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SYSTEMATIC REVIEW

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The effects of adjunctive interventions on cervical skin health post-chemotherapy: a systematic review and meta-analysis

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Abstract

This meta-analysis evaluates the effectiveness of adjunctive interventions, such as lubricants and suppositories, on cervical skin health during or after chemotherapy for cervical cancer patients. Databases, including Ovid Medline and EMBASE, were searched up to April 2024 for studies on the impact of adjunctive treatments on cervical health post-chemotherapy. Eligibility was limited to randomized controlled trials published in English. The methodological quality of the studies was assessed using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Pooled risk ratios (RR) and 95% confidence intervals (CI) were calculated using the Mantel-Haenszel random-effects model, with sensitivity analyses to assess the robustness of the findings. A total of 666 women from six studies were analyzed. The interventions significantly improved symptoms such as vaginal dryness, pain, and inflammation (RR: 0.32 to 0.56, 95% CI varying per symptom, I^2 = 0–24%). However, no significant impact was observed for vaginal discharge (RR: 1.02, 95% CI: 0.47–2.18). Sensitivity analysis confirmed the stability of these results, with minimal heterogeneity observed. This meta-analysis indicates that adjunctive interventions are beneficial for improving certain chemotherapy-related symptoms in cervical cancer survivors. The results support the integration of these treatments into post-chemotherapy care regimens to enhance patient quality of life. Further research is needed to fully address all post-chemotherapy symptomatic needs.

Keywords

Cervical cancer; Chemotherapy; Adjunctive interventions; Vaginal health; Meta-analysis

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1. Introduction

Cervical cancer is a malignant tumor primarily caused by persistent infection with high-risk human papillomavirus (HPV), representing a significant health threat to women [1]. HPV infection can induce abnormal changes in cervical cells that, if left untreated, may progress from pre-cancerous conditions to invasive cancer [2]. The pre-cancerous stage of cervical cancer is typically lengthy, providing ample opportunity for screening and intervention to prevent disease progression. Globally, cervical cancer is the fourth most common cancer among women, with approximately 530,000 new cases annually, accounting for 7.9% of all female cancers [3]. Around 90% of cervical cancer deaths occur in economically disadvantaged nations where screening rates are significantly lower, averaging 19%, compared to 63% in developed countries [4]. The lack of screening and preventive measures in these regions means many women are unaware of the severity of cervical cancer and the importance of early detection, leading to missed opportunities for early treatment. Therefore, there is an urgent need to enhance prevention, screening, and education efforts for cervical cancer, particularly in resource-limited areas.

Cervical cancer treatment, particularly through surgery and radiotherapy, can significantly damage the uterus, affecting its function and structure. Surgical treatments may involve partial or complete removal of the uterus, which directly impacts a woman's fertility. Radiotherapy can lead to the hardening and atrophy of uterine tissue, affecting blood flow and elasticity, and potentially causing painful intercourse and vaginal dryness [5]. Chemotherapy, a cornerstone treatment for advanced cervical cancer, can have systemic side effects that further compromise uterine and vaginal health. Common chemotherapy-induced symptoms include vaginal dryness, pain and inflammation, which can severely impact a patient's quality of life [6, 7]. Therefore, attention to uterine and vaginal health is crucial for women who have undergone cervical cancer treatment. Vaginal care products, such as lubricants and moisturizing suppositories, can alleviate dryness and improve the quality of sexual life [8]. Additionally, regular gynecological examinations and professional medical advice are essential for

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maintaining the health and functionality of the reproductive system.

To better understand and prevent the side effects of cervical cancer treatment, this meta-analysis investigates the ameliorative effects of interventions such as lubricants and moisturizing suppositories on cervical skin health during or post-chemotherapy. By synthesizing data from multiple studies, we aim to provide stronger evidence to support clinical nursing practices and potentially improve treatment outcomes and the quality of life for cervical cancer patients.

2. Methods

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2015 statement [9]. An assessment tool for systematic reviews supplemented the PRISMA explanation and elaboration document. The article selection process is illustrated in the PRISMA flow diagram (Fig. 1).

2.1 Literature search

A literature search was performed using the Ovid Medline and EMBASE electronic databases to retrieve all relevant studies. The search strategy (**Supplementary material**) was developed in consultation with medical information experts.

2.2 Selection criteria

The inclusion criteria were (i) randomized controlled trials (RCTs), (ii) studies conducted up to April 2024 without geographical restrictions, and (iii) studies published in English. The exclusion criteria were case reports, case series, expert opinions, qualitative studies, duplicate publications and studies with incomplete data.

2.3 Data extraction

After eliminating duplicate studies, two researchers independently assessed the relevance of the remaining articles by reviewing their abstracts and titles. Upon reaching a consensus, the full texts of the selected articles were reviewed to confirm eligibility. Both reviewers then extracted relevant information using an Excel spreadsheet, including the first author, publication year, sample size, participant age, disease type, study design, mode and dosage of administration, treatment duration, and follow-up period. Any disagreements were resolved through discussion.

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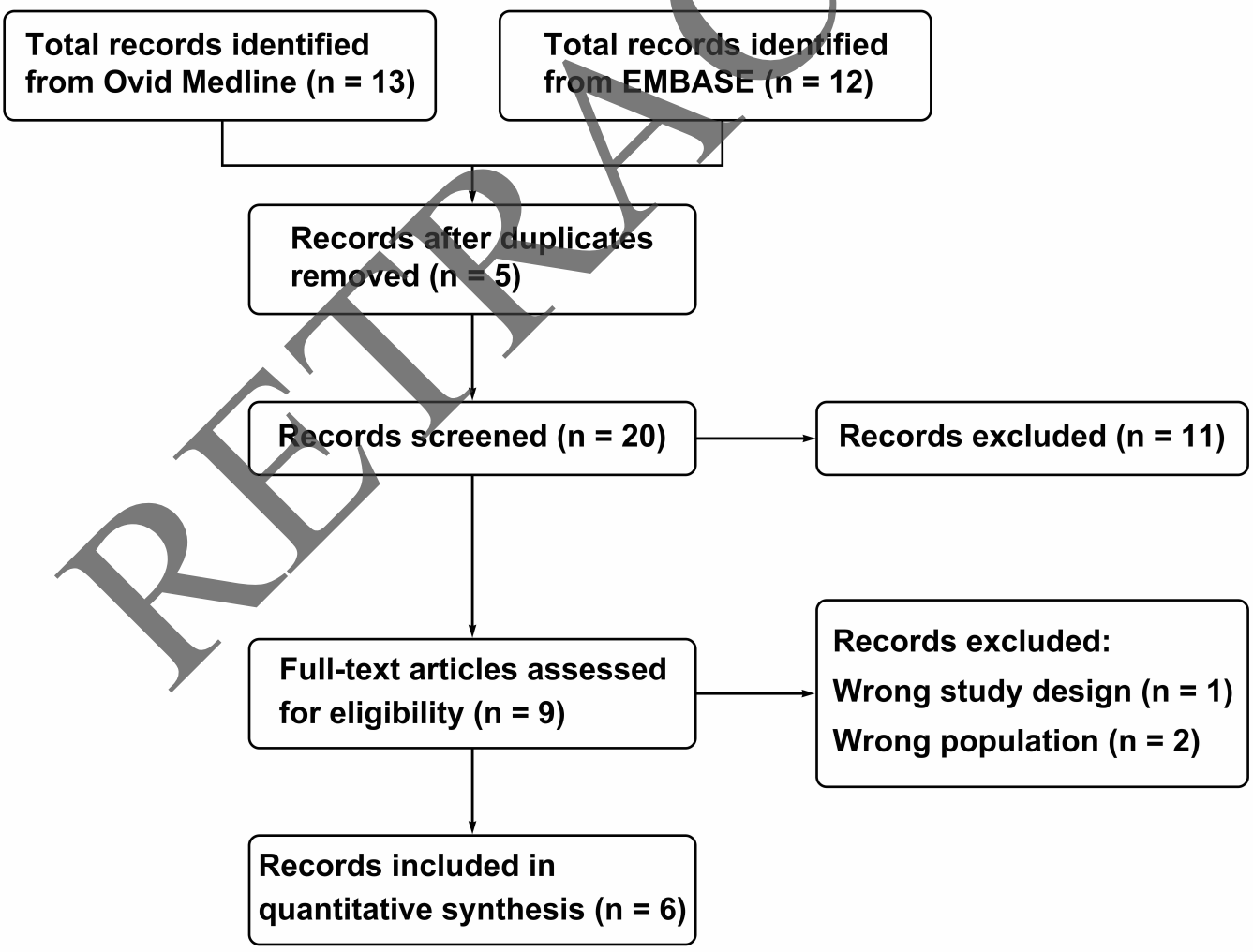


FIGURE 1. Flow diagram of the screening process.

2.4 Data analysis

The Mantel-Haenszel random-effects model was used to calculate the risk ratio (RR) and 95% confidence intervals (CI) between intervention and control groups. Studies that used lubricants, suppositories and other supportive treatments were classified as the intervention group, while those using a placebo or no treatment were considered the control group. Meta-analysis was conducted when at least two studies reported the same outcomes. A leave-one-out sensitivity analysis was performed to assess the impact of individual studies on the overall RR estimation. If excluding a study changed the significance level of the RR, that study was considered for removal. Due to the limited number of included studies, heterogeneity assessment was primarily based on Tau^2 and Higgins's I^2 statistics. All statistical analyses were performed using RevMan Review Manager software version 5.4.1.

3. Results

3.1 Characteristics of the studies

This meta-analysis combined data from six studies with various interventions targeting cervical skin health during or post-chemotherapy [10–15]. The results of the risk of bias in these studies are shown in Fig. 2, illustrating that most studies had a low risk of bias. The pooled sample included 666 women, with a mean age ranging from 32.9 years to 52.78 years, providing a broad demographic representation. The interventions examined included cidofovir, vitamin A and E suppositories, vaginal moisturizers, and the DUDA device (Uterine Device to Dilate the Endocervical Canal). These interventions aimed to alleviate symptoms and minimize the side effects of treatment. The duration of these interventions ranged from 4 weeks to 12 months, allowing for a comprehensive assessment of their efficacy.

Interestingly, the most common route of administration for these interventions was *via* suppositories, except for one study that utilized vaginal dilators as a form of physical intervention. The dosage and quantity varied, reflecting the individualized nature of the treatment regimens. The assessment of outcomes primarily focused on symptomatic relief, with all studies evaluating changes in symptoms as a measure of improvement. One study specifically assessed side effects, highlighting the importance of not only treatment effectiveness but also patient tolerability and quality of life during the intervention period.

A notable finding of this review was the use of a quasi-experimental RCT design by Fernandez (2019), in contrast to the other studies' reliance on prospective RCT frameworks [13]. This diversity in study design underscores the multi-faceted approach to research in this domain (Table 1).

3.2 Vaginal dryness

The pooled risk ratio (RR) for interventions addressing vaginal dryness was 0.56 (95% CI: 0.40–0.79), indicating a statistically significant improvement compared to control groups. Heterogeneity was moderate, with an I^2 value of 24% (Fig. 3).

3.3 Dyspareunia

Interventions showed a promising effect on dyspareunia, with a risk ratio (RR) of 0.52 (95% CI: 0.26–1.01). While the results suggest a trend towards benefit, they did not reach statistical significance. Heterogeneity was moderate, with an I^2 value of 30% (Fig. 4).

3.4 Pain

The interventions were associated with a significant reduction in pain (RR: 0.32; 95% CI: 0.20–0.50), and no heterogeneity was observed (I^2 = 0%) (Fig. 5).

3.5 Vaginal discharge

No significant difference was observed in regard to vaginal discharge between the intervention and control groups, with an RR of 1.02 (95% CI: 0.47–2.18) and no heterogeneity (I^2 = 0%) (Fig. 6).

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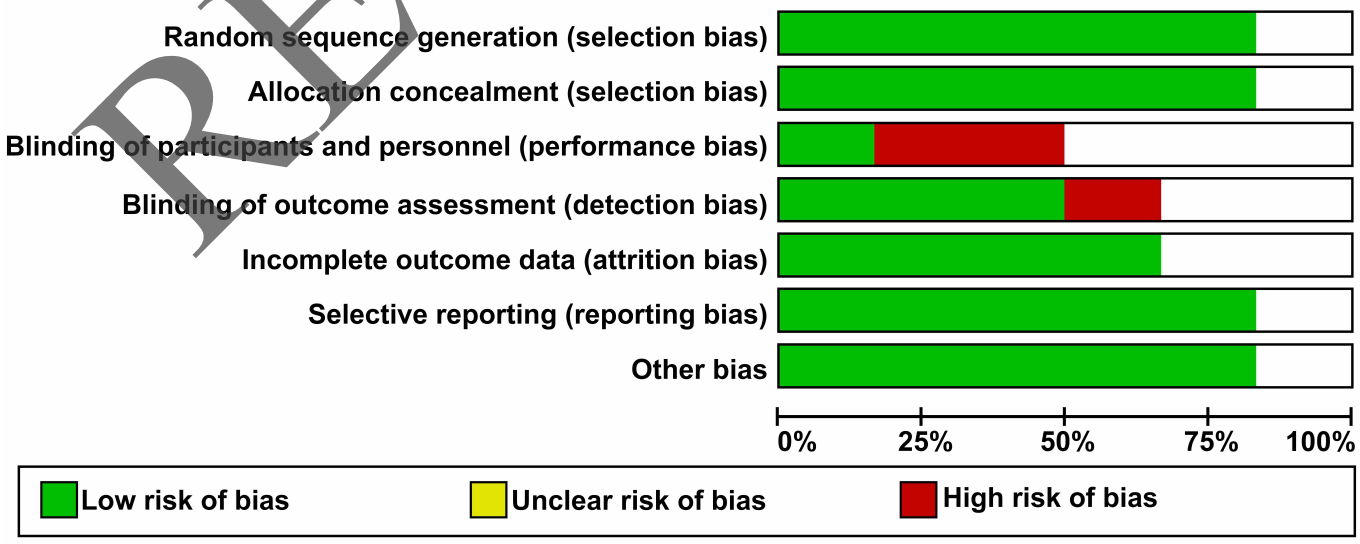


FIGURE 2. Assessment of risk of bias across included studies.

TABLE 1. Basic characteristics of included studies.

Source	Total No. of patients	Age, mean, yr	Subtype	Study type	Intervention/ Control	Number	Quantity, dose	Route of administration	Duration	Outcomes of interest assessed
Van 2009	53	32.9 (28.5–34.1) 24.6 (30.9–38.1)	Cervical intraepithelial neoplasia (CIN 2+)	RCT	Cidofovir/ Placebo	27/26	3 mL of 2% sterile cidofovir were prepared by mixing 0.8 mL of Vistide® (commercially available solution of cidofovir 7.5 w/vol%) with 2.2 mL of the commercially available Intrasite®gel (Smith & Nephew, UK)	Three applications per week	6 weeks	Side effects
Dinicola 2015	38	38 ± 6	Cervical cancer	Prospective RCT	Santes/ Untreated	22/16	5 mg, vitamin E 1 mg, and vitamin A 1 mg (Santes®, Lo.Li. Pharma, Rome, Italy)	Suppositories	4 months	Symptoms
Delia 2019	177	49.7 ± 9.2 50.3 ± 10.3	Cervical cancer	RCT	Santes/ Untreated	88/89	Vaginal suppositories containing HA 5 mg, vitamin E 1 mg, and vitamin A 1 mg (Santes® vaginal suppository, Lo.Li. Pharma, Rome, Italy)	Suppositories	5 weeks	Symptoms
Cerentini 2019	88	42.03 (10.24) 46.49 (14.06)	Cervical cancer	RCT	VD/Control	56/32	-	Vaginal dilators	3 months	Symptoms
Fernandez 2019	89	52.78 ± 12.8	Cervical cancer	Quasi-experimental RCT	Moisture/ Standard care	47/42	-	Moisture	6 months	Symptoms
Vieira 2021	221	34 (21–64) 34 (23–63)	Cervical intraepithelial neoplasia (CIN 2+)	Prospective RCT	DUDA/ Control	111/110	DUDA was placed (Figs. 1,2) on the cervix and secured with four Prolene 2–0 stitches		12 months	Symptoms

RCT: Random Controlled Trial; DUDA: Uterine Device to Dilate the Endocervical Canal; VD: vaginal dilators; HA: hyaluronic acid.

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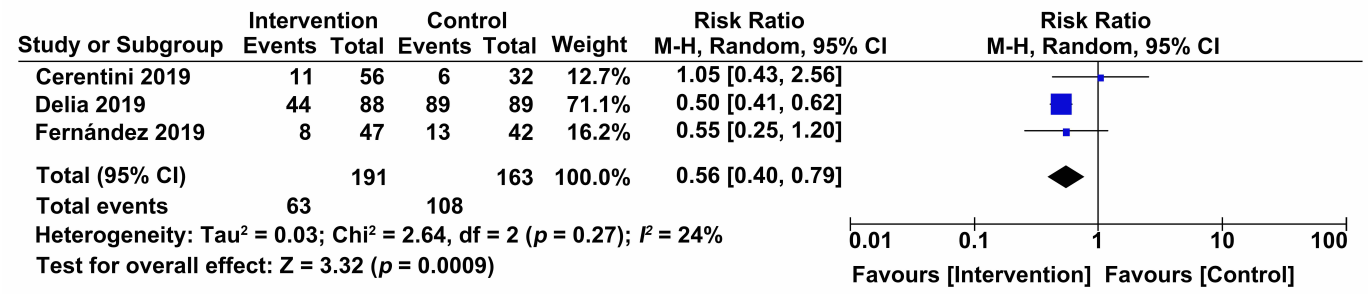


FIGURE 3. Forest plot showing the effects of interventions on vaginal dryness. M-H: Mantel-Haenszel; CI: confidence intervals.

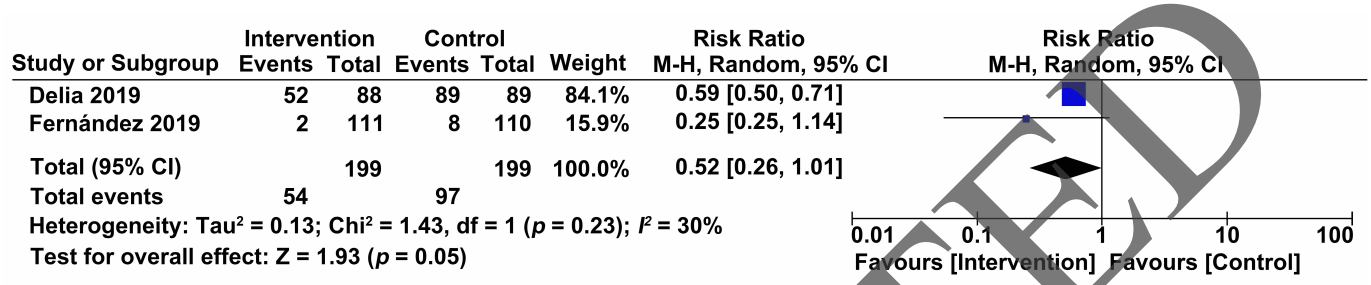


FIGURE 4. Forest plot showing the effects of interventions on dyspareunia. M-H: Mantel-Haenszel; CI: confidence intervals.

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3.6 Inflammation

Further analysis showed that interventions were significantly effective in reducing inflammation, with a risk ratio (RR) of 0.61 (95% CI: 0.52–0.71), indicating a strong association with symptom reduction. No heterogeneity was detected ($I^2 = 0\%$) (Fig. 7).

3.7 Bleeding

Moreover, the intervention group was found to have a reduced risk of bleeding, with a risk ratio (RR) of 0.31 (95% CI: 0.10–0.92), and the heterogeneity was relatively low ($I^2 = 18\%$) (Fig. 8).

Overall, the meta-analysis suggests that interventions targeting symptoms related to cervical cancer treatment can be beneficial. The consistency of results across different symptoms, with low heterogeneity, strengthens the confidence in these findings. However, the impact on vaginal discharge did not show a significant difference, indicating the need for further research in this area.

4. Discussion

In this systematic review and meta-analysis, we synthesized findings from six studies to evaluate the efficacy of interventions aimed at managing symptoms related to cervical cancer treatment [10–15] and observed significant improvements in symptoms such as vaginal dryness, pain and inflammation with the application of interventions compared to control groups. Although these findings could be considered preliminary, they suggest that integrative intervention strategies could indeed be beneficial in the post-chemotherapy care of women with cervical cancer [16, 17].

The interventions, which included pharmacological treatments such as cidofovir and vitamin A and E suppositories, as well as physical interventions like vaginal moisturizers and dilators, showed an overall positive impact on symptom management [18]. Cidofovir is an effective antiviral treatment for multiple HPV-related and resistant viral lesions, requiring only infrequent application due to its long intracellular half-life. Randomized controlled trials (RCTs) have demonstrated cidofovir's inhibitory effect on tumor progression [19]. Vitamin E, a common antioxidant, has been shown in RCTs to improve quality of life and reduce oxidative stress in patients supplementing with it during chemotherapy [20]. These findings align with our study. This multidisciplinary approach to post-treatment care underscores the importance of addressing quality of life issues that are often neglected in the clinical management of cancer [21, 22].

Our study analysis revealed a lack of significant improvement in symptoms such as vaginal discharge, suggesting that not all post-chemotherapy symptoms are equally mitigated by the interventions. Studies have shown that vaginal discharge often occurs alongside pain after chemotherapy, suggesting a possible biological mechanism for this crossover. Metabolomic variant analysis of vaginal secretions may identify potential targets for early warning of cervical cancer [23], highlighting the need for personalized care strategies tailored to the individual symptom profiles of cervical cancer survivors. While the pooled risk ratios for interventions on dyspareunia and vaginal bleeding showed favorable trends, they did not always reach conventional levels of statistical significance. This suggests a potential benefit of the interventions, but further research is required to conclusively determine their efficacy for all symptoms.

Findings from our present meta-analysis highlight several

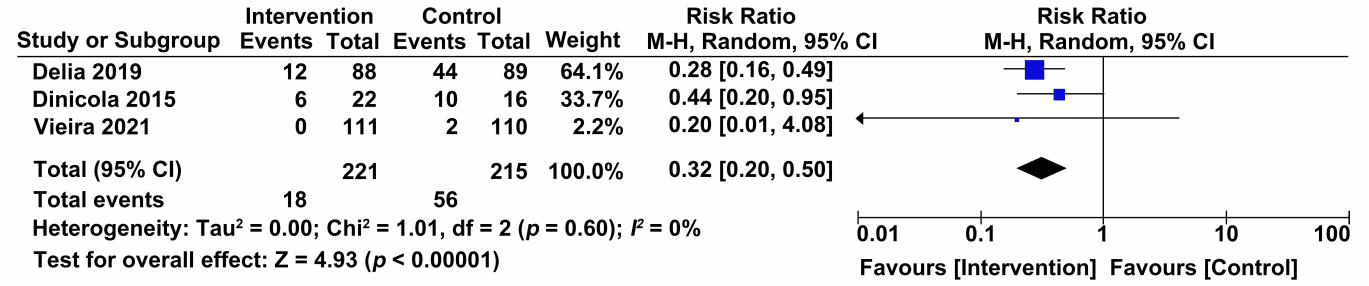


FIGURE 5. Forest plot showing the effects of interventions on pain. M-H: Mantel-Haenszel; CI: confidence intervals.

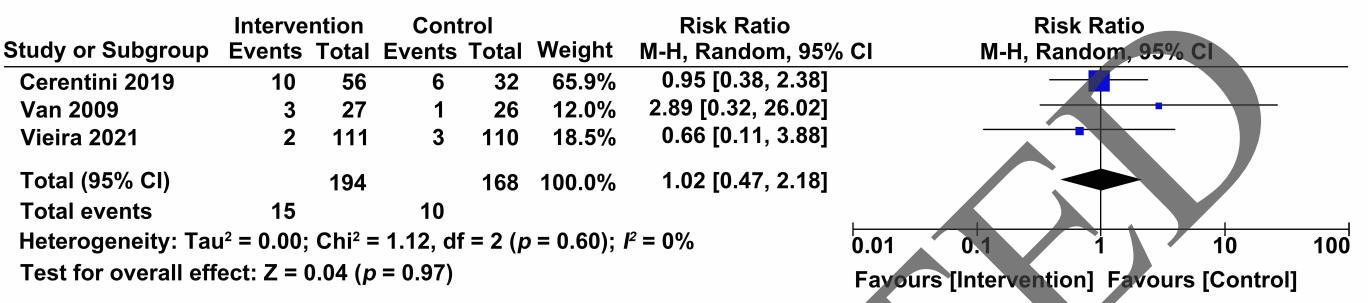


FIGURE 6. Forest plot showing the effects of interventions on vaginal discharge. M-H: Mantel-Haenszel; CI: confidence intervals.

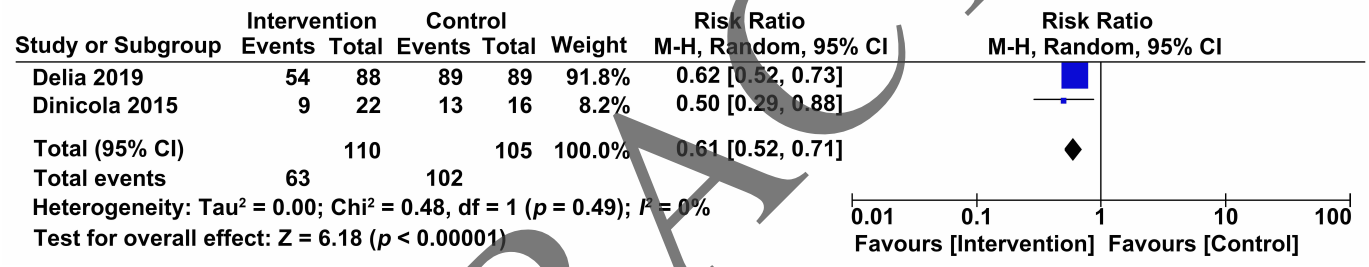


FIGURE 7. Forest plot showing the effects of interventions on inflammation. M-H: Mantel-Haenszel; CI: confidence intervals.

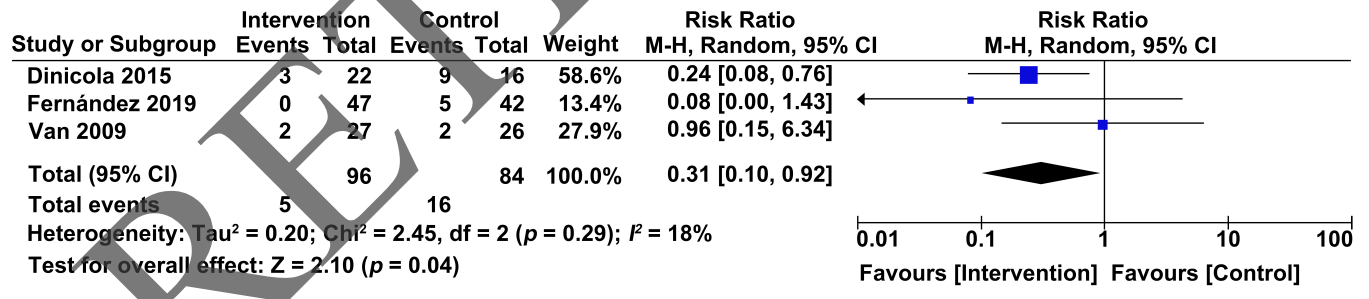


FIGURE 8. Forest plot showing the effects of interventions on bleeding. M-H: Mantel-Haenszel; CI: confidence intervals.

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practical clinical implications. First, the demonstrated efficacy of interventions such as cidofovir and vitamin E suppositories, along with physical interventions such as vaginal moisturizers and dilators, underscores the importance of integrating these treatments into routine post-chemotherapy care for cervical cancer patients. Thus, clinicians could consider these interventions to alleviate symptoms such as vaginal dryness, pain, and inflammation, thereby enhancing the quality of life for these patients [24, 25]. Furthermore, the variability in response to different interventions underscores the necessity of personalized treatment plans. Tailoring interventions based on individual symptom profiles and patient characteristics can optimize outcomes [26]. For symptoms such as vaginal discharge, which did not show significant improvement, further research and targeted strategies are warranted. The potential for early warning of cervical cancer through metabolomic analysis of vaginal secretions suggests a proactive approach in monitoring and managing these patients [27]. Lastly, the

high-quality evidence from RCTs supports the broader implementation of these interventions in clinical practice. However, ongoing research is essential to address the observed heterogeneity and to confirm the long-term benefits of these treatments. By adopting evidence-based, personalized intervention strategies, healthcare providers can significantly improve the post-treatment care and overall well-being of cervical cancer survivors.

The studies included in our meta-analysis used robust randomized controlled trial designs, providing high-quality evidence for the effectiveness of the interventions. However, considerable heterogeneity observed in some symptom categories suggests variability in response, likely due to differences in patient characteristics, intervention modalities, or study designs. In contrast, the low heterogeneity in most symptom categories enhances the reliability of our findings and supports the generalizability of our results. These insights could be essential for informing clinical practice and guiding future research efforts to develop and implement evidence-based interventions for the post-treatment care of cervical cancer patients.

Despite the positive results of our meta-analysis, several limitations must be considered. First, the inherent heterogeneity among the studies regarding participant demographics, types of interventions used, and outcome measures assessed could have influenced the results. Additionally, including only studies that reported outcomes in English may have introduced language bias, potentially overlooking relevant findings published in other languages. The limited number of studies in our analysis may also introduce bias, highlighting the need for additional research to validate our findings. Another limitation is the variable duration of follow-up across studies, which may affect the long-term applicability of the results. Although we methodologically addressed the risk of publication bias, it cannot be entirely excluded, as studies with positive results are more likely to be published. Lastly, our analysis focused on immediate symptom management post-chemotherapy and may not fully capture the complex, long-term care needs of cervical cancer survivors, underscoring the necessity for ongoing research in this area. Collectively, the results of this study suggest that interventions targeting symptoms associated with chemotherapy during the treatment of cervical cancer may improve the health of the patient's uterus.

5. Conclusion

In conclusion, our review indicates that targeted interventions are effective in managing certain chemotherapy-related symptoms in women with cervical cancer. The evidence suggests that a patient-centric approach, which considers individual symptoms and personal preferences, should be a cornerstone of post-chemotherapy care. Further studies are necessary to fill the gaps in our understanding and ensure that all symptomatic aspects of post-chemotherapy care are adequately addressed.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

HXH—designed the study and carried them out; interpreted the data. HXH and HLF—supervised the data collection; analyzed the data; prepared the manuscript for publication and reviewed the draft of the manuscript. Both authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This article does not contain any studies with human participants or animals performed by any of the authors.

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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://oss.ejgo.net/files/article/1823958960947773440/attachment/Supplementary%20material.docx.

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