Position statement of the Latin American Federation of Climacteric and Menopause Societies (FLASCYM) regarding the use of Bioidentical Hormonal Compounds during female mid-life

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ABSTRACT

To date, menopausal hormone therapy (MHT) is the best option for the management of menopausal symptoms, especially vasomotor, genitourinary and also for the prevention of bone loss. Preliminary data of the WHI, regarding one type of regimen, reported a greater risk of breast cancer, cardiovascular disease, cerebrovascular events and thrombosis. Despite this, as years have passed other arms have provide different results. Nevertheless, the use of MHT has never recuperated as before the WHI. In parallel women and physicians have been exploring alternatives. One is bioidentical hormonal compounds. Bioidentical hormonal compounds (BHC) are not approved by the FDA and formulated as galenic preparations promoted as a safer alternative for traditional MHT. The positioning of FLASCYM is that there are inconsistencies in potency, bioequivalence and information regarding the quality of BCHs. The lack of studies regarding their use has raised concerns about the correct doses and efficacy. On the other hand, information related to the possible adverse events is very limited and long-term consequences of the use of BHC are unknown. Therefore, FLASCYM does not recommend the use of BHC.

KEYWORDS

Bioidentical hormonal compounds, bioidentical hormones, alternatives, treatment, menopause.

Introduction

Menopause hormone therapy (MHT) is the best option for the management of vasomotor symptoms, the genitourinary syndrome of menopause (GSM) and the prevention of bone loss [1]. However, in 2002, the preliminary publishing of data of the combined arm estrogen progestogen (E+P) of the Women Health Initiative study (WHI) reporting that women users of MHT, specifically equine conjugated estrogens and medroxyprogesterone acetate, showed a greater risk of breast cancer, cardiovascular disease, cerebrovascular accidents and thrombosis and this unchained mediatic disinformation that didn't take in account that the study was not concluding and that other studies had different results [2].

Before the WHI, more than 90 million women used MHT in the world and, after its publication, prescription decreased in 63% mostly because of fear of breast cancer [3]. With the publication of the preliminary results of the WHI publication, the support of many media personalities and celebrities [4], the coverage of the media and the economic interests of certain health professionals and pharmaceuticals [5] became the perfect scenario for the worldwide growth of industries devoted to the manufacture of bioidentical hormonal, enhanced also by the fact that women wanted an alternative or "natural" therapy for the treatment of their menopause related symptoms.

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Terminology

Sexual steroids bioidentical hormonal therapy: Estradiol and progesterone are the only ones approved by the Food and Drug Administration of the United States (FDA). Bioidentical hormonal compounds (BHC): They are "compounds that have exactly the same chemical and molecular structure than the hormones produced in the human body". Generally, they are steroids of plant origin that are not approved by the FDA for the treatment of menopausal symptoms [6] and they include galenic preparations and the subdermal implants also called "pellets.

Estradiol and progesterone, along with others BHC, have been promoted as a safer and more efficient alternative for traditional MHT, even when many of these formulation lack of the supervision and the endorsement of the FDA. Currently, there is no

scientific evidence that supports that treatment with BHC could be more effective and/or safer than conventional MHT; however, as a result of unfounded affirmations many patients take BHC as natural derivates, falsely believing that they are a safer option [7].

What are bioidentical hormones and what are bioidentical hormonal compounds?

Bioidentical hormones

Bioidentical hormones have the same molecular structure than a hormone that is produced in the body; they are regulated by the state pharmaceutical committees, recently by the FDA, and they have published evidence.

Bioidentical Hormonal Compounds (BHC)

BHCs usually contain estrogens and progesterone, sometimes with testosterone, pregnenolone or dehydroepiandrosterone (DHEA). Formulations include sublingual, oral, transdermal, vaginal ovules, biodegradable subdermal implants or an oral presentation use that is placed between gums and cheeks. BHC preparations include the same ingredients available in the United States pharmacopeia used by the pharmaceutical industry for the massive production of FDA approved hormonal products but they are compounded or prepared in local pharmacies. However, BHC preparations are not subjected to the same federal laws designed to regulate massive produced drugs, since they are considered cosmetic products and not medications in their strict regulation.

Use of Bioidentical Hormonal Compounds

The use of BHC has grown in the last years according to data from a survey published in the Menopause journal; 28 to 68% of women use these kind of compounds [8,9]. Regarding the prescription of bioidentical hormones, published data inform that annually prescriptions of hormonal products with sexual steroids properly approved by the FDA (combination of estrogens + progestogens) increase up to 2.2 million. Interestingly, BHCs that have not been approved by the FDA for their conjoint use (estradiol and progesterone), currently represent 6 million prescriptions for each one and, finally, for BHCs not approved by the FDA as bioidentical compounds (estradiol + progesterone), the estimation is of 21 to 39 million prescriptions a year [10].

Safety of Bioidentical Hormonal Compounds

Recently, the North American Menopause Society (NAMS) and the National Academies of Sciences, Engineering and Medicine (NASEM), as well as the American College of Obstetricians and Gynecologists (ACOG) have expressed their concerns about the use of BHCs, including subdermal implants, also called pellets, as an alternative to the FDA approved hormonal products. Some patients and professionals think BCHs are more effective and safer than FDA approved bioidentical hormones and have become very popular despite the possible risks related to their use [7,11,12].

Inconsistencies of Bioidentical Hormonal Compounds

The contents analysis of BHCs showed important variations regarding their potency; some studies show up to 31% variation in relation to the specified compound. The second evaluation performed to these bioidentical hormonal compounds also showed variations related to their potency of up to 33% [8,13]. The lack of an appropriate labeling and the absence of the regulation of these BHCs allow the inconsistencies observed in their bio-equivalency that represent a risk for users' health. There is limited evidence regarding the organic consequences of the use of BHC, including the risk of endometrial cancer, since the excess of estrogens in combination with an unsuitable dose of progesterone can generate consequences that are harmful to users' health [8,14].

Positioning of international organisms regarding the use of non-FDA approved bioidentical hormonal compounds

In July, 2020, NASEM [15], expressed their concern regarding the safety and efficacy of bioidentical hormonal compounds; this positioning was directly favored by the FDA, that requested NASEM for the evidence recompilation regarding BHC use.

After two years of reviewing literature, NASEM concluded that there is limited evidence that can support the use of non-FDA approved BHCs. The most important issues that were exposed were related to the incorrect labeling of the compounds, the scarce quality of studies related to their pharmacokinetics and bioavailability, the technical difficulty of the manufacturing of "pellets", as well as insufficient quality evidence about safety and clinical effectiveness of these non-FDA approved BHCs. Despite the fact that most of those who promote the use of these non-FDA approved BHCs defend their safety and effectiveness, there are not enough studies that support these statements. One study, published in 2021 [16], shows that BHCs do not have the labeling and the warnings required by the sanitary authorities, in addition to the fact that are produced in a galenic manner in pharmacies that do not have the regulation that is demanded to the pharmaceutical laboratories regarding sterility and Good Manufacturing Practices. It is also showed there that BHCs are commonly prescribed by "antiaging" doctors and not by gynecologists. Even though absence of evidence is not evidence of absence, international scientific committees prefer not to recommend the use of these compounds until there is more research and studies that support their safety and efficacy [7].

The International Menopause Society (IMS) and the ACOG consider that the so called BHC use this name for marketing purposes and due to their ambiguity, since they refer to a hormonal preparation that includes a mixture of several hormones that can include estradiol, estrone, estriol, progesterone, testosterone and dehydroepiandrosterone. The IMS recommends not to prescribe BHCs due to the lack of enough scientific information regarding quality, control and regulation, as well as the fact that patients are not properly informed when coming for consultation asking for these compounds, contrary to orienting them to use already officially regulated products [17].

The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE), published in 2017 their position regarding the management of menopause; both organizations agree on not recommending the use of BHCs because there is not enough information about their safety and efficacy [18].

Recently, in Mexico, the Federal Commission for Protection Against Sanitary Risks (COFEPRIS), warned about the use of

BHC for the treatment of menopausal symptoms since these products are sold as nutritional supplements in the form of gels, powders, gummies, creams, and lack COFEPRIS authorization [19]. Bioidentical hormones used in MHT are approved by medical associations and can be commercially manufactured. This includes hormones like estradiol and progesterone, which are available in FDA-approved combinations.

Conversely, treatment with BHC carries additional risks. Although the hormones are identical to those naturally produced by the body, they may be prepared in combinations that have not been thoroughly studied. For instance, the inclusion of testosterone or other hormones, or the use of estradiol and progesterone in untested ratios, which could increase the risk of endometrial cancer if the progesterone dosage is insufficient.

This is a key concern of medical associations, as they emphasize that such combinations may lack adequate regulation, with inconsistencies in proportions or composition between batches. Additionally, alternative delivery methods, such as hormone pellets, raise concerns due to their uninvestigated pharmacokinetics and pharmacodynamics.

POESIT recommendations

In 2024, the collaborative group POESIT published recommendations regarding the management of body-identical hormones for menopausal symptoms and they emphasized that regulated body-identical hormone therapy (r-BHT), particularly 17β-estradiol (E2) and micronized progesterone (P4), is effective and well-supported by scientific evidence for symptom relief. They highlight findings from the REPLENISH study, which demonstrated that a combination of 1 mg E2 and 100 mg P4 effectively reduced hot flashes, improved sleep quality, and had no significant negative impact on lipid, glucose, or coagulation parameters. The article concludes by advising that non-regulated body-identical hormones could pose safety risks due to the lack of rigorous testing, and they recommend the use of regulated formulations for safer and more effective treatment [20].

Positioning of FLASCYM

- There are inconsistencies regarding potency, bio-equivalency and information regarding the quality of BHCs.
- The lack of scientific essays and studies properly designed regarding the use of bioidentical compounds brings concerns related to the correct doses and efficacy of any BHC.
- Even though there is few information and scarce publications about the possible adverse events related to the use of BHCs, this does not mean that they are not safe, since the current information is very limited. Long term consequences of the use of these BHCs are unknown.
- In agreement with NAMS, IMS, AACE, ACE and ACOG, FLASCYM does not recommend the use of BHCs, specially the implants ("pellets").

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