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Vaginal laser therapy for urogenital symptoms in postmenopausal women and breast cancer survivors

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ABSTRACT

Introduction: Genitourinary syndrome of menopause (GSM) is common after natural menopause as well as in women with induced menopause due to endocrine therapy and/or oophorectomy following breast cancer. Vaginal laser therapy is a nonhormonal treatment option that appears to alleviate GSM symptoms in natural menopause; however, women with induced menopause may respond differently. The aim of this study was thus to evaluate the efficacy and safety of laser treatment on GSM in postmenopausal women and breast cancer survivors.

Methods: A total of 34 women were enrolled in the study, each completing three treatments at monthly intervals. After each treatment, sexual function was assessed with PISQ-12, urinary incontinence and overactive bladder symptoms were measured using ICIQ-UI SF and ICIQ-OAB, and the improvement of urinary incontinence was measured using PGI-I and PGI-S.

Results: At the time of follow-up, one year after the start of treatment the total PISQ-12 score had significantly increased in both groups compared to baseline (33 to 35.5, difference 2.5, 95% CI: 0.9-4.3). As assessed by ICIQ-UI SF scores, vaginal laser therapy also improved urinary incontinence from 5.3 at baseline to 3.4 at one-year follow-up (difference 1.9, 95% CI:0.4-3.1) for the total group. Improved urgency score from 3.1 at baseline to 2.5 at one-year follow-up (difference 0.7, 95% CI:0.02-1.5) and less leakage after urgency 3.1 at baseline to 2.8 at one-year follow-up (difference 0.8, 95% CI:0.05-1.5) were also reported. No complications were observed.

Conclusion: Vaginal laser therapy appears to be safe and may reduce GSM symptoms in postmenopausal women and breast cancer survivors. Separate randomized controlled studies are needed.

Keywords: Lasers; breast cancer; menopause

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INTRODUCTION

Genitourinary syndrome of menopause (GSM) is characterized by sexual dysfunction, vulvovaginal discomfort, and urinary symptoms, and is caused by urogenital atrophy induced by decreases in estrogen and other hormones (1,2). Following natural menopause, GSM is the result of a decline in estrogen synthesis that occurs with aging, while GSM associated with induced menopause after breast cancer is caused by anti-estrogens and/or bilateral oophorectomy (2). Current options for sexual dysfunction include lubricants or moisturizers, together with local and/or systemic estrogens; however, concerns about the long-term safety of this approach arise for women who were treated for breast cancer (3,4). Similarly, local estrogens are well-known to alleviate minor incontinence dysfunctions concomitant with GSM.

In vaginal laser therapy, a series of millimeters-apart laser punctuations extend approximately 1000 um into a systemic grid in the vaginal mucosa (5). This induces a wound-healing process, which may include increased blood flow, remodeling of vaginal connective tissue, and thickening of the mucosa (6,7). Observational studies have reported positive effects; however, concerns have been raised regarding potential negative effects, such as subsequent pain (8). Still, vaginal laser therapy may be an alternative treatment option in GSM when the use of estrogens is not favored, especially since the ACOG recently stressed the safety concern for this approach in breast cancer patients (9). Previous studies have shown improvements by vaginal laser therapy of GSM in postmenopausal women and breast cancer survivors (10-13).

The aim of the prospective pilot study was, to evaluate the safety and efficacy of vaginal laser therapy on GSM in postmenopausal women and breast cancer survivors.

MATERIALS AND METHODS

Two groups of women were included in this prospective study: Women with natural menopause, and women who, following breast cancer treatment, had induced menopause. Eligible cases were referred from general practice, and participants were included from the period of August 1, 2018, to December 31, 2019.

The inclusion criteria for the study were (1) symptomatic GSM with vaginal discomfort and/or dyspareunia secondary to menopausal atrophy due to natural menopause, or (2) induced menopause in breast cancer patients treated with anti-estrogens and/or oophorectomy following initial cytostatic therapy. Exclusion criteria were the use of vaginal non-hormonal treatment within the last month (including lubricants and moisturizers), acute and recurrent urinary tract infections, active genital infection, and any physical and mental illness that could affect compliance with the protocol. Women were asked to discontinue the use of vaginal estrogen, moisturizers, and cream of any kind between treatments for the duration of the trial. In addition, for the first week after treatment, patients were asked to refrain from sex, inserting anything (e.g., tampons) in the vagina, and bathing in pools or tubs.

We registered indication by symptom diagnosis (moderate to severe vaginal dryness, irritation, pain); dyspareunia dependent on their sexual status; hormonal treatment, including type (local or systemic, composition); menopause status; and the use of any pharmacological drugs. In breast cancer survivors, we registered the date of diagnosis, surgery, and chemotherapy completion when relevant, as well as the type of anti-estrogen treatment.

Participants received three vaginal laser treatments at four-week intervals over a total period of eight weeks and a one year follow. Treatments were given with the microablative fractional CO2 laser system (SmarteXide2 V2LR, MonaLisa Touch, DEKA, Florence, Italy) using the following settings: dot power 30-watt, dwell time 1000 µs, dot spacing 1000 µs, and the smart stack parameter 2 (6). The laser probe was gently inserted up to the top of the vagina, and subsequently withdrawn and rotated in order to deliver a complete treatment of the vaginal wall. (5). No anesthesia, local or otherwise, was used. Of the 34 enrolled women, 33 (97%) completed the treatment. The one remaining woman only completed two laser treatments

The following validated questionnaires were used before the start of treatment, and after each laser session: The International Consultation on Incontinence Questionnaire – Urinary Incontinence

Short Form (ICIQ-UI SF), the International Consultation on Incontinence Questionnaire – Overactive Bladder (ICIQ-OAB), the Pelvis Organ Prolapse Urinary Incontinence Sexual Questionnaire (PISQ-12), and the Patient Global Index of Improvement and Severity (PGI-I & PGI-S) (10,14-16). The questionnaires were conducted at baseline and intervals of one, two, six and twelve months after the start of treatment, for a total of five times. The first two evaluations to detect any safety concerns, in particular for breast cancer survivors where previous data are lacking on benefit; the last two evaluations for the persistence of effects as for the overall value for women. Due to a lock-down related to the COVID-19 pandemic, the fourth visit scheduled for six months after the start of treatment was cancelled for two thirds of the study group, resulting in incomplete data for 27 of the 34 patients. Otherwise, all 34 participants answered the questionnaires at the first and second visits, and 33 participants at the third and fifth visits. In question five of the ICIQ-UI SF, "When does urine leak?", the answers were converted to the dichotomy of either 'yes' or 'no' to simplify analysis.

Ethical approval

The study was approved by the Regional Scientific Ethics Committee and the Regional Data Protection Authority (nos. 1-10-72-37-18 and 1-16-02-41-18, respectively). Participants entered the study only after informed written consent.

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics 20. Prior to analysis, the women were divided into two groups; one group for postmenopausal and one group for breast cancer survivors. One woman missed the questionnaire at the time of the second visit, but still fulfilled the treatment.

If the data followed a Gaussian distribution, the Student's t-test was used to test for differences between variable means. Otherwise, Mann-Whitney's U-test was used. For ordinal data from the questionnaires, Pearson's $\chi 2$ and linear-by-linear tests were performed. The use of estradiol (vaginal or oral), smoking, and ongoing letrozole/tamoxifen treatment were used as dichotomous variables in substrata analysis. Paired test with one-way ANOVA was used to evaluate change over time. Groups variables were tested for change over time with two-way ANOVA for parametric and general linear models for non-parametric variables (repeated measurements). Smoking, BMI, parity, and estradiol use were added to the multivariate model as covariates at repeated measurements. Logistic analysis was performed with effect

Table 1: Baseline characteristics of the 34 women

Variable	Breast cancer survivors (n = 16)	Postmenopausal women (n = 18)	Total (n = 34)
Age (y)	56.3 ± 9.1	56.8 ± 3.1	56.6 ± 6.6
Body mass index (kg/m^2)	23.5 ± 3.6	24.3 ± 4.2	23.9 ± 3.9
Smokers			
Yes	1 (6)	0 (0)	1 (3)
Never	11 (69)	10 (56)	21 (62)
Previous	4 (25)	8 (44)	12 (35)
Parity	1 (0-3)	2 (0-5)	2 (0-5)
Age of menopause	46.4 ± 7.4 (n=14)	48.3 ± 3.6 (n=16)	47.4 ± 5.6 (n=30)
Previous hormone therapy (local and systemic)	5 (31)	9 (50)	14 (41)
Time since ended cancer treatment years, median (range)	3.8 (0.8-16)	-	-
Estrogen-receptor positive cancer	15 (94)	-	-
Adjuvant therapy with tamoxifen	8 (50)	-	-
Adjuvant therapy with letrozole	4 (25)	-	-
No adjuvant therapy	4 (25)	-	-
Oophorectomy	4 (25)	-	-
Tamoxifen or letrozole or oophorectomy	12 (75)	-	-

Data are given as mean ±SD, no. (%) or median (range)

on genitourinary symptoms as the dependent variable. If the variable followed a non-Gaussian distribution, Kruskall-Wallis' test was used. A two-sided p-value of < 0.05 was chosen as the level of significance. Data are given as mean ± SD if they followed a Gaussian distribution; otherwise, median (range) are indicated.

RESULTS

A total of 34 women were enrolled in the study; 18 postmenopausal, and 16 breast cancer survivors. Out of the study groups, 14 patients had previously received vaginal hormone therapy (hereof five breast cancer survivors), although with no sufficient effect (Table 1). No differences in baseline clinical characteristics were found between the two groups (Table 1).

Overall, no serious adverse effects were observed during or after the procedure: there were no pain- or intolerance-related disruptions to the procedure, and no participants developed pain, ulcerations, or fistulas after the procedure. The sum of PISQ-12 indicates an improvement in both groups, from 33 at baseline to 35.5 after one year (Fig. 1, difference 2.5, 95% CI: 0.9-4.3 adjusted for BMI, parity, estrogen use and smoking). When breaking down the sum of PISQ-12 the individual questions of dyspareunia and orgasms improved significantly. At baseline, 85% of the 33 women with sexual partners reported dyspareunia either always or often. At the time of follow-up one year later, this symptom was reported by 60% with natural menopause and 65% with induced menopause, respectively. One woman with no partner had recommenced sexual life with masturbation but had not answered the questionnaire at baseline and, similarly, one couple had stopped having sex and further another woman did not fill in PISQ-12 at 12 months' follow-up (Fig.1). The intensity of orgasm improved in both

groups, from 3% at baseline, to 19% after two treatments, and 23% one year after the start of the study. All other variables in the PISQ-12 questionnaire showed no significant change over time. The combined ICIQ-UI SF scores indicated that vaginal laser treatment resulted in an improvement of stress incontinence already at 3rd visit from 5.3 at baseline to 3.5 in the total group of participants (difference 1.9, 95% CI: 0.9-2.9 adjusted for BMI, parity, estrogen use and smoking). After one year the score was 3.4 and the difference 1.8 (95% CI 0.4-3.1). The use of estrogen and smoking were added to the multivariate model as covariates but did not change the conclusions. The individual VAS for GSM symptoms and ICIQ values for pollakiuria improved similarly (data not shown).

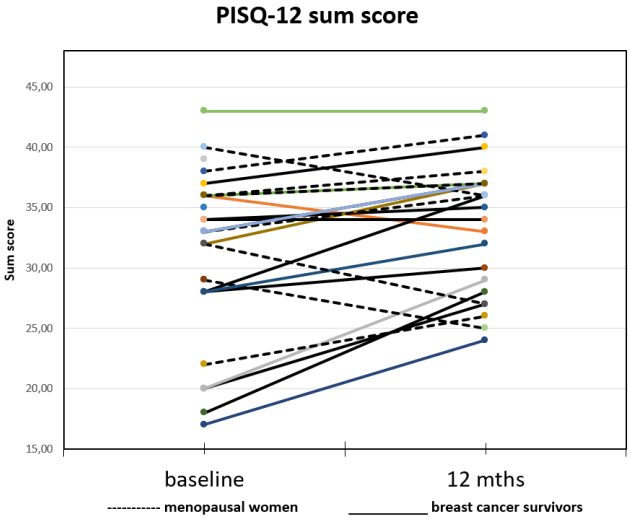

Figure 1: The total PISQ-12 score from start to the follow-up

Urgency incontinence also improved from the third treatment and onwards up to one year (Fig. 2, difference 0.8, 95% CI:0.05-1.5 adjusted for BMI, parity, estrogen use and smoking).

The global impression score showed a tendency towards improvement when rating incontinence (p=0.052).

Results remained similar after adjustment for current and former use of vaginal estrogen, current and former smoking, letrozole and tamoxifen, when analyzed cross-sectionally and for changes over time by repeated measurements.

DISCUSSION

This pilot study evaluated the potential usefulness of vaginal laser therapy in postmenopausal women as well as breast cancer survivors with GSM. The most salient finding was that vaginal laser therapy seems to improve both sexual and urinary tract symptoms associated with GSM, with effects still present at the

one-year follow-up. No complications or side effects were observed.

Our results are in line with the growing evidence that vaginal laser therapy improves sexual function in women with GSM (10). One open-label, randomized study found vaginal laser therapy to be superior to local estrogen treatment, while another open-label, randomized trial found the two therapeutic principles equivalent (14). The double-blinded three-arm study by Cruz et al. compared laser, local estrogen, and combined treatment, and found least efficiency for the laser arm; however, only two vaginal laser treatments were given, as opposed to the three treatments in other studies. Improvements were maintained at the twelve-week follow-up (5,14,17). Our results support these findings and indicate that significant improvement is still found after one year, i.e., 10 months after the last vaginal laser treatment. Previous studies indicate that some effect is still present after twelve months or more, but detailed studies are needed to further investigate the need for, timing, and number of repeat vaginal laser treatments, as well as for the long-term complication profile.

Breast cancer patients undergoing endocrine or surgical anti-estrogen treatment suffer from severe GSM problems that are often overlooked and undertreated (18). Observational studies on GSM in breast cancer patients have revealed the positive effects of vaginal laser therapy, but the present study motivates a more detailed investigation on the number of treatments needed for optimal relief (12,13). The long-term benefits and complications after repeat treatment in larger populations also need to be clarified before recommendations on the use of vaginal laser therapy for sexual dysfunction in breast cancer survivors. We made the deliberate choice to use the PISQ-12 questionnaire instead of the Female Sexual Function Index (FSFI) or Sexual History Form-12 (SHF-12), as we felt that the intervention with laser and previous breast cancer treatment were more analogous to a pre- and post-intervention situation for women with incontinence/prolapse. On the other hand, questions regarding dyspareunia and orgasms are similar in PISQ-12 and FSFI, thus, changes in these modalities would be detected with both methodologies. What is often overlooked is the fact that FSFI was validated on a clinically diagnosed sample of women with female sexual arousal disorder. Furthermore, PISQ-12 is able to distinguish women with poor sexual function in general (19).

Gonzales Isaza et al. were the first to report significant improvements in mild stress urinary incontinence that were maintained after 36 months (20,21). As we did not treat the urethra, it seems that vaginal treatment exerts some effect on the bladder function, better explained in histological studies. The efficacy may be confirmed by the alterations of the vagina wall (6,22). As GSM is associated with minor incontinence disorders, these beneficial side-effects of vaginal laser treatment are, nevertheless, important when treating women who decline hormonal treatment for various reasons.

Ruanphoo Purim et al. and Stefano Salvatore et al demonstrated that vaginal CO2 laser for the treatment of vaginal atrophy was effective compared to sham treatment (23,24). Conversely, Li Fiona et al. and Eduard Mension et al. demonstrated that treatment with fractional CO2 laser versus sham treatment did not improve vaginal symptoms, in postmenopausal woman and breast cancer survivors respectively (25,26).

Our pilot study had several limitations. First, the modest sample size of the cohort, makes it difficult to find statistically differences between the groups. So, we do not claim to have any differences between the groups, but a description over time of similar significant changes. Moreover, the missing follow-up one month after the third vaginal laser treatment may have obscured a further improvement effect of vaginal laser therapy. However, the one-year follow-up showed a stable effect of vaginal laser therapy. Furthermore, the study is not a placebo-controlled study, thus a placebo effect cannot be excluded. We also did not conduct a vaginal examination during the treatment or measure vaginal pH during the laser treatments. However, initially an examination was performed to rule out other pathology including infections. Nevertheless, this is a prospective study with a well-defined group of participants and with reasonable long-term follow-up and minimal dropouts. Moreover, standardized and validated questionnaires were used for measurement of the treatment effects. It will take longer observation

and further investigation, and preferably histological specimens, to confirm whether the changes induced by laser wane off, and if so, when.

CONCLUSION

In conclusion, our pilot study indicates that three vaginal laser treatments given at four-week intervals may improve GSM problems in postmenopausal women as well as in breast cancer survivors. Due to the lack of a placebo group, separate randomized controlled studies are needed to provide evidence before clinical use in Denmark.

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Author contributions:
S Jacobsen: Data analysis, Manuscript writing.
CK Jeppesen: Data collection, Manuscript writing.
HB Christensen: Data collection.
A Forman: Manuscript editing.
FF Lauszus: Data analysis, Manuscript writing
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