It explores the dynamic landscape of hormonal and non-hormonal approaches, integrating recent primary evidence and updated recommendations from specialized medical societies. Menopause, a critical phase in women's lives, is examined through its multifaceted physiological changes and the impact of MHT on symptomatology and long-term health outcomes. Additionally, the review delves into alternative therapies, emphasizing personalized care and tailored interventions for managing menopausal symptoms effectively.

KEYWORDS

Menopausal Hormone Therapy, Climacteric Symptoms, Vasomotor Symptoms, Genitourinary Syndrome of Menopause, Estrogen Replacement, Non-hormonal Therapies.

INTRODUCTION

The diverse array of symptoms experienced during the climacteric phase can be classified into somatic (vegetative), organic, and metabolic categories. Treatment options, pharmacologically, are categorized into hormonal and nonhormonal therapies.[1] Menopausal hormone therapy (MHT), also recognized as hormone replacement therapy (HRT), involves administering sex hormone preparations in instances of low estrogen levels. When estrogen alone is used, it's termed estrogen replacement therapy (ERT or ET), while the combination of estrogens and progestogens is referred to as estrogen–progestogen therapy (EPT). Understanding these distinctions is crucial due to significant differences in their risk-to-benefit profiles.

Effectively utilizing estrogen therapy can alleviate nearly all climacteric symptoms and serve as a strategic approach for long-term prevention of estrogen deficiency and related diseases. In the early menopausal transition, preferred hormone therapies include gestagen substitution, levonorgestrel intrauterine system (LNG-IUS), or low-dose monophasic contraception. Transitioning into later menopausal stages often involves a shift to gestagen-dominated combined sequential EPT, considering factors such as dosage adjustments, patient preferences, treatment duration, and an approximate age threshold of 52 years. In postmenopausal cases, transitioning to combined continuous EPT is recommended, especially for those who have not previously used MHT.[2]

Understanding the use of external hormones, referred to as menopausal hormone therapy (MHT), is crucial for women's health, considering they spend approximately 40% of their lives post-menopause. MHT addresses various post-menopausal symptoms such as hot flashes, sleep disturbances, sexual issues, and urinary problems. It also offers potential benefits for bone health in women, particularly those at risk of fractures.

The utilization patterns of MHT have significantly shifted over time.[3] Following the Women's Health Initiative (WHI) hormone trials, which highlighted increased risks of coronary heart disease (CHD) and stroke in MHT users, its usage steeply declined from the late 1980s to the early 2000s. This decline led to usage rates dropping from approximately 22% in 1999 to as low as 3-5% among women aged 40 or older in the United States by 2010. Despite this decline, recent recommendations, based on updated evidence, have identified specific groups of women for whom the benefits of MHT for symptoms like hot flashes and bone health outweigh the risks.

This narrative review aims to equip clinicians with updated knowledge about MHT and alternative non-hormonal options for managing menopausal symptoms. It integrates recent primary evidence, reevaluates risk-benefit profiles, and incorporates the latest recommendations from specialized medical societies.[4]

Menopause, being a pivotal phase in women's lives, involves profound physiological changes impacting overall well-being. The average duration of Vasomotor Symptoms (VMS) extends to 7.4 years, persisting around 4.5 years post the final menstrual period. Alongside VMS, challenges during the menopausal transition include mood alterations, changes in sexual function, and possibly linked insomnia. Body composition and cardiometabolic alterations, [1] including elevated low-density lipoprotein cholesterol and changes in fat distribution, are associated with menopausal progression and pose increased risks for metabolic syndrome and diminished vascular function. These changes are more attributed to the menopausal transition than simple aging.[5] MHT partially mitigates some metabolic changes but doesn't fully restore the hormonal balance of the premenopausal state due to the complexities of reproductive and biological aging. The benefits and risks of MHT vary based on factors like formulation, dosage, and the patient's risk profile. Research suggests a specific timing to start MHT—initiating before age 60 or within a decade of menopause onset—potentially mitigating the risk of cardiovascular disease (CVD) and achieving a more favorable balance between benefits and risks.

The physiology of menopause involves the cessation of ovarian function for a year, typically occurring around age 51 for most women. Premature (before 40), early (between 40 to 45), and late (after 55) menopause differ physiologically and symptomatically from the standard timing. The transition phase spans 1 to 3 years, involves intricate physiological changes, and doesn't always align hormonal shifts with symptoms, necessitating personalized care.[6] Premature and early menopause pose higher risks of heart disease and earlier mortality, while primary ovarian insufficiency (POI) before 40 allows intermittent ovulation and cycles. Hormone therapy is suggested for women with premature or induced menopause until at least the average age of menopause, if suitable.

Menopause Hormone Therapy

Estrogen administration can take various forms, such as oral ingestion, transdermal patches, gels applied to the skin, injections into muscles, nasal sprays, subcutaneous implants, or localized vaginal application. Each method can be customized to suit individual patients in terms of dosage and timing.

Transdermal delivery, particularly using patches or sprays, becomes preferable when oral treatment isn't suitable due to issues like changes in liver function, diabetes, hypertriglyceridemia, or a risk of thromboembolic disease. This approach avoids the initial liver processing, ensuring improved estrogen absorption, maintaining a consistent long-term estrogen balance, and preserving the natural ratio between estradiol and estrone.[7]

A recent study has highlighted promising outcomes with the latest method, a metered-dose transdermal spray (EMDTS), among

menopausal women. The serum levels of estradiol, estrone, and estrone sulfate increased proportionally with the number of EMDTS 1.53 mg doses. The spray achieves its peak concentration of estradiol around 18–20 hours post-application, establishing a stable level after 7–8 days, providing precise dosing and the safety benefits associated with transdermal application.

Estrogen therapy (ET) suits women who have had a hysterectomy, while those with an intact uterus typically receive combinations of estrogen and progestogen. These combinations involve continuous administration or cyclic dosing for 21 days followed by a 7-day pause.[8] Estrogens, especially at standard and low doses, promote the growth of endometrial cells, requiring their use with progestins in women with an intact uterus to prevent excessive endometrial growth. The choice of progestin and its dosing pattern significantly affects the clinical and metabolic effects of the therapy. [7] Progestogens like micronized progesterone and dydrogesterone are considered to have the most favorable safety profiles. The intrauterine system with levonorgestrel (IUS-LNG) primarily impacts the local endometrium with minimal systemic effects.

Tibolone

Tibolone, a progestogen, exhibits selective estrogenic effects, effectively managing vasomotor symptoms, enhancing mood and libido, and improving vaginal atrophy without affecting the endometrium.[3] Despite its benefits, extended use among older women is associated with an increased risk of stroke and a possible rise in breast cancer recurrence.[9]

Estetrol

Estetrol (E4), a unique steroid estrogen, offers oral bioavailability and potent binding to estrogen receptors. It shows promise in hormone replacement therapy for women post-breast cancer surgery or undergoing aromatase inhibitor treatment.[10]

Selective Estrogen Receptor Modulators (SERMs)

SERMs like tamoxifen act as breast tissue antagonists, aiding in breast carcinoma treatment and prevention. Bazedoxifene (BZA) protects bone mass without affecting breast tissue or the endometrium, offering potential in osteoporosis management.[11]

Nonhormonal Therapy for Vasomotor Symptoms (VMS)

Non-pharmacological approaches like cognitive behavioral therapy, hypnosis, and mindfulness-based stress reduction exist, albeit with limited evidence of efficacy.[11] Herbal therapies and pharmacological options like SSRIs and SNRIs show varying effectiveness in managing VMS.[11]

Nonhormonal Therapies for Climacteric Syndrome

Approaches such as electro-analgesia, spa treatment, physical exercise, and phytoestrogens from plants like soy and red clover are explored for alleviating symptoms, although conclusive evidence is lacking. [3]Black cohosh extract (CRE) demonstrates effectiveness in reducing vegetative symptoms, potentially without impacting plasma hormone profiles.[12]

Pollen Extracts

Pollen extracts offer a non-estrogenic alternative, affecting serotonin reuptake and regulating sleep and thermoregulation, showcasing promise in managing climacteric syndrome.[12]

New Emerging Therapies

Neurokinin B antagonists, particularly fezolinetant, target hypothalamic centers to alleviate VMS and night sweats, currently undergoing evaluation for FDA approval.

Benefits and Risks of Menopause Hormone Therapy

The advantages of menopause hormone therapy (MHT) span across various aspects of women's health during and post-menopause.

1. Vasomotor Symptoms: These symptoms, like hot flashes and night sweats, can severely impact sleep, focus, overall health, and quality of life. Estrogens have demonstrated a remarkable ability to reduce both the frequency (by 75%) and intensity (by 87%) of these symptoms. [13] Different doses of specific estrogens, such as conjugated equine estrogen (CEE) at 0.3 mg, estradiol at 0.5 mg, or estradiol patches at 0.025 mg, typically require 6 to 8 weeks to reach their maximum effect. Gestagen therapy (using medications like medroxyprogesterone acetate at 10 mg per day, megestrol acetate at 20 mg per day, or micronized progesterone at 300 mg) has also shown effectiveness, although long-term safety data are not yet available.[2]
2. Sleeping Disorders: MHT has been shown to improve chronic insomnia among menopausal women. Certain progestogens, especially oral micronized progesterone, seem to have a mild sedative effect, likely due to their action on gamma-aminobutyric acid (GABA) receptors.
3. Sexuality: Estrogens positively impact sexual function by addressing vulvovaginal atrophy (VVA) and reducing vasomotor symptoms. Transdermal estrogens are preferred for women with reduced libido due to their ability to avoid increasing sex hormone-binding globulin (SHBG) levels, thus maintaining testosterone's bioavailability. Continuous testosterone therapy can benefit women diagnosed with hypoactive sexual desire disorders.[14]
4. Premature Ovarian Insufficiency (POI): Early onset of estrogen deficiency in POI heightens the risk of various health issues, including vasomotor symptoms, bone density reduction, mood fluctuations, heart diseases, dementia, and more. Managing POI typically involves Menopausal Hormone Therapy (MHT) alongside calcium supplements, vitamin D, regular exercise, and hormonal contraception without intervals.
5. Quality of Life: Assessing the risks and advantages of MHT concerning outcomes like cancer, cardiovascular disease (CVD), cognitive impairment, venous thromboembolism (VTE), and osteoporosis is crucial. Considering individual patient traits alongside factors like age at initiation, time post-menopause, and treatment duration helps in making informed decisions.[15]

While MHT offers various benefits, it's important to recognize its associated risks. MHT might cause mastodynia, fluid retention, nausea, leg cramps, and headaches with estrogens, while components with gestagens might lead to depression, anxiety, flatulence, and increased appetite. Unwanted bleeding may occur during MHT use, and certain conditions like hypertension, ischemic heart disease, diabetes, migraine, benign breast disease, uterine fibroids, and endometriosis, previously considered problematic, are now seen differently.[9]

Absolute contraindications to MHT include breast cancer, estrogen-dependent malignant carcinoma, active liver disease, history of thromboembolic disease, intolerance to any component in the preparation, among others.[19] Long-term use of MHT (over 10 years) increases the risk of breast cancer and thromboembolic disease. Additionally, there's a heightened risk of endometrial carcinoma with unopposed estrogens but a reduced risk when progestins are added.[16]

Understanding these benefits and risks, tailored treatment approaches, and considering individual patient characteristics are vital in deciding the appropriateness of MHT.[14] Government-regulated bioidentical hormone formulations are recommended due to safety concerns associated with untested compounded ones or unconventional administration methods. Various formulations, doses, and delivery methods exist for MHT, and treatment should be personalized based on patient preferences and needs.[17]

For perimenopausal women, contraception should be considered due to irregular cycles and the possibility of conception. Several birth control methods alongside estrogen can be options for managing contraception during this phase.[18]

Genitourinary Syndrome of Menopause

Skin atrophy resulting from estrogen deficiency, involving the vulva adnexa and vaginal mucosa, manifests as vulvovaginal atrophy (VVA), often accompanied by dyspareunia, pruritus, and chronic vaginitis.

Estrogen replacement stands as the primary treatment and the only definitive therapy for vaginal atrophy. Estriol (E3) is typically initiated at 0.5 mg/24 hours for 2–3 weeks initially, followed by a maintenance dose of 0.5 mg 1–2 times weekly. Estradiol (E2) can be administered via vaginal tablets at 0.01 mg daily for 10–14 days initially, followed by twice-weekly doses.[19]

Long-term use of higher estrogen doses could potentially have adverse trophic effects on the endometrium. However, prescribed doses, such as a total annual dose of 1.14 mg of estradiol, effectively treat vaginal atrophy safely.[17]

Ospemifene, at a daily 60 mg dosage, is approved for VVA treatment in postmenopausal women. It reduces the percentage of parabasal cells in vaginal cytology by 30–40%, increases superficial cells by 5–10%, and decreases vaginal pH. It effectively mitigates dyspareunia, vaginal dryness, and enhances sexual function in postmenopausal women. Ospemifene shows positive effects on the lipid profile without notable adverse effects on hematologic, biochemical, or renal indicators. Common undesirable side effects include hot flushes, vaginal discharge, and muscle spasms.[20]

For women reluctant to undergo hormone therapy, treatments containing hyaluronic acid or prasterone can be considered to enhance vaginal trophic conditions. Some uncontrolled studies also suggest the use of fractional CO2 or erbium lasers. Vaginal moisturizers and lubricants are commonly employed as symptomatic aids during sexual intercourse in older age.[8]

The irreplaceable trophic effect of vaginally administered estrogens makes them an indispensable treatment for vaginal atrophy, either as an individual therapy or in combination for women who may not find systemic MHT or tibolone sufficient.

CONCLUSION

In summary, this review underscores the nuanced understanding required for optimal management of menopausal symptoms, highlighting the pivotal role of MHT while acknowledging its associated risks. It emphasizes the significance of individualized treatment approaches, considering patient characteristics, formulation variations, and delivery methods in navigating the benefits versus risks paradigm. The evolving landscape of menopause therapy necessitates a holistic view, incorporating both hormonal and non-hormonal options, enabling clinicians to tailor interventions that align with patient preferences and health needs. Furthermore, it emphasizes the criticality of evidence-based approaches, endorsing government-regulated formulations and continued research to refine strategies for managing menopausal symptoms effectively.

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