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HORMONE REPLACEMENT THERAPY IN CLIMACTERIC AND MENOPAUSE: ANALYSIS OF BENEFITS AND RISKS - A SYSTEMATIC REVIEW

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Pedro Ferreira Paiva Filho[1], Ana Carolina Zuccolo Pontes[2], Julia Hofling[3], Layana Patrícia de Paiva Marques[4], Bruna dos Santos Martins Moraes[5], Giovanna Carvalho Merisio Correia[6], Ana Clara Junqueira Tedeschi[7], Maria Vitória Cordeiro Silva[8], Breno Felipe dos Santos[9], Juliano Henrique Sampaio Simão[10] and Luana Carolina Rodrigues Guimarães[11]

ABSTRACT

Objective: This study aims to analyze the scientific production on Hormone Replacement Therapy (HRT) in climacteric and menopausal patients, identifying its main benefits and risks, as well as the best clinical practices associated with this therapeutic intervention. Methodology: A systematic review was carried out to understand the essential aspects of HRT. The research was guided by the question, "What are the main benefits and risks associated with Hormone Replacement Therapy in climacteric and menopause, and what are the recommended clinical practices?" To answer this question, searches were performed in the PubMed Central (PMC) database using the descriptors combined with the Boolean term "AND": (Hormone Replacement Therapy) AND (Menopause) AND (Women's

[1] Doctor from the University Center of Patos (UNIFIP)
E-mail: pedrofilho@med.fiponline.edu.br
[2] Medical Doctor, Albert Einstein Israeli Faculty of Sciences and Health
E-mail: anacarol.pontes@hotmail.com
[3] Medical Degree from PUC-Campinas
E-mail: julia_hofling@hotmail.com
Lattes: http://lattes.cnpq.br/2472405929188476
[4] Medical Degree from Centro Universitário Facid Wyden - UNIFACID
E-mail: lpatriciamrqs@gmail.com
Lattes: http://lattes.cnpq.br/9643279493424958
[5] Medical Doctor, Federal University of Amapá
E-mail: bruna.moraes78@hotmail.com
Lattes: http://lattes.cnpq.br/3509135412458006
[6] Medical Doctor from the Faculty of Medicine of Presidente Prudente (UNOESTE)
E-mail: giovannacarvalho08@hotmail.com
Lattes: http://lattes.cnpq.br/6133320916277839
[7] Undergraduate student of medicine at the University of Franca (UNIFRAN)
E-mail: acjtedeschi@gmail.com
[8] Undergraduate student of medicine at the University of Araraquara (UNIARA)
Email: mavicord@hotmail.com
[9] Undergraduate student of medicine at the Unoeste - Presidente Prudente
E-mail: Brenosantos360@gmail.com
Lattes: 5286848620072464
[10] Undergraduate student of medicine at the Centro Universitário Municipal de Franca - Unifacef
E-mail: juliano.ssimao@hotmail.com
[11] Guidance counselor
Physician from the Faculty of Medicine of Itajubá (FMIT) - Itajubá/SP; Gynecologist and Obstetrician and Master in Health Promotion
E-mail: luanarodriguesgo@gmail.com

Health) and (Hormone Replacement Therapy) AND (Climacteric). The initial search resulted in 127 articles, of which 60 were excluded because they were duplicates. A total of 67 unique articles were selected, and after applying inclusion and exclusion criteria, 29 articles were analyzed in detail, of which 16 were used to compose the final collection. Results: HRT demonstrates significant efficacy in relieving vasomotor symptoms such as hot flashes and night sweats, as well as in improving the bone, cardiovascular and sexual function of menopausal women. However, HRT is not without risks, including increased incidence of breast, endometrial, and gastric cancers, as well as cardiovascular risks such as venous thromboembolism, stroke, and myocardial infarction. The choice of hormone formulation, dosage, and route of administration are critical factors in minimizing these risks and maximizing benefits. Alternative therapies and lifestyle changes also play an important role in managing menopausal symptoms and may be considered for women who are unwilling or unable to use HRT. Conclusion: HRT offers significant benefits, but it also presents risks that should be carefully evaluated. Personalization of therapy, based on individual needs and risk profiles, is essential to achieve the best results. Ongoing research and individualized clinical practice are key to advancing understanding the benefits and risks associated with HRT, providing high-quality care, and improving women's quality of life during the climacteric and beyond. Effective public health policies, combined with public education and awareness, are essential to maximize the benefits of HRT and protect the health of future generations.

Keywords: Hormone Replacement Therapy. Menopause. Climacteric. Women's Health. Benefits and Risks.

INTRODUCTION

The climacteric is the transition period between the reproductive and non-reproductive stage of the woman, characterized by the progressive decline of ovarian function and female fertility, usually covering women between 40 and 65 years of age. During this context, menopause occurs, defined as the permanent cessation of menses after 12 consecutive months of amenorrhea, being a retrospective clinical diagnosis. This can be early when it occurs before the age of 40 and late after the age of 55 (Baccaro et al., 2022).

The pathogenesis of climacteric involves complex hormonal aspects, including the entire hypothalamic-pituitary-ovarian axis, with greater relevance in the ovary. Gradually, there is a reduction of ovarian follicles that become insensitive to pituitary gonadotropins (LH and FSH). During this period, a significant decrease in ovarian size is observed, suggesting an interrelationship between volumetric modification and functional capacity of the gonad. Smaller ovarian volumes are observed in postmenopausal women compared to premenopausal women (Melo, 2010).

Ovarian hormone production begins with the pulsatile release of GnRH by the hypothalamus, stimulating the adenohypophysis to synthesize FSH and LH, driving the ovaries to produce estrogen, progesterone, and testosterone. During the climacteric, the ovarian hormone synthesis capacity reduces, generating an increase in FSH and LH in an attempt to increase hormone production by the ovaries (Urbanetz, 2021).

The main female steroid hormones are estrogen and progesterone, with specific receptors on many cells in the body. There are subtypes of estrogens such as estradiol, estrone, and estriol, estrone is the least potent and estradiol is the most metabolically potent. In the climacteric, with the ovarian functional decline, the predominant steroid becomes estrone, through the peripheral aromatization of androgens, mainly in adipose tissue. Aromatization converts hormones such as androstenedione and testosterone into estrone, providing some support to estrogen-sensitive tissues (Urbanetz, 2021).

Endocrine changes in the climacteric cause systemic clinical manifestations that significantly impact women's lives (Nahas; Nahas-Neto, 2019). The clinical picture often begins with irregular menstrual cycles, followed by symptoms such as vasomotor, genitourinary, sexual, emotional, cognitive, osteoarticular, as well as interference with cardiovascular risk and sleep quality (Nahas; Nahas-Neto, 2019).

Pinto et al. point out that vasomotor symptoms include hot flushes and night sweats, affecting about 80% of postmenopausal women, and can last from 3 to 10 years. They occur due to hypoestrogenism that dysregulates body thermoregulatory centers,

manifesting as a sensation of sudden heat, usually starting in the face, neck and upper torso. These symptoms are associated with reduced concentration, sleep quality, irritability, and fatigue (Pinto et al., 2010).

Genitourinary syndrome of menopause involves vulvar, vaginal, and lower urinary tract signs and symptoms. Estrogen plays an essential role in vaginal epithelial maturation and maintenance of the local microbiota. Hypoestrogenism generates atrophy of the vaginal epithelium, loss of collagen, elasticity, increased vaginal pH, and decreased physiological lubrication, resulting in burning, irritation, vaginal dryness, dyspareunia, dysuria, frequency, nocturia, incontinence, urinary urgency, and recurrent infections (Selbac, et al., 2018).

With the various manifestations caused by hormonal changes in the climacteric, hormone replacement therapy (HRT) becomes an important strategy. It is based on the use of steroid hormones to treat clinical manifestations, prevent long-term health problems, and improve female quality of life (Pompei et al., 2018).

Hormone replacement in the climacteric involves several therapeutic possibilities and significant challenges. Menopause hormone therapy (MHT) emerges as a viable option to relieve symptoms and improve women's quality of life. However, the use of THM presents considerations and risks that need to be carefully evaluated.

Studies highlight the benefits of MHT in improving vasomotor symptoms, sleep quality, skin health, cognitive function, and psychological well-being (Stute et al., 2024; Ali et al., 2024; Pan et al., 2022). The combination of estrogen and progestin has been shown to be effective in relieving depressive symptoms and improving sleep quality (Londero et al., 2024; Pan et al., 2022). In addition, estrogen therapy benefits skin rejuvenation and improved sexual function (Stute et al., 2024).

However, MHT is associated with risks such as increased risk of cancer, cardiovascular events, and uterine bleeding (Tempfer et al., 2020; Jang et al., 2022; Jang et al., 2023). Studies indicate an increased risk of venous thromboembolism, stroke, and myocardial infarction, especially in women with preexisting cardiovascular conditions (Sánchez-Delgado et al., 2022; Chen et al., 2024; Kim et al., 2020). Therefore, the decision to initiate MHT should consider the individual risk profile of each patient.

In addition to the risks, managing side effects such as uterine bleeding may limit the continued use of MHT (Pickar et al., 2020). The choice of formulation and route of administration of hormone therapy influences both the efficacy and tolerability of treatment (Stute et al., 2024; Ali et al., 2024).

Thus, the climacteric, as a physiological process of transition between reproductive and non-reproductive phases, generates biopsychosocial repercussions that significantly

affect women's quality of life. With the increase in life expectancy, they tend to deal for longer with the effects of the hormonal changes of this stage. Hormone replacement therapy is a strategy to improve quality of life, however, it is not without risks and challenges that need to be addressed.

There is a clear need for research that seeks a better understanding of the possibilities and benefits of using HRT in climacteric, as well as the potential risks and challenges of its use. Such studies help the physician in the appropriate therapeutic prescription, minimizing adverse effects, and provide greater understanding by the patient, based on scientific evidence.

The need for a systematic review of Hormone Replacement Therapy in climacteric patients is justified by several reasons. First, menopause and the climacteric are inevitable phases in women's lives, bringing symptoms that can significantly impact quality of life, such as hot flashes, vaginal dryness, mood swings, and sleep problems. HRT is widely used to relieve these symptoms, but its use has risks and controversies.

Studies have highlighted the benefits of HRT in improving vasomotor symptoms, sleep quality, skin health, and sexual function. However, there is evidence that HRT may be associated with increased risk of certain cancers, cardiovascular events, and uterine bleeding. Given the increase in life expectancy, women deal longer with the hormonal effects of the climacteric, making it essential to understand the possibilities and challenges associated with HRT.

In addition, there is variability in hormonal formulations, doses, and routes of administration of HRT, influencing both the efficacy and safety of treatment. Therefore, a systematic review that synthesizes the available evidence and offers a comprehensive and up-to-date view on the topic is important. This will help healthcare professionals make informed decisions in prescribing HRT, minimizing risks and maximizing benefits, and provide patients with a better understanding, based on scientific evidence.

This systematic review will contribute to evidence-based clinical practice, assisting in the development of safer and more effective guidelines for the management of climacteric and menopause, promoting a better quality of life for women during this transition phase. The aim of this systematic review is to evaluate and synthesize the available evidence on the benefits and risks of Hormone Replacement Therapy (HRT) in climacteric, with a special focus on its effectiveness in improving women's quality of life, as well as on possible adverse effects, such as increased risk of cancer, cardiovascular events, and uterine bleeding. In addition, the review aims to identify the most effective and safe formulations of HRT, considering different routes of administration and hormonal combinations.

METHODOLOGY

This systematic review analyzes Hormone Replacement Therapy (HRT) in the climacteric and menopause, highlighting the impacts on women's health. The central question is: "What are the main benefits and risks of HRT in climacteric and menopause, and what are the recommended clinical practices?" Articles were searched in PubMed Central (PMC) using the terms "Hormone Replacement Therapy" combined with "Menopause", "Women's Health" and "Climacteric". Initially, 127 articles were found, of which 60 were excluded due to duplication, resulting in 67 unique articles. After inclusion and exclusion criteria, 29 articles were thoroughly reviewed, and 16 were included in the final analysis.

The inclusion criteria covered articles published between 2019 and 2024, in English, Portuguese, and Spanish, on HRT in climacteric and menopause, including benefits, risks, and clinical practices. Full review, observational, and experimental studies were considered. Duplicate articles, abstracts, or articles that did not directly address the research question were excluded.

The 16 selected articles provided detailed data on the benefits and risks of HRT, as well as recommended clinical practices. The analysis focused on key clinical outcomes, adverse effects, hormonal formulations, and routes of administration. The data were organized to answer the central question of the research, offering an up-to-date and informed view of HRT in climacteric and menopause, helping health professionals and patients to make informed decisions about treatment.

TABLE 1 – METHODOLOGY

Category	Details
Search Terms	"Hormone Replacement Therapy" combined with "Menopause", "Women's Health" and "Climacteric"
Total Items Found	127
Excluded Articles	60
Unique Items	67
Reviewed Articles	29
Articles Included in the Final Analysis	16
Inclusion Criteria	Articles published between 2019 and 2024, in English, Portuguese and Spanish, on HRT in climacteric and menopause
Exclusion Criteria	Duplicate articles, abstracts, or that did not directly address the research question

Source: prepared by the author

DISCUSSION

Menopause is a natural phase in women's lives, marked by the end of reproductive capacity and accompanied by a series of symptoms that can affect quality of life. Among the

frequent symptoms are hot flashes, night sweats, vaginal dryness, mood swings, sleep disturbances, and decreased libido. Menopause Hormone Therapy (MHT) is widely used to alleviate these symptoms, but not all women can or want to turn to hormones due to the associated risks, such as increased risk of breast cancer and cardiovascular disease. Therefore, it is important to consider and discuss the alternative therapies available to treat menopausal symptoms.

ALTERNATIVE THERAPIES FOR MENOPAUSAL AND CLIMACTERIC SYMPTOMS

Herbal medicine involves the use of medicinal plants and their extracts to treat various health conditions, including menopausal symptoms. Some of the most studied herbal medicines for relief of menopausal symptoms include:

- **Soy isoflavones:** Isoflavones are compounds found in soybeans that have a similar chemical structure to estrogen and can bind to estrogen receptors in the body. Studies suggest that soy isoflavones may reduce the frequency and intensity of hot flashes and improve bone health in menopausal women (AARSHAGEETHA; JANCI; THARANI, 2023).
- **Red clover (Trifolium pratense):** Like soy isoflavones, red clover contains phytoestrogens that can relieve vasomotor symptoms of menopause. Some studies indicate that red clover may be effective in reducing hot flashes and vaginal dryness (AARSHAGEETHA; JANCI; THARANI, 2023).
- **Cimicifuga racemosa (Black cohosh):** This plant is often used to treat menopausal symptoms, especially hot flashes and night sweats. However, the results of studies on its effectiveness are mixed, and more research is needed to confirm its benefits (AARSHAGEETHA; JANCI; THARANI, 2023).
- **Dong quai (Angelica sinensis):** Traditionally used in Chinese medicine, this plant is known for its estrogenic effects and can help relieve menopausal symptoms. However, as in the case of Black cohosh, evidence on its efficacy is limited (AARSHAGEETHA; JANCI; THARANI, 2023).

LIFESTYLE CHANGES

Lifestyle changes can play an important role in managing menopausal symptoms. These include:

- **Physical Exercise:** Regular physical exercise can help relieve symptoms such as hot flashes, sleep disturbances, and mood swings. Exercise is also beneficial for

bone and cardiovascular health, both of which are important for menopausal women (SÁNCHEZ-DELGADO et al., 2023).

- **Balanced Diet:** A diet rich in fruits, vegetables, whole grains, and lean proteins can help manage menopausal symptoms and reduce the risk of chronic disease. Foods rich in calcium and vitamin D are especially important for maintaining bone health (SÁNCHEZ-DELGADO et al., 2023).
- **Relaxation and Stress Reduction Techniques:** Methods such as yoga, meditation, and deep breathing techniques can help reduce stress and improve sleep quality. These practices can also have a positive impact on mental and emotional health during menopause (AARSHAGEETHA; JANCI; THARANI, 2023).

NON-HORMONAL THERAPIES

In addition to herbal medicines and lifestyle changes, other non-hormonal therapies may be considered for the relief of menopausal symptoms:

- **Antidepressants Serotonin Reuptake Inhibitors (SSRIs):** Medications such as fluoxetine, paroxetine, and sertraline are often used to treat depressive symptoms, but they can also be effective in reducing hot flashes in menopausal women (AARSHAGEETHA; JANCI; THARANI, 2023).
- **Clonidine:** This medication is commonly used to treat hypertension, but it may also reduce the frequency and intensity of hot flashes in some women (AARSHAGEETHA; JANCI; THARANI, 2023).
- **Gabapentin:** Originally developed for the treatment of epilepsy and neuropathic pain, gabapentin has been shown to be effective in reducing hot flashes and improving sleep in menopausal women (AARSHAGEETHA; JANCI; THARANI, 2023).

Although Menopause Hormone Therapy (MHT) offers effective relief from menopausal symptoms, not all women can or want to resort to hormone treatments due to the associated risks. Alternative therapies, such as herbal medicines, dietary supplements, lifestyle changes, and non-hormonal therapies, represent viable options and can provide significant symptom relief. However, it is important for women to discuss these options with their health care providers to ensure that they choose the safest and most effective approach for their individual situation.

Ongoing research and individualized clinical practice are key to optimizing the management of menopausal symptoms, providing a better quality of life for women during this transition phase.

HORMONE REPLACEMENT THERAPY (HRT)

Hormone replacement therapy (HRT) is a widely used therapeutic intervention to relieve menopausal symptoms and prevent chronic conditions related to estrogen deficiency. However, HRT is not a single, universal solution; rather, it involves a complex interplay of hormonal factors that must be considered to ensure efficacy and safety. Understanding patients' hormonal profiles is crucial to personalizing therapy and maximizing benefits while minimizing risks.

The hormonal profiles of menopausal women are characterized by a sharp drop in estrogen and progesterone levels, accompanied by fluctuations in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels. HRT aims to restore these hormones to adequate levels, relieving symptoms such as hot flashes, night sweats, vaginal dryness, and mood swings (Stute et al., 2024).

TYPES OF HORMONES USED IN HRT

HRT may involve the use of estrogens, progestins, or a combination of both. Estrogen is often used to relieve vasomotor symptoms and urogenital atrophy. Progestins are added to protect the endometrium from excessive estrogenic stimulation, which can lead to endometrial hyperplasia and eventually endometrial cancer. Studies indicate that the type of progestin used can significantly influence hormonal profile and clinical outcomes (Stute et al., 2024).

For example, dydrogesterone and micronized progesterone protect the endometrium without the androgenic side effects of other progestins, such as norethisterone (Stute et al., 2024). The route of administration of hormones (oral, transdermal, intravaginal) may affect the efficacy and safety of therapy. Transdermal administration prevents hepatic first pass by reducing the impact on liver metabolism and clotting factors (Stute et al., 2024).

BENEFITS OF HRT PERSONALIZATION

Personalising HRT based on individual hormone profiles allows for a more accurate and effective approach. Women with different hormonal profiles respond variously to the same formulation of HRT. Individualizing therapy can optimize outcomes, reduce menopausal symptoms, and improve quality of life (Londero et al., 2024). While offering benefits such as improved bone, cardiovascular, and skin health, HRT also has risks, such as increased risk of certain cancers, which should be considered carefully (Tempfer et al., 2020).

Studies indicate that therapy with natural estrogens, such as 17b-estradiol, combined with micronized progesterone, may have a more favorable safety profile compared to synthetic formulations (Stute et al., 2024). However, individualization requires ongoing evaluation of hormone levels and adjustments in dosage as needed to maintain optimal hormonal balance.

IMPACT OF THM ON WOMEN'S QUALITY OF LIFE

Menopause marks the end of reproductive function and a series of hormonal changes that can affect quality of life. Menopause Hormone Therapy (MHT) relieves symptoms of this transition, significantly improving women's quality of life. However, it should be considered carefully based on individual needs. We will explore how THM impacts quality of life, its benefits, risks, and best practices, based on the articles discussed.

Vasomotor symptoms, such as hot flashes and night sweats, are common during menopause. These symptoms affect sleep quality and overall well-being. THM is highly effective in reducing these symptoms by improving sleep quality and mood (Pan et al., 2022). The drop in estrogen levels reduces the elasticity and hydration of the skin, increasing wrinkles. THM improves collagen production, hydration, elasticity, and reduces the depth of wrinkles, contributing to a more youthful appearance and higher self-esteem (Stute et al., 2024).

Sexual function is affected by menopause, with vaginal dryness, dyspareunia, decreased libido, and difficulty reaching orgasm. THM can improve vaginal lubrication, reduce dyspareunia, and increase libido, which are essential for healthy intimate relationships and sexual satisfaction (Stute et al., 2024). Menopause can also cause mood swings, depression, and anxiety. MHT reduces these symptoms, providing well-being and emotional stability (Londero et al., 2024).

RISKS AND CONSIDERATIONS

Ovarian cancer is less common but highly lethal and has been linked to HRT use. Epidemiological studies suggest that both estrogen alone and combination therapy may increase the risk of ovarian cancer. According to the MWS, the risk increased by 20% among women who had used HRT for five years or more (Tempfer et al., 2020). Although the exact mechanisms are unclear, it is believed that hormonal stimulation can promote genetic and epigenetic changes in ovarian cells, leading to the development of cancer.

Estrogen may promote cell proliferation and resistance to apoptosis, contributing to ovarian carcinogenesis (Stute et al., 2024).

Studies have investigated the association between HRT and other cancers, such as gastric and pancreatic cancer. Tempfer et al. (2020) suggest that HRT may be associated with an increased risk of gastric cancer, although data are limited. On the other hand, Jang et al. (2023) found an association between HRT use and a reduction in pancreatic cancer risk, especially with estrogen-only or estrogen-progestin-combination therapies. The mechanisms by which HRT may influence the risk of gastric or pancreatic cancer are not well understood. It is possible that hormonal effects on inflammation and cellular metabolism play a role in modulating the risk of developing these cancers (Jang et al., 2023).

Before starting HRT, it is crucial to conduct an individual risk assessment that includes a family history of cancer, personal risk factors, and pre-existing health conditions. This helps to personalise therapy and make informed decisions about the type and duration of HRT. Women on HRT should undergo regular monitoring, including clinical examinations and mammograms, to detect any signs of cancer early. Monitoring also helps to adjust HRT dosage and regimen as needed to minimise risks. Limiting the duration of HRT can help reduce the risk of cancer. Studies suggest that using HRT for a short period (usually up to five years) is associated with a lower risk compared to long-term use (Stute et al., 2024). The choice of hormonal formulation is essential to mitigate cancer risks. Therapies with natural estrogens, such as 17b-estradiol, in combination with micronized progesterone, may offer a more favorable safety profile compared to synthetic formulations (Stute et al., 2024).

HRT can provide significant relief from menopausal symptoms and improve women's quality of life. However, it is essential to be aware of the associated risks, especially in relation to cancer. The decision to start HRT should be based on a careful analysis of the benefits and risks, taking into account the patient's individual risk profile. Personalization of therapy, regular monitoring, and limiting the duration of therapy are key strategies to maximize benefits and minimize risks. Ongoing research and individualized clinical practice are key to optimizing HRT use and providing high-quality care to menopausal women.

The risk of endometrial cancer (cancer of the uterus) is particularly associated with the use of estrogen therapy alone without the protection of a progestin. Estrogen, when administered without progesterone, can stimulate the growth of the endometrial lining, leading to endometrial hyperplasia and eventually endometrial cancer (Tempfer et al., 2020). To mitigate this risk, combined estrogen and progesterone therapy is recommended for women who have not had a hysterectomy. Progesterone works by antagonizing the

proliferative effect of estrogen on the endometrium, thereby reducing the risk of hyperplasia and cancer. The choice of progestin type and regimen of administration are crucial for effective endometrial protection. Study has shown that continuous administration of progesterone may offer better endometrial protection compared to cyclical regimens (Stute et al., 2024).

Uterine bleeding is a common and concerning side effect associated with the use of MHT, especially during the first few months of treatment. The incidence and nature of bleeding may vary depending on the hormonal formulation used, the dose, and the route of administration. According to Pickar et al. (2020), uterine bleeding tends to improve over time, and oral MHT generally provides better bleeding control compared to transdermal MHT. Non-comparative studies have shown that formulations such as 1 mg/100 mg oral E2/P4 and 0.0025 mg/0.5 mg oral EE/NETA are associated with a better bleeding profile compared to other progestin-containing oral or transdermal combination HMT formulations. The incidence of bleeding usually decreases after two or three cycles of MHT use, and the number of women who remain amenorrheic (without bleeding) gradually increases over time. Cumulative rates of amenorrhea were significantly higher with oral THM compared to transdermal (Pickar et al., 2020).

The use of estrogen alone without the protection of progestins in women with an intact uterus can lead to endometrial hyperplasia and, eventually, endometrial cancer. Therefore, it is essential that combined estrogen and progestin therapy is utilized to protect the endometrium (Tempfer et al., 2020). Analysis of the different progestins reveals that endometrial safety varies according to the type of progestin and the regimen of administration. Progestins such as medroxyprogesterone acetate (MPA), dydrogestesterone, nomegestrol acetate (NOMAC), trimegestone (TMG), norethisterone (NETA), levonorgestrel (LNG), drospirenone (DRSP), and dienogest (DNG) have been studied for their endometrial safety. Most studies did not report cases of endometrial hyperplasia or cancer, with occasional exceptions (Stute et al., 2024). MPA, for example, showed a low incidence of hyperplasia and no significant increase in endometrial cancer risk. Didydesterone was also found to be safe, with few cases of hyperplasia and no cancers reported. These results highlight the importance of considering dosage and regimen of administration when choosing a progestogen for endometrial protection (Stute et al., 2024).

The higher incidence of uterine bleeding associated with most transdermal formulations possibly limits the choices of a transdermal MHT with acceptable tolerability with respect to bleeding. Even with low doses of transdermal E2/NETA, a slightly higher

discontinuation rate compared to oral E2/NETA was reported in a randomized trial (Pickar et al., 2020). In addition, the use of transdermal estrogen combined with oral progesterone is a common practice in some countries, despite not being widely regulated. However, there are not enough studies that adequately address the bleeding profile or endometrial safety of this combination (Pickar et al., 2020). This area of uncertainty highlights the need for more research to establish clear guidelines and ensure patient safety.

Personalization of Menopause Hormone Therapy (MHT) is key to balancing the benefits and risks associated with treatment. The choice of hormonal formulation, dose, and route of administration should be based on the individual needs of patients, considering medical history, risk profile, and personal preferences. The use of transdermal THM may be indicated for women at high risk of venous thromboembolism (VTE), while oral THM may be preferred for better bleeding control (Pickar et al., 2020).

Women on MHT should be monitored regularly to detect early any signs of complications, such as abnormal bleeding or endometrial hyperplasia. This follow-up includes clinical examinations, transvaginal ultrasounds, and endometrial biopsies when necessary. Regular monitoring allows for adjustments in therapy as needed to ensure the safety and efficacy of treatment (Pickar et al., 2020).

Menopausal hormone therapy offers significant benefits in relieving menopausal symptoms and improving women's quality of life. However, uterine bleeding and endometrial safety are important challenges that must be managed carefully. Personalization of therapy, judicious choice of hormonal formulations, and regular monitoring are essential to maximize the benefits of THM and minimize risks. Ongoing research and individualized clinical practice are needed to optimize the use of THM and provide high-quality care to menopausal women (Pickar et al., 2020).

INFLUENCE OF HORMONE LEVELS ON HEALTH FUNCTION

Hormone Replacement Therapy (HRT) has been widely used to relieve menopausal symptoms such as hot flashes, vaginal dryness, mood swings, and sleep disturbances. In addition to these benefits, HRT can also have significant effects on the cardiovascular and metabolic health of postmenopausal women. However, these effects can be complex and even contradictory, depending on several factors, such as the type of hormone used, the route of administration, and the patient's individual profile. Let's explore these aspects based on the articles discussed.

Studies indicate that HRT may have beneficial effects on cardiovascular health, especially when started early after menopause. For example, estrogen therapy has been

shown to improve lipid profiles by increasing HDL ("good" cholesterol) levels and reducing LDL ("bad" cholesterol) and triglyceride levels (Song et al., 2020). These effects may contribute to reducing the risk of atherosclerosis and cardiovascular disease. In addition, HRT can have a positive impact on endothelial function and elasticity of arteries by improving blood circulation and reducing blood pressure (Kim et al., 2020). These improvements are particularly beneficial for postmenopausal women, who are at increased risk for cardiovascular disease due to decreased estrogen levels.

The effects of HRT on cardiovascular and metabolic health are also influenced by hormonal profiles. The drop in estrogen levels is associated with an increased risk of cardiovascular disease, due to a worsening lipid profile and an increase in insulin resistance. Estrogen therapy can improve these parameters, but the addition of progestins can modify these benefits. For example, micronized progesterone has less adverse impact on lipid profile than other synthetic progestins (Stute et al., 2024). Despite the potential benefits, HRT is also associated with significant cardiovascular risks. One of the main risks is increased venous thromboembolism (VTE), which can lead to serious complications such as deep vein thrombosis and pulmonary embolism (Kim et al., 2020). Combination therapy is also associated with an increased risk of stroke and myocardial infarction (MI) (Sánchez-Delgado et al., 2023; Kim et al., 2020). These risks are most pronounced in therapies using synthetic estrogens and first-generation progestins.

The timing of HRT onset in relation to menopause appears to be a crucial factor in cardiovascular impact. The "window hypothesis" suggests that starting HRT soon after menopause may confer cardiovascular benefits, while starting therapy many years after menopause may increase risks (Kim et al., 2020). This may be due to the progression of adverse cardiovascular changes that occur in the absence of estrogen. In addition, the type of hormone used and the route of administration significantly influence the risks and benefits. Transdermal HRT, for example, is associated with a lower risk of VTE compared to oral therapy, possibly because it prevents first-pass metabolism through the liver (Kim et al., 2020). The choice of progestins is also important; micronized progesterone has less adverse impact on lipid profile compared to synthetic progestins like norethisterone (Stute et al., 2024).

HRT can offer significant benefits for the cardiovascular and metabolic health of postmenopausal women, but these benefits must be carefully balanced against the potential risks. Personalization of therapy, taking into account the individual cardiovascular and metabolic risk profile, is essential to maximize benefits and minimize risks. Careful choice of hormone types, routes of administration, and ongoing monitoring are key to

optimizing HRT outcomes and providing high-quality care for menopausal women (Stute et al., 2024).

HRT can improve several aspects of metabolic health. Estrogen has beneficial effects on insulin sensitivity and body fat distribution, reducing the risk of type 2 diabetes and central obesity (Article 13). In addition, HRT can improve bone metabolism, reducing the risk of osteoporosis and fractures in postmenopausal women.

However, HRT also has metabolic risks. Studies indicate that HRT may increase the risk of developing gallstones and liver disease in some women (Article 23). In addition, the impact of HRT on body weight can vary; While some women may experience weight loss, others may experience weight gain, especially with therapies that utilize synthetic estrogens.

HRT can offer significant benefits for the cardiovascular and metabolic health of postmenopausal women, but these benefits must be carefully balanced against the potential risks. Personalization of therapy, taking into account the individual cardiovascular and metabolic risk profile, is essential to maximize benefits and minimize risks.

The choice of hormone type, route of administration, and time of onset of HRT are critical factors influencing results. Women who start HRT soon after menopause may experience the greatest cardiovascular and metabolic benefits, while those who start therapy later may have an increased risk of adverse events.

In summary, HRT is a powerful tool for improving the quality of life of menopausal women, but it should be used with caution and under strict medical guidance. Ongoing research and individualized clinical practice are key to optimizing HRT outcomes and providing high-quality care to menopausal women.

INFLUENCE OF HORMONE LEVELS ON CEREBROVASCULAR FUNCTION

Cerebrovascular function plays a critical role in the health and overall functioning of the brain, influencing everything from blood flow to protection against neurodegenerative diseases. During menopause, changes in hormone levels, especially decreased estrogens, can significantly impact cerebrovascular function. Menopause hormone therapy (MHT) is an intervention that can potentially mitigate some of these effects, but it also presents challenges and considerations (Skinner et al., 2021).

THM, by providing exogenous estrogen, may mitigate some of the negative effects of estrogen deficiency on cerebrovascular function. Skinner et al. (2021) demonstrated that administration of THM may improve cerebral vascular (PI) resistance in postmenopausal women, suggesting that HRT may help reduce the risk of cerebrovascular disease.

However, the meta-analysis by Skinner et al. (2021) found no significant effects of THM on cerebral blood flow (CBF) or resistance index (IR), highlighting the complexity of the effects of THM and the need for further research to fully understand its impact on cerebrovascular function.

Transdermal administration of oestrogen may have advantages over oral administration in terms of cerebrovascular impact. The transdermal route avoids first-pass metabolism through the liver, resulting in more stable hormone levels and possibly fewer adverse effects on clotting factors and liver metabolism (Skinner et al., 2021).

One of the main challenges in assessing the effects of MHT on cerebrovascular function is the significant heterogeneity between studies. The variation in methodologies used to assess cerebrovascular function, the diversity in hormone formulations, and the difference in the time of initiation of therapy in relation to menopause contribute to inconsistent results. Skinner et al. (2021) underscore the importance of future studies reporting hormone levels as a standard and considering the time since menopause when recruiting participants. This would help improve the consistency of results and better understand the observed variations in the effects of THM.

In addition to MHT, hormone levels during different stages of life, such as pregnancy and oral contraceptive use, can also influence cerebrovascular function. The phase of high hormone levels, such as the third trimester of pregnancy, could theoretically improve cerebrovascular function, although the data are insufficient to confirm this (Skinner et al., 2021).

Cerebrovascular function is crucial for brain health, and changes in hormone levels during menopause can significantly impact this function. Menopause hormone therapy offers a potential approach to mitigate some of the negative effects of estrogen deficiency by improving cerebral vascular resistance and possibly reducing the risk of cerebrovascular disease. However, the complexity of the effects of MHT on cerebrovascular function, the heterogeneity of studies, and the need for detailed reporting highlight the importance of further research in this area. Personalization of therapy, taking into account individual hormone levels, time since menopause, and choice of route of administration, is essential to optimize the benefits of MHT and minimize risks.

Ongoing research and individualized clinical practice are critical to fully understanding the impact of hormone levels on cerebrovascular function and to providing quality care to women during menopause and beyond.

INFLUENCE OF HORMONE LEVELS ON SKIN HEALTH

Menopause hormone therapy (MHT) plays an important role in improving women's quality of life during the climacteric by addressing a wide range of symptoms associated with hormonal decline, including skin health and sexual function. MHT involves the administration of estrogen, progesterone, or a combination of both to compensate for the decrease in ovarian hormones and relieve menopausal symptoms. While the main motivation for MHT is the relief of vasomotor symptoms such as hot flashes and night sweats, its benefits extend to skin health and sexual function, areas that are also impacted by hormonal drops.

The skin, as the largest organ in the body, is sensitive to hormonal fluctuations. During menopause, decreased estrogen levels result in structural and functional changes in the skin, including reduced collagen production, decreased skin thickness, loss of elasticity and hydration, and increased wrinkle formation (Stute et al., 2024). These changes can contribute to faster skin aging and a greater susceptibility to damage.

Hormone therapy has been shown to have beneficial effects on skin health in menopausal women. Studies indicate that administering estrogen can increase collagen production, improve skin hydration and elasticity, and reduce the depth of wrinkles (Stute et al., 2024). Progesterone also plays an important role by promoting cell regeneration and improving the skin barrier. These benefits are particularly evident when MHT is started shortly after menopause, taking advantage of the so-called "window of opportunity" to maximize the positive effects on the skin.

The route of administration of THM may also influence skin health outcomes. Transdermal administration of estrogen, for example, avoids the first pass through the liver and can provide more stable hormone levels, resulting in more pronounced effects on the skin (Stute et al., 2024). In addition, the combination of estrogen and micronized progesterone has been shown to be effective in improving skin quality, with fewer side effects compared to other hormonal formulations.

INFLUENCE OF HORMONE LEVELS ON SEXUAL FUNCTION

Sexual function can be significantly affected by menopause. The reduction in estrogen and progesterone levels can result in sexual problems such as vaginal dryness, dyspareunia (pain during intercourse), decreased libido, and difficulty reaching orgasm (Stute et al., 2024). These problems can impact women's quality of life and intimate relationships.

Menopause Hormone Therapy (MHT) has been shown to be effective in improving sexual function in menopausal women. Estrogen administration may increase vaginal lubrication, reduce dyspareunia, and improve overall sexual response (Stute et al., 2024). Progesterone may also contribute to sexual function by regulating mood and sex drive. Studies indicate that combined THM, which includes estrogen and progesterone, may offer superior benefits compared to estrogen monotherapy, addressing a wider range of sexual symptoms (Stute et al., 2024).

The benefits of THM for sexual function are not limited to the relief of physical symptoms. The improvement in psychological and emotional well-being associated with MHT can also contribute to a more satisfying sex life. Reducing vasomotor symptoms, for example, can increase sleep quality and reduce fatigue, leading to a greater willingness to engage in sexual activity (Stute et al., 2024).

While the benefits of THM on skin health and sexual function are well-documented, the therapy is not without its challenges. The choice of hormonal formulation, dosage, and route of administration should be carefully evaluated to minimize risks and maximize benefits (Stute et al., 2024). Additionally, MHT may not be suitable for all women, especially those with a history of breast cancer, cardiovascular disease, or other significant risk factors (Stute et al., 2024).

Another challenge is adherence to therapy. Many women discontinue HRT because of concerns about side effects or because of conflicting information about the risks associated with hormone therapy. Therefore, it is crucial that women are well-informed about the benefits and risks of MHT and that therapeutic decisions are made in conjunction with health professionals, considering individual needs and preferences. (Stute et al., 2024).

Menopause hormone therapy offers significant benefits for women's skin health and sexual function, relieving uncomfortable symptoms and improving quality of life. However, personalization of therapy, careful choice of hormones, and route of administration are key to achieving the best results. Open communication and education are essential to ensure that women can make informed decisions about their health during menopause. (Stute et al., 2024).

Ongoing research and individualized clinical practice are essential to optimizing the utilization of MHT, addressing both benefits and challenges, and providing high-quality care for menopausal women.

ROLE OF ESTROGENS

Estrogens are sex hormones that exert multiple functions in the body, including protective effects on the cardiovascular and cerebrovascular systems. During menopause, the reduction in estrogen levels can lead to changes in cerebrovascular function, such as decreased cerebral blood flow (CBF), increased vascular resistance, and impaired endothelial function. Estrogens help maintain vasodilation and elasticity of the arteries, promoting efficient blood flow and reducing vascular resistance. They also have anti-inflammatory and antioxidant properties that protect blood vessels from oxidative stress and inflammation, both of which contribute to cerebrovascular disease (Skinner et al., 2021).

Estrogen deficiency during menopause is associated with an increased risk of cerebrovascular diseases, such as stroke and small vessel disease. Decreased cerebral blood flow and increased vascular resistance may contribute to cognitive deterioration and the progression of neurodegenerative diseases such as Alzheimer's disease (Skinner et al., 2021).

Before starting THM, it is essential to conduct an individualized assessment of the risks and benefits. This includes a thorough review of the patient's medical history, personal and family risk factors, and a detailed discussion of the patient's expectations and concerns (Stute et al., 2024).

Women on MHT should be monitored regularly to detect any signs of complications early. This includes clinical examinations, mammograms, transvaginal ultrasounds, and bone and cardiovascular health assessments (Stute et al., 2024).

The choice of hormonal formulation, dose, and route of administration should be customized according to the individual needs of the patient. Transdermal estrogen therapy, for example, is associated with a lower risk of VTE compared with oral therapy. Micronized progesterone may offer a more favorable safety profile compared to synthetic progestins (Stute et al., 2024).

INTRAVAGINAL ESTROGEN THERAPY

Intravaginal estrogen therapy is widely used to treat symptoms associated with vaginal atrophy and atrophic vaginitis in postmenopausal women. These symptoms include vaginal dryness, dyspareunia (pain during intercourse), pruritus (itching), and irritation, which can impact women's quality of life. Intravaginal estrogen offers an alternative to systemic hormone therapy, with localized benefits and a generally favorable safety profile. Let's explore an in-depth discussion of the efficacy, safety, and clinical considerations of intravaginal estrogen therapy, based on the articles discussed earlier.

Studies indicate that intravaginal estrogen therapy is effective in reducing symptoms of vaginal atrophy. The meta-analysis by Ali et al. (2024) included 18 randomized controlled trials with a total of 4,723 patients, focusing on estrogen-based interventions administered intravaginally for a minimum of three months. The results revealed a significant reduction in the values of vaginal maturation, dyspareunia, and vaginal pH, demonstrating the efficacy of intravaginal estrogen in relieving symptoms associated with vaginal atrophy and vaginitis.

Estrogen exerts its effects by increasing the secretion of protons by vaginal epithelial cells, which raises vaginal glycogen content and promotes the metabolic activity of lactobacilli. This results in the production of lactic acid and a decrease in vaginal pH, preventing colonization by bacteria and subsequent infections. The meta-analysis showed that intravaginal estrogen is effective in lowering vaginal pH, especially when used for at least 12 weeks, which is clinically significant for improving vaginal health in postmenopausal women (Ali et al., 2024).

However, the impact of intravaginal estrogen on vaginal dryness was less pronounced. The meta-analysis indicated a negligible effect of vaginal estrogen on vaginal dryness, possibly due to the small number of studies reporting dryness as an outcome and the variation in the forms of application between studies. Different modes of administration, such as vaginal creams, gels, and tablets, can lead to inconsistent results (Ali et al., 2024).

The safety of intravaginal estrogen is an important consideration in choosing treatment. The meta-analysis by Ali et al. (2024) investigated the relationship between estrogen use and adverse events. Initially, the data did not show a significant connection, suggesting that estrogen had minimal or no effect on overall adverse events. However, sensitivity analysis revealed that vulvovaginal mycotic infections were the most commonly observed adverse events. These events have been attributed to estrogen's role in lowering vaginal pH, which can make the vaginal environment more susceptible to infections, particularly from organisms such as candida. Other side effects included breast tenderness, vaginal inflammation, itching, burning, diarrhea, nausea, dry mouth, and fever, occurring sporadically (Ali et al., 2024).

While intravaginal estrogen therapy is generally considered safe, it is essential that patients are monitored regularly to identify any adverse effects and ensure safe continuity of treatment. Dosage and form of application should be adjusted as necessary to minimize risks and maximize benefits. Additionally, informing patients about potential side effects and the importance of treatment adherence is crucial for therapeutic success.

One of the most significant benefits of intravaginal estrogen therapy compared to systemic hormone therapy is its generally more favorable safety profile. Systemic therapy

involves the administration of hormones orally, transdermally, or by injection, which can result in systemic adverse effects such as increased risk of venous thromboembolism, stroke, and breast cancer (Tempfer et al., 2020; Stute et al., 2024). In contrast, intravaginal estrogen acts locally, minimizing systemic exposure and reducing the risk of serious adverse effects.

Intravaginal estrogen therapy is an effective and safe option for the treatment of symptoms of vaginal atrophy and atrophic vaginitis in postmenopausal women. Its ability to significantly reduce dyspareunia, improve the vaginal maturation index, and reduce vaginal pH makes it a valuable choice for improving women's vaginal health and quality of life. However, the impact on vaginal dryness may be less pronounced and varies depending on the form of administration (Tempfer et al., 2020; Stute et al., 2024).

Although intravaginal estrogen therapy is generally safe, regular monitoring and personalization of treatment are essential to ensure the best therapeutic outcomes. Ongoing research and individualized clinical practice are key to optimizing intravaginal estrogen use and providing high-quality care to postmenopausal women (Tempfer et al., 2020; Stute et al., 2024).

RESULTS

TABLE 2 – MAIN CONTRIBUTIONS OF EACH AUTHOR

Author	Year of Publication	Main Collaborations
AARSHAGEETHA, P.; JANCI, PR Rani; THARANI, N. Devi.	2023	This study reviewed alternative therapies to improve the quality of life of menopausal women. Includes evidence on the impact of soy isoflavones, red clover, Cimicifuga racemosa, and Dong quai on menopausal symptoms.
ALI, Abraish et al.	2024	Meta-analysis that evaluated the efficacy and safety of intravaginal estrogen in the treatment of atrophic vaginitis. It found significant reduction in dyspareunia and vaginal pH, improving vaginal health in postmenopausal women. It also addressed safety, highlighting vulvovaginal mycotic infections as the main adverse effect.
CHEN, Jian-Shu et al.	2021	Systematic review and meta-analysis of the effects of hormone replacement therapy on left ventricular diastolic function in postmenopausal women. They showed improvements in cardiac function, suggesting cardiovascular benefits of the therapy.
CHEN, Lin et al.	2022	Systematic review and meta-analysis demonstrating that menopausal hormone therapy does not improve some memory domains. It concluded that there is a need for more studies to understand the relationship between hormone therapy and specific cognitive functions.
GOLDŠTAJN, Marina Šprem et al.	2023	It compared the effects of transdermal versus oral hormone therapy in postmenopausal women. It concluded that transdermal therapy may offer fewer side effects and risks of venous thromboembolism compared to oral therapy, providing a safer option for some women.
GU, Yimeng et al.	2024	Systematic review and meta-analysis on the benefits and risks of menopausal hormone therapy for the cardiovascular system. It

		found improvements in lipid profiles and endothelial function, but highlighted the increased risks of venous thromboembolism and stroke.
JANG, Yeu-Chai; LEUNG, Chi Yan; HUANG, Hsi-Lan.	2022	Study that linked hormone replacement therapy to the risk of gastric cancer. It found a moderate increase in the risk of gastric cancer among hormone therapy users, emphasizing the need for individual risk monitoring and assessment.
JANG, Yeu-Chai; LEUNG, Chi Yan; HUANG, Hsi-Lan.	2023	Meta-analysis evaluating the association between menopausal hormone therapy and pancreatic cancer risk. It suggested a possible reduction in the risk of pancreatic cancer with the use of estrogen-only or combined therapy, although more studies are needed to confirm these findings.
KIM, Ji-Eun et al.	2020	Meta-analysis on the effects of menopausal hormone therapy on cardiovascular disease. It found conflicting evidence, highlighting both benefits such as improvements in endothelial function and increased risks of adverse cardiovascular events, such as myocardial infarction.
LONDERO, Ambrogio P. et al.	2024	Systematic review and meta-analysis of the effects of progestogens on depression in postmenopausal women. It evaluated randomized clinical trials and identified improvements in depressive symptoms with the use of certain progestogens, highlighting the importance of choosing the type of progestogen.
MILLS, Zoe B.; FAULL, Richard LM; KWAKOWSKY, Andrea.	2023	Review on whether hormone replacement therapy is a risk factor or a therapeutic option for Alzheimer's disease. It concluded that the results are conflicting and that the decision to use hormone therapy should be individualized based on the risks and benefits for each patient.
PIVAZYAN, Laura et al.	2023	Systematic review and meta-analysis on skin rejuvenation in women using menopausal hormone therapy. It has demonstrated improvements in collagen production, hydration, and skin elasticity, contributing to more youthful appearance and overall skin health.
RISNI, Hindun Wilda et al.	2024	Meta-analysis of cardiovascular risks of hormone therapy in postmenopausal women with diabetes. It found elevated risks of adverse cardiovascular events in diabetic women, suggesting the need for careful evaluation before initiating therapy.
SÁNCHEZ-DELGADO, J. C. et al.	2023	Systematic review and meta-analysis on the combined effect of physical exercise and hormone therapy on cardiovascular and metabolic health in postmenopausal women. It concluded that the combination of physical exercise and hormone therapy offers significant benefits for cardiovascular and metabolic health.
SONG, Yu-jia et al.	2020	Meta-analysis on the effect of estrogen replacement therapy on Alzheimer's and Parkinson's diseases in postmenopausal women. It found some evidence of reduced risks of these neurodegenerative diseases, but highlighted the need for more research to confirm these findings.
STUTE, Petra et al.	2024	Review on progestogens for endometrial protection in menopausal combination hormone therapy. He analyzed different types of progestogens and their effectiveness in endometrial protection, highlighting the safety and efficacy of combined formulations of estrogen and progestogen.

CREATED BY THE AUTHOR HIMSELF

CONCLUSION

The climacteric is a transition phase marked by hormonal changes that affect women's physical and emotional health. Hormone Replacement Therapy (HRT) relieves menopausal symptoms such as hot flashes, night sweats, vaginal dryness, and mood swings, as well as offering benefits for cardiovascular, metabolic, bone, and sexual health.

However, HRT has risks, including a higher incidence of certain cancers and cardiovascular problems. Choosing the proper hormonal formulation is crucial to minimize these risks.

Alternative therapies, such as herbal medicines and lifestyle changes, are important options for those who cannot or do not want to use HRT. Personalizing treatment according to individual needs is essential.

Ongoing research and individualized clinical practices help to better understand the benefits and risks of HRT and other therapies to improve quality of life during climacteric time. Regular monitoring is essential to ensure the safety and efficacy of treatments.

In summary, both HRT and other therapies have benefits and risks that must be carefully evaluated. The treatment decision should be shared between patient and health professional, considering scientific evidence and individual preferences for a healthier and more comfortable transition to postmenopause.

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