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# Dienogest Treatment of Symptomatic Adenomyosis: An In-Depth Meta-Analysis

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## ADMINISTRATIVE INFORMATION

**Support -** None.

**Review Stage at time of this submission -** Data extraction.

**Conflicts of interest -** YC, JY, SL, XX and XL have no conflict of interest. S.W.G. is a Board member of the Asian Society of Endometriosis and Adenomyosis, a member of the Scientific Advisory Board of the Endometriosis Foundation of America, Heranova BioSciences, and FimmCyte AG, and has provided paid consultancy advice to the companies, as well as to Sound Bioventures, and BioGeneration, but these activities had no bearing on this work.

**INPLASY registration number:** INPLASY202480119

**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 August 2024 and was last updated on 26 August 2024.

## INTRODUCTION

**Review question / Objective** PICOS Framework: Population: Women with symptomatic adenomyosis, particularly those experiencing dysmenorrhea. Intervention: Treatment with dienogest. Comparator: None. Outcomes: Degree of improvement in dysmenorrhea and differences in response among different patient subgroups. Study Design: Systematic review and meta-analysis.
Review Question: How effective is dienogest in alleviating dysmenorrhea in women with adenomyosis? Are there specific patient subgroups that respond better to dienogest treatment?

**Rationale** Research Background and Purpose:
Adenomyosis is an estrogen-dependent condition characterized by the invasion of endometrial tissue into the uterine muscle layer, leading to dysmenorrhea, heavy menstrual bleeding, chronic pelvic pain, and infertility, which severely impacts the quality of life of affected patients. Traditional treatments, such as surgery, non-steroidal anti-inflammatory drugs (NSAIDs), and hormonal therapy, have shown some effectiveness but are limited due to side effects or their unsuitability for women who wish to preserve fertility. Recently, dienogest, a synthetic progestin with anti-inflammatory and antiproliferative properties, has gained attention for its potential in alleviating adenomyosis-related symptoms, particularly dysmenorrhea.

Research Questions:
How effective is dienogest in alleviating dysmenorrhea in women with adenomyosis?
Are there specific patient subgroups that demonstrate a better response to dienogest treatment?
Hypothesis:

Certain patient subgroups (e.g., based on age, duration of disease, severity of lesions, or other physiological characteristics) may respond better to dienogest treatment.

Research Design and Methods:
Conduct a systematic review and meta-analysis to evaluate the existing literature on the efficacy and safety of dienogest in treating adenomyosis.
Analyze the characteristics and outcomes of different studies to identify patient subgroups that may benefit more from dienogest treatment.
Data Analysis:
Assess the effectiveness of dienogest in alleviating dysmenorrhea.
Use statistical analysis methods, such as subgroup analysis and multivariable regression analysis, to determine the patient characteristics that influence treatment outcomes.
Expected Contributions:
The findings will help clinicians better understand the role of dienogest in treating adenomyosis, particularly in alleviating dysmenorrhea. By identifying specific patient subgroups, the research will contribute to the development of more personalized treatment strategies, enhancing treatment efficacy and patient satisfaction.

**Condition being studied** Adenomyosis is a condition where endometrial tissue grows into the uterine muscle, leading to symptoms such as painful periods, heavy menstrual bleeding, chronic pelvic pain, and infertility. This disorder significantly affects the quality of life for those affected. While surgical options like hysterectomy can effectively manage symptoms, they are not suitable for women who wish to maintain fertility. This has created a demand for effective non-surgical treatments. Among these, dienogest, a synthetic hormone with anti-inflammatory and anti-growth properties, has shown promise in reducing pain and bleeding in women with adenomyosis. However, there is still much to learn about which patients benefit most from this treatment, making further research essential.

## METHODS

**Search strategy** Based on the comprehensive search conducted by Ali et al. in PubMed, Web of Science, Cochrane Library, and Embase databases, we conducted an extensive literature search using the same MeSH terms, keywords, and their combinations: “dienogest and adenomyosis.” Our search focused on studies published in English from January 2024 to August 2024.

**Participant or population** Women with symptomatic adenomyosis, particularly those experiencing dysmenorrhea.

**Intervention** Treatment with dienogest.

**Comparator** None.

**Study designs to be included** Based on the comprehensive search conducted by Ali et al. in PubMed, Web of Science, Cochrane Library, and Embase databases, we conducted an extensive literature search using the same MeSH terms, keywords, and their combinations: “dienogest and adenomyosis.” Our search focused on studies published in English from January 2024 to August 2024.

**Eligibility criteria** Inclusion criteria: based on the comprehensive search conducted by Ali et al. [6]in PubMed, Web of Science, Cochrane Library, and Embase databases, we conducted an extensive literature search using the same MeSH terms, keywords, and their combinations: “dienogest and adenomyosis.” Our search focused on studies published in English from January 2024 to August 2024. After a meticulous screening process, a total of 23 studies were selected for further analysis. Exclusion criteria: (1) reviews, animal experiments, case reports, conference abstracts, conference proceedings, editorial letters, guidelines or commentary; (2) duplicated studies; (3) publications for which full text was not available.

**Information sources** PubMed, Web of Science, Cochrane Library, and Embase databases

**Main outcome(s)** For all retrieved studies, pain scores on dysmenorrhea were designated as the primary outcome, including the initial pain scores and scores following dienogest treatment per the Visual Analogue Scale (VAS) .

**Quality assessment / Risk of bias analysis** We used a modified Newcastle-Ottawa Scale to assess the quality and the risk of bias of the included studies. Each study was evaluated across three categories: selection (up to three stars), comparability (four stars), and outcome (two stars). Selection was assessed based on recruitment bias, selection of consecutive patients, and power calculation. Comparability was evaluated based on adjustments for four confounding factors, including the dose of dienogest administered, concurrent treatments (analgesics and hemostatics), age under 40, and the use of other hormonal contraceptives. The primary outcome was scored based on at least three months of follow-up with

dienogest treatment and the completeness of follow-up (loss to follow-up <10%). We emphasis comparability, setting a threshold of seven stars with at least three in this category.

**Strategy of data synthesis** Stata 17.0 (StataCorp. LLC, College Station, TX, USA) and R version 4.4.0 were used for the data analyses. The heterogeneity of included studies was assessed using the Q test (I2 value). If $p > 0.1$ and $I2 \leq 50\%$, a fixed-effect model was used for meta-analysis; otherwise, a random-effect model was used. The pooled estimate of Δ (reduction in VAS scores after treatment),were calculated based on sample sizes.
Possible publication bias was assessed using funnel plots, in which Δ's were plotted against their corresponding standard errors, a measure of precision [11] and statistically with Begg's and Egger's tests. If bias is absent, small-sized studies would have the Δ estimates that are widely scattered and symmetrically about the true, yet unknown Δ, which would be approximated by larger-sized studies that provide more accurate estimates. In this case, the plot would resemble a funnel with the tip pointing roughly towards the true Δ. If a publication bias is present, the plot would be asymmetric because some negative studies are not published. Sensitivity analysis was also performed.to evaluate the impact of each study on the pooled estimate of Δ.
The comparison of distributions of continuous variables between two groups was made using the Wilcoxon's rank test. Pearson's or Spearman's rank correlation coefficient was used when evaluating correlations between two variables when both variables were continuous or when at least one variable was ordinal. To evaluate which factors were associated with the Δ, multiple linear regression analysis was used. P values of $< 0.05$ were considered statistically significant.

**Subgroup analysis** The subgroup analysis in the meta-analysis included the following aspects:
1) Baseline Severity of Dysmenorrhea:
Patients were categorized based on their baseline dysmenorrhea Visual Analog Scale (VAS) scores.
Severe Dysmenorrhea: Baseline VAS score ≥7.
Mild to Moderate Dysmenorrhea: Baseline VAS score <7.
Treatment Duration:
2) The effectiveness of dienogest was analyzed based on the duration of treatment.
Longer Treatment Duration: ≥12 months.
Shorter Treatment Duration: <12 months.
3) Age of Patients:
The impact of dienogest was analyzed across different age groups.
4) Study Type:
The analysis considered whether the studies were randomized controlled trials, observational studies, or other types of research.
5) Study Quality:
The effectiveness of dienogest was also evaluated based on the quality of the studies included in the analysis.
These subgroup analyses helped determine that dienogest was effective in reducing dysmenorrhea symptoms across various conditions, including different severities of dysmenorrhea, treatment durations, patient ages, study types, and study quality.

**Sensitivity analysis** Sensitivity analysis evaluates the robustness of research findings by systematically excluding individual studies.

**Language restriction** Our search focused on studies published in English.

**Country(ies) involved** China.

**Keywords** Adenomyosis, dienogest, dysmenorrhea.

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