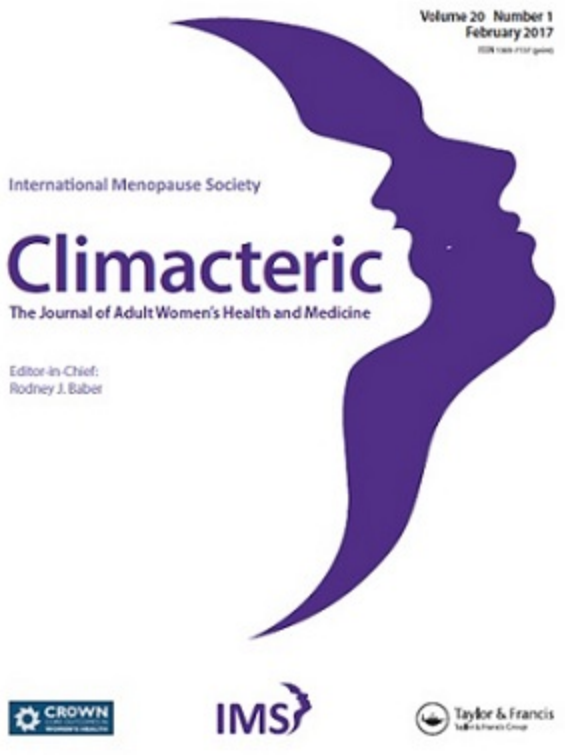

Genitourinary syndrome of menopause in breast cancer survivors:main challenges and promising strate

Journal:	*Climacteric*
Manuscript ID	Draft
Manuscript Type:	Review
Keywords:	Genitourinary syndrome of menopause, atrophic vaginitis, vulvovaginal atrophy, breast cancer, sexual dysfunction

Treating genitourinary syndrome of menopause in breast cancer survivors: main challenges and promising strategies.

Camil Castelo-Branco*, Eduard Mension *, Ines Torras, Isaac Cebrecos, Sònia Anglès-Acedo.

Clinic Institute of Gynecology, Obstetrics and Neonatology, Faculty of Medicine-University of Barcelona, Hospital Clinic-Institut d´Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS); Barcelona, Spain

Running title: Challenges and promising strategies in GSM for BCS.

Correspondence:

Camil Castelo-Branco (orcid.org/0000-0002-9860-8318)

Clinic Institute of Gynecology, Obstetrics and Neonatology,

Hospital Clinic, Villarroel 170, 08036 Barcelona, Spain.

Tel: +34 93 227 54 36. Fax: +39 93 227 93 25.

Mail: castelobranco@ub.edu

* Both authors contributed equally to the work

ABSTRACT

Many breast cancer survivors (BCS) suffer the consequences of antineoplastic treatments that induce a hypoestrogenic state, leading to chronic climacteric symptoms as the genitourinary syndrome of menopause (GSM), arousing significant alteration in their quality of life (QoL).

Non-hormonal therapies (NHT) are first line treatments, safe but with mild efficacy. When facing a moderate-severe GSM, the options to BCS are limited, finding: local estrogen therapy (ET), considered the "gold standard" but with concerns about security; vaginal androgens and prasterone, that seems to trigger an activation of estrogen and androgens receptors of the vaginal epithelium layers, without activating estrogen receptors on other tissues, being potentially safe but still without strong evidence in favor for BCS; vaginal lasers, which appear to improve vascularization of vaginal mucosa by stimulating the remodeling of the underlying connective tissue, but with contradictory results of its efficacy in recent randomized clinical trials; and ospemifene, an oral selective estrogen receptor modulators (SERM) presenting mild vaginal estrogenic potency and anti-estrogenic effect at the endometrial and breast level, but still not recommended for its use in BCS in recent North American Menopause Society (NAMS) guidelines. There is a need to further studies evaluating objectively efficacy and safety of these

promising therapeutic options. On the other hand, sexuality must be seen as a multifactorial issue, where the GSM is only a part of the problem, evidence shows that sexual counselling improves the QoL of BCS.

Finally, there is a need to limit the underdiagnosis and undertreatment of GSM in BCS, the primary goal of BCS treating physicians regarding this issue, have to be the provision of information of what to expect regarding genital and sexual symptoms to BCS.

KEYWORDS

Genitourinary syndrome of menopause; atrophic vaginitis; vulvovaginal atrophy; breast cancer; sexual dysfunction.

1. INTRODUCTION

Overall survival of women who suffer breast cancer (BC) is increasing over the last decades [1], and many of breast cancer survivors (BCS) will receive antineoplastic treatments that may affect their ovarian function or anti-estrogenic treatments [2]. These drugs induce a hypoestrogenic state that usually lead to chronic climacteric symptoms and arousing significant alteration in their quality of life (QoL) that may drive to discontinuation on the adjuvant therapies [3-6].

One of the main complaints of hypoestrogenism is the vulvovaginal atrophy (VVA), which is included in the new concept of genitourinary syndrome of menopause (GSM) [7]. This syndrome, that comprises from genital symptoms as dryness, burning, and irritation, to sexual and urinary symptoms, have a great impact on the quality of life (QOL). It affects up to 50% of postmenopausal women [8], and even more frequently in young patients who receive anti-estrogenic or antineoplastic drugs [9]. Often, these symptoms are under-diagnosed and under-treated due to underreport from the patients and the limited awareness from professionals [10]. And more importantly, if this appeared GSM receive not treatment, worsens over time [11].

Since in many cases BCS suffer from hormonal tumors, they have limited therapeutic strategies to treat GSM. Non-hormonal therapies (NHT) are first line treatments, safe but with mild efficacy and usually with a short-term improvement [12]. When facing a moderate-severe GSM, local estrogen therapy (ET) is considered the “gold standard” therapy for general population, but in respect to BCS, there are concerns about security, particularly due to the possible increased recurrence risk (RR) if systemic absorption occurs [13].

In the recent years new therapeutic options are appearing on the board, such as vaginal laser (VL), ospemifene and androgen local therapy (AT), that could be useful alternatives for those patients where ET are not recommended. Up to date, there is no consensus on how to treat moderate-severe GSM in BCS [14].

The aim of this review is to summarize the current evidence on GSM therapeutic options for BCS and its main future challenges.

2. CURRENT STRATEGIES

At this moment, most of BCS suffering from GSM are not yet diagnosed and therefore are not receiving any treatment. Of those which are treated, most are receiving first line therapies based on NHT [15].

3.1 Non-Hormonal Therapies

The first line treatments for mild-moderate GSM, according to the international guidelines, are NHT. Therefore, these are also the first line treatments in BCS [16]. Within NHT, generally comprise moisturizers mainly based on water or vegetable oil. However, these compounds do not reverse atrophy nor improve vaginal epithelium characteristics; thence, the observed improvement is temporary and short-term. In a specific BCS systematic review the 85% of the trials found on this systematic review described short term efficacy; with a 30 days follow-up or less, and present low risk of potential side effects regarding safety [14].

2.2 Vaginal oestrogen

Since hypoestrogenism is the cause of GSM, the most reasonable treatment would be one based on estrogen, which have proved to be the most effective, since directly eliminate the cause of the atrophy. [17].

However, there are concerns in the literature regarding the possible systemic absorption of vaginal estrogen in BCS. Systemic estrogen administration may increase the risk of breast cancer recurrence [18] and is generally not advised for survivors of breast cancer, although hormone therapy use may be considered in women with severe vasomotor symptoms unresponsive to

nonhormone options, with shared decision-making in conjunction with their oncologists [16-19].

Vaginal estrogen absorption is variable, this absorption appears to decrease once there is improvement in vaginal mucosae [20], but still the use of low dose vaginal estrogen treatment is accepted if there is no improvement using non-hormonal treatments in BCS suffering GSM [16-19]. Different methods of vaginal estrogen administration appear to be equivalent, being estriol preparations the most usually used, which is a weak action estrogen (Table 1).

Therefore, there is some reluctance to use local estrogen therapy in BCS among oncologists, showing in a specialist study that up to 70% of oncologists dealing with BCS do not prescript hormone therapies. Mainly due to fear of interferences with adjuvant treatments that may result in an increased BC recurrence risk [15].

In respect of estrogen use in BCS, recent systematic reviews show clear controversy on this topic, finding trials evaluating short follow-up cohorts of BCS not showing increased recurrence after local estrogen use [21], and conversely, recent prospective designed studies suggesting that the use of vaginal estrogen therapy may increase levels of estrogen serum levels [22].

From our point of view, further studies are needed, controlling confounding factors as variability of vaginal estrogen absorption, and given the controversy, it is recommended to explain risks and benefits, individualizing each case with oncologists before using local estrogen therapies on BCS.

3. PROMISING STRATEGIES

3.1 Vaginal androgens and prasterone

Other options as intravaginal androgens or pre-androgens are getting attention as a potential treatment for GSM in BCS, since androgen receptors have been identified in the vaginal mucosa.

Local androgenic administration at vaginal level of testosterone cream or local pre-androgenic prasterone, seems to trigger an activation of estrogen and androgens receptors of the vaginal epithelium layers, without activating estrogen receptors on other tissues due to the lack of aromatase at this level [23, 24]. A recent pilot study evaluating Dehydrixyepiandrosterone (DHEA) or prasterone was conducted in BCS receiving aromatase inhibitors, observing that serum estradiol was not increased after 6 months of 6.5 mg prasterone every 48h and presenting GSM improvement [25]. But further studies with bigger sample size are needed to document the long-term safety of this treatment.

Table 1.

3.2 Vaginal Lasers

The vaginal laser is nowadays a hot topic in GSM treatment, that appears to improve vascularization of vaginal mucosa by stimulating the remodeling of the underlying connective tissue, which enlarges the vaginal epithelium and allows it to accumulate glycogen. Due to the accumulation of glycogen the vaginal flora is restored, the vaginal pH is reduced, and symptoms of GSM improve [26].

Up to date, we can find three different non-surgical energy-based: fractional microablative CO2 laser, erbium-YAG laser and temperature-controlled radiofrequency. Initial literature strongly suggested that the vaginal laser therapy with either the erbium- laser or the CO_2 laser was an effective therapeutic option to treat GSM symptoms, but recent randomized clinical trials [RCT] evaluating objective outcomes have brought some caution to conclude its efficacy and safety in BCS, since there is a lack of data about BC recurrence and serum estradiol levels were not tested [27, 28].

In 2018 FDA published an alert highlighting that the efficacy and safety of treatments had not been established. Warning the risk of serious adverse events to the patient when using laser and

thermal energy devices used for a range of vaginal symptoms including those related to menopause [29].

Despite this alert, a huge increase of published papers regarding the use of vaginal laser for GSM shows that vaginal laser is been often used as a therapeutic option in the clinical practice, even without strong evidence recommending its use. There is a need for clinical assays evaluating the efficacy and security for this therapy in BCS [30].

3.3 Ospemifene

Ospemifene is an oral selective estrogen receptor modulators (SERM), presenting estrogenic and antiestrogenic effect depending on the tissue where its action takes place. It presents mild vaginal estrogenic potency with capacity to improve the GSM symptoms in a similar way to local estrogenic therapy, and also improves bone mineral density. On the other hand, seems to have an anti-estrogenic effect at the endometrial and breast level, for this reason, appears to be a promising therapy for BCS [31-33].

In 2013, FDA approved the use of ospemifene for dyspareunia and vaginal dryness, but it is not recommended for its use in BCS in recent North American Menopause Society (NAMS) guidelines [34].

3.4 Sexual counseling

Taking into consideration the relevance of psychosocial aspects in the sexual health of patients, some studies have evaluated the use of educational strategies and counselling as a treatment of sexual dysfunction (SD) in BCS [35]. Evidence shows that the sexual health of these women improves with educational interventions specifically focused on sexual aspects, as well as with couple therapy enhancing the communication of SD aspects and cancer. Unfortunately, specialized sexual assessment is not usually performed according to a recent review evaluating sexual disfunction in BCS [36].

4. MAIN CHALLENGES

4.1 Underdiagnose and undertreatment

The main challenge of GSM in BCS is still the underdiagnose and the undertreatment, that prevent the access of many patients to therapies that may significantly improve their daily quality of life. The primary goal of BCS treating physicians regarding this issue, have to be the provision of information of what to expect regarding genial and sexual symptoms in the process of BC treatments, and the early diagnose and treatment of GSM.

4.2 Efficacy and Safety assessment of therapeutic options

Nonetheless, given the current focus on GSM in BCS, there is a need of strong evidence regarding efficacy and safety of the therapeutic options that are appearing on the board, to provide information and best quality options to our patients.

In 2003, the FDA issued a guide outlining possible endpoints for studies assessing topical estrogen to treat GSM: change in severity of symptoms, change in vaginal pH, and change in vaginal maturation index (VMI). But since then, the majority of the studies are still using subjective outcomes such as Vaginal Health Index (VHI), visual analogue scale (VAS) of GSM symptoms and the female sexual function index (FSFI). Instead, not many of the considered objective outcomes such as the VMI are used in the recent literature assessing GSM [37].

There is a need of objective outcomes to test efficacy and compare the new therapeutic options. Some authors have studied vaginal epithelial thickness, composition of the lamina propria, and vaginal compliance as future alternatives [38].

4.3 Sexological approach

The prevalence of sexual dysfunction in BCS oscillate between 40-80%, and vulvovaginal health, directly linked to sexual health, is a key factor for female pleasure, but the treatment of this condition is not always related to an improvement of the SD, since sexuality must be seen as a multifactorial issue, where the GSM is only a part of the problem.

The main symptoms of SD reported by BCS include insufficient lubrication and penetration pain, but also difficulties in arousal or excitation, decreased sexual desire and body image impairment. A recent observational study showed greater SD rate in BCS who receive aromatase inhibitors, presenting greater impairment of sexual desire, arousal, lubrication, orgasm, satisfaction and dyspareunia compared to healthy population, as well as lower scores in FSFI [39].

Evidence shows that BC has the highest rates of lost disability-adjusted life years (DALYs) among all types of cancer; being SD one of the main reasons of this problem. Breast cancer survivors regardless of age, BC stage and ongoing treatment, are concerned about the possible impact of BC treatments on sexual function and are interested in maintaining a good sexual life [40, 41].

Therefore, a combination of a physical treatments and sexual counseling approach, through validated questionnaires and sexual interviews would provide a deeper and more accurate strategy for treating GSM in BCS.

5. CONCLUSION

GSM is the leading cause of sexual dysfunction in BCS and severely limits the quality of life of these patients. The first line treatment in BCS presenting mild-moderate GSM is always using non-hormonal therapies, which appear to be safe but present a limited efficacy and short-term effect. In cases of GSM in BCS refractory to non-hormonal treatment, the next step should include a shared decision-making process centered on patient's expectations and needs, as well as with the oncology team evaluating risks and benefits. Alternatives such as local estrogen therapy, local androgen therapy, vaginal laser or ospemifene could be considered, always with

the patient's awareness of whether there are discrepancies in the data found on the efficacy and safety of all of them. In those BCS with GSM mainly affected by sexual complaints a biopsychosocial sexual approach including sexual counselling should also be offered. High quality clinical studies assessing its efficacy and safety in terms of serum estradiol raise evaluation or relapse evaluation are still lacking in BCS.

6. REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021 May;71(3):209–249.

2. Franzoi MA, Agostinetto E, Perachino M, et al. Evidence-based approaches for the management of side-effects of adjuvant endocrine therapy in patients with breast cancer. Lancet Oncol. 2021 Jul;22(7):e303-e313.

3. Lubián López DM, Butrón Hinojo CA, Sánchez-Prieto M, et al. Sexual Dysfunction in Postmenopausal Women with Breast Cancer on Adjuvant Aromatase Inhibitor Therapy. Breast Care (Basel). 2021 Aug;16(4):376-382.

4. Santen RJ, Stuenkel CA, Davis SR, et al. Managing Menopausal Symptoms and Associated Clinical Issues in Breast Cancer Survivors. J Clin Endocrinol Metab. 2017 Oct 1;102(10):3647-3661

5. Francis PA, Regan MM, Fleming GF. Adjuvant ovarian suppression in premenopausal breast cancer. N Engl J Med. 2015 Apr 23;372(17):1673.

6. Dragvoll I, Bofin AM, Søiland H, et al. Predictors of adherence and the role of primary non-adherence in antihormonal treatment of breast cancer. BMC Cancer. 2022 Dec 2;22(1):1247.

7. Portman DJ, Gass ML; Vulvovaginal Atrophy Terminology Consensus Conference Panel. Genitourinary syndrome of menopause: New terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and The North American Menopause Society. Climacteric 2014;17:557–563.

8. Nappi RE, Seracchioli R, Salvatore S, et al; investigators of the EVES Study. Impact of vulvovaginal atrophy of menopause: prevalence and symptoms in Italian women according to the EVES study. Gynecol Endocrinol. 2019 May;35(5):453-459.

9. Carmen A, Anne O, Monika S, et al. Does the toxicity of endocrine therapy persist into long-term survivorship?: Patient-reported outcome results from a follow-up study beyond a 10-year-survival. Breast Cancer Res Treat. 2022 Nov 23.

10. Moral E, Delgado JL, Carmona F, et al. Genitourinary syndrome of menopause. Prevalence and quality of life in Spanish postmenopausal women. The GENISSE study. Climacteric. 2018 Apr;21(2):167-173.

11. Kingsberg SA, Wysocki S, Magnus L, et al. Vulvar and vaginal atrophy in postmenopausal women: findings from the REVIVE (REal Women's VIews of Treatment Options for Menopausal Vaginal ChangEs) survey. J Sex Med. 2013 Jul;10(7):1790-9.

12. Lee YK, Chung HH, Kim JW, et al., Vaginal pH-balanced gel for the control of atrophic vaginitis among breast cancer survivors: a randomized controlled trial, Obstet Gynecol. 117 (April 4) (2011) 922–927.

13. Wills S, Ravipati A, Venuturumilli P, et al. Effects of vaginal estrogens on serum estradiol levels in postmenopausal breast cancer survivors and women at risk of breast cancer taking an aromatase inhibitor or a selective estrogen receptor modulator, J Oncol Pract. 8 (May 3) (2012) 144–148.

14. Mension E, Alonso I, Castelo-Branco C. Genitourinary Syndrome of Menopause: Current Treatment Options in Breast Cancer Survivors - Systematic Review. Maturitas. 2021 Jan;143:47-58.

15. Biglia N, Bounous VE, D'Alonzo M, et al., Vaginal Atrophy in Breast Cancer Survivors: Attitude and Approaches Among Oncologists, Clin Breast Cancer. 17 (December 8) (2017) 611–617.

16. The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. The 2022 hormone therapy position statement of The North American Menopause Society. Menopause. 2022 Jul 1;29(7):767-794.

17. Naumova I, Castelo-Branco C, Current treatment options for postmenopausal vaginal atrophy, Int J Womens Health. 10 (2018) 387–395.

18. Holmberg L, Anderson H, HABITS steering and data monitoring committees. HABITS (hormonal replacement therapy after breast cancer–is it safe?), a randomised comparison: trial stopped, Lancet. 363 (February 9407) (2004) 453–455.

19. Management of menopausal symptoms in women with a history of breast cancer. Cancer Australia. Publication Date December 2016. Accessed January 12th, 2023.

20. Mariani L, Gadducci A, Vizza E, et al., Vaginal atrophy in breast cancer survivors: role of vaginal estrogen therapy, GynecolEndocrinol. 29 (January 1) (2013) 25–29

21. Le Ray I, Dell'Aniello S, Bonnetain F, et al., Local estrogen therapy and risk of breast cancer recurrence among hormone-treated patients: a nested case-control study, Breast Cancer Res Treat. 135 (September 2) (2012) 603–609.

22. Donders G, Neven P, Moegele M, et al., Ultra-low-dose estriol and Lactobacillus acidophilus vaginal tablets (Gynoflor(®)) for vaginal atrophy in postmenopausal breast cancer patients on

aromatase inhibitors: pharmacokinetic, safety, and efficacy phase I clinical study, Breast Cancer Res Treat. 145 (June 2) (2014) 371–379.

23. Davis SR, Robinson PJ, Jane F, et al., Intravaginal Testosterone Improves Sexual Satisfaction and Vaginal Symptoms Associated With Aromatase Inhibitors, J Clin Endocrinol Metab. 103 (November 11) (2018) 4146–4154.

24. Wang J, Wang L. The therapeutic effect of dehydroepiandrosterone (DHEA) on vulvovaginal atrophy. Pharmacol Res. 2021;166: 105509.

25. Mension E, Alonso I, Cebrecos I, et al. Safety of prasterone in breast cancer survivors treated with aromatase inhibitors: the VIBRA pilot study. Climacteric. 2022 Oct;25(5):476-482.

26. Zerbinati N, Serati M, Origoni M, et al. Microscopic and ultrastructural modifications of postmenopausal atrophic vaginal mucosa after fractional carbon dioxide laser treatment, Lasers Med. Sci. 30 (2015) 429–436.

27. Li FG, Maheux-Lacroix S, Deans R, et al. Effect of Fractional Carbon Dioxide Laser vs Sham Treatment on Symptom Severity in Women With Postmenopausal Vaginal Symptoms: A Randomized Clinical Trial. JAMA. 2021 Oct 12;326(14):1381-1389.

28. Cruff J, Khandwala S. A Double-Blind Randomized Sham-Controlled Trial to Evaluate the Efficacy of Fractional Carbon Dioxide Laser Therapy on Genitourinary Syndrome of Menopause. J Sex Med. 2021 Apr;18(4):761-769.

29. US Food and Drug Administration. FDA warns against use of energy-based devices to perform vaginal 'rejuvenation' or vaginal cosmetic procedures: FDA safety communication. Available at: https://www.fda.gov/medical-devices/safetycommunications/fda-warns-against-use-energy-based-devices-perform-vaginal-rejuvenation-or-vaginal-cosmetic

30. Mension E, Alonso I, Tortajada M, et al. Vaginal laser therapy for genitourinary syndrome of menopause - systematic review. Maturitas. 2022 Feb;156:37-59.

31. Goldstein SR, Bachmann GA, Koninckx PR, et al. Ospemifene 12-month safety and efficacy in postmenopausal women with vulvar and vaginal atrophy. Climacteric. 2014;17(2):173–182.

32. Nappi RE, Panay N, Bruyniks N, et al. The clinical relevance of the effect of ospemifene on symptoms of vulvar and vaginal atrophy. Climacteric. 2015 Apr;18(2):233-40.

33. Lilue M, Palacios S, Del Carmen Pingarrón Santofimia M. Experience with ospemifene in patients with vulvar and vaginal atrophy and a history of breast cancer: case studies. Drugs Context. 2020 Jul 1;9:2020-3-4.

34. The NAMS 2020 GSM Position Statement Editorial Panel. The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. Menopause. 2020 Sep;27(9):976-992.

35. Anglès-Acedo S, Ribera-Torres L, Mension E, et al. Sexual health in breast cancer survivors with genitourinary syndrome of menopause: it is only a dyspareunia issue?,The Journal of Sexual Medicine,Volume 19, Issue 11, Supplement 4,2022,Page S98,ISSN 1743-6095.

36. Castillo H, Mension E, Cebrecos I, et al. Sexual Function in Breast Cancer Patients: A Review of the Literature, Clin. Exp. Obstet. Gynecol. 2022, 49(6), 134.

37. Mension E, Alonso I, Tortajada M, et al. Genitourinary Syndrome of Menopause Assessment Tools. J Midlife Health. 2021 Apr-Jun;12(2):99-102.

38. Castelo-Branco C, Mension E. Are we assessing genitourinary syndrome of menopause properly? Climacteric. 2021 Dec;24(6):529-530.

39. Nimbi FM, Magno S, Agostini L, et al. Sexuality in breast cancer survivors: sexual experiences, emotions, and cognitions in a group of women under hormonal therapy. Breast Cancer. 2022;29:419-428.

40. Bartula I, Sherman KA. The Female Sexual Functioning Index (FSFI): evaluation of acceptability, reliability, and validity in women with breast cancer. Support Care Cancer. 2015;23:2633-2641.

41. Tounkel I, Nalubola S, Schulz A, et al. Sexual health screening for gynecologic and breast cancer survivors: a review and critical analysis of validated screening tools. Sex Med. 2022;10:100498.

42. Kendall A, Dowsett M, Folkerd E, et al. Caution: Vaginal estradiol appears to be contraindicated in postmenopausal women on adjuvant aromatase inhibitors. Ann Oncol. 2006 Apr;17(4):584-7.

43. Pfeiler G, Glatz C, Königsberg R, et al. Vaginal estriol to overcome side-effects of aromatase inhibitors in breast cancer patients. Climacteric. 2011 Jun;14(3):339-44.

44. Melisko ME, Goldman ME, Hwang J, et al. Vaginal Testosterone Cream vs Estradiol Vaginal Ring for Vaginal Dryness or Decreased Libido in Women Receiving Aromatase Inhibitors for Early-Stage Breast Cancer: A Randomized Clinical Trial. JAMA Oncol. 2017 Mar 1;3(3):313-319.

45. Witherby S, Johnson J, Demers L, et al. Topical testosterone for breast cancer patients with vaginal atrophy related to aromatase inhibitors: a phase I/II study. Oncologist. 2011;16(4):424-31.

7. ORCID

Castelo-Branco 0000-0002-9860-8318

Mension 0000-0002-1227-1137

Torres 0000-0001-5961-2843

Cebrecos 0000-0002-9333-3642

Anglès 0000-0002-1909-3759

Study / Year	n	Design	Follow up	Participants	Intervention	Outcomes	Hormonal adjuvant Therapy	Receptor status (ER+)	Results	Conclusion
Kendall et al. Annals of Oncology, 2005[42]	7	Prospective before-after analysis	12 weeks	Patients on adjuvant AI therapy for BC	Estradiol 25mg daily for 2 weeks	Measure estradiol	All women with AI. anastrazole. letrozole or exemestane	Not reported.	2-week analysis: 83% estradiol rise. 10 weeks: 66% E rose 83% improved clinical status	Anastrazole seems to better control estradiol elevation when treated with VET
Pfeiler et al, Climacteric, 2011[43]	6	Prospectivebefore-after analysis	4 weeks	Patients on adjuvant AI therapy for BC	0.5mg vaginal estriol daily for 2 weeks.	Estradiol, FSH and LH serum levels. Clinical improvement (VAS).	All women receiving anastrazole.	All women	No change in estradiol. Increased FHS and LH. Clinical improvement in 83%.	Increase in FHS and LH may indicate systemic estradiol effects.
Wills et al. Journal of Oncology practice, 2012[13]	24 BCS 24 Controls	Prospective clinical study	12 weeks	Patients on adjuvant AI therapy or SERM for BC	Vaginal Estradiol 25ng	E2 serum levels	All women with SERM or AI	Women with ER+ or high risk BC	E2 levels were significantly greater in VET group than in controls.	VET treatment increases E2 levels. Should be used with caution.
Donders et al. Breast Cancer Res Treat, 2014[22]	16	Open label bicentric phase I pharmacokinetic study.	12 weeks	Patients on adjuvant AI therapy for BC	0.03mg Estriol + Lactobacillus.	Estradiol (E2), Estrone (E1), estriol (E3) serumlevels. Clinical improvement (VAS).	All women with AI. letrozole or anastrazole.	All women	No change in E1 and E2. Small transient increase in E3. Clinical improvement in 100%.	E3 + Lactobacillus is safe in BC patients and improves symptoms.
Melisko et al. JAMA Oncology, 2016[44]	76	Randomised non-comparative study	12 weeks	Patients on adjuvant AI therapy for BC	Estradiol ring 7.5ng vs. Testosterone cream at 1% concentration: 1,5mg/week	E2 serum levels VHI	All women with AI	All women	Transient E2 increase in 11% Estradiol group and 12% TST group. Persistent E2 rise in 0% Estradiol group and 12% TST group. Sexual improvement in both groups.	Transient increase in E2 that finally reached normal levels. Meets the primary safety endpoint.
Whiterby et al. The Oncologist, 2011[45]	21	Phase I/II pilot study Before-After study	8 weeks	Patients on adjuvant AI therapy for BC	TST cream for 28 days 300/150ng	E2 and TST levels. Clinical improvement.	All women with AI.	Not reported.	E2 levels remained suppressed Symptom improvement.	They demonstrate clinical efficacy and tolerance.
Mension et al. Cimacteric, 2022[25]	10	Prospective clinical study	6 months	Patients on adjuvant AI therapy for BC	6.5 mg/d of DHEA. use one ovule every night, during the first month, and one ovule every two nights, for the entire 5 resting months.	E2 serum levels FSFI	All women with AI. anastrazole. letrozole or exemestane.	All women.	E2 remained under safety levels Symptom improvement. Sexual improvement	Prasterone meets the primary safety endpoint and demonstrate clinical efficacy and tolerance.

TABLE 1. Estrogen plasma levels after local therapy with sexual steroids.
ER: Oestrogenic Receptors, VET: Vaginal Oestrogenic Therapy, BC: Breast Cancer, AI: Aromatase inhibitors, E: Oestrogen, FSFI: Female Sexual Function Index, VVA: Vulvovaginal Atrophy, TST: Testosterone, VAS: Visual Analogue Scale.