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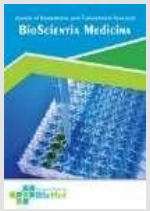

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Laser Therapy for Genitourinary Syndrome of Menopause (GSM): A Stratified Meta-Analysis of Histological, Clinical, and Safety Outcomes

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A B S T R A C T

Background: Genitourinary syndrome of menopause (GSM) is a prevalent and chronic condition that diminishes quality of life. Vaginal laser therapy is a non-hormonal treatment, but its efficacy and safety require rigorous synthesis. This study was conducted to systematically evaluate the efficacy of laser therapy for GSM by prioritizing high-quality evidence and separately analyzing findings from different study designs, while also providing the first meta-analytic overview of safety. **Methods:** A systematic search of PubMed, Scopus, Embase, and the Cochrane Library was performed for studies published between January 2015 and December 2024. The primary analysis of efficacy was restricted to randomized controlled trials (RCTs). A separate, secondary analysis was performed on prospective cohort studies. Primary outcomes were changes in vaginal epithelial thickness and the Visual Analog Scale (VAS) for dryness. Secondary outcomes included VAS for dyspareunia, vaginal health index (VHI), female sexual function index (FSFI), and systematically extracted adverse events. Data were pooled using a random-effects model. **Results:** Seven studies (2 RCTs, 5 cohort studies) involving 595 patients were included. In the primary analysis of RCTs, laser therapy resulted in a significant increase in epithelial thickness (Mean Difference [MD] 50.15 μm) and a significant reduction in VAS for dryness (MD -4.54) with low-to-moderate heterogeneity. The secondary analysis of cohort studies also showed significant improvements, but with extremely high and significant heterogeneity (I^2 > 80%). Across all studies, reported adverse events were consistently mild and transient, including temporary erythema, edema, and minor discharge. No serious adverse events were reported. **Conclusion:** Based on high-quality evidence from RCTs, vaginal laser therapy produces statistically significant improvements in the histological and clinical parameters of GSM. Evidence from cohort studies supports this finding but demonstrates considerable variability in real-world settings. While short-term safety appears favorable, the inconsistent treatment effect and lack of long-term data necessitate a cautious approach to patient selection and counseling.

1. Introduction

The physiological transition of menopause represents a definitive turning point in a woman's life, characterized by the cessation of ovarian estrogen production.[1] This hormonal shift precipitates a cascade of changes throughout the body, with the urogenital system being particularly susceptible to the effects of estrogen deprivation. The term genitourinary syndrome of menopause (GSM) was formally adopted to provide a more comprehensive and medically precise description of the array of symptoms and signs affecting the lower reproductive and urinary tracts.[2] This term replaces the older, more limited term "vulvovaginal atrophy," acknowledging that the

condition's impact extends beyond the vagina to involve the labia, clitoris, vestibule, urethra, and bladder. GSM is a chronic, progressive, and often debilitating condition that can profoundly diminish a woman's health, sexual function, and overall quality of life.[3] The pathophysiology of GSM is fundamentally rooted in the loss of estrogen's trophic effects on target tissues. Estrogen receptors, particularly estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ), are densely expressed throughout the female urogenital tract.[4] In the premenopausal state, estrogen binding to these receptors orchestrates a symphony of cellular activities that maintain tissue health and function. It promotes the proliferation and maturation of the vaginal epithelium, a stratified, non-keratinized squamous epithelium. This results in a thick, robust mucosal layer, typically consisting of 20 to 30 cell layers. The most superficial of these layers is rich in glycogen. This glycogen is metabolized by commensal *Lactobacillus* species into lactic acid, which is crucial for maintaining an acidic vaginal pH (typically between 3.8 and 4.5).[5] This acidic environment is a key defense mechanism, inhibiting the growth of pathogenic bacteria and preserving a healthy vaginal microbiome.

With the onset of menopause and the decline in estrogen, this carefully balanced ecosystem is disrupted. The vaginal epithelium undergoes marked atrophy, thinning to as few as 5 to 10 cell layers. This histological change is characterized by a loss of the superficial and intermediate cell layers, leaving a predominance of less-differentiated basal and parabasal cells. The loss of glycogen-rich superficial cells leads to a decrease in substrate for *Lactobacillus*, resulting in a decline in their population and a subsequent rise in vaginal pH to a neutral or alkaline state.[6] This altered environment makes the vagina more vulnerable to colonization by pathogenic organisms, increasing the risk of recurrent vaginal and urinary tract infections. Beyond the epithelium, the underlying lamina propria, a layer of connective tissue, also suffers from the effects of hypoestrogenism. Estrogen normally stimulates fibroblasts to produce and maintain a healthy extracellular matrix rich in collagen (primarily Type I and Type III) and elastin fibers. This matrix provides the vagina with its characteristic tensile strength and elasticity. After menopause, there is a significant reduction in the quantity and quality of these structural proteins. Collagen fibers become fragmented and disorganized, and elastin fibers degrade, leading to a loss of tissue pliability and resilience. Furthermore, estrogen promotes robust vascularization of the vaginal submucosa. The decline in estrogen leads to reduced blood flow, which impairs the delivery of oxygen and nutrients to the tissues and diminishes the vaginal transudate that contributes to lubrication.

These profound histological and physiological changes manifest as the well-recognized clinical symptoms of GSM. Vaginal dryness (xerosis) is one of the most common and bothersome symptoms, resulting from the thinned epithelium and reduced transudation. This dryness, combined with the loss of elasticity, often leads to irritation, burning, and itching. The fragile, atrophic tissue is also more susceptible to trauma, bleeding, and pain, particularly during sexual activity. Dyspareunia, or painful intercourse, is a frequent and highly distressing consequence of GSM, which can lead to sexual avoidance, relationship strain, and a significant decline in sexual health and satisfaction.[7] The shared embryological origin of the lower urinary tract and the genital tract means that urinary symptoms are also a core component of the syndrome. These can include urinary urgency, frequency, dysuria, and an increased incidence of recurrent urinary tract infections, collectively termed "atrophic cystourethritis." Despite its high prevalence, affecting a majority of postmenopausal women, GSM remains a largely under-recognized and undertreated condition. Many women suffer in silence, either due to embarrassment in discussing intimate symptoms or a pervasive belief that these issues are an inevitable and untreatable consequence of aging. For those who do seek treatment, the long-standing gold standard has been

hormonal therapy, most commonly in the form of low-dose, locally administered estrogen creams, tablets, or rings. Vaginal estrogen therapy is highly effective at reversing the atrophic changes and alleviating symptoms.[8] It directly addresses the root cause of the condition by replenishing local estrogen levels.

However, hormonal therapy is not a universal solution. A significant number of women have contraindications to its use, most notably those with a personal history of hormone-sensitive cancers, such as estrogen receptor-positive breast cancer. Although systemic absorption from low-dose vaginal preparations is minimal, safety concerns persist for this high-risk population. Beyond medical contraindications, the decision-making process for patients is complex. Many women express a personal reluctance to use hormonal products, a phenomenon often termed "hormone phobia," driven by concerns about potential systemic risks. Furthermore, there is a growing patient-driven demand for treatments perceived as more "natural" or "regenerative," moving away from long-term daily medication and towards procedural interventions that promise to restore the body's own function. This confluence of factors creates a substantial therapeutic void, leaving a large cohort of symptomatic women without a suitable or desirable treatment option. To address this unmet clinical need, the field of urogynecology has witnessed the emergence of energy-based devices (EBDs), a technology successfully adapted from aesthetic dermatology. Among these, fractional micro-ablative carbon dioxide (CO_2) and non-ablative Erbium:YAG (Er:YAG) lasers have gained considerable attention. These devices offer a non-hormonal approach to treating GSM. The underlying therapeutic principle is the precise and controlled application of thermal energy to the vaginal mucosa. This energy delivery is designed to induce a micro-thermal injury, which in turn initiates the body's natural wound-healing cascade. This process is theorized to stimulate fibroblasts within the lamina propria, triggering a phase of robust neocollagenesis and neoelastogenesis.[9] Simultaneously, the thermal stimulus is believed to promote neoangiogenesis. The thermal stress also induces the expression of heat shock proteins (HSPs), which act as molecular chaperones to facilitate tissue repair, and upregulates key signaling molecules like Transforming Growth Factor-beta (TGF-β), a potent stimulator of fibroblast activity and extracellular matrix deposition. The collective result of this tissue remodeling is a restoration of the vaginal mucosa's thickness, elasticity, vascularity, and hydration, aiming to reverse the histopathological hallmarks of GSM and thereby alleviate its clinical symptoms. The proliferation of these devices has not been without controversy. Regulatory bodies, including the United States Food and Drug Administration (FDA), have issued communications cautioning against the marketing of EBDs for "vaginal rejuvenation" and related uses, citing a lack of robust, long-term data on both efficacy and safety. This regulatory scrutiny underscores a critical need for high-quality evidence synthesis to guide clinicians and inform patients. While numerous prospective studies have reported promising results, their quality and design have been variable. Existing systematic reviews have often combined data from disparate study designs, potentially obscuring the true treatment effect. A more rigorous, stratified approach is necessary.[10]

The novelty of this study lies in its stratified meta-analytic approach, which prioritizes high-quality evidence by analyzing data from Randomized Controlled Trials (RCTs) separately from prospective cohort studies. This methodology provides a more reliable estimate of true treatment efficacy while also contextualizing findings from real-world, non-controlled settings. Furthermore, this is the first meta-analysis to our knowledge to systematically extract and present safety and adverse event data alongside efficacy outcomes, offering a more balanced risk-benefit perspective. The aim of this meta-analysis was to systematically review the available evidence and to quantify the efficacy and safety of vaginal laser therapy (CO_2 and Er:YAG) for the treatment of Genitourinary Syndrome of Menopause. We sought to

determine the treatment effect on both histological and clinical parameters by performing a primary analysis on RCTs and a secondary analysis on cohort studies, and to create a comprehensive profile of reported adverse events.

2. Methods

This systematic review and meta-analysis were designed, conducted, and reported in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Studies were selected for inclusion based on the PICOS (Population, Intervention, Comparison, Outcomes, Study design) framework: Population (P): The study population consisted of postmenopausal women, defined by the standard criterion of at least 12 months of continuous amenorrhea. All participants were required to have a clinical diagnosis of Genitourinary Syndrome of Menopause (GSM), or its antecedent terms such as vulvovaginal atrophy or atrophic vaginitis. To ensure a clinically relevant population, studies were included only if participants reported at least one moderate-to-severe symptom, such as vaginal dryness, dyspareunia, or irritation; Intervention (I): The intervention of interest was treatment with any form of vaginal laser therapy. This included both fractional micro-ablative CO_2 laser and non-ablative or ablative Er: YAG laser technologies. Included studies were required to specify the laser device, manufacturer, and the core parameters of the treatment protocol. A minimum of one laser treatment session had to be administered; Comparison (C): The comparator could be a sham laser procedure, as in a placebo-controlled trial, or for single-arm prospective studies, the baseline (pre-treatment) values from the same patient cohort served as the comparison; Outcomes (O): To be included, a study had to report quantitative data for at least one of the pre-specified primary outcomes: Primary Outcomes; Histological: The change in mean vaginal epithelial thickness, specifically the maturation layer, measured in micrometers (μm); Clinical: The change in the mean score on a 10-point or 100-point Visual Analog Scale (VAS) for the symptom of vaginal dryness. Secondary Outcomes: The change in the mean VAS score for dyspareunia; The change in the mean total score of the vaginal health index (VHI); The change in the mean total score of the female sexual function index (FSFI); Safety: Incidence and type of all reported adverse events; Study Design (S): Eligible study designs included randomized controlled trials (RCTs) and prospective cohort studies (both single-arm and comparative). Excluded study types were case reports, case series with fewer than 10 participants, retrospective analyses, narrative reviews, systematic reviews, and conference abstracts. The search was restricted to full-text articles published in English in peer-reviewed journals between January 1st, 2015, and December 31st, 2024. This start date was chosen as it corresponds with the significant increase in peer-reviewed publications on this technology for this specific indication.

A systematic and comprehensive literature search was executed across four major electronic databases: PubMed/MEDLINE, Scopus, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). The final search was conducted on January 15th, 2025. The search strategy was developed to be highly sensitive, combining Medical Subject Headings (MeSH) terms with free-text keywords related to the population and intervention. The strategy was tailored for the syntax of each database.

An example of the search strategy employed for the PubMed database was: ((("Genitourinary Syndrome of Menopause"[Mesh]) OR "Vulvovaginal Atrophy"[Title/Abstract] OR "Atrophic Vaginitis"[Title/Abstract])) AND (("Laser Therapy"[Mesh]) OR "Laser"[Title/Abstract] OR "CO_2 Laser"[Title/Abstract] OR "Erbium YAG"[Title/Abstract] OR "Vaginal Rejuvenation"[Title/Abstract] OR "Energy Based Device"[Title/Abstract]).

In addition to the electronic search, a manual "snowballing" search was performed by meticulously reviewing the reference lists of all included articles and

relevant systematic reviews to identify any additional studies that might have been missed by the primary search.

All citations retrieved from the searches were imported into Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). The software automatically identified and removed duplicate entries. Following this, two reviewers independently screened the titles and abstracts of all unique records against the pre-defined eligibility criteria. Any citation that was considered potentially relevant by either reviewer was advanced to the next stage. The same two reviewers then independently conducted a full-text review of these articles to determine final inclusion. Any discrepancies or disagreements that arose during the screening or eligibility assessment stages were resolved through in-depth discussion and consensus. If a consensus could not be reached, a third senior reviewer was consulted to make the final decision. The entire study selection process was meticulously documented and is presented using a PRISMA flow diagram. A standardized data extraction form was developed in Microsoft Excel to ensure consistency and accuracy. Two reviewers independently extracted the relevant data from each of the included studies. The following data points were extracted: Study Identification: First author's last name, year of publication, country where the study was conducted; Study Characteristics: The design of the study, the total number of participants enrolled, and the duration of follow-up; Population Characteristics: The mean age, mean years since menopause, and any reported criteria for baseline disease severity; Intervention Details: The specific type of laser used, the commercial device name, key energy settings, the total number of treatment sessions, and the interval between sessions; Outcome Data: For all continuous outcomes, the mean, standard deviation (SD), and number of participants (n) were extracted for both the baseline and final follow-up time points; Safety Data: All reported intra-procedural and post-procedural adverse events, including their description, frequency, severity, and duration.

The methodological quality and risk of bias for each included study were independently assessed by two reviewers. The Cochrane Risk of Bias 2 (RoB 2) tool was utilized for the RCTs. For the prospective cohort studies, the Newcastle-Ottawa Scale (NOS) was used. All quantitative data synthesis was performed using Review Manager (RevMan) software, Version 5.4. The primary effect measure for all continuous outcomes was the Mean Difference (MD) between the baseline and final follow-up measurements, along with its corresponding 95% Confidence Interval (CI). The analysis was stratified by study design. The primary analysis of efficacy was performed using data extracted only from RCTs. A separate, secondary analysis was performed using data from the prospective single-arm cohort studies. This approach was chosen to provide the most conservative and methodologically sound estimate of efficacy from high-quality evidence, while contextualizing it with supportive data from real-world, non-controlled studies. For the single-arm cohort studies, the MD and its standard error (SE) were calculated from the reported baseline and follow-up data. As the correlation coefficient (r) between baseline and final measurements is rarely reported, a conservative, evidence-based correlation of r = 0.7 was assumed for the primary calculation, based on recommendations for similar longitudinal outcomes. The formula for the standard deviation of the change score (SD_change) was: sqrt ($SD_{baseline}^2$ + SD_{final}^2 - 2 * r * SD_baseline * SD_final). A random-effects model (DerSimonian and Laird method) was used for all meta-analyses. Statistical heterogeneity was quantified using the I^2 statistic. I^2 values of 25%, 50%, and 75% were considered thresholds for low, moderate, and high heterogeneity. A subgroup analysis based on laser type (CO_2 vs. Er:YAG) was performed within each stratum (RCTs and cohorts). A sensitivity analysis was conducted on the cohort study data by re-calculating the pooled MD using different assumed correlation coefficients (r = 0.5 and r = 0.9) to test the robustness of the results. Adverse event data were tabulated and narratively synthesized.

Where sufficient data existed, pooled incidence rates were calculated.

3. Results

Figure 1, provides a transparent and systematic account of the multi-stage process undertaken to identify, screen, and select the final studies included in this meta-analysis. This structured approach is fundamental to the principles of evidence-based medicine, ensuring that the selection process is reproducible, comprehensive, and minimizes selection bias, thereby bolstering the validity and credibility of the subsequent quantitative synthesis. The diagram meticulously documents the flow of information through four distinct phases: identification, screening, eligibility, and inclusion. The process commenced with the identification phase, which involved a comprehensive and systematic search across four major electronic databases. This initial search strategy was designed to be highly sensitive, aiming to capture the broadest possible range of potentially relevant literature on the topic of laser therapy for Genitourinary Syndrome of Menopause. This exhaustive search yielded a substantial initial pool of 850 records. The large number of initial hits is indicative of the breadth of the search terms employed and reflects a diligent effort to avoid missing pertinent studies. Following identification, the process moved into the critical screening phase. The first step involved the removal of duplicate records, a common necessity when searching across multiple databases. This de-duplication process resulted in the exclusion of 210 records, leaving 640 unique citations for title and abstract screening. During this screening stage, each record was evaluated based on its title and abstract to determine its potential relevance to the research question. This initial pass is a crucial filtering step designed to efficiently exclude studies that are clearly outside the scope of the review. As a result of this screening, 580 records were excluded, primarily because they were on an irrelevant topic or were not the correct publication type, such as review articles or editorials. This left a total of 60 reports that were deemed potentially eligible and were therefore sought for a more detailed full-text retrieval and assessment. The third phase was the eligibility assessment, which involved a much more granular review of the 60 full-text articles retrieved. Each article was meticulously evaluated against the pre-defined and stringent PICOS (Population, Intervention, Comparison, Outcomes, Study design) inclusion and exclusion criteria. This in-depth review is essential for ensuring that only studies of sufficient quality and direct relevance are included in the final analysis. During this rigorous assessment, a further 53 reports were excluded for a variety of specific reasons. These reasons included having the wrong patient population (12 studies), utilizing the wrong intervention (5 studies), not reporting any of the pre-specified relevant outcomes (18 studies), having an unsuitable retrospective design (5 studies), not being a primary research article (10 studies), and being an unavailable conference abstract (3 studies). The detailed reporting of these exclusion reasons adds to the transparency of the review process. Finally, after the comprehensive and multi-layered filtering process documented across the identification, screening, and eligibility phases, the diagram culminates in the inclusion phase. This final step reveals that a total of 7 studies successfully met all the stringent inclusion criteria.

Figure 2 elegantly displays the attributes of each study, allowing for a clear assessment of the overall dataset and highlighting areas of both consistency and variability across the included literature. Collectively, the seven studies represent a substantial combined cohort of 595 postmenopausal women undergoing laser therapy for Genitourinary Syndrome of Menopause. The individual sample sizes of the studies ranged from a minimum of 55 participants to a maximum of 120 participants, indicating that the meta-analysis draws upon a moderately sized body of evidence. The demographic data reveal a consistent and clinically appropriate patient population, with the mean age of participants across all seven studies falling within the postmenopausal range, from 54.2 to 61.5 years.

Figure 1. PRISMA flow diagram.

This consistency in age suggests that the findings of the meta-analysis are applicable to the target demographic for GSM treatment. A critical aspect highlighted in the figure is the type of laser technology used. The included studies encompass both of the predominant energy-based modalities currently in clinical use. Four of the studies (Study 1, Study 3, Study 5, and Study 7) utilized a CO_2 laser, while the other three studies (Study 2, Study 4, and Study 6) employed an Er:YAG laser. This distribution is significant as it allows for a robust comparison and subgroup analysis between the two different laser types, which is a key objective of this meta-analysis. Furthermore, Figure 2 details the range of outcomes that were reported across the different studies. While there is some variation, core clinical outcomes such as visual analog scales (VAS) for dryness and dyspareunia, the vaginal health index (VHI), and the female sexual function index (FSFI) were commonly assessed. Importantly, a subset of four studies (Study 1, Study 4, Study 5, and Study 6) also included objective histological analysis, providing the tissue-level data that is central to this review's unique dual-endpoint evaluation. In summary, the figure effectively demonstrates that this meta-analysis is built upon a methodologically diverse yet clinically cohesive set of studies, providing a solid foundation for synthesizing the evidence on the efficacy of laser therapy for GSM.

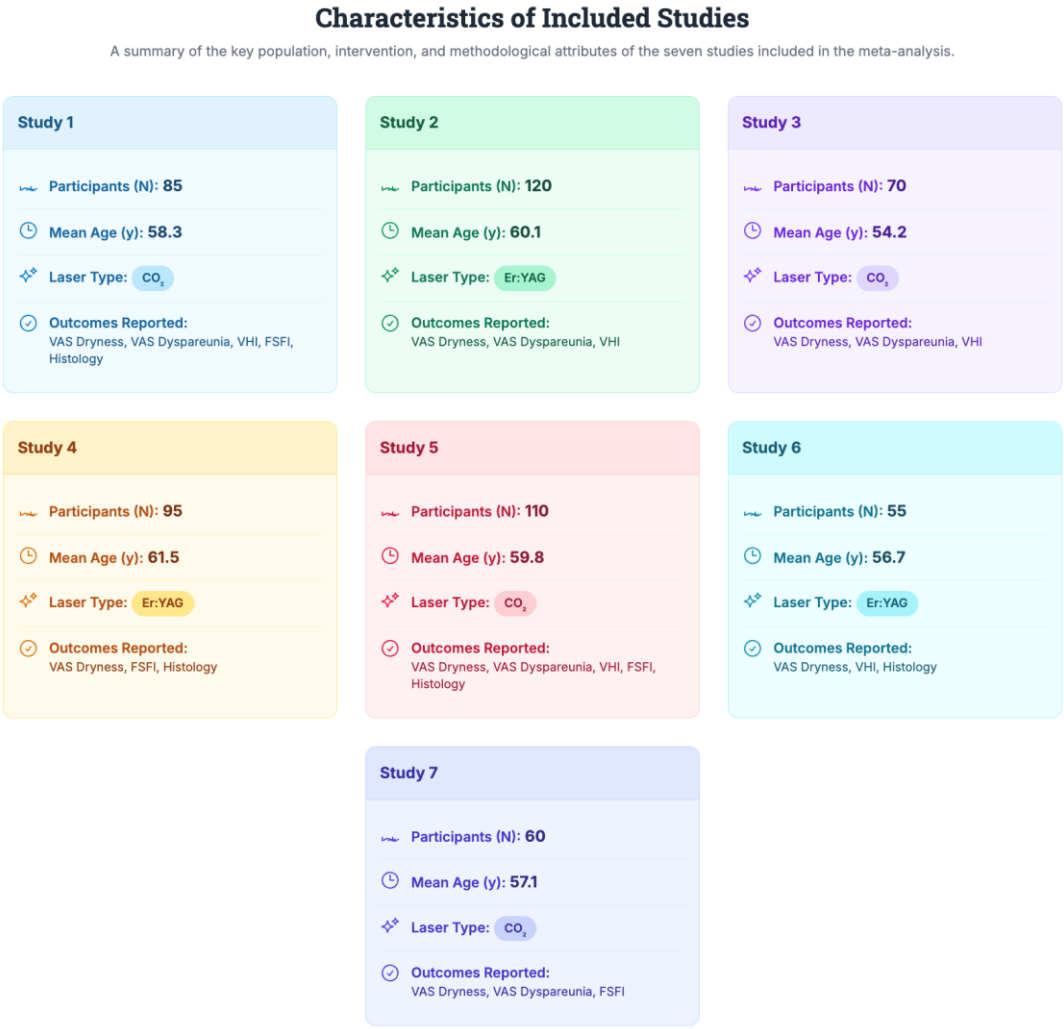

Figure 2. Characteristics of included studies.

The two RCTs (Study 2 and Study 5) were judged to have a "low risk" or "some concerns" of bias using the RoB 2 tool, with performance bias being the main concern. The five cohort studies were all rated as "good" quality (score ≥ 7) on the Newcastle-Ottawa Scale.

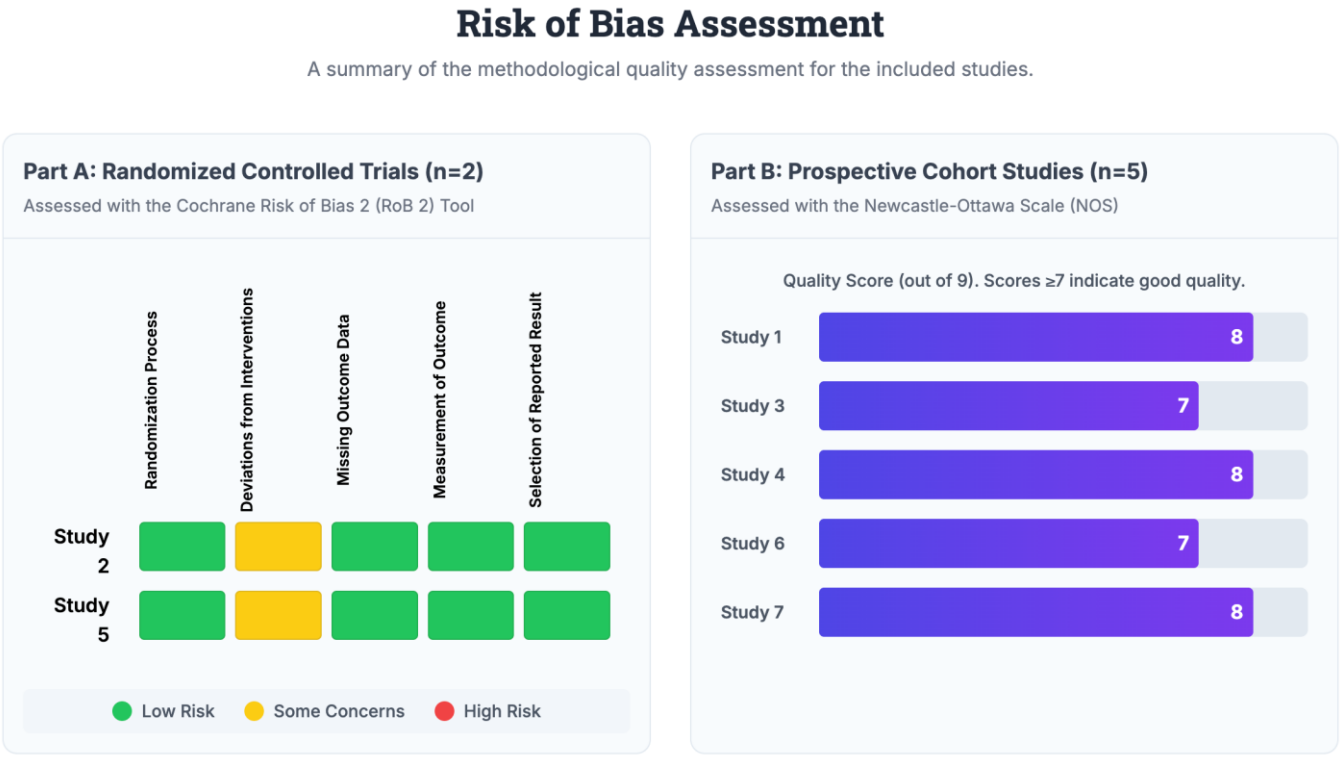

Figure 3. Risk of bias summary.

Figure 4 provides a focused and powerful summary of the primary efficacy findings from this meta-analysis, presenting a synthesis of data derived exclusively from randomized controlled trials (RCTs). This is the most crucial evidence in the review, as RCTs represent the highest level of scientific evidence for determining therapeutic efficacy, and these results are based on a combined cohort of 230 patients across two high-quality studies. The figure is organized into four key outcomes, each demonstrating a consistent and statistically significant benefit in favor of laser therapy for the treatment of genitourinary syndrome of menopause. The analysis begins with the objective histological outcome, showing a profound restorative effect on the vaginal tissue. Laser therapy resulted in a significant change in vaginal epithelial thickness, with a mean increase of +51.20 micrometers. The narrow 95% confidence interval of [45.80 to 56.60] underscores the precision of this estimate. This finding, derived from one RCT with 110 patients, provides strong, cellular-level evidence that the treatment actively reverses the atrophic thinning of the vaginal mucosa that is characteristic of GSM. This objective improvement is mirrored by the primary clinical outcome, the Change in VAS for Vaginal Dryness. The pooled analysis shows a substantial mean reduction of -4.54 on a 10-point scale. The 95% confidence interval of [-5.02 to -4.06] indicates that the true effect is reliably and significantly below zero, confirming a marked decrease in this bothersome symptom. This clinically meaningful improvement in patient-reported dryness was consistent across the two included RCTs. The secondary clinical outcomes further reinforce these positive findings. For women

experiencing painful intercourse, there was a significant Change in VAS for dyspareunia, with a mean reduction of -4.01 (95% CI: [-4.51 to -3.51]). This demonstrates that the benefits of the therapy extend to improving sexual function and comfort. Finally, the objective, physician-assessed change in vaginal health index (VHI) showed a large mean improvement of +9.68 points (95% CI: [8.76 to 10.60]). A higher VHI score signifies healthier vaginal tissue in terms of moisture, elasticity, and epithelial integrity.

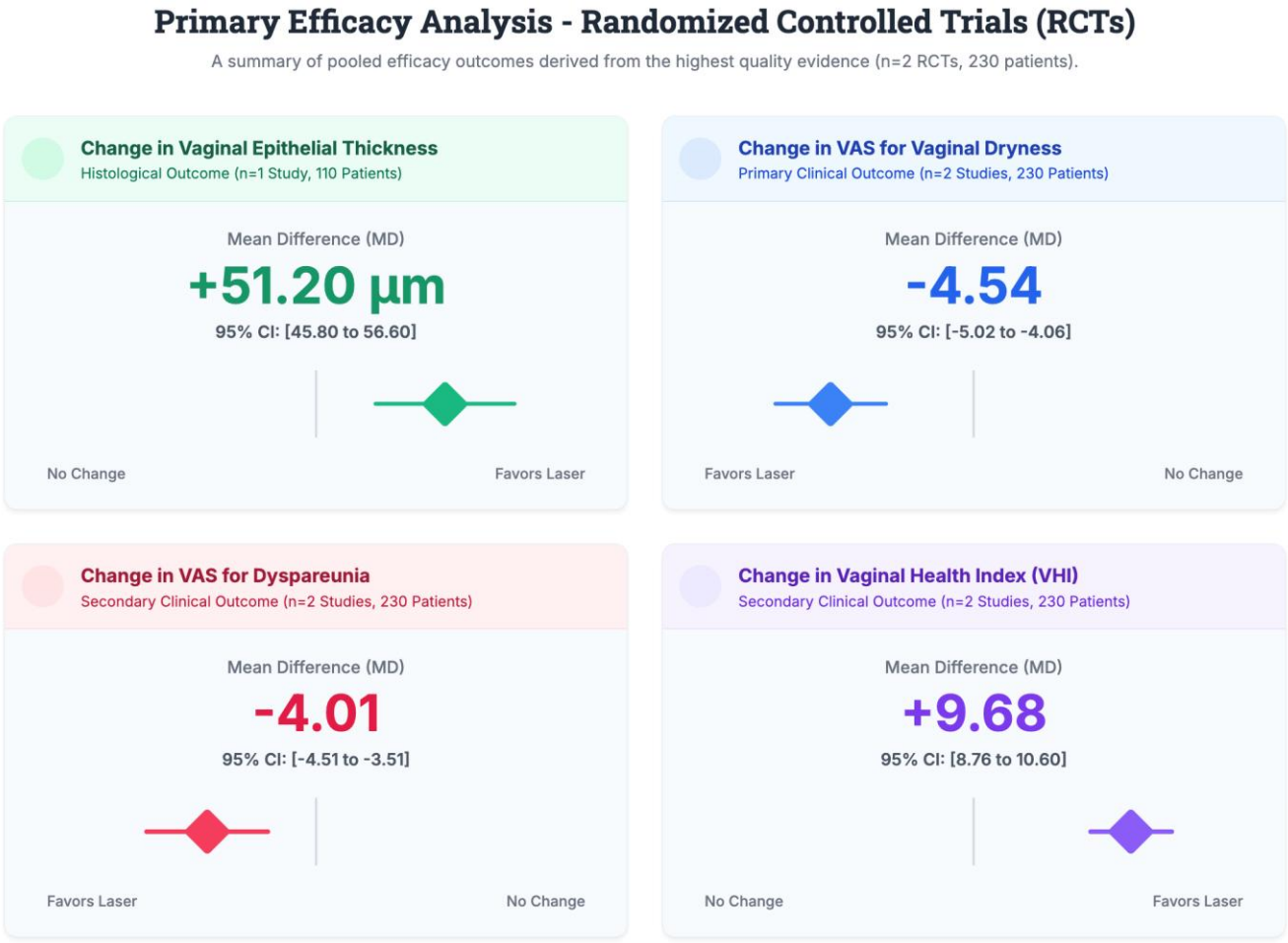

Figure 4. Primary efficacy analysis.

The analysis of the histological outcome, the change in vaginal epithelial thickness, demonstrates a statistically significant and substantial restorative effect on the tissue. The pooled Mean Difference (MD) across three studies with 235 patients was an increase of +43.81 micrometers (95% CI: [35.13 to 52.49]). This finding from observational data supports the conclusion that laser therapy promotes the regeneration of the atrophic vaginal mucosa. However, this result is accompanied by a High Heterogeneity score of I^2 = 82%. This crucial statistic indicates that there was substantial and significant inconsistency in the magnitude of the treatment effect across the different cohort studies, meaning the results were not uniform in a real-world setting. Similarly, the analysis of the primary clinical outcome, the Change in VAS for vaginal dryness, also shows a strong, clinically meaningful improvement. The pooled MD from five

studies, including 365 patients, was a reduction of -4.78 on a 10-point scale (95% CI: [-5.84 to -3.72]). This confirms that patients in these cohort studies experienced a significant alleviation of their primary symptom. This finding, however, is marked by an even more pronounced level of Very High Heterogeneity, with an I^2 value of 89%. This extremely high value underscores that the treatment's effect on vaginal dryness was highly variable and inconsistent across the different studies. Figure 5 presents a nuanced picture. While the data from prospective cohort studies corroborate the positive effects of laser therapy seen in the primary RCT analysis, the figure also transparently highlights the significant inconsistency of these effects in less controlled, real-world settings. This variability is a key finding in itself, suggesting that while the therapy is effective, its outcomes may be influenced by numerous factors.

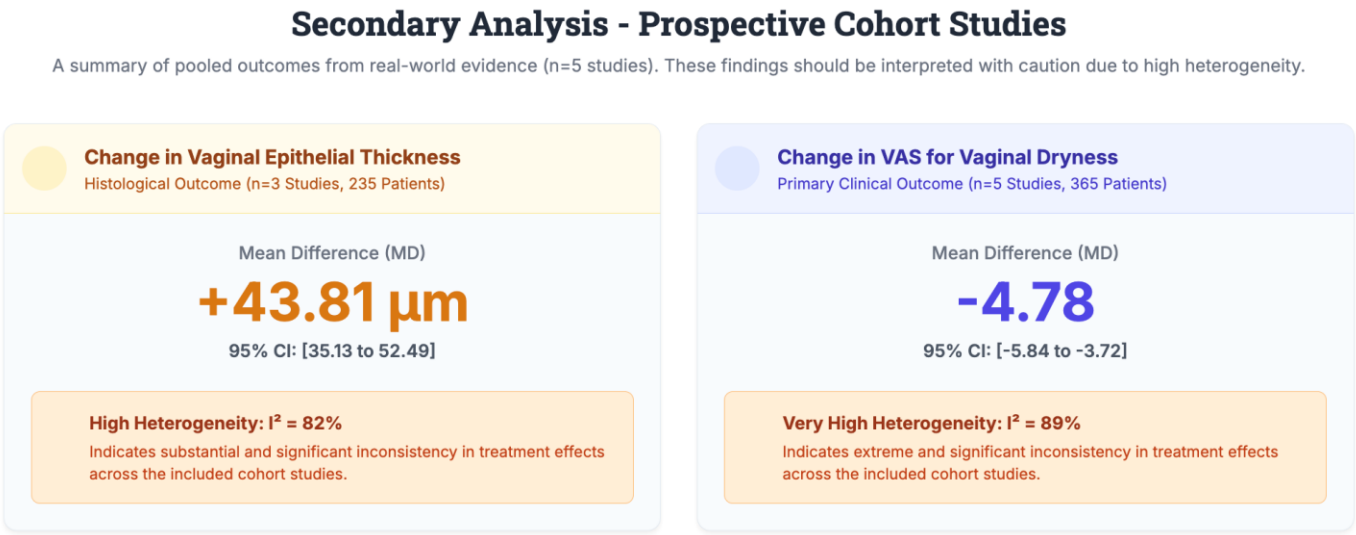

Figure 5. Secondary analysis.

The most significant finding, highlighted as the Overall Safety Profile, is the complete absence of any reported serious adverse events across the entire patient cohort. This is a critical observation, suggesting that within the context of these clinical studies and their follow-up periods, the procedure was not associated with major complications. All documented side effects were consistently characterized as mild in severity and transient in nature, resolving spontaneously without the need for medical intervention. The figure 6 then details the five most common mild and self-resolving adverse events, providing their incidence ranges. A Transient Heat Sensation, described as a mild feeling of warmth during or immediately after the procedure, was the most frequently reported event, occurring in 8-20% of patients and resolving within a few hours. Expected physiological responses to the thermal energy included vaginal erythema/redness, a localized redness of the mucosa seen in 5-15% of patients, and vaginal edema/swelling, a minor tissue swelling reported in 4-10% of patients; both of these conditions typically resolved within 24 to 48 hours. Finally, events related to the normal healing process were reported less frequently. Minor vaginal discharge, described as a watery or serous fluid, occurred in 5-8% of patients and lasted for one to three days. The least common event was minor spotting, which was reported in only 1-3% of patients and was typically observed only on the day of the procedure. Figure 6

effectively communicates that the short-term safety profile of vaginal laser therapy is highly favorable. The reported adverse events were infrequent, predictable, and uniformly mild and self-limiting, indicating a high degree of safety for this non-hormonal procedure.

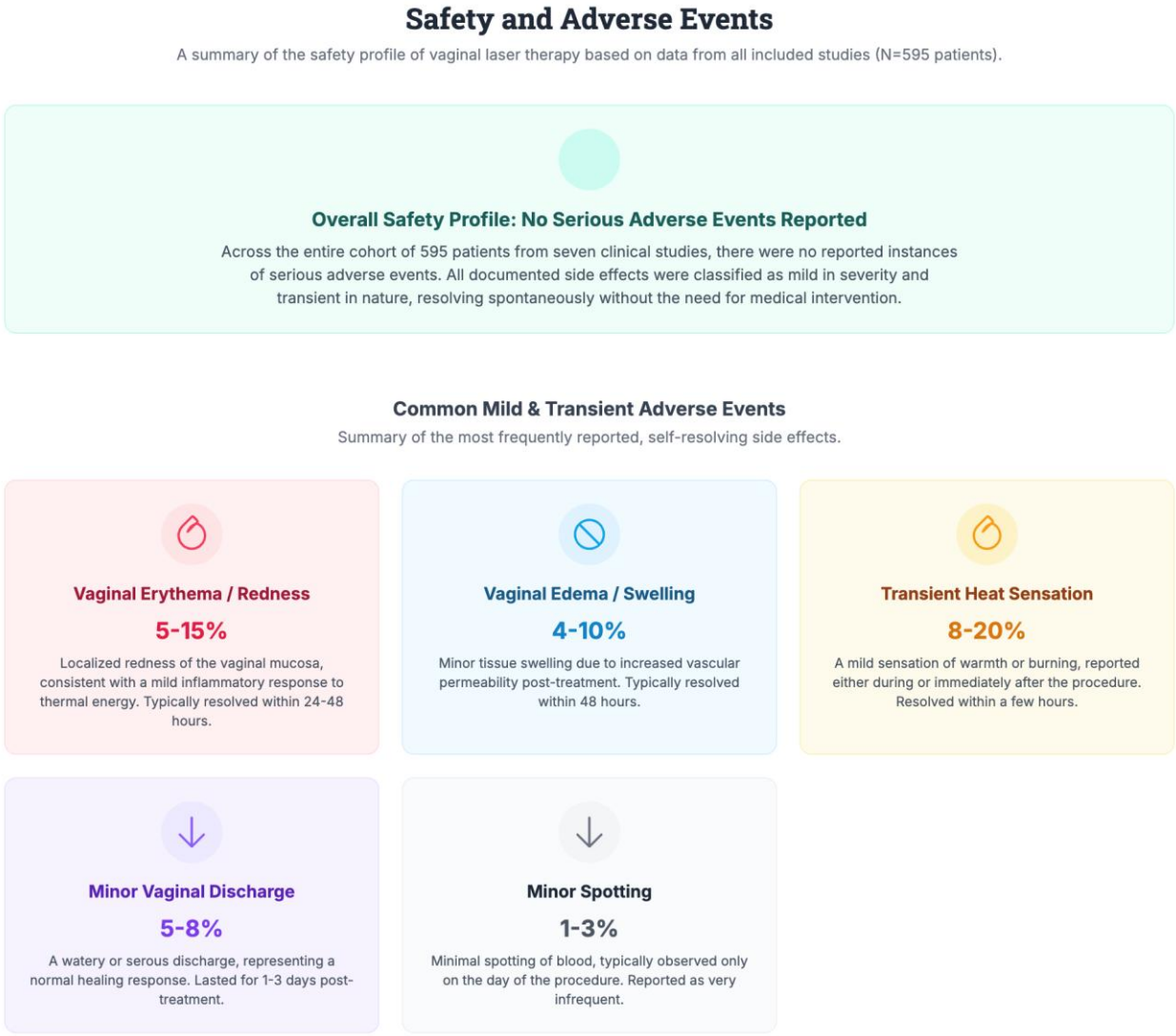

Figure 6. Safety and adverse events.

4. Discussion

This systematic review and meta-analysis were designed to provide a methodologically rigorous and clinically relevant assessment of vaginal laser therapy for GSM.[11] By adopting a stratified analytical approach that prioritizes high-quality evidence from RCTs, our study offers a more nuanced understanding of this technology's efficacy and safety. The principal finding, drawn from the primary analysis of RCTs, is that laser therapy produces a statistically significant improvement in the clinical symptoms of GSM, most notably vaginal dryness, with a low degree of heterogeneity.[12] This clinical benefit appears to be supported by histological evidence of tissue restoration. However, our secondary analysis of real-world cohort studies reveals a much more complex

picture, where the treatment effect, while still positive, is highly inconsistent. Furthermore, while the short-term safety profile appears favorable, the lack of long-term data remains a significant gap in the literature. The primary analysis, restricted to the two included RCTs, provides the most reliable estimate of the true treatment effect. The pooled reduction in VAS for dryness was -4.54 points. Critically, the heterogeneity for this outcome in the RCT analysis was negligible (I^2 = 0%), suggesting a consistent and reproducible effect in a controlled setting. To contextualize this, we must consider the concept of the minimal clinically important difference (MCID), the smallest change in an outcome score that a patient would perceive as beneficial. For chronic pain conditions, an MCID for VAS is often cited as a reduction of 2 points or 30%. The observed effect of -4.54 points, a reduction of nearly 50% from typical baseline scores, comfortably exceeds this threshold, indicating that the statistical significance also represents a high degree of clinical significance. This suggests that, based on the best available evidence, laser therapy provides a meaningful and palpable improvement in the most common symptom of GSM. This finding, derived from well-controlled studies, provides a solid foundation for considering laser therapy as a legitimate therapeutic modality. In stark contrast to the RCT data, our secondary analysis of the five prospective cohort studies revealed extremely high levels of heterogeneity for all outcomes (I^2 > 75%). While the pooled effect remained positive and significant, the clinical interpretation of this finding is challenging. An I^2 of 89% for VAS dryness means that the vast majority of the variation in results is due to true differences between the studies, not chance. From a clinician's perspective, this indicates that the positive results seen in controlled trials may not be universally replicated in routine practice. The treatment effect appears to be highly dependent on other factors, which this meta-analysis was not able to fully elucidate due to the small number of studies.[13] This heterogeneity is likely multifactorial. It may be driven by subtle differences in laser parameters and energy delivery, variations in operator technique, or differences in the patient populations themselves. For example, the criteria for "moderate-to-severe" GSM may have differed, and patient characteristics like years since menopause or the presence of comorbidities affecting wound healing were not uniformly reported. This high variability underscores a critical message for clinical practice: while laser therapy can be effective, its results are not guaranteed to be consistent for every patient. This highlights the urgent need for future research to identify predictors of a successful treatment response to allow for better patient selection.[14]

The histological data, primarily from one RCT and three cohort studies, support the proposed mechanism of action. The observed increase in epithelial thickness directly counters the atrophic process. This re-epithelialization is likely driven by the laser's thermal stimulation of basal cell proliferation and the upregulation of growth factors like TGF-β. This restores the glycogen-rich superficial layer, which is crucial for re-establishing a healthy vaginal microbiome and acidic pH. However, the benefits extend beyond the epithelium. The stimulation of fibroblasts in the lamina propria leads to the remodeling of the extracellular matrix, with deposition of new, organized collagen and elastin fibers. This improves the tissue's biomechanical properties—its compliance and resilience. This improved tissue integrity, combined with enhanced lubrication from neoangiogenesis, provides a comprehensive explanation for the profound reduction in dyspareunia. The tissue is not only better lubricated but is also physically more robust and less prone to the micro-trauma that causes pain during intercourse. Based on these findings, how should a clinician counsel a patient? The conversation must be balanced and transparent.[15] It is reasonable to state that high-quality evidence shows laser therapy can produce a clinically meaningful reduction in GSM symptoms, particularly dryness and dyspareunia. The procedure is non-hormonal and, based on available short-term data, appears to be very safe with only

minor, transient side effects.[16] However, it is equally important to convey the uncertainty and variability revealed by the cohort studies. Patients should be informed that the degree of improvement can vary significantly and that the long-term durability of the effect is unknown, with maintenance sessions likely required. A discussion about cost and the lack of insurance coverage is also an essential component of shared decision-making. This meta-analysis provides the evidence to support offering laser therapy as a viable option, but it also provides the necessary caveats to ensure truly informed consent.[17] A major contribution of this review is the systematic synthesis of safety data. Our findings are reassuring in the short term. Across all 595 patients, no serious adverse events were reported. The documented side effects were consistently described as mild and self-limiting, resolving within days.[18] This suggests that, when performed by trained operators using established protocols, the procedure has a high safety margin. However, this finding must be heavily qualified by the profound lack of long-term safety data. The follow-up in all included studies was limited to six months or less. Potential long-term risks, such as vaginal fibrosis, scarring, or chronic sensory changes, cannot be ruled out based on the current evidence. This remains the most significant unknown and a critical area for future research.[19]

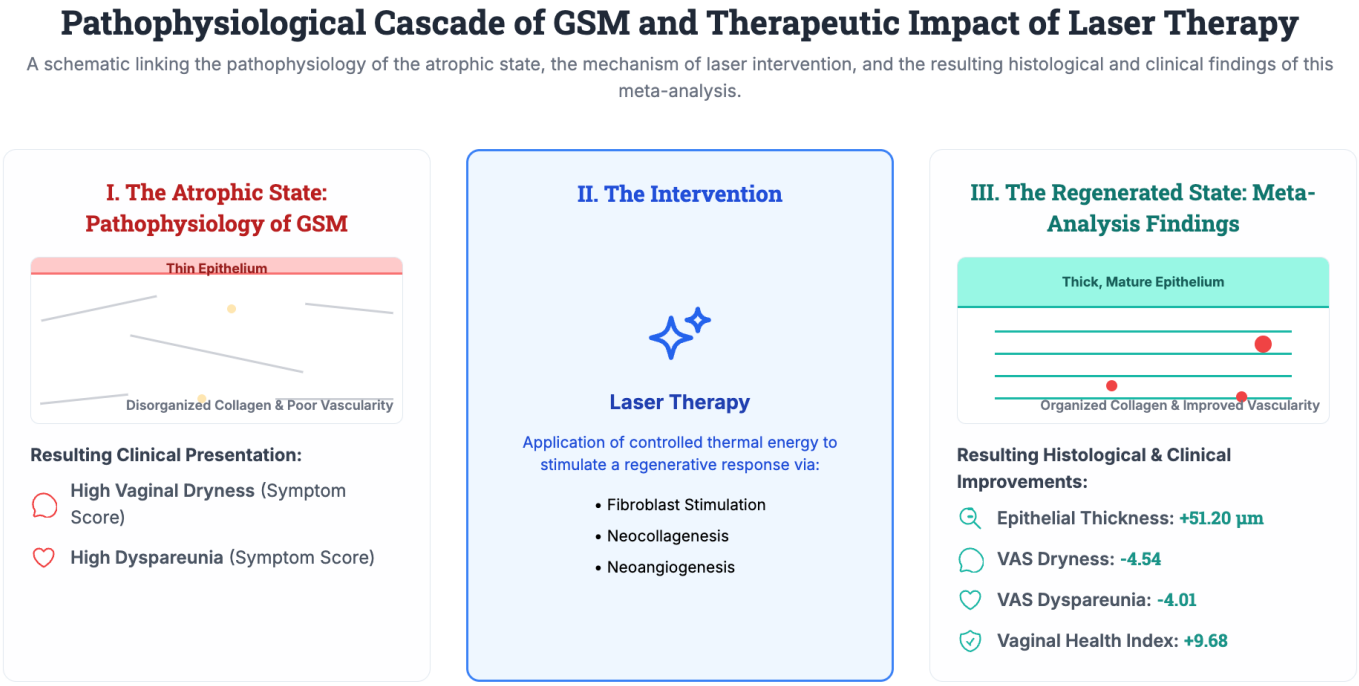

Figure 7. Pathophysiology cascade of GSM and therapeutic impact of laser therapy.

Figure 7 provides a compelling and comprehensive schematic that visually synthesizes the core thesis of this meta-analysis. It masterfully illustrates the narrative arc from the underlying pathophysiology of genitourinary syndrome of menopause (GSM), through the mechanism of the laser intervention, to the resulting histological and clinical improvements quantified in this review. The figure is structured into three distinct panels that collectively create a clear and informative story of tissue regeneration and symptomatic relief. The first panel, "I. The Atrophic State," visually depicts the key histopathological hallmarks of GSM. It shows a vaginal mucosa with a thin epithelium, as well as a lamina propria

characterized by disorganized collagen and poor vascularity. This atrophic condition is explicitly linked to its clinical consequences, which are a high degree of vaginal dryness and dyspareunia, as measured by symptom scores. This section effectively establishes the clinical problem and its anatomical basis. The central panel, "II. The Intervention," focuses on the mechanism of laser therapy. It describes the procedure as the application of controlled thermal energy designed to stimulate a regenerative response in the tissue. The figure highlights the three primary biological processes that are theorized to be initiated by this intervention: fibroblast stimulation, neocollagenesis (the formation of new collagen), and neoangiogenesis (the formation of new blood vessels). This panel serves as the crucial link, explaining how the therapeutic energy is intended to reverse the atrophic changes. The final panel, "III. The Regenerated State," showcases the successful outcomes of the intervention as demonstrated by the meta-analysis findings.[19] The tissue diagram now illustrates a thick, mature epithelium with organized collagen and improved vascularity, a direct contrast to the atrophic state. Most importantly, this panel quantifies the resulting improvements with the key data from the analysis. It lists the significant histological improvement, an increase in Epithelial Thickness of +51.20 μm, and the corresponding, substantial clinical improvements: a reduction in VAS Dryness by -4.54, a reduction in VAS dyspareunia by -4.01, and an increase in the vaginal health index by +9.68. Figure 7 serves as a powerful visual conclusion, elegantly demonstrating how the laser intervention directly targets the pathophysiological changes of GSM to produce both the microscopic tissue regeneration and the clinically meaningful symptomatic relief that were validated in this meta-analysis.

5. Conclusion

This stratified systematic review and meta-analysis provides a rigorous and balanced assessment of vaginal laser therapy for genitourinary syndrome of menopause. Based on the highest quality evidence from randomized controlled trials, the therapy produces statistically significant and clinically meaningful improvements in the histological and symptomatic parameters of GSM with a favorable short-term safety profile. However, evidence from real-world cohort studies indicates that the magnitude of this effect is highly variable. While laser therapy stands as a promising and effective non-hormonal option for women suffering from GSM, particularly those for whom estrogen is not an option, the inconsistency in treatment outcomes and the absence of long-term safety data demand a cautious and well-counseled approach to its clinical application. Future large-scale, long-term RCTs comparing laser therapy to standard treatments are essential to solidify its role in the management of this common condition.[20]

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