SANTEC
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COMPENDIUM DEGLI STUDI SCIENTIFICI

Radiofrequenza in Ginecologia

per

GSM (Sindrome genito-urinaria della menopausa)

Giugno 2024

Bipolar radiofrequency in the treatment of dermatologic imperfections: clinicopathological and immunohistochemical aspects

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PMID: 17941360

Abstract

Background: Rapid progress in the technology for skin rejuvenation has allowed for shorter post-treatment times than ever before. An example of such technology is the radiofrequency (RF) device, which offers nonablative skin rejuvenation, particularly for skin tightening and wrinkle reduction.

Objective: Medical devices that emit RF energy produce a change in the electrical charges of the treated skin creating an electron movement, and the resistance of the tissue to the electron movement generates heat. This article examines the mechanism of action of a new bipolar RF device, which emits RF energy through a handpiece with a bipolar electrode configuration, and assesses the clinical histological and immunohistochemical results on a sample group of patients who underwent a cycle of sessions with this device.

Methods and materials: Thirty patients affected with periocular wrinkles, glabellar wrinkles, slackness of the cheeks with accentuation of the nasogenian furrow, striae distensae at the scapulohumeral joint, abdomen, and gluteal-trochanteric areas, or acne scars were included. These patients underwent a cycle of 6 to 8 sessions with 2-week intervals with the new bipolar RF device undergoing photographic monitoring before treatment and at the end of the cycle of sessions. In addition, 15 patients from the sample group were subjected to 2 biopsies, one at the start of treatment and the other 3 months after the last treatment.

Results: All the patients showed improvement in treated imperfections from the second session onward, and they expressed their satisfaction at the end of the treatment cycle. The most

notable clinical, histological, and immunohistochemical results were observed in the patients with abdominal striae distensae. In most cases, the temporary side effects observed consisted of rashes and ecchymosis. Two patients reported the formation of blisters on the treated area caused by excessively high RF settings.

Conclusion: The new bipolar RF device proved to be effective, noninvasive, and easy to use. The improvement in the treated areas is progressive and continues to be apparent several months after the last session. The duration of the results achieved still remains to be accurately determined.

BMJ Open

Laser and radiofrequency for treating genitourinary syndrome of menopause in breast cancer survivors: a systematic review and meta-analysis protocol

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To cite: Serquiz N, Sarmento ACA, Almeida NR, *et al*. Laser and radiofrequency for treating genitourinary syndrome of menopause in breast cancer survivors: a systematic review and meta-analysis protocol. *BMJ Open* 2023;**13**:e075841. doi:10.1136/bmjopen-2023-075841

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-075841).

Received 19 May 2023
Accepted 20 October 2023

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ABSTRACT

Introduction Breast cancer survivors (BCSs) experience more severe symptoms of genitourinary syndrome of menopause (GSM) than healthy postmenopausal women. As hormonal therapy with oestrogen should be avoided in BCSs, finding an effective and safe therapy to address vaginal symptoms and sexual dysfunction is urgently needed. Physical methods may be promising alternatives for the specificities of this group of women. This review aims to evaluate the efficacy and safety of physical methods (laser and radiofrequency) for treating GSM in BCSs.

Methods and analysis The PubMed, Embase, Web of Science, SciELO, LILACS, Scopus, Cochrane Central Register of Controlled Trials and ClinicalTrials.gov databases will be searched. A search strategy was developed to retrieve clinical trials that evaluate the efficacy and safety of any physical method (laser or radiofrequency) used for GSM in BCSs. No date or language restrictions will be imposed. Two authors will independently select studies by title, abstract and full text to meet the inclusion criteria. Data will be extracted, and the risk of bias will be evaluated using the Cochrane risk-of-bias tool (RoB 2). Review Manager 5.4.1 will be used for data synthesis. The Grading of Recommendations, Assessment, Development and Evaluation will be used to assess the strength of the evidence.

Ethics and dissemination This study reviews the published data; thus, obtaining ethical approval is unnecessary. The findings of this systematic review will be published in a peer-reviewed journal.

PROSPERO registration number CRD42023387680.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Hormonal therapy is contraindicated for breast cancer survivors.
⇒ Physical energy can be an option for urogenital atrophy.
⇒ We intend to evaluate the use of physical energy in breast cancer survivors.
⇒ We will strictly follow the Cochrane recommendations.
⇒ We recognise the risk of obtaining a limited number of studies with small sample sizes.

INTRODUCTION

Description of the condition

Women's life expectation is increasing, and most will experience symptoms of genitourinary syndrome of menopause (GSM).[1] One of the most distressing symptoms reported by women is vulvovaginal atrophy (VVA); up to 70% of breast cancer survivors (BCSs) experience at least one genitourinary symptom due to physiological changes in menopause or adverse effects of oncological treatments (chemotherapy, tamoxifen, aromatase inhibitors and ovarian suppression),[2 3] used to worsen the basal hypoestrogenic state. GSM is a common and underreported condition that results from decreased circulating oestrogen levels in the genital tissue.[4]

Hypoestrogenism leads to the thinning and drying of the vaginal epithelium, a decrease in the number of collagen and elastin fibres, lower vascularisation of the subepithelium, reduced elasticity of the vaginal walls and changes in vaginal pH and commensal flora. All of these modifications lead to functional and sexual changes, including vaginal dryness, dyspareunia, burning and irritation, vulvovaginal pruritus, dysuria and an increased frequency of genitourinary infections. Vaginal changes can lead to chronic symptoms that worsen over time and are unlikely to resolve without treatment.[5] They have been reported to be a major factor in the impairment of quality of life in patients with breast cancer.[6–8]

Topical oestrogen is the most effective treatment for GSM symptoms.[9] However, concerns about systemic absorption limit their use, and clinicians are often hesitant

to prescribe them for BCSs.[10] Non-hormonal therapies, such as lubricants and vaginal moisturisers, are the first-line therapies for BCSs. However, these therapies provide temporary relief, do not reverse urogenital ageing and do not improve vaginal epithelial characteristics.[11 12]

Safe and effective non-hormonal treatments are needed to improve the long-term health of women with breast cancer. Intravaginal energy-based methods (laser and radiofrequency) have recently been proposed as non-pharmacological therapeutical options for managing GSM.

Description of the intervention

New energy-based devices have been the most widely investigated: non-ablative erbium:YAG (Er:YAG laser), fractional microablative CO2 laser and radiofrequency. Its main action is based on thermal effects, resulting in morphological changes in the collagen fibres in the vaginal epithelial tissue.

The CO2 laser works by vaporising tissue columns through the interaction between a specific CO2 pulsed laser and the vaginal area,[13] and the Er:YAG laser has a smooth mode with sequential bursts of erbium pulses without damaging the mucosa.[14] The most popular type of radiofrequency is transcutaneous temperature-controlled radiofrequency, which uses a high-frequency alternating current, resulting in the denaturation of collagen, promoting the contraction of its fibres, activating fibroblasts and leading to neocollagenesis and subsequent remodelling of the tissue.[15 16]

How the intervention may work

They differ in their characteristics and mechanisms of action. However, the fundamental effect is assumed to be a vaginal remodelling pathway involving neocollagenesis and neoangiogenesis, stimulating tissue restructuring and reversing urogenital ageing.[17–19]

The current data suggest promising positive results in improving vaginal health, GSM symptoms (dryness and dyspareunia) and sexual function in postmenopausal women and BCSs, with equivalent efficacy and no significant adverse events.[20 21] However, few systematic reviews have evaluated all physical energy methods for GSM in BCSs, with insufficient evidence and no data on radiofrequency.[8 22 23]

Why it is important to conduct this review

The use of physical energy in clinical practice requires further discussion. Therefore, a systematic review that aims to evaluate and improve the decision-making of all available physical energy interventions for GSM in BCSs and define indications for the use of physical methods through evidence-based medicine will bring many benefits to BCSs where the use of traditional hormone replacement is contraindicated.

OBJECTIVES

This systematic review and meta-analysis aims to evaluate the efficacy and safety of physical methods (laser and radiofrequency) for treating GSM in BCSs.

METHODS AND ANALYSIS

Design and registration

This systematic review protocol followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Protocols.[24] The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO CRD42023387680).

Eligibility criteria

Inclusion criteria

Randomised and quasi-randomised clinical trials that investigate both the efficacy and safety of any intravaginal physical energy (laser and radiofrequency) in non-metastatic BCSs, irrespective of age, who are still sexually active or willing to resume sexual activity with one or more GSM symptoms, will be included.

Exclusion criteria

Studies involving women with recurrent or metastatic cancer, prior reconstructive pelvic surgery involving a mesh for prolapse and active genital infections (diagnosed by Gram staining and multiplex PCR) and studies that do not assess the outcomes will be excluded. Observational studies, case reports, review articles, reports and case series will also be excluded.

Patient, intervention, comparison, outcome and type of study strategy

- Population/participants: BCSs.
- Intervention: intravaginal physical energy (laser or radiofrequency).
- Comparator/control: no treatment, placebo, sham and/or other treatment.
- Outcomes: improvements in vaginal atrophy (dryness, dyspareunia, itching and burning), sexual dysfunction, urinary symptoms (incontinence, urgency and frequency) and vaginal health.
- Type of study: randomised or quasi-randomised clinical trials.

Types of outcome measures

Primary outcome

The primary outcome evaluated will be the improvement of GSM:

- Vaginal atrophy (dryness, dyspareunia, itching and burning) will be assessed by the Visual Analogue Scale (VAS).[25]
- Sexual dysfunction will be assessed by the Female Sexual Function Index (FSFI).[26]
- Frequency, urgency, nocturia and leakage will be assessed by the International Consultation on Incontinence Questionnaire Overactive Bladder (ICIQ-OAB) and Urinary Distress Inventory-6 (UDI-6).[27]

- Urinary incontinence will be assessed by the International Consultation on Incontinence Questionnaire–Short Form (ICIQ-UI SF) and International Consultation on Incontinence Questionnaires (ICIQ-UIF).[28]

Secondary outcomes

- Vaginal health will be evaluated using the Vaginal Health Index (VHI) (epithelial integrity, vaginal elasticity, moisture, fluid volume and vaginal pH).[29]
- Vaginal Maturation Index (VMI) (epithelial maturation, maturation value).[30]
- Vaginal microbiota (Nugent criteria).[31]
- Quality of life.[32]
- Side effects.

Patient and public involvement

Patients and/or the public were not be directly involved in this systematic review, as all relevant metrics will be sourced from original published studies.

Search strategy

A comprehensive search of the PubMed/MEDLINE, Embase, Scopus, Web of Science, Cochrane Central Register of Controlled Trials, CINAHL and clinical trial databases (www.trialscentral.org, www.controlled-trials.com and ClinicalTrials.gov) will be conducted without language or data restrictions. All electronic databases will be searched in January 2024, and we plan to complete our study in January 2025. A combination of Medical Subject Headings terms, text words and keywords will be used to search the database. The search strategy used for PubMed is shown in table 1 (online supplemental table 1).

Other sources

Eligible studies may also be selected from the reference lists of the retrieved articles. The scope of the computerised literature search may be widened based on the reference lists of the retrieved articles.

Data collection and analysis

Selection of studies

After standardised database searches, the studies will be imputed into Rayyan software. Duplicates will be removed. The initial selection of titles and abstracts will be performed independently by three authors (ACAS, NS and KSM), and disagreements will be resolved by the fourth author (AKG). The PRISMA flow diagram (figure 1) will show the selection process.

Data extraction and management

Three authors (ACAS, NS and KSM) will independently extract the study characteristics (author, country, type of study, follow-up, mean age, sample size, type of intravaginal physical energy and outcomes). Disagreements regarding the study acceptability were resolved through discussions among the authors.

Table 1 PubMed search strategy

	MeSH terms and keywords
1	Breast Neoplasm
2	Breast Cancer
3	Female cancer
4	Cancer Survivors
5	Menopause
6	Postmenopause
7	OR / 1–6
8	Laser Therapy
9	Lasers
10	Erbium YAG Laser
11	Lasers, CO2
12	Laser, Carbon Dioxide
13	Radiofrequency Therapy
14	Radiofrequency therapies
15	Therapy, Radiofrequency
16	Radio-Frequency therapy
17	Energy based devices
18	OR / 8–17
19	Genitourinary syndrome of menopause
20	Atrophic vaginitis
21	Atrophy
22	Dyspareunia
23	Sexual health
24	Sexual Disfunctions, Physiological
25	Dysuria
26	Quality of Life
27	OR / 18–26
28	7 AND 18 AND 27

Addressing missing data

In the event of missing data from selected studies, the authors of the article in question will be contacted via email. If it is impossible to retrieve the missing information, the data will be imputed or deleted, which will be covered in the discussion.

Data synthesis

The authors will use Review Manager Software V.5.4.1 to enter the data. Effect sizes will be expressed as risk ratios, ORs or prevalence ratios (for dichotomous data) and weighted (or standardised) mean differences (for continuous data), and their 95% CI will be calculated. In the case of heterogeneity ($I^2 \geq 50\%$), a random-effects model will combine the studies to calculate the OR and 95% CI. The χ^2 test will be used to evaluate the study outcomes (significance level of $p < 0.1$). Heterogeneity will be evaluated according to the Cochrane Handbook criteria using the I^2 statistic. If the I^2 value is <50%, heterogeneity will be considered low, and a fixed-effects model will be used in the analysis. Otherwise, heterogeneity will be considered

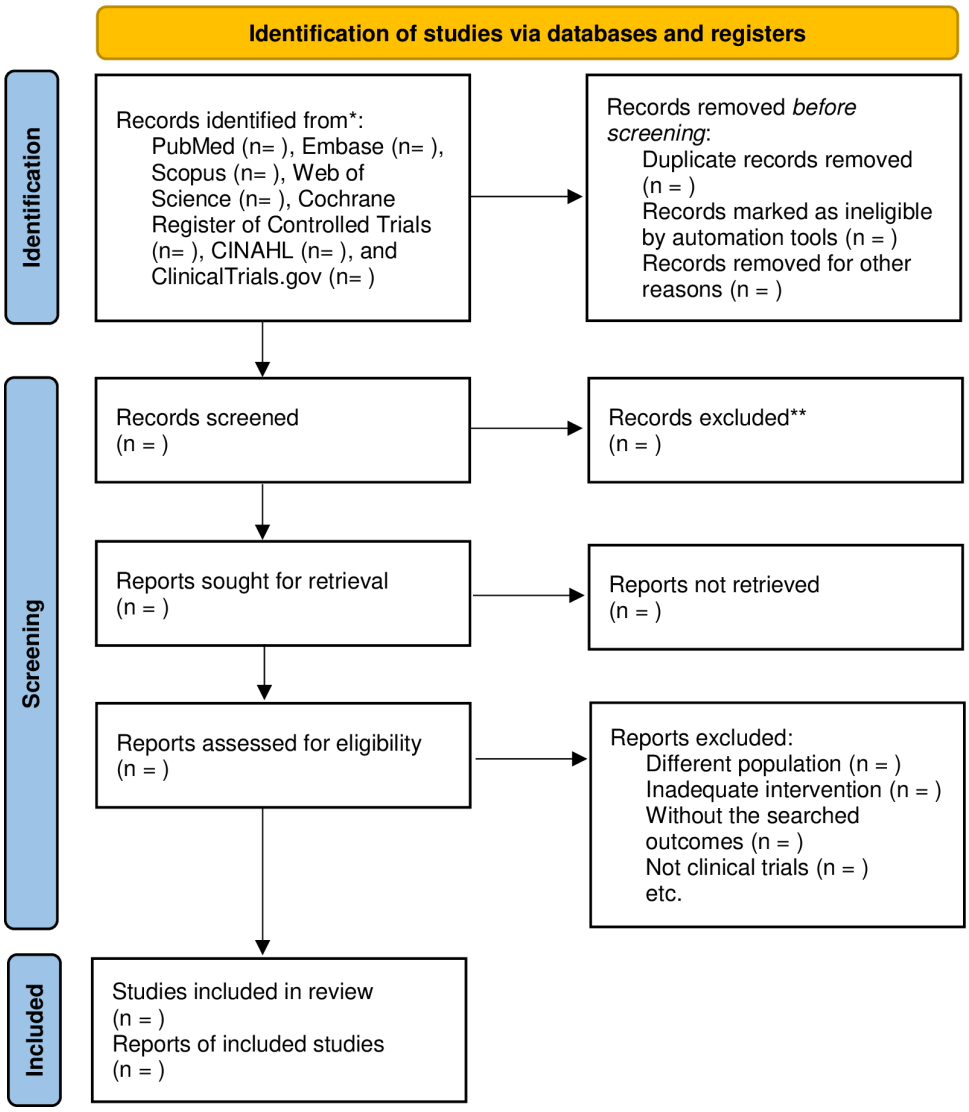

Figure 1 PRISMA flow diagram for the search of eligible studies.

high if the I^2 value is ≥50%; a random-effects model will be used. It is essential to note that this evaluation will be executed if the achievement of the meta-analysis is appropriate. Forest plots will be constructed to show study-specific and pooled risk ratio/OR estimates. Egger's test, Duval and Tweedie's trim-and-fill method and forest plots will be used to plot the data.

Risk of bias assessment

Two authors will independently (NS and ACAS) assess the risk of bias using the Cochrane risk-of-bias tool (RoB 2). The RoB 2 tool is structured into domains through which bias might be introduced into the result; the domains evaluated included randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported results and overall.[33 34]

Egger's funnel plot will assess publication bias, which will be assessed as a judgement (high, low or unclear) if at least ten studies are included in the meta-analysis.

Assessing certainty in the findings

The Grading of Recommendations, Assessment, Development and Evaluation will be used to classify the strength of the evidence obtained by the meta-analysis for each outcome. The quality of evidence will be assessed based on the risk of bias, indirect bias, inconsistency, inaccuracy and publication bias.[35]

DISCUSSION

According to international guidelines, non-hormonal therapies (moisturising or lubricants) are the first-line treatment for mild-to-moderate VVA in BCSs.[11] They are less effective than hormonal therapies, often promote temporary symptom relief and require frequent reapplication. Notably, they do not induce changes in the local epithelium or reverse urogenital ageing.[36 37]

Intravaginal physical energy has been proposed as a non-pharmacological therapeutical alternative for the management of GSM. Several studies have evaluated

the effectiveness and safety of laser and radiofrequency therapy in postmenopausal women with GSM.[38] However, most of them exclude women with breast cancer. Studies on BCSs have a low or very low quality of evidence, with little data on intravaginal radiofrequency therapy,[22] although in 2018, the Food and Drug Administration (FDA) published a statement regarding the use of vaginal devices for 'vaginal rejuvenation, vaginal cosmetic procedures or symptoms of menopause, urinary incontinence or sexual function'.[39]

In response to the FDA warning, a panel of experts pointed out that all devices should be accredited by the regulatory agencies, and only professionals with appropriate skills and who know the precise indications should be allowed to use them. They describe that similar medical and surgical techniques can be associated with adverse effects. Moreover, they agree that long-term safety and efficacy studies are needed before energy-based treatment can be recommended as a standard therapy.[40]

A recent systematic review showed similar improvements in GSM symptoms with vaginal laser therapy versus vaginal oestrogen treatment in terms of the VAS, VHI, VMI and FSFI scores.[21 41 42] However, a survey of health professionals caring for BCSs revealed that only 3% of respondents recommended vaginal lasers for treating GSM. The major concerns and barriers to recommendation were cost, efficacy, safety, availability and lack of knowledge that vaginal laser is an option.[43 44]

We anticipate limitations in this review in the form that most of the studies are performed in the non-breast cancer population and the high heterogeneity of studies investigating the effects and safety of physical methods. Most are single-centre and not blinded, with short-term follow-up.

To date, there is no consensus regarding the treatment of moderate/severe GSM in BCSs. More alternatives for treatment in this group are urgently needed because hormonal therapy is contraindicated, and their symptoms are more intensive with oncological treatments. Robust evidence is warranted to be introduced into clinical practice and improve quality of life and sexual function. We aim to overcome this by placing vast evidence to support different physical methods to treat GSM in BCSs in this systematic review and meta-analysis.

ETHICS AND DISSEMINATION

This study is a systematic review with a possible meta-analysis, which will use data from previously conducted studies; therefore, it does not require ethical approval. The outcome of this research will be submitted for publication in a peer-reviewed journal.

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Contributors NS, ACAS and AKG contributed to the design of this review. NS and ACAS drafted the protocol's manuscript. MLN and RDO contributed additional text and edits. NRA and KSM reviewed the manuscript. NS, APFC and AKG developed the search strategies. NS, KSM, APFC and NRA will be tracked the potential studies, extracted the data and assessed the quality. In case of disagreement between the data extractors, AKG will advise on the methodology and work as a referee. NS and ACAS will complete the data synthesis. All authors approved the final version for publication.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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Journal of Lasers in Medical Sciences

J Lasers Med Sci 2023;14:e32

Original Article

http://journals.sbmu.ac.ir/jlms

doi 10.34172/jlms.2023.32

The Effect of Radiofrequency Therapy on Sexual Function in Female Cancer Survivors (Gynecologic and Breast) and Non-cancer Menopausal Women: A Single-Arm Trial

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Received: April 9, 2023
Accepted: July 1, 2023
Published online September 2, 2023

Abstract

Introduction: Up to 90% of postmenopausal women and female cancer survivors may be affected by the genitourinary syndrome of menopause (GSM), with a negative impact on sexual function and quality of life. A novel energy-based device among the treatment options for GSM is radiofrequency therapy (RFT). RFT is a treatment option that uses energy from radio waves to heat the tissue. The objective of this study was to assess the impact of RFT on sexual function in female cancer survivors (gynecologic and breast) and non-cancer menopausal women.

Methods: In a single-arm prospective trial, the efficacy of RFT in both female cancer survivors (gynecologic and breast) and non-cancer menopausal women with sexual dysfunction at a tertiary and referral center (Imam Hossein Medical Center, Tehran, Iran) was evaluated between April 2022 and December 2022. The study protocol consisted of 3 monthly RFT sessions. Examination was performed at baseline (T0) and 3 months after the last RFT session (T1). The primary outcome was sexual function, which was assessed using the Female Sexual Function Index (FSFI). In addition, adverse events were evaluated during treatment and at T1.

Results: A total of 37 female cancer survivors (mean [SD] age: 49.4 [8.9] years) and 37 non-cancer menopausal women (mean [SD] age: 53.8 [5.5] years) were enrolled. Patients exposed to RFT showed a significant improvement in FSFI scores when compared to baseline scores for both female cancer survivors (13.07, 95% CI: 12.27 - 13.86) and non-cancer menopausal women (13.18, 95% CI: 12.34 - 14.03). There was no difference in FSFI total score improvement between the two groups ($t_{(72)}=0.06$, $P=0.951$). There were no serious adverse events associated with RFT.

Conclusion: The efficacy of RFT as a treatment for sexual dysfunction has been demonstrated in both non-cancer menopausal women and female cancer survivors. In both groups, a significant improvement was confirmed.

Keywords: Radiofrequency therapy; Sexual function; Menopause; Gynecologic cancer; Breast cancer.

Introduction

Breast cancer and gynecologic cancers are the most frequently diagnosed cancers in women, accounting for 24.5% and 15.2% of the newly diagnosed cancers in women worldwide, respectively.[1] Moreover, breast cancer is a major global health concern, given that it is currently the most commonly diagnosed cancer worldwide.[1] Advancements in timely detection and more effective therapies have contributed to a steady increase in the number of female cancer survivors, particularly breast cancer survivors.[2,3] Adjuvant therapy for gynecologic cancer and breast cancer (e.g., systemic chemotherapy and endocrine therapy) can lead to undesirable symptoms that negatively impact on women's quality of life.[4] For example, GSM, previously known as vulvovaginal atrophy (VVA), is a pervasive side effect associated with female sexual dysfunction (FSD).[5,6] FSD refers to a problem that prevents women experiencing the satisfaction of sexual activity and affects approximately 40%-50% of all women and 66% of women with cancer.[7]

GSM is characterized by genital (e.g., vaginal dryness, irritation/burning/itching), urinary (e.g., urgency, dysuria), and sexual symptoms (e.g., decreased lubrication, dyspareunia, impaired function).[5] The GSM

Please cite this article as follows: Arab A, Vasef M, Talayeh M, Hosseini MS, Farzaneh F, Ashrafganjoei T. The effect of radiofrequency therapy on sexual function in female cancer survivors (gynecologic and breast) and non-cancer menopausal women: a single-arm trial. *J Lasers Med Sci.* 2023;14:e32. doi:10.34172/jlms.2023.32.

is highly prevalent, affecting approximately 50% to 90% of post-menopausal women[8-12] and 35% to 91% of breast cancer survivors.[13] Vaginal dryness was the most prevalent GSM-related symptom reported in previous studies both in menopausal women and in breast cancer survivors, with a wide variety in the severity and frequency of the symptom.[9, 12-14] Despite its significant impact on sexual function and high prevalence, GSM is still under-recognized and undertreated.[15] The standard treatment for alleviating GSM-related symptoms includes both non-hormonal therapies, that is, vaginal lubricants and moisturizers, in addition to hormonal therapies, including topical estrogen.[13,16] In recent years, physical methods such as laser therapy and radiofrequency therapy (RFT) have been recruited to manage GSM, especially in women who have been advised against hormone therapy.[16]

Intravaginal laser therapy has emerged as a potential treatment modality for GSM and/or urinary incontinence. The fractional microablative CO2 laser and the non-ablative erbium:YAG (Er:YAG) laser are the two main types of lasers utilized for treating symptoms related to GSM.[16-19] RFT is another modality to alleviate GSM-related symptoms, and its use has become more popular over the last years.[16, 20] There are various types of radiofrequency treatments available, categorized based on energy dissipation and the effect of the electromagnetic wave on tissue.[21] Among these, non-ablative monopolar radiofrequency is the most commonly used method.[22]

A systematic review by Sarmento et al[16] evaluated the use of laser and radiofrequency physical therapies for GSM in pre- and postmenopausal women. They found that laser therapy is a safe and effective treatment for GSM and urinary incontinence in postmenopausal women. Similarly, another review and meta-analysis[23] found that although vaginal laser therapy has shown efficacy in treating GSM in breast cancer survivors in the short term, there is a lack of long-term safety and efficacy data. However, the efficacy and safety of RFT for the treatment of GSM have not been evaluated to the same extent. Considering the above-mentioned points, it is necessary to investigate the effectiveness of RF for the treatment of GSM because most studies only evaluate laser therapy use. In addition, the majority of studies have been conducted on menopausal women, and little is known regarding the efficacy of RFT on FSD among female cancer survivors. Given this background, the current study was performed to examine the effect of RFT in the treatment of FSD, as assessed using the FSFI,[24] in female cancer survivors (gynecologic/breast cancer) and non-cancer menopausal women, and to compare the efficacy of RFT in these two groups of women.

Materials and Methods

Study Design

The study is a single-arm prospective trial and evaluates the efficacy of RFT in both female cancer survivors (Gynecologic and Breast) and non-cancer menopausal women with FSD at a tertiary and referral cancer center (Imam Hossein Medical Center, Tehran, Iran) between April 2022 and December 2022.

Inclusion criteria for the study were as follows: (1) female cancer survivors (Gynecologic Cancer and Breast Cancer), (2) self-reported FSD as defined by a baseline FSFI total score of less than 26.5, and (3) wishing to maintain an active sexual life. In addition, non-cancer menopausal women (at least 12 months after their last menstrual period and/or bilateral oophorectomy) with FSD participated in the study.

The following exclusion criteria were applied: (1) use of hormone replacement therapies, either systemic or local, (2) use of vaginal moisturizers or lubricants, (3) presence of active genital infection such as herpes genitalis or candida, (4) acute or recurrent urinary tract infection, (5) HIV positive status, (6) previous pelvic reconstructive surgery or use of an intrauterine device, (7) current pregnancy, (8) breastfeeding, and (9) presence of any skin disease.

Therapeutic Procedure

All women included in the study were treated with a Physio Vag radiofrequency device, which is based on temperature-controlled transcutaneous radiofrequency that uses monopolar and bipolar modes. There are 4 frequencies (i.e., 420, 500,720 and 1000 kHz) in this device. In this study, a frequency of 720 kHz was used for both monopolar and bipolar modes.

For the application, the women were placed in the lithotomy position. Each session was carried out using two handpieces, one for the external genitalia and another for the vaginal canal. In the external genitalia, the working time was about 10 minutes using an external probe with a frequency of 720 kHz and monopolar mode. In the vaginal canal, the working time was also about 10 minutes using an internal probe with a frequency of 720 kHz and bipolar mode. Each woman underwent three RFT sessions, with an interval of one month between them. Assessments were made at baseline (T0) and 3 months after the last RFT session (T1). The treatment was done by the same trained gynecologist.

Primary Outcome

The primary outcome of the study was sexual function, which was evaluated using the FSFI.[24] The FSFI is a brief, 19-item self-administered questionnaire that measures female sexual function over the preceding four weeks. It evaluates sexual function across multiple domains, including desire, arousal, lubrication, orgasm, satisfaction, and pain, and it provides an overall score for sexual function. The FSFI total score ranges from 2 to 32. A total score of ≤ 26.55 on the FSFI is considered

to be indicative of possible FSD.[25] The Persian version of the FSFI has demonstrated adequate psychometric properties.[26]

Secondary outcome (Side effects)

To examine safety, we considered the adverse events during the treatment and 3 months after the treatment.

Sample Size

The sample size calculation was done using G*Power version 3.1.9.2.[27] With an effect size of 0.7, a power of 0.8 and an alpha value of 0.05, 34 women would be necessary in each group. Assuming a potential dropout rate of 10%, 37 women were needed in each group.

Statistical Analysis

We reported continuous variables as mean (standard deviation (SD), and categorical variables were reported as frequency (percentage). Comparisons of mean scores from FSFI total score and its domain were performed using the paired-samples t-test. The independent-samples t-test was used to compare the improvement of FSFI total and its domain score between female cancer survivors and non-cancer menopausal women. Data analysis was performed using SPSS for Windows, version 16.0 (SPSS Inc., Chicago, IL, USA). Graphs with error bars were generated using GraphPad Prism, Version 8.0.1 (GraphPad Prism Software Inc., San Diego, CA, USA). The *P* value of less than 0.05 was considered statistically significant.

Results

Participants' Characteristics

All women in both groups completed the study, and none were dropped from the study. Table 1 shows the demographic and clinical data of the women. The mean age of the women was 51.58 (SD = 7.68) years.

Table 1. Baseline Characteristics of the Study Participants

	Total	Female Cancer Survivors	Non-cancer Menopause
Age, mean (SD), y	51.58 (7.68)	49.41 (8.94)	53.76 (5.46)
Gravidity, n (%)			
NG	3 (4.1)	2 (5.4)	1 (2.7)
G1	13 (17.6)	9 (24.3)	4 (10.8)
G2	25 (33.8)	16 (43.2)	9 (24.3)
G3	19 (25.7)	4 (10.8)	15 (40.5)
≥G4	14 (18.9)	6 (16.2)	8 (21.6)
Live birth, mean (SD)	2.34 (1.38)	2.11 (1.45)	2.57 (1.28)
Abortion, n (%)			
No	62 (83.8)	30 (81.1)	32 (86.5)
Yes	12 (16.2)	7 (18.9)	5 (13.5)
Type of Delivery, n (%)			
None	6 (8.1)	4 (10.8)	2 (5.4)
NVD	43 (58.1)	16 (43.2)	27 (73.0)
CS	14 (18.9)	10 (27.0)	4 (10.8)
NVD/CS	11 (14.9)	7 (18.9)	4 (10.8)

NVD, Natural vaginal delivery; CS, Caesarean section.
Data are mean (SD) or n (%).

Outcomes

Comparison Between Baseline and 3 Months After the Last RFT Session

As presented in Table 2, female cancer survivors reported a higher FSFI total score after the intervention (Mean = 27.82, SD = 2.13) compared to before the treatment (Mean = 14.75, SD = 2.22). A paired-samples t-test indicated this improvement; 13.07, 95% CI [12.27, 13.86] was statistically significant ($t_{(36)} = 33.25$, $P < 0.001$). Similar results were observed for all FSFI domains among female cancer survivors (see Table 2).

In non-cancer menopausal women, the women's score of total FSFI increased significantly from baseline (M = 14.31, SD = 1.45) to post-intervention (M = 27.94, SD = 2.20) ($t_{(36)} = 31.78$, $P < 0.001$). On average, the total FSFI scores 3 months after the last RFT session were 13.18 [95% CI: 12.34, 14.03] units more than the FSFI scores at baseline. Similar results were observed for all FSFI domains among non-cancer menopausal women (Table 2).

Comparison Between Groups

A comparison of FSFI score improvement between female cancer survivors and non-cancer menopausal women is depicted in Figure 1. There was no difference in FSFI total score improvement between the two groups ($t_{(72)} = 0.06$, $P = 0.951$). The same results were also obtained for Desire ($t_{(72)} = 1.53$, $P = 0.129$), Arousal ($t_{(72)} = 0$, $P = 1$), Lubrication ($t_{(72)} = 0.06$, $P = 0.953$), Orgasm ($t_{(72)} = 0.28$, $P = 0.780$), Satisfaction ($t_{(72)} = 0.08$, $P = 0.933$), and Pain ($t_{(72)} = 0.61$, $P = 0.543$).

Side Effects

All women completed the trial and none was lost to follow-up. There were no serious and unexpected adverse events associated with RFT.

Discussion

GSM in female cancer survivors is a critical and pervasive problem, resulting in FSD and impaired quality of life. However, the appropriate therapy for managing GSM in female cancer survivors is still an inadequately addressed issue. Several systematic reviews have demonstrated the feasibility and safety of laser therapy for treating GSM, as well as improvements in sexual function among both postmenopausal women and breast cancer survivors.[13,17,28] However, evidence regarding the support for the hypothesis of safety and effectiveness of RFT on

Table 2. FSFI Scores at Baseline and 3 Months After the Last RFT Session

	Time		Mean Differences (95% CI)	$t_{(36)}$ / $t_{(72)}$	*P*
	Baseline	Three Months After Last RFT			
Cancer survivors (n = 37)					
Desire	2.42 (0.39)	3.94 (0.62)	1.53 (1.34, 1.72)	16.24	<0.001
Arousal	2.36 (0.40)	4.31 (0.53)	1.95 (1.78, 2.11)	24.01	<0.001
Lubrication	2.38 (0.60)	5.09 (0.49)	2.71 (2.44, 2.97)	20.70	<0.001
Orgasm	2.63 (0.55)	4.59 (0.29)	1.96 (1.74, 2.18)	18.28	<0.001
Satisfaction	2.44 (0.52)	4.80 (0.42)	2.36 (2.16, 2.55)	24.42	<0.001
Pain	2.51 (0.50)	5.08 (0.55)	2.57 (2.33, 2.80)	22.01	<0.001
Total FSFI score	14.75 (2.22)	27.82 (2.13)	13.07 (12.27, 13.86)	33.25	<0.001
Non-cancer menopause (n = 37)					
Desire	2.29 (0.34)	4.05 (0.70)	1.77 (1.51, 2.02)	14.13	<0.001
Arousal	2.21 (0.42)	4.15 (0.63)	1.95 (1.72, 2.17)	17.26	<0.001
Lubrication	2.38 (0.49)	5.10 (0.56)	2.72 (2.46, 2.98)	21.15	<0.001
Orgasm	2.58 (0.35)	4.51 (0.31)	1.92 (1.76, 2.09)	23.53	<0.001
Satisfaction	2.29 (0.38)	4.66 (0.44)	2.37 (2.20, 2.54)	28.30	<0.001
Pain	2.56 (0.44)	5.02 (0.64)	2.46 (2.19, 2.73)	18.48	<0.001
Total FSFI score	14.31 (1.45)	27.49 (2.20)	13.18 (12.34, 14.03)	31.78	<0.001
Total subjects (n = 74)					
Desire	2.35 (0.37)	4.00 (0.66)	1.65 (1.49, 1.80)	20.86	<0.001
Arousal	2.28 (0.41)	4.23 (0.58)	1.95 (1.81, 2.08)	28.22	<0.001
Lubrication	2.38 (0.55)	5.10 (0.52)	2.71 (2.53, 2.90)	29.79	<0.001
Orgasm	2.61 (0.46)	4.55 (0.30)	1.94 (1.81, 2.08)	28.98	<0.001
Satisfaction	2.37 (0.46)	4.73 (0.44)	2.36 (2.24, 2.49)	37.24	<0.001
Pain	2.54 (0.47)	5.05 (0.60)	2.51 (2.34, 2.69)	28.53	<0.001
Total FSFI score	14.48 (1.86)	27.64 (2.34)	13.16 (12.60, 13.73)	46.48	<0.001

SD, Standard Deviation; CI, Confidence Interval; FSFI, Female Sexual Function Index.
Data are mean (SD), unless otherwise specified.

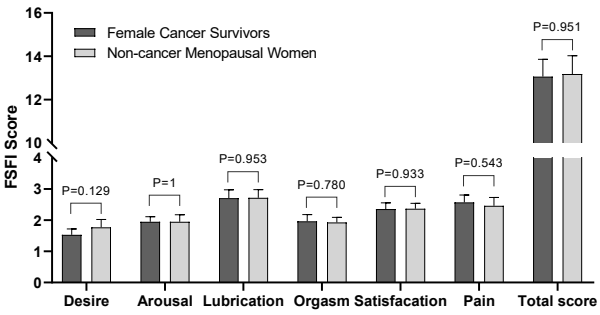

Figure 1. The Improvement (Gain) Score From Baseline to Three Months After the Last Session of RFT in FSFI and its Domain Scores for Female Cancer Survivors and Non-cancer Menopausal Women. *P* values are based on the independent-samples *t*-test

GSM is rare.[16]

Our findings indicate that in women with GSM-related symptoms, either female cancer survivors or non-cancer menopausal women, RFT is effective in significantly improving 6 different domains of sexual function. These results are consistent with other studies that have also found RFT to improve sexual function. In a study performed by Pinheiro et al[22] in Brazil, RFT improved sexual function in 72.7% of participants as assessed by the FSFI. A similar result was obtained in a randomized, single-blind, and sham-controlled study performed by Krychman et al,[29] in nine clinical centers located in Canada, Japan, Italy, and Spain.

Our study utilized three RFT sessions applied at a one-month interval for all women. In previous studies, the treatment protocol included three to five sessions.[22,30-33] There are no guidelines regarding the optimal number of sessions or the intervals between them. Future studies comparing different interval and session protocols might produce the best treatment approaches.

The present study found no serious adverse events associated with RFT during or after the treatment, indicating that RFT may be considered a safe and well-tolerated method for treating GSM. This finding is consistent with the previous studies.[22,30-33] Nevertheless, these results must be interpreted carefully, considering the lack of randomized controlled trials and follow-up on the long-term effect of this therapy.

In the present study, no differences in the efficacy of

RFT on sexual function were found between female cancer survivors and non-cancer menopausal women. Gittens and Mullen's study[34] supports the role of fractional microablative CO2 laser therapy as an effective treatment for FSD in postmenopausal women and breast cancer survivors. However, the group size was too small to allow a direct comparison between postmenopausal women and breast cancer survivors. In a study conducted by Siliquini et al[35] using fractional a CO_2 vaginal laser, GSM symptoms improved slower in breast cancer survivors than in healthy women.

To date, most studies have examined the efficacy of only one physical method for the treatment of GSM. Further comparative research between different RF-based devices and other energy-based devices, such as laser and micro-focused ultrasound, may help establish more specific treatment protocols for GSM.[36]

The limitations of the study include a single-center study, the absence of a control group, and a short follow-up time of up to 3 months. In the present study, subgroup analysis was not designed, particularly due to the small number of subgroups. Further studies using longer follow-up assessments in larger and more diverse populations are useful. In addition, prospective trials to compare RFT with therapeutic alternatives are useful.

Conclusion

RFT effectively treated the symptoms of FSD in gynecologic/breast cancer survivors as well as in non-cancer menopausal women, and no differences in the efficacy of the RFT were observed between the two groups.

Acknowledgements

We would like to express our gratitude to the women who participated in this study, as well as the Clinical Research Development Center at Imam Hossein Educational Hospital, Shahid Beheshti University of Medical Science in Tehran, Iran, for their support.

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Data Availability Statement

The corresponding author can provide the data sets used and/or analyzed in the present study upon request in a reasonable manner.

Ethical Approval

This study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences in Tehran, Iran (Ethics Code: IR.SBMU.RETECH.REC.1401.489). All participating women were fully informed about the study and provided their consent to participate. The trial was registered at www.irct.ir (identifier: IRCT20160531028187N2).

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Systematic Review

Therapeutic Choices for Genitourinary Syndrome of Menopause (GSM) in Breast Cancer Survivors: A Systematic Review and Update

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Citation: Merlino, L.; D'Ovidio, G.; Matys, V.; Piccioni, M.G.; Porpora, M.G.; Senatori, R.; Viscardi, M.F.; Vitale, A.; Della Rocca, C.; on behalf of Policlinico Umberto I Collaborators. Therapeutic Choices for Genitourinary Syndrome of Menopause (GSM) in Breast Cancer Survivors: A Systematic Review and Update. *Pharmaceuticals* **2023**, *16*, 550. https://doi.org/10.3390/ph16040550

Academic Editor: Jolanta Saczko

Received: 9 March 2023
Revised: 21 March 2023
Accepted: 29 March 2023
Published: 6 April 2023

Abstract: (1) Background: Genitourinary syndrome of menopause (GSM) is a medical condition that can affect breast cancer survivors (BCS). This is a complication that often can occur as a result of breast cancer treatment, causing symptoms such as vaginal dryness, itching, burning, dyspareunia, dysuria, pain, discomfort, and impairment of sexual function. BCS who experience these symptoms negatively impact multiple aspects of their quality of life to the point that some of them fail to complete adjuvant hormonal treatment; (2) Methods: In this systematic review of the literature, we have analyzed possible pharmacological and non-pharmacological treatments for GSM in BCS. We reviewed systemic hormone therapy, local hormone treatment with estrogens and androgens, the use of vaginal moisturizers and lubricants, ospemifene, and physical therapies such as radiofrequency, electroporation, and vaginal laser; (3) Results: The data available to date demonstrate that the aforementioned treatments are effective for the therapy of GSM and, in particular, vulvovaginal atrophy in BCS. Where possible, combination therapy often appears more useful than using a single line of treatment; (4) Conclusions: We analyzed the efficacy and safety data of each of these options for the treatment of GSM in BCS, emphasizing how often larger clinical trials with longer follow-ups are needed.

Keywords: genitourinary syndrome of menopause (GSM); breast cancer survivors (BCS); vulvovaginal atrophy (VVA); aromatase inhibitors (AI); vaginal lubricants; vaginal moisturizers; local hormone therapy; vaginal laser therapy

1. Introduction

Breast cancer represents a global issue in public health, ranking as the first most diagnosed cancer in women and the second most common cause of cancer-related death after lung and bronchial cancer [1].

According to data from GLOBOCAN 2020 provided by the International Agency for Research on Cancer (IARC), the incidence is growing worldwide with an estimated number of 2.261.419 new cases per year, while average mortality is constantly decreasing,

accounting for 684.996 deaths, mainly thanks to the recent improvements in early detection techniques and the availability of novel therapeutic agents. [2]. According to the National Cancer Institute's (NCI) definition, every patient who receives a diagnosis of breast cancer is a breast cancer survivor until the end of their lives [3].

For long-term survivors, special concerns about the quality of life and long-lasting side effects, including gynecologic issues, must be considered an increasingly important part of overall care [4].

Breast cancer usually occurs in people without any genetic predisposition (70–80%); however, 5–10% of cases are associated with hereditary syndromes [5,6].

It has been largely demonstrated that pathogenic mutations in the BRCA1 and BRCA2 genes increase the risk of developing breast cancer, respectively, by 65% and 45%, and are responsible for 90% of all hereditary BC cases [4].

Breast cancer is historically classified into four main subtypes: luminal A, luminal B, HER2 overexpression, and basal-like (also known as Triple Negative, TNBC) [7].

The above-mentioned biomarkers have strongly validated prognostic and predictive values, thus playing an essential role in the definition of the best treatment option [8].

However, the treatments used in the management of breast cancer are responsible for the development of GSM. In fact, it has been observed that about 70% of BCS present symptoms attributable to a GSM picture due to the hypoestrogenism they experience [9].

With the term genitourinary syndrome (GSM), we are going to indicate the set of signs and symptoms attributable to the genitourinary tract and caused by a lack of estrogens.

This leads to changes in the lower genitourinary tract, which is responsible for the signs and symptoms of GSM.

As for the symptoms relating to the genital component, we find dryness with poor lubrication, burning and irritation, and vaginal discharge; regarding the urinary component, we have dysuria, urinary urgency, and recurrent urinary infections. To this, we must add dyspareunia. These symptoms determine an important sexual dysfunction.

On physical examination, we can find labial atrophy, vaginal dryness, and clitoral atrophy. The appearance of the vaginal walls, observable with the speculum, may appear friable and hypopigmented; there may be traces of bleeding, which can already be observed upon insertion of the speculum [10].

Vulvovaginal atrophy (VVA) is an important component of GSM [11].

Several studies have shown that the aromatase inhibitor has a central role in determining the symptoms of menopause. In detail, there is evidence that it determines a severe VVA with dyspareunia, significant hot flashes, and musculoskeletal pain.

It is important to be aware of this because it is necessary to make an early diagnosis. The symptoms related to GSM are the cause of a significant decrease in quality of life.

Based on the type of hormonal treatment to which the woman is subjected, there is an increased risk of manifesting a form of secondary amenorrhea, characterized by the absence of previously regular menstruation for three months or previously irregular menstruation for at least six months. Lambertini et al. illustrate in-depth the assessment of the risk of infertility following the administration of the main anti-cancer therapies [12].

The guidelines for BC risk reduction suggest hormonal therapies that lead inevitably to early sterility and premature ovarian failure, which precede the early onset of secondary menopausal symptoms [13].

Chemotherapy has a gonadotoxic effect, causing the destruction of the ovarian follicles. The endocrine therapy used in the treatment of breast cancer causes inhibitory effects on both ovarian and endometrial functions [12].

Pre-menopausal women under therapy will inevitably undergo suppression of ovarian and endometrial function with subsequent manifestations of transient or permanent chemotherapy-induced amenorrhea. In particular, patients under treatment with aromatase inhibitors will be at an increased risk of developing GSM.

On the other hand, young women with a positive pathogenic mutation for BRCA 1 and 2 who agree to undergo preventive bilateral salpingo-oophorectomy will inevitably develop an early surgically induced menopause and a form of secondary permanent amenorrhea.

We are talking about a severe clinical condition that causes a reduction in the quality of life of such patients, so it is important to diagnose and treat it.

Unfortunately, this issue is often underestimated and undertreated, due to a lack of knowledge by health care specialists or due to a fear of BC recurrence and poor familiarity with the various available options. In fact, a study conducted in 2021 by Pearson et al., aiming to improve the understanding of health professionals' knowledge and management of genitourinary symptoms in women with early breast cancer, by administering a survey to 144 oncology health professionals, demonstrated that most respondents recognized it as a common problem, but only 16% felt confident managing these symptoms and prescribing adequate therapies [14].

A similar study on 120 breast oncologists was conducted in 2017 by Biglia's group in Turin: they assessed that, despite the fact that none of the physicians considered VVA a transient event or a secondary problem in BCS, only half of the oncologists (48%) directly illustrated VVA to the patients as a possible consequence. 41% of the oncologists referred BCSs to gynecologists to define VVA treatment, while 35.1% managed it alone [15].

Therefore, we aim to underline the importance of treating this condition in order to enhance BCS's overall care and quality of life.

According to today's knowledge, we have several therapy options:

- Hormonal, systemic, and topical treatments;
- Non-hormonal topical treatments;
- Physical therapy.

The gold standard for this pathology would be the use of estrogen, which is however contraindicated in women with BCS; in fact, the treatment is still the subject of discussion in this population.

According to current guidelines [16], first-line treatment is a non-hormonal therapy, such as moisturizing and lubricating vaginal creams, which appear to be useful in treating vaginal dryness and lead to an improvement in symptoms. If there is no response, local hormonal treatments are carried out: low-dose intravaginal ovules or intravaginal cream based on testosterone or DHEA. However, the problem is represented by estrogen-based creams and vaginal rings in subjects receiving aromatase inhibitor therapy because systemic absorption has also been demonstrated [16].

The revolution in this area is represented by physical therapies such as electroporation and radiofrequency with the possibility of conveying different active ingredients inside the tissues or even by laser therapy, which allows for improved tropism of the vulvovaginal mucosa.

The objective of this systematic review of the literature is to analyze the various types of treatment currently present with regard to GSM in BCS and understand how to combine them in the best way.

2. Materials and Methods

A systematic review of the literature on SGM management and therapeutic options in BCS was conducted on PubMed, Medline, and the Cochrane Library using the following search terms: genitourinary syndrome of menopause (GSM); breast cancer survivors (BCS); menopause; vulvovaginal atrophy (VVA); aromatase inhibitors (AI); vaginal lubricants; vaginal moisturizers; local hormone therapy; vaginal laser therapy.

Recommendations from international scholarly societies were also taken into account. The North American Menopause Society (NAMS) https://www.menopause.org (accessed on 24 February 2023); https://www.asco.org (accessed on 24 February 2023), the American Society of Clinical Oncology (ASCO); the International Menopause Society (IMS) https://www.imsociety.org (accessed on 24 February 2023); the Canadian Menopause Society https://www.sigmamenopause.com (accessed on 24 February 2023); the European

Menopause and Andropause Society (EMAS) https://www.emas-online.org (accessed on 24 February 2023); the International Society for the Study of Women's Sexual Health (ISSWSH) https://www.isswsh.org (accessed on 24 February 2023).

Using PRISMA guidelines [17] for systematic review, we initially identified through database searches 648 records; after duplicates were removed, the records were 633; 577 of them were excluded based on the title and the abstract, so we assessed 76 full-text articles for eligibility. Full text excluded because it did not meet the review criteria was 47. Finally, we included in our systematic review 38 studies, all in English (Figure 1).

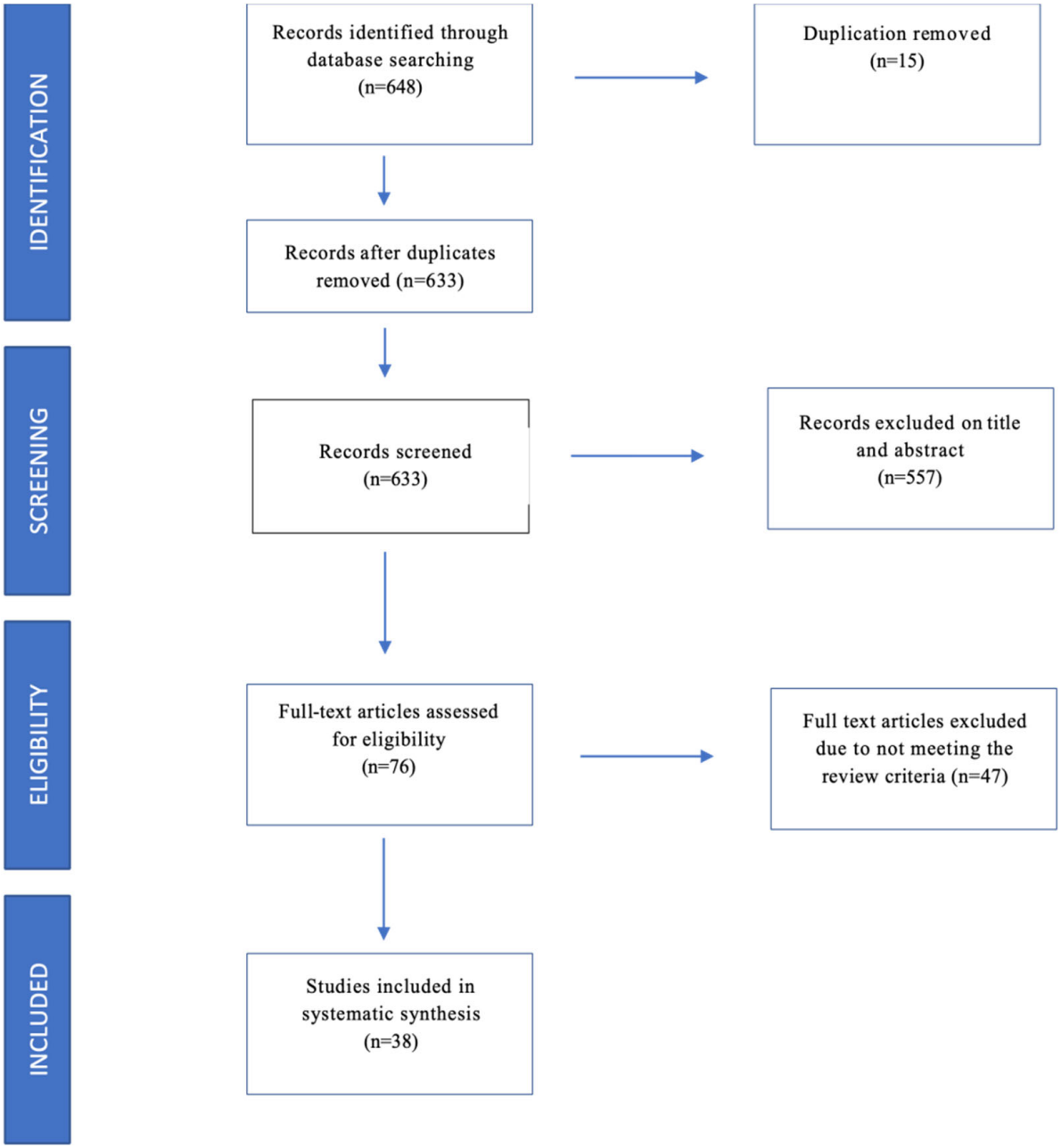

Figure 1. PRISMA flowchart [17].

3. Discussion

The first-line treatment for vulvovaginal atrophy as well as for BCS is represented by non-hormonal therapies [18].

The group of non-hormonal therapies includes numerous categories of drugs and others that can play an optimal role in the treatment of pain during the sexual act and in general for vaginal well-being. Regarding GSM non-hormonal treatments in BCS, we have:

- Moisturizers and lubricants;
- Hyaluronic acid;
- Polynucleotides;
- Phytoestrogens;
- Vasodilators;
- Mechanical (dilators and sexual activity);
- Vaginal vitamin D and E;
- Vaginal/oral probiotics;
- Laser radiofrequency.

Moisturizers and lubricants: the role of vaginal moisturizers is to maintain the integrity and elasticity of the vagina; these are products that must be used regularly, therefore independently of sexual activity. Lubricants, on the other hand, are useful in reducing the sensation of discomfort during sexual acts. As far as lubricants are concerned, the WHO recommends using lubricants that have the following characteristics: osmolarity lower than 1200 mOsm/kg; this is because higher values are toxic and irritating to the vaginal mucosa. Glycerol content in the lubricant <9.9% mass fraction; propylene <8.3% mass fraction; if a glycol mixture is used, the limit must be less than 8.3% of the mass balance. The product must also be free from parabens, chlorhexidine, and polyquaternary compounds [19].

Hyaluronic acid (HA): linear polymer with large dimensions; it is flexible and extremely polar. It is a compound that we find to be the main component of the extracellular matrix (ECM), together with collagen, elastin, and fibronectin. It is one of the main constituents of the connective tissue of humans and mammals [20]. In the last 20 years, several studies have been carried out aimed at understanding the role of HA in both physiological and pathological conditions, and the biological mechanisms that regulate its synthesis, degradation, and metabolic activities have been analyzed. HA is synthesized on the inner surface of the plasma membrane and then extruded extracellularly; the synthesis is mediated by hyaluronic acid synthetase (HAS); we have 3 types of this enzyme with different functions: HAS1 and 2 polymerize HA of similar length, and HAS3 synthesizes HA with a short chain [21]. Long-chain HA has been shown to promote cell quiescence and only superficially support cellular integrity; low-molecular-weight HA instead promotes tissue repair. Taking into account what has been said, low molecular weight HA finds application both in the gynecological and urological fields. Several studies have shown that the topical use of ovules containing low molecular weight hyaluronic acid (LMW-HA) is a valid alternative in the short- and long-term treatment of problems such as itching, burning, dyspareunia, and dryness, symptoms therefore caused by alterations in the vaginal mucosa resulting both from treatments such as laser therapy, cryotherapy, and radiotherapy and from a lack of estrogen and therefore a GSM [22].

Polynucleotides: they are a mixture of low-molecular-weight fractions that form a linear polymer of deoxyribonucleotides joined by phosphodiester bonds. These are molecules capable of activating fibroblasts by activating purinergic receptors; they also stimulate growth by acting on CD39 receptors [23].

Phytoestrogens: they are substances of vegetable nature that are non-steroids, able to bind to estrogen receptors but with a weaker effect, from 100 to 1000 times a day. They also have antioxidant, anti-inflammatory, and antihypertensive properties. In the phytoestrogen family, isoflavones are of particular interest in the treatment of menopause, in particular genistein, contained in soy. Although the information and studies available are still very few, it has been seen that this molecule could be useful in the management of menopause problems both in the short and long term and therefore could also find utility in the treatment of GSM in BCS women [24].

Vasodilators: the extractive pyranocoumarin is a molecule with a vasodilating action. It interacts with the type 1 calcium channels at the level of the smooth muscles, causing

an increase in the local flow. It has been observed that the local administration of a spray based on visnadine 10 minutes before sexual intercourse has a positive effect, so it is also a candidate among the non-hormonal alternatives to be used in the treatment of GSM in BCS [25].

Vaginal vitamin D and E: a study was conducted to understand the effect of vaginal suppositories based on vitamin E and D on vaginal atrophy in BCS. It is a randomized controlled trial. The result was an improvement in vaginal atrophy by administering these vaginal suppositories every night for 8 weeks [26].

Vaginal/oral probiotics: the vaginal microbiota (in detail, Lactobacillus spp.) plays a very important role in the health of the lower genitourinary tract, and a decrease has been observed during menopause. It has been observed that postmenopausal women with a vaginal microbiota dominated by Gardnerella vaginalis and low Lactobacillus develop vaginal atrophy much more easily than postmenopausal women with a microbiota high in Lactobacillus [27]. The administration of probiotics orally or vaginally is still the subject of a strong debate today, but on the basis of what they report, it certainly finds its usefulness.

Platelet-rich plasma: although there are few studies in the literature to date, it has been deduced that the use of platelet-rich plasma in the treatment of GSM, both as a single treatment and as an adjuvant, appears to be promising and has a good safety profile [28].

Mechanical (dilators and sexual activity): the use of dilators has been shown to support and help women suffering from genital pelvic pain and penetration disorders, which can be present in women with GSM [29].

The main problem with these substances, however, is that they are not able to regenerate the vaginal barriers or improve their characteristics. They can only slow down the evolution of the pathological picture, and the improvements obtained tend to be lost quickly after suspension. These are generally creaming moisturizers or lubricating gels composed mainly of water, vegetable oils, or silicone derivatives [30].

The main advantages related to non-hormonal therapy instead are represented by having practically no side effects; consequently, they can be used for long periods of time without the need for suspension periods. On the other hand, long periods are necessary for these treatments to start to take effect.

All non-hormonal therapies used in GSM therapy for breast cancer patients are summarized in Table 1.

From an etiopathogenic point of view, we know that the cause of vaginal atrophy, even in BCS patients, is caused by a drop in estrogen levels; consequently, a therapeutic treatment based on hormonal supplementation would seem logical. Local estrogen administration has been shown to be the most effective method. The effect consists of an improvement in the tropism of the vaginal mucous membranes and in tissue regeneration with the formation of new vessels and an increase in cell layers with the restoration of adequate local flora and an adequate pH [31].

The methods of administration of estrogens are numerous; there are solutions in cream, vaginal rings, ovules, or gels. The estrogen that is most frequently used in the treatment of vaginal atrophy is estriol.

Conversely, other recent prospective studies have suggested that the use of vaginal estrogen therapy may increase serum estrogen levels, resulting in a possible increased risk of BC recurrence. Santen et al. reported that an increase in serum estradiol levels produced by vaginal estrogens may not exceed the normal range of postmenopausal serum estradiol [32]. Some works in the literature suggest the use of estriol instead of estradiol for BCS since its metabolic clearance is faster. Estriol is not FDA-approved for any indication and should be used as an off-label hormone option [33]. Surely other studies are needed to validate the safety of hormone therapy with clear certainty, considering that the vaginal walls are extremely vascularized and that the use of local therapy does not exclude with certainty the entry into the circulation of hormones. Surely, from our point of view, we would like to specify that a case-by-case evaluation is necessary.

Table 1. Non-hormonal treatments.

Study	Year	Study Design	Follow Up	Median Age	n.	Participants	Intervention	Primary Outcome	Hormonal BC Therapy	Receptor Status (ER +)	Results	Conclusions
Carter et al. Supportive Care in Cancer	2021	Single-arm, prospective longitudinal trial	6 months	55 years old	101	HR+ breast cancer treated with AI or HR+ endometrial cancer treated with surgery and postopera-tive radiation.	HLA daily for the first 2 weeks, and then 3×/week until weeks 12–14; dosage was then increased to 5×/week for non-responders.	VAS, VuAS, FSFI, MSCL	AI	All	VAS/VuAS scores significantly improved at all assessment points (all $p < 0.001$). MSCL scores similarly improved (all $p < 0.001$). FSFI scores significantly improved from T1 to T2 ($p < 0.03$), T3 ($p < 0.001$), and T4 ($p < 0.001$). Severe vaginal pH (>6.5) decreased from 26% at T1 to 19% at T4 ($p = 0.18$).	HLA moisturization improved the vulvovaginal health/sexual function of cancer survivors. While HLA administration 1–2×/week is recommended for women in natural menopause, a 3–5×/week schedule appears to be more effective for symptom relief in cancer survivors.
Keshavarzi et al. Supportive Care in Cancer	2019	Randomized triple-blind study	8 weeks	43.2 years old	96	Patients with diagnosed BC on adjuvant therapy with TAM.	Vit D (1000 UI), Vit E (1 mg), or placebo sup-positories	To investigate the effect of vitamin D and E vaginal suppositories on vaginal atrophy in women with breast cancer receiving tamoxifen.	TAM	-	Increase in VMI of the groups receiving Vit E and D compared with placebo ($p < 0.001$); vaginal pH and subjective symptoms reduced in the two groups compared with placebo.	These data support that vitamin D and E vaginal suppositories were beneficial in improving vaginal atrophy in women with breast cancer receiving tamoxifen.
Chatsiproios et al. PlosOne	2019	Open, prospective, multicentric, observa-tional study.	28 days	52 years old	128	Patients with diagnosed BC managed with chemotherapy or hormonal therapy.	Oil-in-water emulsion during 28 days.	Subjective Symptoms; safety and tolerability.	-	-	The difference in symptom frequency before-after the treatment was significant ($p < 0.0001$).	This treatment seems to improve VVA symptoms with a short treatment.

Table 1. *Cont.*

Study	Year	Study Design	Follow Up	Median Age	n.	Participants	Intervention	Primary Outcome	Hormonal BC Therapy	Receptor Status (ER +)	Results	Conclusions
Hersant et al. Menopause	2018	Prospective, comparative (before/after) pilot study	6 months	60.8 years old	20	Patients with diagnosed BC	A-PRP and evaluated at 0,1,3 and 6 months.	Evaluated vaginal mucosa changes using Vaginal Health Index.	-		Significant increase 10.7 to 20.75 ($p < 0.0001$) at 6 months.	A-PRP improves vaginal mucosa within 6 months of treatment according to VHI criteria.
Marschalek et al. Breast Care	2017	Randomized Controlled Trial, Double Blinded Pilot study	2 weeks	59 years old	11 Lacto-bacillus 11 placebo	Patients with diagnosed BC managed with chemother-apy or hormonal therapy	Vaginal lactobacillus capsules vs. placebo	Nugent score	-		Not reported. Differences between groups: 4.73 vs. 4.0 ($p = 0.038$).	Lactobacillus improves microbiota in BCS.
Juliato PT et al. Climacteric	2016	Randomized Trial	30 days	50.5 years old	25 Poly-acrylic acid 27 lubricant	Patients with diagnosed BC treated with tamoxifen.	Polyacrylic acid vs. Lubricant	FSFI	-	-	Both showed improvement. Acid: 96 to 24% ($p = 0.0001$). Lubricant: 88.9 to 55.6% ($p = 0.0027$).	Polyacrylic acid was superior to lubricant.
Goetsch et al. Journal of Clinical Oncology	2015	Randomized Controlled Trial, Double Blinded	4 weeks	56.6 years old	23 Lido-caine 23 Saline	Patients with diagnosed BC	4% aqueous lidocaine vs. placebo 3 min before vaginal penetration.	Pain (VAS scale)	-	-	Significative differences between groups ($p < 0.007$).	It is a safe option for painful intercourse.
Juraskova et al. J Sex Med	2013	Phase I/II Prospective Study	26 weeks	51 years old	16	Patients with diagnosed BC treated with AI	Pelvic floor muscle (PFM) relaxation exercises twice/day, polycarbophil-based vaginal moisturizer three times/week, and olive oil as a lubricant during intercourse.	Dyspareunia, sexual functioning, quality of life, distress, and pelvic floor muscles (PFMs) functioning	All	-	OVERcome resulted in significant improvements in dyspareunia, sexual function, and quality of life over time (all $p < 0.001$). PFM relaxation training was reported to be effective ($p < 0.001$). Maximum benefits were observed in week 12.	Efficacy in improving dyspareunia and sexual function following breast cancer was demonstrated.

Table 1. *Cont.*

Study	Year	Study Design	Follow Up	Median Age	n.	Participants	Intervention	Primary Outcome	Hormonal BC Therapy	Receptor Status (ER +)	Results	Conclusions
Lee YK et al. ACOG	2011	Randomized Controlled Trial, Double Blinded	12 weeks	45.8 years old	44	Patients with diagnosed BC managed with chemotherapy or hormonal therapy	pH balanced gel vs. placebo for 12 weeks	Vaginal dryness and dyspareunia	-	-	There was a significant difference in the variable dryness with pain ($p = 0.001$), and in the variable dyspareunia ($p = 0.04$).	A vaginal pH-balanced gel could relieve vaginal symptoms.

The administration of HRT should be limited to topical use; in fact, international guidelines do not recommend systemic administration [34].

Promestriene (3-propyl ethyl, 17β-methyl estradiol) is a synthetic estrogen analog with minimal systemic absorption for the topical treatment of vaginal atrophy, which can be used in BCF patients due to its poor activity on the breast. Studies by mass spectrometry have confirmed the low systemic activity even after months of therapeutic doses in women with high-grade estrogen receptor-positive breast tumors [35]. However, in vitro studies concluded that the potential estrogen-like properties of promestriene to stimulate the growth of estrogen receptor-reactive breast cancer cell lines, especially under conditions of estrogen deprivation, suggest caution when prescribing for vaginal atrophy in postmenopausal BCS. Its ability to activate growth and gene expression in ER-BC cells deserves further study.

Women who underwent surgery for luminal early breast cancer are all candidates to receive endocrine adjuvant systemic treatment, which was clearly related to a significant improvement both in progression-free survival (PFS) and overall survival (OS) [36,37].

In ER and PgR-positive BC, estrogens induce the proliferation of tumor cells and support the progression of the disease. Hormone therapy is administered in order to decrease the levels of circulating estrogens by using drugs active on the hypothalamic-pituitary-ovarian axis and the estrogen receptors [38,39].

Mechanisms and sites of synthesis of sexual hormones change over a woman's life depending on reproductive age. In pre-menopausal women, estrogens are mainly produced by the granulosa cells of the ovary, whereas in post-menopausal women, the primary mechanism of production is the peripheral aromatization of C19-steroids by aromatase located in the adipose tissue [40].

Based upon these biological assumptions, pre- and post-menopausal women are candidates to receive different treatment options.

Two randomized trials, TEXT and SOFT, demonstrated that the use of LHRH-analogues (e.g., triptorelin, goserelin, and leuprorelin) in association with tamoxifen or exemestane resulted in a significant survival benefit for premenopausal women [41].

The ATAC and BIG 1–98 trials showed that in post-menopausal patients, monotherapy with aromatase inhibitors (e.g., anastrozole, letrozole) yielded better outcomes when compared with tamoxifen. In this group, the use of LHRH analogs is not recommended because ovarian production of estrogens is supposed to be physiologically abolished [42,43].

About 95% of patients exposed to endocrine therapy experience at least one drug-induced adverse event (AE), among whom 25–30% reach grade 3 or 4. The early discontinuation rate because of AEs is approximately 20%. Most common AEs include increased cardiovascular and thromboembolic risk, osteoporosis, and those issues that come under the name of genitourinary syndrome of menopause (GSM) [41].

Systemic loss of estrogen results in physiological and structural modifications within the genital structures and vaginal mucosa. Changes include reduced cervical gland secretions, deterioration of tissue, a decrease in blood flow, loss of elasticity, thinning of tissue and epithelium, and an increased pH. These changes are responsible for vaginal dryness and irritation, dyspareunia, decreased libido, frequent urinary tract infections, and urinary incontinence, which together are known as vulvovaginal atrophy or GSM [44,45].

All these symptoms have a great impact on quality of life and need to be properly recognized and managed by the treating physicians, often requiring a multidisciplinary approach. For a long time, this condition has gone undiagnosed and untreated due to a lack of awareness and the paucity of evidence about a safe and effective therapy. From an analysis of the literature and from daily clinical practice, it emerged that there is a lot of difficulty on the part of doctors in administering hormone replacement therapy in patients with previous breast cancer, due to the possible repercussions and side effects. The main fears are related to the risk of interfering with adjuvant therapy, thus favoring any relapses. Numerous works in the literature explain how the risk of tumor reactivation or recurrence is very low [46].

Currently, the cornerstone of treatment for GSM in patients receiving antiestrogen therapy is non-hormonal products. These kinds of solutions are not able to reverse atrophy once it has occurred but can help alleviate symptoms by increasing vaginal moisture, thus avoiding the use of any hormone-based compounds [47].

When non-hormonal products fail to control symptoms, estrogen-based therapy is the only effective option available.

The detrimental effect of systemic estrogen administration was established by two randomized trials. The HABITS trial enrolled 434 patients taking AIs with GSM and randomly assigned them to receive hormone therapy (estradiol hemihydrate and norethisterone) for 2 years or the best symptomatic treatment [48]. The Stockholm trial randomized 378 patients with the same characteristics to receive estradiol and medroxyprogesterone acetate or non-HT. Both studies demonstrated that systemic expositions to estrogens are associated with a significantly increased risk of recurrence of breast cancer (HR 3.5) or new primary development, thus contraindicating the use of this strategy in breast cancer survivors [49].

Although the role of systemic HT is well known, the debate about the safety of its administration is still open. When asked, 71% of oncologists mentioned that the main reason not to prescribe vaginal estrogens is the concern about the potential systemic absorption and the consequent possibility of increased risk of recurrence [15].

Dew et al., in a small cohort study, and Le Ray et al., in a case-control study, of 340 patients with early BC, investigated the BC recurrence risk associated with the use of vaginal estrogen therapy [50,51]. In both works, there is no evidence of an increased risk of recurrence.

In a Danish observational study, a cohort of postmenopausal women with early-stage invasive estrogen receptor-positive nonmetastatic BC who received no treatment or 5 years of adjuvant endocrine therapy were followed over time to evaluate the recurrence and mortality that each had and according to VET, MHT, or no therapy received. The authors concluded that in postmenopausal BCS, neither VET nor MHT was associated with an increased risk of recurrence or mortality. A subgroup analysis revealed an increased risk of recurrence, but not mortality, in patients receiving VET with adjuvant aromatase inhibitors [52].

However, the studies had several limitations, including a small sample size and a short follow-up.

Therefore, it remains unclear whether VET or MHT is safe for women treated for BC [53,54].

Among women without a history of BC, a meta-analysis from the Collaborative Group on Hormonal Factors in Breast Cancer reported an increased risk of primary BC among women treated with MHT compared with never-users, whereas VET was not associated with an increased risk of BC [55,56].

When discussing circulating estrogen levels, it is important to highlight that there is no validated safe threshold, but it is commonly assumed that post-menopausal levels must be achieved. There is not a shared opinion about what specific estradiol or estrone levels should raise concern for breast cancer survivors. In postmenopausal women not receiving hormone therapy, average estradiol levels reach 14.1 pg/mL and estrone levels 27.5 pg/mL; it is unclear if keeping values within the typical postmenopausal range is sufficient to decrease the risk of BC recurrence [57].

Estradiol systemic absorption is dose-dependent, and it is influenced by dose, formulation, and positioning in the vagina. During the last few years, several clinical trials were designed to analyze the pharmacokinetics of different vaginal devices to assess safety and efficacy [58].

Eugster-Hausmann et al. conducted a study in which 58 postmenopausal women received 10 mg or 25 mg estradiol vaginal tablets. The trial proved that systemic estradiol absorption with the 10 mg tablet was lower when compared with the 25 mg tablet. Furthermore, after 1 year of treatment with the 10 mg vaginal tablet, levels of estrogen in the body

were within the menopausal range (2.44 to 12.08 pg/mL), indicating minimal absorption and a potentially safe alternative in breast cancer survivors receiving AIs [59].

Other treatments that have been considered include intravaginal androgens, based on the concept that administration may act on androgen receptors that have been identified in the wall of the vagina. Local administration of testosterone at the vaginal level appeared to trigger the activation of estrogen and androgen receptors in the vaginal epithelial layers without activating estrogen receptors in other tissues due to the lack of aromatase at this level. Testosterone can induce proliferation of the vaginal epithelium, but the conversion of testosterone to estrogen is blocked by Ais, and thus, it may be effective in reversing the atrophic changes without increasing circulating estrogen levels and compromising aromatase inhibitor therapy [60].

Some recent studies are evaluating the effects of a new androgen, dehydroepiandrosterone (DHEA), in the treatment of vaginal dryness in patients with previous BC [61]. Labrie et al. (2017) in their randomized clinical trial demonstrated the efficacy of prasterone (administered intravaginally at 0.50% 6.5 mg) in postmenopausal women suffering from moderate to severe dyspareunia due to vulvovaginal atrophy. In particular, an average 35.1% decrease over placebo in the percentage of parabasal cells ($p < 0.0001$), an average 7.7% increase in the percentage of superficial cells ($p < 0.0001$), and a mean 0.72 pH unit decrease in vaginal pH ($p < 0.0001$) were observed. Moreover, a very positive evaluation was obtained on the acceptability of the technique of administration of the insert, whereas the male partners reported a very positive evaluation of the changes observed in their sexual partners [62].

At present, this androgen appears to be the only one approved by the FDA for the treatment of GSM in the form of prasterone, the synthetic analog of DHEA.

Barton et al. conducted a phase III randomized clinical trial that evaluated vaginal administration of DHEA at the doses of 3.25 or 6.5 mg compared with plain moisturizer in postmenopausal women with a history of breast (97%) or gynecologic cancer who could be receiving HT (56%). Peripheral blood sample analysis showed that circulating estradiol was significantly increased in those receiving 6.5 mg/d DHEA but not in those receiving 3.25 mg/d DHEA or AI therapy. In both arms, mean estradiol concentrations remained lower than 5 pg/mL. Assuming that hormone concentrations, even though slightly increased, remain in the lowest half or quartile of the postmenopausal range, the FDA has approved vaginal DHEA for the treatment of GSM [63]. However, the prasterone technical data sheet includes a warning against its use in BCS.

There are no studies directly comparing vaginal DHEA to vaginal estrogens in terms of efficacy or studies comparing systemic hormone levels; therefore, there can be no recommendation for one over the other in BCS. Vaginal testosterone cream and an estradiol-releasing vaginal ring also proved to safely improve GSM symptoms in BCS. A study by Witherby et al. supported the safety of vaginal testosterone at the dose of 150 mg or 300 mg daily for treating vulvovaginal atrophy in patients with breast cancer receiving AI therapy, not detecting any significant elevation in serum estradiol levels (<8 pg/mL) at either dose of testosterone [64].

Melisko et al. conducted a randomized phase II trial evaluating the safety and efficacy of intravaginal testosterone cream or a vaginal ring for 12 weeks in postmenopausal women receiving AIs who had symptoms of vulvovaginal atrophy. The intervention was considered unsafe if more than 25% of patients had elevations in serum estradiol greater than 10 pg/mL and at least 10 pg/mL above baseline after treatment initiation. Both interventions met the primary safety end point and improved vaginal atrophy, sexual interest, and dysfunction [65].

In conclusion, according to the American College of Obstetricians and Gynecologists (ACOG) recommendations, the first-line approach to managing GSM in BCS receiving HT is non-hormonal options, but when refractory or severe symptoms occur, the use of vaginal estradiol or DHEA can be considered a safe option to be offered to patients to improve their quality of life [54,57].

Novel emerging approaches, including SERMs, TSECs, estriol, and neurokinin B-inhibitors, showed promising activity in managing GSM symptoms with a hypothetical neutral activity on BC. Further investigations in women affected by BC are required to assess the safety and efficacy of these compounds [66].

Another emerging therapy for the treatment of VVA is the vaginal laser. The first studies were performed using a CO_2 fractional laser approved by the Food and Drug Administration (FDA) as a therapy for GSM [67]. The mechanism of action of the laser consists in stimulating progressive neo-collagenases and fibroblast activation with the production of new trabecular-type collagen. The active fibroblasts in the lamina propria also determine an increase in elastin. The use of reverse transcriptase with PCR allowed to demonstrate of a significant increase of pro-collagen mRNA and interleukin-b and TGF-b1, with epithelial reactivation and cellular differentiation [68].

Subsequently, the Erbium laser was introduced, which is better at promoting vascularization of the vaginal mucosa due to a direct correlation between energy density and penetration depth. In fact, Erbium has a non-ablative photothermal effect with less discomfort and less blood loss capable of improving the local accumulation of glycogen and promoting the restoration of an adequate local pH [69]. Another type of laser that finds application in the treatment of vulvovaginal atrophy is the CO_2 laser. The CO_2 laser, unlike the Erbium laser, is able to act on the more superficial collagen, improving the vascularization of the tissues in order to obtain better integrity and elasticity of the tissues. Additionally, CO_2 lasers have been shown to improve stress urinary incontinence and vaginal prolapse, as well as vaginal dryness and dyspareunia. A recent meta-analysis by Salvatore et al. conducted in 2022 analyzed the CO_2 laser therapy efficacy for the treatment of GSM, no matter whether the patients were postmenopausal or BCS. They demonstrated that in all scores (FSFI, WHIS, and VMV scores), laser CO_2 therapy has led to a significant reduction in VVA and/or GSM symptoms. Its application showed a beneficial safety profile, and no major adverse events were reported [70].

However, the available data are short-term, and the efficacy, as well as the safety of repeated applications, are unclear. Furthermore, CO_2 laser treatment is very expensive and a procedure that is not yet widely performed by gynecologists; therefore, access to this method may be limited [71].

In 2018, Becorpi et al., in a prospective study, analyzed a sample of 20 patients for one month, treating them with CO_2 laser. They demonstrated that the laser caused changes both at a biomolecular and morphological level in the tissues by activating anti-inflammatory mechanisms [72]. Subsequently, two more prospective studies were conducted, the first by Quick et al. in 2022 and the second and most recent by Mension et al. in 2023. Both studies demonstrated that CO_2 laser is safe and effective, respectively, after 6 months and 2 years of follow-up in patients with previous BC [73,74]. Squilini's group retrospectively analyzed a cohort of 45 BCS patients, comparing them to 90 control group patients for one year. They found that fractional CO_2 vaginal laser led to a long-term improvement in GSM symptoms, even in BCS [75].

The only RCT in the literature that analyzes laser therapy in patients with GSM is the one conducted in 2021 by Gold and Collab. These were analyzed for 3 months on a group of 43 patients treated with Erbium laser or local hyaluronic acid. Both treatments were effective for patients with previous breast cancer [76]. Even if the effectiveness of vaginal lasers using both CO_2 and Erbium is confirmed in most studies, there are no studies that demonstrate their real long-term effectiveness. We have summarized the various laser therapies in Table 2.

Table 2. Laser therapy.

Study	Year	Study Design	Follow Up	Median Age	n.	Participants	Intervention	Primary Outcome	Hormonal BC Therapy	Receptor Status (ER +)	Results	Conclusions
Mension et al. JAMA Network	2023	Prospective double-blind sham-controlled Randomized Clinical Trial	6 months	52.6 years old	72	BC patients on adjuvant AI therapy	5 monthly sessions of fractional CO_2 laser therapy (CLT) or sham laser therapy (SLT).	FSFI, VHI, Objective improvement	-	-	Both groups showed improvement in FSFI, but there was no significant difference in subjective and objective outcomes between CLT and SLT groups. Tolerance to treatment was significantly lower in the CLT group than in the SLT group.	Vaginal laser treatment was found to be safe and effective after 6 months of follow-up.
Quick et al. J of Clin Med	2022	Prospective study	2 years	59.3 years old	33	Patients with diagnosed BC on adjuvant therapy (AI or trastuzumab)	3 sessions of micro ablative CO_2 laser 30–45 days apart	Long-term efficacy: VAS, FSFI, UDI	AI or trastuzumab	-	No statistically significant difference in VAS score, FSFI, and UDI score between 4 weeks follow-up and 2 years follow-up.	Breast cancer survivors treated with fractional CO_2 laser therapy have sustained improvement in sexual function two years after treatment completion, suggesting potential long-term benefits.

Table 2. *Cont.*

Study	Year	Study Design	Follow Up	Median Age	n.	Participants	Intervention	Primary Outcome	Hormonal BC Therapy	Receptor Status (ER +)	Results	Conclusions
Gold et al. Maturitas	2021	Randomized controlled trial	3 months	54 years old	43	Patients with diagnosed BC	2 sessions of Erbium YAG Laser therapy one month apart or vaginal hyaluronic acid, daily for 10 days then 3 times/ week for three months	VHIClinical and sexual improve-ment	-	-	VHI improved significantly in both groups (p = 0.001) with no differences between treatment groups (p = 0.232). Clinical and sexual improvements in both groups without differences.	Both vaginal hyaluronic acid and Ervium Yag Laser are effective to treat GSM in BCS.
Squillini et al. The Breast J	2021	Retrospective study	12 months	59.5 years old	45 BC patients 90 controls	Patients with diagnosed BC	3 sessions of fractional micro ablative CO_2 laser every 30 days	VHI, VVHI, dyspareunia, and vaginal dryness	Previous endocrine therapy 51.4% Current endocrine therapy 48.6%		BCS are most likely to present severe GSM symptoms compared with the comparison group. VHI and VVHI were improved in both groups.	Fractional CO_2 vaginal laser leads to a long-term improvement in GSM symptoms, even in BCS.
Angioli et al. Intern J of Gynecol Cancer	2020	Retrospective multicentric study	3 months	53 years old	165	Patients with diagnosed Breast, Ovary, Uterus, or Cervical Cancer	3 sessions of fractional micro ablative CO_2 laser 30 days apart	Objective and subjective im-provement	-		Dryness improved by 66%, dyspareunia improved by 59%, burning improved by 66%, pain at the introitus improved by 54%, and itching improved by 54%.	An effective strategy in the management of the symptoms of genitourinary syndrome in post-menopausal women and survivors of gynecological cancer.
Areas et al. Menopause	2019	Open, prospective study	4 months	53.7 years old	24	Patients with diagnosed BC	3 sessions of Vaginal Erbium YAG Laser every 30 days.	Clinical and Sexual im-provement: VAS scale—Objective VHI.	-	-	Improvement in clinical and sexual scores. Last follow-up vs. Basal VHI: significant reduction ($p < 0.001$).	The treatment seems to improve sexual function and vaginal atrophy.

Table 2. *Cont.*

Study	Year	Study Design	Follow Up	Median Age	n.	Participants	Intervention	Primary Outcome	Hormonal BC Therapy	Receptor Status (ER +)	Results	Conclusions
Pearson et al. Breast Cancer Research and Treatment	2019	Single-arm pilot study Before-After Study	12 weeks	56 years old	26	Patients with diagnosed BC	3 sessions of Fractional Microablative CO_2 Laser every 30 days.	Clinical and Sexual improvement: VAS scale and FSFI	96% Hormonal Therapy	-	Improvement in VAS after 3 sessions ($p < 0.001$). Improvement in FSFI after 3 sessions ($p < 0.01$).	The treatment seems to improve sexual function and vaginal atrophy.
Quick et al. Supportive Care in Cancer	2019	Single-arm feasibility study	1 month	57.4 years old	64	Patients with diagnosed BC on adjuvant therapy	3 sessions of micro ablative CO_2 laser 30–45 days apart	Feasibility, adverse events	AI 68%	63% ER/PR+/Her2-	No women presented serious adverse events. VAS, FSFI, and UDI improved to follow-up.	Fractional CO_2 laser treatment for breast cancer survivors is feasible and appears to reduce GSM symptoms across treatment and follow-up.
Becorpi et al. Lasers in Medical Science	2018	Prospective study	1 month	58.2 years old	20	Patients with diagnosed BC	2 sessions of fractional CO_2 laser	Objective and subjective improvement, Microbiome analysis, Vaginal cytokine analysis	-	-	Statistically significant improvement for VHI, FSFI. Higher levels of IL-18, CTACK LIF, M-CSF, and IL-17. The Shannon diversity index H and equitability comparison before and after treatment did not yield any statistically significant results.	Efficacy of laser on GSM in BCS due to the biochemical and morphological changes of the epithelial vaginal cells which are associated with the expression of specific cytokines involved, in the anti-inflammatory process. Maintenance of a positive local balance is able to favor the colonization of commensal microorganisms.
Pagano et al. Menopause	2018	Observational retrospective study	3 months	44 years old	82	Patients with diagnosed BC	3 sessions of Fractional Microablative CO_2 Laser every 30 days.	Clinical improvement: VAS scale	74% Hormonal adjuvant treatment; 61% AI; 39% TMX	-	Improvement in VAS after 3 sessions ($p < 0.001$).	The treatment seems to be effective.

Table 2. *Cont.*

Study	Year	Study Design	Follow Up	Median Age	n.	Participants	Intervention	Primary Outcome	Hormonal BC Therapy	Receptor Status (ER +)	Results	Conclusions
Mothes et al. Journal of Cancer Research and Clinical Oncology	2018	Retrospective study	6 weeks	71 years old	16	Patients with diagnosed BC and surgery for pelvic organ prolapse	1 session of Vaginal Erbium YAG Laser.	Clinical improvement: VAS scale	-	-	Last follow-up vs. Basal VHI: significant reduction ($p = 0.01$).	The treatment seems to be effective.
Gambacciani et al. Menopause	2017	Pilot study Before-After study		50.8 years old	43	Patients with diagnosed BC	3 sessions of Vaginal Erbium Laser every 30 days.	Clinical improvement: VAS scale—Objective VHI.	-	-	Last follow-up vs. Basal VAS: significative reduction ($p < 0.01$). Last follow-up vs. Basal VHI: significative reduction ($p < 0.01$).	The treatment seems to be effective.
Pagano et al. Menopause	2016	Observational retrospective study	3 months	42 years old	26	BC patients on adjuvant TMX or AI therapy	3 sessions of Fractional Microablative CO_2 Laser every 30 days.	Clinical improvement: VAS scale—Objective VHI.	All	All	Significant improvement of clinical variables.	The treatment seems to be effective and with good tolerance.
Pieralli et al. Arch Gynecol Obstet	2016	Prospective Before-After study	11 months	53.3 years old	50	Patients with diagnosed BC	3 sessions of Fractional Microablative CO_2 Laser every 30 days.	Clinical improvement: VAS scale—Objective VHI.	4% AI; 40% TMX; 56% Not adjuvant therapy	-	Improvement in VAS after 3 sessions ($p < 0.0001$).	The treatment seems to be feasible and effective.

The last family of drugs that we are going to examine is selective estrogen receptor modulators (SERMs). It is a class of drugs that have activity on estrogen receptors, the most representative of which in the therapy of GSM in BCS are Tibolone, Bazedoxifene, and Ospemifene.

The LIBERATE (The Livial Intervention following Breast Cancer; Efficacy, Recurrence, and Tolerability Endpoints) study was designed to establish the safety of tibolone in women operated on for breast cancer suffering from severe menopause symptoms. The study, a double-blind, non-inferiority, multicenter RCT conducted on 3148 postmenopausal women (mean age 53 years) with a history of surgically treated breast cancers, compares therapy with tibolone (2.5 mg/day) versus placebo in terms of breast cancer recurrences. After a median follow-up of 3.1 years, a statistically significant increase in the incidence of tumor recurrence was observed in the tibolone group (237 cases vs. 165 in the placebo group; HR 1.4; CI 95% 1.1–1.7) [77].

In the literature, there are two RCTs that evaluated the activity of bazedoxifene combined with estrogens of animal origin. In the first study, healthy, postmenopausal, non-hysterectomized women (n = 652) with symptoms of moderate to severe vulvar/vaginal atrophy treated with a drug or placebo were considered. It was seen that the drug treatment had a decidedly positive efficacy in the treatment of vulvar atrophy and consequently also on the sexual hygiene of the patients, improving their quality of life. However, bazedoxifene alone, not combined with estrogen, has not been shown to improve symptoms [78].

The second study presented by Kagan et al. showed similar results in another RCT; however, neither study evaluated the safety of the drug in patients with previous breast cancer, so at present, there are no recommendations for the administration of this drug [79].

Ospemifene is a drug belonging to the class of SERMs that has the ability to act on various organs: an agonist action on the brain, vaginal epithelium, and bone; an anti-estrogenic activity on the breast; and it would appear to have no activity on the endometrium or the cardio-circulatory system.

The activity on the vaginal epithelium favors epithelial thickening, favoring its lubrication.

There are no clinical data demonstrating that ospemifene would increase the risk of BC; indeed, its anti-estrogenic activity in the breast could be protective against a possible recurrence. However, the follow-up periods of these studies were too short to conclude the long-term effects of ospemifene [80]. Barton et al. (2017) conducted a three-arm randomized controlled trial on patients with previous breast cancer or gynecological patients using DHEA gel at two different doses or a placebo. What they found is that daily use of the gel has the ability to improve vaginal dryness after 12 weeks of treatment but is unable to impact sexual function [63]. Subsequently, in a randomized double-blind study, Davis' group demonstrated that the administration of testosterone locally by ointment or cream is able to promote sexual function compared to a placebo in a group of BCS patients [66].

The latest randomized study in the literature of 2020 is the result of the activity of Hirschberg's group. This is a large multicenter prospective randomized double-blind placebo-controlled phase II study, which analyzed a group of 61 patients treated with local estrogens for 12 weeks. What was achieved was that there were no significant differences in FSH between groups ($p = 0.104$) with a slight increase in LH in the treatment group. No changes in E1 and E2 were observed in estrogen-treated patients, other than a slight transient increase in E3 within the first 3 weeks. It is therefore possible to state that administration of 0.005% estriol gel is safe in BCS receiving NSAI and provides clinical improvement of vaginal symptoms and signs of VVA [81]. The observational study proposed by Cold et al. included a nationwide cohort of postmenopausal women diagnosed between 1997 and 2004 with early-stage invasive estrogen receptor-positive nonmetastatic BC who received no treatment or 5 years of adjuvant endocrine therapy. We evaluated the mortality and risk of relapse associated with VET and MHT use versus no use using multivariable models adjusted for potential confounders. The study concluded that in postmenopausal women treated for early-stage estrogen receptor-positive BC, neither

VET nor MHT was associated with an increased risk of recurrence or mortality. A subgroup analysis revealed an increased risk of recurrence but not mortality in patients trained on adjuvant aromatase inhibition [52].

Below, in Table 3, all the local hormone treatments are listed.

In conclusion, we deem it appropriate to say a few words about patients with non-luminal BC. Patients with non-luminal BC (HER2-positive and triple-negative) are not candidates for adjuvant HT because there has long been a consensus that they are completely independent of the estrogen signaling pathway. Chemotherapy and anti-HER2 agents are the gold standards of treatment.

Even if they do not receive AI or tamoxifen, women with non-luminal BC may experience GSM as a consequence of chemo-induced ovarian failure or age-related menopause. At first glance, the use of estrogen compounds in this population could be considered absolutely safe; however, there is no conclusive evidence in the literature to support this hypothesis [82].

According to Kenemans et al. [83], there is no significant adverse effect of HRT in the subgroup analysis of patients with ER-negative BC exposed to HRT, whereas Holmberg et al. [48] showed an increased, but not statistically significant, risk of recurrence.

Preclinical evidence has also recently demonstrated that estrogen and progesterone can circumvent the absence of their respective traditional nuclear receptors in TNBC and play an active role in cancer progression [84]. Most of the evidence comes from retrospective cohorts or subgroup analyses of studies designed primarily for luminal BC. In conclusion, there is insufficient evidence to allow the use of systemic HRT for GSM in patients with TNBC. In our daily clinical practice, the treatment of symptoms in this subset of patients should be guided by the same guidelines approved for luminal BC, preferring non-hormonal or local therapy to systemic administration [85].

Table 3. Local hormonal treatments.

Study	Year	Study Design	Follow Up	Median Age	n.	Participants	Intervention	Primary Outcome	Hormonal BC Therapy	Receptor Status (ER +)	Results	Conclusions
Cold et al. J Natl Cancer Inst	2022	Observational Cohort Study	20 years	61 years old	1957 VET 133 MHT (+/− VET) 6371 never-user	BC patients on adjuvant AI or TAM or no therapy	"VET": "MHT": "never-user"	Recurrence Mortality	TAM, AI, both, or none	All	VET risk of recurrence was similar to never-users (HR 1⁄4 1.08, 95% CI 1⁄4 0.89 to 1.32). The use of VET in patients who received AI was associated with an elevated risk of recurrence (HR 1⁄4 1.39, 95% CI 1⁄4 1.04 to 1.85). The cumulative incidence of recurrence was 19.2% in never-users, 15.4% in VET users, and 17.1% in users of MHT. Never-users of VET or MHT had an absolute 10-year overall survival of 73.8% compared with 79.5% and 80.5% among the women who used VET or MHT, respectively.	VET or MHT is not associated with an increased risk of recurrence or mortality. In patients treated with VET and adjuvant AIs (but not TAM or no endocrine adjuvant therapy), increased risk of recurrence but not mortality. Overlapping overall survival in the three groups.
Streff et al. Supportive Care in Cancer	2021	Prospective trial	16 weeks	55 years old	8 treated 6 controls	BC patients on adjuvant AI therapy	"Estring": estradiol 2 mg ring placed vaginally over 90 days	Estradiol serum level; clinical improvement	AI (anastrozole, letrozole or exemestane)	All	Estradiol level was <10 pg/mL in all patients; the week-4-estradiol level was >10 pg/mL in 6 cases (75%) but decreased to <10 pg/mL by week 14.	No significant change in serum estradiol level in BCS treated with AI from baseline to week 16.

Table 3. *Cont.*

Study	Year	Study Design	Follow Up	Median Age	n.	Participants	Intervention	Primary Outcome	Hormonal BC Therapy	Receptor Status (ER +)	Results	Conclusions
Hirschberg et al. J North American Menopause Society	2020	Phase II prospective randomized double-blind placebo-controlled multicentric trial	12 weeks	59 years old	61	BC patients on adjuvant AI therapy	Estriol gel 50 mg daily for 3 weeks and twice weekly for 6 weeks vs. placebo	FSH, LH, estrogens serum levels; clinical improvement	AI (anastrozole or letrozole) + evtl TAM + evtl LHRH agonist	All	No significant differences in FSH between groups ($p = 0.104$); a slight rise of LH in the treatment group; no change in E1 and E2; slight E3 rise transiently within the first 3 weeks; clinical improvement. A significant difference in favor of the TST group.	0.005% estriol gel preparation is safe in BCS receiving NSAI and provides a clinical improvement in vaginal symptoms and signs of VVA.
Davis et al. J Clin Endocrinol Metab	2018	Double-blind randomized placebo-controlled trial	26 weeks	56.4 years old	44	BC patients on adjuvant AI therapy	TST cream for 26 weeks 300 ng vs. placebo	FSFI	AI		A significant difference in favor of the TST group.	TST improves sexual function compared to placebo.
Barton et al. Support Care Cancer	2017	Three-arm randomized controlled trial	12 weeks	57.4 years old	353	BC or gynecological patients on adjuvant TAM or AI therapy	DHEA gel 3.25 mg vs. DHEA gel 6.5 mg vs. Placebo, administred daily	FSFI	AI or TAM		Overall clinical improvement in all arms but not significantly different between arms. Women in the DHEA arms reported significant improvement in the sexual health measure. DHEA 6.5 mg, improved symptoms more quickly, with a significant difference at 8 weeks.	Daily use of a vaginal moisturizer has the ability to improve vaginal symptoms over 12 weeks but may not sufficiently positively impact overall sexual function.

Table 3. *Cont.*

Study	Year	Study Design	Follow Up	Median Age	n.	Participants	Intervention	Primary Outcome	Hormonal BC Therapy	Receptor Status (ER +)	Results	Conclusions
Melisko et al. JAMA Oncology	2016	Randomized non-comparative study	12 weeks	56 years old	76	BC patients on adjuvant AI therapy	"Estring" Estradiol ring 7.5 ng vs. TST cream at 1% 1.5 mg/week	E2 serum levels; VHI	AI	All	Transient E2 rise in the estradiol group and 12% in the TST group. Persistent E2 rise of 0% in the estradiol group and 12% in the TST group. Sexual improvement in both groups.	Transient increase in E2 with "Estring". Meets the primary safety endpoint.
Dahir et al. Sexual Medicine	2014	Pilot Study	8 weeks	59.7 years old	13	BC patients on adjuvant AI therapy	TST cream for 28 days 300 ng	FSFI	AI (anastrozole, letrozole or exemestane)	92% ER+ 84% PR+	Clinical improvement.	Improvement in FSFI scores.
Donders et al. Breast Cancer Res Treat	2014	Open-label bicentric phase I pharmacokinetic study	12 weeks	57 years old	16	BC patients on adjuvant AI therapy	Estriol 0.03 mg + Lactobacillus	E2 (estradiol), E1(estrone), E3(estriol) serum levels; clinical improvement	AI	All	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.
Wills et al. Journal of Oncology practice	2012	Prospective clinical study	12 weeks	60 years old (BCS) 68 years old (Controls)	24 therapy 24 controls	BC patients on adjuvant AI therapy or SERM	(14 p) Vaginal Estradiol tablet 25 mcg daily for 14 days, then twice a week (10 p) "Estring" Estradiol ring	E2 serum levels	AI or SERM	All	E2 was significantly greater in the VET group. Mean E2 levels of controls: 3.72 pmol/L Mean E2 levels 12 h post tablet insertion: 76 pmol/L (significantly higher than controls $p < 0.001$). Mean E2 levels 60 days post ring insertion: 15 pmol/L ($p < 0.014$).	VET increases E2 levels. Should be used with caution.
Le Ray et al. Breast Cancer Res Treat	2012	Retrospective cohort study	3.5 years	63.7 years old	13.479	917 BC recurrence patients 8885 Controls	Vaginal estrogen cream and tablets	Recurrence	TAM or AI	All	Recurrence RR 0.78 (95% CI: 0.48–1.25).	VET is not associated with an increase in BC recurrence in patients treated with TAM or AI.

Table 3. *Cont.*

Study	Year	Study Design	Follow Up	Median Age	n.	Participants	Intervention	Primary Outcome	Hormonal BC Therapy	Receptor Status (ER +)	Results	Conclusions
Whiterby et al. The Oncologist	2011	Phase I/II pilot study	8 weeks	56 years old	21	BC patients on adjuvant AI therapy	TST cream for 28 days 300/150 ng	E2 and TST levels; clinical improvement	AI	-	E2 levels remained suppressed. Clinical improvement.	Clinical efficacy and tolerance.
Pfeiler et al. Climateric	2011	Prospective before-after analysis	4 weeks	65 years old	6	BC patients on adjuvant AI therapy	"Ovestim" 0.5 mg vaginal estriol daily for 2 weeks	Clinical improvement, serum estradiol level	Anastrozole	All	Clinical improvement in 83%, with no increased serum estradiol levels at 2 weeks.	VET improves clinical VVA and appears to be safe.
Biglia et al. Gynecological Endocrinology	2010	Prospective study	12 weeks	54 years old (VET) 46 years old (Replens)	31	BCS in menopause: 18 receiving VET 8 receiving moisturizers	Estriol 0.25 mg Estradiol 12.5 ng 2.5 g Replens	Clinical Improvement, Objective vaginal mucosa evaluation Estradiol, FSH, and LH serum levels	TAM and GnRH	72% Estriol 87% Estradiol	Improved symptoms in both VET groups ($p = 0.02$, $p = 0.01$) No change in estradiol, increased FSH and LH.	VET is effective in improving symptoms and objective evaluation. An increase in FSH and LH may indicate a systemic estradiol effect.
Kendall et al. Annals of Oncology	2005	Prospective before-after analysis	12 weeks	52 years old	7	BC patients on adjuvant AI therapy	"Vagifem": Estradiol 25 mg daily for 2 weeks	Estradiol serum levels	AI (anastrozole, letrozole or exemestane)	-	2 weeks: 83% estradiol rise 10 weeks: 66% estradiol rise.	Serum estradiol levels increased short term.
Dew et al. Climateric	2003	Retrospective Cohort Study	5.5 years	53.8 years old	69	69 BC patients with VVA 1403 BC patients without VVA	Estriol 0.5 mg cream and pessaries (n = 33) Estradiol 25 mcg tablets (n = 33)	Disease-free Interval Recurrence	48% TAM	Positive in 12/33 (36%)	DFI HR = 0.57 (95% CI: 0.29–1.58, $p = 0.28$). 6 (9%) vs. 330 (22.4%).	VET does not seem to be associated with increased RR of BC.

4. Conclusions

In BCS patients, vaginal atrophy is one of the main causes of reduced quality of life, both for individuals and couples. Patients with mild atrophy can be treated with therapy based on non-hormonal substances; however, these medicines need a long time to act and are relatively effective. In patients' refractory to non-hormonal therapy, local, low-dose estrogen administration has been shown to be the most effective treatment. Although there is strong skepticism about the use of hormone therapy in patients with previous breast cancer, this seems to be the most effective therapy to date in restoring adequate vaginal tropism. Some studies suggest a possible increase in serum estrogen levels, which may lead to an increased risk of BC recurrence. In the new guidelines, further new therapeutic strategies with mechanical and non-pharmacological action are considered, such as the vaginal laser. However, more studies are needed to evaluate. More studies are needed to evaluate the effectiveness of these new therapies.

Author Contributions: Conceptualization, L.M., C.D.R. and M.G.P. (Maria Grazia Piccioni); methodology, G.D.; formal analysis, M.F.V. and A.V.; investigation, V.M.; writing—original draft preparation, G.D.; writing—review and editing, M.G.P. (Maria Grazia Porpora) and Policlinico Umberto I Group; visualization, M.G.P. (Maria Grazia Piccioni); supervision, R.S., M.G.P. (Maria Grazia Piccioni) and M.G.P. (Maria Grazia Porpora). All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not Applicable.

Informed Consent Statement: Not Applicable.

Data Availability Statement: Data sharing is not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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DOI: https://doi.org/10.5114/pm.2018.81743

Menopause Rev 2018; 17(4): 180-184

REVIEW PAPER

Genitourinary syndrome of menopause treatment using lasers and temperature-controlled radiofrequency

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Abstract

Perimenopausal changes caused by oestrogen deficiency are accompanied by a decrease in the content of collagen and elastin in the tissues, leading to thinning of the epithelium and the resultant disappearance of the superficial layer, which leads to smooth muscle dysfunction as well as connective tissue degradation. This aetiopathogenetic chain results in a set of symptoms experienced by approximately 50% of women in the peri- and postmenopausal period. Symptoms of dryness, burning, dyspareunia and urgency contribute to a significant reduction in the quality of sexual function and general comfort of life due to recurrent infections of the vagina, vulva and urinary tract. Different therapeutic methods may benefit genitourinary syndrome of menopause (GSM), while innovative methods such as lasers or radiofrequency deserve further study in this area.

Key words: genitourinary syndrome of menopause, vulvovaginal atrophy, sexual health, lasers, radiofrequency.

Introduction

Genitourinary syndrome of menopause (GSM) is a new term, which is used to describe a variety of menopausal symptoms and signs that are related to physical changes of the vulva, vagina, and lower urinary tract. Until 2014 terms such as *vulvovaginal atrophy* and *atrophic vaginitis* were widely used, but were considered to be insufficient for the constellation of symptoms and signs associated with genitourinary changes after menopause. In early 2014 the Board of Directors of the International Society for the Study of Women's Sexual Health (ISSWSH) and the Board of the North American Menopause Society (NAMS) formally adopted the term "genitourinary syndrome of menopause".

GSM is characterised by a set of symptoms and signs connected with oestrogen insufficiency involving changes in the labia, introitus, clitoris, vagina, urethra and bladder [1]. Approximately 50% of menopausal women manifest signs and symptoms of GSM [2].

As a result of postmenopausal oestrogen deficiency the following, anatomic and histological changes are noted in female genital tissues:

1) symptoms of GSM:
- vaginal dryness, irritation and dryness,
- burning sensation,
- dyspareunia,
- feeling of pressure,
- yellow malodorous discharge,
- pressure, tenderness,
- urinary frequency,
- incontinence,
- urgency,
- urinary tract infections (UTIs),
- difficulty in sexual arousal,
- inadequate lubrication during arousal,
- vaginal bleeding from fragile atrophic skin,
- dryness of labia;

2) physical signs of genitourinary syndrome of menopause:
- pale, smooth or shiny vaginal epithelium,
- loss of elasticity or turgor of skin,
- sparseness of pubic hair,
- fusion of labia minora,
- introital stenosis,
- pelvic organ prolapse,
- vulvar dermatoses,
- pH changes,
- loss of labial and vulvar fullness.

Many women are seriously affected by these symptoms, which cause physical and psychological discomfort, poor quality of sexual life or even avoidance of intimacy.

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Submitted: 20.12.2018
Accepted: 27.12.2018

Vulvovaginal atrophy (VVA) is a component of GSM [3]. VVA is very common; it affects up to 84% of menopausal women, according to some studies [4]. In a cross-sectional, population-based study of American women in the age range 40 to 65 years, symptoms corresponding to VVA occurred in 57% of sexually active women [5]. In a study of 913 post-menopausal women, who visited a gynaecologist for a routine examination, GSM was diagnosed in 65% of women just one year after menopause and in 85% women six years after menopause [6]. The most common symptoms reported by these women included vaginal dryness (100%), dyspareunia (78%), burning (57%), itching (57%) and dysuria (32%) [7].

Treatment of genitourinary syndrome of menopause

Given that GSM may have a significant impact on a women's lives, gynaecologists need to talk to their patients and help relieve their symptoms. All menopausal women should be screened for GSM. There are various methods listed below by which it is possible to improve the quality of life in menopausal patients:

- non-pharmacologic therapies – sexual counselling, dilatators, stress reduction therapy;
- non-hormonal OTC products – vaginal lubricants or moisturizers, herbal products,
- prescription products – oral oestrogens, transdermal oestrogens, intravaginal oestrogens, vaginal creams, vaginal tablets, vaginal rings, tibolone.

In this article, the authors will focus on CO_2 lasers, YAG lasers, and a transcutaneous temperature-controlled radiofrequency device.

Lasers

Albert Einstein in 1917 discovered that under certain conditions, atoms could absorb light and be stimulated to shed their energy, although it was not until 1959 that the name LASER (light amplification by stimulated emission of radiation) was introduced by Gordon Gould into the literature [8].

The Food and Drug Administration (FDA) has approved laser therapy for several medical indications (e.g. dental procedures, ophthalmology, including refractive eye surgery, tumour and cataract removal, and cosmetic surgery). In 2014, the FDA approved the use of fractional microablative CO_2 laser therapy for genitourinary surgery, but not for the treatment of GSM.

In relation to GSM therapy, the micro-ablative fractional CO_2 laser, or the non-ablative vaginal erbium YAG laser (VEL), can be considered as a therapeutic option that enables women to avoid hormonal interventions. Also other non-ablative electromagnetic energy, radiofrequency (e.g. low-energy dynamic quadripolar radiofrequency – DQRF) could be considered for this particular indication [9].

Laser therapy improves the vascularization of the vaginal mucosa, stimulates the synthesis of new collagen, extracellular matrix ground substances in the vaginal connective tissue, thickens the vaginal epithelium with the formation of new papillae, replenishes glycogen in the vaginal epithelium, and restores the balance in the mucosa, which reduces the symptoms of vulvovaginal atrophy. Available data suggest that inducing morphologic changes in vaginal tissue with laser and DQRF intervention can relieve the symptoms of vaginal dryness and dyspareunia accompanying GSM [10-12].

CO_2 laser, or VEL treatment, usually consists of a series of 3-4 treatments, 4-6 weeks apart, taking about 1-2 min per session, as an in-office procedure.

Various measurements are used for evaluating the effectiveness of laser GSM treatment:

- Visual Analogue Scale – VAS 0-10,
- Female Sexual Function Index (FSFI), which measures sexual function evaluating 6 domains (desire, arousal, lubrication, orgasm, satisfaction and pain), and provides a total score; higher scores define better sexual function. Vaginal Health Index Score (VHIS): elasticity, fluid volume, pH and epithelial integrity. The sum of the 5 components can provide an upper score of 25 and a lower of 5. A score of ≤ 15 defines the presence of vaginal atrophy,
- a cytological evaluation: calculation of the vaginal maturation value (VMV): $\leq$ 40% defined atrophy on the vaginal smears.

According to Athanasioua *et al.*, who examined 55 postmenopausal women with GSM symptoms, CO_2 laser therapy may enable complete regression of dyspareunia, dryness and reestablishment of normal sexual function after 3 laser sessions. The improvement of vaginal health was reflected by the subjective measurements of VAS and FSFI. The VMV increased following each subsequent therapy, resulting in 80-100% of participants surpassing the thresholds of non-atrophic clinical findings. The study identified several limitations in its design [13].

Among recent publications, a short-term Brazilian clinical trial of the CO_2 laser, compared with 1 mg oestriol cream, in a cohort of 45 women, suggests general efficacy of laser alone or in combination with oestriol after 20 weeks. Although patients experienced alleviation in symptoms in every oestriol treatment group, a significant increase in dyspareunia was noted only in the laser group [11]. In one of the pioneering studies, Salvatore *et al.*, using the same laser system and parameters as used in this study, showed significant improvement in pain and other symptoms by the 12th week [10].

Laser application in postmenopausal breast cancer survivors may be a reasonable alternative, given that

hormonal topical therapy is contraindicated. Pagano *et al*. published a retrospective series of case studies of 82 survivors of breast cancer, who failed to have adequate relief of their GSM symptoms with non-estrogenic local treatments. These women were treated with 3 cycles of CO_2 laser and demonstrated significant improvements in genital sensitivity during intercourse, vaginal dryness, decreased itching or stinging, dyspareunia, dysuria, bleeding, and movement-related pain [14].

Laser therapies lack adequate RCTs and long-term safety. Efficacy data may be considered in women who prefer non-hormonal treatments after a discussion of potential risks, benefits, and need for ongoing treatments, and costs. NAMS recommendations for management of GSM in specific patient populations: women at high risk for breast cancer, women with oestrogen-receptor positive breast cancers, women with triple-negative breast cancers, and women with metastatic disease – choose lasers as a first line therapy [15].

It is necessary to acknowledge that laser therapy for GSM is not FDA-approved at this time. The American College of Obstetricians and Gynecologists in its most recent position statement on laser therapy, dated May 2016, emphasizes the importance of accurately informing patients of a treatment's FDA status. The statement emphasizes that procedures which use lasers and other energy-based devices, such as radiofrequency, when applied to destroy or reshape vaginal tissue "may have serious risks and don't have adequate evidence to support their use for these purposes" according to the FDA Commissioner, Scott Gottlieb. It also should be stressed that the FDA has cleared laser and energy-based devices for destroying abnormal or precancerous cervical or vaginal tissue, as well as condylomas (genital warts) and other serious conditions [16].

The reason for the FDA statement is a lack of larger studies demonstrating long-term safety and efficacy, as well as an analysis of cost-effectiveness in laser GSM therapy. Despite the publication of the first RCT, it is evident that RCTs in vaginal laser treatment for GSM with a true placebo arm are urgently needed [17].

Buttini *et al.* focus in their publication on laser GSM therapy side effects. Clinicians should remain aware of the fact that vaginal laser therapy, as administered in this trial, can also worsen pain, and therefore topical vaginal oestrogen therapy remains the gold standard [17].

According to the FDA, vaginal burns, scarring, pain during sexual intercourse, and recurring or chronic pain can affect women undergoing a laser procedure in GSM therapy. In July 2018, the FDA released a press statement in an effort to safeguard women's health from deceptive health claims and significant risks related to devices being marketed for use in medical procedures for "vaginal rejuvenation" [18].

Slight spotting, scarring and discomfort during the procedure may be related to an atrophic, narrow vestibule and vagina, and the discomfort seems to be transitional. The issue of persistent vulvar pain and dyspareunia cannot be ignored. Unfortunately, GSM symptoms are similar to vulvodynia (dryness, dyspareunia, soreness, dysuria) [19].

On the basis of carefully taken history, if GSM-like symptoms appear before menopause, the clinician can suspect a pre-existing condition. Vulvodynia, in most cases, is caused by pelvic floor muscle dysfunction/hypertonic state. The laser intravaginal shockwave may aggravate muscle spasms and increase side effects, so the procedure is contraindicated in such patients. All of these potential risks require further confirmation, to reduce side effects and promote safe use of the procedure.

Vulvodynia could be suspected in every GSM patient when topical oestrogen is not effective. According to NAMS recommendations, non-hormonal treatment is the first choice, especially when oestrogens are contraindicated (e.g. breast cancer survivals). Moisturizers and lubricants, pelvic floor physical therapy (e.g. manual therapy, biofeedback) dedicated also for vulvodynia patients, and dilator therapy are first-line treatments for GSM symptoms [15, 20].

Radiofrequency

There are different types of radiofrequencies; the most popular is transcutaneous temperature-controlled radiofrequency (TTCRF).

In gynaecology monopolar radiofrequency is commonly used – in this configuration there are two electrodes. One of them, a passive (grounding) electrode, is in contact with the patient's body and the second emits radio frequency radiation that reaches through the body to the passive electrode. Depth and the heating area in this method are larger than in others (bipolar, multipolar). In 2010, Millheiser and colleagues demonstrated the efficacy of monopolar radiofrequency on vaginal laxity after childbirth. This study found that radiofrequency safely improved laxity and sexual function up to 6 months after treatment [21]. This is one of the first articles published about radiofrequency; it was published in 2010. Currently there are a number of new reports on the effectiveness of this method.

TTCRF is safe, tolerable and effective for vulvovaginal rejuvenation. Evidence suggests applications in the treatment of atrophic vaginitis, orgasmic dysfunction, and stress incontinence [22]. Recently, a vaginal probe (ThermiVa) was developed for treatment of vulvovaginal tissues using this technology. TTCRF brings numerous benefits for the treatment of vagina laxity and GSM symptoms. The aim of treatment is to heat vaginal/vulvar epithelium to approximately 40-45°C for a defined treatment time, with each zone being treated for 3-5 minutes, for a total time of 25-30 minutes per treatment session [23]. These sessions may be repeated at

4-6 week intervals [24]. Ultrasound gel is needed during the treatment process. The effect of TTCRF on vaginal epithelium is that it restores most vaginal functions such as secretion, absorption, elasticity, lubrication, and vaginal epithelium thickness.

Mechanism of rejuvenation

The heat generated in the skin under the influence of radio waves, depending on the time and power, shortens and densifies collagen or its partial denaturation. With age, there are fewer collagen fibres in the dermis. These fibres stretch and their structure becomes disordered. Heating the skin results in the re-tensioning of collagen fibres and stimulation of fibroblasts to create new collagen and elastin. The generation of heat in the tissues further extends the blood vessels, which improves the nutrition and oxygenation of skin, as well as its metabolism. As a result, the skin and mucosa become firmer.

In a prospective nonrandomized trial by Monigue *et al.*, 10 female patients with mild-to-moderate vulvovaginal laxity (VVL), with or without atrophic vaginitis (AV), orgasmic dysfunction (OD) and/or stress urinary incontinence (SUI), underwent 3 courses of TTCRF at 4-week intervals. Assessment was performed at baseline and days 10, 30, 60 and 120. One patient was discontinued from the study because of noncompliance with the study protocol.

Radiofrequency energy was applied to the vagina and the labia majora and minora using a special probe. The electrode tip was passed back and forth slowly with wide movements over each treated area for 3 to 5 minutes, for a total treatment time of 30 minutes. The temperature setting was 42°C to 45°C depending on patient tolerance. Overall satisfaction at the final visit (day 120) showed that 77.8% of patients (7 of 9) were "satisfied" or "very satisfied", and 77.8% indicated that they would recommend the procedure to friends and family. A total of 42.9% (3 of 7) reported at least 50% improvement in symptoms of OD and 55.6% (5 of 9) had at least 50% improvement in SUI, while 57.1% (4 of 7) reported a 51-75% improvement in AV. By the last visit at day 120, all patients reported significant satisfaction with their overall sexual life [25].

Alinsod performed a very similar study with 23 patients participating in a prospective study (age range 26-58 years, mean 43.6, and median vaginal births was 2) [22]. All patients reported mild to moderate primary or secondary vulvovaginal laxity. All of them also had associated secondary conditions (orgasmic dysfunction, stress incontinence, or atrophic vaginitis). All patients were treated using TTCRF. The clinical endpoint was achievement of the target temperature range of 40°C to 45°C for approximately 3-5 minutes per zone (or longer, depending on heat tolerance). Total treatment time was less than 30 minutes. A complete course of therapy consisted of three treatments with the TTCRF device, at an interval of approximately 4-6 weeks. Patients were offered up to three treatments. Outcome measures for this study included: subject assessment via the Vaginal Laxity Questionnaire (VLQ), rating on a 7-point scale (where 1 = very loose and 7 = very tight), and the Sexual Satisfaction Questionnaire (SSQ) rating on a six-point scale (where 1 = none and 6 = excellent), as well as noting of associated conditions such as incontinence, atrophic vaginitis, and orgasmic dysfunction. The results showed a median improvement of 5 points on the VLQ scale and 2.5 points on the SSQ scale, with a statistically significant improvement ($p < 0.05$) [22].

Conclusions

GSM is a very common problem among post-menopausal women which severely impacts quality of life. Patients may be reluctant to talk about vaginal dryness, and the specialist may need to initiate a discussion to reduce discomfort. Treatment has to be individualised. The presence or absence of systemic symptoms and comorbidities has to be considered when choosing the best therapy for a patient. Local oestrogen therapy and vaginal moisturizers are highly effective, but there is also laser or radiofrequency therapy, which may be successful. Intra-vaginal, non-ablative, energy-based devices seem to be a promising alternative for the treatment of mild to moderate symptoms related to GSM.

Disclosure

The authors report no conflict of interest.

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New concept for treating female stress urinary incontinence with radiofrequency

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INTRODUCTION

The prevalence of stress urinary incontinence (SUI) in the adult female population varies widely, ranging from 4% to 35% (1, 2). SUI has a high impact on the health condition of patients, with personal and social consequences and high negative impact on psychological and relational well-being (3, 4). This justifies a continuous search for a therapy.

The first line of treatment is pelvic floor muscle training. Medication, or even surgery, could also be recommended. The success rate of therapeutic treatment varies from 25 to 90%, depending on severity, cause and timing of reassessment (5).

Theetiology of SUI is multifactorial, and SUI may be caused by inadequate support of the pelvic organs and anterior vaginal wall suspension and/or a possible change in the intrinsic urethral closure mechanism itself (6, 7). In addition to that, histological studies observed a reduction of collagen in urethra walls in case of loss of urethral support and/or sphincter dysfunction (8), making therapy with radiofrequency an option.

A current treatment proposal is the use of radiofrequency, which is a diathermic process generated by the radiation of an electromagnetic spectrum, resulting in an immediate retraction of existing collagen and subsequent activation of fibroblasts causing neocollagenesis (9). In studies using radiofrequency to treat SUI, a therapeutic response of 50% was shown (10). Elser et al., used the probe by inserting it in the intra urethral or intravaginal region. Although this technique is minimally invasive, it presented a rate of adverse or side effect of 0.9% to 9.5%, and the need for antibiotic prophylaxis, oral sedation, local anesthesia, while increasing the risk of urinary tract infections and its costs (11, 12).

Female urethra is known for having a maximum length of five centimeters, and its anatomical structure and length justifies the use of radiofrequency on the external urethral meatus. Radiofrequency waves can reach a sufficient depth to induce collagen production in the whole urethra. The hypothesis of this innovative study is that radiofrequency treatment on the urethral meatus reduces urinary loss, in a safe manner and with low risk. Our main objective is to evaluate the clinical response and adverse effects of radiofrequency on the urethral meatus in the treatment of stress urinary incontinence in women.

MATERIALS AND METHODS

These are results of a phase one study, approved by the Ethics Committee and Research of the Bahia School of Medicine and Health Public (CAAE: 20333213.1.0000.5544). Conformed to the standards set by the Declaration of Helsinki. It was registered at ClinicalTrials.gov (NTR: 02623842). All participants provided written informed consent.

The age of the women involved varied from 43 to 66 years, with an average of 53.1±7.1 years. Eligible women were at least 18 years of age, with SUI as the main clinical complaint, without any urgency symptoms (clinical complaint plus voiding diary per three days), and urinary loss of more than 1g in a one hour Pad Test. Patients with organ prolapses, neurological chronic degenerative diseases, residual voiding, pacemakers, copper intrauterine devices, or those who underwent other treatment for SUI (medical, surgical or physical therapy) as well as pregnant women, were excluded.

Evaluation of patients

Initially an anamnesis questionnaire was carried out to assess the presence of comorbidities, associated urinary symptoms and fecal urinary symptoms. After the questionnaire was done, physical examination took place to assess the function of the muscles of the pelvic floor. The examination comprised digital palpation quantified by the modified Oxford scale (13).

Device and procedure description

The non-ablative radio frequency device Spectra G2 - Tonederm®, has been adjusted for use on the urethral meatus. The device consists of an electromagnetic wave generator - high frequency wave, 0.5MHz - which is connected to a monopolar active electrode with a diameter of 0.5cm, and a passive metal electrode, the return plate (Figure-1). Only equipment with the approval of the national organ (ANVISA) can be used for this treatment method.

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Figure 1

Details of the electrodes used in the radiowfrequency apparatus Spectra G3 Tonederm®.

The undressed patient lays in lithotomy position, the return plate is placed under the sacrum and the active electrode is positioned on the external urethral meatus.

When starting the passage of electromagnetic waves, the active electrode is placed on the urethral meatus and moved in circles (Figure-2). The active electrode is removed regularly to perform the temperature check. The temperature is monitored with an infrared thermometer, and after reaching 39-41°C, this temperature and the motions are maintained for 2 minutes. We used the same principle of the monopolar radiofrequency that is used for tissue repair to genital regions (14). All patients had 5 sessions of treatment, with a weekly frequency, and did not undergo any other therapeutic treatment for urinary incontinence. Women currently taking medications such as hormones, diuretics, or other medications, remained on their usual dose of medicine throughout the study period.

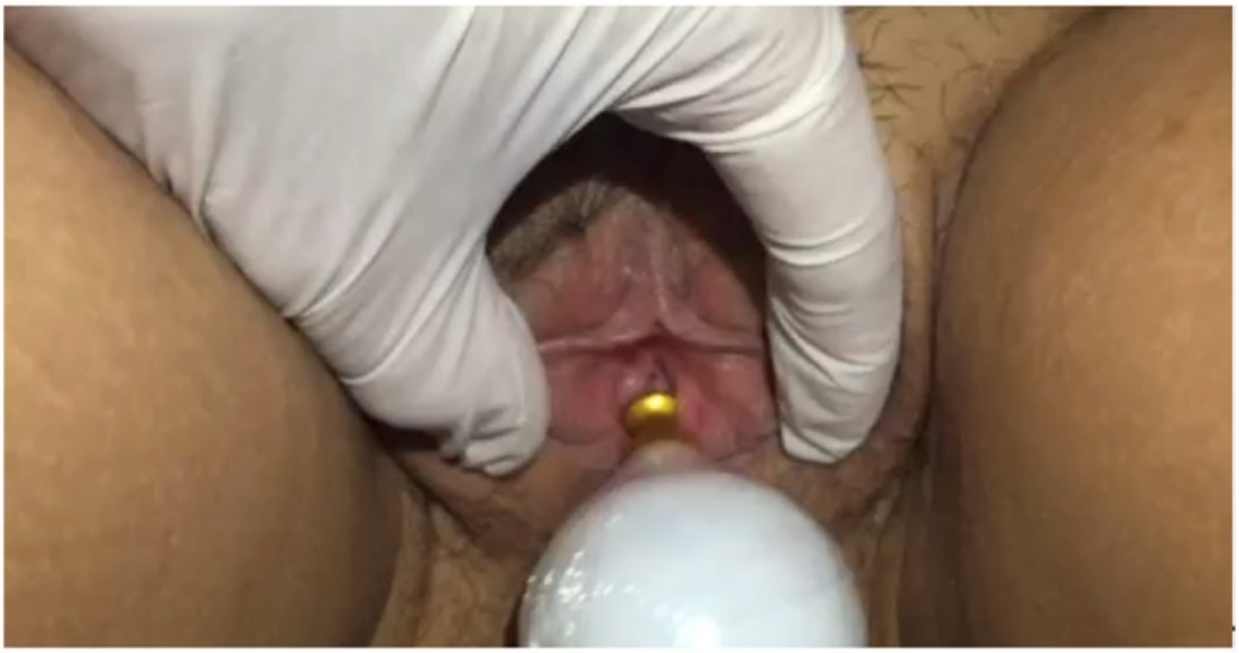

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Figure 2

Demonstration of application of non-ablative radiofrequency in external urethral meatus.

Assessment of response to therapy

As objective evaluation, the Pad test was repeated immediately after the last radiofrequency treatment, and as follow-up one-, two- and three months after the treatment. The categories used in the classification of urinary loss are: loss of 1 to 10g represents mild incontinence, 11 to 50g represents moderate incontinence and >50g represents severe incontinence (3).

As subjective evaluation, the level of patient satisfaction was measured using a 5-point Likert scale, which measured the response to treatment as follows: 1) very dissatisfied, 2) dissatisfied 3) neutral; 4) satisfied; 5) very satisfied.

The expected adverse effects were edema, redness, increased local temperature or presence of secretion.

Statistical Design

To prepare the database and descriptive analysis, the Statistical Package for Social Sciences software (SPSS Inc., Chicago, IL, USA) version 14.0 for Windows, was used. The results are presented in tables and graphs. Categorical variables (patient satisfaction level) are expressed as frequencies and percentages -n (%). Continuous variables with normal distribution are expressed as mean and standard deviation; and those with non-normal distribution, as median and interquartile range. The normality of the numerical variables was assessed using descriptive statistics, graphical analysis and the Shapiro -wilk test.

The analysis of the mean Pad Test comparison was performed by ANOVA repeated measures, and compared the loss in grams at the begginning, the end, after one-, two-, and three months of treatment, considering a significance level of 5% ($p < 0.05$).

RESULTS

The sample consisted of 10 patients with a mean age of 53.10±7.08 years. The clinical characteristics are shown in Table-1. The result of the initial Pad test evaluation showed four (40%) participants classified as having experienced a slight loss, five (50%) a moderate loss and one (10%) a severe loss.

Table 1

Clinical characteristics of 10 patients who underwent non-ablative radiofrequency treatment on the external urethral meatus, Salvador - BA, 2015.

Patient	Age	Pelvic floor muscle strength*	Pregnancies	Normal deliveries	Surgeries	Medicins for CNS and LUTS	Hormonal status	Smoki
01	56	4	0	0	Hemorrhoidectomy	HRT	Menopause	No
02	62	1	5	5	TAH	HRT	Menopause	No
03	49	4	4	4	No	High blood pressure Clordalidone Elanapril	Fertile	No
04	43	3	2	1	Myomectomy	Captopril pressure Puran t4	Fertile	No
05	47	4	2	0	Caesarean section	OC, Nifedipine, Hydrochlorothiazide	Fertile	No
06	49	3	3	3	TAH	No	Fertile	No
07	51	2	6	4	No	No	Menopause	No
08	57	1	7	5	No	No	Menopause	Yes
09	66	1	8	4	TAH	Losartan, Hydrochlorothiazide	Menopause	No
10	51	4	2	1	TAH + Perineoplasty	Estradot + Testosterone	Menopause	Yes

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CNS = Central Nervous System; **AO** = Anticoncepcional Oral; **OC** = Oral Contraceptive; **LUT** = Lower Urinary Tract; **TAH** = Total Abdominal Hysterectomy

*measure by modified Oxford scale.

In assessing the final Pad test, seven (70%) showed a reduction of urinary loss, two (20%) showed no further loss and three (30%) a worsening of urinary loss.

Figure-3 shows reduction of the urine loss in grams (g) Pad test at the begginning-, end-, and after one-, two - and three months of treatment (p=0,028).

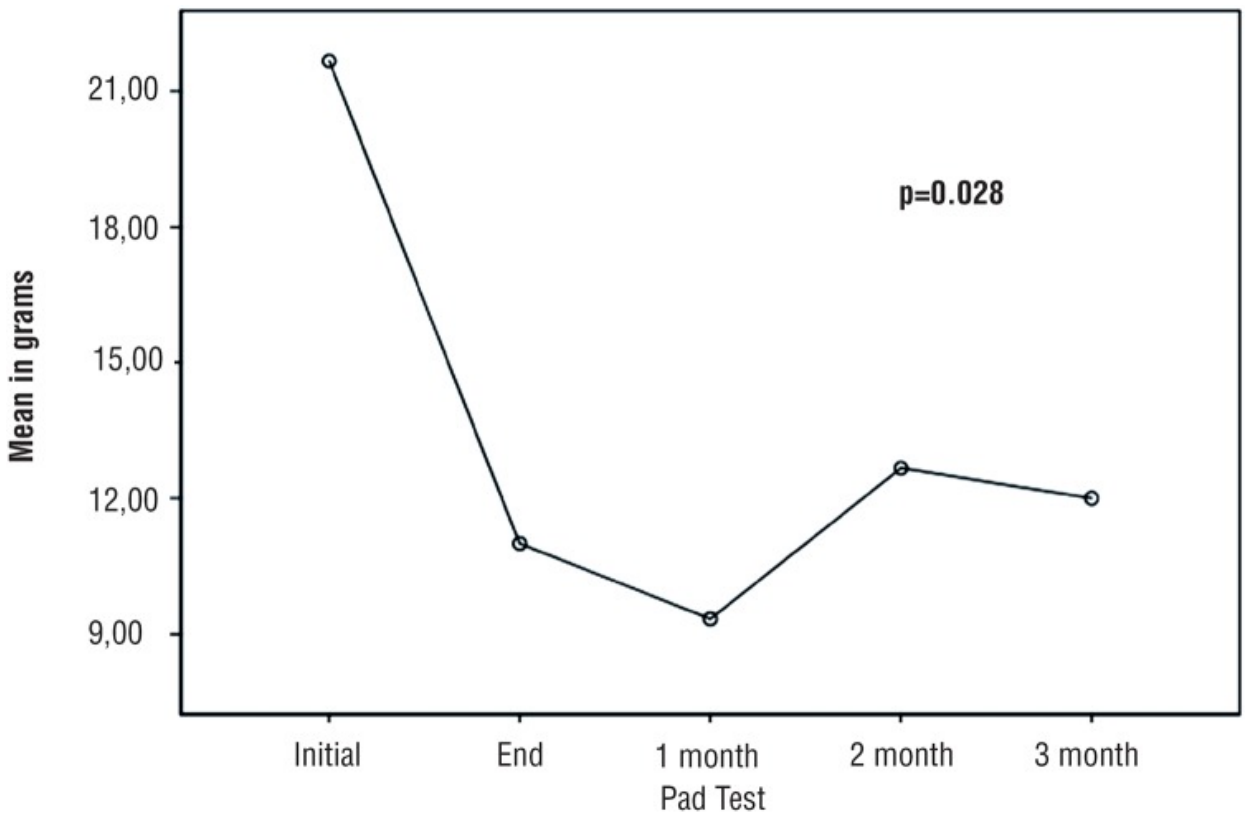

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Figure 3

Comparison of mean urinary loss in grams (g) Pad Test at the begginning-, end-, and after one-, two- and three months of treatment.

After one month, all participants showed an improvement in the results of Pad test, compared to the initial examination: two (20%) had no loss, three (30%) had a slight loss, four (40%) had a moderate loss and none had severe loss. One participant did not return for a follow-up review after one month (Table-2).

Table 2

Results of urinary loss in grams (g) of 10 patients who underwent non-ablative radiofrequency treatment on external urethral meatus measured by Pad Test, Bahia, 2015.

Patient	Initial Pad test (g)	Final (End) Pad test (g)	Pad test after 1 month (g)	Pad test after 2 months (g)	Pad test after 3 months (g)
01	2	1	0	2	2
02	6	2	0	5	4
03	13	23	10	12	--
04	16	21	10	31	29
05	7	2	5	3	--
06	6	3	5	11	--
07	11	10	4	3	6
08	25	27	20	19	16
09	70	5	22	16	15
10	16	0	--	2	--

While assessing patient satisfaction, nine (90%) participants reported to be satisfied with the treatment. One patient indicated to be little satisfied with the treatment as an answer to the Likert questionnaire.

Assessing whether the use of non-ablative radiofrequency on urethral meatus is regarded safe, nine (90%) out of 10 participants presented no adverse or side effects. One participant indicated to have felt an unexpected burning sensation in the area of the urethral meatus, just after the menstrual period. This participant returned for the radiofrequency treatment a week later, without any complaints.

During her physical examination, there was no edema, redness, increased local temperature or presence of secretion. Nothing was prescribed in order to improve this discomfort. No other complications were observed. All patients completed the five sessions.

DISCUSSION

We present a new technique of a conservative treatment of SUI. It follows a principle that already exists, but applied in a different way. We applied the technique on the urethral meatus after an animal experimental study has demonstrated the possibility of increasing collagen production of anal sphincter (9) and we used temperatures ranging from 39 to 41°C, as it was proved to be safe and effective in the human genital region (14).

We demonstrated that the method is painless and reliable. Besides the fact that we indicate its lower risk of adverse effects during the technical treatment; only one patient reported a burning sensation during a session right after menstruation. In this case, a possible difference in resistance of tissue could be due to friction of the pad with a change in impedance of the passage of electric waves. For the electric current to perform the desired action on the tissue, it needs to overcome the barrier imposed on its flow and reach the target tissue in the right intensity. This is what we call tissue impedance. The impedance is composed of the extra flow resistance and capacitive reactance of cell membranes. The electric current will always take the path of least resistance. The tissue impedance may change the density, intensity and path of the current and of the biological response (15).

The method has no adverse effects; the observed results were similar to those of the studies of Meillheiser et al. where radiofrequency was used for treatment of the vaginal introitus to treat vaginal laxity; and a pilot study conducted to test tolerance and safety showed that there has been no adverse effect (using frequency 75-90 Joules/cm^2) (16). In addition to the low risk, one advantage of this new treatment technique is that it is not necessary to place the device in the urethra, which reduces the side effects and eliminates the need for prophylactic antibiotics or the use of anesthetics, as used in prior studies. In the systematic review on the intraurethral radiofrequency technique, a relative risk (RR) of 5.76 of pain / burning-, a RR of 1.36 of a hyperactive destrusor-, and a RR of 0.95 of urinary retention was found (17).

The clinical response related to urinary loss was satisfactory for this group of patients studied. This is a very small number of patients to show therapeutic effectiveness, but considered a necessary phase study when to present a new therapy. Randomized clinical trials are being developed by our group to assess the effectiveness of the method.

The improvement in urinary loss is shown in the final Pad test. Seven out of ten participants showed an improvement in reducing stress urinary incontinence. By treating with radiofrequency, local temperatures increase, which enables vasodilation and the opening of capillaries, the gain of oxygen, and an improved drainage. This phenomenon can improve the circulation of the venous plexus which is a layer of spongy erectile tissue, that contributes to the urethral closure mechanism (7). The decrease in urinary loss measured by the Pad test was most evident one month after the radiofrequency treatment. The result we found is probably due to the period of collagen denaturation and neo production that remains until 28 days after treatment. Since those collagen changes favor the urethral closure mechanism (18), it could be explained why there was a better response on the pad test after one month. Rechberger et al. demonstrated that collagen content has been correlated with the urethral pressure, the length of the urethra and maximum closure pressure of the urethra (19).

Nine out of ten patients indicated to be satisfied with the treatment, although seven out of ten patients experienced a reduction of urinary loss after treatment with radiofrequency. This finding shows that satisfaction is not only linked to the therapeutic outcome, but possibly also to the level of expectations of the people involved. This means that degrees of satisfaction do not always correspond to the results. However, the degree of satisfaction should be measured to stablish a subjective response of patients. Satisfaction is the feeling of pleasure or disappointment which resulted from comparing a perceived performance or outcome against one's expectations. When considering the answers of patients on satisfaction, the Hawthorne-effect can be taken into consideration. Hawthorne said that when individuals believe they are experiencing a form of treatment, they are more likely to respond to be satisfied with therapeutic responses (20). Another factor that should be taken into consideration is that the complaint regarding urinary loss is not directly proportional to the volume of urine loss (21, 22).

A disadvantage of this new technique is that qualified professionals are required to perform the procedures. Another issue is a need to schedule five sessions, however, there is no consensus on parameters and treatment frequency in literature regarding radiofrequency treatment.

Hence, it can be considered a conceivable perspective to carry out a clinical trial to measure the response to radiofrequency treatment on the external urethral meatus of woman with SUI, with a control on variables such as age, parity, degree of muscle strength, BMI, and with a long-term control of the response to therapy on the external urethral meatus. A limitation found was the loss of 4 patients during the follow-up phase, due to their lack of finances to finish the study.

CONCLUSIONS

The preliminary results of our study (phase 1) look promising. However, to increase the validity of the study, larger clinical trials are warranted. Our study showed that the treatment of stress urinary incontinence with radiofrequency on the urethral meatus had no adverse effects and reduced urinary loss in women.

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Article

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Special Issue

Hydrogels in Biomedical Applications

Edited by

Prof. Dr. Chun Gwon Park and Prof. Dr. Jung Seung Lee

MDPI

https://doi.org/10.3390/ph15121571

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Hyaluronic Acid and Radiofrequency in Patients with Urogenital Atrophy and Vaginal Laxity

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Citation: Kolczewski, P.; Parafiniuk, M.; Zawodny, P.; Haddad, R.; Nalewczyńska, A.; Kolasa, A.K.; Wiszniewska, B.; Menkes, S.; Bader, A.; Stabile, G.; et al. Hyaluronic Acid and Radiofrequency in Patients with Urogenital Atrophy and Vaginal Laxity. *Pharmaceuticals* **2022**, *15*, 1571. https://doi.org/10.3390/ph15121571

Academic Editors: Chun Gwon Park and Jung Seung Lee

Received: 25 September 2022
Accepted: 12 December 2022
Published: 16 December 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Abstract: Vaginal laxity (VL) and genitourinary syndrome of menopause (GSM), as well as aesthetic changes in the vulvar skin, often occur together and cause physical, psychological, and functional problems for women and their partners. The current study evaluated the efficacy of a nonsurgical radiofrequency device (RF) procedure combined with hyaluronic acid (HA) injection into the skin of the labia majora on clinical, histological, and aesthetic levels. Twenty women with GSM and VL, aged between 36 and 72 (mean age 53.4), were treated with bipolar RF SECTUM, vaginal and vulvar application, as well as with a hyaluronic acid (HA) injection into the skin of the labia majora. The Vaginal Laxity Questionnaire (VLQ), Vaginal Health Index (VHI), and Female Sexual Function Index (FSFI) were used to examine the clinical effects of the operations. The Global Aesthetic Improvement Scale was utilized to measure patient satisfaction. On a histochemical level, the concentrations of elastin and collagen in the vaginal wall and vulvar skin were examined. Results: There was significantly higher patient satisfaction and a considerable clinical improvement across all areas of analysis. On the histochemical level, elastin and collagen fiber concentration increased after the treatment protocol both in the vulvar skin and in the vaginal wall: elastin in the vaginal wall, 11.4%, and in the vulvar skin, 61%; collagen in the vaginal wall, 26%, and in the vulvar skin, 27%. The current study demonstrated the efficacy and safety of this nonsurgical RF procedure combined with a hyaluronic acid (HA) injection into the skin of the labia majora on clinical, histochemical, and aesthetic levels.

Keywords: hyaluronic acid; radiofrequency; urogenital atrophy; vaginal atrophy; vaginal laxity

1. Introduction

Menopause-related hypoestrogenism negatively affects vaginal and urinary health, often leading to genitourinary syndrome of menopause (GSM) [1]. The lack of estrogens causes floppy, droopy vulvar skin, and an atrophic, pale vaginal epithelium with petechiae, dryness, burning, irritation, and sexual symptoms such as discomfort, pain, and reduced sexual function. This disorder, called vulvovaginal atrophy (VVA), commonly causes urine incontinence, dysuria, urgency, and recurrent UTIs [2]. VVA is a chronic illness that

worsens if left untreated, unlike menopausal vasomotor symptoms. According to the latest study, VVA affects 36% to 90% of perimenopausal and postmenopausal women [3,4]. The treatment of VVA comes down to long-acting vaginal moisturizers when there are mild and topical estrogens in moderate to severe VVA [5]. Systemic replacement does not always relieve vaginal dryness symptoms and requires topical estrogen [6–8].

Pregnancy and childbirth are thought to cause vaginal laxity [VL] [9]. There is a correlation between objective indicators of pelvic floor function in the postpartum period [10] and the loss of physical feeling and diminished sexual satisfaction following vaginal birth. It is now commonly acknowledged that vaginal delivery can cause trauma to the pelvic floor, particularly the levator ani muscle [11–13]. In a worldwide survey of urogynecologists, 83% of 553 respondents identified vaginal laxity as underreported by their patients. Most described it as a self-reported uncomfortable condition that compromises sexual function and relationships [14–16]. VL is linked to less vaginal feeling and a poorer sexual life [17]. A total of 46% of women with VL met the criteria for sexual distress and 65% met the criteria for female sexual dysfunction [18].

VL can be treated with Kegel exercises and surgery [9,16]. Vaginoplasty and perineoplasty are often performed for this reason, but like any surgical treatment, there are sometimes complications. Scarring or nerve damage can induce dysesthesia, hypercorrection, and dyspareunia [19,20], hence, the need to look for effective mini invasive treatment.

Radiofrequency and laser technologies can also improve laxity and atrophy of the vaginal wall [21,22]. RF devices increase tissue molecular mobility, causing heat [21]. Monopolar, bipolar, and multipolar RF devices operate on the principle of the radiofrequency current flow through tissue, which resists creating a rising temperature up to 43 degrees centigrade. This heat activates heat shock proteins and initiates the inflammatory cascade, causing fibroblasts to make collagen and elastin. RF was studied in a vaginal sheep model using a monopolar Viveve applicator. Three months later, collagen production and fibroblast development had increased. This ovine model lacked elastin [23]. In a pig model, BTL Industries' Exilis Ultra 360 monopolar intravaginal applicator also improved vaginal tissue. Neocollagenesis and neoelastinogenesis were identified [24].

In our study (non-published) on swine's vaginal wall, we evaluated the effects of bipolar RF Sectum 360 with a vaginal applicator (Berger and Kraft Medical). Vaginal radiofrequency (RF) exposure was administered twice every 4 weeks and the vaginas were removed after slaughter, four weeks after the last radio frequency exposure. We demonstrated a substantial rise in the concentration of elastin and collagen fibers in the zones exposed to radiofrequency up to 1.3 mm of the thickness of the vaginal wall. There was a 52.8% rise in elastin concentration and a 103.6% rise in collagen concentration in the RF-exposed areas of the vaginal wall. Studies of women with VL and VVA have shown that RF therapy is safe and effective in improving VL and VVA [25–30]. However, the optimal technique of RF therapy is still unclear [28].

The labia majora are also subject to changes characteristic to VVA. With age and parity, the labia majora decrease their volume and tone, and change their coloration because vascularization rapidly decreases after menopause. Following the loss of follicular activity, the external genitalia lose subcutaneous fat, and connective tissue relaxes and becomes less elastic; this is associated with pain during sexual intercourse [31]. Moreover, for these reasons, an increasing interest in the aesthetic appearance of female genitalia has also been observed in the field of cosmetic medicine. In the last years, the industry has developed new dermal fillers for facial and body treatments. Hyaluronic acid (HA) filler is the most common due to its good outcomes, ease of administration, and lack of side effects [32]. Hyaluronic acid (HA) can also be safely injected during a simple outpatient procedure to augment the labia majora, providing youthful and natural results [33,34].

Several studies [35–37] have evaluated combined HA and RF treatment regimens. The reason for their combined use results from the fact that RF therapy delivers homogeneous heat to the dermis, which remodels collagen and tightens the skin, but it cannot restore lost volume. In a study of RF treatment on soft-tissue fillers in an animal model, England

et al. [37] found that several passes of RF treatment directly over filler-injected skin did not cause immediate adverse reactions and did not significantly affect treatment duration. Goldman et al. [38] reported that humans can safely receive laser, RF, and intense pulsed light therapy after HA therapy.

No study has shown how HA and RF acting together can affect the labia majora skin. To address the limits of both modalities and assume a synergistic impact, our patients were treated with a radiofrequency (RF) device before HA filler injections (filler 28 mg/mL PEG-crosslinked) and, subsequently, with three consecutive vulvar and vaginal RF applications every 3–4 days. Zerbinati et al. [34] found that infiltration of the labia majora with HA-based PEG-crosslinked filler is reproducible, complication-free, reversible, and 96.6% patient-satisfying.

We predicted RF therapy can boost HA's efficacy, especially in the vulvar region. This study evaluated the efficacy and safety of RF therapy combined with HA injection in women with VL and VVA.

2. Materials and Methods

Twenty women with VL and VVA aged between 36 and 72 (mean age 53.4) participated in this non-randomized, prospective study. The study was approved by the Research Ethics Committee under number 09/KB/VII/2020, and conducted according to the guidelines recommended by the 2000 Declaration of Helsinki, updated in 2008. Demographic data, number of deliveries, menopause, and pharmacologic treatments were recorded. Hypotrophy of the labia majora was preoperatively staged according to classification by Fasola considering both the adipose tissue and the cutaneous layer [33]. The inclusion criteria were patients with symptoms of VVA and VL as vaginal and vulvar complaints, vulvar skin laxity and hypotrophy perimenopause, menopause or surgical menopause, and cervical cytology test negative for cancer. The exclusion criteria were use of hormone therapy (either systemic or topical) or long-acting moisturizers within the last 6 weeks prior to the initial assessment; patients with active or recurrent genital infection (e.g., genital herpes, candidiasis, bacterial vaginosis); patients with human immunodeficiency virus; recurrent urinary tract infection; pelvic radiation therapy or brachytherapy; reconstructive pelvic surgery and previous vaginal or vulvar treatment with energy-based devices and/or hyaluronic acid fillers. After history taking and physical examination, patients were selected and instructed about the procedure, and, after giving informed consent and authorization for photographic documentation, they answered the following questionnaires: Female Sexual Function Index (FSFI) and Vaginal Laxity Questionnaire (VLQ). The vaginal status was examined with the use of Vaginal Health Index (VHI). The aesthetic appearance of the vulva was evaluated by Global Aesthetic Improvement Scale (GAIS) and the comfort of the protocol was assessed for each procedure separately by visual analogue scale (VAS). The treatment course consisted of injection of HA into the skin of labia majora, 1–1.5 mL per side followed by 4 vaginal and vulvar applications of radio frequency (RF) with an interval of 3–4 days.

2.1. Hyaluronic Acid

In our study, we used a well examined area , the monophasic hydropolymer that was created with 28 mg/mL of HA crosslinked with polyethylene glycol (PEG) (Neauvia® Intense Rose, Matex Lab, Switzerland) [34]. PEGylation also seems to offer considerable advantages in the field of fillers for aesthetic use, both in terms of safety and of gel performance [39–41]. Both PEG and hyaluronic acid are polymers, and their union allows creation of matrices with scaffold architecture; that is, a three-dimensional weft consisting of large meshes that offer high assimilation of the gel into the tissue, and the possibility to include and gradually release molecules that are useful for skin rejuvenation [41–43].

The procedure involves administering HA filler to the subcutaneous tissue of labia majora (between tunica dartos and fibrous layer of an adipose sac) through an injection, using an 18 G cannula. Blood vessels and nerves supplying the vulva are located within the

lower pole of labia majora, therefore caution is advised when the first injection is carried out at the lower pole. The depth of injection plays an important role, as accessing too deep structures may result in administering the filler to the adipose sac, thus disrupting its effect.

The first step involves a decontamination and anesthetizing of the area to be injected. Local anesthesia is used with approximately 2 mL of 2% lidocaine administered along the labia in a single injection per side. Firstly, a 16 G needle is used to access the labia. Then, the 18 G cannula is used to administer the filler to the lower pole of the labia. A linear, upward application mode should be followed. It is important to administrate the product in the whole length of the labia in the way that enables creation of a natural shape by dividing this as one-fourth of the syringe at the top pole, two-fourths in the middle, and one-fourth at the lower pole. No more than 1.5 mL of hydrogel 28 mg/mL PEG-crosslinked HA was injected on each side for all the patients treated.

2.2. Radiofrequency (RF)

We used a disposable gynecological applicator with a bipolar radio frequency Sectum 360 degrees (Berger and Kraft Medical). The RF therapy schedule included four treatment sessions separated by three to four days. Each therapy session included vaginal and vulvar application (labia majora and perineum).

During the vulvar treatment, the current is released in a continuous mode and the applicator is set in motion mode using slow circular movement over the vulvar skin for 10 min (both sides). The energy set up was between 5–10 W and was adjusted based on patient's feedback (comfortable or uncomfortable).

The intravaginal application involves placing an applicator to the vaginal canal behind the hymenal ring and warming vaginal wall over the length of approximately 10 cm over the course of 3–7 min. The energy setup was between 15–20 and, similarly to vulvar application, was adjusted based on patient's feedback. Unlike vulvar application, in the vaginal procedure, the current was released in a pulse mode (500 ms), which means that there was no need to move the applicator back and forth in a vaginal canal, which can be embarrassing for both a patient and a doctor performing a procedure. To affect the vaginal wall evenly, the vagina was divided into three 3 cm sections, and when performing a procedure, the tip of an applicator (two rings part) was placed for 3 min in each section.

Before each RF procedure, a specially designed for this purpose gel, containing glycerin without no water, was applied (Neauvia Gel).

2.3. Histochemical Analysis

To measure changes in collagen and elastin concentration, specimens were obtained from one patient under local anesthesia with 2% lidocaine (lignocaine 2% 20 mg/mL Polfa Warszawa S.A.) Punch biopsies of the skin of labia majora and vaginal wall in the RF-exposed areas were used to gather samples before and six weeks after the last RF application. The samples were stained to look for collagen and elastin concentration according to the included staining procedure instructions (Mallory Trichrome (Bio Optica, Milan, Italy, cat. no.: 04-020802), and orcein Bio Optica, Italy, cat. no.: 04-055802, Sirius red picrate, Italy, cat. No.:04-121873) Each specimen was computationally processed by the KS 300 (Zeiss) scanner and evaluated according to the selected region of interest. The evaluated area embraced the vaginal wall layers just under the lamina propria of the vaginal epithelium (up to 1.3 mm of the thickness of the vaginal wall). We used a magnification of 400×. Smaller magnifications would embrace the layers beyond the zone of interest and would interfere with the measurement. After threshold values were established, the recorded pictures were segmented by counting the areas of the objects designated for segmentation. Quantitative measures were performed by the summation of separate areas in pixels. Due to the fact that values of segmented areas in pixels were extremely high, a logarithmic scale was used.

3. Results

3.1. Outcome Measures and Statistic Evaluation

The Friedman test, anon-parametric equivalent of the repeated measures ANOVA, was used to compare the outcomes (numerical variables) between data points. In post hoc analysis, the Wilcoxon signed rank test was used for pairwise comparisons between all time points. For qualitative data, Cochran's Q test followed by McNemar's post hoc procedure were used. False Discovery Rate (FDR) adjustment was used to account for multiple comparisons. FDR was calculated using the Benjamini–Hochberg method. An FDR-adjusted p value < 0.05 was considered significant. Statistical analysis was performed and figures created using R statistical environment (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/ (accessed on 1 September 2022).

The sample size was calculated using GPower (3.1.9.6). A sample size of n = 20 was sufficient to detect large effects (corresponding to eta-squared of 0.14), assuming alpha error 0.05, power of 80%, number of groups 1, and number of measurements 4.

3.2. VL

Vaginal laxity was assessed by a non-standardized subjective vulvovaginal laxity questionnaire (VLQ) using a 7-point Likert scale. Participants were eligible if they self-reported a perception of vaginal introital laxity defined as "very loose", "moderately loose", or "slightly loose" on a seven-point Likert scale [17,18,27]. Data were collected before the first treatment and during the consecutive follow-up visit. The average improvement was calculated. VL changed significantly over time (Figure 1, $p < 0.0001$). Post hoc comparisons revealed that significant differences were found between study entry and follow-up visits but not between follow-up visits.

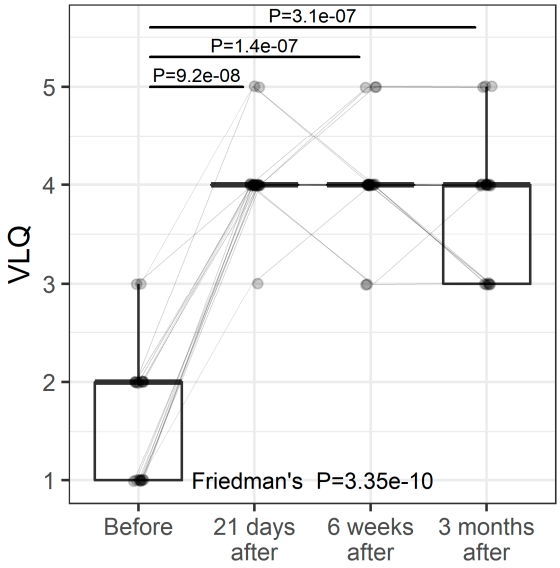


Figure 1. VLQ at study entry and follow-up visits (individual values and summary statistics). Individual values are represented by points joined by lines. Summary statistics are shown using box plots. The middle line of the box plot is median, the lower and upper hinges correspond to the first and third quartiles (the 25th and 75th percentiles). The upper whisker extends from the hinge to the largest value (no further than 1.5*IQR from the hinge, IQR is the interquartile range—distance between the first and third quartiles). The lower whisker extends from the hinge to the smallest value (no further than 1.5*IQR of the hinge). Median line overlaps with lower and upper hinges. p-values were determined using Friedman's test, followed by pairwise post hoc Wilcoxon test with FDR adjustments for multiple testing correction.

3.3. FSFI

The FSFI is a widely accepted, global evaluation used in female sexual medicine trials [44]. The FSFI is a 19-item questionnaire divided into six domains: desire, arousal, lubrication, orgasm, satisfaction, and pain, which evaluate a woman's recent state of sexual function (within the past 4 weeks). The domain scores combine to create a total score (range 2–36). A change in the FSFI during the study was significant (Figure 2a, $p < 0.0001$). A six-week follow-up demonstrated a significantly improved FSFI score (from 26.5 (9.3) to 32 (4), median (IQR), $p < 0.0001$) and remained significantly better at the 3-month follow-up (32 (4), $p < 0.0001$ versus baseline, Figure 2). A total FSFI score of 26 is recognized in the medical literature as indicating female sexual dysfunction (FSD). We also observed significant improvements in women without FSD (Figure 2b).

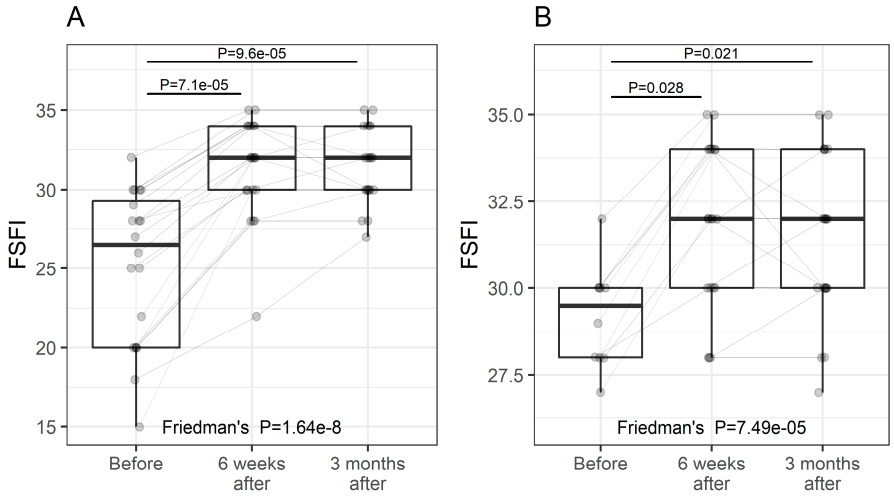


Figure 2. FSFI at study entry and follow-up visits (individual values and summary statistics). (**A**)—all participants, (**B**)—participants with FSFI score > 26. Individual values are represented by points joined by lines. Summary statistics are shown using boxplots. The middle line of the boxplot is median, the lower and upper hinges correspond to the first and third quartiles (the 25th and 75th percentiles). The upper whisker extends from the hinge to the largest value (no further than 1.5*IQR from the hinge, IQR is the interquartile range—distance between the first and third quartiles). The lower whisker extends from the hinge to the smallest value (no further than 1.5*IQR of the hinge). *p*-values were determined using Friedman's test, followed by pairwise post hoc Wilcoxon test with FDR adjustments for multiple testing correction.

We also defined a clinically significant change in women with no FSD, Figure 2b, for an FSFI posttreatment total score of at least 2 points regardless of the participant's score at study entry. We based this on a similar calculation and methodology to that previously reported [45,46]. All participants exhibited a clinically significant change with a median change of 5 and 50% of women ranging from 4 to 8.

3.4. VHI

Vaginal health linked to VVA was evaluated by the Vaginal Health Index (VHI). The VHI consists of the clinical analysis during the specular examination of five parameters and is graded from 1 to 5. The sum of the values of the parameters evaluated results in the total vaginal health score. The VHI gives scores of vaginal moisture, vaginal fluid volume, vaginal elasticity, pH, and vaginal epithelial integrity. The lower the score, the higher the atrophy. The sum of the values of the evaluated parameters results in the total vaginal health score. When the overall score is less than 15, the vaginal mucosa is considered atrophic [47,48]. VHI was measured at baseline and three follow-up visits (Figure 3). Overall, there was a significant improvement in the VHI score over time with the greatest and most significant change taking place between the baseline and 21-day follow-

up (p = 0.006). The VHI score leveled off after the 21-day follow-up and no significant changes were found between follow-up visits thereafter.

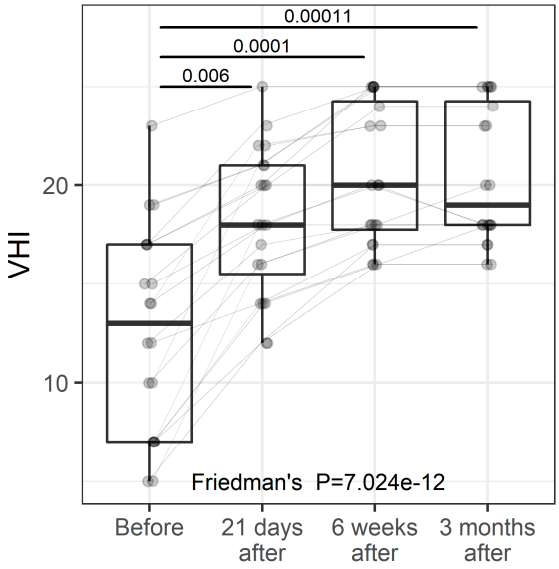


Figure 3. VHI at study entry and follow-up visits (individual values and summary statistics). Individual values are represented by points joined by lines. Summary statistics are shown using boxplots. The middle line of the boxplot is median, the lower and upper hinges correspond to the first and third quartiles (the 25th and 75th percentiles). The upper whisker extends from the hinge to the largest value (no further than 1.5*IQR from the hinge, IQR is the interquartile range—distance between the first and third quartiles). The lower whisker extends from the hinge to the smallest value (no further than 1.5*IQR of the hinge). p-values were determined using Friedman's test, followed by pairwise post hoc Wilcoxon test with FDR adjustments for multiple testing correction.

3.5. GAIS

The patient rated the aesthetic improvement in the vulva or lack of it on the Global Aesthetic Improvement Scale (GAIS) ranging from −1 (worsening) to 5 (very much improved) at 6 weeks after the procedure and 12 weeks after the procedure with a preoperative digital picture. Patients were asked to write their score on a form, analogously identified by a number from the GAIS. The forms were collected and analyzed once all evaluations were accurately recorded at the interval follow-up visits at 6 and 12 weeks and 6 months. There were only two categories of the GAIS score: an improvement and a marked improvement. Their distribution changed significantly with time (Figure 4, $p < 0.0001$). Marked improvement was found in 85% at 2 weeks, 90% at 6 weeks, and 80% of participants at 12 weeks, and in none of the participants 6 months after. The post hoc analysis revealed that the percentages of marked improvement were significantly higher when compared with the 6-month follow-up (0.000112, 0.000112 and 0.000127 for 2 weeks, 6 weeks, and 12 weeks, respectively) but not between each other.

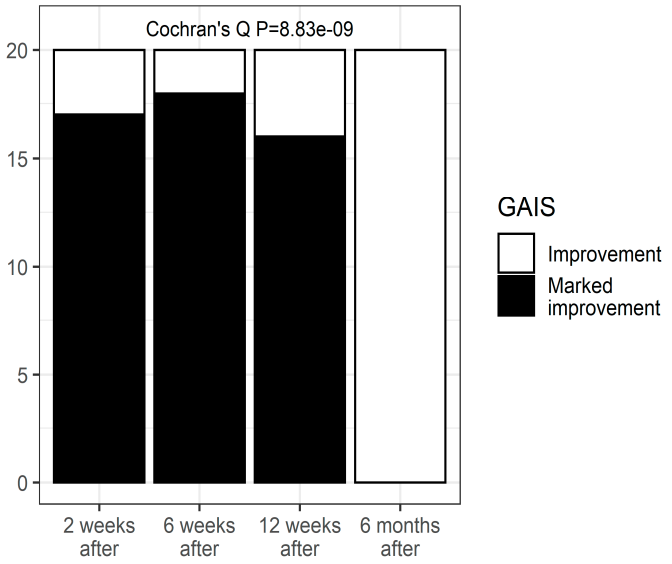
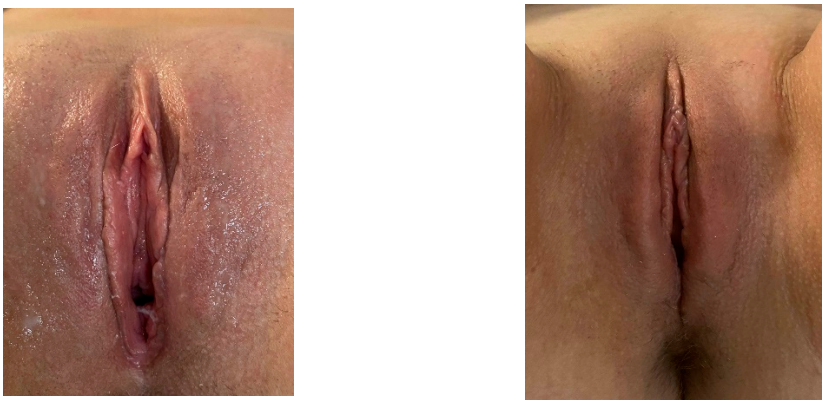
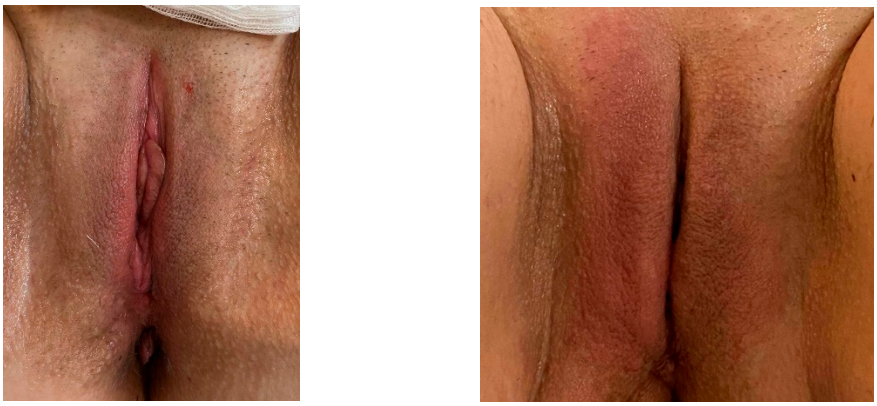


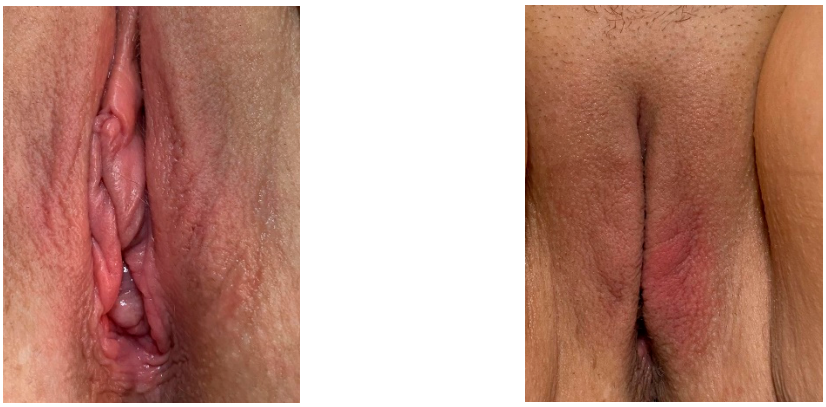
Figure 4. The aesthetic improvement in vulva or lack of it on the Global Aesthetic Improvement Scale (GAIS).



Clinical case 1 before and after the procedure.



Clinical case 2, before the and after the procedure.



Clinical case 3, before and after the procedure.

3.6. VAS

A preponderance of evidence demonstrates that the visual analog scale (VAS) is by far the most frequently used assessment instrument to evaluate the analgesic effects of various therapies (Figure 5). From a structural standpoint, we believe that anyone who is cognitively capable of grasping the parameters and following instructions from a doctor can utilize the VAS. Indeed, the VAS's success is typically credited to it being simple and convenient in a hectic clinical environment [49,50].

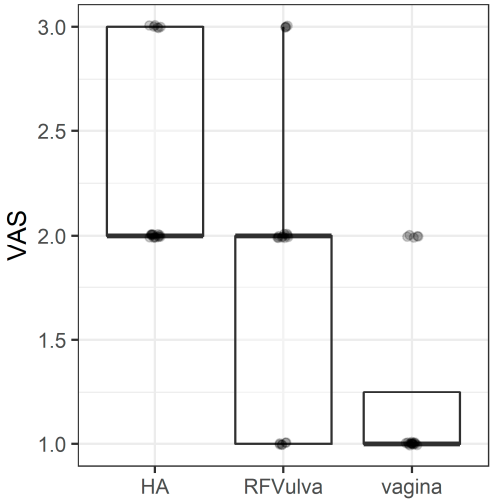


Figure 5. The visual analog scale (VAS) to evaluate analgesic effects of various therapies. The middle line of the boxplot is median, the lower and upper hinges correspond to the first and third quartiles (the 25th and 75th percentiles). The upper whisker extends from the hinge to the largest value (no further than 1.5*IQR from the hinge, IQR is the interquartile range—distance between the first and third quartiles). The lower whisker extends from the hinge to the smallest value (no further than 1.5*IQR of the hinge). Median line overlaps with lower and upper hinges.

3.7. Histochemical Staining Results

The paragraph gives an explanation of the charts (Figures 6–23). The *y*-axis indicates the intensity of the staining reaction in the histological preparation; the units and scale are assigned routinely and automatically by the imaging analyzer (KS 300) and this applies to the 2D and 3D diagrams for all histochemical methods used. This allows not only a quantitative comparison of the histochemical reaction but also their specific distribution in the tissue structures, and this is visible in the 3D graphs.

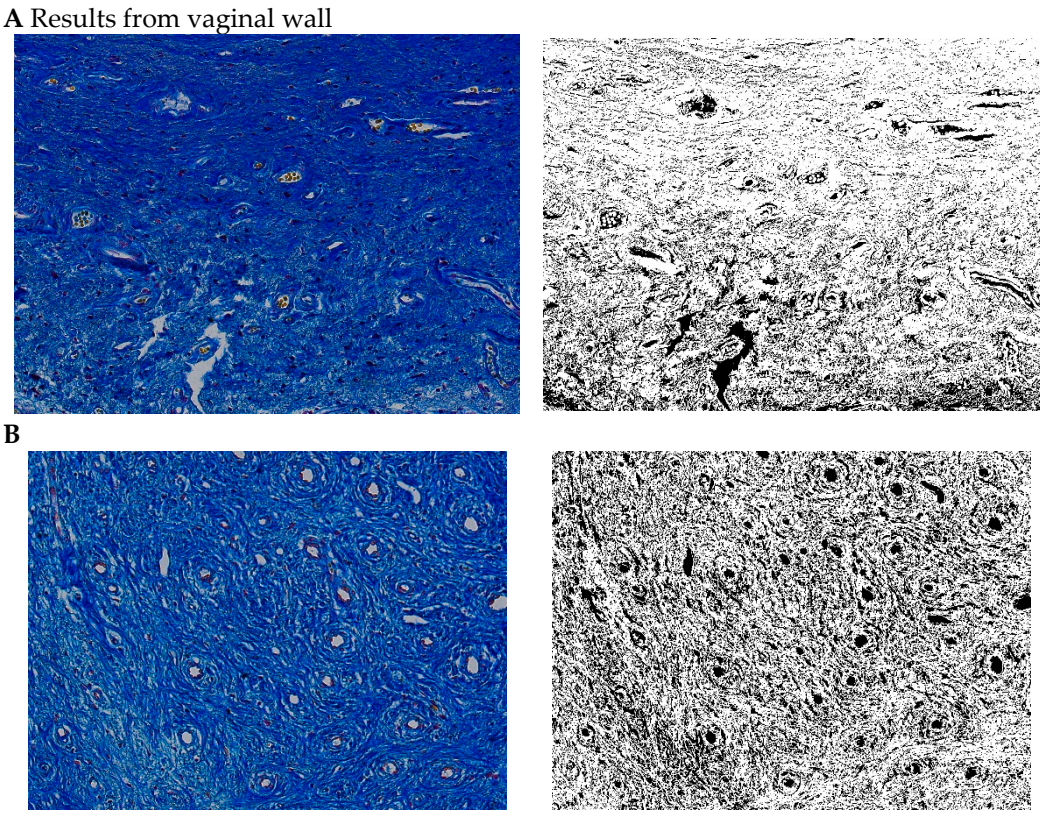


Figure 6. Segmentation before (**A**) and after (**B**) treatment (Mallory trichrome).

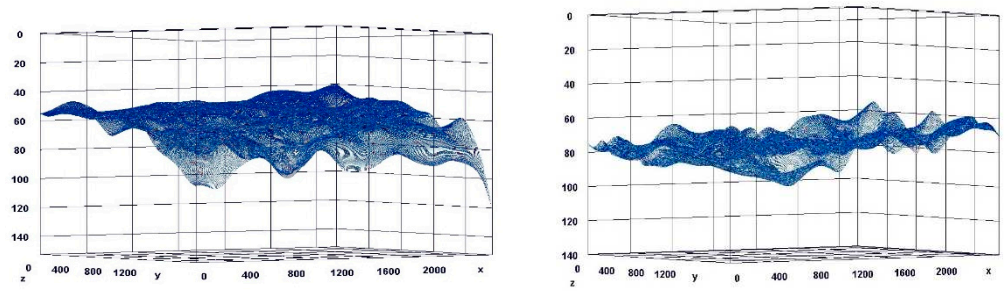


Figure 7. Visualization of the differences in collagen concentration before and after treatment (computer program IMAGEL).

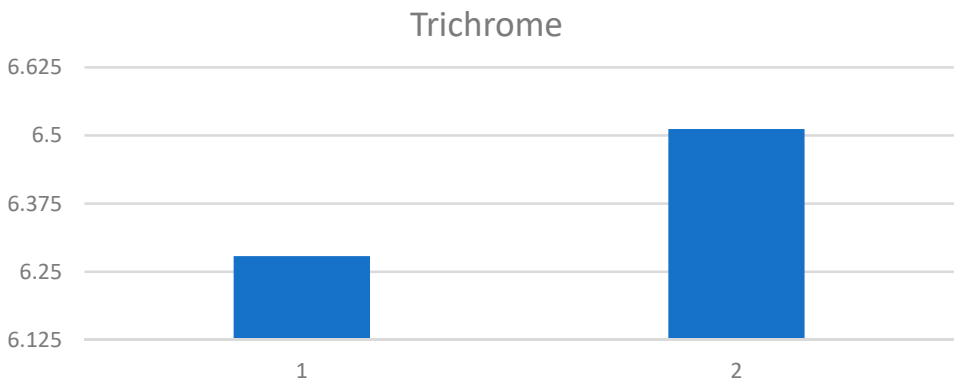


Figure 8. The comparison of specimens before and after the treatment revealed 26.6% rise in collagen concentration.

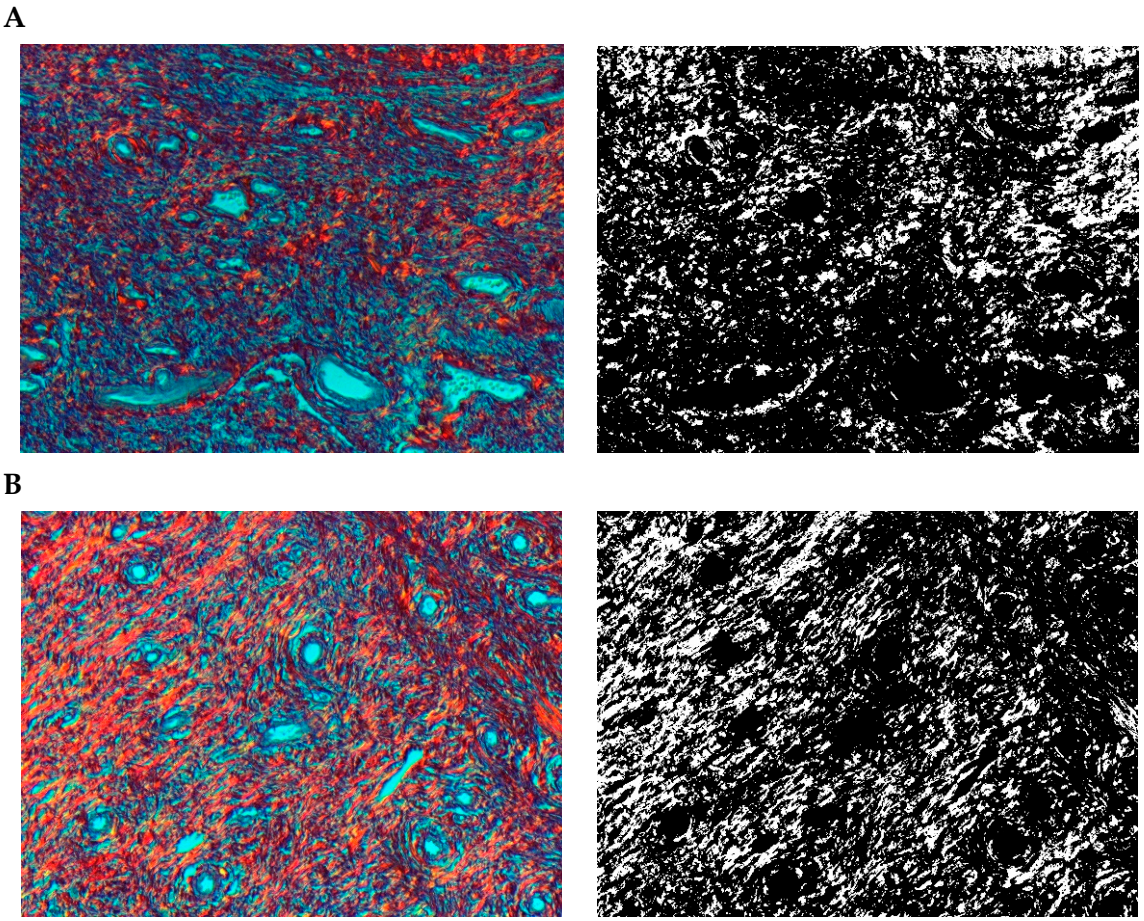


Figure 9. Segmentation before (**A**) and after (**B**) treatment (picrosirius red staining).

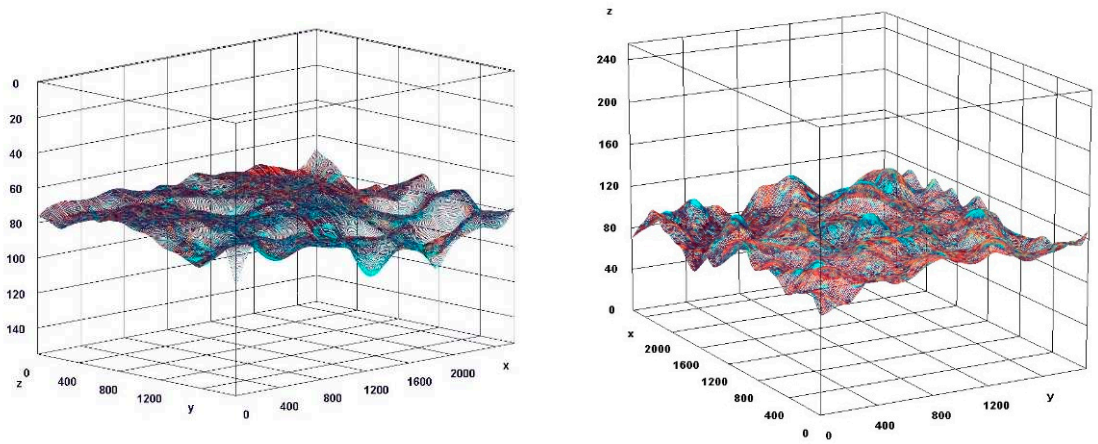


Figure 10. Visualization of the differences in collagen concentration before and after treatment.

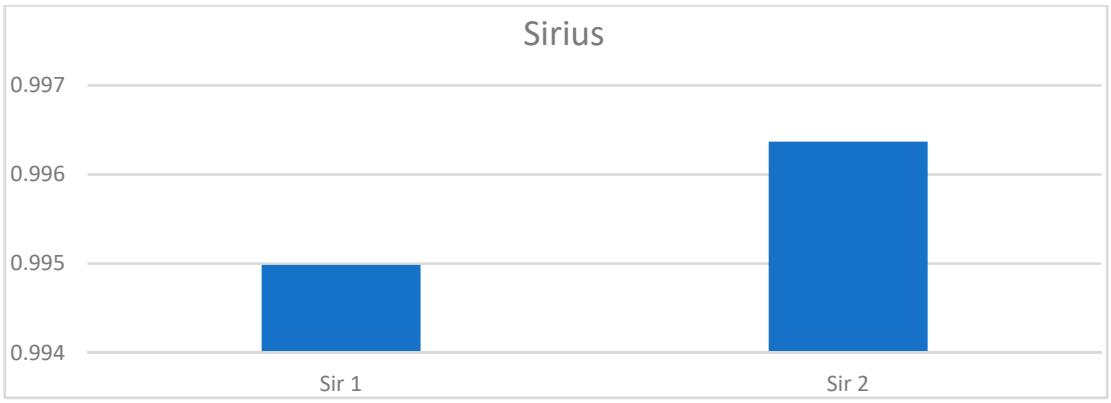


Figure 11. The comparison of specimens before and after the treatment revealed 26.4% rise in collagen concentration.

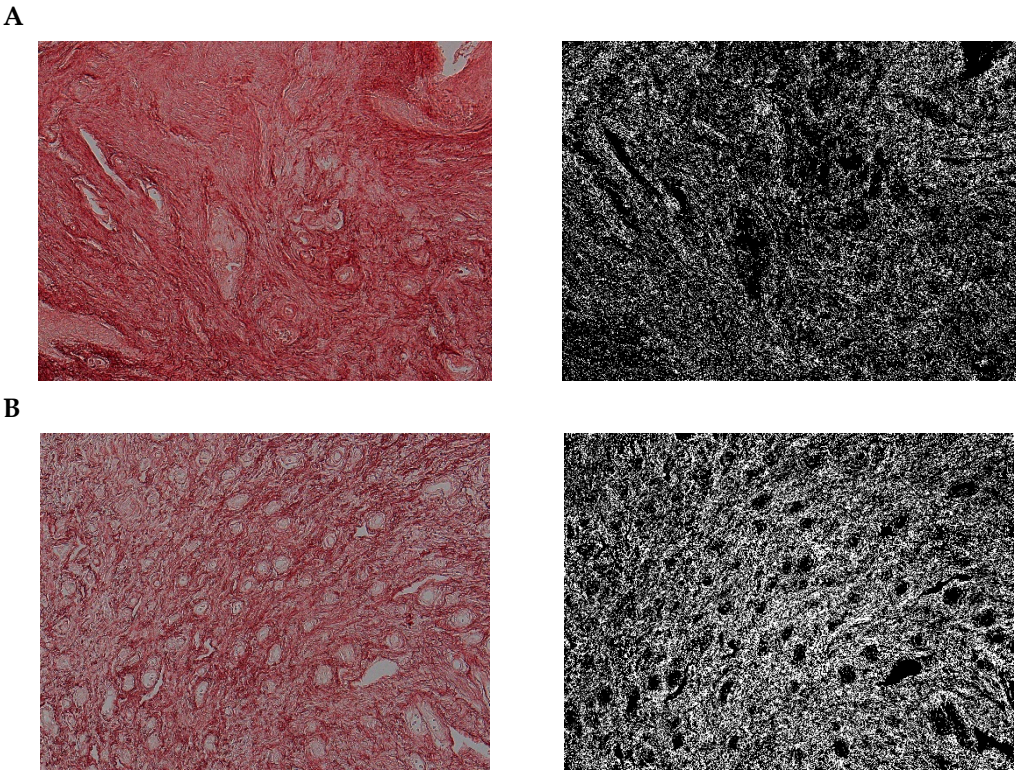


Figure 12. Segmentation before (**A**) and after (**B**) treatment (orcein).

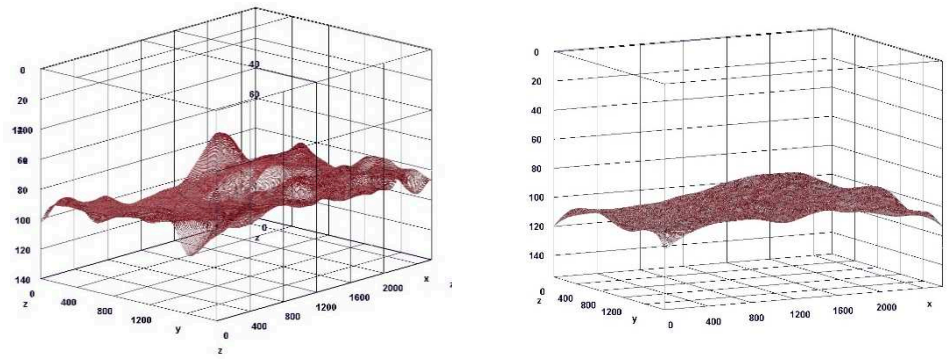


Figure 13. Visualization of the differences in elastin concentration before and after treatment.

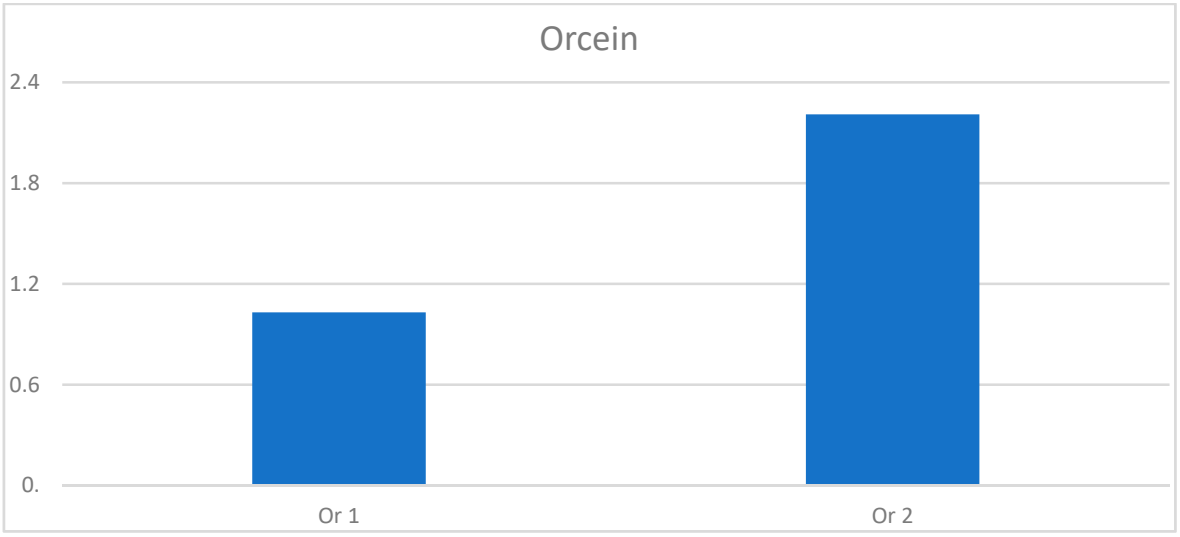
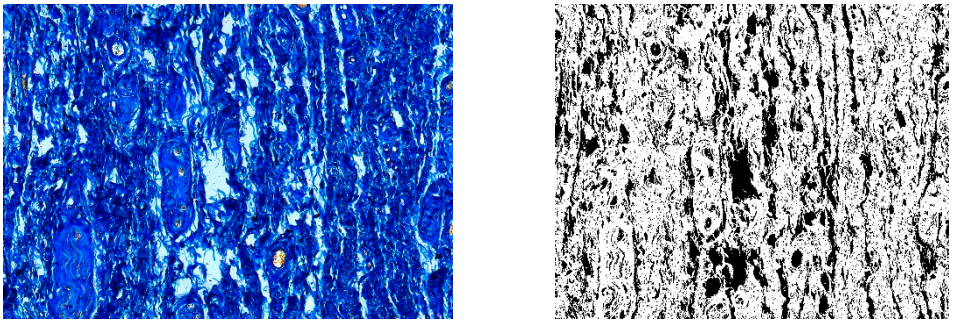


Figure 14. The comparison of specimens stained with orcein before and after the treatment revealed 11.43% rise in elastin concentration.

A



B Results from the skin of the labia majora

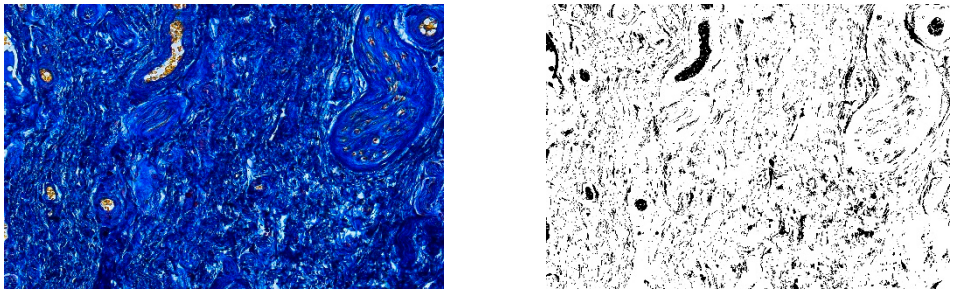


Figure 15. Segmentation before (**A**) and after (**B**) treatment (Mallory trichrome).

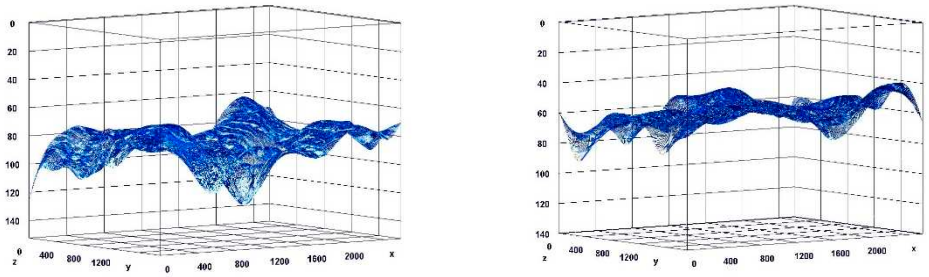


Figure 16. Visualization of the differences in collagen concentration before and after treatment (Trichrome).

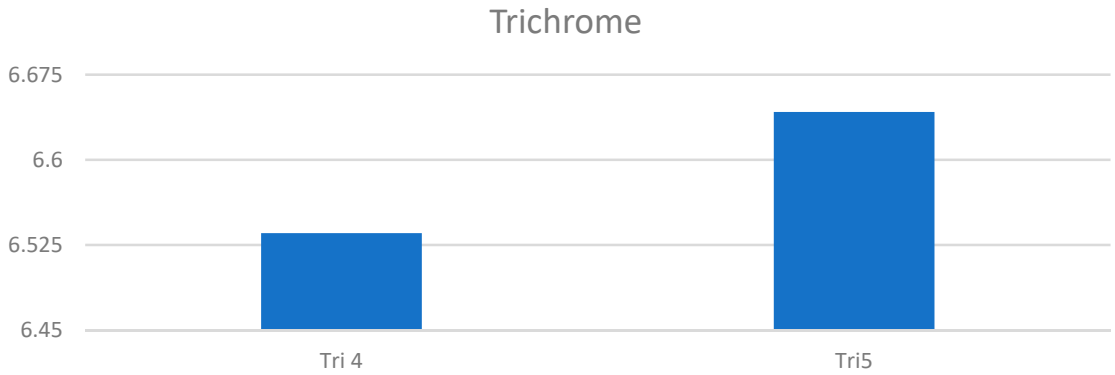


Figure 17. The comparison of specimens stained with trichrome before and after the treatment revealed 27.8% rise in collagen concentration.

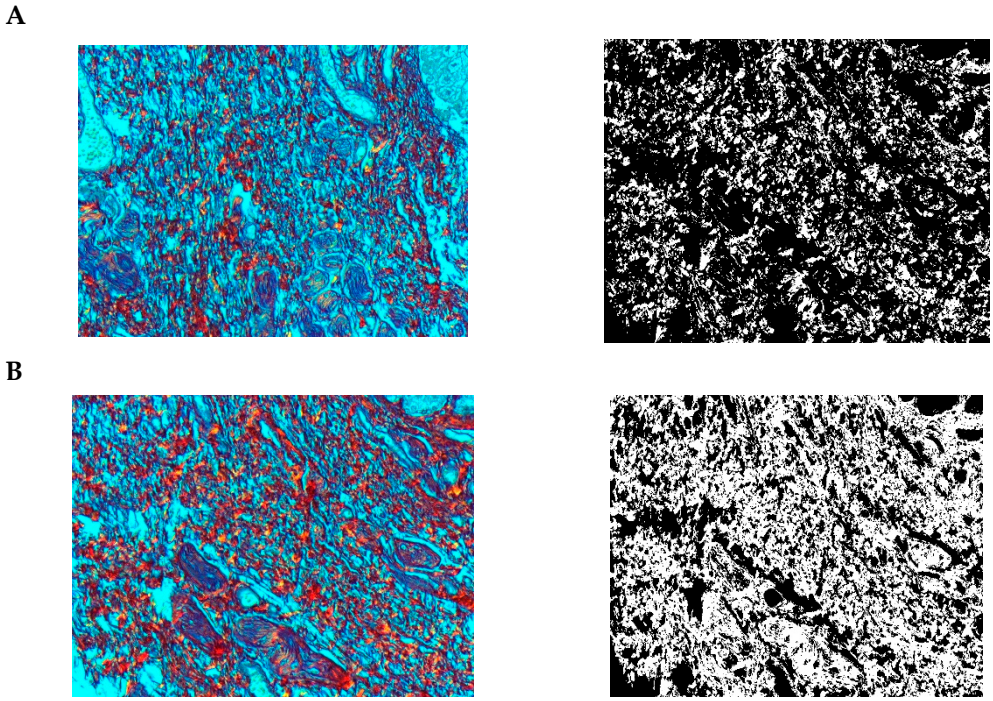


Figure 18. Segmentation before (**A**) and after (**B**) treatment (picrosirius red staining).

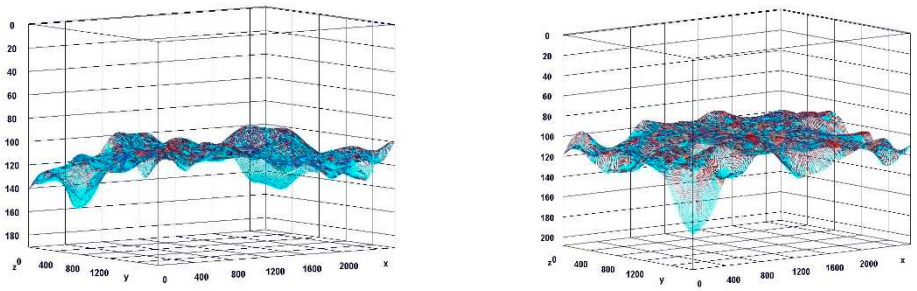


Figure 19. Visualization of the differences in collagen concentration before and after treatment.

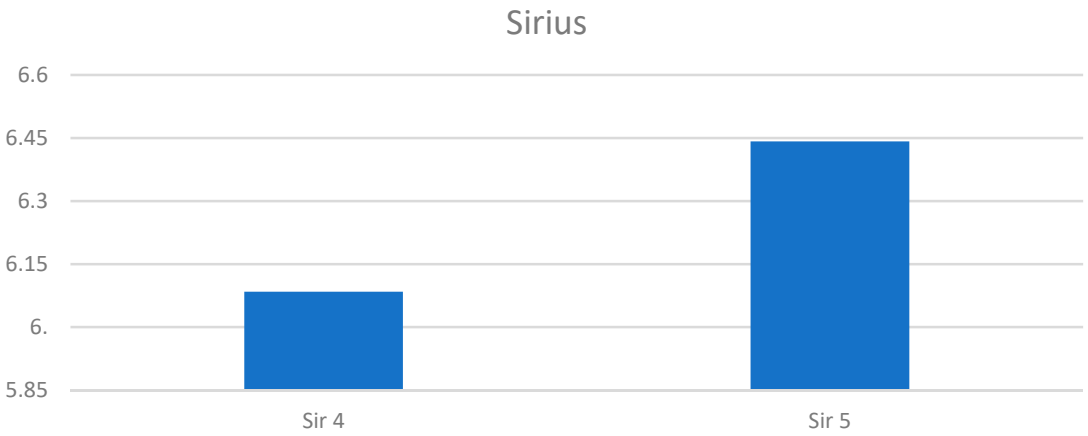


Figure 20. The comparison of specimens stained with trichrome before and after the treatment revealed 26.7% rise in collagen concentration.

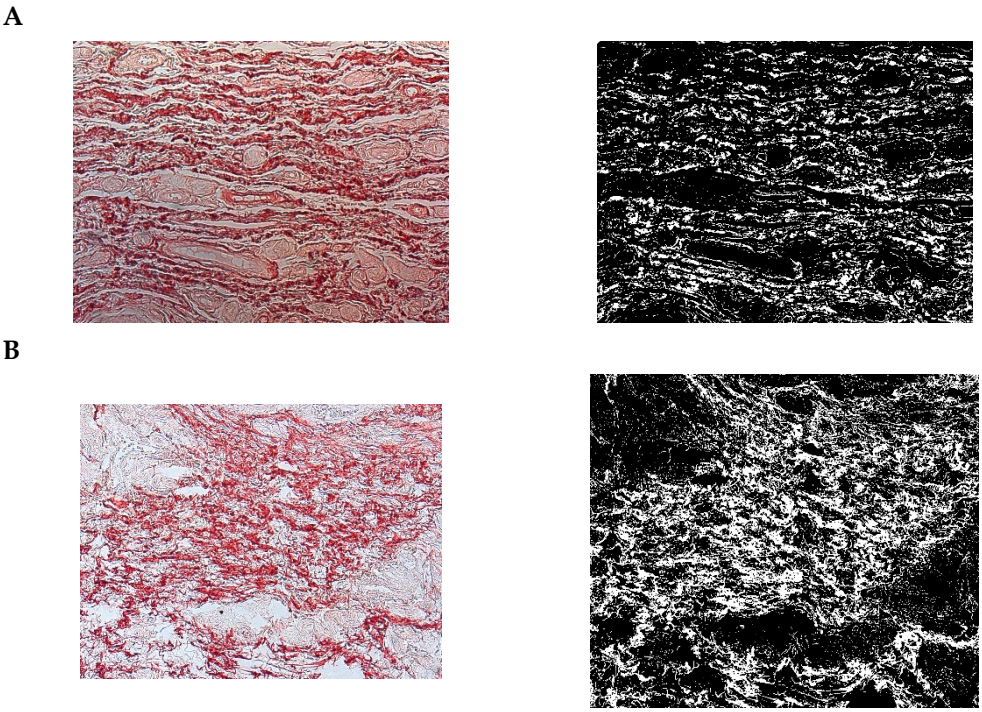


Figure 21. Segmentation before (**A**) and after (**B**) treatment (orcein).

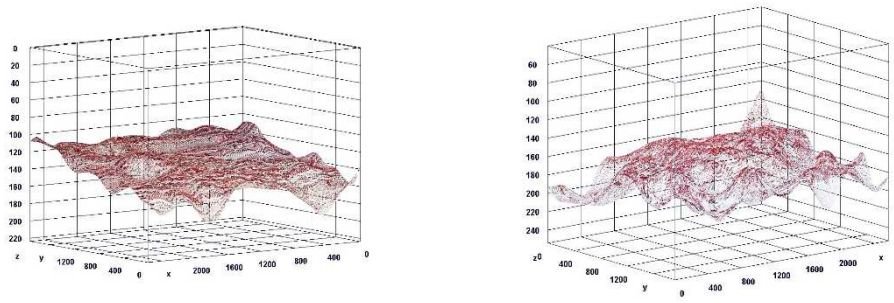


Figure 22. Visualization of the differences in elastin concentration before and after treatment.

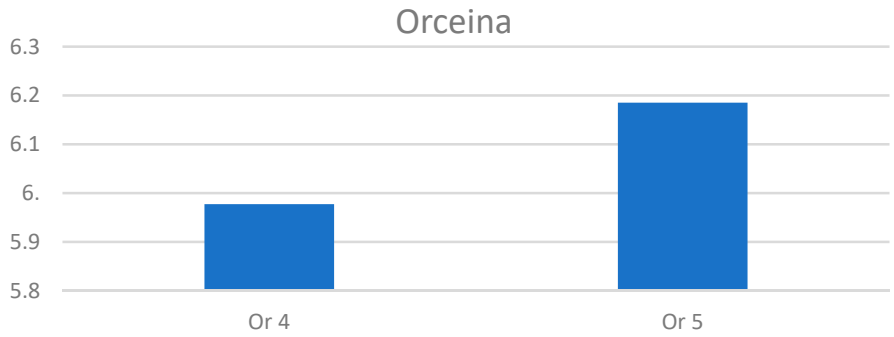


Figure 23. The comparison of specimens stained with orcein before and after the treatment revealed 61.8% rise in elastin concentration.

4. Discussion

Over the past decade, there has been an increase in the use of energy-based devices for sexual dysfunction, vulvovaginal laxity, and GSM, as well as to improve the appearance of external genitalia. Recently, the use of radiofrequency for the treatment of vaginal laxity, sexual dysfunction, and genitourinary syndrome of menopause (GSM), has shown promising treatment outcomes [25,26,29].

As a part of a urogenital function, the appearance deteriorates too. There are two studies showing the efficacy, effectiveness, and safety of an injection of HA into the skin of the labia majora [33,34] as well as the combination of the treatment in the region of the nasolabial folds and perioral rhytides with monopolar radiofrequency [37].

In our study, RF therapy performed four times, combined with HA injection improved all evaluated domains statistically significantly: vaginal laxity, female sexual disorder, sexual function, and genitourinary symptoms of menopause and labia majora hypotrophy. We also showed at the histochemical level an increase in collagen and elastin concentrations in both the vaginal wall and vulvar skin. The efficacy, safety, and comfort of the procedure were similar to other studies quoted above [25–27,29].

What distinguishes our research is the use of a bipolar radiofrequency and combining it with an HA injection into the skin of the labia majora to enhance the aesthetic effect. We have not encounter this combination of RF and HA in the skin of the labia majora in the literature.

In our opinion using bipolar RF seems to be safer then monopolar (the current goes between two rings, not between the active electrode and grounding pad under a patient's back , and as a result, a current flows in a not too well defined area). Another facet is the possibility of launching an RF current out of the handpiece in two ways: a pulse mode and a continuous mode. When we use external, vulvar application, the continuous mode, in motion, is recommended and we used it in our protocol.

The pulse mode is devised to be used in a vaginal application with no need to move the handpiece. With the monopolar devices accessible on the market, there is a need to move the vaginal handpiece back and forth in the vaginal canal, which can be embarrassing for the patient and the doctor performing the procedure.

The combined treatment turned out to be safe and painless with no side effects and with a statistically significant improvement between the baseline and findings 3 months after treatment. Apart from clinical efficacy, we also exhibited an aesthetic effect, evident in the pictures before and after, as well as evaluated by the GAIS.

5. Conclusions

The current study demonstrated the efficacy of this nonsurgical RF procedure combined with a hyaluronic acid (HA) injection into the skin of the labia majora on clinical, histological, and aesthetic levels.

Our study provides further evidence for the clinical utility, and direction for further evaluation. Since this is a pilot study with a small number of patients, further studies are

required to corroborate our findings and evaluate the long-term effects of the combined treatment of hyaluronic acid and radiofrequency.

Author Contributions: Conceptualization, N.Z. and P.K.; methodology, M.P.; software, M.P.; validation, P.Z., A.K.K. and B.W.; formal analysis, G.S.; investigation, R.H.; resources, A.N.; data curation, S.M.; writing—original draft preparation, P.K.; writing—review and editing, G.S.; visualization, A.B.; supervision, N.Z.; project administration, N.Z. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was approved by the Research Ethics Committee under number 09/KB/VII/2020, and conducted according to the guidelines recommended by the 2000 Declaration of Helsinki, updated in 2008.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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Radiofrequency treatment of vaginal laxity after vaginal delivery: nonsurgical vaginal tightening

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PMID: 20584127 DOI: 10.1111/j.1743-6109.2010.01910.x

Abstract

Introduction: All women who have given birth vaginally experience stretching of their vaginal tissue. Long-term physical and psychological consequences may occur, including loss of sensation and sexual dissatisfaction. One significant issue is the laxity of the vaginal introitus.

Aim: To evaluate safety and tolerability of nonsurgical radiofrequency (RF) thermal therapy for treatment of laxity of the vaginal introitus after vaginal delivery. We also explored the utility of self-report questionnaires in assessing subjective effectiveness of this device.

Methods: Pilot study to treat 24 women (25-44 years) once using reverse gradient RF energy (75-90 joules/cm(2)), delivered through the vaginal mucosa. Post-treatment assessments were at 10 days, 1, 3, and 6 months.

Main outcome measures: Pelvic examinations and adverse event reports to assess safety. The author modified Female Sexual Function Index (mv-FSFI) and Female Sexual Distress Scale-Revised (FSDS-R), Vaginal Laxity and Sexual Satisfaction Questionnaires (designed for this study) to evaluate both safety and effectiveness, and the Global Response Assessment to assess treatment responses.

Results: No adverse events were reported; no topical anesthetics were required. Self-reported vaginal tightness improved in 67% of subjects at one month post-treatment; in 87% at 6 months ($P<0.001$). Mean sexual function scores improved: mv-FSFI total score before treatment was 27.6 ± 3.6, increasing to 32.0 ± 3.0 at 6 months ($P < 0.001$); FSDS-R score before treatment was 13.6 ± 8.7, declining to 4.3 ± 5.0 at month 6 post-treatment ($P < 0.001$). Twelve of 24 women who

expressed diminished sexual satisfaction following their delivery; all reported sustained improvements on SSQ at 6 months after treatment (P = 0.002).

Conclusion: The RF treatment was well tolerated and showed an excellent 6-month safety profile in this pilot study. Responses to the questionnaires suggest subjective improvement in self-reported vaginal tightness, sexual function and decreased sexual distress. These findings warrant further study.

BMC Women's Health

RESEARCH

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Intravaginal nonablative radiofrequency in the treatment of genitourinary syndrome of menopause symptoms: a single-arm pilot study

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Abstract

Background: Genitourinary syndrome of menopause (GSM) involves vaginal dryness (VD), pain during sexual activity (SAPain), vaginal itching (VI), burning, pain, and symptoms in the urinary organs. Non-ablative radiofrequency (RF) is a type of current with electromagnetic waves with a thermal effect that generates an acute inflammatory process with consequent neocolagenesis and neoelastogenesis. We aimed to describe the clinical response to VD, SAPain, vaginal laxity (VL), VI, burning sensation, pain in the vaginal opening, urinary incontinence, sexual dysfunction, cytological changes, and adverse effects of non-ablative RF in patients with GSM.

Methods: This single-arm pilot study included 11 women diagnosed with GSM with established menopause. Patients with hormone replacement initiation for six months, who used a pacemaker, or had metals in the pelvic region, were excluded. Subjective measures (numeric rating scale of symptoms, Vaginal Health Index-VHI) and objective measures (vaginal maturation index-VMI, vaginal pH, sexual function by the FSFI, and urinary function by the ICIQ-SF) were used. A Likert scale measures the degree of satisfaction with the treatment. Five sessions of monopolar non-ablative RF (41°C) were performed with an interval of one week between each application. The entire evaluation was performed before treatment (T0), one month (T1), and three months (T2) after treatment. Adverse effects were assessed during treatment and at T1 and T2.

Results: The symptoms and/or signs were reduced after treatment in most patients (T1/T2, respectively): VD 90.9%/81.8%, SAPain 83.3%/66.7, VL 100%/100%, VI 100%/100%, burning 75%/87.5%, pain 75%/75%, and VHI 90.9%/81.9%. Most patients did not show changes in VMI (54.5%) and pH (63.6%) at T1, but there was an improvement in VMI in most patients (54.5%) at T2. Nine patients were satisfied, and two were very satisfied at T1. The treatment was well tolerated, and no adverse effects were observed. There was an improvement in sexual function (72.7%) and urinary function (66.7% in T1 and 83.3% in T2).

Conclusion: Intravaginal RF reduced the clinical symptoms of GSM in most patients, especially during T1, and women reported satisfaction with treatment. The technique showed no adverse effects, and there were positive effects on sexual and urinary function.

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Trial registration This research was registered at clinicaltrial.gov (NCT03506594) and complete registration date was posted on April 24, 2018.

Keywords: Genitourinary syndrome of menopause, Menopause, Radiofrequency

Background

Genitourinary syndrome of menopause (GSM) is traditionally defined as a set of signs and symptoms due to altered estrogen production, both physiologically or as a result of a therapeutic approach. It involves physical and sensory changes in the external and internal genitalia and lower urinary tract region, such as loss of collagen and elastin, altered smooth muscle cell function, reduction in the number of blood vessels, and an increase in connective tissue, leading to epithelial thinning, decreased blood flow, and reduced elasticity [1]. Women may have some or all the signs and symptoms. The most common symptoms are vaginal dryness (VD), pain during sexual activity (SAPain), and urinary incontinence (UI) [2]. It is estimated that 10%- 45% of these women live with some discomfort due to GSM. However, only 25% seek treatment, and symptoms are unlikely to improve spontaneously [2–4].

GSM treatment aims to alleviate symptoms and reverse atrophic anatomical changes. Hormonal therapy is the current gold standard treatment that can be administered systemically or locally [1, 5, 6]. However, there are contraindications such as history of breast cancer, coronary artery disease, previous venous thromboembolic event or stroke, and adverse effects, such as vaginal bleeding, endometrial hyperplasia, breast pain, and perineal pain, which limit its use [3, 6, 7]. Approximately 23% of women using hormonal therapy reported that they felt incomplete or no relief of vaginal/vulvar symptoms and 36% of patients noted that the vagina did not restore their natural state [8].

With the contraindications and limitations of standard therapy for GSM, a search for new therapeutic options for GSM management is needed. Radiofrequency (RF), a new alternative technique for GSM [9], is a high-frequency current used for therapeutic purposes, based on the mechanism of heat production by conversion, that is, ionic and molecular mobilization, favoring oxygenation, nutrition, and vasodilation of tissues [10]. The heating of the tissues also promotes the denaturation of collagen with a subsequent contraction of its fibers, retraction of fibrous septa, and activation of fibroblasts. Neocolagenization, neoelastogenesis, and reorganization of collagen fibers may occur, resulting in tissue remodeling [10–12].

Based on the knowledge of the physiological responses of the tissues submitted to RF and on the results of its use on the treatment of genitourinary signs and symptoms related to GSM, this research aimed to describe the clinical response (VD, SAPain, vaginal laxity (VL), vaginal itching (VI), burning sensation, pain in the vaginal opening, UI, and sexual dysfunction), cytological changes, and adverse effects of non-ablative RF in patients with GSM.

Materials and methods

Study design

This was a single-arm pilot study preceding a randomized controlled trial (RCT) in progress, followed the precepts of the Declaration of Helsinki, with the approval of the Ethics and Research Committee of the Bahiana School of Medicine and Health (EBMSP) with CAAE 72147317.9.0000.5544 on September 5, 2017, and registered at clinicaltrial.gov (NCT03506594) and complete registration date (first date posted) on April 24, 2018. Written informed consent was obtained from all patients.

Adult women with established menopause (at least 12 months after their last period and/or bilateral oophorectomy) and who had complaints of at least one of the symptoms of GSM (VD, SAPain, VL, VI, burning sensation, and pain in the vaginal opening) participated in the study. The women were referred by gynecology services, and the service took place at the teaching outpatient clinic of the Physiotherapy Clinic at EBMSP. For inclusion in the study, they should have a vaginal pH of ≥ 5 and vaginal cytology from the last 12 months, or three previous normal tests, without any malignancy and/or atypia. We excluded patients with hormone replacement initiation for six months, who used a pacemaker, or had metals in the pelvic region, hemophiliacs, using vasodilators and/or anticoagulants, and those with chronic neurological degenerative diseases and/or diagnosis of current vaginal infection.

Assessment procedures

Initially, we administered a basic anamnesis questionnaire for collecting sociodemographic and clinical data. Each participant subjectively assessed their symptoms (VD, SAPain, VL, VI, burning sensation, and pain in the vaginal introitus) using the **Numeric Rating Scale (NRS)**, which consists of a scale from 0 to 10 points, with 0 indicating no symptoms and 10 indicating as many symptoms as possible.

The physical examination was to assess the **vaginal health index (VHI)**, which consists of a graduated scale from 1 to 5 for each item (vaginal elasticity, fluid volume,

pH, epithelium integrity, and humidity). Vaginal elasticity varies between 1 (no elasticity) and 5 (excellent elasticity), assessed through mucosal distention upon palpation and in the placement of the speculum. Fluid volume, assessed at inspection, varies between 1 (no secretion) and 5 (normal secretion) (white flocculent). Epithelium integrity varies between 1 (petechiae already detected on inspection) and 5 (tissue not friable and normal mucosa). Moisture varies between 1 (no moisture detected in the inspection and presence of an inflamed mucosa) and up to 5 (normal humidity). The pH was quantified using a pH indicator strip between 0 and 14 (MColorpHast™—pH-indicator strips) which was placed directly on the right lateral vaginal wall for one minute, giving 1 point for the pH of 6.1, and 5 for the pH $\leq$ 4.6, in which the last one was considered normal. The sum of all items represents the vaginal health score, with 25 representing the best vaginal health [13].

The **Vaginal Maturation Index (VMI)** was evaluated from a vaginal secretion collection, in the middle third of the vaginal canal, fixed in absolute alcohol and sent to a laboratory, in which a biomedical doctor performed the percentage counting of the parabasal (P), intermediate (I), and superficial (S) cells, characterizing the vaginal epithelium in hypotrophic (I > S), normotrophic (I = S), hypertrophic (I < S), mild atrophic (I > P), moderate atrophic (I > = P) and marked atrophic (I < P). The sum of the three cell types totals 100% and is presented as follows: P/I/S [14].

Participants answered the **Female Sexual Function Index (FSFI)** [15] questionnaire to objectively assess sexual function, gathering responses in six different domains: desire, arousal, lubrication, orgasm, satisfaction, and discomfort/pain. The cut-off point of $\leq$ 26.5 was considered for sexual dysfunction and the increase in the score was considered an improvement. The **Sexual Quotient-Female Version (QS-F)** assessed women's sexual activity. This questionnaire was developed and validated in 2006, specifically for the Brazilian population [16]. Through ten self-answering questions, the QS-F assesses all phases of the sexual response cycle with a total index ranging from 0 to 100. Higher values indicate better sexual performance and satisfaction.

To assess the impact of UI on quality of life and characterize urinary loss, we used the **International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF)** [17], composed of five questions that assess the frequency, severity, and impact of UI, in addition to a set of eight items of self-diagnosis related to UI situations experienced by patients. The maximum sum of the response values indicates a score of 21 points, referring to the high impact of UI on an individual's life.

At the end of the treatment, the participants were asked about their degree of satisfaction with the treatment using a five-point Likert scale, which classified the patient's level of satisfaction as 1 (very dissatisfied), 2 (dissatisfied), 3 (unchanged), 4 (satisfied), 5 (very satisfied) [18].

To assess the clinical response, we considered an improvement when there was a decrease in values in self-reported symptoms, verified by the NRS; the increase in the value of the VHI; the decrease in parabasal cells (deep) and/or increase in superficial cells evaluated by VMI, a decrease in vaginal pH, an increase in FSFI and QS-F scores, a decrease in the sum of the ICIQ-SF questions, and improved satisfaction according to the five-point Likert scale.

We used all outcome measures before, one month, and three months after the end of treatment, respectively, times T0, T1, and T2, performed by the same initial evaluators.

To test safety, we considered existing adverse effects if they had erythema, ulcers, fistulas, burns, blisters, bleeding, and/or pain. They were evaluated during each application at T1, T2, or at any contact by the patients' self-reports. We considered it to be at risk if it had one or more of these effects. If an adverse effect occurs, the patient was referred for evaluation and treatment by the team's gynecologist. The RF treatment would be interrupted, and the data are presented in the results.

Therapeutic procedure

RF was used in the form of capacitive electrical transfer, monopolar configuration (Capenergy® device, model C500), which has two electrodes: an intracavitary active electrode placed in the vagina with a non-lubricated condom and water-soluble gel and another electrode, dispersive, positioned in the lumbosacral region (Fig. 1). For the

Fig. 1 Radiofrequency device (Capenergy®)

application, the participants were placed in the supine position with the lower limbs abducted and the knees bent. The temperature was set at 41°C, with a frequency of 1 MHz and power of 75 kJ. When the established temperature was reached, the physiotherapist maintained it for 2 min with semicircular movements on the anterior wall of the vagina. The movement and time on the posterior vaginal wall was repeated, totaling 4 min of after reaching the established temperature (Fig. 2). Each patient underwent five RF sessions, with an interval of seven days between them.

Data analysis

For the elaboration of the database, we used the software Statistical Package for Social Sciences (SPSS), version 14.0 for Windows. The results were reported descriptively in the text or through tables and graphs; categorical variables are expressed as absolute and percentage values—n (%), and continuous variables with normal distribution in mean and standard deviation (± SD), and those with asymmetric distribution in the median and interquartile range (IQ).

Results

Sociodemographic and clinical characteristics

The sample consisted of 11 patients with GSM, with an average age of 59.6 ± 3.93 years, with data collected from October 2017 to August 2018. Table 1 presents the sociodemographic and clinical characteristics of the study population. The main characteristic was VD, as they all had this symptom. Menopause duration ranged from two to 17 years, with a median of 14 years (6–15).

Fig. 2 Radiofrequency application (Capenergy®) intracavitary with semicircular movements

Symptoms of GSM

We observed the clinical improvement of GSM in the NRS scores of the symptoms of VD, SAPain, VL, VI, burning, and vaginal pain, as shown in Table 2, especially in T1.

Vaginal Health Index (VHI)

Ten patients (90.9%) showed an increase in the VHI score in T1, which represents an improvement, and one worsened (patient five). Regarding pre-treatment, in T2, nine patients (81.8%) had an increase in VHI, while two (18.2%) had a reduction in this index during the initial value (Table 3).

Vaginal pH

In T1, most patients (7–63.6%) did not change, three (27.3%) showed a decrease in pH, representing improvement, and one (9.1%) showed an increase. In T2, there was also a predominance of maintaining baseline values (Table 3).

VMI

The cytological analysis showed that six patients (54.5%) remained unchanged in the cell count, and five (45.5%) showed an improvement in T1, with two patients of the latter changing their category from moderate or severe atrophic to mild atrophic. In T2, six patients (54.5%) showed improvement compared to the beginning, three (27.3%) remained at the beginning, and two (18.2%) worsened. One patient maintained the category of severe atrophy, and the other went from hypotrophic to severe atrophy (Table 3).

Sexual function

In the FSFI analysis, all patients experienced sexual dysfunction during pre-treatment. There was an increase in the total index in nine patients (81.8%) in T1, with three patients without sexual dysfunction. In T2, eight patients (72.7%) had improved compared to the beginning, but half had a decrease compared to T1, and two continued without sexual dysfunction. According to the **QS-F,** seven patients (63.6%) had sexual dysfunction at T0. Ten (90.9%) and seven (63.6%) patients improved their scores at T1 and T2 respectively, compared to the beginning. We observed worsening of the two periods evaluated in Patient 11 (Table 3).

Urinary symptoms

In this study, six patients had pre-treatment urinary complaints. When assessing the impact of UI on quality of life (QoL) using the ICIQ-SF questionnaire, we found a decrease in the score in four patients (66.7%) in T1, one of whom had no symptoms; two (33.3%)

Table 1 Sociodemographic and clinical characteristics of 11 patients with GSM

Sociodemographic characteristics	
	Mean ± *SD*
Age	59.6 ± 3.93
Education level	n (%)
Complete higher education	5 (45.5)
Complete high school	4 (36.4)
Complete Elementary school	1 (9.10)
Illiterate	1 (9.10)
Marital status	
Married	4 (36.4)
Divorced/separated	3 (27.3)
Single	2 (18.2)
Widow	2 (18.2)
Self-reported skin color	
Brown	7 (63.6)
Black	2 (18.2)
White	2 (18.2)
Clinical characteristics	**n (%)**
Body mass index	
Low weight	1 (9.10)
Normal	3 (27.3)
Overweight	6 (54.5)
Obesity	1 (9.10)
Hormone replacement	5 (45.5)
Gynecological surgeries	9 (81.8)
Constipation	4 (36.4)
Number of deliveries	
Nulliparous	1 (9.10)
Primiparous	1 (9.10)
Multiparous	9 (81.8)
Type of delivery	
Vaginal	5 (45.5)
Cesarean	5 (45.5)
Symptoms of GSM	
Vaginal dryness	11 (100)
Pain during sexual activity	6 (54.5)
Vaginal laxity	6 (54.5)
Vaginal itching	6 (54.5)
Vaginal burning	8 (72.7)
Vaginal pain	4 (36.4)
Urinary incontinence	6 (54.5)
Vaginal intercourse/penetration/coitous	
No	6 (54.5)
Sexual dysfunction	8 (72.7)
Vaginal color	
Whitish	6 (54.5)
Normal	5 (45.5)

Table 2 Numerical Rating Scale of the symptoms of Genitourinary Syndrome of Menopause before treatment, 1 month and 3 months after 05 radiofrequency sessions

Patient	Pre-treatment						1 month						3 months					
	VD	SAPain	VL	VI	B	Pain	VD	SAPain	VL	VI	B	Pain	VD	SAPain	VL	VI	B	Pain
1	10	10	0	5	10	0	3	5	0	0	0	0	7	7	0	5	6	7
2	9	8	0	0	0	0	3	0	0	3	0	0	6	0	0	4	0	0
3	10	0	8	10	9	10	7	0	6	9	10	6	5	0	2	9	10	2
4	5	0	10	7	5	0	0	0	8	0	0	0	0	0	7	0	2	0
5	8	2	5	0	0	2	4	0	1	0	1	0	8	1	4	0	0	0
6	7	7	0	0	0	0	1	1	1	0	0	0	1	0	0	0	0	1
7	10	0	3	2	4	0	2	0	0	0	0	1	1	0	0	0	0	0
8	10	0	2	0	4	0	1	0	0	0	2	0	1	8	0	0	2	0
9	7	7	0	6	5	7	7	7	2	5	5	7	7	0	3	4	4	7
10	9	8	5	5	8	8	1	0	0	0	0	0	1	0	0	0	0	0
11	10	0	0	0	9	0	5	0	2	0	4	0	1	0	1	0	1	0

VD vaginal dryness, *SAPain* pain during sexual activity, *VL* vaginal laxity, *VI* vaginal itching, *B* burning

Table 3 Vaginal Health Index, Vaginal Cytology, Vaginal pH, FSFI, Sexual Quotient, and ICIQ in 11 patients with GSM, pre-treatment, 1 month, and 3 months after 05 radiofrequency sessions

Patient	PRE						1 month						3 months					
	VHI	pH	VMI %B/I/S	FSFI	QS	ICIQ	VHI	pH	VMI %B/I/S	FSFI	QS	ICIQ	VHI	pH	VMI %B/I/S	FSFI	QS	ICIQ
1	14	5.5	0/90/10	8.5	14	0	25	4.0	0/90/10	14.7	28	0	21	5.0	10/90/0	11.7	30	0
2	12	6.5	40/60/0	3.0	22	0	23	5.0	6/90/4	2.4	24	0	19	5.0	5/95/0	5.0	22	0
3	18	5.0	0/95/5	3.4	16	14	21	5.0	0/80/20	6.2	44	13	22	5.0	0/95/5	6.2	44	11
4	18	6.0	100/0/0	3.0	18	3	20	6.0	20/70/10	7.0	28	7	17	6.0	90/10/0	4.8	44	0
5	18	6.5	100/0/0	24.3	64	0	15	7.0	100/0/0	27.4	72	0	14	6.5	90/10/0	24.4	64	0
6	14	5.0	0/95/5	4.4	66	8	22	5.0	0/95/5	4.0	74	11	20	5.0	0/95/5	3.8	74	9
7	11	7.0	90/10/0	2.6	20	11	13	6.0	90/10/0	20.4	76	0	15	6.0	95/5/0	4.7	18	0
8	17	6.0	100/0/0	23.8	50	12	18	6.0	95/5/0	27.9	60	7	23	5.0	5/90/5	28.2	62	4
9	16	5.0	0/95/5	3.2	24	0	17	5.0	0/90/10	3.2	46	11	19	5.0	0/68/32	10.6	34	13
10	16	5.0	0/95/5	22.7	70	6	20	5.0	0/95/5	31.8	88	4	22	5.0	0/90/10	31.8	90	4
11	22	5.0	0/90/10	4.4	86	0	24	5.0	0/90/10	4.8	60	0	23	5.0	0/90/10	3.6	76	0

VHI Vaginal Health Index, *pH* vaginal pH, *%B/I/S* % basal/intermediate/superficial cells, *FSFI* Female Sexual Function Index, *QS* sexual quotient—female version, *ICIQ* International Consultation on Incontinence Questionnaire—Short Form, *VMI* Vaginal Maturation Index

increased the score and one who had no symptoms started to complain (patient nine). In T2, almost all patients (five—83.3%) had an improvement in the beginning, in which two had their symptoms disappeared, and two had a higher score than the initial one (Table 3).

Satisfaction with treatment

Regarding treatment satisfaction, nine patients (81.8%) reported being satisfied and two (18.2%) were very satisfied at T1. In T2, nine patients (81.8%) remained satisfied, one (9.1%) very satisfied, and one (9.1%) very dissatisfied (Fig. 3). The patient who reported being

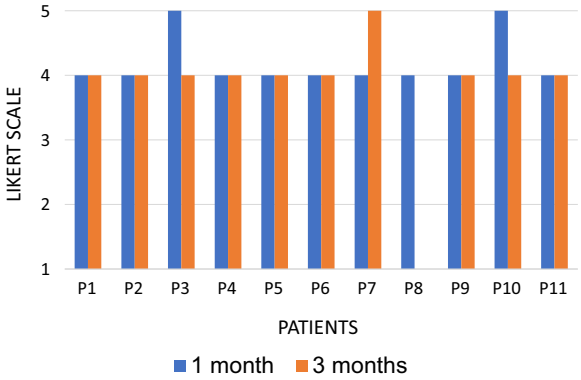

Fig. 3 Satisfaction with the treatment of 11 patients with GSM, 1 month and 3 months after 05 radiofrequency sessions

very dissatisfied with the reassessment during T2 showed improvement in all other parameters evaluated and reported being satisfied after one month.

Adverse effects

We did not observe erythema, ulcers, fistulas, blisters, burns, bleeding, and/or pain at any time during treatment or follow-up. The treatment was well tolerated. One patient reported a little discomfort in the lower abdominal region during the first two sessions, which ceased in the third application.

Discussion

We found an improvement in genitourinary symptoms such as VD, SAPain, VL, VI, burning sensation, pain in the vaginal opening, UI, and sexual dysfunction in most patients, especially in T1, in this pilot study that used non-ablative RF in postmenopausal women with GSM. The application of RF was considered safe because only one light adverse effect in one patient was found up to T2. To our knowledge, this is the first study to assess symptoms of GSM associated with cytological analysis and patient satisfaction after using non-drug and non-ablative treatment with intracavitary monopolar RF.

VD was the main symptom reported by patients in this study and showed an important improvement when assessed by both self-report and by VHI. Based on the histological changes observed in previous studies, the process of neocolagenesis and neoelastogenesis that occurs after exposure to controlled RF thermal energy in the vaginal tissue restores most vaginal functions such as secretion, absorption, elasticity, lubrication, and tissue consistency, which are decreased in GSM [9, 19, 20]. This hypothesis is supported by previous knowledge that this high-frequency current induces collisions and movements between atoms and molecules, resulting in energy transfer to the tissue in the form of heat and a consequent controlled increase in temperature, promoting an increase in the arterial circulation, and vasodilation, and improving tissue oxygenation [21].

VD can generate or contribute to SAPain, just as abstinence from intimate relationships is involved in the decline of lubrication, often forming a cycle. Vaginal trophism is fundamental for a comfortable sexual intercourse, which depends on the lubrication promoted by vasodilation of the lamina propria and the vaginal epithelium [22, 23]. In this study, a patient who did not have SAPain in the pre-treatment started to report this symptom in T2. An assumption is that an increase in the frequency of sexual activity may favor the appearance of this symptom. To confirm this hypothesis, an investigation of sexual frequency before and after treatment must be included. We are developing an RCT in which this variable has been included and, therefore, we may soon have this information. The increase in sensory perception by neurogenesis can occur after using RF [20], which can lead to a greater perception of the vagina; therefore, some patients may start to report these symptoms. However, further morphometric investigations of neuronal analysis are necessary.

Other studies have also found positive results for SAPain. Alinsod (2015) studied RF with controlled temperature (TTCRF) with intra- and extra-vaginal application in six menopausal women and 10 in the perimenopausal period with SAPain symptoms, demonstrating the safety and beneficial effects of the treatment [24]. An RCT with 20 postmenopausal women applied three sessions of intra- and extra-vaginal TTCRF (ThermiVa) once a month with reduced VD and SAPain [25].

RF has also been widely used to improve collagen levels. Its diathermic effects cause the collagen denaturation. As the temperature rises, some of the cross-links are broken, causing the triple helix to unwind. Thus, there is a consequent activation of fibroblasts, with subsequent neocolagenesis, neoelastogenesis, and tissue remodeling [26]. Coad et al. (2013) evaluated the histological effect of non-ablative RF on the vaginal introitus of sheep before, after seven, 30, and 90 days. There was a significant increase in the activation of the submucosa fibroblasts and an increase in collagen compared to the control group [27]. In a histological study in multiparous sows, a significant progressive increase in the amount of elastin and collagen in the vaginal mucosa was observed. The treatment consisted of weekly intravaginal radiofrequency administrations for three weeks, with follow-up at both one week and one month after treatment [28]. The evaluation of the vaginal wall, performed by ultrasound, showed an increase in thickness, but it was not statistically significant [28]. In our study, the NRS was used to grade VL, and all patients noted improvement. Three patients who did not have the complaint initially reported mild intensity in the reassessments, which can also be justified by the increase in sensory perception after treatment. Assessing the symptoms of GSM is challenging because of its subjective nature. The development of a specific score with a cut-off point for the quantification of these symptoms and clinical improvement may be of great relevance to better evaluate these patients and verify the treatment effect.

Previous studies have obtained positive results with the use of monopolar RF with cryogenic surface cooling in pre-menopausal women with a history of at least one vaginal delivery and complaints of vulvovaginal atrophy/symptoms of GSM or VL [26, 29]. Alinsod (2015) used the TTCRF in 23 pre-menopausal women with VL, with

improvement on a seven-point scale, called the vaginal laxity questionnaire (VLQ) [30]. Krychman et al. (2017) carried out a multi-center study with 189 premenopausal women complaining of VL during sexual intercourse with significant improvements in self-report and sexual function by FSFI [29].

Symptoms such as VI, burning, and pain are common complaints in GSM. Hypoestrogenia results in reduced number of epithelial layers and vessels, thinning of smooth muscles [31], and an increase in nociceptive sensory afferents [32]. In addition, the increase in tissue friction caused by the decrease in trophism and moisture causes greater mucosal fragility, contributing even more to the condition [22, 33]. In this study, there was an important improvement in these symptoms. This clinical improvement is supported by the thermal effect of RF, which significantly affects the tissue layers. As a consequence of local peripheral vasodilation and increased blood flow, there is an improvement in trophism, oxygenation, cellular metabolism, and lubrication [10, 34]. High-frequency thermal therapy seems to act through the effects of analgesia, but the mechanisms by which RF controls pain are still unclear, seemingly involving the transduction of C fiber signals [35].

The analysis of vaginal cytology through the VMI and the measurement of pH are well-used measures to establish diagnostic parameters of GSM [36, 37], but have not yet been analyzed in RF research in GSM. Brizzolara et al. (1999) carried out a study in 70 postmenopausal women determining a specific vaginal pH range that correlates with high levels of parabasal cells in the VMI, defined as at least 20%, and found a correlation between these two objective measures [38]. In this study, pH values ≥ 6.0 were compatible with a greater number of parabasal cells ($\geq 20\%$). However, these results showed that there was no pattern of clinical/objective findings with the symptoms reported by the patients. VMI and pH, unlike NRS, remained similar in most patients (six-54.6% and seven-63.3%, respectively) in T1. In T2, most patients showed an improvement in VMI (54.6%) and in pH (36.4%). Vaginal cytology, in part, has been inconsistent with clinical findings [36]. A smaller-scale and more sensitive tape is recommended to detect minor variations.

Two patients presented with worsening VMI, which may have happened at random, because it is a small sample or due to the aging process. This change could be better controlled by an RCT. In the literature, there is no evaluation made of the agreement between evaluators of the VMI, which is a dependent evaluation instrument.

GSM has adverse effects on sexual function and general well-being. The FSFI is an instrument used worldwide to assess sexual function. In this study, it improved in most of the samples in T1 (81.8%) and T2 (72.7%). Patients were also evaluated using QS-F, a questionnaire specifically developed for the Brazilian population [16]. In terms of the total score, we observed an increase in QS-F in most of the participants. The promising results and the last position statements published by the European Society of Sexual Medicine [39] stimulated our group to carry out an RCT of RF in the treatment of signs and symptoms of GSM that is in progress. Using the non-ablative RF technique, Lordelo et al. (2016) carried out an RCT with 43 women dissatisfied with the appearance of their genitalia. They applied RF to the external genitalia, with an improvement in sexual function by 3.51 points in the group treated in the evaluation by FSFI [11].

RF is considered one of the most innovative non-surgical modalities for treating UI and VL [40]. In addition to modifying the trophism of the vaginal canal, it also targets the urethral mucosa and seems to improve not only the symptoms of GSM but also those of UI. This change could be better controlled by an RCT. In our study, although the type of UI has not been classified, 66.7% and 83.8% of the patients improved urinary symptoms at T1 and T2, respectively. Lalji & Lozanova (2017) in a pilot study, conducted three treatment sessions with monopolar RF, intra- and extra-cavitary, in 27 women with stress urinary incontinence (SUI). They found that 96.3% decreased the frequency of urinary loss by at least one level, and 59.3% reported a decrease in the amount of loss [41]. Another study with 10 patients with SUI showed improvement in the pad test one month after treatment with monopolar non-ablative RF in the urethral meatus [42]. Despite different outcome measures and application forms, RF therapy appears to be a good alternative for the treatment of SUI. Histological studies have observed a reduction in collagen in the urethral walls in the event of loss of urethral support and/or internal sphincter dysfunction [43], which supports the use of RF in this dysfunction.

Treatment satisfaction was assessed using a five-point Likert Scale, with most patients reporting satisfaction with treatment. This was reinforced by the decrease in symptoms recorded in that study. On the other hand, we observed that although most of the outcome measures have improved, the indication of patient satisfaction was greater, showing that the degree of satisfaction do not always correspond to the clinical results. Thus, satisfaction is not only linked to the therapeutic result, but also to the level of expectations of the people involved. It is important to consider the Hawthorne effect, which states that when individuals believe they are experiencing a form of treatment, they are more likely to respond and be satisfied with therapeutic responses [44]. In this sense, we also justified carrying out an RCT to better assess this issue.

Our safety analysis showed that the technique was well tolerated by patients and no side effects were observed or reported. In one patient, only mild discomfort was noted in the first two sessions. Also in the study by Lalij and Lozanova (2017), using intravaginal and extracavitary radiofrequency, no side effects were reported [41]. In this study, no description about possible side-effects was given either. The parameters of this study were also different from ours (e.g.: we measured temperature; had five treatment sessions instead of three; applied RF laterolateral instead of longitudinal; and we included a follow-up after three months). Because it was not entirely clear to what extent the different therapeutic parameters would influence safety, we decided to include a safety assessment in our research. We therefore chose to initially conduct a single-arm pilot study with patients presenting GSM. And we only moved on to a Phase 2 trial with a control group and sample calculation [45] once the therapeutic protocol was found to be safe and if there was a therapeutic response. In a safety study conducted in an animal model in treated sows, additional aspects were evaluated, such as the presence of edema, histological changes in the composition of the vaginal wall, change in urination frequency, erythema, and antalgic position, and no side effects were found [28]. A long-term effect that was not evaluated in our study and, to our knowledge, in any other study in the literature, is the possibility that non-ablative radiofrequency enhances the development of tumor cells. A biological effect takes place in the treated area as the electromagnetic field causes a temperature increase [10], and an increased blood circulation. The possibility of cell multiplication is hypothesized, including malignant cells [46]. Therefore, as a safety inclusion, patients had to undergo a vaginal cytology test and show a normal outcome, prior to treatment. For many years the literature has described the effect of thermotherapy (including radiofrequency), which, at a temperature of 41°C or more, and if maintained for at least 30 min, brings a possible therapeutic effect against cancer cells by reducing cellular DNA and RNA synthesis and respiratory depression [47]. The application of radiofrequency in the present study took place at a temperature of 41ºC, but the total treatment time was lower than the recommended time to treat cancer cells, and for this reason it may be important to perform a new long-term cytopathological evaluation to confirm the safety of the treatment technique.

Although some of the patients continued to show improvement in their symptoms in T2, some symptoms were accentuated in that period. Studying the frequency of reapplication after the end of treatment to maintain clinical improvement is essential in future studies, especially since we already have evidence from histological studies (in animals) that show that the peak of RF action occurs within 21 days after its application [10].

Strengths and limitations

This is a pioneer research on the application of intracavitary non-ablative radiofrequency (RF), in women with Genitourinary Syndrome of Menopause (GSM). The study combines clinical symptoms of GSM, including sexual and urinary functions, with cytological results, patient satisfaction and treatment outcomes.

As it is a non-medicated pharmacological approach, applied locally, it opens up a new field for the treatment of this syndrome. In addition to being a new field for physiotherapy professionals.

As limitations of the study, we found a short follow-up time, the use of independent symptom outcome measures (such as sexual and urinary function questionnaires) for symptoms associated with a syndrome, the use of evaluator dependent indices (VHI and VMI) and a subjective index (VHI).

Based on these limitations, we understand the need to create a specific rating scale for GSM symptoms, intra- and inter-rating comparisons for rater-dependent scales for longer follow-up period and, since intracavitary non-ablative RF has been proven safe, the realization of an RCT.

Conclusions

The symptoms of VD, SAPain, VL, VI, burning sensation, pain in the vaginal opening, UI, and sexual dysfunction of GSM with non-ablative RF showed clinical improvement in most of the patients, with improvement in the self-report of the symptoms and the VHI, especially at T1. The cytological analysis, through the VMI, remained unchanged in most evaluations in T1, but there was a greater improvement in T2. There was no change in vaginal pH in most patients after RF treatment. There was no adverse effect in the 11 patients evaluated, which is considered a safe and well-tolerated technique, and patients reported satisfaction with treatment.

Abbreviations

B: Burning; EBMSP: Bahiana School of Medicine and Health; FSFI: Female Sexual Function Index; GSM: Genitourinary syndrome of menopause; ICIQ-SF: International consultation on incontinence questionnaire—short Form; IQ: Interquartile range; NRS: Numeric Rating Scale; QS-F: Sexual quotient—female version; RF: Radiofrequency; SAPain: Pain during sexual activity; SD: Standard deviation; SUI: Stress urinary incontinence; TTCRF: Radiofrequency with controlled temperature; UI: Urinary incontinence; VD: Vaginal dryness; VHI: Vaginal Health Index; VI: Vaginal itchy/pruritus; VL: Vaginal laxity; VLQ: Vaginal laxity questionnaire; VMI: Vaginal Maturation Index.

Acknowledgements
All authors would like to thank the members of the Pelvic Floor Care Center (CAAP), the Bahian School of Medicine and Public Health, and the government institutions, CNPQ and FAPESB, for promoting this research.

Authors' contributions
C.P. and P.L. developed the project concept and wrote the main manuscript text, R.A, R.C., R.B., and T.A, collected data and A.T. and A.Q. prepared Figs. 1, 2 and 3 and tables. All authors read and approved the final manuscript.

Funding
This study was funded through Public Notice No. 10/2014 of the Emerging Nucleus Support Program—PRONEM/FAPESB/CNPQ.

Availability of data and materials
The data is available if requested by the corresponding author.

Declarations

Ethics approval and consent to participate
All patients signed or fingerprint signature an informed consent form and followed the precepts of the Declaration of Helsinki; the study was approved by the ethics and research committee of the Bahiana School of Medicine and Health (EBMSP) with CAAE 72147317900005544 and registered with clinicaltrial.gov (NCT03506594). The fingerprint signature as informed consent procedure was approved by the ethics and research committee of the EBMSP.

Consent for publication
Consent for publication and use of the image was obtained from all participants.

Competing interests
All authors declare that there is no competition from financial and/or non-financial interests concerning the work described.

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Received: 15 February 2021 Accepted: 18 October 2021
Published online: 30 October 2021

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Publisher's Note

Three-Dimensional Radiofrequency Tissue Tightening: A Proposed Mechanism and Applications for Body Contouring

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Introduction

Radiofrequency (RF) thermal-induced contraction of collagen is well known in medicine and is used in ophthalmology, orthopedic applications, and treatment of varicose veins. Each type of collagen has an optimal contraction temperature that does not cause thermal destruction of connective tissue but induces a restructuring effect in collagen fibers. The reported range of temperatures causing collagen shrinkage varies from 60 to 80°C [1–7]. At this temperature tissue contraction occurs immediately after tissue reaches the threshold temperature. The shrinkage of tissue is dramatic and can reach tens of percent of the heated tissue volume. This type of contraction is well studied in cornea [1], joints [2], cartilage [4, 7], and vascular tissue [5] but its application for skin, subdermal tissue, and subcutaneous tissue tightening has not been studied.

Noninvasive RF and lasers have been used for skin-tightening effects since the mid-1990s [6, 8–12]. Because of superficial thermal safety concerns, the skin surface temperature is maintained below 45°C. To increase the temperature in the deep dermis the skin is heated with RF or laser energy penetrating into the tissues deeper than 1.5 mm, with simultaneous skin surface cooling. This sophisticated method of transepidermal, noninvasive RF thermal delivery provides a variable and controversial tightening effect, which is not usually apparent, if at all, until dermal remodeling occurs a few months after the treatment. Noninvasive tissue tightening treatments have an inherent safety limitation because energy is delivered through the skin surface and the threshold epidermal burn temperature is significantly lower than the optimal temperature for the collagen contraction. Studies indicate that deeper penetrating energy provides better skin contraction and RF energy, by penetrating deeper than laser radiation, is a superior method, not only for treatment of facial rhytides and laxity, but also for body tightening [6, 9, 12]. It is the physical and biological characteristics of RF that explain its superior three-dimensional mechanism of skin tightening.

Recently, the use of thermal-induced tissue tightening was expanded to minimally invasive treatments [13–16]. Using laser-assisted liposuction (LAL) or radiofrequency-assisted liposuction (RFAL), physicians have attempted to achieve reduction of subcutaneous tissue with simultaneous tissue contraction [13, 16]. DiBernardo [13] reported 17% skin surface shrinkage measured at 3 months follow-up after LAL treatment. RFAL technology provides much higher power and more efficient energy transfer than laser energy systems and thus allows the treatment of larger volumes of subcutaneous tissue with optimal thermal profiles, facilitating the significant tightening of the tissue. Paul and Mulholland [16] introduced a RFAL and soft tissue contraction technology that showed tremendous promise for thermal contouring. Invasive thermal treatments are superior because the RF conduit (RFAL emitting cannula) targets the whole volume of treated tissue with critical thermal energy, not only the superficial subdermal layer, and the invasive RF treatments can heat deep adipose and subcutaneous tissue to much higher temperatures without compromising skin safety.

When considering skin contraction we have to differentiate two-dimensional horizontal x-axis tightening of the skin surface from three-dimensional x-y-z tissue tightening of the subcutaneous tissue, where the skin is also more firmly connected and adjacent to the deeper anatomical structures. If two-dimensional contraction is a function of collagen structure changes in the dermis, the three-dimensional tissue-tightening changes involve contraction of different types of collagenous tissue. We can separate the following types of collagen tissue in the subcutaneous space:

- Dermis: papillary and reticular
- Fascia: relatively thick layer of connective tissue located between muscles and skin
- Septal connective tissue: thin layers of connective tissue separating lobules of fat and connecting dermis with fascia
- Reticular fibers: framework of single collagen fibers encasing fat cells

One of the main objectives of this study was to evaluate the possibility of immediate thermal-induced subcutaneous tissue contraction and to estimate the thermal threshold of the effect. In this study we compare the threshold temperature and contraction level of different types of ex vivo collagenous tissue samples and the clinical results based on RFAL results for body contouring.

Materials and Methods

Ex Vivo Experiment Setup

An ex-vivo study was conducted to measure subcutaneous collagenous tissue contraction with simultaneous monitoring of local tissue temperature to determine the threshold temperature of the collagen shrinkage. Three types of collagenous tissue were studied for thermal-induced contraction: (1) adipose tissue with septal and reticular connective tissue, (2) dermis, and (3) fascia.

Samples of ex vivo human tissue were taken from an abdominoplasty surgery and were tested within 10 min of excision. Immediate thermal testing was performed to minimize changes in tissue related to long storage and temperature variation or change of liquid content, including blood and lymphatic content. The tissue samples were placed between the two BodyTite™ (Invasix Ltd., Israel) RF electrodes, where the small-area, internal RF-active electrodes (cannula) were placed in contact with the studied tissue and the other large-area electrode was applied to the opposite side, or epidermal side, of the sample. Large samples of subcutaneous tissue were used, allowing observation of any contraction behavior in the tissue's native environment in connection with its entire matrix structure. Two marks were placed 1 cm from the active internal electrode to visualize tissue displacement. The experiment design setup is shown in Fig. 1.

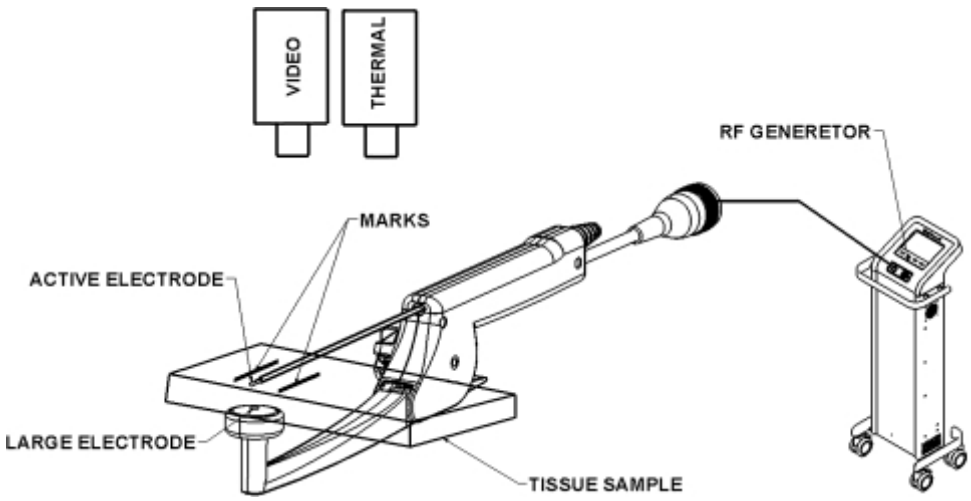

Fig. 1

Ex vivo experimental setup

RF energy was delivered by the BodyTite device. The delivered power was 70 W at 1 MHz, and energy was delivered until evaporation of water from the adipocytes was observed. Video and thermal cameras (FLIR A-320) were used to monitor tissue displacement and temperature change during the treatment. The start of tissue displacement was correlated with tissue temperature to determine the contraction thermal threshold. Each experiment was repeated three times for each type of tissue to sample tissue averages and avoid measurements of random events.

In Vivo Evaluation with Radiofrequency-Assisted Liposuction (RFAL)

Twenty-four consecutive patients, 22 female and 2 male, underwent RFAL to the abdomen and hips. The average age was 39.7 years (range = 19-52 years). The average preoperative weight was 71 kg. The selected patients were typical patients indicated for a liposuction procedure. All patients were healthy anesthetic risks and active with no significant medical diseases. Fifteen of 24 patients had a normal BMI (<25), while 9/24 patients were moderately overweight (BMI = 25–30) and 3 patients were obese (30 < BMI < 32).

RFAL was performed using the BodyTite device. The BodyTite device deploys a handpiece to deliver radiofrequency energy to the adipose tissue and skin. The internal cannula is coated with dielectric material and has a conductive tip that emits RF energy into the adipose tissue toward the skin surface. RF energy flows between the tip of the internal cannula and external electrode creating a localized, confined thermal effect between them. The internal cannula is inserted into the pretumesced fat to be contoured and is moved gently back and forth at various predetermined and controlled depths for uniform heating of the treated volume. There is also an external electrode that moves along the surface of the skin in tandem vertical alignment with the tip of the internal cannula (Fig. 2). The subcutaneous tissue and skin between the electrodes experience a significant thermal effect which is maximal near the tip of the internal cannula and decreases in intensity toward the skin electrode The operator controls the depth of the internal cannula within a predetermined range of 5–50 mm and moves the handpiece back and forth through the desired fat volume to be contoured. The RF energy coagulates the adipose, connective, and vascular tissues in the vicinity of the internal cannula tip and gently heats the dermis below the external electrode. The internal electrode also serves as an asynchronous internal suction cannula, aspirating the coagulated adipose, vascular, and fibrous tissues.

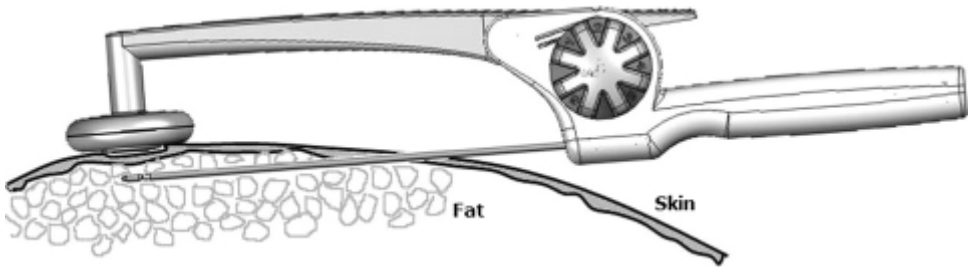

Fig. 2

Schematic drawing of RF handpiece inserted into the body

The RF power, in the range of 40–70 W, was used for uniform heating throughout a thick subcutaneous flap. The average total energy of about 72 kJ was delivered to the abdominal area. The temperature around the tip of the cannula reached 70-80°C. This internal temperature was observed using thermography on tissue cross section for preabdominoplasty patients treated with RFAL when the skin surface temperature reached 38–42°C (see Fig. 3, cross section of lower abdominal tissue showing the thermal image of the skin surface and tissue incision allowing visualization of the thermal profile of the internal subcutaneous temperature). The target skin temperature was monitored and controlled with a thermal sensor built into the external electrode. The sensor provides continuous real-time epidermal temperature monitoring and feedback loop control of RF power. The system was set to a target temperature of 38–42°C, which was maintained for 1–3 min. The strong and sustained tissue heating during the procedure results in thermal stimulation of the subdermal layer, the entire matrix of adipose tissue, and the vertical and oblique fibrous septa, eliciting a powerful three-dimensional retraction and contraction of the entire soft tissue envelope.

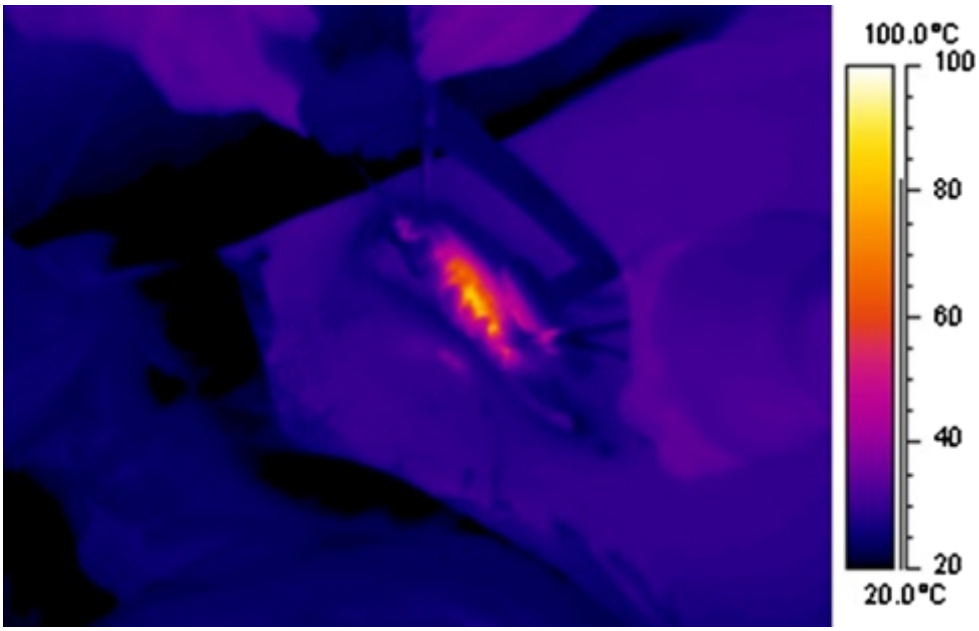

Fig. 3

Temperature profile inside adipose tissue during the RFAL treatment

The distance between the internal and external electrodes was controlled with an eccentric spring-loaded mechanism that keeps the external electrode on the surface of the skin at all times. The device also controls vaporization and prevents carbonization around the tip of the cannula. When evaporation around the internal cannula occurs, the tissue impedance rises and exceeds the online monitored high impedance and the device shuts off the RF energy.

All patients had their treatment area infiltrated with tumescent anesthesia prior to the RFAL procedure. Tumescent anesthesia is critical in the technique as the RF current travels through tissue most efficiently in a salinated environment.

The objective of this in vivo portion of the study was to optimize treatment parameters and correlate treatment soft tissue contraction results with procedure and patient variables, including amount of deposed RF energy, body mass index (BMI) of the patients, and amount of aspirated fat.

A zone measuring as large as 15 × 10 cm (150 cm^2) may be heated to critical target temperature within 3–8 min depending on the thickness of the treated fat layer and then uniform volumetric heating can be safely performed to reach uniform temperature distribution over the entire treated volume.

All patients from the study were followed up at 6, 12, and 24 weeks. To measure linear contraction, the distance between two fixed points was measured preoperatively and then at the 24-week postoperative visit. Distances between incision ports and natural “fixed” anatomical registration points, such as moles or the umbilicus, were measured before the treatment, after the treatment, and at 3- and 6-month follow-up visits. The linear contraction was measured as relative change of distance between two points over the curved surface of the body. Distances were measured using a flexible ruler applied over the skin surface. For the abdominal area, at least three measurements were taken between three different points and average linear contraction was calculated (Fig. 4).

Fig. 4

Before and after RFAL and intraoperative two-point linear contraction registration points from pubic RFAL incision point to the lower pole of the umbilicus

Pre- and postoperative photography, weights, and circumferential reduction data were obtained on all patients. One RFAL study patient had a biopsy of the thermally treated skin 12 months after the procedure during which epidermal skin temperatures of 40°C had been attained and there was an area contraction of 43% at 6 months.

Results and Discussion

Ex Vivo Tissue Contraction Experiments

The adipose tissue with septal and reticular collagen behavior is shown in Fig. 5. The experiments showed that the marker movement (contraction) started within 2 s after the start of RF energy delivery. Tissue contraction was not symmetrical as the displacement from one side was 8 mm and from the other side the average displacement was 3 mm. Adipose fibrous septal tissue coagulation and vaporization started to be observed at 13 s after the initiation of RF energy. Nonsymmetrical behavior can be explained by the nonuniform structure of connective tissue and the nonsymmetrical geometry of the studied tissue sample. The average marker migration and tissue contraction for the three experiments with adipose tissue was 6.5 mm.

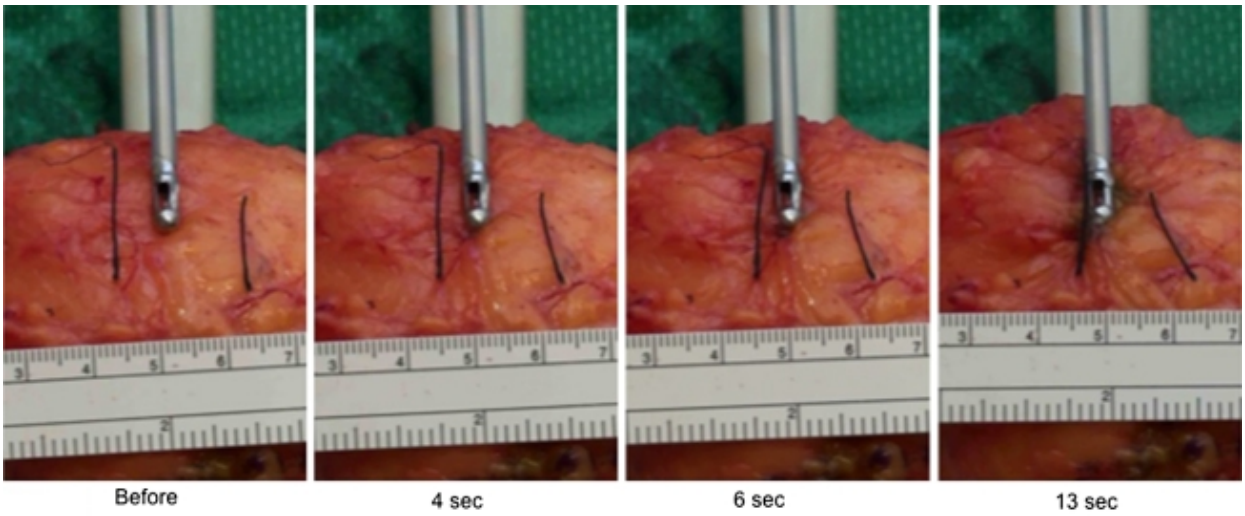

Fig. 5

Adipose-septal tissue behavior during RF energy delivery at different time points

Figure 6 shows thermal images of the same sample taken before the treatment, at the beginning of tissue displacement, and at the end of the treatment showing the rise in thermal profile with time and onset of contraction. For fascial tissue, contraction started when the maximal adipose tissue temperature near the active internal electrode reached 69.4°C. Adipose fibrous septal tissue coagulation and vaporization started when tissue temperature reached 90-100°C and is most probably associated with boiling of adipocyte water content.

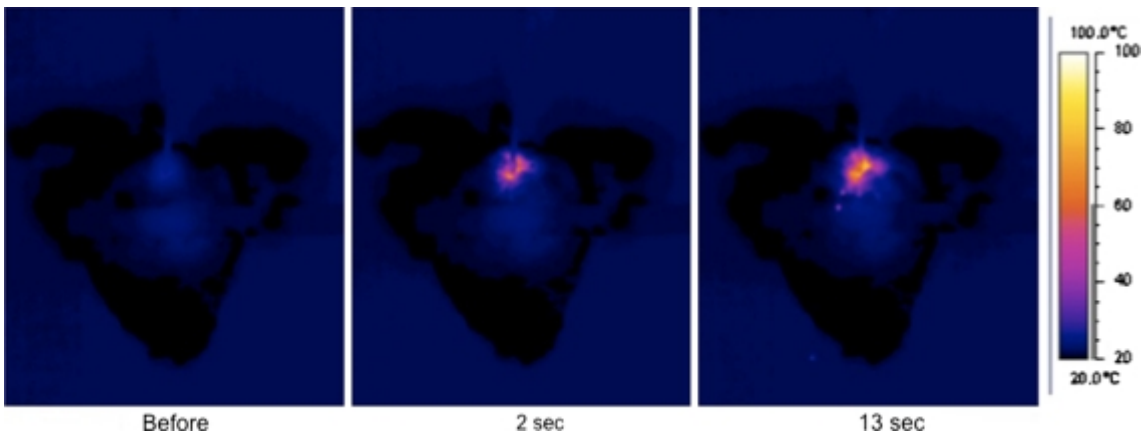

Fig. 6

Adipose-fibrous septal tissue thermal behavior during RF energy delivery at different time points

Fascia contraction is demonstrated in Fig. 7. The displacement of the markers and tissue contraction in fascia were significantly less than in adipose tissue. The average movement was 2.75 mm or approximately 2.5 times less than the mark migration and tissue contraction observed in adipose tissue. The marker migration and medial contraction started after 3.5 s and maximal temperature near the active electrode at this moment was 61.5°C.

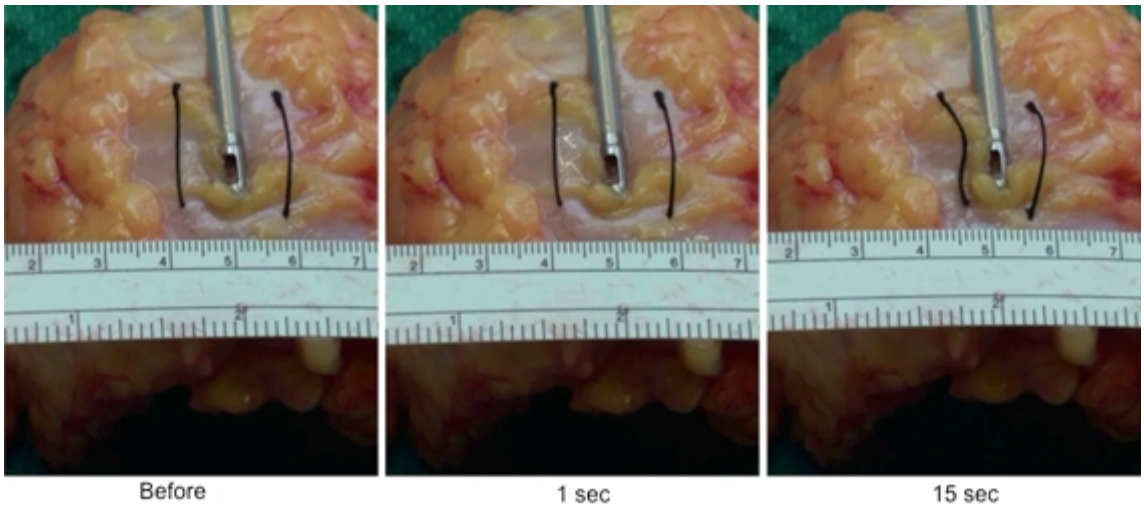

Fig. 7

Fascia contraction behavior during RF energy delivery at different time points

Skin behavior is presented in Fig. 8. The migration of markers and medial displacement and tissue contraction on the skin were similar to the fascia. The average movement was 2.0 mm or approximately 3 times less than the marker migration and contraction observed in adipose tissue. The medial marker movement started after 2.5 s and the maximal temperature near the active electrode during this contraction was 81.9°C.

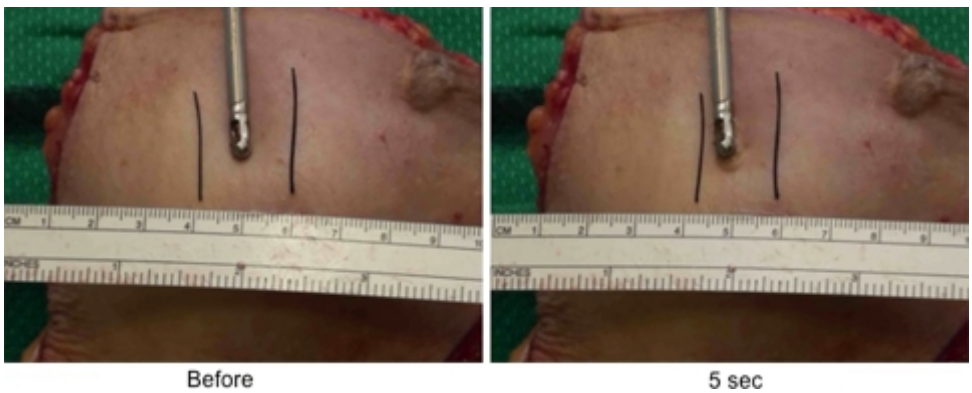

Fig. 8

Skin contraction behavior during RF energy delivery at different time points

Table 1 summarizes the results on subcutaneous tissue contraction. From the results one can see that the strongest contraction response was observed in adipose tissue containing septal connective tissue and reticular collagen fibers encasing fat cells. The contraction temperature threshold was the highest for dermis. It is clear that the immediate contraction of dermal collagen is not possible to achieve without a skin burn, which happened when the epidermal temperature exceeded 45°C [13]. Fascia and septa can be heated to these high, optimal contraction temperatures, but it can be done only in a minimally invasive transcutaneous manner that deposits the thermal RF energy directly into the adipose tissue and subdermal space, thus avoiding heating the epidermal surfaces.

Table 1

Average displacement and contraction threshold

	Dermis	Fascia	Septa/Adipose tissue
Average displacement (mm)	2	2.75	6.5
Threshold temperature (°C)	81.9	61.5	69.4
Time before start of contraction (s)	2.0	2.9	2.1
Delivered energy before start of contraction (J)	140	203	147

The contraction temperatures of collagen in our ex vivo study were in the same range reported for other collagenous tissues. We observed tissue contraction in the area with a diameter of 2 cm, which corresponds to a spherical contraction volume of 4.2 cm^3. Knowing the tissue volume and deposited energy before the start of contraction, we can estimate the energy density required for each cubic centimeter of treated tissue to reach tissue contraction effects. We can calculate that for 1 L of adipose tissue up to 48.3 kJ is required to start to see immediate and significant collagen contraction. These calculations of tissue energy needed to initiate adipose contraction are consistent with empirical data obtained with LAL treatment where energy from 50 up to 100 kJ is recommended for treatment of the abdominal area.

In vivo clinical monitoring of temperature in the adipose tissue and on the epidermal surface should allow the physician to predict more accurately the thermal treatment times and reduce the risk of thermal injuries.

In Vivo Clinical RFAL Results

The skin biopsies taken from an RFAL study patient at 12 months show normal dermal architecture with healthy collagen (Fig. 9) and elastin fibers (Fig. 10) in the deep reticular dermis and no evidence of scar tissue or abnormal collagen fibers. All RFAL patients demonstrated some level of contraction. From 8 to 15% linear tightening was observed at the end of the surgery on the operating table. It then increased dramatically during the first week when most of the swelling was reduced. The linear and area contraction process continued for weeks and maximum contraction was noted at the last follow-up visit 24 weeks after the treatment.

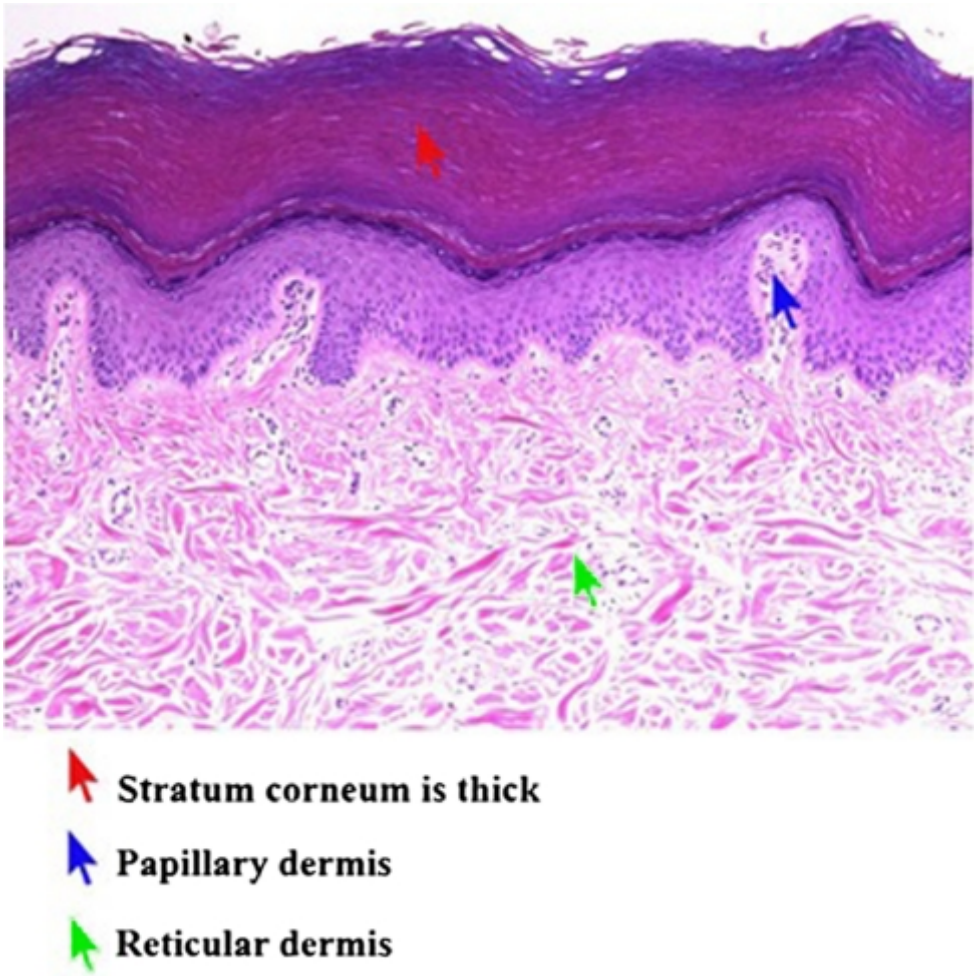

Fig. 9

Normal skin histology 12 months following optimal RFAL thermal end point

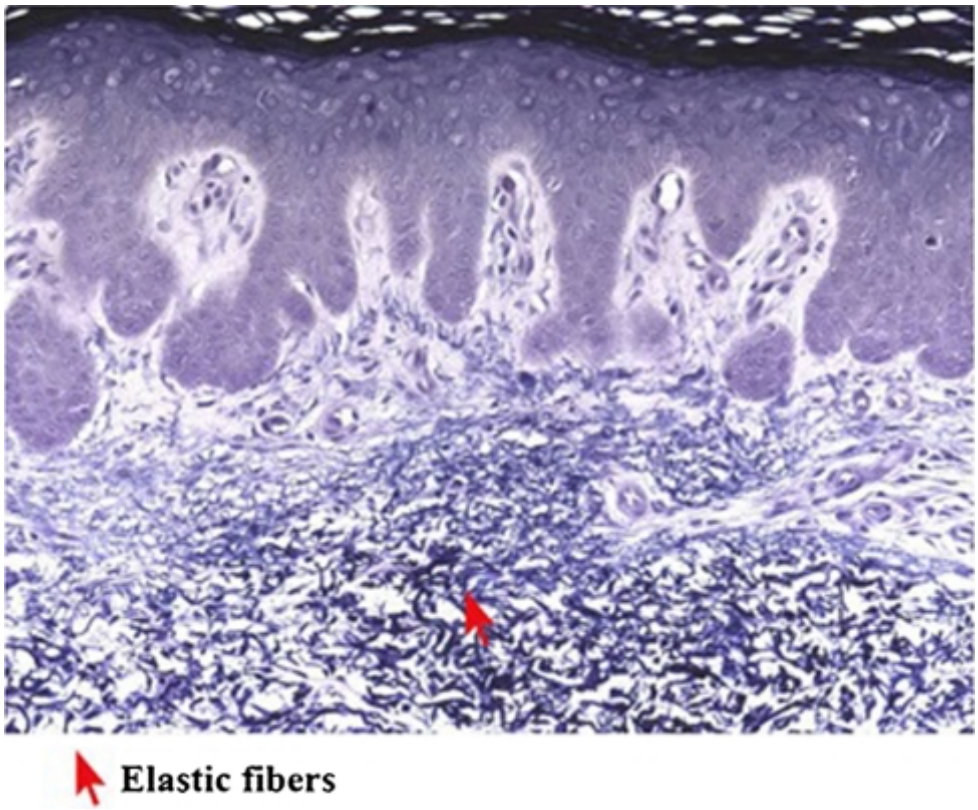

Fig. 10

Same RFAL patient with 43% contraction and normal elastic fiber content

Linear contraction observed at 6 months follow-up was much more significant than reported with any other technology and varied from 12.7 up to 47% depending on patient and treatment variables. It is important to note that soft tissue area contraction can be calculated as the square of the linear contraction and represents much higher numbers. The measured linear contraction was then correlated with three parameters: (1) aspirated volume that ranged from 0.5 to 3.4 L, with an average volume of 2.0 L, (2) BMI that varied from 20.8 to 31.7, with an average index of 25.7, and (3) deposed RF energy that varied from 60 to 96 kJ per abdominal area, with an average RF energy of 72 kJ.

For statistical analysis of the correlation between the measured variables and linear contraction, the Pearson product moment correlation coefficients were calculated. The closer the coefficient is to 1, the higher the linear correlation between the measured variable and tissue contraction. Analysis shows no or very weak correlation between aspirated volume and linear skin contraction. The Pearson coefficient is about 0.22. Figure 11 shows the correlation between these values and has a random distribution. The Pearson coefficient for correlation between contraction and patient BMI is much higher and equal to 0.64. Figure 12 demonstrates a much stronger connection between these parameters and it is easy to understand that a patient with a larger volume of adipose tissue would have more tissue available to undergo contraction.

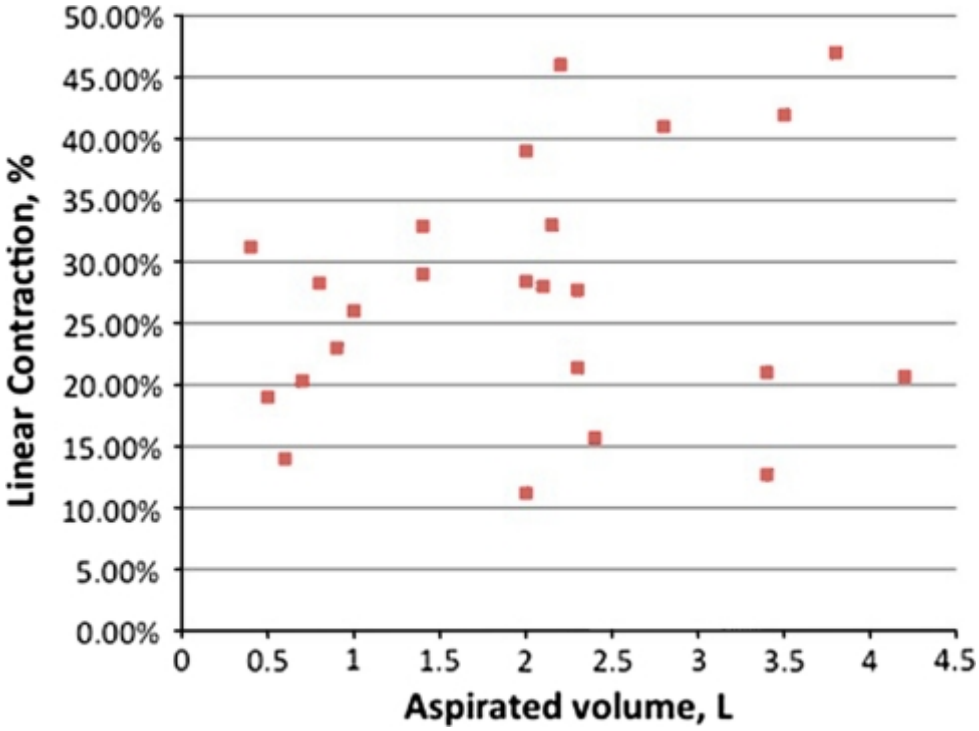

Fig. 11

Correlation between aspirated volume and linear contraction

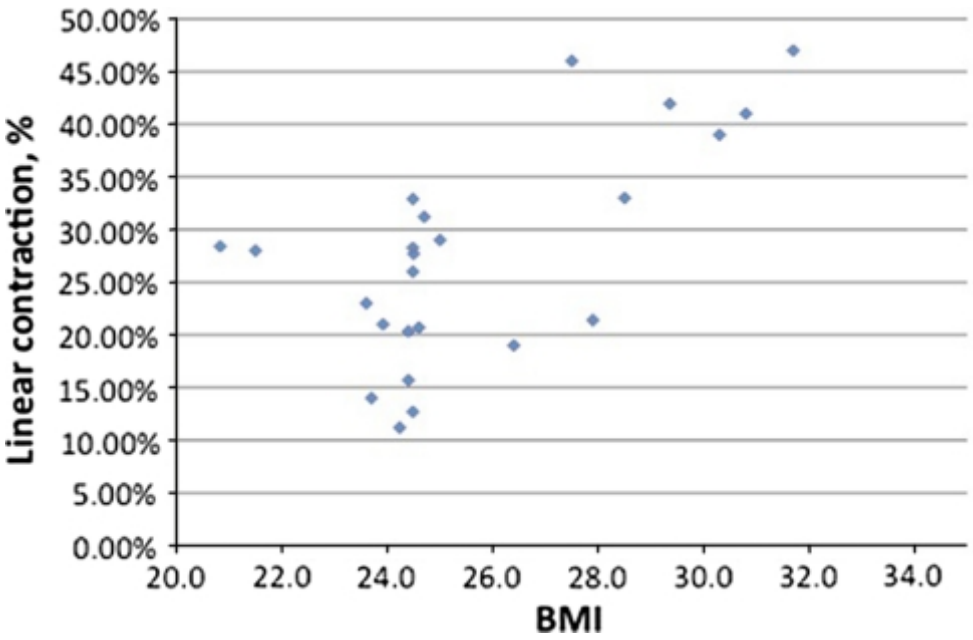

Fig. 12

Correlation between BMI and linear contraction

The highest correlation (0.86) was obtained between deposed RF energy and skin contraction. Figure 13 shows measurement results that have an almost linear function between these two parameters. The more energy deposited, the more linear contraction that was observed. In spite of improved contraction obtained at higher energies, the amount of energy used during treatment can and should be measured and controlled to avoid side effects such as seroma and skin burn and still achieve optimal linear and area contraction.

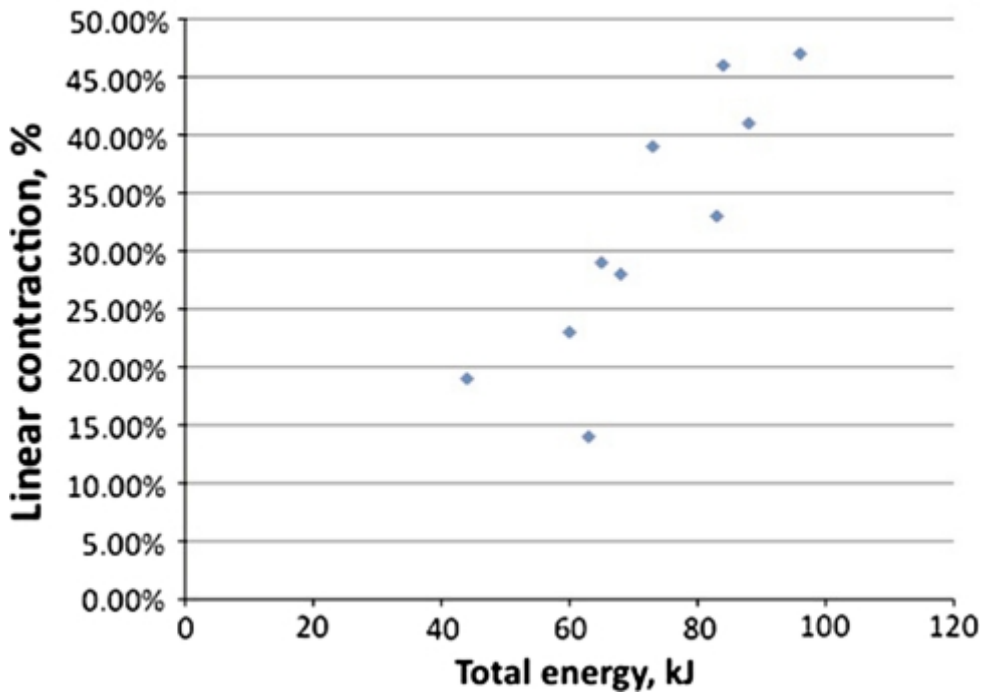

Fig. 13

Correlation between total energy and linear contraction

Features of an ideal liposuction procedure would include reduced ecchymosis, pain, and edema from preaspiration coagulation of adipose and vascular tissue, followed by less forceful and traumatic extraction forces, as well as significant soft tissue contraction when host tissue elasticity is compromised. Thermal-based lipoplasty appears to hold this potential.

In the present study based on volumetric heating, we reached an average local linear contraction of 31% that is statistically significantly higher than that reported with other energy-emitting liposuction technologies. Overall area contraction was much higher than linear contraction. We believe that these in vivo results confirm our proposed mechanism of RF-based tissue tightening and recruitment of the vertical and oblique fibrous adipose matrix. Our biopsy at 7 months suggests that the papillary and reticular dermis is populated with normal collagen and elastin that have been stimulated and remodeled by subnecrotic subdermal RFAL temperatures.

About 30% of patients noted minor weight loss but it is premature to correlate it with the treatment procedure.

The in vitro experiments produced different degrees of contraction for septal and dermal tissues which emphasizes the balance between these processes for optimal aesthetic results. Lower two-dimensional contraction of the skin and significant three-dimensional contraction of subdermal adipose connective tissue may cause wrinkling of the skin surface in high-volume liposuction patients.

During this study we had one case of a seroma that was treated with closed serial aspiration. Seroma is not a rare side effect for energy-assisted liposuction, especially for high-volume treatment and may necessitate a lower threshold for closed drainage systems in selected patients.

Conclusions

We believe the study results confirm the hypothesis of Kenkel [17], i.e., skin tightening and elasticity changes following thermal lipoplasty are mostly a result of subdermal tissue contraction but not dermal, which experiences lower heating during the treatment. It is clear that 40–42°C on the skin surface cannot result in an immediate contraction effect. Deep dermal remodeling may account for some horizontal contraction over time. It is possible that the dermal-fat junction experiences higher temperatures, but this process requires future investigation. We believe that the mechanism of subcutaneous collagen contraction during RF-assisted liposuction is similar to that witnessed in other types of collagen in that the contraction process has thermal contraction thresholds in the range of 60–70°C.

It is likely more accurate to talk about tissue contraction rather than skin tightening because significant area contraction is a result of the strong contribution of deeper adipose fascial layers. Further studies with accurate 3D area measurements will tell us more about the RF-mediated area contraction in this RFAL technology. This RFAL thermal process and contraction can be effectively applied during a liposuction treatment in selected cases, improving patient satisfaction and extending liposuction procedures to higher-weight patients and patients with compromised skin conditions.

Review > Int Urogynecol J. 2021 Jun;32(6):1345-1350. doi: 10.1007/s00192-021-04735-9. Epub 2021 Mar 4.

Clinical utility of radiofrequency energy for female genitourinary dysfunction: past, present, and future

Anne M Stachowicz [1], Mallorie L Hoover [2], Mickey M Karram [2]

Affiliations + expand

PMID: 33661319 DOI: 10.1007/s00192-021-04735-9

Abstract

Introduction and hypothesis: Radiofrequency (RF) energy has been delivered in a variety of methods to the vagina, bladder, and periurethral tissue to improve myriad genitourinary complaints. Currently, practitioners are promoting transvaginal RF treatments with a minimal understanding of the various platforms and data to support or refute their utilization. This review explores how various RF technologies create desired tissue effects, review the published literature reporting outcomes of various treatment regimes, and peer into potential future uses of this technology in urogynecology.

Methods: A comprehensive literature review was performed for articles pertaining to RF energy use in women for genitourinary complaints with regard to stress urinary incontinence (SUI), genitourinary syndrome of menopause (GSM), female sexual dysfunction (FSD), and overactive bladder (OAB).

Results: Radiofrequency energy devices heat tissues via direct or micro-needling applications with the goal of stimulating collagen remodeling, neovascularization, and potentially modulation of nerve function. By altering the approach and location of energy application, many new devices have been marketed for treatment of conditions such as SUI, GSM, FSD, and OAB. Available studies demonstrate promising efficacy and favorable safety; however, interpretation of studies is greatly limited by poor study quality and reporting.

Conclusions: Despite a lack of high-quality evidence for efficacy, safety, and durability in the literature, practitioners around the world continue to promote RF technology for a variety of genitourinary complaints. Currently, it appears that RF energy can potentially treat a variety of genitourinary conditions, but more robust data are needed to substantiate evidence-based use.

Keywords: Genitourinary syndrome of menopause; Overactive bladder; Physiological sexual dysfunction; Stress urinary incontinence; Technology; Women's health.

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Review Semin Cutan Med Surg. 2018 Dec;37(4):226-232. doi: 10.12788/j.sder.2018.052.

Device-based treatment for vaginal wellness

Macrene Alexiades [1] [2]

Affiliations + expand

PMID: 30475926 DOI: 10.12788/j.sder.2018.052

Abstract

Genitourinary syndrome of menopause (GSM), encompassing the disorders of atrophic vaginitis, urinary incontinence, and pelvic prolapse, affects the majority of postmenopausal women, as well as patients who are undergoing breast cancer treatement, post-ovarectomy, post-radiation, and breast-feeding. There is a need for better treatment options for these common conditions that adversely affect physical function and quality of life and that are often underserved by existing options. Lasers have been used to treat genitourinary tissue for over 40 years, and over the past decade, several lasers and radiofrequency devices have been developed and clinically tested for the treatment of GSM, with an accumulating body of evidence demonstrating their safety and efficacy. Fractional lasers, including carbon dioxide, erbium: YAG and hybrid technologies, as well as monopolar radiofrequency devices, work by resurfacing and/or stimulating via heat the vaginal lining resulting in a re-epithelialization, neovascularization, and remodeling of the vaginal tissue from an atrophic postmenopausal state to a thickened, glycogen-rich and well-vascularized state similar to premenopausal vaginal lining. These changes are correlated clinically with improved function on a variety of validated vaginal health scales and urinary incontinence tests. Currently cleared for general application to genitourinary tissue, clinical trials are underway for FDA clearance or approval for specific GSM indications.

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MeSH terms

- Atrophy / pathology
- Atrophy / surgery
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Genitourinary syndrome of menopause treatment using lasers and temperature-controlled radiofrequency

Jadwiga Wańczyk-Baszak [1], Sławomir Woźniak [1], Bartosz Milejski [2], Tomasz Paszkowski [1]

Affiliations + expand

PMID: 30766466 PMCID: PMC6372847 DOI: 10.5114/pm.2018.81743

Abstract

Perimenopausal changes caused by oestrogen deficiency are accompanied by a decrease in the content of collagen and elastin in the tissues, leading to thinning of the epithelium and the resultant disappearance of the superficial layer, which leads to smooth muscle dysfunction as well as connective tissue degradation. This aetiopathogenetic chain results in a set of symptoms experienced by approximately 50% of women in the peri- and postmenopausal period. Symptoms of dryness, burning, dyspareunia and urgency contribute to a significant reduction in the quality of sexual function and general comfort of life due to recurrent infections of the vagina, vulva and urinary tract. Different therapeutic methods may benefit genitourinary syndrome of menopause (GSM), while innovative methods such as lasers or radiofrequency deserve further study in this area.

Keywords: genitourinary syndrome of menopause; lasers; radiofrequency; sexual health; vulvovaginal atrophy.

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Rationale and design for fractional microablative CO_2 laser versus photothermal non-ablative erbium:YAG laser for the management of genitourinary syndrome of menopause: a non-inferiority, single-blind randomized controlled trial.
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Microablative Fractional **Radiofrequency** as a Therapeutical Option for Genitourinary Syndrome of Menopause: Perspectives.
Kamilos MF, et al. Front Reprod Health. 2021. PMID: 36303987
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Review of non-invasive vulvovaginal rejuvenation.
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To date, three non-surgical energy-based therapies have been proposed: fractional microablative CO(2) laser, erbium:YAG laser and temperatur ...

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Review. Int J Gynaecol Obstet. 2023 Dec 16. doi: 10.1002/ijgo.15304. Online ahead of print.

Physical energies for the management of genitourinary syndrome of menopause: An overview of a systematic review and network meta-analysis

Ayane Cristine Alves Sarmento [1], Juliana Dantas de Araújo Santos Camargo [1], Cijara Leonice de Freitas [1], Kleyton Santos Medeiros [1 2], Ana Paula Ferreira Costa [1 2], Ana Katherine Gonçalves [1 3]

Affiliations + expand

PMID: 38102987 DOI: 10.1002/ijgo.15304

Abstract

Background: Energy-based devices (laser and radiofrequency) have been used to treat genitourinary syndrome of menopause (GSM).

Objectives: To evaluate the efficacy and safety of physical energy use in managing GSM symptoms.

Search strategy: Five databases were searched from inception to December 2022. Language restrictions were not imposed.

Selection criteria: We included all Cochrane and non-Cochrane systematic reviews with or without meta-analyses that described postmenopausal women with symptoms of GSM treated with physical energy.

Data collection and analysis: We performed a network meta-analysis using frequentist methods to calculate standardized mean differences (SMDs) and their corresponding 95% confidence intervals (CIs). Methodological and reporting quality were assessed using the Assessment of Multiple Systematic Reviews (AMSTAR 2).

Main results: Nine reviews were included in the overview, six of which were meta-analyses. Four randomized controlled trials, representing 218 participants and nine different study arms, met the criteria for inclusion in our component network meta-analysis. Confidence in review findings was low in six reviews and critically low in three. Our network meta-analysis results showed that premarin (SMD 2.60, 95% CI 7.76-3.43), conjugated estrogens (SMD 2.13, 95% CI 1.34-2.91), carbon dioxide laser (SMD 1.71, 95% CI 1.10-2.31), promestriene (SMD 1.41, 95% CI 0.59-2.24), and vaginal lubricant (SMD 1.37, 95% CI 0.54-2.20) were more effective than sham for reducing sexual dysfunction, with a consequent increase in Female Sexual Function Index (FSFI). Two studies showed a high risk of bias, owing to a lack of blinding.

Conclusion: Several gaps in the use of physical energy for managing GSM still need to be addressed. The small number of blind clinical trials made the results fragile.

Keywords: atrophy; laser therapy; menopause; network meta-analysis; overview; radiofrequency therapy.

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Int J Gynaecol Obstet. 2021 May;153(2):200-219. doi: 10.1002/ijgo.13561. Epub 2021 Feb 22.

Physical methods for the treatment of genitourinary syndrome of menopause: A systematic review

Ayane C A Sarmento [1], Juliana F Lírio [2], Kleyton S Medeiros [1], Camila Marconi [3], Ana P F Costa [1], Janaina C Crispim [4], Ana K Gonçalves [1 5]

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PMID: 33354773 DOI: 10.1002/ijgo.13561

Abstract

Background: Genitourinary syndrome of menopause (GSM) negatively affects sexual function and quality of life. Techniques like laser and radiofrequency are being used to manage GSM, particularly in women with contraindications for hormone therapy.

Objectives: To verify whether the physical methods of laser and radiofrequency can be recommended as safe and effective options for the treatment of GSM/urinary urgency or incontinence in pre- and postmenopausal women.

Search strategy: Databases were comprehensively searched using combinations of the following keywords in any language: "postmenopause"; "genitourinary syndrome of menopause"; "vaginal atrophy"; "radiofrequency"; and "laser."

Selection criteria: Full articles of case-control, cross-sectional, cohort, randomized clinical trials, and quasi-randomized or controlled clinical trials were included.

Data collection and analysis: All authors independently evaluated the design of the studies for quality of reporting, risk of bias, and quality of evidence.

Main results: Of the included 49 studies, 37 were on the CO_2 laser, 10 on the Erbium laser, and two on radiofrequency.

Conclusions: Laser and radiofrequency therapy could be promising and safe therapeutic options for GSM/urinary incontinence. However, the study findings cannot be generalized until new randomized clinical trials are performed that confirm the strength of the evidence. This review has been registered with PROSPERO: CRD42020141913.

Keywords: atrophy; erbium; female urogenital diseases; laser therapy; menopause; radiofrequency.

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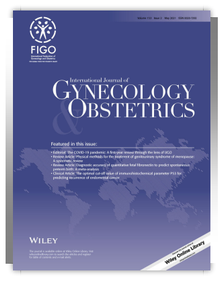

Volume 153, Issue 2
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REVIEW ARTICLE

Physical methods for the treatment of genitourinary syndrome of menopause: A systematic review

Ayane C. A. Sarmento, Juliana F. Lírio, Kleyton S. Medeiros, Camila Marconi, Ana P. F. Costa, Janaina C. Crispim, Ana K. Gonçalves

First published: 22 December 2020 | https://doi.org/10.1002/ijgo.13561 | Citations: 18

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Abstract

Background

Genitourinary syndrome of menopause (GSM) negatively affects sexual function and quality of life. Techniques like laser and radiofrequency are being used to manage GSM, particularly in women with contraindications for hormone therapy.

Objectives

To verify whether the physical methods of laser and radiofrequency can be recommended as safe and effective options for the treatment of GSM/urinary urgency or incontinence in pre- and postmenopausal women.

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Data collection and analysis

All authors independently evaluated the design of the studies for quality of reporting, risk of bias, and quality of evidence.

Main results

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Conclusions

Laser and radiofrequency therapy could be promising and safe therapeutic options for GSM/urinary incontinence. However, the study findings cannot be generalized until new randomized clinical trials are performed that confirm the strength of the evidence. This review has been registered with PROSPERO: CRD42020141913.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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Randomized Controlled Trial > Climacteric. 2024 Apr;27(2):210-214.
doi: 10.1080/13697137.2024.2302425. Epub 2024 Jan 22.

Randomized trial: treatment of genitourinary syndrome of menopause using radiofrequency

A Joris [1], V Di Pietrantonio [1], J Praet [1], K Renard [1], A-C Verduyn [1], F Buxant [1], S Rozenberg [2]

Affiliations + expand

PMID: 38251861 DOI: 10.1080/13697137.2024.2302425

Abstract

Objective: A randomized controlled study was conducted to evaluate the safety and efficacy of radiofrequency treatment in postmenopausal women not willing to use or presenting a contraindication for menopause hormone therapy (MHT) and suffering from genitourinary syndrome of menopause (GSM).

Methods: A prospective randomized open study evaluated the effect of radiofrequency treatment versus a gel (control group) in postmenopausal women suffering from GSM. Patients were assessed at baseline and after 10-12 weeks of treatment for severity of vulvovaginal atrophy, dyspareunia, pH, vaginal smear maturation index, Vaginal Health Index and Female Sexual Function Index. The difference at baseline and after 10-12 weeks of treatment and the difference in improvement were tested between groups by a two-sample *t*-test and the Mann-Whitney test.

Results: Due to the COVID-19 pandemic, we were only able to treat 48 patients (24 patients using radiofrequency and 24 patients using a gel). Globally, at the end of the study, there were no differences in changes of the measured outcomes between the group of women treated with radiofrequency and the control group.

Conclusion: Radiofrequency treatment was found to be safe, but was not superior to a gel, although the study lacked power. The study was registered at ClinicalTrials.gov (NCT03857893).

Keywords: Menopause; genitourinary syndrome of menopause; low-energy radiofrequency; randomized trial; vulvovaginal atrophy.

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Review J Eur Acad Dermatol Venereol. 2020 Apr;34(4):716-726. doi: 10.1111/jdv.16066. Epub 2019 Dec 5.

Review of non-invasive vulvovaginal rejuvenation

L Photiou [1], M J Lin [2], D P Dubin [2], V Lenskaya [3], H Khorasani [2]

Affiliations + expand

PMID: 31714632 DOI: 10.1111/jdv.16066

Abstract

Vulvovaginal atrophy (VVA) or genitourinary syndrome of menopause (GSM) may affect up to 90% of menopausal women. Features include vulvovaginal atrophy, vulvovaginal laxity, vulvovaginal dryness and irritation, dyspareunia, anorgasmia and urinary symptoms. The vulva, vagina and bladder are oestrogen-responsive tissues, but oestrogen replacement therapy is not possible in women who have hormone-responsive cancers or normal oestrogen levels. Therefore, there is a role for alternative treatments. To date, three non-surgical energy-based therapies have been proposed: fractional microablative CO_2 laser, erbium:YAG laser and temperature-controlled radiofrequency (RF). Our objective was to assess the available evidence for the safety and efficacy of erbium:YAG laser, microablative fractional CO_2 laser and RF in the treatment of VVA/GSM. The authors reviewed the current published literature evaluating these therapies. All three therapies appear safe; however, all the studies were uncontrolled and used different protocols and outcome measurements. Therefore, comparison of treatments is difficult. It appears that there is more evidence in favour of the CO_2 laser than the erbium:YAG laser. Both lasers have more evidence than RF. In conclusion, microablative CO_2 laser, erbium:YAG laser and RF may be offered to patients suffering from VVA/GSM as an alternative or adjunct to conventional therapies. Further well-conducted controlled studies are needed.

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Genitourinary syndrome of menopause treatment using lasers and temperature-controlled **radiofrequency**.
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Different therapeutic methods may benefit genitourinary syndrome of menopause (**GSM**), while innovative methods such as lasers or **ra** ...

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Review > Menopause. 2021 Feb 1;28(5):579-588. doi: 10.1097/GME.0000000000001728.

The genitourinary syndrome of menopause

Nancy A Phillips [1], Gloria A Bachmann

Affiliations + expand

PMID: 33534428 DOI: 10.1097/GME.0000000000001728

Abstract

Genitourinary syndrome of menopause (GSM) refers to a collection of symptoms resulting from diminished hormonal, primarily estrogenic stimulation to the vulvovaginal or lower urinary tract and may affect up to 50% of postmenopausal women. Symptoms, which are typically progressive and unlikely to resolve spontaneously, may include, but are not limited to, vulvovaginal dryness, burning or irritation, dyspareunia, or urinary symptoms of urgency, dysuria or recurrent urinary tract infection. These symptoms are typically progressive and unlikely to resolve spontaneously. Diagnosis is clinical. Telemedicine may play a role in diagnosis, initiation of treatment, and follow-up of women with GSM. Effective treatments include moisturizers and lubricants, local hormonal therapy with estrogen or dehydroepiandrosterone, and oral selective estrogen receptor agonists. Laser or radiofrequency procedures, although currently utilized, are being studied to comprehensively understand their overall effectiveness and safety. Additionally, the influence and effect of the vaginal microbiome, as well as potential of treatment via its manipulation, is being studied. We performed a literature search of PubMed, Google Scholar, and Ovid with search terms of vulvovaginal atrophy and GSM and reviewed major US Society Guidelines to create this narrative review of this topic. The literature suggests that healthcare providers can make a significant impact of the health and quality of life of women by being proactive about discussing and providing interventions for GSM. A systematic approach with consideration of current guidelines and attention to developing protocols for interventions should be employed.

Plain language summary

Video Summary:http://links.lww.com/MENO/A702 .

Conflict of interest statement

Financial disclosure/conflicts of interest: None reported.

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Meral Ö, et al. Bratisl Lek Listy. 2016. PMID: 28125894
RESULTS: Cytochrome c and AIF levels were not altered, but all caspase activities were increased in female infant rabbits that exposed to 18 ...

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Review > Pharmaceuticals (Basel). 2023 Apr 6;16(4):550. doi: 10.3390/ph16040550.

Therapeutic Choices for Genitourinary Syndrome of Menopause (GSM) in Breast Cancer Survivors: A Systematic Review and Update

Lucia Merlino [1], Giulia D'Ovidio [1], Viviana Matys [1], Maria Grazia Piccioni [1], Maria Grazia Porpora [1], Roberto Senatori [2], Maria Federica Viscardi [1], Antonio Vitale [3], Carlo Della Rocca [4], On Behalf Of Policlinico Umberto I Collaborators

Affiliations + expand

PMID: 37111307 PMCID: PMC10142093 DOI: 10.3390/ph16040550

Abstract

(1) Background: Genitourinary syndrome of menopause (GSM) is a medical condition that can affect breast cancer survivors (BCS). This is a complication that often can occur as a result of breast cancer treatment, causing symptoms such as vaginal dryness, itching, burning, dyspareunia, dysuria, pain, discomfort, and impairment of sexual function. BCS who experience these symptoms negatively impact multiple aspects of their quality of life to the point that some of them fail to complete adjuvant hormonal treatment; (2) Methods: In this systematic review of the literature, we have analyzed possible pharmacological and non-pharmacological treatments for GSM in BCS. We reviewed systemic hormone therapy, local hormone treatment with estrogens and androgens, the use of vaginal moisturizers and lubricants, ospemifene, and physical therapies such as radiofrequency, electroporation, and vaginal laser; (3) Results: The data available to date demonstrate that the aforementioned treatments are effective for the therapy of GSM and, in particular, vulvovaginal atrophy in BCS. Where possible, combination therapy often appears more useful than using a single line of treatment; (4) Conclusions: We analyzed the efficacy and safety data of each of these options for the treatment of GSM in BCS, emphasizing how often larger clinical trials with longer follow-ups are needed.

Keywords: aromatase inhibitors (AI); breast cancer survivors (BCS); genitourinary syndrome of menopause (GSM); local hormone therapy; vaginal laser therapy; vaginal lubricants; vaginal moisturizers; vulvovaginal atrophy (VVA).

Conflict of interest statement

The authors declare no conflict of interest.

Figures

Figure 1 PRISMA flowchart [17].

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Vaginal Rejuvenation: A Retrospective Review of Lasers and **Radiofrequency** Devices.
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Moreover, the present review also summarizes available literature in this subject, reports and studies which will help to form guidelines fo ...

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Review > Dermatol Surg. 2021 Apr 1;47(4):489-494. doi: 10.1097/DSS.0000000000002845.

Vaginal Rejuvenation: A Retrospective Review of Lasers and Radiofrequency Devices

Margit L W Juhász [1], Dorota Z Korta [2], Natasha Atanaskova Mesinkovska [1]

Affiliations + expand

PMID: 33165070 DOI: 10.1097/DSS.0000000000002845

Abstract

Background: Vaginal rejuvenation is a topic of interest to multiple specialties, including dermatologists, plastic and reconstructive surgeons, urologists, and gynecologists. Evidence suggests that minimally invasive, energy-based devices-radiofrequency and laser therapy-are effective at vaginal tightening and decreasing symptoms of genitourinary syndrome of menopause (GSM) and/or vulvovaginal atrophy (VVA).

Materials and methods: A systematic review was completed using PubMed in November 2018 with search terms "vaginal" or "vagina" and "rejuvenation" or "tightening" or "laxity" or "radiofrequency" or "laser," as well as "genitourinary syndrome of menopause," "pelvic prolapse," "atrophic vaginitis," "vulvovaginal atrophy," "sexual function," "urinary incontinence," and "radiofrequency" or "laser." Inclusion criteria were articles written in English and clinical trials or case reports/series dealing with human subjects.

Results: We identified 59 studies (3,609 women) treated for vaginal rejuvenation using either radiofrequency or fractional ablative laser therapy. Studies report improvement in symptoms of GSM/VVA and sexual function, high patient satisfaction, and minor adverse events, including treatment-associated pain, swelling, or vaginal discharge.

Conclusion: This review demonstrates radiofrequency and laser are efficacious for the treatment of vaginal laxity and/or atrophy. Further research needs to be completed to determine which specific pathologies can be treated, if maintenance treatment is necessary, and long-term safety concerns.

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