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ORIGINAL RESEARCH

Efficacy of Oral Zinc Sulfate for the Clearance of Cervical Low-Grade Squamous Intraepithelial Lesions: A Randomized Controlled Trial

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Abstract

Background: Low-grade squamous intraepithelial lesions (LSIL) of the cervix are commonly managed with surveillance because of their high spontaneous regression rate. Zinc has been proposed as a potential therapeutic agent owing to its immunomodulatory and antioxidant properties. This study evaluated the efficacy of oral zinc sulfate in promoting the regression of cervical LSIL compared with standard follow-up. **Methods:** In this randomized controlled trial, Thai women aged ≥20 years with histopathologically confirmed cervical LSIL diagnosed by colposcopy-directed biopsy were randomly assigned to receive either oral zinc sulfate (440 mg daily for 12 weeks) or standard follow-up alone. The primary outcome was the clearance of abnormal cervical cytology at 12 and 24 weeks after treatment initiation. **Results:** At 12 weeks, abnormal cervical cytology had cleared in 58.2% of participants in the zinc group and 65.4% in the control group (risk ratio (RR,0.83; 95% CI: 0.51 to 1.33; p=0.43). At 24 weeks, clearance rates were 49.2% and 61.8%, respectively (RR,1.26; 95% CI: 0.90 to 1.77; p=0.18). No statistically significant differences were observed between the two groups at either follow-up time point. No serious adverse events related to zinc supplementation were reported. **Conclusions:** Oral zinc sulfate administered at a dose of 440 mg daily for 12 weeks did not improve the regression of cervical LSIL compared with standard follow-up. These findings do not support the routine use of high-dose oral zinc sulfate as a therapeutic intervention for women with established LSIL, particularly in populations without evidence of zinc deficiency.

Keywords: Cervical intraepithelial lesions, low-grade squamous intraepithelial lesion, LSIL, zinc sulfate

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Introduction

Cervical cancer remains one of the most common malignancies among women in Thailand and represents a major public health concern despite the availability of effective screening programs [1]. The Royal Thai College of Obstetricians and Gynecologists (RTCOG) recommends cervical cancer screening for women aged 25 years and older using cervical cytology (Pap smear), primary human papillomavirus (HPV) testing, or co-testing with both methods [2]. For women with low-grade squamous intraepithelial lesions (LSIL), current guidelines recommend either repeat cytological testing at 6 and 12 months or colposcopic evaluation followed by repeat screening after one year if no significant lesions are identified [3]. These recommendations are consistent with the 2021 guidelines of the American Society for Colposcopy and Cervical Pathology (ASCCP) [4]. Although conservative follow-up remains the standard management strategy for LSIL, a 2021 systematic review reported that approximately 60% of cervical intraepithelial neoplasia grade 1 (CIN 1) lesions regress spontaneously within 24 months. Nevertheless, approximately 11% progress to CIN 2 or higher and 2% to CIN 3 or higher, underscoring the need for careful surveillance and the potential value of interventions that could enhance lesion regression [5].

Zinc is an essential trace element that plays a critical role in both innate and adaptive immune function. It contributes to host defense by regulating intracellular signaling pathways, maintaining epithelial integrity, and modulating inflammatory responses through

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suppression of pro-inflammatory cytokines [6-10]. Several observational studies have reported significantly lower serum zinc concentrations in women with cervical dysplasia or cervical cancer compared with healthy controls, suggesting a possible association between zinc deficiency and cervical carcinogenesis [11-15]. In addition, zinc serves as a cofactor for numerous enzymes and transcription factors involved in antioxidant defense, DNA repair, cell proliferation, and immune regulation, providing a biological rationale for its potential role in preventing HPV persistence and promoting regression of premalignant cervical lesions [16, 17].

Despite these biological mechanisms, clinical evidence supporting zinc supplementation for the treatment of LSIL remains limited. To date, only one randomized controlled trial has evaluated oral zinc sulfate in women with HPV infection and abnormal cervical cytology, including LSIL and atypical squamous cells of undetermined significance (ASC-US). That study reported a significantly higher clearance rate of abnormal cervical cytology after 12 weeks of zinc supplementation compared with the control group, without serious adverse effects [18]. However, the findings have not been independently validated, and evidence from different populations remains scarce.

Therefore, this randomized controlled trial aimed to evaluate the efficacy of oral zinc sulfate in promoting the clearance of cervical LSIL compared with standard follow-up care among Thai women. The findings may help clarify whether oral zinc supplementation offers a clinically meaningful therapeutic benefit and whether it should be considered as an adjunctive management strategy for women with established LSIL.

Materials and Methods

Study Design and Participants

This open-label randomized controlled trial was conducted at the gynecology clinic of Bhumibol Adulyadej Hospital (BAH), Bangkok, Thailand, between May 2025 and June 2026. The study protocol was approved by the Institutional Review Board of Bhumibol Adulyadej Hospital (IRB No. 26/68) and registered with the Thai Clinical Trials Registry (TCTR20250406002).

Eligible participants were Thai women aged ≥20 years who had abnormal cervical cancer screening results requiring colposcopy and a histopathological diagnosis of low-grade squamous intraepithelial lesion (LSIL). Exclusion criteria included: (1) colposcopic findings suggestive of high-grade lesions (HGL) or more severe disease; (2) pre-colposcopy cervical cytology showing atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H), or more severe abnormalities; (3) use of zinc-containing medications or dietary supplements within the preceding three months; (4) known allergy or contraindication to oral zinc sulfate; and (5) immunocompromising conditions, including human immunodeficiency virus (HIV) infection or autoimmune diseases.

Following receipt of their colposcopy biopsy results, all eligible patients received standard counseling regarding LSIL management and routine follow-up according to institutional practice. The attending physician, who also served as the principal investigator, subsequently introduced the study as an optional research opportunity. To minimize potential coercion arising from the physician–patient relationship, a research nurse was present throughout the recruitment process as an independent observer. Participants were clearly informed that participation was entirely voluntary and that declining participation would not affect their clinical care. Adequate time was provided to review the participant information sheet and ask questions before written informed consent was obtained.

Randomization and Intervention

After providing written informed consent, participants were assigned sequential study numbers from 1 to 110. Allocation concealment was achieved using sequentially numbered opaque sealed envelopes containing group assignments generated by a computer-based block randomization sequence with a block size of four. Participants were randomly allocated in a 1:1 ratio to either the treatment group (oral zinc sulfate) or the control group (standard follow-up without medication).

Baseline blood samples were collected from all participants to determine serum zinc concentrations before initiation of the intervention. Participants assigned to the treatment group received oral zinc sulfate 440 mg daily, administered in two divided doses, for 12 consecutive weeks. The full 12-week medication supply was dispensed at enrollment by hospital pharmacists who were not involved in study conduct or outcome assessment. Participants in the control group received standard follow-up care without zinc supplementation.

Throughout the intervention period, participants were instructed to avoid all nutritional supplements containing zinc or other micronutrients. They were also provided with direct telephone access to the principal investigator to report adverse events or seek clarification regarding medication administration.

Follow-up and Outcome Assessment

Participants in both groups underwent repeat cervical cytology at 12 and 24 weeks after enrollment. The primary outcome was the clearance of abnormal cervical cytology, defined as the proportion of participants with a cytological result of negative for intraepithelial lesion or malignancy (NILM) at each follow-up visit.

At the 12-week follow-up, participants in the treatment group were interviewed regarding treatment adherence and adverse events. Medication adherence was assessed by self-report and pill count based on the number of remaining tablets. Adverse events specifically evaluated included headache, nausea, vomiting, diarrhea, abdominal discomfort, and neurological symptoms.

Sample Size Calculation

The sample size was calculated based on the comparison of two independent proportions using data reported by Ayatollahi et al. [18]. Assuming LSIL

clearance rates of 25% in the control group and 52.5% in the zinc sulfate group, with a two-sided α level of 0.05 and 80% statistical power, the required sample size was estimated at 50 participants per group. To compensate for an anticipated 10% loss to follow-up, the final target sample size was increased to 55 participants per group (110 participants in total).

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range [IQR]), as appropriate, while categorical variables were presented as frequencies and percentages.

Baseline characteristics were compared between the treatment and control groups using the independent-samples Student's t-test for normally distributed continuous variables, the Mann–Whitney U test for non-normally distributed variables, and the Pearson chi-square test or Fisher's exact test, as appropriate, for categorical variables.

The primary outcome was the clearance rate of abnormal cervical cytology at 12 and 24 weeks. Between-group differences were evaluated by calculating the risk ratio (RR) with corresponding 95% confidence intervals (CIs) and p values.

To account for potential confounding, multivariable logistic regression analysis was performed using cervical cytology clearance as the dependent variable. Variables demonstrating baseline imbalance or showing a p value <0.20 in the univariable analysis were entered into the multivariable model. Results were reported as adjusted odds ratios (AORs) with 95% CIs.

All statistical tests were two-sided, and a p value <0.05 was considered statistically significant.

Results

A total of 110 participants were enrolled and randomly assigned in a 1:1 ratio to the treatment group (n = 55) or the control group (n = 55) (Figure 1). Baseline demographic and clinical characteristics, including age, baseline serum zinc level, parity, contraceptive method, baseline cervical cytology, HPV status, and HPV vaccination history, were comparable between the two groups (Table 1). However, the mean body mass index (BMI) was significantly higher in the treatment group than in the control group (24.2 ± 6.2 vs. 22.2 ± 5.7 kg/m², p = 0.009).

At the 12-week follow-up, the cytological clearance rate to negative for intraepithelial lesion or malignancy (NILM) was 58.2% (32/55) in the zinc sulfate group and 65.4% (36/55) in the control group. There was no statistically significant difference between the groups (RR,0.83; 95% CI: 0.51 to 1.33; p=0.43). (Table 2).

At the 24-week follow-up, the cytological clearance rate was 49.2% (27/55) in the treatment group and 61.8% (34/55) in the control group. Similar to the 12-

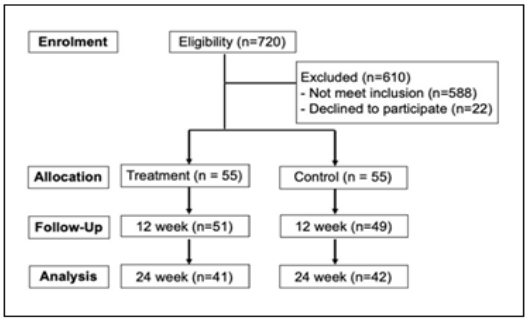

Figure 1. Study flow diagram of participant enrollment, randomization, intervention, and follow-up. Abbreviations: NILM, negative for intraepithelial lesion or malignancy; T/C, treatment/control; NS, not statistically significant; S, statistically significant.

Table 1. Baseline Demographic and Clinical Characteristics of Women with Histologically Confirmed Low-grade Squamous Intraepithelial Lesions (LSIL)

Characteristic	Treatment (n = 55)	Control (n = 55)	p value
Age (years)†	42.0 ± 8.6	39.2 ± 10.5	0.13
Body mass index (kg/m²)‡	24.2 (22.1–28.3)	22.2 (20.0–25.7)	0.009
Serum zinc level (µg/dL)‡	79.0 (71.2–90.4)	80.7 (71.0–96.9)	0.53
Nulliparous	13 (23.6)	22 (40.0)	0.07
No contraception	25 (45.5)	25 (45.5)	0.88
Baseline cervical cytology			0.98
• NILM	20 (36.4)	18 (32.7)	
• ASC-US	17 (30.9)	18 (32.7)	
• LSIL	13 (23.6)	14 (25.5)	
Baseline HPV status			0.22
• Negative	1 (1.8)	0 (0.0)	
• HPV 16/18	17 (30.9)	23 (41.8)	
• Other high-risk HPV	27 (49.1)	18 (32.7)	
No prior HPV vaccination	49 (89.1)	45 (81.8)	0.59

Data are presented as n (%), †mean ± standard deviation (SD), or ‡median (interquartile range [IQR]), as appropriate. Abbreviations: BMI, body mass index; HPV, human papillomavirus; NILM, negative for intraepithelial lesion or malignancy; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion.

Table 2. Cervical Cytology Outcomes at 12 and 24 Weeks in Women with Histologically Confirmed Low-grade Squamous Intraepithelial Lesion (LSIL) Randomized to Oral Zinc Sulfate or Standard Follow-up

Outcome	Treatment (n = 55)*	Control (n = 55)*	Risk Ratio (95% CI)	p-value
12 weeks				
NILM	32 (58.2)	36 (65.4)	0.83 (0.51-1.33)	0.43
LSIL	8 (14.5)	4 (7.3)	—	—
Abnormal cytology†	11 (20.0)	9 (16.4)	—	—
Lost to follow-up	4 (7.3)	6 (10.9)	—	—
Cytology clearance rate (%)	58.2	65.4	0.83 (0.51-1.33)	0.43
24 weeks				
NILM	27 (49.2)	34 (61.8)	1.26 (0.90-1.77)	0.18
LSIL	7 (12.7)	1 (1.8)	—	—
Abnormal cytology†	7 (12.7)	7 (12.7)	—	—
Lost to follow-up	14 (25.4)	13 (23.6)	—	—
Cytology clearance rate (%)	49.2	61.8	1.26 (0.90-1.77)	0.18

* Values are presented as n (%) unless otherwise indicated. † Abnormal cytology includes cytological abnormalities other than NILM and LSIL (e.g., ASC-US or higher, according to study classification). Abbreviations: NILM, negative for intraepithelial lesion or malignancy; LSIL, low-grade squamous intraepithelial lesion; CI, confidence interval.

Table 3. Univariable and Multivariable Logistic Regression Analyses of Factors Associated with Cervical Cytology Clearance in Women with Histologically Confirmed low-grade Squamous Intraepithelial Lesion (LSIL) (n = 110)

Variable	Univariable OR (95% CI)	p-value	Multivariable* AOR (95% CI)	p-value
Age (years)	1.03 (0.99–1.07)	0.13	1.01 (0.97–1.06)	0.67
BMI (kg/m²)	1.10 (1.01–1.20)	0.03	1.08 (0.98–1.19)	0.09
Serum zinc level	0.99 (0.97–1.02)	0.59	—	—
Nulliparity	2.15 (0.95–4.91)	0.07	0.60 (0.24–1.49)	0.26
Contraceptive method				
• No contraception	Reference	—	—	—
• Hormonal	1.14 (0.46–2.83)	0.77	—	—
• Mechanical	0.88 (0.35–2.17)	0.77	—	—
Baseline cervical cytology				
• NILM	Reference	—	—	—
• ASC-US	1.11 (0.28–4.47)	0.88	—	—
• LSIL	0.94 (0.23–3.85)	0.94	—	—
Baseline HPV status				
• Negative	Reference	—	—	—
• HPV 16/18	1.91 (0.71–5.14)	0.2	—	—
• Other high-risk HPV	0.94 (0.34–2.58)	0.91	—	—
No prior HPV vaccination	0.55 (0.19–1.64)	0.29	—	—

* Variables with $p < 0.20$ in the univariable analysis (age, BMI, and parity) were entered into the multivariable logistic regression model. Abbreviations: OR, odds ratio; AOR, adjusted odds ratio; CI, confidence interval; BMI, body mass index; NILM, negative for intraepithelial lesion or malignancy; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HPV, human papillomavirus.

week findings, no statistically significant difference was observed between the groups (RR,1.26; 95% CI: 0.90 to 1.77; p=0.18) (Table 2).

To identify independent predictors of cytological clearance and adjust for baseline differences, univariable and multivariable logistic regression analyses were performed (Table 3). In the univariable analysis, higher BMI was significantly associated with cytological clearance (OR = 1.10, p = 0.03), whereas age (p = 0.13) and parity (p = 0.07) met the predefined criterion ($p < 0.20$) for inclusion in the multivariable model. However, after adjustment, BMI was no longer significantly associated with clearance (AOR = 1.08, 95% CI: 0.98–1.19; p = 0.09). Likewise, neither age (AOR = 1.01, 95% CI: 0.97–1.06; p = 0.67) nor parity (AOR = 0.60, 95% CI: 0.24–1.49; p = 0.26) was independently associated with cytological clearance. Overall, oral zinc sulfate supplementation did not demonstrate a statistically significant therapeutic benefit over standard follow-up during the study period.

The intervention was generally well tolerated. No serious adverse events, including neurological complications, were reported. No participants were withdrawn after randomization, and there were no losses to follow-up or crossover between study groups, resulting in complete outcome data for all randomized participants.

Discussion

The primary objective of this randomized controlled trial was to evaluate whether oral zinc sulfate could improve the clearance of cervical low-grade squamous intraepithelial lesions (LSIL). Contrary to our hypothesis, administration of 440 mg of oral zinc sulfate daily for 12 weeks did not significantly increase the rate of cytological clearance to negative for intraepithelial lesion or malignancy (NILM) compared with standard follow-up. Although spontaneous regression of LSIL was observed in both groups at 12 and 24 weeks, zinc supplementation did not provide an additional therapeutic benefit.

Our findings are consistent with those reported by Şahin et al. [19], who evaluated an oral probiotic–zinc combination in women with histologically confirmed LSIL. After 12 weeks of treatment, the cytological clearance rate was approximately 69%, with no statistically significant difference between the intervention and control groups. Similarly, Kim et al. [20] found that a vaginal suppository containing zinc citrate administered for 12 weeks did not improve cytological clearance compared with the control group (51.8% vs. 45.3%). In contrast, Ayatollahi et al. [18] reported that oral zinc sulfate (440 mg/day for 12 weeks) significantly increased the clearance rate of abnormal cervical cytology compared with standard management (52.5% vs. 25.0%).

Several methodological differences may explain these inconsistent findings. In the studies by Kim et al., Şahin et al., and the present trial, participants were enrolled based on histopathologically confirmed LSIL, whereas Ayatollahi et al. recruited women based solely on abnormal cervical cytology [18–20]. Histological confirmation generally provides greater diagnostic accuracy and may identify lesions with different biological behavior than cytology alone. In addition, while the present study, Ayatollahi et al., and Şahin et al. evaluated oral zinc supplementation, Kim et al. investigated vaginal zinc administration, making direct comparisons difficult. Furthermore, outcome assessment differed across studies: most relied on repeat cervical cytology, whereas Şahin et al. used histological regression as the primary endpoint. A comparison of the major characteristics and findings of these studies is presented in Table 4.

The high spontaneous regression rate of LSIL presents an inherent challenge when evaluating therapeutic interventions. Most low-grade lesions regress without treatment, making it difficult to demonstrate additional benefit from adjunctive therapies. Consequently, any intervention intended to accelerate lesion regression requires sufficient statistical power and sensitive outcome measures to detect relatively small treatment effects.

Several limitations of the present study should be acknowledged. First, although adequately powered according to the initial sample size calculation, the study may still have been underpowered to detect modest differences between groups. Second, HPV testing was not repeated during follow-up, precluding evaluation of viral clearance, which is an important biological endpoint in the management of cervical precancerous lesions. Third, although baseline serum zinc concentrations were measured and found to be within the normal range in both groups, serum zinc levels were not reassessed after treatment to confirm adherence or biological response to supplementation. It is possible that zinc supplementation provides greater benefit in women with zinc deficiency rather than those with adequate baseline zinc status. Finally, the open-label design may have introduced performance bias, although the primary outcome was based on objective cytological assessment.

Overall, the findings of this trial do not support the routine use of high-dose oral zinc sulfate as an adjunctive treatment for women with histologically

Table 4. Summary of Previous Studies Evaluating Zinc Supplementation and Cervical Cytology Clearance in Women with Low-grade Squamous Intraepithelial Lesion (LSIL)

Characteristic	Kim et al.	Ayatollahi et al.	Şahin et al.	Present study
Year	2011	2022	2025	2026
Study design	Prospective	Randomized controlled trial	Retrospective	Randomized controlled trial
Country	South Korea	Iran	Türkiye	Thailand
Treatment/Control (n)	76/118	40/40	100/102	55/55
Participant selection	Histology	Cytology	Cytology/Histology	Histology
Outcome assessment	Cytology	Cytology	Cytology/Histology	Cytology
Route of zinc administration	Vaginal	Oral	Oral	Oral
Zinc dose (mg/day)	8.61	440	7.5	440
Follow-up (weeks)	12	12	24	12 and 24
Cytology clearance rate (%)				
12 weeks	51.8 / 45.3 (NS)	52.5 / 25.0 (S)	66.7 / 69.9 (NS)	58.2 / 65.4 (NS)
24 weeks	—	—	45.0 / 31.3 (NS)	49.2 / 61.8 (NS)

Abbreviations: NILM, negative for intraepithelial lesion or malignancy; T/C, treatment/control; NS, not statistically significant; S, statistically significant.

confirmed LSIL and normal baseline zinc levels. Current guideline-recommended surveillance remains the most appropriate management strategy for these patients. Future randomized trials with larger sample sizes, serial HPV testing, post-treatment zinc measurements, and stratification according to baseline zinc status may help identify patient subgroups that could potentially benefit from zinc supplementation.

In conclusion, although zinc plays an important role in immune function and may contribute to the prevention of HPV-related cervical disease, the findings of this randomized controlled trial do not support the routine use of high-dose oral zinc sulfate as a therapeutic intervention for women with established low-grade squamous intraepithelial lesions (LSIL) who have adequate baseline serum zinc levels. Standard guideline-based surveillance remains the preferred management strategy, given the high spontaneous regression rate of LSIL. Future studies should stratify participants according to baseline zinc status, incorporate serial HPV DNA testing and liquid-based cytology (LBC), and evaluate whether specific subgroups of women may derive benefit from zinc supplementation.

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Conflict of Interest

The authors declare that they have no conflicts of interest related to this study.

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Author Contributions

T.W., K.S., and W.A. conceived and designed the study. T.W. collected the data. W.A. verified the analytical methods. All authors contributed to data interpretation, critically revised the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request for up to five years after publication.

Ethics Statement

This study was approved by the Institutional Review Board of Bhumibol Adulyadej Hospital (IRB No. 26/68) and was registered with the Thai Clinical Trials Registry (TCTR20250406002). Written informed consent was obtained from all participants before enrollment, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

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