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Original Article

Comparison of the Effect of Dienogest Alone and Dienogest Combined with Zinc on Pain and Quality of Life in Patients with Endometriosis

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BRIEF TEXT

Background and Objective

Endometriosis is a chronic, estrogen-dependent inflammatory disease characterized by the presence of endometrial-like tissue outside the uterine cavity, predominantly affecting women of reproductive age. This condition is associated with a wide range of symptoms, including chronic pelvic pain, refractory dysmenorrhea, dyspareunia, and pain [1]. … [2, 3]…. [3, 4] …. [5].

Treatment options for endometriosis vary depending on symptom severity, patient age, desire for fertility preservation, and response to previous therapies, and include a spectrum of medical and surgical approaches. Medical treatments are primarily based on hormone therapy using agents such as combined estrogen–progestin oral contraceptives, progestins, GnRH agonists, danazol, and non-steroidal anti-inflammatory drugs [6, 7]. … [7, 8].

These interventions are generally suppressive rather than curative; therefore, symptom recurrence is commonly reported upon discontinuation of therapy [9].

In recent years, dienogest, an oral progestin with high selectivity for the progesterone receptor, favorable bioavailability, and acceptable safety profile, has been widely used in the management of endometriosis. Its effectiveness in reducing pain and improving patients' quality of life has been demonstrated in various studies [10]. … [11-17].

In contrast, the role of micronutrients, particularly zinc, in modulating inflammatory responses and oxidative stress has gained attention. This raises the question of whether adding zinc supplementation to a dienogest regimen could lead to greater improvements in pain and quality of life among women with endometriosis [18]. … [19-22]. Based on this hypothesis, the present study was designed to evaluate the effects of concurrent administration of dienogest and zinc on pain intensity and quality of life in women with endometriosis.

Materials and Methods

This single-blind, randomized clinical trial enrolled 72 women with endometriosis who attended the Fatemieh Hospital outpatient clinic in Hamadan in 2025. Patients were evaluated according to standard diagnostic criteria for endometriosis, and after an initial gynecological assessment, they were screened based on the inclusion and exclusion criteria. Eligible participants who provided informed consent were enrolled. They were then randomly assigned to two groups, A and B .

In Group A, participants received oral dienogest at a dose of 2 mg daily for 4 months. In Group B, in addition to receiving the same dose and duration of dienogest, participants were administered 50 mg of oral zinc daily.

Pain intensity was assessed using the Visual Analog Scale (VAS), with participants rating their pelvic pain at baseline and after 4 months of treatment on a 10-cm VAS line. To evaluate endometriosis-related quality of life, the validated and disease-specific Endometriosis Health Profile-30 (EHP-30) questionnaire was used, which assesses multiple dimensions of quality of life, including functioning, control and empowerment, pain perception, social support, body image, and sexual function. The questionnaire was completed at baseline and after four months.

Extended Abstract

The collected data were coded and entered into SPSS (version 26) and analyzed using appropriate statistical tests.

Results

At baseline, there were no significant differences between the two groups in demographic characteristics or initial pain intensity, indicating homogeneous pre-treatment conditions. After four months of intervention, both groups exhibited a significant reduction in pain intensity; this decrease was highly significant in within-group analysis ($P < 0.001$) (Figure 1). However, pain reduction was greater in the dienogest plus zinc group than in the dienogest-only group, supporting the enhanced efficacy of the combined regimen .

Regarding quality of life based on the EHP-30 questionnaire, findings showed significant improvement across most quality-of-life domains in both groups after the intervention. However, the extent of improvement was significantly greater in all domains among participants receiving dienogest plus zinc ($P < 0.05$) (Table 1).

Quality of life scores improved across all domains before and after treatment, with the combination group showing greater improvement than the dienogest-only group. This difference was statistically significant in the pain, control, social support, and self-image domains ($P < 0.001$). Only in the emotional domain was there no significant difference in improvement between the two groups (Table 2).

Regarding adverse effects, the frequency of side effects was 16.7% in the dienogest-only group and 11.1% in the combined group, with no statistically significant difference ($P = 0.496$), indicating that adding zinc did not significantly increase drug-related side effects (Figure 2).

Discussion

The findings of this randomized clinical trial demonstrate that dienogest alone is effective in reducing pain and improving quality of life in women with endometriosis; however, adding zinc supplementation at a daily dose of 50 mg to the dienogest regimen can lead to greater reductions in pain severity and broader improvements across multiple quality-of-life dimensions, without significantly increasing adverse effects.

… [23]… [24]… [25]… [26]. Given the chronic and recurrent nature of endometriosis, these results are clinically meaningful, as enhanced pain control and quality of life improvement are primary therapeutic goals. The potential role of zinc in modulating inflammatory responses, reducing oxidative stress, and regulating immune function [27, 28] may partially explain its additive effects alongside dienogest, although the precise mechanisms require further laboratory and clinical investigation .

Additionally, the lack of a significant increase in adverse events in the combination group suggests that this therapeutic combination may be a relatively safe option, particularly for patients requiring long-term symptom management, where treatment tolerability is essential [29, 30]. However, the results should be interpreted with limitations, such as the relatively small sample size, the four-month follow-up period, and the single-center design. Future studies with larger sample sizes, longer follow-up durations, multicenter settings, and assessments of additional outcomes—such as fertility parameters and inflammatory biomarkers—are recommended.

Conclusion

Based on the present findings, zinc supplementation alongside dienogest may be considered a promising adjunctive approach for managing pain and improving the quality of life in women with endometriosis.

REFERENCES

1. Bijlani S, Sonawane P. Epidemiology of endometriosis" in. Current Practice in Obstetrics and Gynecology. *Endometriosis*. 2012:9-13. Link
2. Ferreira ALL, Bessa MMM, Drezett J, de Abreu LC. Quality of life of the woman carrier of endometriosis: systematized review. *Reprodução & Climatério*. 2016;31(1):48-54. DOI: 10.1016/j.recli.2015.11.002
3. Simoens S, Dunselman G, Dirksen C, Hummelshoj L, Bokor A, Brandes I, et al. The burden of endometriosis: costs and quality of life of women with endometriosis and treated in referral centres. *Human Reprod*. 2012;27(5):1292-9. PMID: 22422778 DOI: 10.1093/humrep/des070
4. Santulli P, Bourdon M, Presse M, Gayet V, Marcellin L, Prunet C, et al. Endometriosis-related infertility: assisted reproductive technology has no adverse impact on pain or quality-of-life scores. *Fertil Steril*. 2016;105(4):978-87.e4. PMID: 26898717 DOI: 10.1016/j.fertnstert.2016.01.014
5. Makari S. Value of endometrial nerve fiber detection in diagnosing

endometriosis: Lithuanian University of Health Sciences (Lithuania); 2012. Link
6. Falcone T, Flyckt R. Clinical management of endometriosis. *Obstetrics & Gynecology*. 2018;131(3):557-71. PMID: 29420391 DOI: 10.1016/j.fertnstert.2016.01.014
7. Brøns N, Baandrup L, Dehlendorff C, Kjaer SK. Use of nonsteroidal anti-inflammatory drugs and risk of endometrial cancer: a nationwide case–control study. *Cancer Causes & Control*. 2015; 26: 973-81. PMID: 25895439 DOI: 10.1007/s10552-015-0597-2
8. Lier MC, Vlek SL, Ankersmit M, van de Ven PM, Dekker JJ, Bleeker MC, et al. Comparison of enhanced laparoscopic imaging techniques in endometriosis surgery: a diagnostic accuracy study. *Surgical Endoscopy*. 2020; 4(1): 96-104. PMID: 31028547 DOI: 10.1007/s00464-020-07503-4
9. Guo S-W. Recurrence of endometriosis and its control. *Human Reprod Update*. 2009;15(4). PMID: 19279046 DOI: 10.1093/humupd/dmp009
10. Schindler AE. Dienogest in long-term treatment of endometriosis. *Int J Women's Health*. 2011:175-84. PMID: 21792339 DOI: 10.2147/IJWH.S18266
11. Agarwal A, Gupta S, Sharma RK. Role of oxidative stress in female reproduction. *Reprod Biol Endocrinol*. 2005;3:1-21. PMID: 16018814 DOI: 10.1186/1477-7827-3-28
12. Harlev A, Gupta S, Agarwal A. Targeting oxidative stress to treat endometriosis. *Expert Opin Ther Targets*. 2015;19(11):1447-64. PMID: 26256952 DOI: 10.1517/14728222.2015.1059929
13. Scutiero G, Iannone P, Bernardi G, Bonaccorsi G, Spadaro S, Volta CA, et al. Oxidative stress and endometriosis: a systematic review of the literature. *Oxidative Medicine and Cellular Longevity*. 2017;**2017**(1):7265238. PMID: 29057034 DOI: 10.1155/2017/7265238
14. Prasad AS. Zinc: an antioxidant and anti-inflammatory agent: role of zinc in degenerative disorders of aging. *Journal of Trace Elements in Medicine and Biology*. 2014;**28**(4):364-71. PMID: 25200490 DOI: 10.1016/j.jtemb.2014.04.004
15. Prasad AS. Zinc: role in immunity, oxidative stress and chronic inflammation. *Current Opinion in Clinical Nutrition & Metabolic Care*. 2009;**12**(6):646-52. PMID: 19710611 DOI: 10.1097/MCO.0b013e3283311457
16. Fukada T, Yamasaki S, Nishida K, Murakami M ,Hirano T. Zinc homeostasis and signaling in health and diseases: Zinc signaling. *JBIC*. 2011;**16**(7):1123-34. PMID: 21660546 DOI: 10.1007/s00775-011-0810-0
17. Prasad AS. Zinc: role in immunity, oxidative stress and chronic inflammation. *Current Opinion in Clinical Nutrition and Metabolic Care*. 2009;**12**(6):646-52. PMID: 19710611 DOI: 10.1097/MCO.0b013e3283311457
18. Lai GL, Yeh CC, Yeh CY, Chen RY, Fu CL, Chen CH, et al. Decreased zinc and increased lead blood levels are associated with endometriosis in Asian Women. *Reprod Toxicol*. 2017;**74**:77-84. PMID: 28889936 DOI: 10.1016/j.reprotox.2016.11.009
19. Yılmaz BK, Evliyaoğlu Ö, Yorgancı A, Özyer Ş, Üstün YE. Serum concentrations of heavy metals in women with endometrial polyps. *J Obstet Gynaecol*. 2020;**40**(4):541-5. PMID: 31478412 DOI: 10.1080/01443615.2019.1704461
20. Singh AK, Chattopadhyay R, Chakravarty B, Chaudhury K. Altered circulating levels of matrix metalloproteinases 2 and 9 and their inhibitors and effect of progesterone supplementation in women with endometriosis undergoing in vitro fertilization. *Fertil Steril*. 2013;**100**(1):127-34. PMID: 23557756 DOI: 10.1016/j.fertnstert.2012.10.003
21. Messalli EM, Schettino M, Mainini G, Ercolano S, Fuschillo G, Falcone F, et al. The possible role of zinc in the etiopathogenesis of endometriosis. *Clin Exp Obstet Gynecol*. 2014;**41**(5):541-6. PMID: 25864256
22. Oberweis D, Madelenat P, Nisolle M, Demanet E. A pilot double-blind, randomized, placebo-controlled trial of the efficacy of trace elements in the treatment of endometriosis-related pain: Study design and methodology. *Nutr Diet Suppl*. 2016:1-8. DOI: 10.2147/NDS.S96893
23. Strowitzki T, Faustmann T, Gerlinger C, Seitz C. Dienogest in the treatment of endometriosis-associated pelvic pain: a 12-week, randomized, double-blind ,placebo-controlled study. *Eur J Obstet Gynecol Reprod Biol*. 2010;**151**(2):193-8. PMID: 20444534 DOI: 10.1016/j.ejogrb.2009.12.004
24. Huang Y, Wei Y, Liang F, Huang Y, Huang J, Luo X, et al. Exploring the link between dietary zinc intake and endometriosis risk: insights from a cross-sectional analysis of American women. *BMC Public Health*. 2024;**24**(1):2935. PMID: 39443887 DOI: 10.1186/s12889-024-18313-5
25. Caruso S, Cianci S, Caruso G, Sareri MI, Gulino FA, Palumbo M. Comparative study on the effects of combined oral contraceptives and dienogest in women with endometriosis-associated chronic pelvic pain. *Eur J Obstet Gynecol Reprod Biol*. 2025;**304**:10-5. DOI: 10.1016/j.ejogrb.2024.11.037
26. Semenyna H, Hrytsko M, Doroshenko-Kravchyk M, Korytko O, Fartushok T. New opportunities for correction of hormonal disorders and oxidative stress in women with genital endometriosis. *Int J Endocrinol (Ukraine)*.

2024;**20**(1):41-7. DOI: 10.22141/2224-0721.20.1.2024.1352
27. Nasiadek M, Stragierowicz J, Klimczak M, Kilanowicz A. The role of zinc in selected female reproductive system disorders. *Nutrients*. 2020;**12**(8):2464. PMID: 32824334 DOI: 10.3390/nu12082464
28. Guerrero CÁH, Montenegro LB, de la Jara Díaz J, Cabrera JM, Valencia PB. Endometriosis and deficient intake of antioxidants molecules related to peripheral and peritoneal oxidative stress. *Ginecología y obstetricia de México*. 2006;**74**(01):20-8. PMID: 16634350
29. Uludag SZ, Demirtas E, Sahin Y, Aygen EM. Dienogest reduces endometrioma volume and endometriosis-related pain symptoms. *J Obstet Gynaecol*. 2021;**41**(8):1246-51. PMID: 33629621 DOI: 10.1080/01443615.2021.1910509
30. El Taha L, Musa AA, Khalifeh D, Khalil A, Abbasi S ,Nassif J. Efficacy of dienogest vs combined oral contraceptive on pain associated with endometriosis: Randomized clinical trial. *Eur J Obstet Gynecol Reprod Biol*. 2021;**267**:205-12. PMID: 34826668 DOI: 10.1016/j.ejogrb.2021.04.033

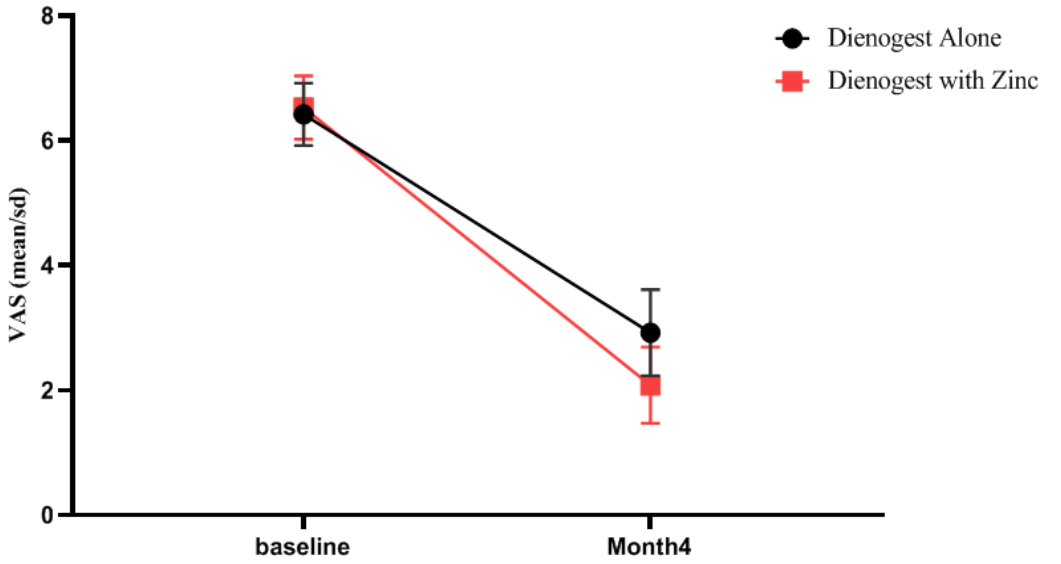

Figure 1. Mean and Standard Deviation of Endometriosis-Related Pain Scores (VAS) Before Initiation of Treatment and at the End of the Fourth Month After Treatment in the Dienogest-Only Group and the Dienogest-Plus-Zinc Group

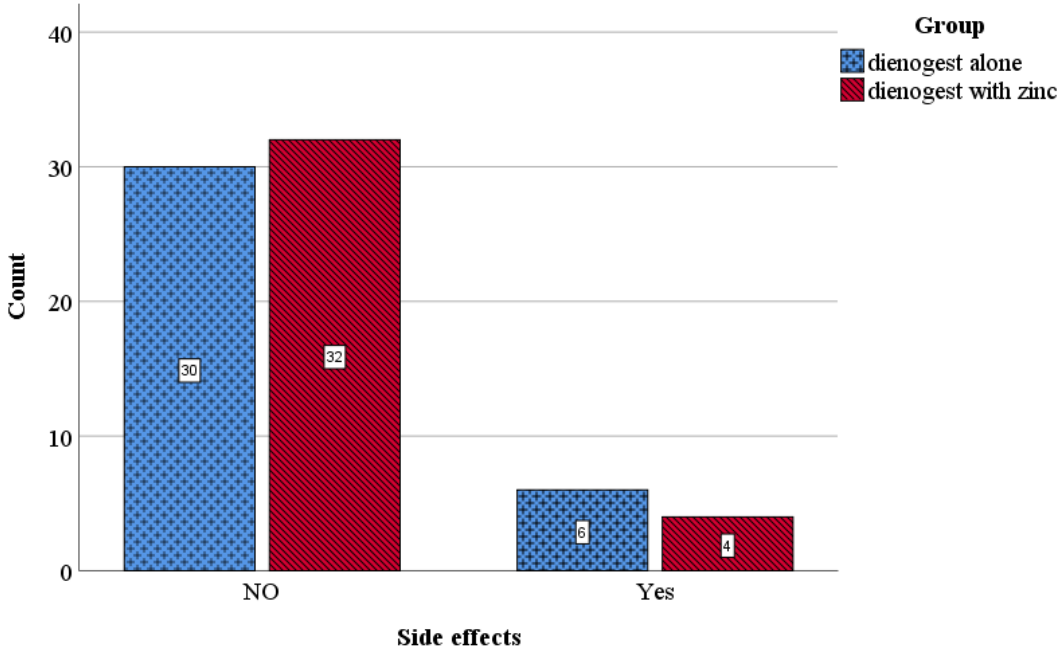

Figure 2. Frequency of Drug Adverse Effects in the Two Treatment Groups: Dienogest Alone versus Dienogest Plus Zinc

Extended Abstract

Table 1. Mean EHP Questionnaire Scores in Endometriosis Patients by Treatment Type and Assessment Time

P Value	Treatment Type		Time of Assessment	EHP
	Dienogest + Zinc Mean ± SD	Dienogest alone Mean ± SD		
0.233	56.31 ± 3.20	55.39 ± 3.26	Pretest	Pain
< 0.001	33.39 ± 1.96	36.14 ± 2.23	Posttest	
0.241	54.75 ± 3.49	54.11 ± 3.20	Pretest	Control
< 0.001	32.03 ± 2.41	34.94 ± 2.39	Posttest	
0.672	51.69 ± 5.74	52.31 ± 6.44	Pretest	Emotional well-being
< 0.001	29.22 ± 3.59	31.81 ± 1.62	Posttest	
0.099	51.61 ± 4.20	50.03 ± 3.82	Pretest	Social support
0.017	36.06 ± 3.96	38.08 ± 2.22	Posttest	
0.310	36.63 ± 9.18	37.50 ± 3.43	Pretest	Self-image
< 0.001	21.44 ± 1.83	26.25 ± 1.78	Posttest	

Table 2. Differences in Mean EHP Questionnaire Scores between Baseline and the Fourth Month After Treatment Initiation in Endometriosis Patients by Treatment Type

P Value	Treatment Type		Time of Assessment	EHP
	Dienogest + Zinc Mean ± SD	Dienogest alone Mean ± SD		
< 0.001	-21.92 ± 1.34	-19.25 ± 1.13	0-100	Pain
< 0.001	-22.72 ± 1.28	-19.16 ± 0.97	0-100	Control
0.098	-22.47 ± 5.26	-20.50 ± 4.91	0-100	Emotional well-being
< 0.001	-15.56 ± 1.40	-11.94 ± 1.78	0-100	Social support
< 0.001	-15.39 ± 1.46	-11.25 ± 0.91	0-100	Self-image