



Overview on Hormonal Replacement Therapy in Menopause

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i39A32152

Editor(s):

(1) Dr. Dharmesh Chandra Sharma, G. R. Medical College & J. A. Hospital, India.

Reviewers:

(1) Kalpana S. Dudhal, MUHS University, India.

(2) Vijaya Chandra Reddy Konda, Sri Venkateswara Institute of Medical Sciences, India.

Complete Peer review History: <https://www.sdiarticle4.com/review-history/71578>

Review Article

Received 20 May 2021

Accepted 24 July 2021

Published 30 July 2021

ABSTRACT

Hormone replacement therapy (HRT) is defined as a therapy that could allow women to free themselves from the malediction of estrogen loss and conserve their femininity. The study aims to summarize the updated evidence regards types, indication, contraindication, and untoward effects of hormonal replacement therapy among menopausal women. There are several different drug classes comprising estrogens, progestogens, and estrogen + progestogen combinations. Estrogen is the primary active component of HRT, treating menopausal symptoms, particularly vasomotor symptoms. There are several adverse effects of hormone replacement therapy that manifest in many different ways depending on the route of administration, and whether that route has local or systemic effects. Further research is needed to study the risks of menopausal HRT and pharmacological studies are needed to lower these risks and make its use safer with less side effects.

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Keywords: Menopause; hormone replacement therapy; estrogens; progestogens; estrogen and progestogen combinations.

1. INTRODUCTION

Menopause is defined as the cessation of menstruation which reflects cessation of ovulation due to a loss of ovarian follicles, which in turn lead to reduced ovarian production of estradiol, the most biologically active form of estrogen [1] as well as increased circulating concentrations of follicle-stimulating hormone (FSH) and decreased concentrations of inhibin, which inhibits FSH release [2,3].

Although menopause is a universal phenomenon among women, the timing of the onset and the duration of the menopausal transition and the timing of the final menstrual period are variable from one woman to another [4].

Results from cross-sectional studies have indicated that endocrine changes characteristic of the onset of the perimenopause begin at around age 45 [5]. The median age at menopause among white women from industrialized countries ranges between 50 and 52 years and at onset of the perimenopause is 47.5 years [6] with slight evidence of increasing age at menopause over time [7,3]. These onsets seem to vary by race and ethnicity and are affected by demographic and lifestyle factors [8].

The clinical conditions associated with menopause were identified as "Hormone Deficiency Syndrome" [9], which included, besides hot flashes, other late onset chronic diseases such as osteoporosis, cardiovascular events, Alzheimer's disease, and vaginal atrophy. Food and Drug Administration (FDA) approved an estrogen product for the first time for the treatment of hot flashes at the beginning of the 20th century [10]. A bestselling book published in 1966 ("feminine forever"), with its claim that "menopause is a hormone deficiency disease, curable and totally preventable, just take estrogen" [11].

Hormone replacement therapy (HRT) was presented as a therapy that could allow women to free themselves from the malediction of estrogen loss and conserve their femininity. In the 1970s, the finding that unopposed estrogen supplements were associated with an increased risk of endometrial cancer had a bad impact on HRT's reputation [12,13]. Ziel et al. [12] observed a probable connection between the

administration of conjugated estrogen alone and the development of endometrial cancer. Nevertheless, in the following years, researchers discovered that reducing the dosage of estrogen and combining it with progesterone could reduce the risk of endometrial cancer [14]. Such combined therapy was recommended for women with an intact uterus, raising renewed enthusiasm for HRT treatment. The FDA initially approved HRT only for the treatment of hot flashes and not for the prevention of chronic conditions, but in 1988 the prevention of osteoporosis was included among the FDA-approved indications [15,16].

2. OBJECTIVE

The study aims to summarize the updated evidence regarding types, indications, contraindications, and the side effects of hormonal replacement therapy among menopausal women.

2.1 Types of Hormonal Replacement Therapy (HRT) during Menopause

There are several different drug classes comprising estrogens, progestogens, and estrogen + progestogen combinations. Estrogen is the primary active component of HRT and is the recognized 'gold standard' for treating menopausal symptoms, particularly vasomotor symptoms, estrogens used for HRT include conjugated equine estrogens (CEEs), synthetic conjugated estrogens, micronized 17 β -estradiol, estriol, estradiol valerate and oestradiol hemihydrates [17], and they can be administered orally, transdermally or through cream, patch, vaginal inserts, or subdermal pellets.

Each route of administration has advantages and disadvantages. Oral estrogen: Any estrogen administered orally results in increased the resistance of activated protein-C, increasing the risk of a blood clot [18]. Oral estradiol lead to induction of the liver to form matrix metalloprotease 9, which reduce the formation and rupture of atherosclerotic plaque. Transdermal estrogen, bypasses the hepatic metabolism which produces activated protein-C resistance, and the risk for blood clotting is negated. Progestin administration is usually through the oral route, although a few are

available in combination with estrogen patches . Progesterone is available orally [19] that can also be used vaginally for non-FDA-approved uses. Specialized pharmacies make compounded estrogen and progesterone creams, sublingual troches, and vaginal inserts, but these are not FDA approved [17,18].

2.2 Indications of Hormonal Replacement Therapy

Vasomotor symptoms (VMS) in menopause are associated with sleeping disorders, concentration disorders, and lowered quality of life and overall health condition (cardiovascular risk, cognitive functions, bone loss). They last on average for 7.4 years. Estrogens reduce the frequency of symptoms by 75% and their intensity by 87% [19]. Also used in chronic insomnia in menopausal women. Some progestogens (especially oral micronized progesterone) have a slight sedative effect probably due to their agonistic action on gamma-aminobutyric acid (GABA) receptors [20]. Hormonal replacement therapy (HRT) has a good role in resolving vulvovaginal atrophy (VVA), Systemic HRT and low-dose vaginal estrogen therapy ET, are effective in treating urogenital atrophy and improve sexual function by increasing vaginal lubrication, blood flow, and sensory function.

By using transdermal estrogens which are preferred to oral estrogens in women with vulvovaginal atrophy and lowered libido because they do not increase the level of sex hormone-binding globulin (SHBG) and thus do not reduce bioavailability of testosterone [21]. Continuous testosterone therapy has benefits for women diagnosed with hypoactive sexual desire disorders [22]. Also using these medications in Premature ovarian insufficiency (POI), shows great benefits, premature onset of estrogen deficiency is associated with a risk of persistent VMS, bone loss, VVA, mood swings, ischemic cardiac disease, dementia, cerebrovascular accidents, Parkinsonism, eye disorders, and increased overall mortality [22]. POI is a mandatory indication for hormone therapy.

(HRT) increases quality of life by eliminating VMS symptoms [23]. Estrogens modify the course of inflammation and regeneration of the epithelium. They improve the quality of skin [24]. (HRT) increases the risk of dry eye syndrome but reduces the risk of cataract and glaucoma [25]. Based on a meta-analysis, of existing observational studies, hormone

replacement therapy cause reduction in the risk of coronary artery disease by 28 percent and the mortality risk by 38 percent for current users [26]. A standard dose of estrogen prevents bone loss by inhibition of osteoclast activity and reducing bone turnover, and reduces the number of osteoporosis fractures in different sites, even in women without osteoporosis. However, HRT is not first-line therapy position for osteoporosis, but is helpful in prevention of osteoporosis. Studies about the effect on joints have inconsistent results but the positive effect dominates [27].

The effect of HRT on frailty syndrome is positive particularly in combination with exercise [28]. HRT improves mood and has a positive effect on menopause-associated depression [29]. Cognitive functions also improve by HRT but only in case of an early start (critical window hypothesis, healthy cell bias hypothesis) [30]. On the contrary, at the age over 65, it increases the risk of dementia and Alzheimer's disease [30].

2.3 Contraindication of HRT

Hormone replacement therapy, which includes estrogen therapy taken either by oral route or transdermally, has numerous contraindications that correlate with the adverse effects and relative toxicity of estrogen-based formulations. These include patients who have a known or suspected history of any form of breast or uterine cancer, a history of deep vein thrombosis (DVT) or pulmonary embolism, a history of stroke or myocardial infarction (MI) or a history of blood clotting disorders [31] those patients who have a history of stroke, particularly ischemic stroke events, might benefit from estrogen therapy because the current literature on the contraindication in patients with stroke is controversial [32].

These contraindications do not apply to estrogen taken by transvaginal route, as in the form of creams or suppositories, because the serum level of estrogen through this route is too low to generate any effect [33]. Combined preparations that include both estrogen and progestin are contraindicated in acute pelvic inflammatory disease, or history of pelvic inflammatory disease (unless there has been a subsequent intrauterine pregnancy), postpartum endometritis or infected abortion within past three months, known or suspected uterine or cervical malignancy, untreated acute cervicitis or vaginitis (including bacterial vaginosis) or other lower genital tract infections until the infection is controlled,

conditions which increase susceptibility to pelvic infections [34].

In women with risk factors for VTE or breast cancer (e.g. family history, obesity, smoking, physical inactivity, genetic factors, older age), the risk–benefit balance of HRT must be considered carefully before prescribing [35]. In women without risk factors such as normal weight, the risk profiles of oral and transdermal HRT appear to be equivalent. In women at increased risk for VTE, transdermal HRT and oral therapy are preferred as they may attenuate risk by avoiding first-pass metabolism [36].

2.4 Untoward Effects of Hormonal Replacement Therapy among Menopausal Women

There are several adverse effects of hormone replacement therapy that manifest in many different ways depending on the route of administration, and whether that route has local or systemic effects. A study exhibiting the adverse effects of hormone replacement therapy showed that unopposed estrogen correlates with high risk of occurrence of endometrial and breast cancer. A large prospective study exhibited that there is a positive relationship between estrogen, used in the form of estradiol, and increased breast cancer risk [37]. This study concluded that the relative risk was 1.7 (95 % CI 1.1 to 2.7) for women who used estrogen for more than nine years and 1.8 (95% CI 0.7 to 4.6) for those who used estradiol for more than six years. Another study showed that there is a correlation between estrogen therapy and the risk of stroke, but still not confirmed [38].

Hormone replacement therapy, as in estrogen therapy, has also been associated with increased risk of developing venous as well as pulmonary thromboembolism. Patients taking estrogen therapy for hormone replacement purposes should be thoroughly evaluated and considered on an individual level to assess whether the benefits of estrogen therapy outweigh the risks. Additionally, the most common adverse effects experienced by women taking estrogen only comprise breast tenderness, nausea, bloating, headaches, leg cramping, and vaginal "breakthrough" bleeding [39].

Studies have shown that side effects of estrogen replacement therapy include endometrial cancer, hypertension, gallbladder disease, angina pectoris, bloating, breast swelling, tenderness,

headaches, mood changes, nausea and vaginal bleeding. Progesterone is well tolerated, and many clinical studies have reported no side effects [38]. Side effects of progesterone may include abdominal cramps, back pain, breast tenderness, constipation, dizziness, nausea, edema, bleeding from vagina, hypotension, fatigue, dysphoria, depression, and irritability, among others, CNS depression, such as sedation and cognitive/memory impairment, can also occur [40].

Vaginal progesterone have also been associated with vaginal irritation, itchiness, and discharge, decreased libido, painful sexual intercourse, vaginal bleeding or spotting in association with cramps, and local warmth or a "feeling of coolness" without discharge. Intramuscular injection may lead to mild-to-moderate pain at the site of injection. High intramuscular doses of progesterone have been associated with high body temperature, which may be relieved with paracetamol treatment [41].

Undesirable off-target hormonal activity does not present in progesterone use, unlike various progestins, as a result, it is not associated with androgenic, antiandrogenic, estrogenic, or glucocorticoid effects [39]. Conversely, progesterone can still produce side effects related to its antimineralocorticoid and neurosteroid activity. There are fewer reports of breast tenderness with progesterone, compared to the progestin medroxyprogesterone acetate. In addition, the magnitude and duration of vaginal bleeding with progesterone are reported to be less longer than that with medroxyprogesterone acetate [42].

3. CONCLUSION

There are several different drug classes comprising estrogens, progestogens, and estrogen + progestogen combinations. Estrogen is the primary active component of HRT and is the recognized 'gold standard' for treating menopausal symptoms, particularly vasomotor symptoms. Vasomotor symptoms in menopause are associated with sleeping disorders, concentration disorders, and lowered quality of life and overall health condition (cardiovascular risk, cognitive functions, bone loss). They last on average for 7.4 years. Estrogens reduce the frequency of symptoms by 75% and their intensity by 87%. There are several adverse effects of hormone replacement therapy that manifest in many different ways depending on

the route of administration, and whether that route has local or systemic effects. Some of its serious side effects are: increased risk of endometrial and breast cancer, hypertension, gallbladder disease, angina pectoris, and increased risk of developing venous as well as pulmonary thromboembolism. Further research is needed to study the risks of menopausal HRT and pharmacological studies are needed to lower these risks and make its use safer with less side effects.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:

*The peer review history for this paper can be accessed here:
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