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Systematic Review

Efficacy of Fractional CO_2 Laser Versus Intravaginal Estrogen for Controlling the Genitourinary Syndrome of Menopause (GSM) Especially Sexual Dysfunctions—A Systematic Review and Meta-Analysis

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Abstract

Background: Fractional CO_2 laser (FCL) has been gradually used in the management of genitourinary syndrome of menopause (GSM) in recent years, but the results remain uncertain. We aimed to estimate the efficacy and safety of FCL as a novel treatment for controlling the GSM, especially sexual dysfunction, compared with intravaginal estrogen. **Methods**: The following digital databases were searched, including PubMed, Web of Science, Cochrane Library, and Embase. All the studies were limited to randomized controlled trials (RCTs). Included literatures must be in English, without limitation about region and race. The pooled dates were analyzed by Review Manger version 5.4 (Cochrane Collaboration's Information Management System, London, UK). **Results**: 3 RCTs were included, which involved 160 patients, 79 of whom received FCL treatment, 81 received intravaginal estrogen treatments. This meta-analysis results showed no statistical significance existed in improving the patient's vaginal health index (VHI) (mean difference (MD) = 0.59; 95% confidence interval (95% CI): –1.07~2.25; p = 0.49) after FCL treatment. In terms of the female sexual function index (FSFI) total scores, we observed no improvement without statistical significance (MD = –0.13; 95% CI: –3.32~3.06; p = 0.94). Furthermore, all the FSFI domains showed no statistical significance. No serious complications were reported in all included trials. **Conclusions**: FCL therapy was an interesting and novel treatment for menopausal female sexual dysfunction. However, no statistical evidence existed, which recommended that FCL was superior to intravaginal estrogen. Our results will be confirmed by high-quality and multicentric RCTs in the future.

Keywords: fractional CO_2 laser (FCL); female sexual function index (FSFI); vaginal health index (VHI)

1. Introduction

Menopause can exert severe effects on a woman's quality of life, especially with regard to the genitourinary system. Genitourinary syndrome of menopause (GSM) is a chronic, aggressive, and progressive disease status that affects at least 27% to 84% of postmenopausal women globally [1]. Vulvovaginal dryness, burning, and irritation were symptoms related to GSM, which caused enormous harm to females psychologically and physically [2,3], especially with regard to sexual dysfunction [4]. Sexual dysfunction is defined as a reduction in lubrication, arousal, erotism, sensation, pain during intercourse, and difficulty reaching orgasm. In a previous study, Simon *et al*. [5] reported that 66% to 74% of menopausal women were dissatisfied with their sexual life, 62% to 70% reported reduced sexual spontaneity, and 53% to 69% reported a loss of intimacy. A study have shown that such females feel ashamed and reluctant to attend hospital for professional consultations [6]. Indeed, according to Simon *et al*. [5], 40% of such women waited one year or more after symptom onset. Regrettably, 37% of these women said they would not share their problems with others [5].

Moisturizers and lubricants are both Food and Drug Administration (FDA)-approved medical devices, which act transiently and provisionally in sexual activity. These products cause no fundamental changes with regards to the pathological and physiological conditions of the vagina [7]. Multiple studies have reported that postmenopausal estrogen replacement therapy (ERT) is effective for the treatment of sexual dysfunction [4,8,9]. However, ERT is known to be associated with many side effects [10]. Individuals diagnosed with hormone-dependent malignancies (especially breast and endometrial cancer), abnormal uterine bleeding, severe hypertension, recent myocardial infarction within 6 months, and diabetes mellitus should exercise caution when undergoing ERT. According to a prior systematic review, intravaginal estradiol, estrogen, or conjugated estrogens have been found to have a substantial impact on

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improving the vaginal microenvironment [11]. Levels of intravaginal estrogen absorption by vaginal epithelial cells have yet to be fully elucidated, and related research studies are scarce. Thus, appropriate consideration is required when using intravaginal estrogen products [9].

As for the laser, the FDA clearance in 2014 allowed for widely used as follows: for incision, excision, ablation, vaporization and coagulation of body soft tissues in medical specialties including aesthetic (dermatology and plastic surgery), podiatry, otolaryngology (ENT), gynecology, neurosurgery, orthopedics, general and thoracic surgery (including open and endoscopic), dental and oral surgery and genitourinary surgery. CO_2 lasers have been widely used in recent years for GSM/vulvovaginal atrophy (VVA) [12]. Fractional CO_2 laser (FCL) used in gynecology for GSM are using ablative regime, drilling micro-holes in the vaginal mucosa producing micro-injuries and achieving the tissue regeneration through the mechanism of wound healing [13]. The effectiveness and safety of FCL in treating sexual dysfunction in postmenopausal women have been widely discussed in the literature [14]. Salvatore *et al.* [15] conducted the first pilot study in 2014, followed by a randomized sham-controlled trial [16] in 2021, both of which demonstrated the efficacy of FCL in alleviating symptoms associated with GSM in postmenopausal women, particularly in relation to sexual dysfunction. Filippini *et al.* [17] conducted a meta-analysis and reported that FCL can greatly improve symptoms related to GSM and the female sexual function index (FSFI) scores were significantly improved. However, all of the included trials were carried out in a single center and were non-randomized [18]. The aim of this systematic review and meta-analysis was to assess the effectiveness and safety of FCL as an interesting and novel approach to managing GSM, particularly in comparison to intravaginal estrogen, with a specific focus on sexual dysfunction. The primary outcomes was changes in FSFI scores when compared to baseline, and the secondary outcomes was changes in vaginal health index (VHI) scores.

2. Method

2.1 Search Strategy

We searched several databases for relevant literature, including PubMed, the Cochrane Library, Web of Science, and Embase. All the included studies were limited to randomized controlled trials (RCTs). The references cited in the included literature were checked to ensure that all eligible articles were included. The included articles needed to be written in English without geographical and ethnic restrictions. We screened all published literature up to the 17th of January 2022. The search strategies were performed using a combination of medical subject headings (MeSH) terms and free words, including "postmenopause", "period, postmenopausal", "post menopause", "post-menopauses", "vaginal atrophy", "atrophic vaginitis", "sexual difficulties", "sexual dysfunction/dysfunctions", "sexual disorders", "genitourinary syndrome of menopause", "GSM", "laser Therapies", "CO_2 laser", "lasers" and "Fractional CO_2 laser". Electronic searches and eligibility were assessed by two independent authors (CL and FPY). Disagreements were solved by discussion with a third author (YYC). This study was previously registered with PROSPERO (CRD: 42021291280) and followed PRISMA guidelines.

2.2 Inclusion and Exclusion Criteria

Inclusion criteria: all included studies needed to meet the following criteria: (I) participants who lacked menstruation for at least 12 months; (II) study type needed to be a RCT; (III) intervention needed to be FCL; (IV) the control group were treated with intravaginal estrogen; and (V) data needed to include mean and standard deviation.

Exclusion criteria: (I) contraindications for estrogen treatments, including hormone-dependent cancer (especially breast and endometrial cancer), abnormal uterine bleeding, severe hypertension, myocardial infarction within 6 months, diabetes mellitus, and thrombophlebitis; (II) vulval pathology, condyloma, vaginal intraepithelial neoplasia (VIN), carcinoma of the vulva, leukoplakia vulvae, lichen planus, and lichen sclerosis; (III) acute and chronic urinary tract infections; (IV) various types of vaginitis such as bacteria, fungal and trichomonad; (V) history of malignant neoplasm, pelvic radiotherapy, and bilateral oophorectomy; (VI) chronic conditions that prevented patient compliance; (VII) pelvic organ prolapse $>$ stage II (according to the Pelvic Organ Prolapse Quantitation, PQP-Q system); (VIII) human immunodeficiency virus (HIV)-positive; (IX) duplicated literature and literature that was not available in full text with a full dataset; and (X) inappropriate statistical methods that could not be corrected.

2.3 Quality Assessment

Two independent researchers (CL and FPY) assessed the quality of the included RCTs using the Cochrane risk of bias tool, which encompassed 7 domains: sequence generation and allocation sequence concealment (selection bias), blinding of participants and personnel, blinding of outcome assessments, selective reporting (reporting bias), incomplete outcome data (attrition bias), and other sources of bias (e.g., funding assistance and baseline comparability). Each domain was evaluated as "low risk", "high risk", or "unclear risk". Subsequently, we utilized Review Manger 5.4 (Cochrane Collaboration's Information Management System, London, UK) to analyze the risks and applicability of the included studies.

2.4 Data Extraction

All data were screened and extracted by two authors (CL and FPY) independently from the included studies, in order to ensure the integrity and accuracy for the extracted data, if any disagreements existed among the two

Table 1. Characteristics of qualified studies.

First author	Year	Country/Age (Years)	Simple size Trial/Control	Experimental group	Control group	Follow-up
Paraiso *et al.*	2019	USA. 61.0 ± 8.0, 60.0 ± 7.0	30/32	Fractional microabltive CO_2 laser, once a month for 3 months; Dot power: 30 W; Dwell time: 1.000 ms; Dot spacing: 1.000 mm	Intravaginal premarin cream 0.5 g daily for 14 days followed by 0.5 g twice weekly for 24 weeks	24 weeks
Politano *et al.*	2019	Brazil. 57.8 ± 5.0, 57.2 ± 5.3	24/24	Fractional microabltive CO_2 laser, once a month for 3 months; Dot power: 40 W; Dwelling time: 1.000 ms; Dot spacing: 1.000 mm	Intravaginal 1 g cream and 10 mg promestriene 3 times a week for 14 weeks	14 weeks
Eftekhar *et al.*	2020	Iran. 54.6 ± 8.2, 57.0 ± 6.4	25/25	Fractional microabltive CO_2 laser, once a month for 3 months; Dot power: 40 W; Dwelling time: 1.000 ms; Dot spacing: 1.000 mm	Intravaginal premarin vaginal cream (0.625 mg) with a third of the applicator 3 nights a week for 3 months	12 weeks

researchers, a final decision was made with a third author (YYC). The extracted information was shown in Table 1 including authors, date of publication, country, sample size, mean age, instrument model, intervention procedure for control/experimental groups, and durations of follow-up. If necessary, the authors within the eligible trials were contacted by phone, fax, or e-mail to obtain missing information.

2.5 Statistical Analysis

We performed meta-analysis by using RevMan 5.4. The mean and standard deviation (SD) were used to calculate the mean difference (MD) and 95% confidence interval (95% CI) of the continuous data. The risk ratio (RR) with 95% CI was applied to analyze the dichotomous data among the two groups. $p < 0.05$ represented a statistical significance in all indicators. I^2 statistic test was used to detect the heterogeneity among the included studies. When the results showed more than 50%, we use the random-effects model (inverse-variance method) in our meta-analysis. Conversely, we used the fixed-effects model (inverse-variance method) to analyze. Unfortunately, only 3 RCTs were included in our review, and sensitivity analysis and publication bias were not conducted.

3. Results

3.1 Characteristics of the Included Studies

After applying the strict inclusion/exclusion criteria, a total of 42 articles were identified from the databases. In the first step, we removed 12 repeated studies. Then, we screened the titles and abstracts, which led the removal of 12 articles, and 10 unavailable full texts articles, resulting in 8 studies screened. 1 article was eliminated as the outcomes were expressed by the median, 2 studies were removed as they included non-RCTs, and 2 articles were eliminated for the including breast cancer patients. Finally, this meta-analysis included 3 high-quality RCTs that involved 160 patients, 79 of whom received FCL treatment. Fig. 1 described the selection process by a flowchart. Basic information about the included article is shown in Table 1.

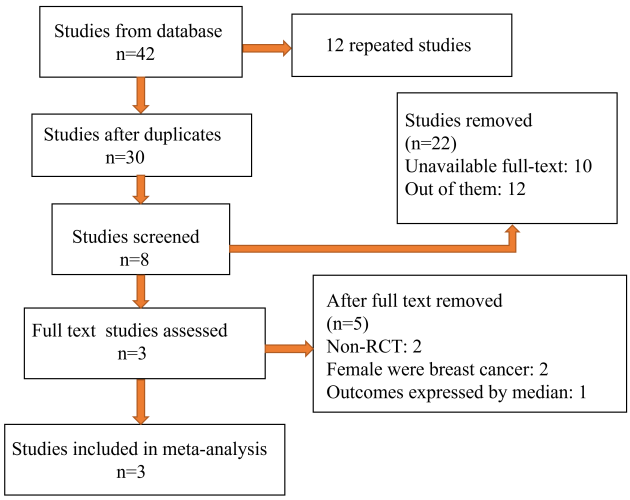

Fig. 1. Flowchart of the selection process. RCT, randomized controlled trail.

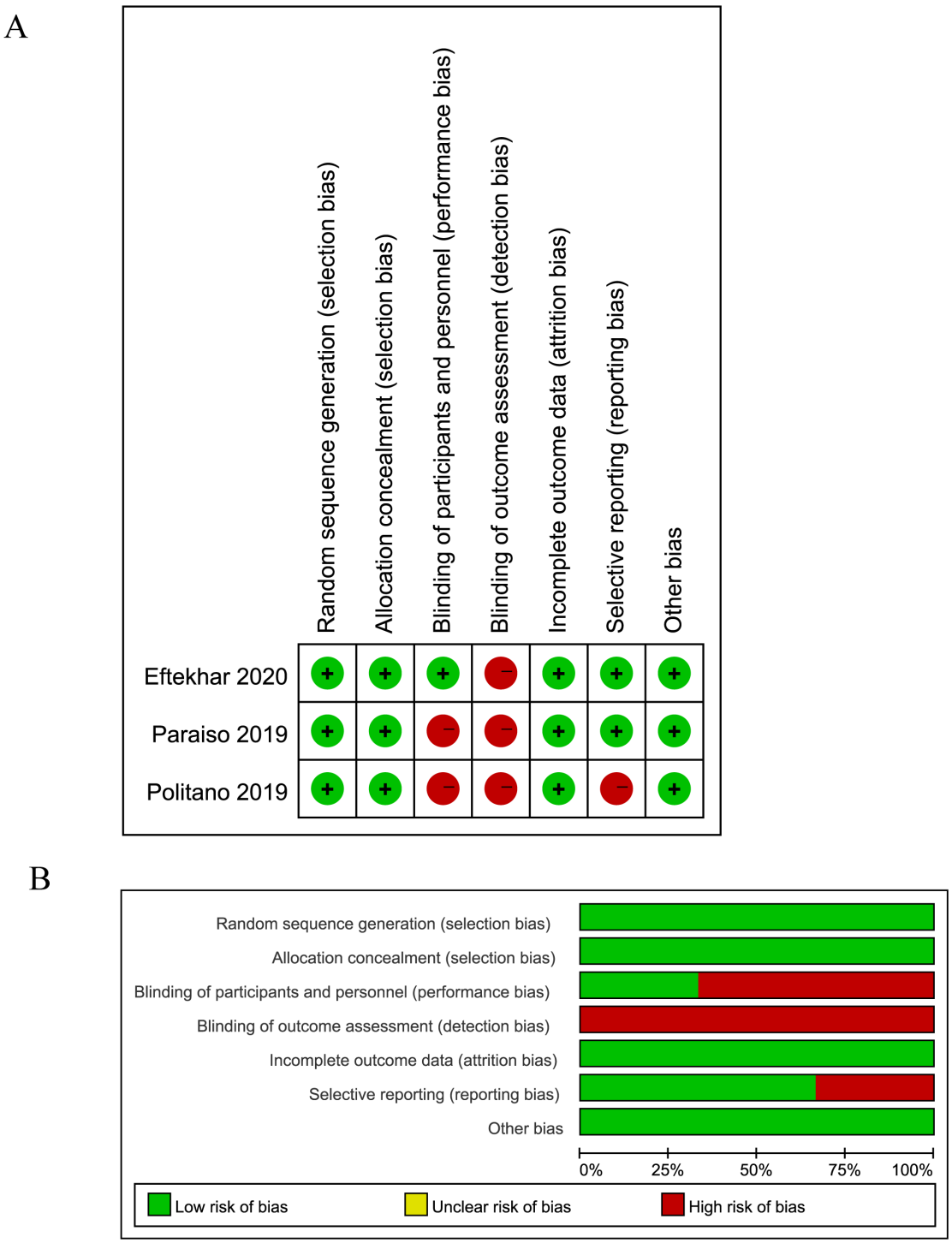

Fig. 2. Risks and quality of included studies. (A) Risk of bias summary: review authors' judgements about each risk of bias item for each included study. (B) Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

3.2 Risks of Bias

Fig. 2 showed the detailed quality of the included three RCTs by using the Cochrane risk of bias assessment tool. Among the included RCTs, two studies [19,20] showed high risk in performance bias. As for the others, all were in high-risk account for insufficient samples and follow-up.

3.3 Narrative Review

A RCT conducted by Politano *et al.* [19] enrolled 72 postmenopausal women, 24 in the FCL group, 24 in control group 1 with intravaginal promestriene (estrogen cream), and 24 in control group 2 with intravaginal lubrication. After 14 weeks of follow-up, results showed that

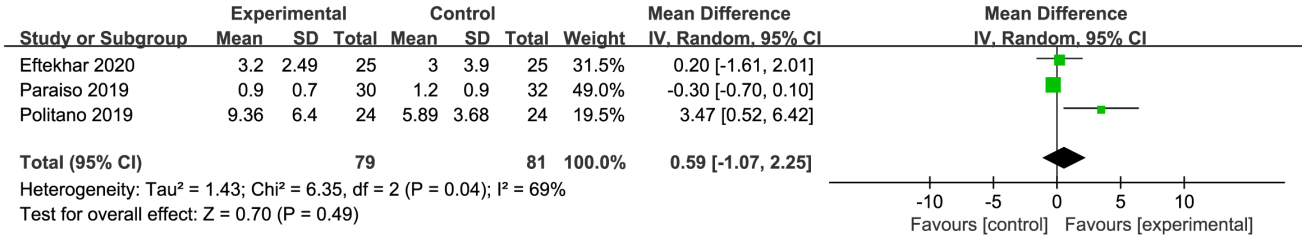

Fig. 3. Forest plot showed the effect of fractional CO_2 laser (FCL) on the vaginal health index (VHI) change as compared. SD, standard deviation; 95% CI, 95% confidence interval.

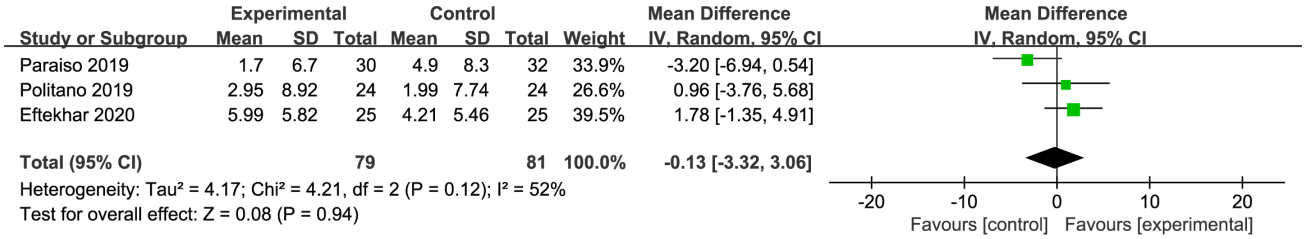

Fig. 4. Forest plot showed the effect of FCL on the female sexual function index (FSFI) total changes as compared. SD, standard deviation; 95% CI, 95% confidence interval.

VHI scores had improved significantly in the experimental group when compared with both control groups. No statistical differences existed for total FSFI scores across three groups, only desire and lubrication scores improved when compared with the two control groups. With regard to vaginal maturation, basal cells were significantly reduced, and superficial cells were significantly increased, in the FCL group compared with the two control groups. These authors also observed an improvement in vaginal elasticity, volume, moisture, and pH in the FCL and intravaginal promestriene groups. Finally, no side effects were reported for any of the three groups. FCL for GSM was superior to intravaginal estrogen or lubricants, especially with regard to vaginal health; however, there was no improvement in terms of sexual dysfunction. Paraiso *et al.* [20] conducted a multicenter randomized trial in which 30 women were randomly assigned to FCL group, and 32 to intravaginal estrogen cream group. After 6 months of follow-up, the FSFI total scores showed no significant improvement, although the vaginal maturation index scores remained higher in the intravaginal estrogen group when compared with the FCL group. Based on the findings of these authors, it can be inferred that FCL and intravaginal estrogen exhibited comparable enhancements in GSM symptoms associated with urinary and sexual functions, thereby indicating that FCL cannot be deemed superior to estrogen. Eftekhar *et al.* [21] involved 50 postmenopausal women. After a 3-month follow-up period, the authors noted that the impact of FCL treatment surpassed that of the intravaginal estrogen group in terms of sexual desire, orgasm, satisfaction, and alleviated pain during sexual activity. Nevertheless, VHI scores exhibited improvement in both groups without any significant statistical disparities. The authors reached the conclusion that FCL could potentially surpass intravaginal estrogen in enhancing sexual function among postmenopausal women.

3.4 Patients' Perception

Politano *et al.* [19] and Eftekhar *et al.* [21] failed to describe patients' subjective perceptions, and only used some experiential scales such as VHI score, FSFI score and the frost index (which objectively evaluated the differential count of each cell group to determine the degree of atrophy). Paraiso *et al.* [20] reported from patients' global impressions, the results showed that 71.9% of FCL participants rated their improvement as "better or much better" and 75.8% reported being either "satisfied or very satisfied" compared to 82.8% and 75.9% in the control group. Finally, no statistical significance existed on the number of people who reported sexually active after treatments in the two groups.

3.5 Meta-Analysis

3.5.1 Meta-Analysis about VHI

Three RCTs enrolling 160 patients (79 in the FCL group and 81 in the intravaginal estrogen group) reported the changes in VHI scores after FCL treatment. In Fig. 3, the pooled results showed VHI scores improved without statistical significance compared to controls (MD = 0.59; 95% CI: –1.07~2.25; $p = 0.49$).

3.5.2 Meta-Analysis about the FSFI Scores

Three RCTs reported the changes of FSFI total scores after FCL treatment. In Fig. 4, the pooled results showed that the FSFI scores were not improved in comparison with

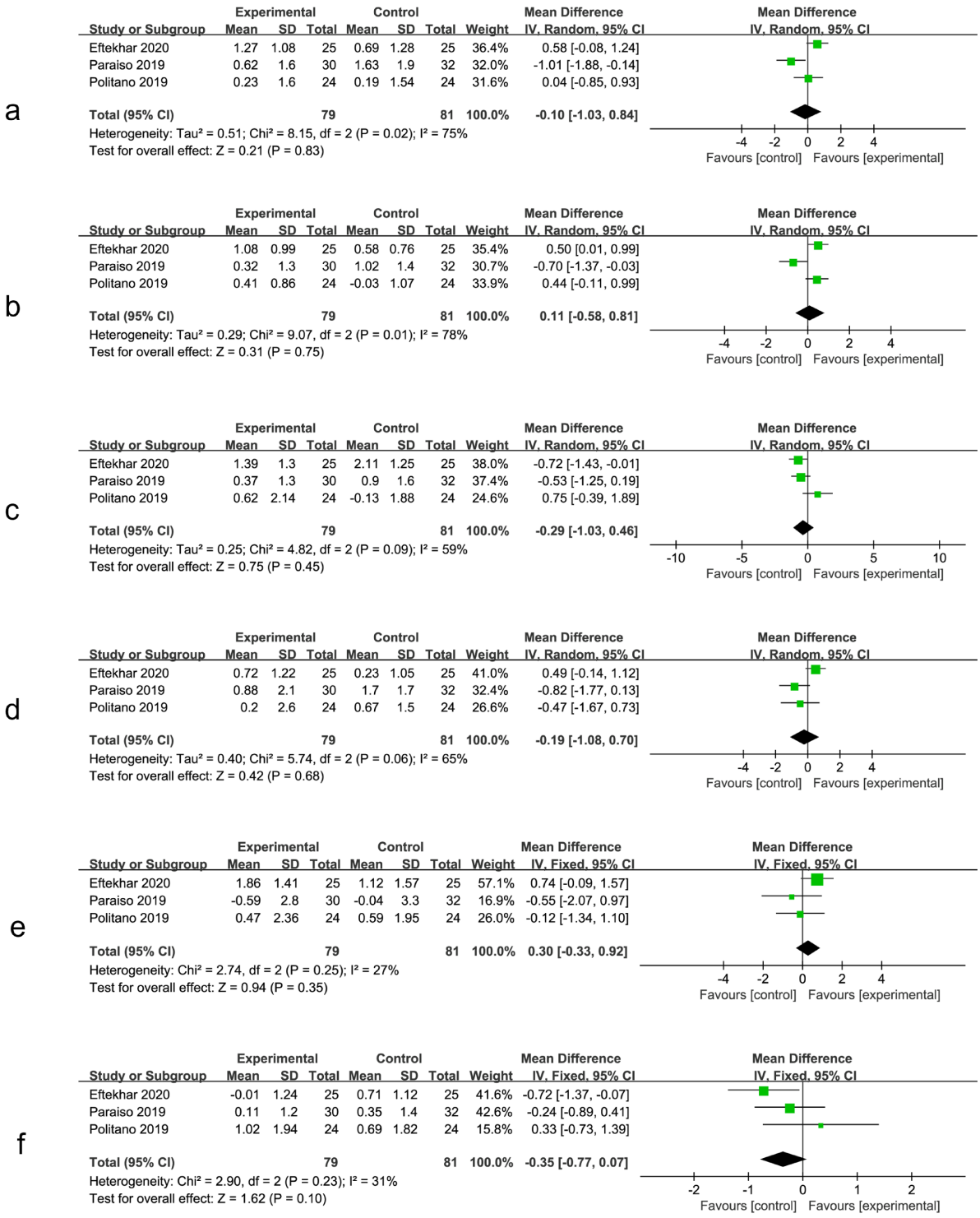

Fig. 5. Forest plot showed the effect of FCL on 6 domains of FSFI changes as compared. (a) Arousal. (b) Desire. (c) Orgasm. (d) Satisfaction. (e) Pain. (f) Lubrication. SD, standard deviation; 95% CI, 95% confidence interval; FCL, fractional CO_2 laser; FSFI, female sexual function index.

the control group (MD = –0.13; 95% CI: –3.32~3.06; p = 0.94). FSFI is formed from 6 domains including desire, arousal, lubrication, orgasm, satisfaction, and pain. As shown in Fig. 5, none of them were improved statistically compared with the control group.

3.6 Adverse Side Effects

There were no serious adverse effects noted, but only mild to moderate and transient/short lasting and resolved without any intervention. Paraiso *et al.* [20] reported that 10 women (5 in FCL and 5 in control group) suffered

from mild or moderate to adverse events, including vaginal bleeding, vaginal pain, vaginal discharge, urinary tract infection, breast tenderness, migraine, and abdominal cramping.

4. Disscussion

Menopause can severely affect a woman's quality of life especially female sexual functions. Sexual dysfunction means a decline in sexual desire and stimulation, pain during coitus, and the presence or difficulties to reach orgasm. Our meta-analysis revealed no statistical evidence supporting the superiority of FCL over intravaginal estrogen in terms of changes in FSFI and VHI scores. Even in all domains of FSFI, no statistical significance existed. No serious adverse reactions were reported in all participants. Clinicians should be cautious when choosing FCL therapy.

The genitourinary tract is extremely sensitive to estrogen. Indeed, this hormone can increase blood flow in the mucosa of the genitourinary tract, maintain the balance of the vaginal flora, resist pathogens and increase vaginal secretion. Hypoestrogenic conditions can arise from dysfunctional ovaries, thus leading to changes in the vaginal microenvironment, including vaginal dysbacteriosis, increased vaginal pH, atrophy of the vaginal orifice and clitoris, and reduced vaginal length and volume. These conditions can also lead to the vaginal wall becoming vulnerable to injury and induce vaginal dryness [5,22,23].

The local use of estrogen in the vagina effectively improves symptoms related to GSM. Other treatment options include the use of vaginal lubricants. Local estrogen administration can ameliorate the microenvironment of the urogenital tract. Local estrogen therapy may also improve sexual genital arousal and orgasmic function. However, the safety of estrogen is still not thoroughly investigated at present. Currently, one of the major concerns in clinical practice is the use of vaginal estrogen for women with a history of hormone-dependent cancer. Despite the localized administration of estrogen, the extent of its systemic absorption has not been thoroughly studied. Therefore, cautious consideration is still required when prescribing vaginal estrogen in patients with high-risk factors [24]. A Cochrane's systematic review [25] comparing vaginal estrogen with placebo and found that vaginal estrogen significantly improved symptoms associated with vaginal atrophy compared to placebo. However, low-quality evidence suggested that localized estrogen use might be associated with increased endometrial thickness. Various formulations of vaginal estrogen are available, including tablets, rings, capsules, pessaries, creams, gels, and ovules, but this study did not observe significant differences in efficacy among these formulations. Patient compliance with the use of vaginal estrogen is also a crucial factor to consider in clinical practice.

A meta-analysis [26] conducted in 2022, which only incorporated three RCTs, showed that FCL was better than sham laser when treating and managing GSM. Furthermore, vaginal local estrogen can significantly reduce the symptoms of GSM and improve sexual function. However, the credibility of the evidence is limited because the included studies are still too few. As such and importantly enough, we are the first to compare the efficacy and safety of FCL with intravaginal estrogen for the treatment of sexual dysfunction in postmenopausal women. No unified duration or intensity of laser treatment is here specified. However, this meta-analysis has certain limitations. The largest shortcoming is the inadequate number of included studies and overall sample size. Narrow inclusion and very broad exclusion criteria limited the inclusion of studies. Thus, we were unable to perform sensitivity analysis and determine publication bias. We were unable to analyze the four subindicators that constitute the VHI. Because of the different follow-up periods, we chose the last evaluation time as the end point, which could caused bias. Furthermore, heterogeneity between the studies was obvious. The included studies were all RCTs, however, most of the studies were monocentric with short-term follow-ups. Finally, the status of the sexual partner can also influence sexual satisfaction. Furthermore, Athanasiou *et al*. [27] reported that the number of sessions can also influence the efficacy of the FCL. Future clinical trials should focus more on the pathophysiology of the vaginal mucosa after FCL treatment. Further high-quality multicenter RCTs are now required to confirm our findings.

5. Conclusions

FCL therapy is an interesting and novel concept for treating and managing GSM, especially with regard to sexual dysfunction. However, there is no statistical evidence to suggest that FCL treatment is superior to intravaginal estrogen in terms of FSFI scores in females and VHI. Due to the lack of relevant RCTs and sufficient patients at present, our conclusions need to be carefully confirmed by high-quality and multi-center RCTs in the future.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Author Contributions

CL and XYN designed the study. CL and FPY conducted the selection of relevant studies and data extraction separately. CL and FPY evaluated the quality of each study independently. CL and YYC performed the statistical analysis. CL and FPY drafted the manuscript. CL and LM contributed to the interpretation of the results and critically checked the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.ceog5102040.

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