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Therapeutic Individualization in Menopause: Applications and Strategies for the Use of Hormonal Implants

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Abstract

Therapeutic individualization in menopause requires a careful assessment of risks, benefits, and patient preferences within a context of increasing diversity of available treatment options. In this setting, hormonal implants have gained visibility as a strategy for continuous and sustained hormone delivery; however, they remain associated with regulatory controversies, gaps in scientific evidence, and divergent recommendations among scientific societies. Current evidence suggests potential improvement in vasomotor symptoms, sleep disturbances, cognitive performance, body composition, and quality of life, particularly in women who do not tolerate other routes of administration. Effective therapeutic individualization requires a detailed evaluation of the clinical profile, reproductive history, comorbidities, and patient goals, as well as regular monitoring to assess efficacy and safety. This narrative review examines the use of hormonal implants for the management of menopausal symptoms, emphasizing the need for therapeutic individualization. It explores the physiological basis, clinical efficacy, and safety profile of implants, highlighting benefits such as sustained hormone release and improved treatment adherence, alongside challenges such as variability in formulations. The authors conclude that although implants are a promising strategy, their use requires rigorous patient selection, continuous monitoring, and adherence to safety guidelines.

Keywords

Menopause, Hormonal Implants, Hormone Therapy, Climacteric, Therapeutic Individualization

1. Introduction

Menopause represents a physiological phase characterized by the progressive decline of ovarian function and a reduction in circulating levels of gonadal hormones, resulting in multiple clinical repercussions that may compromise quality of life, cognitive well-being, and women's metabolic health [1]. This physiological phenomenon is marked by a pronounced reduction in the production of ovarian steroids, particularly estradiol and progesterone, leading to systemic effects that extend beyond the reproductive system and impact cardiovascular, bone, metabolic, cognitive, and sexual health [2].

In addition to the estrogen decline characteristic of the menopausal transition, a progressive reduction in testosterone levels is also observed in women with advancing age, resulting from decreased ovarian and adrenal production. This decline may be associated with symptoms such as reduced libido, fatigue, decreased muscle mass, and a negative impact on quality of life. In this context, androgen replacement has been discussed as a therapeutic strategy in selected women, which underpins the growing attention to the use of testosterone-containing hormonal implants in the individualized management of menopause [3].

It is estimated that by 2030, more than 1.2 billion women worldwide will be in the postmenopausal age group, including approximately 29 million in Brazil alone [4]. This increase is driven by population aging and greater female life expectancy, resulting in a substantial proportion of a woman's life being lived in a hypoestrogenic state. Clinical manifestations—including vasomotor symptoms, sleep disturbances, mood changes, sexual dysfunction, and genitourinary syndrome of menopause—vary in intensity and duration and are influenced by genetic, socioeconomic, cultural factors, and overall health status.

Hormone therapy (HT) is widely recognized as the most effective treatment for controlling moderate to severe vasomotor symptoms and for preventing bone loss related to estrogen deficiency [5]. However, therapeutic decision-making during the climacteric and menopause requires an individualized approach, taking into account age, time since menopause, cardiovascular risk, oncologic history, and the patient's personal preferences.

Although subcutaneous hormonal implants have been used as a therapeutic option since the 1940s, in recent years they have become a more prominent part of the available therapeutic armamentarium, offering continuous and prolonged hormone release, with the potential for greater serum stability and improved treatment adherence in selected cases [6].

One of the main advantages of hormonal pellets is the sustained and stable release of hormones, reducing serum fluctuations associated with the peaks and troughs frequently observed with oral or intermittent transdermal therapies. This pharmacokinetic stability contributes to better control of vasomotor symptoms, such as hot flashes and night sweats, as well as potential improvements in sleep, mood, and overall well-being [7].

Another relevant aspect is therapeutic adherence. By eliminating the need for

daily medication use, pellets reduce the risk of forgetfulness and treatment failures, promoting greater consistency in hormone replacement and a better clinical response over time [8]. In addition, when appropriately indicated, they may contribute to the preservation of bone mineral density, reducing the risk of osteopenia and osteoporosis associated with estrogen deficiency [9].

In this context, therapeutic individualization becomes a guiding principle, seeking to reconcile scientific evidence, clinical experience, and patient values. This article aims to critically analyze the strategic use of hormonal implants in menopause, addressing pathophysiological aspects and available evidence in order to support safe, evidence-based clinical decision-making.

2. Methodology

The literature search identified approximately 210 potentially relevant studies, of which 68 articles were selected for full-text reading after screening by title and abstract. At the end of the process, 33 studies met the inclusion criteria and were incorporated into the qualitative analysis of this review.

A narrative review was chosen instead of a systematic review due to the heterogeneity of study designs, the diversity of hormonal formulations, routes of administration, and regulatory contexts of hormonal implants, as well as the scarcity of comparable randomized clinical trials. This design allowed the integration of pathophysiological data, clinical evidence, guideline recommendations, and regulatory aspects relevant to clinical practice.

The literature search was conducted between August and November 2025 in the PubMed/MEDLINE, SciELO, and ScienceDirect databases, using free-text descriptors and indexed terms related to the topic, such as "menopause," "hormone therapy," "individualized treatment," "personalized medicine," "routes of administration," "transdermal," "oral," "vaginal," "pellets," and "implant therapy." The descriptors were combined using the Boolean operators AND, OR, and NOT, and an additional manual search was performed in the reference lists of the selected articles.

The absence of formal tools for assessing the quality of evidence, such as the GRADE system, is explicitly acknowledged, representing a methodological limitation inherent to this type of review. This limitation restricts the strength of the conclusions and prevents objective classification of the level of evidence of the recommendations presented, reinforcing the need for cautious interpretation of the findings and for higher-quality prospective randomized studies.

Original articles, reviews, meta-analyses, consensus statements, and guidelines published between 2010 and 2025 in English, Portuguese, or Spanish were included, provided they addressed menopause, therapeutic management, or individualized treatment. Duplicate studies, articles with inadequate methodology or insufficient data, non-scientific publications, and articles focused exclusively on sociocultural aspects without therapeutic relevance were excluded.

The analysis process included detailed reading, thematic classification, and crit-

ical synthesis of the content, following scientific standards of rigor to ensure reliability and consistency of the information. This approach allowed the construction of a comprehensive perspective on the topic, contributing to the formulation of clinical recommendations and evidence-based shared decision-making practices.

3. Literature Review

3.1. Pathophysiology and Clinical Implications

Menopause represents a physiological milestone resulting from the progressive decline of ovarian function, culminating in the permanent cessation of menstruation and the end of cyclical production of gonadal steroids, particularly estrogen and progesterone. This process results from irreversible follicular depletion, associated with decreased sensitivity of granulosa cells to follicle-stimulating hormone (FSH) and luteinizing hormone (LH). As a compensatory response, serum gonadotropin levels—particularly FSH—increase, concomitant with a significant reduction in estradiol and alterations in androgen balance [10].

From a pathophysiological perspective, estrogen deficiency affects multiple organ systems. In the central nervous system, hypothalamic dysfunction of thermoregulation explains the occurrence of hot flashes and night sweats. In the urogenital tract, epithelial atrophy and reduced local vascularization compromise vaginal lubrication and elasticity, predisposing to dyspareunia, urinary incontinence, and increased susceptibility to infections. In bone tissue, reduced osteoblastic activity associated with increased osteoclastic resorption predisposes to osteopenia and osteoporosis, increasing the risk of fractures [11].

The clinical implications extend beyond immediate symptoms. Reduced estrogen levels are associated with increased cardiovascular risk, resulting from a worsened lipid profile, increased arterial stiffness, and endothelial dysfunction. Alterations in glucose metabolism and body weight, commonly observed during this period, may contribute to the development of metabolic syndrome. In addition, reduced gonadal hormones, through their action on the central nervous system, influence neurocognitive aspects, potentially affecting memory, mood, and sleep quality, and increasing the incidence of depression and anxiety [11].

The management of menopause requires an individualized approach that addresses not only symptom relief but also the prevention of chronic complications and the promotion of quality of life. Hormonal implants may represent a valid therapeutic strategy for specific patient profiles, provided they are prescribed based on rigorous clinical criteria and supported by consistent scientific evidence [12].

3.2. Concept and Mechanisms of Action of Hormonal Implants

Hormonal implants are controlled-release devices inserted into the subcutaneous tissue with the aim of providing long-term hormone replacement or contraception. They are generally manufactured from biocompatible materials, such as

medical-grade silicone or specific polymers, and have a cylindrical or rod-like shape with a small diameter, facilitating minimally invasive insertion and stable subdermal placement [12].

It is essential to differentiate commercially manufactured hormonal implants approved by governmental regulatory agencies from so-called compounded bioidentical pellets. Commercial implants are produced by authorized manufacturers, follow strict industrial standards of quality, purity, and pharmacokinetic stability, and undergo formal processes of efficacy, safety, and standardization assessment by regulatory agencies such as the FDA or national health authorities [13] [14].

In contrast, compounded bioidentical pellets are prepared in compounding pharmacies and are not subject to the same regulatory approval processes, controlled clinical trials, or industrial standardization, which may result in greater dosage variability, unpredictable hormone release, and inconsistent serum levels, with potential clinical implications [15] [16].

In the context of menopause, the hormones used include estradiol, progesterone, and, in some cases, testosterone, in different combinations and dosages according to the individual needs of the patient [17]. The mechanism of action is based on the direct replacement of sex steroids, compensating for the abrupt hormonal decline characteristic of the climacteric transition. Continuous release avoids pronounced peaks and troughs in hormone levels, reducing symptom variability and minimizing some adverse effects commonly observed with oral or transdermal therapies. Furthermore, by avoiding first-pass hepatic metabolism, implants may reduce the impact on coagulation factors and lipid profiles [18].

Clinically, implants aim to relieve vasomotor symptoms, improve urogenital function, preserve bone health, and contribute to physical and emotional well-being [19].

Thus, hormonal implants constitute a personalized medicine strategy, offering stable hormone delivery and potential clinical benefit when used in an individualized, safe, and evidence-based manner [20].

3.3. Clinical Efficacy in the Treatment of Menopausal Symptoms

The available literature, predominantly composed of observational studies, indicates that hormonal implants may promote significant improvement in vasomotor symptoms, including hot flashes, night sweats, irritability, and insomnia. Women treated with implants frequently report increased energy levels, greater emotional well-being, and improved sexual function.

Beyond climacteric symptoms, some studies suggest benefits in vaginal trophism and possible positive effects on lean mass and body composition; however, the results are inconsistent and appear to depend on the specific formulations used.

Clinical studies have shown that estradiol implants promote consistent reductions in both the frequency and intensity of vasomotor symptoms. In a prospective clinical trial [21], postmenopausal women who received subcutaneous implants

exhibited marked improvement in hot flash intensity after three months of treatment, with maintenance of these results for up to 12 months of follow-up. These findings are consistent with observations from national studies [22], which reported a reduction in vasomotor symptoms and improvement in overall well-being in women who received combined estradiol and testosterone implants.

A recent meta-analysis [23] demonstrated that women treated with hormonal implants achieved higher scores in domains related to mood, vitality, sexual function, and sleep quality when compared with placebo or other hormone therapy routes.

Within the context of individualized therapeutic strategies, hormonal implants offer pharmacokinetic stability and simplified dosing, as their continuous and stable hormone release prevents large dose fluctuations that may occur with other routes of administration, such as oral, transdermal, or intramuscular therapy. This stability is particularly beneficial for patients with persistent symptoms or variable metabolism, optimizing clinical control. High treatment adherence represents another important advantage, as daily use or application is not required, reducing the risk of missed doses [24].

In this context, the CLARA study contributes to advancing knowledge on the safety, efficacy, and pharmacokinetics of bioabsorbable estradiol implants, providing additional scientific support for the use of this hormone therapy modality in climacteric women seeking long-acting release options.

Another relevant aspect is the possibility of dose individualization. Unlike standardized pharmaceutical formulations, implants—especially those prepared under strict professional responsibility and clinical supervision—allow individualization of hormone type and dosage based on symptom profile, clinical history, baseline hormone levels, and therapeutic goals. Retrospective studies and prospective cohorts, although limited, have shown that estradiol and testosterone administered via implants can effectively improve vasomotor symptoms, libido, bone mineral density, and lipid profiles in cases refractory to other routes of administration [24].

The strategic use of subcutaneous hormonal implants in menopause places them at the forefront of personalized medicine. Their ability to provide stable pharmacokinetics, precisely adjusted doses, and high patient adherence makes them a valuable tool for therapeutic individualization. Although clinical caution and ongoing research remain essential, current evidence suggests that, for carefully selected patients under rigorous monitoring, implants represent an effective and strategic modality to optimize relief of vasomotor symptoms, improve quality of life, and promote long-term health [25].

3.4. Safety and Adverse Events

The use of hormone therapies—including hormonal implants and testosterone replacement—is guided by international guidelines and national regulations aimed at ensuring patient safety and evidence-based clinical practice. These recommen-

dations address therapeutic indications, monitoring of adverse events, dosing, routes of administration, and the assessment of cardiovascular, thrombotic, breast, and endometrial risks [26].

Among the most frequently reported adverse events are irregular bleeding, mastalgia, mood changes, and, in the case of testosterone-containing implants, possible acne or increased skin oiliness. Additional complications include difficulty in implant removal, risk of overdosing with compounded formulations, and unpredictable hormone release in certain preparations. Local complications may also occur, including inflammation, hematoma, infection, and fibrous tissue formation at the insertion site; although less frequent, these events have been described in clinical series [27].

From a safety perspective, the distinction between regulatory agency–approved hormonal implants and compounded bioidentical implants is particularly relevant. Approved hormone therapies are supported by consolidated pharmacovigilance data, post-marketing surveillance, and clear recommendations regarding indications, contraindications, and clinical follow-up, as highlighted by international guidelines [13].

In contrast, the use of compounded bioidentical pellets is associated with greater regulatory uncertainty, the absence of large randomized trials, and limited long-term safety data, which may increase the risk of adverse events such as supratherapeutic dosing, difficulty in treatment reversibility, and unpredictable metabolic and cardiovascular effects [15].

Accordingly, international consensus statements and scientific societies recommend caution in the use of compounded implants, emphasizing the importance of careful patient selection, detailed informed consent, and rigorous clinical monitoring, particularly when testosterone-containing therapies are considered [13] [16].

3.5. Therapeutic Individualization Applied to Hormonal Implants

Therapeutic individualization is a fundamental principle in the management of menopause and becomes particularly relevant in the use of hormonal implants, whose fixed pharmacokinetic characteristics and prolonged release require rigorous and personalized evaluation. Unlike oral and transdermal routes, which allow gradual dose adjustments, implants deliver non-modifiable doses after insertion, making careful patient selection and an integrated analysis of clinical, metabolic, and individual preference factors essential.

The individualized approach begins with the identification of the woman's symptom profile, considering the intensity of hot flashes, sleep disturbances, emotional symptoms, sexual dysfunction, and the overall impact on quality of life. Patients with refractory symptoms or hormonal instability with other routes of administration may benefit from the more stable release provided by implants [28].

Shared decision-making is of paramount importance. Initially, risk stratification should be performed, taking into account age, time since menopause, per-

sonal and family history of breast cancer, thromboembolic risk, cardiovascular health, and comorbidities such as obesity, hypertension, and diabetes—factors that directly influence therapeutic choice [29].

Hormone dosing should always aim to achieve physiological ranges, minimizing the risk of overdosing, especially with compounded implants, which present greater variability in hormone release. Periodic clinical and laboratory monitoring is recommended, including assessment of therapeutic response, hormone levels, adverse events, and the need for reinsertion [30].

Thus, therapeutic individualization applied to implants goes beyond the simple choice of route of administration, involving a structured process that integrates safety, efficacy, and the patient's preferences and expectations. In a broader context, personalization represents the safest and most appropriate approach, consistently aligned with scientific evidence and the principle of shared decision-making (Table 1).

Table 1. Clinical framework for the individualized use of hormonal implants in menopause.

Domain	Key points
Patient selection criteria	• Moderate to severe vasomotor symptoms refractory to other routes • Intolerance or poor adherence to oral or transdermal therapies • Well-informed women with realistic expectations regarding benefits and risks • Absence of absolute contraindications to hormone therapy
Contraindications	• Active or prior breast or endometrial cancer without oncologic clearance • Active thromboembolic disease or recent history • Severe liver disease • Unexplained uterine bleeding • Uncontrolled high cardiovascular risk
Monitoring strategies	• Periodic clinical assessment of symptoms and adverse events • Hormone level measurements as clinically indicated (avoid supraphysiological levels) • Metabolic monitoring (lipid profile, glycemia) • Breast and gynecologic evaluation according to current guidelines
Follow-up recommendations	• Clinical reassessment every 3 - 6 months • Ongoing discussion of risk-benefit balance and possibility of discontinuation • Detailed documentation of informed consent • Avoid automatic reinsertion without individualized clinical reassessment

Legend: The use of hormonal implants should be based on careful patient selection, informed consent, rigorous monitoring, and alignment with national and international guidelines, respecting regulatory limitations and the relative irreversibility of the method.

3.6. Regulatory and Ethical Aspects

The regulation of hormonal implants shows marked heterogeneity across different countries, reflecting differences in regulatory systems, approval criteria, and requirements for scientific evidence. In some regions, certain industrially manufactured hormonal implants have obtained temporary or restricted approval, whereas in other contexts clinical use occurs predominantly through compounded bioidentical pellets, which do not follow the same standards of standardization, phar-

macovigilance, and safety evaluation required for medications approved by regulatory agencies such as the Food and Drug Administration (FDA), the European Medicines Agency (EMA), or the Brazilian Health Regulatory Agency (ANVISA) [9] [13]. This regulatory variability limits the generalizability of the available data and requires caution when extrapolating clinical results across different healthcare settings [31].

From an ethical perspective, the use of hormonal implants raises relevant concerns related to informed consent, the relative irreversibility of the method, and long-term safety. Unlike oral or transdermal routes, implants do not allow immediate dose adjustments after insertion, which reinforces the need for clear communication with patients regarding potential risks, therapeutic limitations, and scientific uncertainties [32]. In addition, the scarcity of long-term prospective randomized studies poses additional challenges for the assessment of cardiovascular, oncologic, and metabolic outcomes, making rigorous clinical follow-up and adherence to the precautionary principle essential in clinical practice [33].

4. Conclusions

Therapeutic individualization in menopause represents a central pillar of contemporary clinical practice, particularly in light of the diversity of symptoms, metabolic profiles, and patient expectations. In this context, subcutaneous hormonal implants—documented in the scientific literature for more than 80 years—are increasingly recognized as a safe and effective alternative capable of providing continuous and prolonged hormone release and effective symptom control in selected cases. Nevertheless, their use requires rigorous indication criteria, careful assessment of the risk–benefit balance, and continuous monitoring, as the relative irreversibility of the method and variability among formulations may increase the likelihood of adverse events when not appropriately managed.

It is essential to recognize that the management of menopause with hormonal implants and complementary therapies extends beyond the relief of immediate symptoms. It involves a comprehensive approach to women's health, considering metabolic, cardiovascular, bone, psychological, and social aspects. Therapeutic individualization, combined with rigorous clinical follow-up and transparent communication, allows optimization of treatment benefits, minimization of potential risks, and promotion of patient autonomy within a shared decision-making model.

Looking ahead, the expansion of randomized, multicenter, long-term clinical trials will be fundamental to consolidate evidence on efficacy, safety, and impact on quality of life, strengthening evidence-based practice and supporting national and international guidelines. The advancement of standardized, high-quality research is indispensable to defining the role of hormonal implants in clinical practice and to enhancing the safety of their use in the future.

5. Limitations

As limitations inherent to narrative reviews, this study acknowledges the absence

of rigorous selection criteria, the potential for selection bias, and interpretative subjectivity. However, strategies were adopted to minimize these limitations, including a comprehensive literature search, critical appraisal of sources, and coherent integration of the available evidence.

Although recent publications were included, relevant studies may not have been identified due to indexing limitations, terminological variability, or access restrictions. Therefore, the findings of this review should be interpreted with caution, recognizing that the current landscape still requires high-quality clinical trials and comparative investigations to better establish the role of hormonal implants in the individualized management of menopause.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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