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CO2-Laser therapy and Genitourinary Syndrome of Menopause: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Genitourinary syndrome of menopause (GSM) is a widespread condition with a great impact on quality of life and self-image.

Aim: We aimed to systematically review the current literature on CO2-Laser therapy efficacy for the treatment of GSM.

Methods: MEDLINE and Embase databases were systematically queried in December 2020 Studies included women with a diagnosis of Vulvo-Vaginal Atrophy (VVA) or GSM without an history of gynaecological and/or breast cancer, pelvic organ prolapse staged higher than 2, pelvic radiotherapy or Sjogren's Syndrome. The quality of the evidence was assessed with the Cochrane risk of bias tool. This study is registered on PROSPERO, number CRD42021238121.

Outcomes: Effects of CO2-Laser therapy on GSM symptoms assessed through subjective or objective efficacy measurement methods.

Results: A total of 803 articles were identified. Of these, 25 studies were included in this review for a total of 1,152 patients. All studies showed a significant reduction in VVA and/or GSM symptoms (dryness, dyspareunia, itching, burning, dysuria). The pooled mean differences for the symptoms were: dryness -5.15 (95% CI:-5.72,-4.58; $P < .001$; I^2:62%; n = 296), dyspareunia -5.27 (95% CI:-5.93,-4.62; $P < .001$; I^2:68%; n = 296), itching -2.75 (95% CI:-4.0,-1.51; $P < .001$; I^2:93%; n = 281), burning -2.66 (95% CI:-3.75, -1.57; $P < .001$; I^2:86%; n = 296) and dysuria -2.14 (95% CI:-3.41,-0.87; $P < .001$; I^2:95%; n = 281). FSFI, WHIS and VMV scores also improved significantly. The pooled mean differences for these scores were: FSFI 10.8 (95% CI:8.41,13.37; $P < .001$; I^2:84%; n = 273), WHIS 8.29 (95% CI:6.16,10.42; $P < .001$; I^2:95%; n = 262) and VMV 30.4 (95% CI:22.38,38.55; $P < .001$; I^2:24%; n = 68). CO2-Laser application showed a beneficial safety profile and no major adverse events were reported.

Clinical Implications: Vaginal laser treatment resulted in both a statistically and clinically significant improvement in GSM symptoms. FSFI improved significantly in all 8 included studies but it reached a clinically relevant level only in 2 of them.

Strengths & Limitations: The strength of the current meta-analysis is the comprehensive literature search. We reported data from a high number of patients (1,152) and high number of laser applications (more than 3,800). The main limitations are related to the high heterogeneity of the included studies investigating laser effects. Moreover, most of them are single center and nonrandomized studies.

Conclusion: The data suggest that CO2-Laser is a safe energy-based therapeutic option for the management of VVA and/or GSM symptoms in postmenopausal women; however, the quality of the body of evidence is "very low" or "low". **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.**

Key Words: Genitourinary Syndrome of Menopause (GSM); Menopause; Vaginal CO2-Laser; Vulvo-Vaginal Atrophy (VVA)

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INTRODUCTION

Genitourinary Syndrome of Menopause (GSM) is a condition encompassing changes resulting from loss of oestrogen production on the female genitourinary tract.

The nomenclature was proposed in 2014 during a consensus conference of experts, The International Society for the Study of Women's Sexual Health (ISSWSH) and The North American Menopause Society (NAMS).[1] They revised the term Vulvo-Vaginal Atrophy (VVA) introducing a new one that more accurately and appropriately describes this condition. However, some authors continue to adopt the term VVA to refer to this syndrome.

GSM is a chronic condition progressing when not treated. Principal symptoms include vaginal or vulval dryness, burning, itching, dyspareunia, dysuria, urinary urgency, increased frequency of urination and recurrent urinary tract infections. These symptoms impact on daily activities and interferes with sexual life with negative consequences on couple's relationship.[2,3]

GSM is estimated to affect approximately 50% of postmenopausal women.[4,5] As the average life expectancy continues to grow, many women spend more than one third of their lives in menopause.

Despite the frequency of this condition and its impact on quality of life (QoL), GSM is underdiagnosed and undertreated. This is both due to the belief that GSM symptoms are natural part of aging and considered something to live with[6] and the physicians' poor awareness about GSM prevalence and symptoms.[7]

A variety of treatment strategies for GSM are available to alleviate VVA symptoms and to restore urogenital physiology. First-line treatment for symptomatic women with GSM is represented by local oestrogen. If this therapy fails, moisturizers and lubricants treatment should be considered to mitigate the symptoms.[8]

Furthermore, daily topical use of dehydroepiandrosterone can also be considered in the treatment of VVA and sexual associated symptoms.[9] Physical methods for the treatment of GSM, like laser or radiofrequency therapy, represent a non-pharmacological second line option particularly useful in women who are nonresponsive and/or noncompliant and in those who have contraindications to hormones. All this considered the use of laser is gaining ground during the last years.

Mainly two different types of lasers are available: The Erbium: YAG Laser and the CO2-Laser. The former has thermal properties, while the latter has thermal and micro-ablative properties. CO2-Laser, with its capacity to reach deep layers of the vagina, can stimulate collagen synthesis and angiogenesis.

CO2-Laser has been introduced in 2014 and its use has spread quickly. Histological findings from ex vivo and biopsied atrophic vaginal tissue CO2-Laser application has showed that CO2-Laser is associated to a regenerative effect on the vagina because it determines stimulation and neo-formation of collagen and elastic fibres in postmenopausal women.[10,11]

Nowadays different devices using CO2-Laser technology are available on the market.

Technical characteristics are summarized in Table 1. Devices' settings and features have been collected from manufacturers' advertising literature.

At the moment different reviews have been published on physical methods for the treatment of GSM; many of them focus on their efficacy without performing a sub-analysis for each physical method.[12–14]

Moreover in a meta-analysis published by Pitsouni et al. in 2017, the authors analysed the effect CO2 or Erbium: YAG Laser showing that the quality of the reported data is low or very low.[15]

For this review with we decided to focus only on CO2-Laser therapy.

Two reviews exclusively focusing on CO2-Laser are already available in literature but they are neither systematic nor meta-analyses, missing a critical appraisal of the evidence with validated tools.[16,17]

The main aim of this review and meta-analysis was to systematically search the literature to find all the studies analysing CO2-Laser therapy in postmenopausal women in order to assess the efficacy and safety of this treatment on GSM.

Moreover, we aimed to provide evidence-based strategies and recommendations in current clinical practice.

The Population, Intervention, Comparison, and Outcome framework for the review included[1] population of interest: postmenopausal women with symptoms of VVA (vaginal dryness, irritation, soreness, or dyspareunia);[2] interventions: CO2-Laser;[3] comparison: type of laser, setting, therapeutic protocol; and[4] outcome: objective and subjective measurements of GSM symptoms and clinical signs.

METHODS

Reporting

The reporting of this systematic review is performed accordingly to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) guidelines.[18,19]

Eligibility Criteria

Inclusion criteria were original clinical studies and clinical trials, written in English language and published within the last 6 years. We included both randomised controlled trials and non-randomised studies to provide a complete summary of the effects of CO2-Laser therapy.

Studies analysing other energy modalities were not considered. We excluded case reports, conference abstracts and articles without full text publication and unpublished material. "Grey literature" was not searched.

Table 1. Technical characteristics of different laser devices

Devices	Manufacturer and location	Technical characteristics
MonaLisa Touch SmartXide^2 V^{2}LR	DEKA; Florence, Italy	A laser beam is emitted fractionally, creating small spots called DOTs, which stand for Dermal Optical Thermolysis. This refers to the pattern of microscopic channels made in the mucosa by the laser, separated by healthy tissue. The pulses are distributed over the vaginal wall and are spaced (DOT spacing) to cover the entire treatment area. The Stack mode controls the number of successive pulses in the same point, from one to five, leading to a deeper tissue effect with a reduction of side effects. DEKA pulse (D-pulse) mode consists of a constant high peak power, that produce ablation of the atrophic mucosa, followed by a lower peak power and a longer emission time that allows laser to penetrate further into the mucosa.[57]
CO_2RE Intima	Syneron Candela; Massachussetts, USA	Operates by creating a 10,600nm wavelength beam, with a maximum peak power of 60 watts. It delivers the laser energy by using a pulsed emission mode.[58]
FemTouch AcuPulse system	Lumenis; Israel	It uses a 10,600nm laser beam and provides three power and time exposure modes: SuperPulse, Pulser and Continuous Wave (CW) mode for low, moderate and higher thermal effects on tissue. SuperPulse mode consists of a series of short duration and high peak power pulses; Pulser mode involves constant frequency with variable pulse lengths and CW mode consists of a continuous beam of energy. The maximum peak power is 40 watts.[59]
FemTouch AcuPulse DUO system	Lumenis; Israel	Is a combination of CO2-Laser fibre and free beam energy in a single device. In the treatment of GSM, it has the same features of AcuPulse one.[59]
SmaXel multi-functional fractional CO2-Laser	IDS laser; South Korea	Operates by using a double part pulse called SmartPulse. It consists of a first step in which a high-power ablative pulse with short duration sends laser energy into tissue at optimal depth and this short duration pulse is followed by a lower power pulse with longer duration that sends thermal energy deep into tissue.[60]
Aphrodite	BH LASER; France	It delivers the laser energy to the target tissue by offering two different usage patterns: Ultra Pulse and continuous wave. The maximum peak power is 75 watts.[61]

Participants of the included studies were postmenopausal women with GSM diagnosis.

Patients with an history of gynaecological and/or breast cancer, pelvic organ prolapse staged higher than 2, vulvodynia, vulvovaginitis and with vaginal dryness and dyspareunia due to any cause other than GSM (ie, pelvic radiotherapy or Sjogren's Syndrome) were excluded.

Animal, cadaveric and ex vivo studies were excluded.

Information Sources

A literature search was done up to December 2020 using two electronic databases: MEDLINE and Embase.

Relevant literature was extracted using MeSH-terms (Medical subject headings) in MEDLINE and Emtree-terms (Embase subject headings) in Embase along with synonyms for both databases. Trial registers was not searched. The references of all selected papers were cross-checked to identify other potentially relevant reports.

Search Strategy

Literature search was performed using the following key words: Genitourinary Syndrome of Menopause, Vulvo-Vaginal Atrophy, Laser and CO2-Laser.

Details of the search strategy can be found in online supplemental Appendix 1.

Selection Process

Independent review of the full-text manuscripts of the selected studies was performed by two authors (MF and IP) to check if the selected full-text papers met the inclusion criteria. Cases of disagreement were solved by asking a third researcher (SS).

Data Collection Process and Data Items

Two authors (MF and IP) independently extracted and collected data into a table. A third author (SS) double checked the table.

We collected data on:

- the report: author and year
- the participants: number of patients, sample characteristics,
- the research design: study design, adherence, length of follow-up (FU)
- the intervention: type of laser and laser setting, treatment protocol, outcomes and outcomes measures and adverse events

The outcome of laser therapy can be assessed through subjective or objective efficacy measurement methods.

Subjective measurements consist in standardized specific tools:

1 Visual Analogue Scale (VAS), or numerical scale response, is used to measure vaginal atrophy symptoms intensity. VAS could range from 0 to 10 or from 0 to 3. In VAS 0-10, a score of 4−7 indicates moderate symptoms and a score of 8−10 indicates severe symptoms. In VAS 0-3, a score of one indicates mild symptoms, two indicates moderate symptoms and three indicates severe symptoms.
2 Female Sexual Function Index (FSFI) is a 19−item questionnaire used to evaluate sexual function. It investigates 6 domains: desire, arousal, lubrication, orgasm, satisfaction and pain. The threshold of 26.55 has been set to define the presence or absence of sexual dysfunction.[20]
3 Short Form 12 (SF-12) assesses physical (PCS12) and mental (MCS12) components giving a score of quality of life (QoL).[21]
4 Vaginal dryness score of International Consultation on Incontinence Modular Questionnaire-Vaginal Symptoms questionnaire (ICIQ-VS) is a tool to assess the severity of vaginal symptoms. It consists of 14 items divided into three blocks: vaginal symptoms, sexual matter, and QoL. Item number seven regards vaginal dryness and it is used to assess symptoms of vaginal atrophy.[22]
5 Objective measurements consist in scores that evaluate vaginal tissue aspects:
6 Vaginal Health Index Score (VHIS) evaluates five components of vaginal epithelium: elasticity, fluid volume, pH, epithelial integrity, and moisture. A score from 1 to 5 can be given to each component were score 1 is the poorest condition. The sum of the five components represents the total VHI score. A score ≤15 defines the presence of vaginal atrophy.
7 Vaginal Maturation Value (VMV) is a cytological evaluation of the percentage of superficial, intermediate and parabasal epithelial cells on the vaginal smear. Threshold of 40 defines vaginal atrophy.

Study Risk of Bias Assessments and Levels of Evidence

Risk of bias and quality assessments of the included studies were determined for nonrandomized studies using the Risk of bias in Non- Randomized Studies of Intervention (ROBINS-I) tool and for randomized controlled trials using the revised Cochrane Risk of Bias Tool for Randomized Trials (Rob2).[23,24]

Quality of the body of evidence was assessed by the GRADE system for the outcomes that could be meta-analysed.[25]

Data Synthesis and Statistics

We performed a qualitative and quantitative analysis of data collected from the studies comparing laser effect before and after treatment in the same patients. The meta-analysis was conducted using RevMan version 5.4.1 (Cochrane Training, London, United Kingdom). Pooled mean difference with 95% confidence intervals (CIs) from random-effects models were calculated using inverse variance as statistical method. Heterogeneity between studies was assessed using I^2 statistic, with I^2 less than 25% is considered low and I^2 more than 75% is considered high.

Patient and Public Involvement

As this is a systematic review of the literature, patients and the general public were not involved in the development of the research question or choice of outcome measures that we wanted to assess.

RESULTS

Study Selection

A total of 25 studies were included in the present review. (Figure 1)

The search strategy provided a total of 803 citations. After adjusting for duplicates, 320 articles were screened for title and abstract. Those not corresponding to the study selection criteria were excluded.

We examined 40 full-text articles, of which only 25 met the inclusion criteria.

The references of all selected papers were cross-checked, but any additional material was identified.

Study Characteristics

Out of the 25 total included studies, five were randomized controlled trials (141 patients)[26−30] and twenty were non-randomized studies (1,011 patients). Of the non-randomized studies, two were retrospective (144 patients),[31,32] seventeen were prospective observational (817 patients) and one was a prospective controlled case (50 patients).[33]

All studies were written in English and published between 2015 and 2020.

Countries of origin of the different work teams were USA (n = 7), Italy (n = 5), Greece (n = 5), Brazil (n = 2), Greece and Italy (n = 1), France (n = 1), Australia (n = 1), Thailand (n = 1), Iran (n = 1) and Perú (n = 1).

Results reported in individual studies are displayed in Table 2.

The included studies recruited a total of 1,152 women with an average of 46 participants per study (minimum 15 and maximum 140). All included patients were postmenopausal women with a median age of 57.9 years, ranging from 54 and 61.7 years.

All studies include women with a diagnosis of GSM without an history of gynaecological and/or breast cancer, pelvic organ prolapse staged higher than 2, pelvic radiotherapy or Sjogren's Syndrome.

Different laser CO2-Laser technologies have been adopted: MonaLisa Touch SmartXide^2 V^{2}LR by DEKA in 18 studies, CO_2RE Intima by Syneron Candela in two studies; FemTouch AcuPulse system by Lumenis in two studies. FemTouch AcuPulse DUO system by Lumenis, SmaXel multi-functional fractional CO2-Laser by IDS laser and Aphrodite, BH LASER, France in one study each.

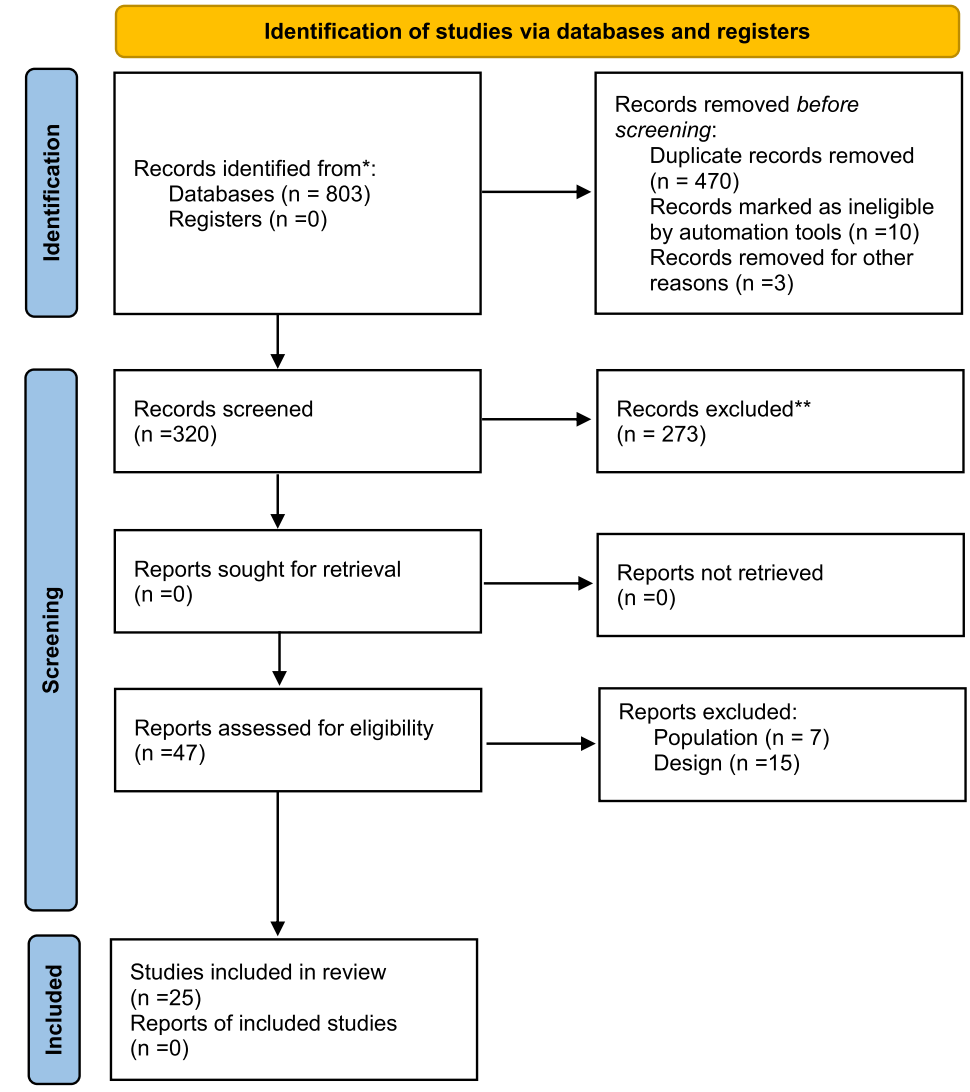

Figure 1. Flow diagram of the study selection.

Different therapeutic protocols were adopted in the included studies with the following characteristics.

The number of laser applications was variable, in most of studies (20 out of 25) the standard protocol of three sessions was adopted. In 3 studies only two laser sessions were set and in other 3 studies the number of laser sessions varied from 3 to 5. Interval between each session was four weeks in 20 studies and 6 weeks in 5 studies with an average of 4 weeks and 4 days. Settings of the lasers varied. All but one study[34] provided information about laser setting details.

Outcome measures of laser therapy are reported using subjective and objective measurement tools. Eighteen studies evaluate both subjective and objective outcomes while seven studies evaluate only one of the two aspects (six report only subjective outcomes and one only objective ones).

In 17 studies GSM symptoms were assessed using the VAS 0-10. In one study the VAS 0-3 was adopted.[29] In seven studies VAS score was not calculated. Eighteen studies assessed the effect of laser treatment on sexual functions with FSFI questionnaire. Satisfaction with the procedure was evaluated in ten studies: eight of them used a five-point Likert scale, one used a 7-point Likert scale and one study assessed satisfaction not using a validated tool.

A change in Quality of Life from baseline was assessed in five studies. Four of them used SF-12 score and one used a self-assessment score of QoL concerning genitourinary symptoms.

Table 2. Characteristics of the studies included in this review

Year	First author, Country	Type of CO2-Laser	Laser setting	Design	No of patients	Mean age	Characteristics of participants	Therapeutic protocol	Assessments	Follow up (Months)
2020	Adabi, Iran [62]	Smaxel	Fractional density:4-5% Energy level of 50 to 60 mJ	Prospective observational	140	56.8	Sexually active women. Symptoms of VVA (vaginal dryness, irritation, soreness, or dyspareunia)	3 laser-therapies (1/4 weeks)	Subjective: - SF-12 - FSFI Objective: - VHIS	3
2020	Alexiades, USA [35]	CO_2RE Intima, Syneron Candela	Square pattern: 7.8 × 7.8 mm, Fractional density:5%, Energy level: 50mJ, Fluence: 283 J/cm2.	Prospective observational	18	54 ± 7	Symptoms of VVA (vaginal dryness, irritation, soreness, or dyspareunia)	3 laser-therapies (1/4 weeks)	Subjective: - FSFI - 5−point Likert scale Objective: - VHIS	1; 3; 6; 12
2016	Athanasiou, Greece [44]	SmartXide^2 V^{2}LR, Monalisa Touch, DEKA.	D-Pulse; Power 40W; Dwell time 1000μs; Spacing 1000μs; SmartStak: 1-3	Prospective observational	53	57.2 ± 5.4	≥1 moderate/severe symptom of GSM, pH of vaginal fluid >4.5, superficial epithelial cells on vaginal smear <5%.	3 laser-therapies (1/4 weeks)	Objective: - PH of vaginal fluid - Microscopy of wet mount - Cultures for bacteria species	1
2017	Athanasiou, Greece [45]	SmartXide^2 V^{2}LR, Monalisa Touch, DEKA.	NR	Prospective observational	55	57	Moderate/severe symptoms of dyspareunia	3-5 laser-therapies (1/4 weeks)	Subjective: - VAS [0-10] - FSFI Objective: - VHIS - VMV	1
2018	Athanasiou, Greece [31]	SmartXide^2 V^{2}LR, Monalisa Touch, DEKA.	D-Pulse; Power 30 or 40 W; Dwell time 1000μs; Spacing 1000μm; SmartStak: 1 to 3.	Retrospective observational	94	57	≥1 moderate/severe symptom of GSM	3-5 laser-therapies (1/4 weeks)	Subjective: - VAS [0-10] - FSFI	1; 3; 6; 12
2017	Behnia-Willison, Australia [46]	SmartXide^2 V^{2}LR, Monalisa Touch, DEKA.	D-Pulse; Power 30 W; Dwell time 1000μs; Spacing 1000μm. SmartStak:2.	Prospective observational	102	61	≥1 GSM symptoms:[1] vaginal dryness, and/or[2] dyspareunia	3 laser-therapies (1/6 weeks)	Subjective: - GSM symptoms - Australian Pelvic Floor Questionnaire	12; 24
2017	Cruz, Brazil [26]	SmartXide^2 V^{2}LR, Monalisa Touch, DEKA.	Power 300W; Dwell time 1000μs; Spacing 1000μs; SmartStak:2	RCT	45 15 CO2 laser (L); 15 Estriol (E); 15 CO2 laser + Estriol (LE)	55.9 ± 5.2	≥1 moderate symptom of VVA (dyspareunia, dryness, or burning)*	2 laser-therapies (1/4 weeks)	Subjective: - VAS [0-10] - FSFI Objective: - VHIS - VMV	1; 4
2020	Di Donato, Italy [36]	FemTouch Lumenis AcuPulse DUO system	Energy: 7.5- 12.5 mJ; Density: 5%- 15%.	Prospective observational	53	58.1 ± 7.4	≥1 symptom of VVA (itching, burning, reduced lubrication, superficial mild and/or severe dyspareunia).	3 laser-therapies (1/4 weeks)	Subjective: - 7-point Likert scale for pain during procedure - 7-point Likert scale for satisfaction	6
2018	Eder, USA [37]	FemTouch Lumenis AcuPulse system	Energy: 7.5 - 12.5 mJ	Prospective observational	28	60.1 ± 5.55	≥1 VVA-related symptoms (dryness, itching, burning, dysuria or dyspareunia)	3 laser-therapies (1/4 weeks)	Subjective: - VAS [0-10] - FSFI - 5-point Likert scale Objective: - VHIS	1; 3; 6
2019	Eder, USA [38]	FemTouch Lumenis AcuPulse system	Energy: 7.5- 12.5 mJ	Prospective observational	20	60.1 ± 5.55	≥1 VVA-related symptoms (dryness, itching, burning, dysuria or dyspareunia)	3 laser-therapies (1/4 weeks)	Subjective: - VAS [0-10] - FSFI - 5-point Likert scale Objective: - VHIS	12; 15; 18
2019		Aphrodite, BH LASER.		Case control		58	VVA symptoms (vaginal dryness, burning sensation, local	2 laser-therapies (1/6 weeks)		3; 6

(continued)

Table 2. Continued

Year	First author, Country	Type of CO2-Laser	Laser setting	Design	No of patients	Mean age	Characteristics of participants	Therapeutic protocol	Assessments	Follow up (Months)
	Marin, France [33]		Energy 18 W; On time: 320 ms, Off time 1200 ms, smaller spot: 70–80 m		50 25 non-menopausal; 25 menopausal		itching) and/or sexual impaired function (dyspareunia, decrease in sexual satisfaction, excitation)		Subjective: - FSFI - QoL	
2019	Paraiso, USA [27]	SmartXide^2 V^{2}LR, Monalisa Touch, DEKA.	Power 30W; Dwell time 1000μs; Spacing 1000μs; SmartStak: 1 (baseline), 3 (6 weeks and 3 months)	RCT	62 30 CO2 laser (L); 32 Estriol (E)	61 ± 7	Vaginal dryness ≥ 7 on VAS scale	3 laser-therapies (1/6 weeks)	Subjective: - VAS [0-10] - Patient global impression - Satisfaction - FSFI Objective: - VHIS - VMV	6
2014	Perino, Italy [39]	SmartXide^2 V^{2}LR, Monalisa Touch, DEKA.	D-Pulse; Power 40 W; Dwell time 1000μs; Spacing 1000μm; SmartStak: 2	Prospective observational	48	56	≥1 VVA symptoms (e.g., itching, burning, reduced lubrication, superficial and/or severe dyspareunia)	3-5 laser-therapies (1/4 weeks)	Subjective: - VAS [0-10] - 5-point Likert scale Objective: - VHIS	1
2016	Pitsouni, Greece [34]	SmartXide^2 V^{2}LR, Monalisa Touch, DEKA.	NR	Prospective observational	53	57.2 ± 5.4	≥1 moderate-severe symptom of GSM (dyspareunia, genital dryness, burning, itching, dysuria, urinary frequency, urgency)[†]	3 laser-therapies (1/4 weeks)	Subjective: - FSFI - VAS [0-10] Objective: - VMV - VHIS	1
2017	Pitsouni, Greece [32]	SmartXide^2 V^{2}LR, Monalisa Touch, DEKA.	D-Pulse; Power 30-40 W; Dwell time 1000μs; Spacing 1000μm; SmartStak: 1- 3	Retrospective case-control	50 25 at 30 W power; 25 at 40 W power	56.3 ± 5.1 56.8 ± 3.6	Severe dyspareunia and dryness[†]	3 laser-therapies (1/4 weeks)	Subjective: - VAS [0-10] - FSFI Objective: - VMV - VHIS	1
2019	Politano, Brazil [28]	SmartXide^2 V^{2}LR, Monalisa Touch, DEKA.	D-Pulse; Power 40 W; Dwell time 1000μs; Spacing 1000μm; SmartStak:2	RCT	72 24 CO2 laser (L); 24 Estriol (E); 24 vaginal lubricant (vl)	57.83 ± 5.01	Symptoms of vaginal dryness ± dyspareunia, vaginal burning, or pruritus.	3 laser-therapies (1/4 weeks)	Subjective: - FSFI Objective: -VMV -VHIS	1
2020	Ruanphoo, Thailand [29]	SmartXide^2 V^{2}LR, Monalisa Touch, DEKA.	D-Pulse; Power 40 W; Dwell time 1000μs; Spacing 1000μm; SmartStak: 1-3	RCT	88 44 CO2 laser; 44 sham	61.73 ± 8.01	Moderate to severe intensity of VVA symptoms	3 laser-therapies (1/4 weeks)	Subjective: - VAS score [0-3] - ICIQ-VS for vaginal dryness - 5–point Likert scale Objective: - VHIS	1
2020	Salvatore, Greece and Italy [30]	SmartXide^2 V^{2}LR, Monalisa Touch, DEKA.	D-Pulse; Power 30 W; Dwell time 1000μs; Spacing 1000μm; SmartStak: 1-3. Energy, 43.2-86.4-129.6mJ at 1^,2^ and 3^ session.	RCT	58 28 CO2 laser (L); 30 sham	57	GSM diagnosis. Dryness and dyspareunia had to be the two most bothersome symptoms in all women.	3 laser-therapies (1/4 weeks)	Subjective: - VAS [0-10] - FSFI	1
2014	Salvatore, Italy [43]	SmartXide^2 V^{2}LR, Monalisa Touch, DEKA.	D-Pulse; Power 30 W; Dwell time 1000μs; Spacing 1000μm; SmartStak: 1- 3.	Prospective observational	77	60.6±6.2	Symptoms of VVA (vaginal dryness and/or dyspareunia rated as moderate/severe most bothersome symptoms)[63]	3 laser-therapies (1/4 weeks)	Subjective: - FSFI - SF-12 - VAS [0-10]	1
2014	Salvatore, Italy [40]	SmartXide^2 V^{2}LR, Monalisa Touch, DEKA.	D-Pulse; Power 30 W; Dwell time 1000μs; Spacing 1000μm; SmartStak:1 to 3.	Prospective observational	50	59.6±5.8	Symptoms of VVA (vaginal dryness and/or dyspareunia rated as moderate/severe most bothersome symptoms)[63]	3 laser-therapies (1/4 weeks)	Subjective: - VAS [0-10] - SF-12 - 5–point Likert scale	3

(continued)

Table 2. Continued

Year	First author, Country	Type of CO2-Laser	Laser setting	Design	No of patients	Mean age	Characteristics of participants	Therapeutic protocol	Assessments	Follow up (Months)
									Objective: -VHIS	
2014	Salvatore, Italy [64]	SmartXide^2 V^{2}LR, Monalisa Touch, DEKA.	D-Pulse; Power 30 W; Dwell time 1000μs; Spacing 1000μm; SmartStak: 1- 3.	Prospective observational	15	57.3±3	Dyspareunia related to GSM	3 laser-therapies (1/4 weeks)	Subjective: - VAS [0-10] - SF-12 - FSFI Objective: -VHIS	1
2018	Samuels, USA [47]	CO_2RE Intima, Syneron Candela	Square pattern; Fractional density: 4-5%, Energy level: 50-60 mJ	Prospective observational	40	56 ± 8	Symptoms of VVA (vaginal dryness, irritation, soreness, or dyspareunia)	3 laser-therapies (1/4 weeks)	Subjective: - NSR [0-10] - FSFI Objective: - VHIS - Biopsy samples	3; 6; 12
2016	Sokol, USA [41]	SmartXide^2 V^{2}LR, Monalisa Touch, DEKA.	D-Pulse; Power 30 W; Dwell time 1000μs; Spacing 1000μm; SmartStak: 1- 3.	Prospective observational	30	58.6±8.8	GSM symptoms	3 laser-therapies (1/6 weeks)	Subjective: - VAS [0-10] - FSFI - 5-point Likert scale - Vaginal wall elasticity Objective: - VHIS - Vaginal pH	3
2017	Sokol, USA [42]	SmartXide^2 V^{2}LR, Monalisa Touch, DEKA.	D-Pulse; Power 30 W; Dwell time 1000μs; Spacing 1000μm; SmartStak: 1- 3.	Prospective observational	30	58.6±8.8	GSM symptoms	3 laser-therapies (1/6 weeks)	Subjective: - VAS [0-10] - FSFI - 5-point Likert scale Objective: - VHIS	12
2019	Tovar-Huamani, Perù [48]	SmartXide^2 V^{2}LR, Monalisa Touch, DEKA.	Power 40 W; Dwell time 1000μs; Spacing 1000μm; Fluence 2.68 Jl/cm2	Prospective observational	60	55	VVA symptoms	3 laser-therapies (1/4 weeks)	Subjective: - VAS [0-10] - FSFI Objective: - VHIS -VMV	1

*Participants rated each of three VVA symptoms from 0 (no symptom) to 10 (very severe symptom) using the Visual Analog Scale (VAS) and symptoms were considered moderate if reported to be equal to or greater than 4 in VAS.

†Assessed using a 10-cm Visual Analogue Scale (VAS 0–10). Zero defined absence of symptoms, rates of >0 and <4 mild symptom intensity, ≥4 and <8 moderate intensity, and ≥8 severe intensity. NR = not reported; RCT = randomized controlled trial.

Clinical findings were assessed using VHIS (18 studies) and VMV (seven studies). Other questionnaires and methods adopted to evaluate outcomes are listed in the Table 2.

Outcome assessment was performed before the first and after the last session of laser.

Follow-up length ranged between different studies from a minimum of one month to a maximum of 24 months, with an average of 5.5 months. Six studies reached FU period ≥ 12 months for a total of 304 patients.

Adverse effects of laser treatment were assessed in 23 studies out of 25 and described in Table 4.

Risk of bias in studies and levels of evidence

The risk of bias analysis was performed for each study ranging from low to critical and it is summarized in Figures 2 and 3.

The risk of bias assessment resulted to present "some concern" for 3 out of the 5 (60%) RCTs while the other two emerged to have a low risk of bias.

The risk of bias analysis performed for the 20 nonrandomized studies, showed that 17 (85%) had a moderate risk of bias while 3 (15%) had a serious risk of bias.

The quality of the body of evidence rated "very low" for dryness, dyspareunia, itching, burning, dysuria, FSFI and WHIS. Quality of evidence rated "low" for VMV (Appendix 2).

Results of Syntheses

Comparison of GSM Symptoms and Scores Before and After Laser Treatment. Study outcomes are presented in

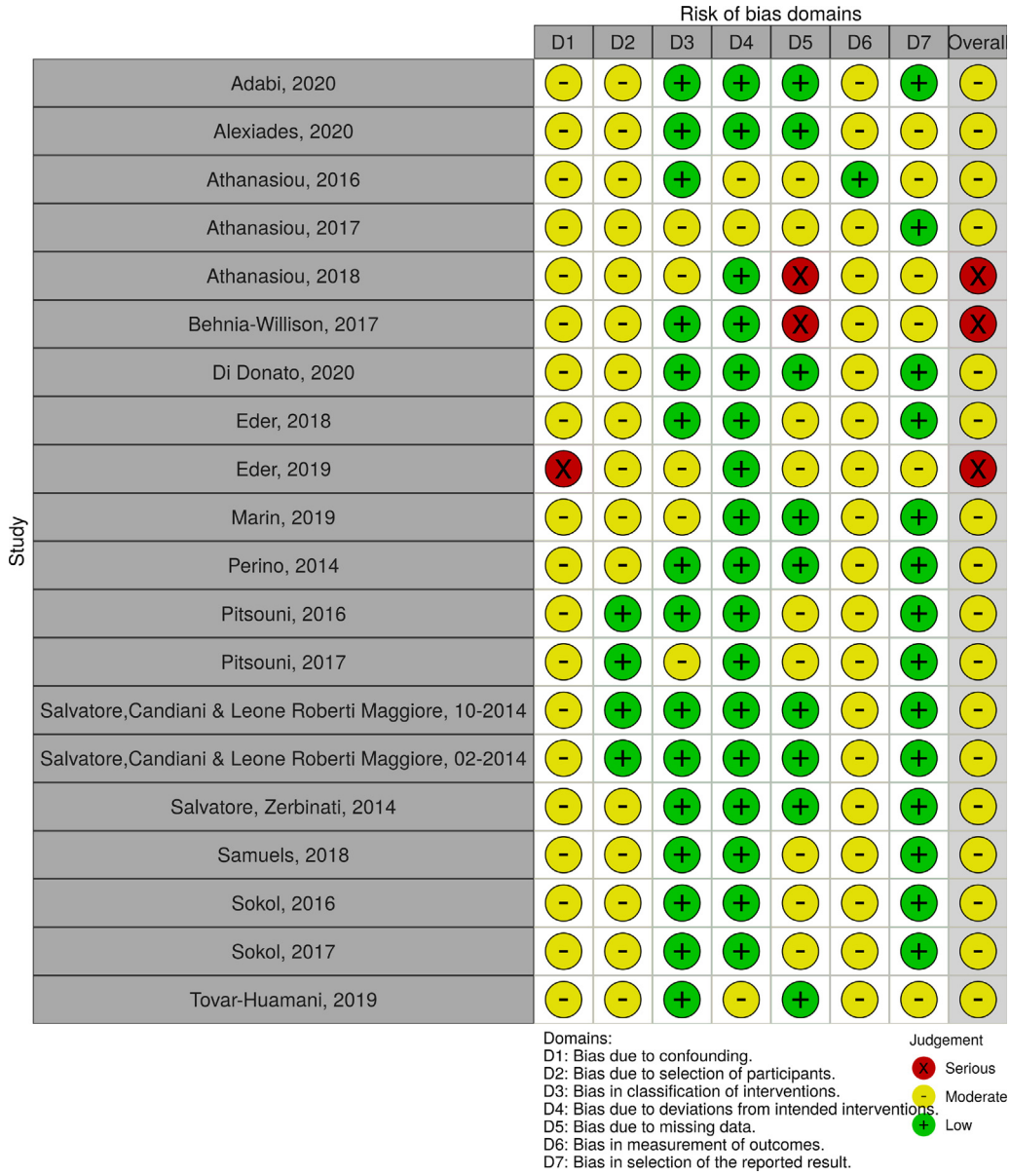

Figure 2. Risk of bias, nonrandomized trials.

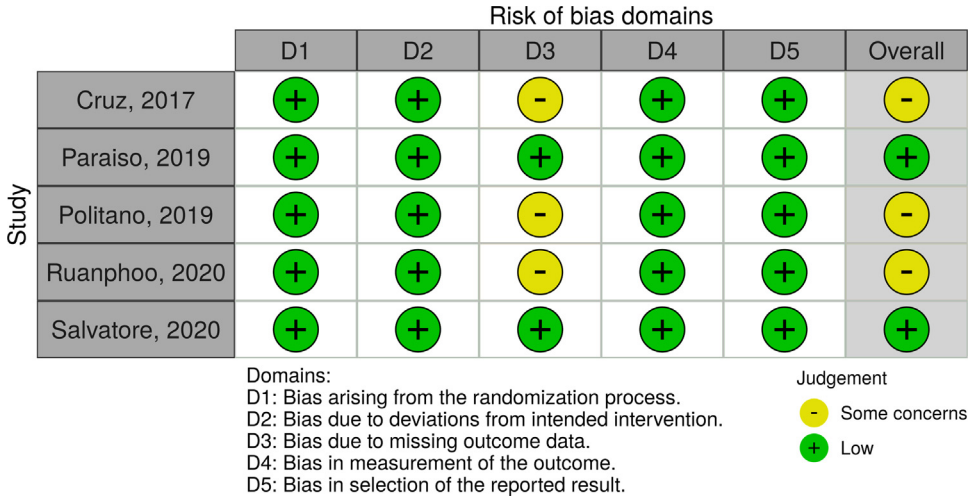

Figure 3. Risk of bias, randomized trials.

Table 3. The forest plots of the meta-analyses at 1 month follow-up are presented in Figure 4 and 5. All GSM symptoms (dryness, dyspareunia, itching, burning, dysuria) decreased significantly in all studies and FSFI, WHIS and VMW scores increased significantly.

Comparison to Sham Procedure. Recently 2 double blind RCTs[29,30] have been published comparing CO2-Laser therapy (study group) to sham procedure (control group).

Ruanphoo et collaborators showed that 12 weeks after therapy patients in the study group reported a significant improvements in VHI score ($P < .001$) and in VAS score ($P = .03$) for dryness, irritation, soreness, and dyspareunia, whereas those in the control group had no significant improvements for all measurements.[29]

Salvatore et al. investigated the effect of laser therapy on sexual function. Study group participants reported a significant improvement in dryness, dyspareunia and FSFI at four months FU ($P < .005$).[30]

Comparison to Standard Therapies. Current literature provides three RCTs[26–28]comparing the efficacy of CO2-Laser with local vaginal oestrogen for GSM treatment. Meta-analysis of these data was not performed due to lack of homogeneous outcome measures in the three RCTs.

The first RCT was published by Cruz et al. in 2017. They randomized 45 patients to three arms: CO2-Laser alone, local estriol alone and combination of both. After 20 weeks they showed that the combination group had the most significant change in VHI and that both laser and combination groups had a relevant improvement in all GSM symptoms: dryness ($P < .001$), dyspareunia ($P = .009$) and burning ($P = .002$). While patients in the oestrogen only group reported a significant improvement only in vaginal dryness ($P < .001$).[26]

Paraiso et al. published the results of the VELVET trial which evaluated the improvement in VAS vaginal dryness score, vaginal atrophy, QoL and sexual function comparing fractionated CO2-Laser therapy to topical oestrogens. Both treatments resulted in similar improvement in GSM symptoms and sexual function at six months FU.[27]

Lastly, Politano et al. performed a RCT comparing the efficacy of CO2-Laser with that of local oestrogens and vaginal lubricants. They focused on vaginal health objective parameters (VHIS and VMI) and they observed a greater increase in total VHIS after laser application compared to the other treatments. Regarding vaginal maturation, laser group patients showed a significant reduction in vaginal basal cells and an increase in superficial vaginal cells after treatment.[28]

Satisfaction with the Procedure. Ten studies reported patient satisfaction with the procedure. 87.9% of the questioned patients affirmed to be satisfied or very satisfied with the procedure (310 patients out of 352 questioned).[27,29,35–42]

Sexual Function. Sexual function parameters (FSFI and satisfaction with sexual life) were investigated in 18 out of the 25 included studies. In the subgroup-analysis of the CO2-laser effect on FSFI, the pooled mean difference was 10.8 (95% CI:8.41,13.37; $P < .001$; I^2:84%; n = 273), Figure 5.

In four studies, 85%[43], 98%[34,44] and 100%[45],[31] of women who reported to be sexually inactive before treatment due to GSM symptoms, resumed a normal sex life one month after last laser session. In another study this has been reported in 89% of women six months after last laser session.[37]

Duration of Effect. Salvatore et al. reported a persistence of GSM symptoms improvement and a good VHIS at 12-week FU.[40]

Table 3. Outcomes of the included studies in the systematic review and meta-analysis

First autor	No of patients	Dryness	Dyspareunia	Itching	Burning	Dysuria	FSFI	VHIS	VMV
Adabi[62]	140	NA	NA	NA	NA	NA	NA	NA	NA
Alexiades[35]	18	NA	NA	NA	NA	NA	B: Mean 14.4,SD 8.8 A (1m): Mean 24.8, SD 7.2 A (3m): Mean 25.7, SD 7.8 A (6m): Mean 25.8, SD 9.3 A (12m): Mean 25.3, SD 9.5	B: Mean 9.9, SD 2.2 A (1m): Mean 20.6, SD 3.3 A (3m): Mean 21.7, SD 1.7 A (6m): Mean 22.2, SD 1.7 A (12m): Mean 20.5, SD 2.2	NA
Athanasiou[44]	53	NA	NA	NA	NA	NA	NA	NA	NA
Athanasiou[45]	55	B: Median 8, IQR 4 A(1 m): Median 2, IQR 4	B: Median 8, IQR 4 A(1 m): Median 2, IQR 3	NA	NA	NA	B: Median 13.4, IQR 15.7 A(1 m): Median 25.3, IQR 5.9	B: Median 8, IQR 3 A(1 m): Median 20, IQR 6	B: Median 0, IQR 30 A(1 m): Median 50, IQR 17.5
Athanasiou[31]	94	B: Median 8 A(1 m): Median 2	B: Median 8 A(1 m): Median 2	B: Median 5 A(1 m): Median 0	B: Median 5 A(1 m): Median 0	NA	B: Median 9.2 A(1 m): Median 24.6	NA	NA
Behnia-Willison[46]	102	NA	NA	NA	NA	NA	NA	NA	NA
Cruz[26]	45 15 CO2laser (L); 15 Estriol (E); 15 CO2laser + Estriol (LE)	L group B: Mean 8, SD 2.6 A (1m): Mean 3.6, SD 2.6 E group B: Mean 5.6, SD 2.9 A (1m): Mean 2.4, SD 2.0 LE group B: Mean 7.9, SD 3.0 A (1m): Mean 3.3, SD 2.9	L group B: Mean 4.9, SD 3.7 A (1m): Mean 2.9, SD 2.9 E group B: Mean 3.2, SD 3.4 A (1m): Mean 0.6, SD 1.7 LE group B: Mean 6.5, SD 3.9 A (1m): Mean 2.5, SD 3.8	NA	L group B: Mean 3.9, SD 4.5 A (1m): Mean 1.0, SD 2.0 E group B: Mean 0.9, SD 1.6 A (1m): Mean 0.1, SD 0.5 LE group B: Mean 4.9, SD 3.8 A (1m): Mean 1.2, SD 2.7	NA	L group B: Median 18.6, IQR 16.4-24.6 A (1m): Median 18, IQR 11.4-20.7 E group B: Median 23.6, IQR 17.5-29.8 A (1m): Median 22.9, IQR 8.4-29.7 LE group B: Median 18.7, IQR 7.2-22.6 A (1m): Median 22.6, IQR 11.3-26.3	NA	L group B: Mean 42.4, SD 24 A (1m): Mean 64.5, SD 23.1 E group B: Mean 36.9, SD 29.7 A (1m): Mean 65.6, SD 6.5 LE group B: Mean 48.4, SD 25.3 A (1m): Mean 65, SD 10.5
Di Donato[36]	53	NA	NA	NA	NA	NA	NA	NA	NA
Eder[37]	28	B: Mean 5.04, SD 3.16 A (1m): Mean 1.99, SD 1.84	B: Mean 6.29, SD 3.23 A (1m): Mean 2.13, SD 2.49	B: Mean 1.22, SD 2.06 A (1m): Mean 0.56, SD 0.9	B: Mean 1.68, SD 2.52 A (1m): Mean 0.39, SD 0.73	B: Mean 1.35, SD 2.31 A (1m): Mean 0.44, SD 0.79	B: Mean 13.78, SD 7.70 A (1m): Mean 22.36, SD 10.40	B: Mean 11.93, SD 3.82 A (1m): Mean 17.07, SD 4.24	NA
Eder[38]	20	NA	NA	NA	NA	NA	NA	NA	NA
Marin[33]	50 25 non-menopausal; 25 menopausal	NA	NA	NA	NA	NA	B: Median 19 A (1m): Median 27	NA	NA
Paraiso[27]	62 30 CO2 laser (L); 32 Estriol (E)	NA	NA	NA	NA	NA	NA	NA	NA
Perino[39]	48	B: Median 8, IQR 2 A(1 m): Median 2, IQR 1	B: Median 8, IQR 2 A(1 m): Median 3, IQR 1	B: Median 6, IQR 1.75 A(1 m): Median 2, IQR 0.75	B: Median 6, IQR 2 A(1 m): Median 2, IQR 1	NA	NA	B: Median 10.5, IQR 3 A (1m): Median 21.5, IQR 2	NA
Pitsouni[34]	53	B: Mean 6.1, SD 3.1 A(1m): Mean 1.7, SD 1.9	B: Mean 7.7, SD 2.5 A(1m): Mean 2.3, SD 2.2	B: Mean 1.7, SD 3.2 A(1m): Mean 0.3, SD 1.2	B: Mean 1.3, SD 2.9 A(1m): Mean 0.3, SD 0.9	B: Mean 0.9, SD 1.7 A(1m): Mean 0.3, SD 0.7	B: Mean 13.7, SD 8.1 A(1m): Mean 25.9, SD 4.6	B: Mean 8.4, SD 2.5 A(1m): Mean 20.1, SD 3	B: Mean 11.7, SD 15.6 A(1m): Mean 44.2, SD 13.7
Pitsouni[32]	50 25 at 30 W power; 25 at 40 W power	NA	NA	NA	NA	NA	NA	NA	NA
Politano[28]	72 24 CO2 laser (L); 24 Estriol (E); 24 vaginal lubricant (vl)	NA	NA	NA	NA	NA	L group B: Mean 17.28, SD 8.46 A (1m): Mean 20.55, SD 8.68 E group B: Mean 15.35, SD 7.57 A (1m): Mean 18.04,	L group B: Mean 9.5, SD 2.59 A (1m): Mean 18.68, SD 3.2 E group B: Mean 9, SD 2.52 A (1m): Mean 15.11,	NA

(continued)

Table 3. Continued

First autor	No of patients	Dryness	Dyspareunia	Itching	Burning	Dysuria	FSFI	VHIS	VMV
							SD 9.46 vl group B: Mean 15.84, SD 7.66 A (1m): Mean 17.79, SD 7.13	SD 3.98 vl group B: Mean 9.79, SD 3.09 A (1m): Mean 10.44, SD 2.78	
Ruanphoo[29]	88 44 CO2 laser; 44 sham	NA	NA	NA	NA	NA	NA	L group B: Mean 14.18, SD 3.39 A (1m): Mean 17.45, SD 2.61 sham group B: Mean 14.66, SD 2.91 A (1m): Mean 16.08, SD 3.27	NA
Salvatore[30]	58 28 CO2 laser (L); 30 sham	L group B: Mean 8.0, SD 1.7 A(1m): Mean 2.4, SD 2.9 sham group B: Mean 7.5, SD 1.9 A (1m): Mean 5.6, SD 2.9	L group B: Mean 8.6, SD 1.5 A(1m): Mean 2.6, SD 2.6 sham group B: Mean 8.7, SD 1.4 A (1m): Mean 7.6, SD 1.9	L group B: Mean 3.9, SD 3.1 A(1m): Mean 1.0, SD 2.1 sham group B: Mean 3.1, SD 3.2 A (1m): Mean 1.8, SD 2.6	L group B: Mean 3.6, SD 3.0 A(1m): Mean 1.4, SD 2.4 sham group B: Mean 4.6, SD 3.4 A (1m): Mean 3.7, SD 3.4	L group B: Mean 1.6, SD 2.4 A(1m): Mean 0.6, SD 1.5 sham group B: Mean 0.9, SD 1.6 A (1m): Mean 0.6, SD 1.2	L group B: Mean 11.4, SD 8.2 A(1m): Mean 23.8, SD 6.6 sham group B: Mean 9.7, SD 7.8 A (1m): Mean 12.1, SD 8.3	NA	NA
Salvatore,Candiani & Leone Roberti Maggiore, 10-2014[43]	77	B: Mean 8.4, SD 2.0 A(1m): Mean 2.8, SD 1.8	B: Mean 8.4, SD 2.4 A(1m): Mean 2.8, SD 2.1	B: Mean 6.4, SD 2.7 A(1m): Mean 2.1, SD 2.0	B: Mean 6.2, SD 2.7 A(1m): Mean 2.2, SD 2.8	B: Mean 5.7, SD 2.8 A(1m): Mean 2.6, SD 1.9	B: Mean 14.8, SD 7.7 A(1 m): Mean 27.2, SD 5.6	NA	NA
Salvatore,Candiani & Leone Roberti Maggiore, 02-2014[40]	50	B: Mean 8.3, SD 2.1 A(1m): Mean 2.7, SD 1.9	B: Mean 8.1, SD 2.8 A(1m): Mean 3.3, SD 2.3	B: Mean 6.1, SD 3 A(1m): Mean 1.5, SD 1.7	B: Mean 6.4, SD 2.7 A(1m): Mean 2.9, SD 2.4	B: Mean 5, SD 2.4 A(1m): Mean 1.1, SD 1.1	NA	B: Mean 13.1, SD 2.5 A(1m): Mean 23.1, SD 1.9	NA
Salvatore, Zerbinati, 2014[64]	15	B: Mean 7.2, SD 1.1 A(1m): Mean 1.7, SD 0.9	B: Mean 8.7, SD 1 A(1m): Mean 2.2, SD 1	B: Mean 5.6, SD 1.3 A(1m): Mean 1.6, SD 0.7	B: Mean 6.9, SD 2.7 A(1m): Mean 1.5, SD 1.9	B: Mean 5.1, SD 0.9 A(1m): Mean 0.8, SD 1	B: Mean 12.2, SD 1 A(1m): Mean 27.3, SD 0.9	B: Mean 12.9, SD 3 A(1m): Mean 22.1, SD 2.3	NA
Samuels[47]	40	NA	NA	NA	NA	NA	NA	NA	NA
Sokol[41]	30	B: Mean 7.5, SD 2.5 A(3m): Mean 1.4, SD 2.5	B: Mean 8.2, SD 1.7 A(3m): Mean 3.0, SD 2.9	B: Mean 1.9, SD 2.1 A(3m): Mean 0.5, SD 1.3	B: Mean 2.3, SD 3.3 A(3m): Mean 0.9, SD 1.9	B: Mean 1.1, SD 2.5 A(3m): Mean 0.0, SD 0.2	B: Mean 11.5, SD 7.8 A(3m): Mean 20.1, SD 11.0	B: Mean 14.4, SD 2.9 A(3m): Mean 21.4, SD 2.9	NA
Sokol[42]	30	B: Mean 7.5, SD 2.5 A(12m): Mean 1.5, SD 2.0	B: Mean 8.2, SD 1.7 A(12m): Mean 3.1, SD 3.1	B: Mean 1.9, SD 2.1 A(12m): Mean 0.5, SD 1.1	B: Mean 2.3, SD 3.3 A(12m): Mean 0.5, SD 1.9	B: Mean 1.1, SD 2.5 A(12m): Mean 0.4, SD 1.3	B: Mean 11.5, SD 7.8 A(12m): Mean 21.3, SD 11.5	B: Mean 14.4, SD 2.9 A(12m): Mean 21.7, SD 3.6	NA
Tovar-Huamani[48]	60	B: Median 9, IQR 8–10 A(12m): Median 4, IQR 3–5.5	B: Median 8, IQR 5–10 A(12m): Median 4, IQR 2–5	B: Median 6, IQR 4–8 A(12m): Median 0, IQR 0–2	B: Median 8, IQR 5–9 A(12m): Median 1.5, IQR 0–3	B: Median 5.5, IQR 3–7 A(12m): Median 0, IQR 0–2	B: Median 5, IQR 2–14 A(12m): NA	B: Median 13, IQR 10–15 A(12m): NA	B: Median 28, IQR 24–31 A(12m): NA

A = After ± the last laser-therapy; B = Before ± the initiation of laser-therapy; NA = Not applicable

In 12 studies data were reported as mean ± standard deviation. In 1 study[31] data were reported as median and in 3 studies[39,45,48] data were reported as median and interquartile range(interquartile is presented in the parentheses). The time of outcome assessment after the last laser-therapy is presented in the parenthesis (e.g 1 m, 12 m) (m: months).

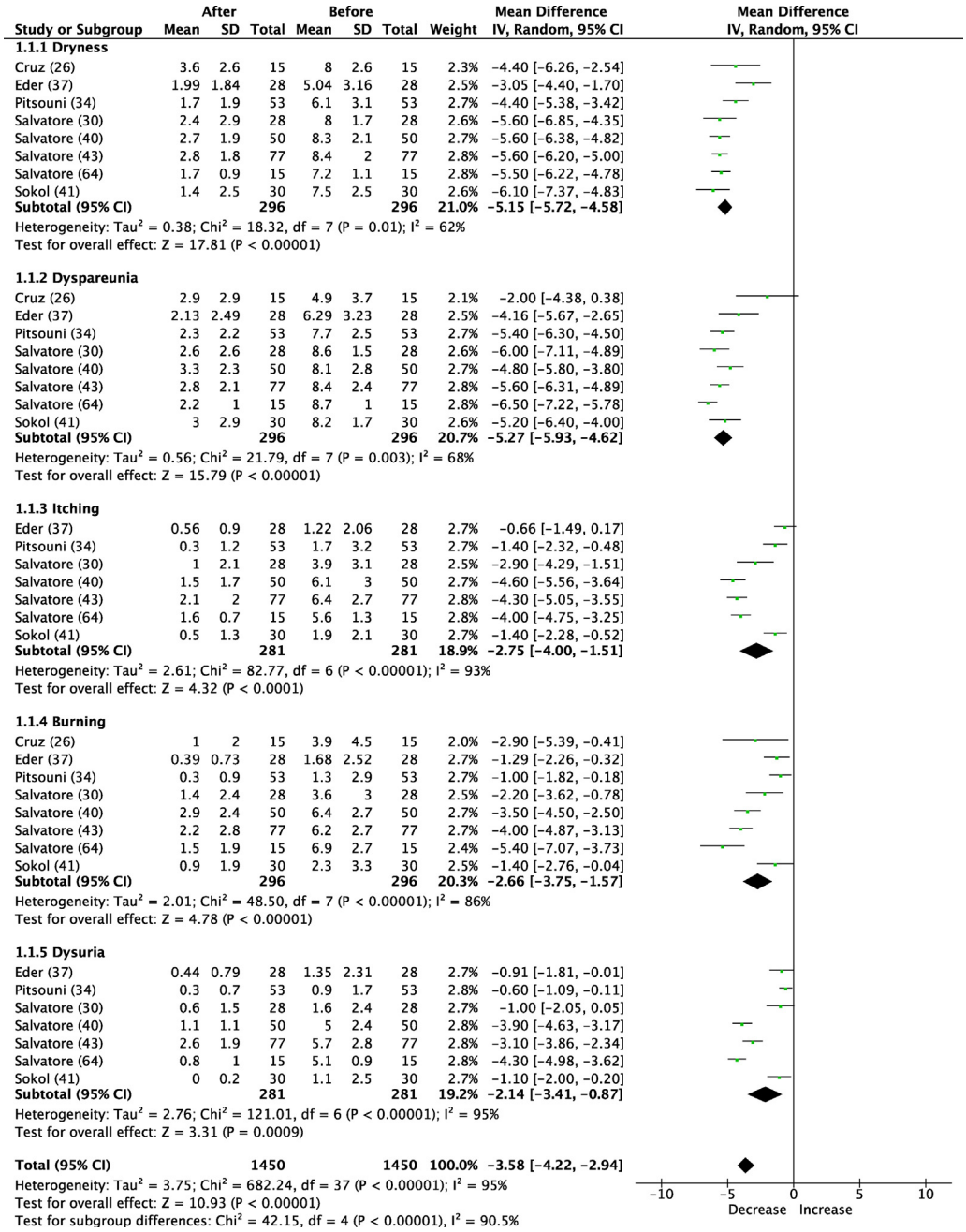

Figure 4. Forest plots showing mean differences between values before and 1-month after the last laser-therapy (1-3 months follow-up) for dryness, dyspareunia, itching, burning, dysuria (assessed by Visual Analogue Scale 0–10).

Sokol and Karram evaluated the efficacy of three sessions of fractional CO2-Laser at 12 months FU and they demonstrated that the positive effect on VVA symptoms, FSFI and VHI lasted for all the FU period.[41,42]

In 2017, Behnia-Willison et al. investigated the long-term efficacy of fractional CO2-Laser treatment at 12 to 24 months FU. 84% of the participants reported a persistence of GSM symptoms improvement and high sexual function scores at the end of FU.[46]

Number of Laser Sessions. Standard protocols used GSM symptoms management usually consists in three laser sessions.

Athanasiou et al. suggest that one or two extra sessions might be beneficial in women with moderate to severe GSM symptoms in order to obtain a satisfying GSM symptoms control and higher symptom-free rates.[45]

MonaLisa Touch instructions for users available on DEKA website report the possibility to modulate the number of cycles (3, 4 or 5) on the base of VVA severity.

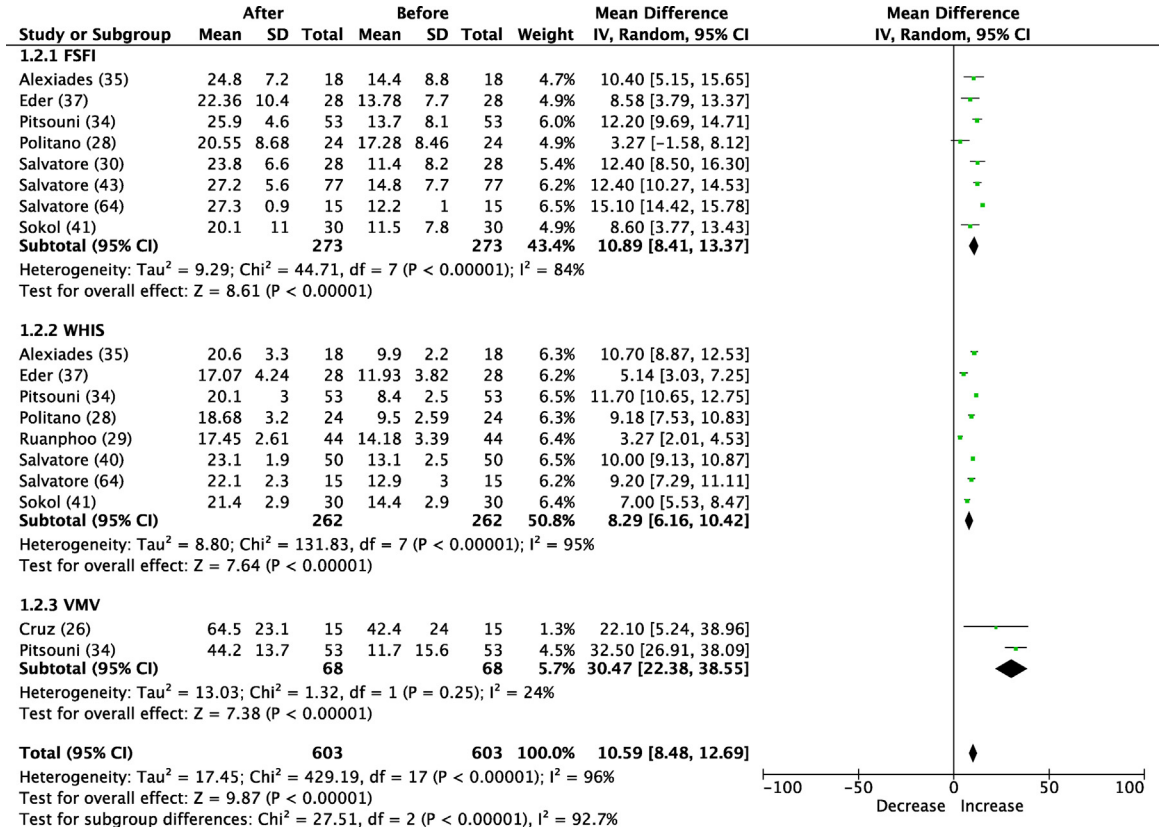

Figure 5. Forest plots of mean differences between values before and 1-month after the last laser-therapy (1-3 months follow-up) for FSFI, VHIS, VMV scores.

Energy Power Setting. Pitsouni et al. compared 30 vs 40 W power of CO2-Laser in a retrospective case-control study where MonaLisa Touch instrumentation was employed. The difference in GSM symptoms and signs improvement resulted to be non-statistically significant between the two groups.[32]

Microbiota. Athanasiou et al. firstly observed that CO2-Laser had a beneficial effect on the vaginal microenvironment with a significant increase of lactobacilli prevalence and a reduction of vaginal fluid ph. The maintenance of an acid mantle is useful to protect vaginal epithelium from erosion, atrophy and vaginal infections.[44]

Adverse Events (AEs). Fifteen studies reported some AEs after treatment[27,29–31,33,35–37,41,44,46–48], eight studies observed no AEs, and in two studies AEs data lack.

AEs related to laser procedure are divided as reported during application, immediately after, days after and months after (Table 4).

Overall, the majority of adverse events reported were mild and no major adverse events was experienced by treated patients. Moreover, no patient discontinued CO2-Laser therapy due to treatment associate AEs.

Low Dose Laser Energy Approach. Marin et al. reported a low dose protocol of CO2-Laser where laser energy applied was set to 18W and only 2 sessions at 6 weeks interval were accomplished. Their results show a significant improvement in FSFI and QoL scores at 6 months FU.[33]

DISCUSSION

The available literature we reviewed show that CO2-Laser is effective and safe intervention for the relief of GSM in symptomatic postmenopausal women.

This systematic review included all clinical studies adopting CO2-Laser therapy and investigating its effects in women postmenopausal symptoms. We excluded patients with a history of breast cancer because of their premature and usually more severe atrophic condition compared with those of menopausal patients. The severity of symptoms in those oncological patients is due to the effect of endocrine therapy, such as tamoxifen, aromatase inhibitors or gonadotropin-releasing hormone agonist, all commonly used for the treatment of estrogen receptor-positive breast tumors to improve disease-free survival.[4,49–51]

Previous studies demonstrated that the efficacy of the 3 laser sessions standard protocol was reduced in women with a history of breast cancer treated with endocrine therapy compared with

Table 4. Adverse events

Type of CO2-Laser	Timing	Complications	Number of patients and percentage	Reference
FemTouch Lumenis	DURING APPLICATION	Low Pain/discomfort	NA	36,37
		Minor bleeding related to tip introduction and rotation	1/53; (1.9%)	36
	IMMEDIATELY AFTER	Dizziness	1/53; (1.9%)	36
	DAYS AFTER	Dysuria	2/53; (3.7%)	36
		Vaginal discharge/ infection	1/53; (1.9 %)	36
Monalisa Touch, DEKA	IMMEDIATELY AFTER	Mild vulvar irritation, oedema, erythema	28/28; (100%)	30
		Mild Irritation of introitus, oedema, erythema	NA	44,45
		Minor vaginal bleeding	4/60; (6.7%)	27,41
	DAYS AFTER	Dysuria	1/60; (1.6%)	48
		Post-coital urinary tract infections	3/102; (2.9%)	46
		Urinary tract infections	1/30; (3.3 %)	27
		Vaginal discharge/ infection	4/176; (2.3%)	28,29,46
		Lower pelvic pain	3/102; (2.9%)	46
		Pain after procedure	5/74; (6.7%)	29,41
		Recurrence of genital herpes	1/102; (0,98%)	46
	MONTHS AFTER	Vaginal spotting/bleeding	2/102; (1,9%)	46
CO_2RE Intima, Syneron Candela	DURING APPLICATION	Heating sensation	2/40; (5%)	47
	IMMEDIATELY AFTER	Mild vulvar irritation, oedema, erythema	NA	35,47
		Mild Irritation of introitus, oedema, erythema	NA	35
		Minor vaginal bleeding	1/40; (2.5%)	47
Aphrodite, BH LASER	DURING APPLICATION	Heating sensation	16/25; (66%)	33
	IMMEDIATELY AFTER	Mild vaginal oedema	2/25; (8%)	33
		Leukorrhea	22/25; (90%)	33
		Itching	25/25; (100%)	33

menopausal patients.[52] Salvatore et al proposed a specific protocol with an increased number of laser session (5 rather than 3) and a progressive increase in laser energy for the treatment of symptoms in these oncological patients. Results of he study showed that this approach was both safe and effective in the VVA symptoms treatment.[53]

The included literature considered a total of 1,152 patients who underwent more than 3,800 laser applications.

We identified 5 randomized controlled studies. Two of them compared vaginal laser with sham procedure both providing evidence that CO2-Laser treatment is superior to placebo in reducing GSM symptoms. The other 3 RCTs analysed the efficacy and safety of CO2-Laser when compared to standard topical therapy. They demonstrated that CO2-Laser have a similar efficacy, no AEs and the benefit of being hormone-free. However, when administered in combination, laser therapy associated with topical medicaments can result in an even more pronounced GSM symptoms improvement.

Vaginal laser treatment does result in an improvement in symptom scores, as assessed by VAS. Symptoms improvement was the highest for dryness and dyspareunia, both of them considered to be the most bothersome GSM symptoms at baseline. However, all VVA symptoms achieved a VAS score less than 4 after laser-therapy, which reflects not only a statistically significant improvement in symptoms, but also clinically significant one.

Subjective symptoms improvement mirrors the improvement of objective tissue findings (VHIS and VMV).

In studies investigating the impact of CO2-Laser therapy on quality of life and the satisfaction with the procedure data reported are positive.

Sexual function measured by the FSFI were significantly improved in all studies. FSFI less than 26.55 defines sexual dysfunction.[20] In our systematic review and meta-analysis, even though an overall significant improvement in FSFI was reported after CO2 laser therapy, the clinically meaningful level was achieved only in 2 out of the 8 studies. During the evaluation of these results, it's important to consider the multifactorial nature and the complexity related to the assessment of sexual wellbeing in women in menopause. Indeed, sexual function is impaired by

many factors such as the reduction in both oestrogen and androgen production (which has an impact on tissue and libido), changes in body image perception along with the impact of social and psychological factors.

Moreover, FU results seem to show that the benefits of a standard course of CO2-Laser therapy is usually long lasting with effects still reported at 12 months FU.

This is the first systematic review published that analyses the effect of laser therapy on GSM symptoms focusing specifically on CO2-Laser treatment that represents one of the most studied and adopted laser technology. We report data from a high number of patients (1,152), high number of laser applications (more than 3,800) along with a detailed description of laser settings for each study and a systematically and clear interpretation of the analysed outcomes.

Furthermore, it includes five recent randomized controlled trials assessing CO2-Laser therapy in GSM.

This systematic review has also some biases and limitations (as summarized in Figures 2 and 3).

Most studies are single centre studies and nonrandomized studies (20 articles = 80% of studies). Some of them have no control group for comparison, hence possible placebo effect of the treatment cannot be ruled out. In 64% (16/25) of studies no power analysis was made.

A high level of heterogeneity of laser effect was found between the various studies. This could possibly be explained by the lack of detailed information regarding the outcome measures of participants included in the analysis (Figures 4 and 5). Some authors include patients referred to be generically postmenopausal women with symptoms of GSM or VVA without reporting the intensity of symptoms or reporting symptoms as "moderate/severe" without defying different GSM grade.

Five RCTs included are well conducted, three of them presented "some concern" bias due to the missing outcome data of patients lost during follow-up.

Number of laser sessions was not homogeneous (ranging from 2 to 5) even though 80% of the included studies adopted a standard three sessions protocol. However, it seems that in this range, especially when modulated on the base of symptoms severity, any laser protocol resulted to be effective apparently without differences in AEs rate.

The mean FU time of the included studies is 5.5 months (ranging from 1 to 24 months). Even though all studies with at least 12 months FU report persistence of effects 1 year after therapy insufficient data are available on long term effects. The need of subsequent repeated cycles of therapy could be evaluated.

Concerning CO2-Laser safety profile our review showed that this treatment is generally well tolerated and when associated to AEs they are reported as mild and transient local adverse effects graded I according to the Clavien-Dindo classification.[54]

Despite this, vaginal lasers received criticism from regulatory agencies such as the FDA.

On July 30, 2018 the FDA published a warning against the use of vaginal devices for vaginal rejuvenation, vaginal cosmetic procedures and for treatment of symptoms related to menopause, of urinary incontinence and of sexual disfunction because of safety concerns.[55]

The year after a panel of experts published a letter in response to this FDA Communication. In this letter they pointed out that only clinicians with specific skills and expertise should be allowed to administer a Class III medical device and that all devices must have the accreditation of the Regulatory Agencies. Moreover, they want to remind that any medical or surgical procedure can be associated to some adverse effects.[56]

It is difficult to perform a real evaluation of laser side effects because of the low quality of reported data.

In fact, seven out of the 25 studies analysed in the present review reported AEs without providing the exact rate. This makes it impossible to evaluate the incidence of AEs for each single laser technology.

In conclusion, CO2-Laser treatment appears to be an effective hormone-free option for GSM treatment.

Even though data concerning laser-related side effects are of low quality, no major AEs have been reported, neither during nor after laser administration. Safety of this therapy is strictly related to adhesion of manufacturers suggested settings, operator skills and experience. Therefore, in carefully selected patients, CO2-Laser procedure could represent a safe and effective procedure for GSM, despite quality of the body of evidence is "very low" or "low".

Different CO2-Laser devices and technologies are commercially available; however, every device has a specific mode of action with related tissue bioactivation and remodelling properties.

Our review includes all studies describing the use of CO2-Laser technology for VVA/GSM. MonaLisa Touch laser emerged to be the most adopted technology (reported in 18 out of the 25 studies), or at least the one with the highest number of papers in international literature.

REGISTRATION AND PROTOCOL

This systematic review has been registered in the international prospective register of systematic reviews (PROSPERO) on 21 March 2021 under the registration number: CRD42021238121.

ETHICS APPROVAL

Not applicable.

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STATEMENT OF AUTHORSHIP

All the authors conform to the International Committee of Medical Journal Editors (ICMJE) criteria for authorship, contributed to the intellectual content of the study, and gave approval for the final version of the article. S Salvatore, M Filippini, M Candiani and I Porcari: Study Conceptualization. M Filippini, I Porcari and A F Ruffolo: Methodology. M Filippini, I Porcari, A F Ruffolo and A Casiraghi: Resources and Data Curation. M Filippini, I Porcari, S Salvatore and A F Ruffolo: Writing the Original Draft. M Filippini, I Porcari and S Salvatore: Writing, Review and Editing. S Salvatore, M Candiani, M Farinelli, S Uccella and M Franchi: Visualization and Supervision. All authors contributed to the interpretation of results, as well as reviewed and approved the final version.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jsxm.2021.12.010.