REVIEW ARTICLE

Rediscovering Hormone Replacement Therapy in Menopause: Understanding the Balance of Benefits and Risks through Landmark Studies

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Abstract

Menopause represents an inevitable transition in a woman's life, presenting with vasomotor symptoms, mood disorders, sleep difficulties, and prolonged risks such as osteoporosis and cardiovascular diseases. Hormone replacement therapy emerged as the cornerstone of menopausal management, particularly for alleviating symptoms and preventing postmenopausal osteoporosis.

However, findings from the Women's Health Initiative (WHI) study in 2002 highlighted increased risks of breast cancer, cardiovascular disease, and stroke associated with hormonal replacement treatment, leading to a significant global decline in its usage. Consequently, numerous women were deprived of essential therapy, endangering their health and quality of life.

This review presents the findings of the WHI study, discusses its methodological errors, and evaluates its benefits and harms. We explore landmark studies that have reestablished the benefits and risks of hormone replacement therapy over the past two decades. Guidelines supported by these findings are presented in this review.

Despite advancements, public perception of hormone replacement treatment remains influenced by outdated findings, limiting its utilization in many regions, especially in developing countries. Our objective is to provide evidence that misconceptions about hormone replacement therapy significantly impact women's general health and quality of life, as well as to clarify the short-term and long-term impacts of hormone replacement therapy.

We conclude that hormonal replacement treatment is effective and safe when administered according to established guidelines. Access to information, coupled with knowledgeable physicians who consistently interact with women, is as vital as the contributions of menopause healthcare specialists. Conflicting information from outdated professionals can likely lead to treatment failure in patients.

Keywords: menopause, women's health, estrogens, progestins, quality of life

INTRODUCTION

Menopause represents a transitional phase in a woman's life, marked by the cessation of ovarian function and the consequent decrease in estrogen levels. The most common symptoms associated with menopause are vasomotor symptoms (VMS), mood disorders, anxiety, depression, and sleep difficulties. Prolonged risks of menopause are most often osteoporosis and cardiovascular diseases. Vasomotor symptoms affect 30 to 80% of women (1). They are closely related to depression (2, 3) and reduced quality of life (4).

Throughout history, menopause has been inadequately researched and often seen as a natural phase of aging. This led to a lack of adequate medical and psychosocial support for most women. A key milestone in the field was the WHO Report on Menopause Research in the 1990s, which underscored menopause as a public health problem (5). This report emphasized the correlation between osteoporosis and cardiovascular risks during menopause, indicating that the prevalence of osteoporosis and heart disease nearly doubles within ten years post-menopause (5).

Hormone replacement therapy (HRT) has since then been considered as a gold standard for alleviating menopausal symptoms and mitigating postmenopausal osteoporosis. In the United States, roughly 38%–40% of postmenopausal women utilized hormone replacement therapy, equating to almost 15 million women annually in the late 1990s. However, everything changed when the results of the Women's Health Initiative study were released in early 2000, and for the last two decades, HRT has been rediscovered.

Our objective is to provide evidence that misconceptions about hormone replacement therapy significantly impact women's general health and quality of life, as well as to clarify the short-term and long-term impacts of hormone replacement therapy.

RESULTS OF THE WOMEN'S HEALTH INITIATIVE STUDY

The Women's Health Initiative (WHI) study included over 161,000 postmenopausal women. The primary goal of the study was to examine the impact of hormone therapy on cardiovascular health and bone density, and the incidence of breast cancer due to the fear of a connection between estrogen and breast cancer. Two interventions were used: combined estrogen-progestin therapy for women with a uterus and estrogen-only therapy for women without a uterus. The results, published in 2002, had significant impact at menopause management.

The WHI found that women on combined HRT had a 26% increased risk of breast cancer Furthermore, there was a twofold increase in the incidence of venous thromboembolism and an increased risk of coronary heart disease and stroke (7).

Women on estrogen-only therapy (who did not have a uterus) did not show a significant increase in the risk of breast cancer but did show increased risk of stroke and venous thromboembolism (8).

These findings contradicted earlier observational studies that suggested a cardioprotective effect of hormone replacement treatment (7). The study confirmed the efficacy of hormone therapy in reducing the risk of osteoporosis-related fractures by addressing fracture frequency and improving bone density (7).

WOMEN'S HEALTH INITIATIVE STUDY IMPACT

The negative findings of the study attracted significant attention and raised concerns within both medical and public domains. The media indicated that hormone replacement therapy presents more hazards than advantages for all women. Following such an impact, there was a swift decline in the prescription of hormone therapy. In the United States, the utilization of HRT diminished by around 50% over the subsequent two years (9).

Subsequent years saw the emergence of skepticism over the findings of the WHI study. The study was considered to have methodological and statistical flaws. The selection of subjects was unacceptable, as the study involved elderly women who experienced menopause over a decade ago, putting the implications of cardiovascular illnesses and breast cancer inapplicable to healthy younger women. Subsequently, only one type of conjugated estrogen (CEE) and progestin (medroxyprogesterone acetate) were evaluated. The risks associated with these formulations cannot be generalized to other formulations, including transdermal estrogen and micronized progesterone. Regardless, the results of this study caused considerable harm prior to being reevaluated. A large number of physicians stopped prescribing hormone replacement therapy, which resulted in a concomitant decrease in the number of women utilizing this treatment.

KEY PITFALLS OF THE WOMEN'S HEALTH INITIATIVE STUDY

Although the Women's Health Initiative (WHI) study was groundbreaking, it has met with significant criticism for its methodology, population selection, and interpretation of results. The main pitfalls are as follows:

1. Inclusion of Older Participants

The subjects in the study were women between the ages of 50 and 79, with an average age of 63. Therefore, its results cannot be generalized to the risk of cardiovascular disease and breast cancer in younger women (10).

2. Neglected Time Hypothesis

Most of the women were 10 or 20 years after menopause. Which means that the study did not take into account the "temporal hypothesis", according to which the impact of HRT on cardiovascular status depends on the time of initiation of therapy. HRT was introduced to participants even a decade or more after menopause; therefore, it resulted in increased cardiovascular risk. The applicability of these results to women who started therapy closer to menopause is limited (11).

3. Use of Conjugated Equine Estrogens (CEE) and Medroxyprogesterone Acetate (MPA)

The study used CEE and MPA, which do not cover all HRT formulations. Modern formulations, such as transdermal estradiol and micronized progesterone, show a reduced risk. Therefore, these results are not applicable to newer and safer regimens of hormone replacement therapy (12).

4. Overestimated Breast Cancer Risks

In this study, the risks associated with HRT and the risk of breast cancer are overemphasized. The association of these risks did not take into account the type of replacement therapy, duration, or time of introduction. On the other hand, therapy with estrogen alone did not lead to an increase in the risk of cancer, but these results were not sufficiently presented (13). Furthermore, the reported 26% increase in breast cancer cases corresponds to a total of 8 additional cases per 10,000 patients. This translates to an increase in absolute risk of 0.08% for breast cancer (14).

5. Ethnic and Demographic Limitations

The subjects were predominantly white postmenopausal women, which limits the applicability of the findings to other ethnic groups. The results do not represent a different population of menopausal women worldwide (15).

Short Follow-Up for Primary Outcomes

Postmenopausal women treated with combined therapy were observed for an average of 5.2 years, whereas those receiving estrogen therapy alone were observed for 7.1 years, which is insufficient for a thorough evaluation of long-term risk. The brief follow-up period may have compromised the evaluation of long-term cardiovascular risks, as well as those related to osteoporosis and dementia (16).

Media Misinterpretation of Results

Media reports after the release of the WHI study results outlined the risks of hormone therapy for all women in general, lacking appropriate context. This resulted in increased fear, and many women then denied therapy, resulting in increased risks of osteoporosis, cardiovascular disease, and diminished quality of life (6).

LANDMARK STUDIES BEHIND THE CURRENT STANCE

Over the past two decades, research on menopause has focused on challenging the findings of the WHI study. The new studies provided important insights into the true risks and benefits. Their findings outline the significance of initiating hormone replacement therapy in younger women, ideally within 10 years post-menopause—while considering individual risk assessments. This approach has minimized risks and optimized benefits. Our review outlines significant studies that have influenced the current understanding of the safety and efficacy of hormone replacement therapy.

CURRENT GUIDELINES ON HORMONE REPLACEMENT THERAPY: COMBINED NICE AND NAMS PERSPECTIVES

The National Institute for Health and Clinical Excellence (NICE) guidelines highlight the importance of an individual approach to hormone replacement therapy taking into account woman's age, symptoms, and associated risk factors. Estrogen-only therapy is safer for women lacking uterus, whereas combined estrogen-progestogen therapy is essential for those with a uterus to avert endometrial hyperplasia. NICE confirms the effectiveness of HRT in alleviating vasomotor symptoms and preventing osteoporosis. However, it is recommending against its use

Table 1. Landmark post-WHI studies on menopause overview

Trial	Sample	Findings
KEEPS (Kronos Early Estrogen Prevention Study) (2005-2010) (17)	727 healthy women in early postmenopausal aged 48 to 58	low doses of oral and transdermal estrogen improve vasomotor menopausal symptoms and quality of life; no negative cardiovascular risks were observed; based on this research, low-dose hormone replacement therapy is safe and effective for younger, healthy postmenopausal women
Danish Osteoporosis Prevention Study (DOPS) (1990-2010) (18)	2016 healthy women aged 45-58	overall fracture risk and the risk of forearm fractures were significantly reduced in woman using HRT
WHI Follow-Up Studies (2013, 2017, 2020) (19)	27000 women aged over 13	HRT in women younger than 60 or within ten years after menopause does not significantly increase cardiovascular risk while providing relief of symptoms and improving quality of life
ELITE (Early versus Late Intervention Trial with Estradiol) Study (2005-2011) (20)	643 postmenopausal women divided into two groups: early and late postmenopausal	progression of atherosclerosis was significantly reduced in women who started HRT 6 years before the onset of menopause: this protective effect was not found in women who started therapy six years after the onset of menopause
Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC) (2019) (13)	meta-analysis of 54 studies in 26 countries included 53,297 women with breast cancer and 100,239 women without breast cancer	small increase in breast cancer risk in current users of combined oral contraceptives (COC) and in women who had stopped use in the past 10 years, without evidence of an increased risk in more than 10 years after stopping use.
The ESTHER Study (1998-2018) (21)	271 women over 20 years evaluated transdermal estrogen treatment compared to oral HRT	transdermal estrogen was associated with a lower risk of venous thromboembolism compared to oral formulations
WHI Estrogen-Alone Trial (2004, Follow-Up 2020) (11)	10,739 postmenopausal women over seven years	20% reduction in breast cancer incidence on conjugated equine estrogen monotherapy
SWAN Study (1996-present) (22)	3302 ethnically diverse women aged 42–52 investigated physiological changes related to menopause	–5% annual decline in bone mineral density (BMD) during early postmenopause and significant associations between hormonal changes and increased risks of osteoporosis, cardiovascular disease, anxiety, depression, and metabolic syndrome
Cognitive Health and Dementia Studies (2021) (23)	more than 8,000 postmenopausal women	HRT may contribute to cognitive improvement and reduce the risk of dementia when started early

for the primary prevention of cardiovascular disease or dementia (24).

The Menopause Society, formerly the North American Menopause Society (NAMS), guidelines are consistent with NICE in endorsing hormone replacement therapy for symptomatic women, especially those under 60 or within a decade of menopause onset. They recommend utilizing low doses for the minimal duration required while also taking into account newer hormone replacement therapy formulations, such as transdermal estradiol and micronized progesterone, because of their advantageous safety profiles (25). Both organizations highlight the significance of shared decision-making grounded in individual benefits and risks.

Key Recommendations of NAMS Hormone Therapy Position Statement

- Hormone replacement treatment is the most efficacious treatment for vasomotor and genitourinary symptoms of menopause and mitigates bone loss and fractures.
- The risk associated with hormone therapy is dependent upon the type, dosage, duration, mode of administration, and the time of therapy initiation. A personalized strategy yields the optimal benefit-risk ratio.
- The advantages of the therapy surpass the possible hazards when administered to women under 60 years of age or within 10 years of starting menopause.
- For genitourinary symptoms that do not respond to systemic hormone therapy, recommend using low-dose vaginal estrogen or alternative approved treatments like vaginal DHEA or oral ospemifene (25).

DISCUSSION

The Women's Health Initiative study showed a strong association between the risk of breast cancer, cardiovascular events and stroke, and hormone replacement therapy. These results were followed by a significant reduction in the HRT use.

Over the past two decades, there has been a renewed interest in hormone replacement therapy. Subsequent research showed numerous flaws in WHI study and pointed out to the effectiveness and safety of HRT if the approach is individualized, especially if it takes into account age, time of introduction of therapy, associated diseases, and HRT formulation. Today, we possess robust evidence regarding the risks and benefits of HRT, as well as evidence-based guidelines for its use.

Studies such as DOPS, WHI Follow-Up Studies, and the Global Consensus Statement on Menopausal Hormone Therapy have not observed a significant increase in breast cancer risk (18, 19). The results from the Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC) show that combined estrogen-progestogen therapy in combiner oral contraceptives is linked to a slightly higher risk, but the absolute risk is still very low (13). The estrogen and progestin used in combined oral contraceptives are different from the estrogen and progesterone used in hormone replacement therapy. COCs contain conjugated hormones, while HRT contain regulated bioidentical hormones. The doses in HRT are also much lower because it is not aimed at stopping ovulation, which is the main goal of COCs. On the other hand, the WHI estrogen-alone trial found a 20% reduction in breast cancer incidence in estrogen treatment only, and long-term follow-up confirms continued safety (8). Several studies, such as KEEPS, ELITE, and DOPS, supported the "timing hypothesis" (18), suggesting that starting hormone therapy nearer to menopause may provide cardiovascular advantages and lower risks (17, 18, 20).

When considering the type of HRT formulation, findings from KEEPS, ESTHER, and WHI follow-up studies may be beneficial. Findings stated that transdermal estrogen improved vasomotor menopausal symptoms and quality of life with no increase in cardiovascular risk. The findings revealed a lower associa-

tion between transdermal estrogen and venous thromboembolism when compared to oral formulation. These findings also provide reassurance regarding the risk of breast cancer (18, 25). Hormone therapy clearly benefits bone health and reduces fracture risk (16, 19). Furthermore, research such as SWAN and Cognitive Health and Dementia Studies (2021) indicates that the early commencement of hormone therapy may help maintain cognitive function (19, 23).

A key takeaway from post-WHI research is the necessity of customized HRT approaches. This approach leads us to a personalized, evidence-based practice that balances risks and benefits.

Bosnia and Herzegovina is a developing country. Despite the medical profession's efforts to align with contemporary medicine on critical topics, several matters remain unaddressed – menopause being one of them. In our society, women's health during menopause is often viewed as a luxury rather than a fundamental necessity. The addition of prejudice-based treatment to this fact creates a vicious cycle that affects menopausal women. For medical professionals, breaking this cycle with knowledge is essential to paving the way for a medically evidence-based approach that ensures a fulfilling and balanced midlife experience for women. This review is significant as it represents an initial step in this direction, setting a starting point for further progress and research in this field in our country.

CONCLUSION

Regardless of numerous studies and results obtained in the last twenty years, the public's opinion about HRT is mostly unchanged, especially in developing countries. This outdated view has adversely impacted the health and quality of life of women in many regions globally.

Menopausal hormone therapy is the most effective intervention for vasomotor symptoms. There is no alternative that is as effective as hormone replacement therapy in treating menopause symptoms and preventing diseases such as cardiovascular disease, cognitive decline, and osteoporosis. However, currently, hormone replacement therapy is only approved for VMS and osteoporosis prevention.

Unless there are contraindications, clinicians should thoroughly evaluate the short- and long-term benefits and risks before providing treatment to women seeking HRT. Research indicates that hormone therapy is both safe and effective for women under 60 years of age, with menopause onset within 10 years. The risk is further minimized with treatment duration of less than 5 years, along with the use of micronized progesterone (for women with uterus) and transdermal preparations of estrogen.

Enhanced access to information in less developed countries, coupled with knowledgeable physicians who consistently interact with women, is as vital as the contributions of menopause healthcare specialists. Conflicting information from outsourced medical professionals can likely lead to a treatment failure in patients.

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