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Hormone Replacement Therapy in Menopause: A Comprehensive Review

Michalina Cyrulik
University Hospital in Poznań
Przybyszewskiego 49, 60-355 Poznań
https://orcid.org/0009-0008-9174-801X
michalina.cyrulik@onet.pl

Natalia Ramlau
University Hospital in Poznań
Przybyszewskiego 49, 60-355 Poznań
https://orcid.org/0009-0006-3595-1529
naramlau@gmail.com

Dominika Kolenda
S.T. Dąbrowski Hospital in Puszczykowo
Józefa Ignacego Kraszewskiego 11, 62-040 Puszczykowo
https://orcid.org/0009-0007-9243-6723
dominika.kolenda98@gmail.com

Zuzanna Fischer
Hospital in Ostrow Wielkopolski
Limanowskiego 20-22, 63-400 Ostrów Wielkopolski
https://orcid.org/0009-0008-3530-5660
zuzannakrysciak@gmail.com

Marcin Podolak
Medical Center HCP
28 czerwca 1956 r. nr 194, 61-485 Poznań
https://orcid.org/0009-0000-2839-728X
marcin.podolak2@gmail.com

Michał Hładki
Medical Center HCP
28 czerwca 1956 r. nr 194, 61-485 Poznań
https://orcid.org/0009-0000-2420-2203
hladki.mt@gmail.com

Michalina Simachi
University Hospital in Poznań
Przybyszewskiego 49, 60-355 Poznań
https://orcid.org/0009-0002-9137-0535
skrzypem97@gmail.com

Michalina Janiszewska
University Hospital in Poznań
Przybyszewskiego 49, 60-355 Poznań
https://orcid.org/0009-0001-1321-8565
janiszewska.michalina@gmail.com

Beata Imbirska
Regional Hospital in Poznań,
Juraszów 7/19, 60-479 Poznań
https://orcid.org/0009-0002-2941-3418
beata.imb@gmail.com

Marta Prager-Zimny
University Hospital in Poznań
Przybyszewskiego 49, 60-355 Poznań
https://orcid.org/0009-0000-6412-3745
marta.prager98@gmail.com

Key words

Menopause, Hormone Replacement Therapy, estrogens, progestogens, vasomotor symptoms, bone health

Abstract

Menopause is a natural, physiological milestone in a woman's life. It is defined by the permanent end of menstruation, which follows the depletion of ovarian follicles and a decline in estrogen and inhibin levels. This hormonal transition can give rise to numerous symptoms, including hot flashes, night sweats, mood swings, sleep disturbances, vaginal dryness, and decreased libido. These symptoms can significantly impair quality of life. Hormone therapy

(HT) is the most effective treatment for alleviating vasomotor and genitourinary symptoms, and it offers protective benefits for bone health by reducing the risk of osteoporosis. However, HT is also associated with an increased risk of venous thromboembolism and certain hormone-dependent cancers, such as breast and endometrial cancer. Therefore, careful evaluation is necessary before initiating treatment. Emerging evidence highlights the positive effects of non-hormonal strategies, such as physical activity and diets rich in phytoestrogens. These strategies may serve as alternatives to or complements of HT for managing menopausal symptoms. Ultimately, treatment plans must be tailored to each woman's symptoms, health status, and preferences to optimize therapeutic outcomes and improve quality of life during menopause.

Keywords

Menopause, Hormone Replacement Therapy, estrogens, progestogens, bone health

1.Introduction

Menopause is a physiological process characterized by the irreversible cessation of menstruation, typically confirmed after twelve consecutive months without a menstrual period. It results from the natural decline in ovarian function and estrogen production, rather than from any pathological condition. This transition marks the end of spontaneous ovulation and a woman’s reproductive capacity. In Western populations, the average age of menopause is approximately 51 years [1,2]. This period of transition is often accompanied by a range of physical, emotional, and metabolic symptoms that may clearly reduce a woman’s quality of life. Common manifestations include hot flashes, vasomotor symptoms, sleep irregularities, mood fluctuations, vaginal dryness or irregular uterine bleeding, and increased bone resorption leading to reduced bone density [2].

Hormone replacement therapy (HRT) remains the most effective treatment for moderate to severe menopausal symptoms, particularly vasomotor disturbances and urogenital complaints.

It has been shown to significantly reduce the frequency and intensity of hot flashes and night sweats, while also alleviating symptoms related to estrogen deficiency when administered locally. Moreover, HRT contributes to the preservation of bone mineral density, thereby decreasing the risk of osteoporotic fractures. Observational studies additionally suggest that postmenopausal hormone therapy may offer protective benefits against cognitive decline, although further research is needed to confirm these associations [3,4]. Despite its proven therapeutic benefits, HRT has been the subject of long-standing controversy due to concerns about its safety—especially regarding the risk of cardiovascular diseases, hormone-sensitive cancers, and thromboembolic events [5]. Current guidelines highlight a personalized approach to HRT, taking into account the woman's age, time since menopause onset, and comorbid conditions. In recent years, growing attention has been given to individualizing treatment and developing safer hormone therapy regimens tailored to each patient's risk profile [6]. In view of the evolving body of evidence and the continual refinement of clinical guidelines, this review aims to present a thorough and up-to-date analysis of hormone replacement therapy (HRT) in menopausal women. It explores the physiological basis for HRT, outlines available therapeutic options, and examines current indications and contraindications for treatment. Particular emphasis is placed on critically evaluating the benefits and potential risks associated with HRT, as well as summarizing contemporary recommendations from leading medical organizations.

2.Physiology of Menopause

Menopause is a natural and terminal transition in a woman's reproductive life. It is marked by permanent cessation of menstruation, which follows the depletion of ovarian follicular activity. This process begins with a progressive decline in the quantity and quality of ovarian follicles, which leads to reduced secretion of estradiol and inhibins [7,8]. Inhibin B, which is produced by the granulosa cells of early antral follicles, plays a critical role in negatively regulating the secretion of follicle-stimulating hormone (FSH). During the menopausal transition, the shrinking pool of follicles causes a significant decrease in inhibin B levels even before notable changes in estradiol concentrations become apparent [9]. This early inhibin B decline removes its inhibitory effect on the anterior pituitary, resulting in an increase in FSH levels — a defining hormonal characteristic of perimenopause [9]. The loss of inhibin A, which is produced by the

corpus luteum and dominant follicles, contributes to the variability of FSH levels and menstrual cycle irregularity, as ovulatory cycles become less frequent [9].

Together, these changes in inhibin secretion and diminished estradiol and inhibin B disrupt the hypothalamic-pituitary-ovarian axis, resulting in loss of negative feedback and elevated gonadotropins, particularly FSH and, to a lesser extent, LH [7, 8]. After menopause, estrone, which is derived primarily from the peripheral aromatization of androstenedione in adipose tissue, becomes the main circulating estrogen; however, its levels are significantly lower than premenopausal estradiol concentrations [10, 11]. The abrupt decline in ovarian estrogen production, combined with relative androgen excess due to continued adrenal secretion, underlies many of the somatic and psychological symptoms associated with menopause [8,12]. Additionally, the hypoestrogenic state has long-term physiological consequences. These include changes in bone remodeling dynamics, alterations in lipid metabolism, and modifications in vascular endothelial function. All of these consequences contribute to an increased risk of osteoporosis and cardiovascular disease in postmenopausal women [8, 10].

3.Types and Administration of Hormone Therapy

There are various forms of hormone therapy available for menopausal symptoms, each with distinct advantages and associated risks[14]. Studies show that oral and transdermal estrogen administration had similar improvements in bone mineral density, glucose metabolism, and lipid profiles. However, the most significant clinical distinction is the increased risk of venous thromboembolism (VTE) associated with oral estrogen administration. Transdermal hormone replacement therapy (HRT) is considered safer in this respect [13].

For individuals with an intact uterus adding progestogens—administered orally, via combination patches, or through intrauterine systems—is essential to prevent endometrial hyperplasia and reduce the risk of endometrial cancer [14]. Estrogen and progestogens can be administered continuously to eliminate menstrual bleeding or sequentially to mimic the natural cycle with monthly withdrawal bleeding, which is often preferred in the early perimenopausal phase [14]. The appropriate type and avenue of hormone therapy should be selected based on the frequency and severity of menopausal symptoms, the patient's age, and underlying health

risks. This ensures that treatment decisions are personalized to maximize therapeutic benefits and minimize potential harms [14].

4.Indications and Contraindications for Hormone Therapy

Hormone replacement therapy (HRT) is considered the most effective treatment for moderate to severe menopausal symptoms such as hot flashes, night sweats, and sleep disturbances, particularly in women younger than 60 or within 10 years of menopause, when the benefits clearly outweigh the risks and the therapy is supported by strong clinical evidence [15,16]. HRT is also recommended for managing genitourinary syndrome of menopause, which can cause vaginal dryness, pain during intercourse, and recurrent urinary tract infections, as it helps restore moisture and elasticity to the vaginal tissues [15,16]. Additionally, hormone therapy is indicated for women who experience premature menopause or ovarian failure before the age of 45, as prolonged estrogen deficiency in these women significantly increases the risk of osteoporosis and cardiovascular disease [15,17].

However, certain conditions make HRT unsafe. Absolute contraindications include active or previous breast cancer, hormone-dependent endometrial cancer, unexplained vaginal bleeding, a history of deep vein thrombosis or pulmonary embolism, active liver disease, uncontrolled high blood pressure, or previous cardiovascular events such as heart attack or stroke [15,16]. Relative contraindications involve a high decennial cardiovascular risk (over 10%), starting HRT more than 10 years after menopause, migraine with aura, severe hypertriglyceridemia, or obesity combined with other cardiovascular risk factors [15,17]. In these situations, the decision to initiate HRT should be made individually, through a shared decision-making process that considers the woman's health history, symptom severity, and personal preferences, ensuring that the potential benefits of treatment clearly outweigh the risks [15–17].

5.Risks of Hormone Therapy

Although hormone therapy offers significant benefits for many women, it is essential to carefully consider its potential risks. Consequently, a comprehensive evaluation of each case is

imperative to ascertain the most suitable formulation and treatment regimen, meticulously customized to the patient's specific requirements [15].

Hormone therapy, especially when taken orally, increases the risk of venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism. Studies have shown that oral hormone therapy nearly doubles the risk of these events compared to placebo. However, this risk depends on the formulation and method of administration: transdermal hormone therapy does not appear to raise the risk of VTE, and certain types of progestogens may be associated with a lower risk than traditional synthetic options. Therefore, selecting the appropriate formulation and route can help reduce the risk of thrombotic complications associated with hormone therapy [15].

Hormone therapy has been associated with an increased risk of ischemic stroke, particularly when started many years after menopause. Data from the WHI trial showed a higher risk of stroke in women aged 50–79 taking oral conjugated estrogens alone or with progestogen, without clear differences across age groups. However, longer-term follow-up suggested this elevated risk was not statistically significant over time. Importantly, systematic reviews, including the Cochrane analysis, indicate that women who begin hormone therapy before age 60 or within 10 years of menopause do not appear to have an increased risk of stroke. These findings highlight the importance of timing when considering hormone therapy to minimize the risk of cerebrovascular events [18].

Estrogen-only therapy, meaning the use of estrogen without adding a progestogen, has been consistently shown to increase the risk of endometrial cancer in women with an intact uterus. According to recent analyses, estrogen-only HT raises endometrial cancer risk by 45% to more than fourfold, with the risk increasing further with longer duration of therapy and higher doses. In contrast, adding a synthetic progestogen to hormone therapy significantly reduces this risk by counteracting estrogen’s proliferative effects on the endometrial lining. These findings highlight the importance of including a progestogen component in HT regimens for women with an intact uterus to minimize the risk of endometrial hyperplasia and cancer. Therefore, individualized treatment planning that ensures adequate endometrial protection is crucial when considering hormone therapy in menopausal women [19].

Long-term use of hormone therapy, especially combined estrogen-progestogen treatments, has been consistently associated with an increased risk of breast cancer in women. Evidence indicates that the longer hormone therapy is used, the higher the risk becomes, with some analyses showing a doubling of breast cancer risk in women who used hormone therapy for ten years compared to those who used it for five years. These findings underscore the importance of carefully weighing the duration of therapy and individual risk factors when considering hormone treatment in menopausal women to minimize the potential for developing breast cancer [20].

6.Benefits of Hormone Therapy

Hormone therapy has a positive effect on alleviating menopausal symptoms by effectively reducing hot flashes, night sweats, and other discomforts, thereby significantly improving women's quality of life [21].

Hormone therapy provides significant benefits for bone health in postmenopausal women by reducing bone resorption, preserving bone mineral density, and decreasing the risk of osteoporotic fractures. Data from the Women's Health Initiative demonstrated that systemic hormone therapy reduced the overall risk of fractures by 28%, major osteoporotic fractures by 40%, and hip fractures by 34% compared to placebo. These findings confirm that hormone therapy is an effective option for preventing osteoporosis-related fractures in women who are at an appropriate age and stage of menopause to benefit from treatment. However, the decision to use hormone therapy for bone protection should always consider the individual's risk profile and balance potential benefits against known risks [22].

Local vaginal estrogen has long been considered the treatment of choice for postmenopausal women experiencing vulvovaginal symptoms of menopause, as it effectively addresses

genitourinary syndrome of menopause (GSM) using significantly lower estrogen doses than systemic therapy. Studies show that even a third of women receiving systemic hormone therapy may still require additional local estrogen for persistent GSM symptoms. The selection of a specific local estrogen preparation should be tailored to the severity of symptoms and the patient's preferences. Systematic reviews of efficacy and safety consistently demonstrate that local estrogen therapy is superior to placebo in improving vaginal dryness, dyspareunia, and other urogenital symptoms, while also achieving objective improvements in vaginal epithelial health, pH normalization, and restoration of beneficial Lactobacillus populations. What is more, by relieving vaginal dryness and discomfort during sexual activity, local estrogen therapy can significantly enhance sexual satisfaction and overall quality of life for postmenopausal women [23].

Weight gain and central fat redistribution are common after menopause, often resulting in increased abdominal fat, insulin resistance, dyslipidemia, and higher cardiovascular risk due to the decline in estradiol levels. Although hormone therapy (HT) is generally weight neutral in postmenopausal women, it has been shown to positively influence body composition by increasing lean body mass and reducing visceral fat. For example, in the Women's Health Initiative, women receiving conjugated estrogens plus medroxyprogesterone acetate experienced significant reductions in BMI and waist circumference during the first year of therapy compared to placebo. Furthermore, meta-analyses have demonstrated that HT increases HDL cholesterol while reducing LDL cholesterol, the LDL/HDL ratio, and lipoprotein (a), leading to an overall improvement in lipid profiles. These metabolic benefits may be more pronounced with oral formulations compared to transdermal preparations, highlighting the importance of selecting the appropriate type and route of therapy for each individual patient [15].

The role of physicians and healthcare providers is to clearly inform patients about both the benefits and the limitations of HRT, taking into account patients' preferences and concerns. Above all, it is important to implement proven preventive measures, including regular breast self-examination (although controversial), clinical breast examinations, annual mammography, and adequate calcium and vitamin D intake, as well as adopting an appropriate exercise regimen and a low-fat diet [24].

7.Current recommendations for hormone therapy

According to recent guidelines, menopausal hormone therapy (MHT) is the most effective treatment for relieving moderate to severe vasomotor symptoms (VMS) and genitourinary syndrome of menopause, particularly in women younger than 60 years or within 10 years of menopause onset, when the benefits outweigh the risks [25,26]. Therapy should always be individualized, taking into account symptom severity, time since menopause, medical history, cardiovascular and thromboembolic risk, and the patient's preferences [25,26]. Low-dose and transdermal estrogen formulations are preferred for women with elevated cardiovascular or metabolic risk profiles, as these routes are associated with a lower risk of adverse events [26]. In women with an intact uterus, combining estrogen with a progestogen is essential to protect against endometrial hyperplasia, while estrogen-only therapy is appropriate for those who have undergone hysterectomy [25]. Regular reassessment of therapy's necessity and safety, as well as shared decision-making between healthcare providers and patients, are emphasized to ensure effective and safe long-term treatment [25,26].

8.Alternatives to hormone therapy: exercise, nutrition, and pharmacologic options

Physical activity is a valuable non-hormonal strategy for alleviating menopausal symptoms and enhancing overall quality of life in postmenopausal women. Sedentary lifestyle is common after menopause and is associated with declining health and reduced well-being. Encouragingly, studies have shown that engaging in regular exercise—such as Pilates, weight training, or aerobics—can significantly reduce vasomotor, psychological, and physical symptoms related to menopause. Even a relatively short, 8-week Pilates program has been shown to effectively decrease these symptoms, highlighting that lifestyle interventions can serve as practical and accessible alternatives or complements to hormone therapy. While urogenital symptoms may require longer or additional interventions, regular physical activity remains a key component of non-hormonal management strategies for menopausal women [27].

Nutrition also plays a crucial role in menopausal health and can help alleviate menopausal symptoms. Phytoestrogens, naturally occurring plant compounds with estrogen-like properties, represent a promising non-hormonal alternative for symptom relief. Notably, St. John's wort (Hypericum perforatum) and fennel (Foeniculum vulgare) stand out for their potential benefits. St. John's wort contains phytoestrogens along with other bioactive compounds, such as flavonoids and phenolic acids, which together may help reduce psychological symptoms of menopause, including mood disturbances and anxiety, through their combined antidepressant and estrogenic effects. Meanwhile, fennel, rich in isoflavones and phenolic compounds, has been shown to alleviate vasomotor symptoms, improve vaginal dryness, enhance sexual satisfaction, and support better sleep quality, making it a valuable option for women who cannot or prefer not to use hormone therapy [28].

In addition to lifestyle and dietary interventions, pharmacologic options like selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) offer another non-hormonal alternative. Studies indicate that these medications can reduce the frequency and severity of hot flashes by 10% to 64%, depending on the specific agent and study population. Escitalopram, extended-release paroxetine, and extended-release venlafaxine have shown the highest efficacy among these drugs. Although generally less effective than hormone therapy, SSRIs and SNRIs provide a viable option for women seeking to avoid or who are ineligible for hormone-based treatments. Common side effects, such as nausea, constipation, and dry mouth, are typically mild and tend to resolve within the first week of therapy [29].

9.Future perspectives and research directions

Future research should focus on determining which subgroups of women benefit most from hormone therapy and how best to tailor the formulation, dosage, and administration method for individual patients [30]. Studies should also explore combined interventions, such as integrating lifestyle modifications with pharmacologic or hormonal treatments, to enhance symptom management while minimizing risks [31]. Additionally, large-scale, long-term trials comparing hormone therapy to non-hormonal alternatives are needed to clarify the efficacy, safety, and patient satisfaction associated with each approach. Expanding research on alternative therapies

like phytoestrogens, SSRIs/SNRIs, and exercise will support the development of comprehensive, personalized strategies for menopause management [27-29].

10.Conclusion

Menopausal hormone therapy is currently the most effective approach for managing the vasomotor and genitourinary symptoms of menopause. It provides many women with substantial improvements in quality of life [3]. However, therapy should be tailored to each patient, considering factors such as age, time since menopause, comorbidities, and personal preferences, in order to balance the benefits with the potential risks, such as venous thromboembolism (VTE), stroke, endometrial cancer, and breast cancer [15]. Non-hormonal alternatives, including exercise, diets rich in phytoestrogens, and pharmacological options such as SSRIs and SNRIs, can effectively relieve symptoms for women who cannot or prefer not to use hormone therapy. Open communication between healthcare providers and patients is essential for making informed decisions and achieving optimal treatment outcomes [31].

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10. Data were obtained from

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11. Author Contributions:

- Conceptualization: Michalina Cyrulik
- Methodology: Marcin Podolak, Michalina Cyrulik
- Software: Marta Prager, Michalina Skrzypek
- Check: Marcin Podolak, Natalia Ramlau
- Formal Analysis: Beata Imbirska, Michalina Skrzypek
- Investigation: Michalina Cyrulik, Michał Hładki
- Resources: Natalia Ramlau, Zuzanna Fischer

- Data Curation: Beata Imbirska, Zuzanna Fischer
- Writing – Original Draft Preparation: Michalina Cyrulik
- Writing – Review & Editing: Michalina Janiszewska, Michalina Cyrulik
- Visualization: Natalia Ramlau, Zuzanna Fischer
- Supervision: Michał Hładki, Michalina Cyrulik
- Project Administration: Michalina Cyrulik

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