




THERAPEUTIC MANAGEMENT OF MENOPAUSE: HORMONAL APPROACH AND NON-HORMONAL ALTERNATIVES

MANEJO TERAPÊUTICO DA MENOPAUSA: ABORDAGEM HORMONAL E ALTERNATIVAS NÃO HORMONAIS

MANEJO TERAPÉUTICO DE LA MENOPAUSIA: ENFOQUE HORMONAL Y ALTERNATIVAS NO HORMONALES

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ABSTRACT

Menopause is a physiological milestone characterized by the loss of ovarian follicular activity, often associated with vasomotor symptoms (VMS) and genitourinary syndrome of menopause (GSM). Although Menopausal Hormone Therapy (MHT) is the most effective intervention for symptomatic relief and prevention of bone loss, its use is limited by contraindications in specific subgroups, such as breast cancer survivors and patients with a history of endometriosis, requiring individualized approaches. Diagnosis is clinical and retrospective, but Anti-Müllerian Hormone (AMH) is a sensitive biomarker of ovarian reserve, useful in predicting impending menopause, despite persistent inaccuracy in determining the exact timing. Advances in non-hormonal alternatives represent a promising frontier, including neurokinin receptor antagonists such as fezolinetant and elinzanetant for VMS, and topical therapies such as vaginal hyaluronic acid and laser (CO₂ and Er:YAG) for GSM/vulvovaginal atrophy, which demonstrate comparable efficacy in patient-centered outcomes, with favorable safety profiles for patients at oncologic risk. In addition, MHT has been shown to optimize weight loss response when

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combined with GLP-1 agonists such as semaglutide. However, therapeutic management of menopause still lacks long-term data regarding the cardiovascular, skeletal, and oncologic safety of new non-hormonal therapies, reinforcing the need for prospective studies to consolidate safe and individualized strategies during the climacteric period.

Keywords: Menopause. Hormone Therapy. Non-Hormonal Alternatives. Vasomotor Symptoms. Genitourinary Syndrome of Menopause. Anti-Müllerian Hormone.

RESUMO

A menopausa é um marco fisiológico caracterizado pela perda da atividade folicular ovariana, frequentemente associado a sintomas vasomotores (VMS) e à síndrome geniturinária da menopausa (GSM). Embora a Terapia Hormonal da Menopausa (THM) seja a intervenção mais eficaz para o alívio sintomático e prevenção da perda óssea, seu uso é limitado por contraindicações em subgrupos específicos, como sobreviventes de câncer de mama e pacientes com histórico de endometriose, exigindo abordagens individualizadas. O diagnóstico é clínico e retrospectivo, mas o Hormônio Anti-Mülleriano (AMH) é um biomarcador sensível da reserva ovariana, útil na predição da menopausa iminente, apesar da persistente imprecisão na determinação do momento exato. O avanço em alternativas não hormonais representa uma fronteira promissora, incluindo antagonistas dos receptores de neuroquinina (como fezolinetant e elinzanetant) para VMS, e terapias tópicas como o ácido hialurônico vaginal e laser (CO₂ e Er:YAG) para GSM/atrofia vulvovaginal, que demonstram eficácia comparável em desfechos centrados na paciente, com perfis de segurança favoráveis para pacientes de risco oncológico. Além disso, a THM tem demonstrado otimizar a resposta à perda de peso com agonistas de GLP-1, como a semaglutida. No entanto, o manejo terapêutico da menopausa ainda carece de dados de longo prazo sobre a segurança cardiovascular, óssea e oncológica das novas terapias não hormonais, reforçando a necessidade de estudos prospectivos para consolidar estratégias seguras e individualizadas no climatério.

Palavras-chave: Menopausa. Terapia Hormonal. Alternativas Não Hormonais. Sintomas Vasomotores. Síndrome Geniturinária da Menopausa. Hormônio Anti-Mülleriano.

RESUMEN

La menopausia es un hito fisiológico caracterizado por la pérdida de la actividad folicular ovárica, frecuentemente asociada a síntomas vasomotores (VMS) y al síndrome genitourinario de la menopausia (SGM). Aunque la Terapia Hormonal de la Menopausia (THM) es la intervención más eficaz para el alivio sintomático y la prevención de la pérdida ósea, su uso está limitado por contraindicaciones en subgrupos específicos, como sobrevivientes de cáncer de mama y pacientes con antecedentes de endometriosis, lo que exige abordajes individualizados. El diagnóstico es clínico y retrospectivo, pero la Hormona Antimülleriana (AMH) es un biomarcador sensible de la reserva ovárica, útil en la predicción de la menopausia inminente, a pesar de la persistente imprecisión en la determinación del momento exacto. El avance en alternativas no hormonales representa una frontera prometedor, incluyendo antagonistas de los receptores de neuroquinina como fezolinetant y elinzanetant para los VMS, y terapias tópicas como el ácido hialurónico vaginal y el láser (CO₂ y Er:YAG) para el SGM/atrofia vulvovaginal, que demuestran eficacia comparable en desenlaces centrados en la paciente, con perfiles de seguridad favorables para pacientes con riesgo oncológico. Además, la THM ha demostrado optimizar la respuesta a la pérdida de peso cuando se combina con agonistas de GLP-1 como la semaglutida. No obstante, el



manejo terapéutico de la menopausia aún carece de datos a largo plazo sobre la seguridad cardiovascular, ósea y oncológica de las nuevas terapias no hormonales, reforzando la necesidad de estudios prospectivos para consolidar estrategias seguras e individualizadas durante el climaterio.

Palabras clave: Menopausia. Terapia Hormonal. Alternativas No Hormonales. Síntomas Vasomotores. Síndrome Genitourinario de la Menopausia. Hormona Antimülleriana.



1 INTRODUCTION

Menopause is a physiological milestone in a woman's life, characterized by the permanent cessation of menstrual cycles due to the loss of ovarian follicular activity. This transitional process is often accompanied by a myriad of symptoms that significantly impact quality of life, including vasomotor symptoms (VMS) such as hot flashes and night sweats, in addition to genitourinary menopause syndrome (GSM) (Johnson et al., 2023; Panay et al., 2024).

It can be characterized by hormonal changes associated with vasomotor, genitourinary, metabolic, and psychosocial symptoms, which can significantly compromise women's quality of life. Although hormone therapy is considered one of the most effective options for managing these symptoms, its use is limited by clinical contraindications, potential risks, and individual preferences. In this context, recent studies have investigated non-hormonal alternatives, including local therapies such as vaginal hyaluronic acid for genitourinary syndrome of menopause and non-hormonal drugs targeting the neuroendocrine mechanisms of vasomotor symptoms. These approaches expand the available therapeutic options and reinforce the need for individualized strategies in the care of climacteric women (Agrawal et al., 2024; Johnson et al., 2023; Panay et al., 2025).

The main characteristic of a woman's reproductive function is that it has a clearly finite duration. The terminal transition to a post-reproductive phase of life is overly apparent to women in the form of menopause, when menstruation ceases, although this is preceded by subtle changes, including a decline in fertility, being apparent approximately a decade and a half earlier (TeVelde and Pearson, 2002). Thus, with the increase in life expectancy and the average age of menopause being 49 years, ranging from 46 to 52 years, and depending on ethnicity (Gold, 2011; Schoenaker et al., 2014), women will spend nearly half of their lives in a postmenopausal state. However, for some, this will be substantially higher, as 4% of women experience premature ovarian failure (POI; menopause before the age of 40) (Golezar et al., 2019) and 8% experience early menopause (menopause before the age of 45) (Mishra et al., 2017).

The diagnosis and prediction of the onset of menopause have evolved with the use of biomarkers, with Anti-Müllerian Hormone (AMH) being identified as a robust tool to assess ovarian reserve and estimate the time remaining until the last menstruation (Nelson et al., 2023). While Menopause Hormone Therapy (MHT) remains the gold



standard for symptomatic relief, its prescription requires caution in specific subgroups, such as breast cancer survivors or women with a history of endometriosis (Glynne et al., 2024; Cassani et al., 2024). Untreated POI is characterized by progressive bone loss (leading to osteoporosis and fragility fractures), central and adipositive predisposition to type 2 diabetes, early cardiovascular disease, and premature death, as well as infertility (Shuster et al., 2010; Torrealday, Kodaman and Pal, 2017; Anagnostis et al., 2019a). At the same time, the search for safe and effective non-hormonal alternatives has advanced, driven by the need to treat patients with formal contraindications to estrogens or who opt for hormone-free therapies (Panay et al., 2024). New classes of drugs, such as neurokinin receptor antagonists, and non-hormonal topical approaches to vaginal health represent promising frontiers in current therapeutic management (Johnson et al., 2023; Agrawal et al., 2024).

2 METHODOLOGY

This research is a narrative review of the literature, structured with the purpose of examining and synthesizing recent advances in the diagnosis and treatment of menopause. The bibliographic search was carried out through the PubMed database, using the descriptors "Menopause", "Treatment" and "Diagnosis", articulated by the Boolean operators AND and OR, following the MeSH standardization. The selection included original articles and systematic reviews published in the period between the last five years, with full text available and written in English. Studies that did not have a direct link with therapeutic management or clinical diagnosis, duplicates, and publications without clear methodological grounds were excluded. The initial screening was carried out by the analysis of titles and abstracts, followed by the full evaluation of the texts to ensure relevance to the central theme. The extracted data were grouped thematically to enable an integrated discussion of the evidence.

3 RESULTS AND DISCUSSION

3.1 DIAGNOSIS AND PREDICTION OF MENOPAUSE

The diagnosis of menopause is defined retrospectively after 12 consecutive months of amenorrhea in women over 40 years of age, in the absence of other causes (such as pregnancy, hyperprolactinemia, or systemic diseases) (Crandall et al., 2023).



Accurate identification of the transition to menopause is essential for clinical planning. Anti-Müllerian Hormone (AMH) stands out as the most sensitive biomarker to reflect follicular decline. Evidence demonstrates that low AMH levels are reliable predictors of impending menopause, outperforming other traditional hormonal markers in assessing the age at which menopause occurs (Nelson et al., 2023). In addition, the integration of AMH dosage to the patient's age and menstrual history allows the creation of predictive models that aid in the personalized estimation of the time remaining until menopause, although individual variability is still a diagnostic challenge (Nelson et al., 2023).

However, laboratory evaluation, including FSH or estradiol measurement, is not recommended for diagnosis in women in this age group, as hormone levels vary widely during the menopausal transition and only stabilize years after the last menstrual cycle. (Crandall and colab., 2023) The accuracy of AMH increases as women approach menopause, standing out among other laboratory markers. In addition, elevated AMH levels in young women may indicate an increased risk of primary ovarian failure, however, it has limited utility in accurately predicting menopause in young women. (Nelson et al., 2023; Karaviti et al., 2025).

In summary, diagnosis is clinical and retrospective, and prediction of the exact time of menopause remains inaccurate, even with the use of hormonal markers. Early recognition of vasomotor symptoms and changes in the menstrual cycle can help identify the menopausal transition. (Crandall and colab., 2023).

In the clinical aspect, menopause is usually accompanied by different symptoms, which can vary greatly in intensity and form of presentation between women. Among the most impactful changes are those that affect the genital region and sex life, gathered in what we call genitourinary syndrome of menopause (GSM). It is a chronic and complex condition, which involves changes in the vulva, vagina, lower urinary tract and sexual function. It is estimated that between 26% and 85% of women after menopause have some of these symptoms, the most common being vaginal dryness, pain during sexual intercourse (dyspareunia), and vaginal irritation or itching (Agrawal et al., 2024).

3.2 HORMONAL APPROACH: BENEFITS AND CHALLENGES IN COMPLEX CASES

Menopause hormone therapy (MHT), also called hormone replacement therapy, is recognized as the most effective intervention for the control of vasomotor symptoms and



for the prevention of bone loss in postmenopausal women. Evidence shows that MHT significantly reduces the incidence of osteoporotic fractures, and is especially recommended in women with early or premature menopause, a group that has a higher risk of cardiovascular diseases and fractures throughout life. In these situations, estrogen replacement up to the expected age of natural menopause is indicated, as long as there are no clinical contraindications (Glynne et al., 2024).

However, as discussed by Glynne et al., the use of MHT in women with a history of breast cancer remains contraindicated. This restriction is based on the role of estrogen as a tumor growth stimulating factor, in addition to historical and contemporary evidence demonstrating improved overall survival associated with the reduction or elimination of estrogen exposure after breast cancer diagnosis. Randomized controlled trials reinforce that endocrine manipulation is an essential therapeutic pillar in this population, making hormone reintroduction potentially harmful.

Additionally, the route of administration of THM influences the risk profile, since oral formulations of estrogen are associated with a higher risk of venous thromboembolism and stroke, while transdermal estradiol does not seem to significantly increase these events, as it avoids first-pass hepatic metabolism. Still, this benefit does not extend to women with previous breast cancer.

Against this backdrop, Glynne et al. emphasize the preference for non-hormonal approaches to the management of menopausal symptoms in breast cancer survivors. Antidepressants, anticonvulsants such as gabapentin and pregabalin, as well as non-hormonal local therapies, may offer symptomatic relief, although they have limited efficacy and potential adverse effects, including sexual dysfunction. Thus, the management of menopause in this population requires therapeutic individualization, rigorous weighing between risks and benefits, and a multidisciplinary approach.

MHT is highly effective in controlling VMS, preserving bone mineral density, reducing the risk of mortality, myocardial infarction, and heart failure. In patients with endometriosis, management during menopause is delicate, as hormonal therapies can reactivate foci of the disease or increase the risk of malignant transformation, requiring an individualized approach that considers cardiovascular and oncological risks, aiming to promote quality of life. Studies suggest that the use of combination hormone therapy or tibolone is preferable to the use of estrogen alone in these patients to minimize the risk of reactivation of endometriotic foci and reduce the chance of transformation to



endometriosis-associated ovarian cancer (Cassani et al., 2024). In this context, the isolated use of estrogens as MHT is associated with the aforementioned risks, such as reactivation of endometriosis and malignant transformation of ovarian cysts. Therefore, combinations that are estrogen and progesterone, such as Tibolone, become safer alternatives for these women, controlling vasomotor and bone effects and, at the same time, acting on the endometrium. Also considering cardiovascular risks, patients with endometriosis have increased risks, with a higher probability of angina and infarctions (Cassani et al., 2024). In breast cancer survivors, systemic MHT is generally avoided due to the potential risk of recurrence, which makes non-hormonal options crucial for this group (Glynne et al., 2024). For these women, the decision to initiate any form of hormone therapy should be based on a multidisciplinary discussion that weighs the severity of climacteric symptoms against oncological safety data, always prioritizing non-hormonal alternatives as the first line (Glynne et al., 2024). Exposure to estrogen (such as MHT) in peri- or postmenopausal times may recreate an environment that favors cancer growth, reducing survival, and increasing the risk of death in women with a history of estrogen receptor-positive (ER-positive) breast cancer primarily. However, despite the harms, patients with a history of the cancer in question can choose to adopt MHT according to their preferences and values in order to ensure quality of life, as long as the doctor informs them about the increased risks of hormone therapy in this case (Glynne et al., 2024).

In addition, the interaction between THM and metabolism has been explored. Studies suggest that hormone therapy does not negatively interfere with the response to weight loss mediated by GLP-1 receptor agonists, such as semaglutide, indicating that women using hormones may obtain metabolic benefits similar to those who do not use such therapy (Hurtado et al., 2024).

The transition to menopause is associated with changes in body composition, including increased fat mass, decreased lean mass, and increased abdominal adiposity. Consequently, changes in weight and body composition increase the risk of cardiometabolic diseases, as evidenced by the increased prevalence of type 2 diabetes mellitus, dyslipidemia, steatotic liver disease associated with metabolic dysfunction, and cardiovascular disease, and is also associated with higher risks of morbidity and mortality (Hurtado et al., 2024).



At the start of semaglutide treatment in postmenopausal women, the use of hormone therapy (HT) plus it demonstrated approximately 30% greater weight loss. After twelve months, HT use was associated with a higher likelihood of achieving the weight loss goal $\geq 5\%$ and $\geq 10\%$ total body weight loss (Hurtado et al., 2024). The weight loss observed is associated with an improvement in cardiometabolic risk markers, regardless of the use of hormone therapy. However, the use of hormone therapy causes improvement in vasomotor symptoms and may therefore lead to improved sleep, physical activity, and overall quality of life, factors that may affect the response to weight loss interventions (Hurtado et al., 2024).

3.3 INNOVATIONS IN NON-HORMONAL THERAPIES

For vasomotor symptoms, neurokinin (NK) receptor antagonists emerge as a therapeutic revolution. Fezolinetant, a selective NK3 receptor antagonist, has demonstrated a significant reduction in the frequency and severity of hot flashes in phase 3 clinical trials, with a favorable long-term safety profile (Johnson et al., 2023). Safety data indicate that fezolinetant is not associated with changes in endometrial thickness or serious hepatic adverse events, making it a robust option for long-term use (Johnson et al., 2023).

Similarly, elinzanetant, which acts as a dual antagonist of NK1 and NK3 receptors, has shown efficacy in improving sleep and reducing VMS at 52 weeks, consolidating itself as a viable alternative for women who cannot or do not wish to use hormones (Panay et al., 2024). Elinzanetant has also been shown to improve health-related quality of life and reduce the interference of hot flashes with daily activities, remaining effective and well-tolerated for up to one year of treatment (Panay et al., 2024).

In the field of urogenital health, GSM treatment also offers non-hormonal alternatives. The topical use of vaginal hyaluronic acid has shown comparable efficacy to vaginal estrogen in reducing symptoms such as dryness and dyspareunia, without the systemic risks associated with hormone absorption, offering a safe option for patients at high cancer risk (Agrawal et al., 2024). Although vaginal estrogen is superior in restoring vaginal physiology (pH and cell maturation), hyaluronic acid is a non-inferior alternative in subjective symptom relief, which is critical for treatment adherence in patients with hormonal contraindications (Agrawal et al., 2024).



In a pilot randomized clinical trial, the efficacy of vaginal hyaluronic acid (a non-hormonal alternative) to vaginal estrogen in the treatment of GSM over 12 weeks was compared. No clinically significant differences were observed between the groups regarding the overall improvement of vulvovaginal symptoms, as assessed by the *Vulvovaginal Symptom Questionnaire* (VSQ). Both treatments resulted in significant improvement in patient-reported symptoms, including vaginal dryness and dyspareunia, with more than 90% of participants reporting overall clinical improvement (Agrawal et al., 2024)

Although vaginal estrogen demonstrated a greater impact on objective outcomes, such as the vaginal maturation index, patient-centered outcomes (considered increasingly relevant in the therapeutic evaluation of GSM) were similar between groups. In addition, both treatments had a good safety profile, with no serious adverse events related to the intervention (Agrawal et al., 2024).

These findings suggest that vaginal hyaluronic acid may represent an effective and safe therapeutic option for women who do not want or cannot use vaginal estrogen, reinforcing the need for larger and appropriately sized studies to confirm its non-inferiority to standard hormone therapy.

Also in the context of the treatment of genitourinary syndrome of menopause (GSM), specifically vulvovaginal atrophy (VVA), laser therapy has emerged as a non-hormonal alternative for women who do not get a response, have contraindications, or do not comply with available therapies (Benine et al., 2022).

There are two main types of lasers currently used for the treatment of VVA, they are the fractional micro-ablative CO₂ laser and the non-ablative photothermal laser Erbium:YAG. Both lasers promote improvement of vaginal atrophy through tissue stimulation and remodeling. Er:YAG acts by controlled and non-ablative thermal heating of the deep vaginal mucosa, inducing the contraction of collagen fibers, remodeling, and neocollagenesis, with consequent increase in vaginal elasticity and tone. The micro-ablative CO₂ laser, on the other hand, produces controlled thermal microlesions in the lamina propria by vaporization of intracellular water, triggering neocollagenesis and neovascularization, associated with improved humidity, pH, blood flow, and vaginal trophicity (Benine et al., 2022).

Regarding the results of the use of lasers, the CO₂ laser was shown to be long-lasting, with maintenance of clinical improvement for up to 12 to 36 months without the



need for retreatment. On the other hand, in the Er:YAG laser, long-term data are scarcer, suggesting a gradual return of parameters to baseline levels after 18 to 24 months. Regarding safety, no serious adverse events were reported, the most common side effects were mild and transient such as burning sensation and discomfort during the procedure. Despite the favorable results, it is noteworthy that the FDA (the food and drug administration) of the United States issued a warning against the use of energy-based devices for unapproved genital indications in 2018, reinforcing the need for caution, adequate patient selection, and greater methodological robustness in future studies (Benine et al., 2022).

4 CONCLUSION

In view of the above, despite important advances in the diagnosis and management of menopause, there are still relevant limitations in the available evidence. Anti-Müllerian hormone functions as a marker of ovarian reserve, but has limited accuracy in predicting the individual timing of menopause, especially in young women. Similarly, emerging non-hormonal therapies have symptomatic efficacy but lack robust data from longer-term studies on cardiovascular, bone, and oncological safety. Thus, prospective studies with longer follow-up time and direct comparisons between therapeutic approaches are needed in order to consolidate safe, effective strategies based on individualized care for climacteric women.

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