ORIGINAL STUDY

Superficial dyspareunia treatment with hyperstacking of erbium: yttrium-aluminum-garnet SMOOTH laser: a short-term, pilot study in breast cancer survivors

Tiziana Fidecicchi, MD,¹ Adrian Gaspar, MD,² and Marco Gambacciani, MD, PhD³

Abstract

Objective: This prospective pilot study aimed to evaluate the effects of a modified vaginal erbium laser (VEL) protocol, using the hyperstack mode on the vaginal vestibulum and introitus to treat superficial dyspareunia in postmenopausal breast cancer survivors suffering from the genitourinary syndrome of menopause.

Methods: In this pilot, prospective, randomized study, two groups of postmenopausal women suffering from superficial dyspareunia were included: 34 women (VEL group) were treated with erbium laser crystal yttrium-aluminumgarnet (XS Fotona SMOOTH; Fotona, Ljubljana, Slovenia) with a wavelength of 2,940 nm; for the other 34 (hyperstack group), a modified second step of the VEL protocol for the treatment of vestibulum and introitus was used, with hyperstacked (repeating a number of) subablative, long pulses with very low fluences. For each group, three laser applications at 30-day intervals were performed. Symptoms were assessed before, after each application, and after 1 and 3 months from the last laser application, using the visual analog scale score for superficial dyspareunia.

Results: Superficial dyspareunia improved in both groups over time (P < 0.001), regardless of age and years since menopause status. The reduction in visual analog scale score after the third laser application was 58% in VEL versus 73.5% in hyperstack. The hyperstack group, since the first laser application, showed a greater (P < 0.001) and persistent improvement of superficial dyspareunia.

Conclusions: The hyperstack treatment of the introitus and vestibulum in breast cancer survivors leads to a more significant improvement in superficial dyspareunia than the VEL alone.

Key Words: Genitourinary syndrome of menopause - Superficial dyspareunia - Vaginal erbium laser.

Video Summary: http://links.lww.com/MENO/B60.

In postmenopausal women suffering from the genitourinary syndrome of menopause (GSM), bothersome symptoms often lead to poorer sexual relationships and reduced quality of life.¹ Standard therapies include hormone and nonhormone approaches.² In breast cancer survivors, severe GSM is often due to antiestrogen treatment, and its management is critical for their well-being and quality of life. In these women, postmenopausal hormone use is currently contraindicated, including

low-dose local estrogen administration.³ In recent years, erbium:yttrium-aluminum-garnet (Er:YAG) laser at a wavelength of 2,940 nm, using the SMOOTH mode (vaginal erbium laser [VEL], FOTONA SP Dynamis, SMOOTH mode; Fotona, Ljubljana, Slovenia), has been reported to improve GSM symptoms in healthy postmenopausal women⁴⁻¹⁵ and in breast cancer survivors.¹⁰ Vaginal erbium laser, as a nonablative, minimally invasive thermal-only treatment, is intrinsically safe. Laser parameters are set to achieve a controlled deep thermal effect, without ablation and carbonization of the tissues, avoiding the risk of perforation with accidental lesions of the vaginal mucosa, urethra, bladder, or rectum. A worldwide analysis including more than 113,000 women confirmed that VEL treatment is safe, presenting only rare, minor, and usually transient adverse effects.⁷

However, superficial dyspareunia, defined as pain at the vaginal opening during intercourse, is a problematic symptom to treat as it usually does not fully respond to any treatment, particularly in breast cancer survivors. Recently, we reported that the association of VEL protocol with the treatment of the posterior

Received July 5, 2022; revised and accepted September 16, 2022.

From the ¹Department of Obstetrics and Gynecology, Pisa University Hospital, Pisa, Italy; ²Uroclinica, Department of Gynecology, University of Mendoza, Mendoza, Argentina; and ³Menopause and Osteoporosis Unit, San Rossore Clinical Center, Pisa, Italy.

Funding/support: None reported.

Financial disclosure/conflicts of interest: None reported.

Supplemental digital content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's Website (www.menopause.org).

Address correspondence to: Marco Gambacciani, MD, PhD, Menopause and Osteoporosis Unit, San Rossore Clinical Center, Viale delle Cascine, 152/f, 56122 Pisa, Italy. E-mail: margamba54@gmail.com

commissure with neodymium: YAG laser with the PIANO mode (Fotona) can improve superficial dyspare unia more than the VEL alone.¹⁶

The aim of the present pilot study was to investigate the efficacy of a modified VEL protocol, treating vaginal vestibulum and introitus with the hyperstack mode, that is, hyperstacked (repeating a number of) subablative, long pulses with very low fluences.

METHODS

In this pilot, prospective, comparative, single-blind study, we enrolled women attending the Menopause Clinic of Pisa University Hospital and with a history of treated breast cancer and suffering from GSM with superficial dyspareunia (ie, pain at the vaginal opening during intercourse). Inclusion criteria were the presence of superficial dyspareunia in sexually active women with a hormonal profile diagnostic for menopause status (follicle-stimulating hormone greater than 40 U/L; estradiol less than 25 pg/mL) and a negative Papanicolaou smear.

Exclusion criteria were as follows: scars, lesions, or infection, active or recent (in the last 30 days) of the genitourinary tract; use of lubricants, local preparations, hormones, or other treatments to alleviate menopausal symptoms in the 3 months before the study; abnormal uterine bleeding; use of photosensitizing drugs or history of photosensitivity disorders; genital prolapse (grade II-III of the classification Pelvic Organ Prolapse Quantification system); and conditions that could interfere with our protocol.

All procedures were performed in accordance with the ethical standards of the Committee on Institutional Human Experimentation and with the Helsinki Declaration of 1975, as revised in 1983. During a screening visit (T0), 68 women were selected according to the inclusion and exclusion criteria. For all of them, clinical information (age at menopause, chronological age, and years since menopause status) was collected. Informed consent was signed before the treatment. Participants were randomly assigned to two different groups of therapy, without being informed about which treatment they were receiving. The block randomization method was used to randomize participants into groups with a balance in sample size (www.randomization. com). Two to 4 weeks after this screening visit, women were treated with three laser applications (L1, L2, L3) every 30 days. Superficial dyspareunia was evaluated by a visual analog scale (VAS) score. The VAS consists of a 10-cm line, with two endpoints representing 0 ("no pain") and 10 ("pain as bad as it could possibly be"). The women were asked to rate the pain level by placing a mark on the line during the screening visit, after each laser application, and at the follow-up visits. Follow-up evaluations were performed after 1 month (T1) and 3 months (T3) from the last laser application. The laser procedures were performed without anesthesia in an outpatient clinical setting. Neither pretreatment nor posttreatment medications were needed. Treatments were undertaken by a single physician (M.G.). Before the procedure, the vagina was cleaned with a disinfectant solution and dried with a swab. After treatment, all women were instructed to avoid sexual intercourse for 1 week.

Thirty-four women (VEL group) were treated with VEL Renovalase (FOTONA SP Dynamis, SMOOTH mode; Fotona) with a wavelength of 2,940 nm. Laser parameters were set in a two-step protocol, as previously described.⁹ In the first step, a specifically designed glass vaginal speculum was used to perform a full beam, 360° circular treatment of the vaginal wall, with seven pulses given every 5 mm. The laser spot size was 7 mm, with a pulse frequency of 1.6 Hz and a fluence of 6.0 J/cm². This procedure was repeated three times up to the vaginal vestibule. In the second step, the vestibule and the introitus were treated with the PS03 probe, set up at a spot size of 7 mm, at a frequency of 1.6 Hz, releasing two stacks of 10 J/cm² for each spot.⁹

The other 34 women (hyperstack group) underwent the same first step. Then, they were treated with a modified second step for the treatment of the vestibulum and introitus: the PS03 probe with a spot size of 7 mm, at a frequency of 1.6 Hz, with a fluence of 1.5 J/cm was used. For each spot, 27 stacks were released.

Statistical analysis

The primary outcome was to assess whether the hyperstack protocol can improve superficial dyspareunia. Secondary outcomes were to (i) study the differences between the VAS score of the two groups over time, (ii) evaluate if the effect of time was present in both groups, (iii) describe the trend of the curves of the VAS score over time, and (iv) explore the influence of age and years since menopause status on the results obtained.

In this pilot study, the sample size was not calculated with a statistical method. During the follow-up period, 12 women dropped out. This was not related to adverse events. The data are presented from the 34 valid completers in each group.

The results are reported as mean \pm SDs. A Mann-Whitney U test was used to compare the between-groups baseline (T0) data. The impact of the two laser protocols on superficial dyspareunia was analyzed with a linear mixed model for repeated measures over time¹⁷: fixed effects were time, group, and interaction between time and group, and the dependent variable was the VAS score, whereas random effects were the participants. The Bonferroni correction was used as a post hoc test for the interaction between time and treatment. Simple effects of time for different groups were estimated in each group; then, we performed a trend analysis to explore how time affects the VAS score to provide information about which trend (linear, quadratic, or cubic) better describes the observed effect and if different trends are present in the two groups. The trends' modeling is informative of the response kinetics to the examined parameter, adding information to the treatment comparison.

The difference between T0 scores and T3 ($\Delta_{T0/T3}$) was then calculated, and a multiple linear regression model was used to study how women's characteristics (age and years since menopause status) and the treatment may influence the $\Delta_{T0/T3}$. Variables in the regression model were chosen upon the biological inherency to the hypothesis and the dependent variable.

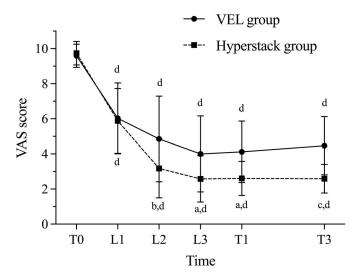


FIG. 1. Mean VAS score over time for the two treatment groups. VEL group (n = 34) and hyperstack group (n = 34) VAS scores were compared using the post-hoc test with Bonferroni correction. ${}^{a}P < 0.05$ versus the corresponding time of the VEL group. ${}^{b}P < 0.01$ versus the corresponding time of the VEL group. ${}^{c}P < 0.001$ versus the corresponding time of the VEL group. ${}^{d}P < 0.001$ versus the corresponding group. L1, laser session 1; L2 laser session 2; L3 laser session 3; T0, baseline; T1, after 1 mo from the end of treatment; T3, after 3 mo from the end of treatment; VAS, visual analog scale; VEL, vaginal erbium laser.

Data were analyzed with the open-source statistical software Jamovi version 2.0.0.0 (The Jamovi Project, Sydney, Australia). P < 0.05 was considered statistically significant.

RESULTS

No significant differences in age (59.11 ± 6.48 years in the VEL group vs 59.53 ± 7.64 years in the hyperstack group, P = 0.829), age at menopause (48.59 ± 5.43 years vs 50.50 ± 4.84 years, P = 0.167), years since menopause status (10.52 ± 6.08 vs 9.00 ± 5.47 years, P = 0.243), and basal superficial dyspareunia VAS scores (9.59 ± 0.66 vs 9.74 ± 0.67 points, P = 0.150) were present in the two groups before the study.

Figure 1 and Table 1 show the VAS scores for superficial dyspareunia over time. The VAS scores showed a significant decrease in both groups. The VAS values in the VEL group decreased from pretreatment values of 9.59 ± 0.66 to 6.03 ± 2.02 ; 4.85 ± 2.44 and 4.00 ± 2.16 after the first, second, and third treatments, respectively (P < 0.001 vs basal values, Table 1, Fig. 1). Superficial dyspareunia VAS values in the hyperstack

group decreased from pretreatment values of 9.74 ± 0.67 to 5.88 ± 1.84 ; 3.18 ± 1.68 and 2.58 ± 1.32 after the first, second, and third treatments, respectively (P < 0.001 vs basal values, Table 1,Fig. 1). The decrease in VAS scores was significant in both groups after the first laser treatment. Still, from the second laser treatment, the VAS score was significantly lower in the hyperstack group (Fig. 1, Table 1). $\Delta_{T0/T3}$ of the two groups of treatments was significantly different (-5.12 ± 2.13 points in the VEL group vs -7.15 ± 1.16 points in the hyperstack group, P < 0.001).

An R^2 marginal of 0.688 and an R^2 conditional of 0.819 emerged from the linear mixed model. The *F* tests for group, time, and group-time interaction were statistically significant (Table 1). The VAS score measurements compared in the two treatment groups and versus baseline (T0) are reported in Figure 1 and Table 1.

Both treatments significantly affected VAS score over time according to the simple effect test (VEL group and hyperstack group, P < 0.001). However, the effect of the treatment in the

VAS score with different types of treatment			Mixed-model analysis with interactions		
Measurement	VEL group $(n = 34)$	Hyperstack group $(n = 34)$	Effect	F	Р
Т0	9.59 ± 0.66	9.74 ± 0.67	Group	14.86	< 0.001
L1	6.03 ± 2.02^{a}	5.88 ± 1.84^{a}			
L2	4.85 ± 2.44^{a}	$3.18 \pm 1.68^{a,b}$	Time	284.54	< 0.001
L3	4.00 ± 2.16^{a}	$2.58 \pm 1.32^{a,c}$			
T1	4.12 ± 1.75^{a}	$2.61 \pm 0.97^{a,c}$	Group-time interaction	8.35	< 0.001
Т3	4.47 ± 1.66^{a}	$2.59 \pm 0.82^{a,d}$			

TABLE 1. Results of the linear mixed model for repeated measures over time

Fixed effects were time, group, and interaction between time and group; the dependent variable was the VAS score, whereas random effects were the subjects. The VEL group and hyperstack group VAS scores were compared using the post hoc test with Bonferroni correction. Fixed-effect test results are reported for time, group of treatment, and group-time interaction, and they are described as F test value and P value. P < 0.05 was considered statistically significant.

L1, laser session 1; L2 laser session 2; L3 laser session 3; T0, baseline; T1, after 1 mo from the end of treatment; T3, after 3 mo from the end of treatment; VAS, visual analog scale; VEL, vaginal erbium laser.

 $^{a}P < 0.001$ versus T0 of the corresponding group.

 $^{b}P < 0.01$ versus the corresponding time of the VEL group.

 $^{c}P < 0.05$ versus the corresponding time of the VEL group.

 $^{d}P < 0.001$ versus the corresponding time of the VEL group.

TABLE 2. Characteristics of overall trend of means observed in the two groups

	VEL group		Hyperstack group		
Trend	Estimate	95% CI	Estimate	95% CI	
Linear Quadratic Cubic	-3.85^{a} 2.70 ^a -0.66^{c}	-4.26 to -3.43 2.29 to 3.11 -1.07 to -0.24	$-5.52^{a,b}$ 3.28^{a} -0.78^{a}	-5.93 to -5.10 2.87 to 3.70 -1.19 to -0.36	

Both slopes show significant linear, quadratic, and cubic shapes. The parameter estimates with their 95% CI are reported. P < 0.05 was considered statistically significant.

VEL, vaginal erbium laser.

 $^{a}P < 0.001$ versus VEL group.

 $^{b}P < 0.001$ versus VEL group.

 $^{c}P < 0.01$ versus VEL group.

hyperstack group seems to be slightly higher, with an *F* test of 190 versus an *F* test of 103 in the VEL group. In both curves, on average, the VAS score tends to decrease over time (linear trend P < 0.001 for both curves), and the decrease rate diminishes over time (quadratic trend P < 0.001), but the flatting-out of the trend fluctuates a bit from time to time (cubic trend P < 0.01 for the VEL group and P < 0.001 for the hyperstack group), as shown in Table 2. However, the linear trend (P < 0.001) of the curves was significantly different (Fig. 1): the two groups start at the same height but end up at a different level, with a more pronounced decrease in the VAS score in the hyperstack group. The fluctuation captured by the quadratic (P = 0.05) and the cubic (P = 0.681) trends is the same in the two groups (Table 2).

The multiple linear regression model considering as variables the age at treatment, the number of years since menopause, status and the treatment showed an R^2 of 0.268. Both age at treatment (estimate: -0.02; 95% CI, -0.13 to 0.08; P = 0.653) and years since menopause status (estimate: 0.02; 95% CI, -0.07 to 0.10; P = 0.686) did not affect the $\Delta_{T0/T3}$. Only the laser treatment performed was shown to influence the results (estimate: -2.07; 95% CI, -2.93 to -1.21; P < 0.001). No serious adverse events were recorded during the study. Some women reported a transitory warm, not burning, sensation during treatment and, in a few cases, self-limiting leukorrhea for a few days after treatment.

DISCUSSION

In this pilot study, an innovative hyperstack VEL protocol has been studied as a new laser approach for superficial dyspareunia. Our primary outcome was to explore the hyperstack protocol's efficacy in treating superficial dyspareunia. In general, women showed a significant improvement in the VAS score when treated with hyperstack since the first laser application. After comparing the two groups, it emerged that the hyperstack mode induced a more significant reduction of superficial dyspareunia than the standard VEL protocol. Hyperstack caused a 73.5% reduction in VAS score after the third laser treatment, and the mean $\Delta_{T0/T3}$ was -7.15 ± 1.16 points. In a clinical setting, this may translate into an almost complete resolution of superficial dyspareunia, with a lasting relief for at least 3 months. The VEL group showed a 58% reduction in VAS score after the third laser treatment, and the mean $\Delta_{T0/T3}$ was -5.12 ± 2.13 points; this means that they had pain relief but not the complete resolution of the symptom (VAS score after three laser sessions was 4.00 ± 2.16 vs

 2.58 ± 1.32 in the hyperstack group). This different effect was evident since the second laser session, and the difference between the two treatments was maintained over time. As we can see from the analyses of the trends of the curves, both treatments showed a significant linear reduction in the VAS score. However, comparing the two curves, the slope (linear trend) of the curve obtained with hyperstack was significantly higher than that obtained with VEL alone, confirming the overall more relevant effect of hyperstack in reducing the VAS score. Both curves flatten over time and undergo some oscillation. Still, the flattening (quadratic trend) and the oscillations (cubic trend) were similar in the two curves, with no rebound of the effect after the end of the laser sessions in both groups. Therefore, present data suggest that the hyperstack step, treating the vestibule and introitus with repeated pulses at low fluence, can produce further benefits in postmenopausal breast cancer survivors, suffering from superficial dyspareunia. These results are independent of age and years since menopause, as demonstrated by the multiple regression model: the only significant effect on VAS score was caused by the treatment performed. Therefore, the present study suggests that hyperstack treatment could help all postmenopausal women, regardless of the time since menopause status and age.

Although this is a randomized study of two laser treatment modalities in breast cancer survivors with dyspareunia, it does not include a placebo group. The present results are similar to those already reported by our group using neodymium: YAG laser in healthy postmenopausal women.¹⁶ The hyperstack treatment seems to be a straightforward solution with a better improvement in superficial dyspareunia, avoiding using an additional laser wavelength.¹⁶ Other energy-based devices, such as radiofrequency, have been proposed to treat GSM.13 A recent trial reports that postmenopausal women treated with vaginal CO₂ laser therapy do not have a significant benefit over sham treatment,18 contrary to other prospective clinical trials, systematic reviews, and meta-analyses.^{19,20} Conversely, a multicenter, robust, placebo-controlled, blinded trial demonstrates that VEL therapy is beneficial for stress urinary incontinence with minimal adverse effects,²¹ as previously reported in a small, short-term, randomized trial.¹¹ These randomized trials confirm the positive effects of VEL on vaginal tissues, already described in many longitudinal nonrandomized studies.4,5,14-16,6-13

In our study, no significant adverse effects were reported. The hyperstack protocol applies the same VEL technology, the nonablative SMOOTH mode, already demonstrated to be safe,⁷ but with an extremely lower fluence (1.5 vs 10 J/cm). This is reassuring about the safety of this new protocol. All women reported only a mild heat sensation on the posterior commissure, and no special prelaser or postlaser treatment was necessary.

CONCLUSION

This short-term, pilot study suggests that adding the hyperstack treatment protocol to the usual VEL treatment may enhance the beneficial effects on superficial dyspareunia in breast cancer survivors. However, long-term, comparative results are not yet available. Larger studies are needed to assess the noninferiority of this novel laser treatment to hormone or nonhormone therapies.

REFERENCES

- Portman DJ, Gass MLS. Genitourinary syndrome of menopause. Menopause 2014;21:1063-1068. doi: 10.1097/GME.00000000000329
- Palacios S, Castelo-Branco C, Currie H, et al. Update on management of genitourinary syndrome of menopause: a practical guide. *Maturitas* 2015; 82:308-313. doi: 10.1016/j.maturitas.2015.07.020
- The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. *Menopause* 2020;27:976-992. doi: 10. 1097/GME.00000000001609
- Elia D, Gambacciani M, Berreni N, et al. Genitourinary syndrome of menopause (GSM) and laser VEL: a review. *Horm Mol Biol Clin Investig* 2019;41. doi: 10.1515/hmbci-2019-0024
- Gambacciani M, Levancini M, Russo E, et al. Long-term effects of vaginal erbium laser in the treatment of genitourinary syndrome of menopause. *Climacteric* 2018;21:148-152. doi: 10.1080/13697137.2018.1436538
- Gambacciani M, Albertin E, Torelli MG, et al. Sexual function after vaginal erbium laser: the results of a large, multicentric, prospective study. *Climacteric* 2020;23:S24-S27. doi: 10.1080/13697137.2020.1804544
- Gambacciani M, Cervigni M, Gaspar A, et al. Safety of vaginal erbium laser: a review of 113,000 patients treated in the past 8 years. *Climacteric* 2020; 23:S28-S32. doi: 10.1080/13697137.2020.1813098
- Gambacciani M, Palacios S. Laser therapy for the restoration of vaginal function. *Maturitas* 2017;99:10-15. doi: 10.1016/j.maturitas.2017.01.012
- Vizintin Z, Lukac M, Kazic M, Tettamanti M. Erbium laser in gynecology. *Climacteric* 2015;18:4-8. doi: 10.3109/13697137.2015.1078668
- Gambacciani M, Levancini M. Vaginal erbium laser as second-generation thermotherapy for the genitourinary syndrome of menopause: a pilot study in breast cancer survivors. *Menopause* 2017;24:316-319. doi: 10.1097/ GME.0000000000000761
- Blaganje M, Šćepanović D, Žgur L, et al. Non-ablative Er: YAG laser therapy effect on stress urinary incontinence related to quality of life and sexual function: a randomized controlled trial. *Eur J Obstet Gynecol Reprod Biol* 2018;224:153-158. doi: 10.1016/j.ejogrb.2018.03.038

- Lee MS. Treatment of vaginal relaxation syndrome with an erbium:YAG laser using 90° and 360° scanning scopes: a pilot study & short-term results. *Laser Ther* 2014;23:129-138. doi: 10.5978/islsm.14-OR-11
- Tadir Y, Gaspar A, Lev-Sagie A, et al. Light and energy based therapeutics for genitourinary syndrome of menopause: consensus and controversies. *Lasers Surg Med* 2017;49:137-159. doi: 10.1002/lsm.22637
- Gambacciani M, Levancini M, Cervigni M. Vaginal erbium laser: the second-generation thermotherapy for the genitourinary syndrome of menopause. *Climacteric* 2015;18:757-763. doi: 10.3109/13697137.2015. 1045485
- Gaspar A, Brandi H, Gomez V, Luque D. Efficacy of erbium: YAG laser treatment compared to topical estriol treatment for symptoms of genitourinary syndrome of menopause. *Lasers Surg Med* 2017;49:160-168. doi: 10.1002/ lsm.22569
- Gambacciani M, Fidecicchi T. Short-term effects of an erbium/neodymium laser combination in superficial dyspareunia: a pilot study. *Climacteric* 2022;25:208-211. doi: 10.1080/13697137.2021.2014809
- Bell ML, Rabe BA. The mixed model for repeated measures for cluster randomized trials: a simulation study investigating bias and type I error with missing continuous data. *Trials* 2020;21:148. doi: 10.1186/s13063-020-4114-9
- Li FG, Maheux-Lacroix S, Deans R, et al. Effect of fractional carbon dioxide laser vs sham treatment on symptom severity in women with postmenopausal vaginal symptoms. JAMA 2021;326:1381-1389. doi: 10.1001/jama.2021.14892
- Khamis Y, Abdelhakim AM, Labib K, et al. Vaginal CO₂ laser therapy versus sham for genitourinary syndrome of menopause management: a systematic review and meta-analysis of randomized controlled trials. *Menopause* 2021;28:1316-1322. doi: 10.1097/GME.000000000001845
- Filippini M, Porcari I, Ruffolo AF, et al. CO₂-laser therapy and genitourinary syndrome of menopause: a systematic review and meta-analysis. *J Sex Med* 2022;19:452-470. doi: 10.1016/j.jsxm.2021.12.010
- O'Reilly B, Phillips C, Toozs-Hobson P, et al. Vaginal erbium laser for SUI—a prospective multicentre randomized placebo-controlled trial to evaluate efficacy and safety of non-ablative Er:YAG laser for treatment of stress urinary incontinence (SUI). *ICS 2021 Melb Online* 2021:218. Available at: https://www.ics.org/2021/abstract/218. Accessed November 18, 2022.