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Review

Position of the Spanish Menopause Society regarding the management of menopausal symptoms in breast cancer patients

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ABSTRACT

Breast cancer is the most common female cancer in Spain. Its high prevalence, its high survival rate, and its incidence are the reasons treatment is increasingly sought for common problems by young women who have survived it. Besides the contraception and fertility issues, many breast cancer survivors develop sexual disorders and menopausal symptoms, whether as a consequence of treatment-induced menopause or side effects of treatment. For such reasons, a panel of experts from the Spanish Menopause Society has met to develop usage recommendations for the relief of vasomotor symptoms and for sexual and reproductive health in patients with breast cancer based on the best evidence available.

Contents

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1. Introduction

More than 20,000 new cases of breast cancer (BC) are diagnosed annually in Spain. BC is the most common type of cancer (28.7% of all cancers) and has the highest mortality of all cancers in women (18.2%). However, survival has also increased in recent years as a result of early detection programmes and advances in treatment; consequently, BC also has the highest survival rate among cancers affecting women [1].

New clinical demands are often difficult to manage and present a challenge because survival and improved quality of life have been interpreted as conflicting interests. In fact, BC patients suffer more hypoestrogenism symptoms than women who reach menopause naturally, in some cases because chemotherapy (CT) has induced early menopause and in others because of the anti-estrogenic effects of adjuvant treatments [2]. This position paper aims to present recommendations for symptomatic patients with BC based on the best scientific evidence available [3,4].

2. Treatment of vasomotor symptoms in patients with BC

2.1. Hormone therapy (HT)

Although hormone therapy (HT) is considered the most effective treatment for the relief of vasomotor symptoms, the suspicion that it could increase the risk of recurrence, especially in oestrogen receptor (ER)-positive tumours, limits its use in patients with BC [5]. We only recommend it for patients with severe symptoms or those who are refractory to other treatments, and we always take into account other favourable factors (e.g., patients with early-stage or ER-negative tumours or with a prolonged disease-free survival) and inform the patient about the risks and benefits. In these cases, the duration and dose of HT should be minimised where possible [6].

The available evidence is limited and of poor quality; although there are many non-randomised observational studies in which prognosis does not worsen (and, in some cases, improvements are described) for women on oestrogen therapy (ET), the selection bias of no-randomisation affects the validity of the conclusions.

While the HABITS (Hormone Replacement Therapy after Breast Cancer: Is It Safe?) [7] trial found an increase in BC recurrences after HT (*hazard ratio* (HR), 3.3; 95% CI, 1.5–7.4), the Stockholm trial did not (HR, 0.82; 95% CI, 0.35–1.9). Possible explanations for these differences are the different doses, the type of progestogen used, or the concomitant use of tamoxifen (TMX) [8]. However, an analysis of the data revealed a slight increase in the risk of recurrence, and the two randomised clinical trials (RCTs) were prematurely ended in 2003[9].

Consequently, HT is not advisable for symptom relief in women with a history of BC.

2.2. Progestogens

High-dose progestogens may be effective for the relief of hot flashes without increasing the recurrence of BC. However, to date, there are no data on their long-term safety in patients with BC.

Megestrol acetate is a synthetic progestogen used to treat BC. In a study with TMX, an oral dose of 20 mg/day of megestrol acetate decreased the frequency of hot flashes by 85%. Weight gain is the main side effect, but glucocorticoid activity and the risk of adrenal insufficiency are also cause for concern [10].

In a trial comparing a single dose of 400 mg of intramuscular medroxyprogesterone acetate (MPA) to venlafaxine, the reduction of hot flashes was higher with venlafaxine than with MPA (80 vs. 55%). Venlafaxine is also associated with more side effects, such as nausea, loss of appetite, dizziness, constipation, dry mouth, and drowsiness [11].

2.3. Tibolone

Tibolone is a drug with complex, tissue-specific action that exhibits a combination of estrogenic, progestogenic and slight androgenic activity. Due to generally positive results regarding the breast [12], the LIBERATE (*Livial Intervention following Breast Cancer; Efficacy, Recurrence, and Tolerability Endpoints*) study was designed to compare the effectiveness and safety of tibolone against the placebo in the treatment of the vasomotor symptoms of 3148 women who had overcome the disease. After an average follow-up of 3 years, 237 of the 1156 women (15%) using tibolone experienced a recurrence of breast cancer, in comparison with 138 of the 1213 (11.4%) in the placebo group (HR 1.40, 95% CI 1.1–1.79), for which reason the study was halted 6 months before the planned date [13].

Consequently, although tibolone alleviates vasomotor symptoms and improves BMD, the use of this medication is not recommended in women with a history of breast cancer.

2.4. Isoflavones

Isoflavone intake poses a special dilemma for women with BC. First, by acting on ERβ (their affinity for ERα is very low), isoflavones could stimulate the growth of BC. However, it has been suggested that isoflavones can act as selective oestrogen receptor modulators (SERMs), blocking the effects of other more potent estrogens on breast cells.

Meta-analyses that examine isoflavones' effectiveness on vasomotor symptoms have been performed mostly in healthy populations. In patients with BC, isoflavones have not demonstrated any efficacy, although studies examining isoflavones in BC patients are scarce and short-term and include variable numbers of women being treated with TMX.

No BC recurrences have been observed for soy intake, and soy isoflavones might possibly have a synergistic effect with TMX. A meta-analysis of over 1200 patients has shown a reduced risk of recurrence in women who ate more soy isoflavones (RR = 0.84; 95% CI, 0.70–0.99), although in the stratified analysis, statistical significance was only evident for postmenopausal patients (RR = 0.78; 95% CI, 0.68–0.97) [14].

In any case, the available evidence is insufficient, and further prospective studies are required to recommend their use for the relief of vasomotor symptoms in women with a history of BC.

2.5. Black cohosh

Black cohosh does not bind to ERs, but it relieves hot flashes through the release of serotonin and dopamine. Purified products containing black cohosh without estrogenic pollutants do not cause an increase in breast density or endometrial stimulation.

In laboratory studies, black cohosh decreases local oestrogen synthesis and increases the apoptosis of breast tissue. However, RCTs are needed to confirm these experimental data. Some studies even suggest that black cohosh exerts a therapeutic effect by extending disease-free time. Moreover, the alleged cohosh black hepatotoxicity was not confirmed in a critical review published in 2010 [15].

Studies in patients with BC have yielded inconsistent results, most likely because of the methodological variability in the dosages and extracts analysed.

The interaction of black cohosh with antineoplastic treatments is also relevant. *In vitro* data show positive interactions with doxorubicin and docetaxel, neutral interactions with 4-hydroxycyclophosphamide or with radiotherapy, and negative interactions with cisplatinum [16].

Therefore, given black cohosh's lack of estrogenic action, it could be used safely in patients with BC regardless of whether they are also being treated TMX.

3. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs)

In addition to SSRIs and SNRIs' primary antidepressant effects, which are useful in many patients with BC, their capacity to relieve vasomotor symptoms is also relevant. These vasomotor effects are even faster and require a smaller dose than that required for the antidepressant action. These drugs' efficacy has been studied in RCTs, and they are a good alternative for women who cannot undergo HT [17–21]:

In two RCTs, paroxetine (10–25 mg/day) showed a 40–65% reduction of symptoms.

Fluoxetine (20 mg/day) has shown different results. One paper's findings that fluoxetine was not proven to be effective may have resulted because baseline data were measured on the first day of treatment, which underestimates the medication's effect because all SSRIs quickly relieve hot flashes starting the first day of administration.

Some studies have shown that low doses of citalopram (10–20 mg/day) decrease hot flashes compared to placebo. The drug is well tolerated, and 20 mg seems to be the optimal dose at which sleep, mood, and quality of life also improve.

Escitalopram (10–20 mg/day) is also effective for the relief of hot flashes. In an 8-week trial, its results were slightly better than those of a placebo (47 vs. 33%).

Sertraline has not proven to be effective for hot flashes.

Venlafaxine reduced hot flashes in women with BC.

Desvenlafaxine, a new SNRI approved for the treatment of depression, also appears to be effective for hot flashes. In a study of 707 symptomatic women, both 100 mg of desvenlafaxine and a placebo reduced the number of hot flashes per day; the mean difference between desvenlafaxine and placebo was approximately 1.5 hot flashes per day.

A meta-analysis showed that after 4 weeks, hot flashes were reduced by 9–18% for sertraline, 13% for fluoxetine, 13–41% for paroxetine, and 33% for venlafaxine compared with placebo [22].

SSRIs–SNRIs may be accompanied by side effects, such as decreased libido, weight gain, dry mouth, anorexia, nausea and constipation, dizziness, insomnia, and somnolence, which must be taken into account in patients with BC in whom these symptoms are also common.

3.1. Clonidine

Clonidine is an alpha-adrenergic agent that has demonstrated efficacy in relieving vasomotor symptoms in women with BC, but its use is not recommended because of frequent adverse effects (drowsiness, dizziness, and dry mouth).

3.2. Gabapentin

Gabapentin's mechanism of action is still unknown. It binds to an unknown receptor instead of simulating the physiological effects of the neurotransmitter gamma-aminobutyric acid (GABA), for which it was designed. It is approved for the treatment of seizure disorders and post-herpetic neuralgia, but it appears to be effective in reducing hot flashes outside its indication.

Three RCTs have shown that 300 mg of gabapentin every 8 h reduce hot flashes by 50% after a month of use. Gabapentin's effect is greater at higher doses (2700 mg/day). Gabapentin has an added hypnotic-sedative effect, and a single dose of 300–600 mg at night was useful for the relief of night sweats and sleep disturbances and minimising the side effects reported during the day. In a multicentre cross-sectional study with venlafaxine and gabapentin, both treatments reduced hot flashes by 66%, although patients preferred venlafaxine to gabapentin because of the side effects reported with the latter, which included bloating, weight gain, and sedation [23].

3.3. Others

Other medications, such as Vitamin E, veralipride, and methyldopa, are currently not being prescribed, either because of side effects or low efficacy.

4. Use of drug therapies in patients treated with TMX or aromatase inhibitors (AIs)

The efficacy of HT is limited in patients receiving TMX, possibly because of competition with ERs, a phenomenon that is not observed with progestogens.
The use of isoflavones may exert a competitive action on ERs and decrease their effect. The few studies that have analysed this effect are inconsistent. The concomitant use of isoflavones and AIs has only been tested in one human study, which found an inverse relationship between dietary intake and BC recurrence, suggesting a synergistic action between them [24].
Regardless of the fact that black cohosh is not bound to ERs, it does not interact with TMX or with AIs.
Paroxetine is a potent inhibitor of the CYP2D6 enzyme, which metabolises TMX to endoxifen, its active metabolite; therefore, paroxetine is not recommended for patients being treated with TMX. This precaution is especially important for women with certain genetic polymorphisms of the gene that expresses CYP2D6. Overall, SSRIs should be used with caution in women receiving TMX because of these inhibitory actions, though not all SSRIs have an equally inhibitory capacity: paroxetine and fluoxetine are strong inhibitors, sertraline and duloxetine are moderate inhibitors, and citalopram and escitalopram are weak inhibitors. SSRIs' impact on BC recurrence is unknown [25].
Venlafaxine is prominent among SNRIs. It has proved to be moderately effective and interferes only minimally with CYP2D6, and thus, its use is compatible with TMX. The same is true for desvenlafaxine, but its use is not approved by the European Medicines Agency.
Gabapentin does not interfere with TMX.

4.1. Non-pharmacological therapies

Given the importance of vasomotor symptoms in many women with BC, and because there are no effective and safe pharmacological therapies, other non-pharmacological interventions have been explored.

4.2. Lifestyle changes

Lifestyle changes can be effective for the relief of vasomotor symptoms and can enhance the physical and mental health of patients with BC. Women with BC are advised to follow a healthy lifestyle with a balanced diet and an exercise programme and to avoid being overweight or smoke or consume alcohol in excessive amounts.

4.3. Alcohol consumption

Studies of alcohol consumption in patients with BC show little consistency. The LACE (Life after Cancer Epidemiology) study found that women who ingested more than 6 g of alcohol daily had more recurrences (HR 1, 35; 95% CI, 1.0–1.83) and higher BC mortality (HR 1.51; 95% CI, 1.0–2.29) compared with women who consumed less than 0.5 g per day [26]. However, alcohol increases body temperature, and thus, reduced consumption is recommended to avoid hot flashes.

In short, we recommend consuming fewer than five alcoholic drinks per week to reduce BC recurrence and mitigate the effect of hot flashes.

4.4. Exercise

Numerous studies recommend exercise to improve BC survival, improve fitness, decrease fatigue, and improve quality of life, cardiopulmonary function, and bone mass; however, its effect on vasomotor symptoms is less consistent. In the SWAN (Study of Women's Health across the Nation) study, reduced physical activity was associated with more hot flashes; however, this finding has not been confirmed in other RCTs and meta-analyses and may be related to the increased body temperature after exercise [27].

4.5. Diet

Numerous studies suggest that obesity worsens the prognosis of BC. Moreover, although obese women have higher levels of circulating estrone, they are also more likely to have hot flashes [28]. As a general dietary guideline, we recommend avoiding the intake of hot drinks, spicy food, and alcohol.

4.6. Others

Environmental temperature affects the frequency and severity of hot flashes. Apart from the use of air conditioning or ventilation, we recommend wearing cotton clothing, which is cooler and allows skin perspiration.
Quitting smoking helps to reduce the intensity and frequency of hot flashes because tobacco is hypoestrogenic.
In two pilot studies, hypnosis reduced the intensity and frequency of hot flashes (by 60% and 70%, respectively) after five self-hypnosis training sessions. Hypnosis offered the added benefits of improved sleep quality and relief of anxiety and depression [29,30].
A meta-analysis found a trend towards significance with acupuncture and suggested that longer or more intense acupuncture regimens could be more effective than shorter and less intense ones [31].
Controlled relaxation techniques have shown positive results in reducing hot flashes by reducing physiological activation and stress. Abdominal slow breathing, for example, may reduce hot flashes by 40%. In another study on the therapeutic use of yoga in patients with BC, a moderate relief from hot flashes, joint pain, fatigue, and insomnia was found.
The stellate ganglion blockade has been the subject of several studies. The procedure has demonstrated outstanding effects on hot flashes and sleep disorders, but its mechanism of action is unknown [32].

In Fig. 1 the therapeutic options for the treatment of hot flashes are displayed in order of priority

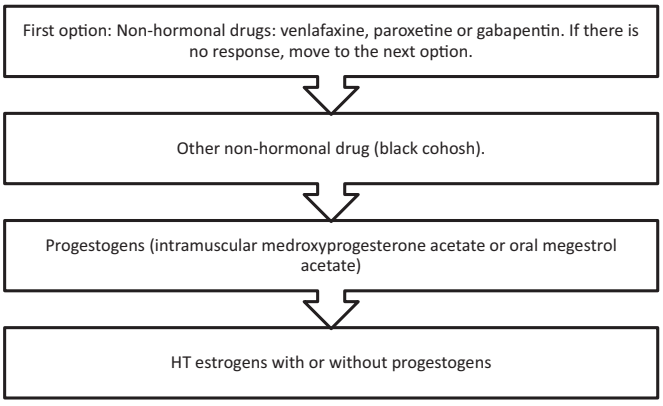

Fig. 1. Treatment options for hot flashes in women with BC.

5. Sexual and reproductive health

BC treatments often cause major physical changes (hair loss, breast or chest disfigurement, lymphedema, change in skin texture, vaginal irritation, hot flashes and weight gain or loss), which generate feelings of vulnerability and a loss of self-esteem and femininity.

All the physical and emotional changes inherent to BC have an influence on sexuality; however, doctors often do not fully address these changes because they are more focused on their patients' survival.

Sexual dysfunction is common among women with BC (it occurs in 25–66% of cases), especially among those who are receiving CT in the immediate postoperative period and those who experience vaginal dryness. In addition, the early onset of menopause caused by the action of CT increases vaginal dryness and the loss of libido, arousal and orgasm [33].

The symptoms ensuing from vaginal atrophy are common among women with BC, particularly those undergoing treatment with TMX or AIs [34]. These symptoms add to the stress and psychological consequences of the disease itself, which justifies the view that sexuality issues deserve to be approached from a multidisciplinary perspective.

5.1. Vaginal oestrogen therapy (VET)

VET, available as tablets or creams, is very effective for the treatment of genital atrophy. However, early systemic absorption when the tissue is still atrophic is a safety concern for patients with BC, even when blood levels only reach the minimum level observed for a normal ovarian cycle [35]. No recurrences have been observed with the use of VET; estriol instead of estradiol has been proposed for women with BC because estriol has a faster clearance [36].

The use of VET in women with BC will remain controversial until we have long-term safety studies, and the patient and her oncologist must agree about its use.

Additionally, we do not have data on VET's interaction with TMX or AIs. In premenopausal women, TMX shows anti-estrogenic effects and, in postmenopausal women, weak estrogenic effects on the vagina, although some patients also experience symptoms of atrophy.

In our opinion, it is reasonable to use low doses of VET to treat women who are taking TMX and showing symptoms of dryness. The small amount that is absorbed is likely to be blocked by TMX. However, we suggest not using it in women taking AIs, in which case the minimisation of systemic oestrogen levels is a goal.

5.2. Testosterone

In a group of 300 pre- and post-menopausal women with symptoms of relative androgen deficiency, continuous testosterone alone, delivered by subcutaneous implant, was effective for the relief of hormone deficiency symptoms [37]. However, there are limited data on the use of topical testosterone in women with BC, but no oestrogen increase in the peripheral blood has been observed in women taking AIs [38].

5.3. Non-hormonal options

Non-hormonal vaginal lubricants and moisturiser creams are the treatments of choice for women with BC, as they improve dryness and vulvovaginal blood flow. In an RCT, a lactic acid-spiked gel reduced vaginal irritation, dryness, and dyspareunia, although further studies are needed to validate these results [39].

In another RCT with placebo, pilocarpine, a cholinergic agonist used to treat Sjögren's syndrome, did not improve the symptoms of vaginal dryness.

It must be remembered that sexual activity may be an option for these women, and it has been found that women who engage in normal sexual activity (intercourse or masturbation) have less vaginal dryness.

5.4. Fertility and pregnancy after BC

Young women who overcome BC may have fertility problems resulting from CT's toxic effect on follicular endowment, delayed attempts to conceive, or the effects of anti-estrogenic treatments [40].

There is little data on the safety of pregnancy in these women, although most studies have not found an increase in the risk of recurrence or death. There are even studies that associate pregnancy with lower rates of recurrence, although selection biases are suspected, such as the fact that the women in these studies had BCs with a better prognosis [41].

Although data do not clearly show that pregnancy is dangerous, we recommend waiting 2 years after completing adjuvant therapy before attempting to become pregnant to avoid pregnancy at the time of greatest recurrence risk. However, it has not been shown that having suffered BC or having received any treatment for it carries an increased risk of malformations to the offspring.

5.5. Contraception

Pregnancy is not recommended while on CT or until 2 months after stopping methotrexate (MTX). Although premenopausal women treated with CT have a higher risk of premature ovarian failure, a birth control method is still needed until menopause is confirmed.

The safety and efficacy of hormonal contraceptives (HCs) have not been well studied in women with BC, as these patients have been traditionally excluded from efficacy studies. In the absence of prospective data, we adopt the World Health Organisation (WHO) eligibility criteria, which suggest that women with a history of BC avoid HCs. Instead, the use of non-hormonal methods (condoms, diaphragms or intrauterine devices [copper IUDs]) is advised. For women with BC (BRCA) gene mutations, bilateral oophorectomy provides permanent contraception and reduces the risk of ovarian cancer. Of the hormonal contraceptives, only the levonorgestrel-releasing intrauterine device (LNG-IUD) has been evaluated in women with a history of BC, given its low absorption of progestogen. The LNG-IUD can be a good form of birth control while protecting the endometrium from the effects of TMX [42,43].

Contraceptive decision-making algorithm for premenopausal women with BC is shown in Fig. 2.

6. List of recommendations

The *Spanish Menopause Society* considers it appropriate to develop its own recommendations based on the GRADE (*Grading of Recommendations Assessment, Development and Evaluation)* system to elaborate clinical practice guidelines and to classify the quality of the evidence and the strength of the recommendations [44].

A summary of the Gynaecologic sequelae associated with BC and its treatment is shown in Table 1.

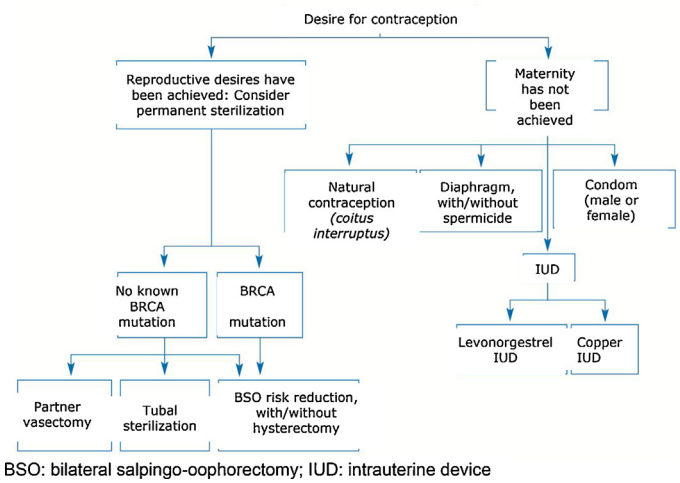

Fig. 2. Contraceptive decision-making algorithm for premenopausal women with BC.

6.1. Recommendations

6.1.1. Vasomotor symptoms

HT is the most effective method for the relief of vasomotor symptoms, but its use is not recommended in women with BC because it increases the risk of recurrence (Grade 2B).
Tibolone is not recommended for the same reason (Grade 2B).
Alternative therapies with gabapentin, SSRIs, and clonidine have proven to be effective for treating hot flashes (Grade 2B).
Because hot flashes gradually disappear without treatment in most postmenopausal women, the dose of any drug can be gradually reduced after one to 2 years of continued prescription.
SSRIs should be used with caution in women with BC receiving adjuvant treatment with TMX as some are potent inhibitors of CYP2D6 that reduce the availability of its active metabolite, endoxifen.
Black cohosh can be considered an alternative treatment to SSRIs (Grade 2C).

Table 1
Gynaecologic sequelae associated with BC and its treatment.

Diagnosis	Treatment
Abnormal uterine bleeding caused by TMX	Endometrial sampling LNG-IUD[a] Hysterectomy[b]
Vaginal atrophy	Vaginal lubricants Non-hormonal lubricants Vaginal estradiol Vaginal estriol
Fertility preservation	Gonadotropin-releasing hormone agonists Cryopreservation of oocytes Cryopreservation of embryos
Hot flashes	Observation Avoid triggers Loose clothes, cool environment Lifestyle modification (exercise, healthy diet) Relaxation techniques Isoflavones, black cohosh SSRI–SNRI Gabapentin
Decreased libido	Moisturisers and vaginal lubricants Counselling with sexologist

[a] The IUD should be removed after menopause.
[b] Consisder only if bleeding affects the patient significantly.

Diet and exercise can promote wellness and improve survival. We recommend that all women with BC maintain a healthy lifestyle that includes eating a balanced diet, following an active exercise programme, minimising the consumption of alcohol, and abstaining from smoking (Grade 1B).

6.1.2. Vaginal atrophy

The first-line treatment of vaginal atrophy symptoms in women with BC includes non-hormonal options. We recommend the regular use of vaginal moisturisers and the use of lubricants during intercourse (Grade 2B).
VET in low doses is recommended for women being treated exclusively for vaginal atrophy and for whom non-hormonal treatments are inadequate (Grade 1B).
The use of VET in low doses is reasonable in women with a low risk of recurrence and those taking TMX.
We do not recommend VET for women being treated with AIs (Grade 2C).
The use of vaginal testosterone in women with BC is a topic of current research.

6.1.3. Contraception

CT and anti-oestrogen therapy are teratogenic. Premenopausal women should use safe contraception measures during treatment.
Although data are limited, studies do not indicate an increased risk of recurrence for pregnant women with a history of BC. Children born to women who have been treated for BC do not have an increased risk of malformations.
According to the WHO eligibility criteria, HCs are not recommended for women with a history of BC (Grade 2B).
The contraception methods of choice for women with BC are barrier methods or the copper IUD.
The use of progestogen-only methods may be considered for women with a history of BC if the benefits outweigh the risk of recurrence (Grade 2B).

Contributors

Rafael Sánchez-Borrego and Nicolás Mendoza: conception and design of the idea, data interpretation and preparation of manuscript.

All authors participated in the statement and approved the final version of the manuscript.

Competing interest

None.

Provenance and peer review

Not commissioned peer reviewed Spanish Menopause Society Position Statement.

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