Asian Journal of Health Research
Journal Homepage: https://a-jhr.com
Published by Ikatan Dokter Indonesia Wilayah Jawa Timur

OPEN ACCESS

Systematic Review/Meta-Analysis

Efficacy of Dienogest on Pelvic Pain and Dyspareunia: Comprehensive Meta-Analysis and Systematic Review

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ARTICLE HISTORY
Received: 18 November 2022
Revised: 4 February 2023
Accepted: 12 March 2023

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KEYWORD
Dienogest; Combined Oral Contraceptive; Endometriosis; Pelvic Pain; Dyspareunia

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ABSTRACT

Introduction: *Endometriosis* is a severe disorder marked by endometrial tissue outside the uterus and linked to infertility, although typically manifesting as discomfort in the form of dysmenorrhea, dyspareunia, and pelvic pain. Dienogest is indicated as a first-line hormone treatment for endometriosis-related discomfort. The aim of this study is to analyze the efficacy of Dienogest on treating pelvic pain and dyspareunia compared to placebo or combined oral contraceptives (COC) in women with endometriosis.

Methods: A systematic search is conducted in PubMed, ScienceDirect, and Google Scholar. The PRISMA 2020 rules were used to screen the articles that were obtained. For the review, studies that examined how using dienogest in improving endometriosis were exposed to were taken into consideration. In a meta-analysis utilizing a random-effects model, odds ratios with their 95% confidence intervals (CI) were provided.

Results: Five studies that met the criteria for inclusion were determined to be pertinent to the association between using dienogest in improving endometriosis (n=711). The Dienogest group had substantially improve pelvic pain with a mean difference of 1.01 (95% CI 1.2, 0.82; p<0.00001) and dyspareunia with a mean difference of 0.58 (95% CI 1.09, 0.08; p=0.02) compared to placebo. Compared to combined oral contraceptives, COC had substantially improves dyspareunia with a mean difference of 0.99 (95% CI 0.62, 1.37; p<0.00001) and pelvic pain with a mean difference of 1.15 (95% CI 0.23, 0.83; p=0.01).

Conclusion: Dienogest should be considered as an alternate treatment for endometriosis-related symptoms. In double-blind research, DNG efficacy was compared to placebo.

Cite this as: Sutrisno S, Firdaus WA (2023) Efficacy of Dienogest on Pelvic Pain and Dyspareunia: Comprehensive Meta-Analysis and Systematic Review. *Asian J Heal Res.* 2 (1): 89–95. doi:https://doi.org/10.55561/ajhr.v2i1.73

INTRODUCTION

Endometriosis is a severe disorder marked by endometrial tissue outside the uterus [1]. It is considered an estrogen-dependent disorder that affects women during their reproductive years. Some women with endometriosis exhibit no symptoms. Nonetheless, it affects several women's physical, mental, and social health. Endometriosis is linked to infertility [2–5], although typically manifesting as discomfort in the form of dysmenorrhea, dyspareunia, and pelvic pain. Other symptoms include dyschezia and dysuria in people with bowel or bladder involvement [6,7].

Despite the great variety in the recommendations and methodological quality of the guidelines for endometriosis [8], several guidelines concur that despite the availability of surgical management options, this chronic illness requires long-term medical care. The control of symptoms is the major objective of endometriosis treatment. Therefore, endometriosis should be diagnosed based on clinical symptoms, and empirical therapy with hormonal therapies is advised for women with suspected symptoms [9].

Progestins (Dienogest), a unique fourth-generation synthetic progestogen, exclusively binds to progesterone receptors. Progestins is a selective progestin advised by international standards as the first-line treatment for

long-term endometriosis care. It has high tolerability, anti-androgen action, modest hypothalamic-pituitary-ovarian (H-P-O) axis inhibition, moderate estrogen level decrease, and little effect on estrogen, sugar, salt, or lipid metabolism, and indicated as a first-line hormone treatment for endometriosis-related discomfort [10–12]. Dienogest binds to the progesterone receptor, reduces systemic gonadotropin production, and exerts local antiproliferative and anti-inflammatory effects on endometriotic lesions when administered continuously, which is extremely selective for progesterone receptors (PGRs) and limits blood estrogen levels by stopping ovulation. Additionally, it encourages death and inhibits the growth of endometriotic cells [13–15].

This review presents an expert analysis of the data regarding the use of dienogest in the long-term treatment of endometriosis compared to placebo and oral contraceptives.

MATERIAL AND METHODS

Literature Search

This systematic review and meta-analysis were carried out to ascertain the relationship. The following databases were searched using Google Scholar, ScienceDirect, and PubMed. The following Medical Subject Heading (MeSH) terms were entered individually or in combination in the search: "Dienogest" AND "Endometriosis" for this evaluation, all publications up through August 3rd, 2022, were located and evaluated. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Eligibility Criteria

The following were the inclusion criteria :

1. Experimental study
2. Studies within the last ten years
3. Subjects were women with endometriosis treated by dienogest as the case group and women with endometriosis treated by combination oral contraceptive (COC) or placebo as the control group
4. Having the same unit of measurement. If the units are different, it is equated with a standardized calculation.

However, the exclusion criteria include:

1. Experimental study, such as supplementation during the study.
2. Review articles/case series, letter in response, and conference abstract
3. Study with irrelevant titles/abstract
4. No full text available
5. Language other than English

The unit of measurement is not mentioned/ incomplete data.

Study Selection and Screening

Revman v. 5.4 exported all citations found by our search approach, and duplicate articles were removed. Two independent reviewers then evaluated the titles and abstracts of the chosen papers, and relevant research was incorporated for further analysis. Before data extraction, the whole texts of the selected papers were collected and carefully reviewed to guarantee their eligibility. If the two reviewers were unable to agree, a consensus-building meeting was organized, and the third reviewer was consulted.

Data extraction

The following data were taken from the RevMan v. 5.4 files:

1. First author's name
2. Publication year
3. Country

The following data were taken from the methodology section:

1. Endometriosis
   Endometriosis is defined as endometrial glands and stroma-like lesions outside the uterus. The lesions may be peritoneal, superficial implants or cysts on the ovary or disease with deep infiltration.
2. Dienogest
   A progestin of the fourth generation that combines the pharmacological properties of 19-nortestosterone and progesterone derivatives, offering a pronounced local effect on endometriotic lesions, with little androgenic, estrogenic, glucocorticoid, or mineralocorticoid activity and minimal impact on metabolic parameters.
3. Study design.
   Eligible studies can be in the form of case-control dan randomized-double-blind-pilot-study
4. Subject age range.
5. Gestational age range.
6. Biochemical method used.

Statistical Analysis

We compile the relevant research for each trace element in Microsoft Excel. The strength of the association between dienogest and endometriosis treatment was evaluated statistically using Review Manager (RevMan) v.5.4 and standardized mean difference (SMD) with a 95% confidence interval (CI). To measure heterogeneity, I2 was utilized. Low heterogeneity was defined as an I2 of less than 25%, moderate heterogeneity as an I2 of between 25% and 75%, and high heterogeneity as an I2 more significant than 75%.

A random-effects model was used in the research population was highly diverse. Significant P values are those with a value less than 0.05. Additionally, a subgroup analysis based on race was conducted to look

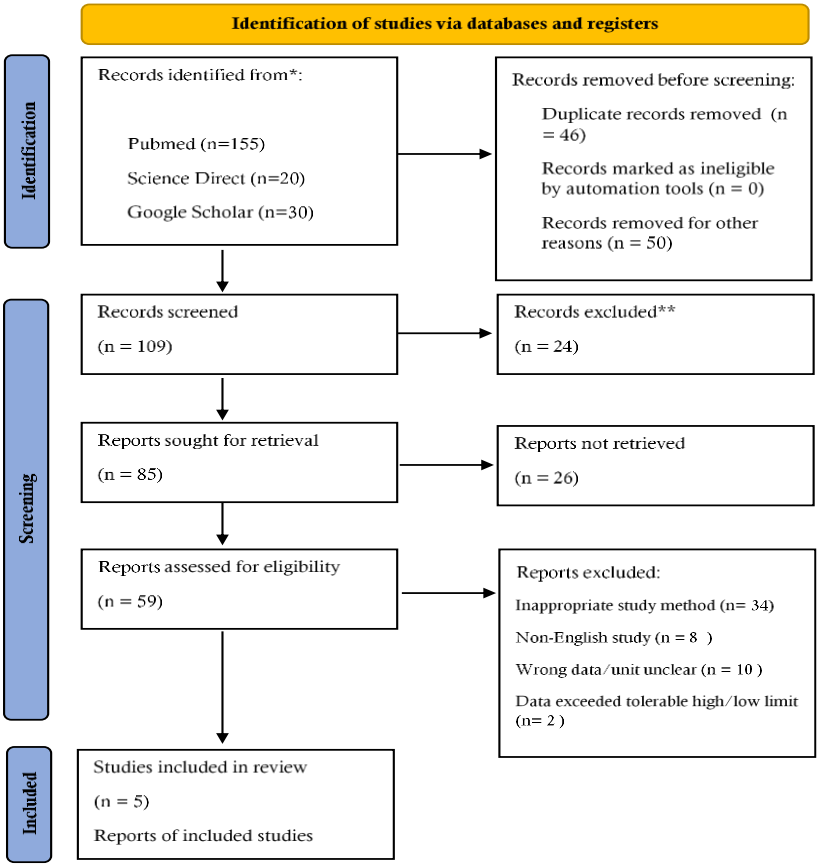


Fig. 1. PRISMA Flowchart of the Literature Selection

at potential variables that may significantly affect between-study heterogeneity if sufficient studies were available.

RESULTS

Overview of Literature Searching

Through searching databases from PubMed, ScienceDirect, and Google Scholar, 205 studies were found. After deleting duplicate titles and abstracts from 109 submissions, we evaluated the remaining 59 studies, which we then chose and examined for qualitative synthesis.

Study Characteristics

In this review, five randomized, double-blind studies were included. A total of 90 [16], 210 [17], 88 [18], 70 [19], and 253 [20] participants were enrolled in the study of dienogest for endometriosis improvement, respectively (Table 1).

Summary Mean Difference of Dienogest and Endometriosis Improvement Subgroup Results

In this sub-group analysis, three papers compared the pelvic pain improvement in endometriosis between the dienogest group and placebo, and two studies compared the pelvic pain in endometriosis between the dienogest group and combination oral contraceptives. Two studies comparing the dyspareunia in endometriosis between the dienogest group and placebo group and two studies comparing the dyspareunia in endometriosis between the dienogest group and combination oral contraceptive were included. Dienogest group had substantially reduce pelvic pain than placebo, with a mean difference of 1.01 (95% CI 1.2, 0.82; p<0.00001), which is dienogest treatment gives an improvement in pelvic pain 1.01 (95% CI 1.2, 0.82; p<0.00001) than placebo group significantly (Fig.2).

When compared with a combined oral contraceptive, dienogest didn't give a better improvement in pelvic pain. Combined oral contraceptive had substantially better pelvic pain change than the dienogest treatment, with a mean difference of 1.15 (95% CI 0.23, 0.83; p=0.01), which is COC treatment gives a better improvement in pelvic pain 1.15 (95% CI 0.23, 2.08; p=0.01) than dienogest group significantly (Fig.3). The Dienogest group had substantially better dyspareunia improvement than the placebo group, with a mean difference of 0.58 (95% CI

Table 1. Characteristics of the included study

Country	Authors	Year	Study Design
Iran	Niakan, G et al. [16]	2021	Randomized, double blind, placebo-controlled clinical trial
Korea	Kim, S et al.[17]	2016	Non-randomized prospective study
Iran	Mehdizadeh, Abolfazl et al.[18]	2018	Case-control
Lebanon	El taha, et al. [19]	2021	Randomized, double-blinded, parallel clinical trial
China	Lang, Jinghe et al. [20]	2017	Randomized, double-blind, placebo-controlled multicenter

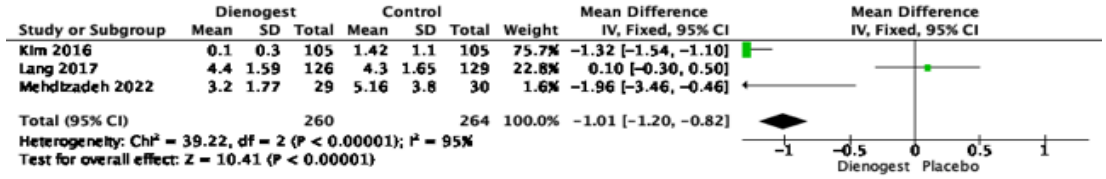


Fig 2. Summary mean difference of dienogest for pelvic pain improvement in endometriosis of dienogest and placebo group

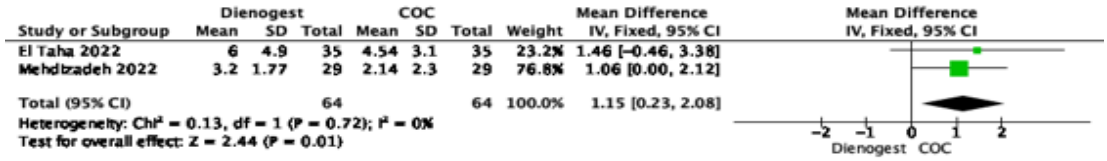


Fig 3. Summary SMD of dienogest for pelvic pain improvement in endometriosis of dienogest and COC group

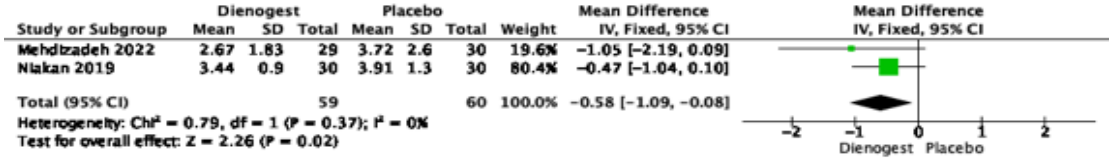


Fig 4. Summary SMD of dienogest for dyspareunia improvement in endometriosis of dienogest and placebo group

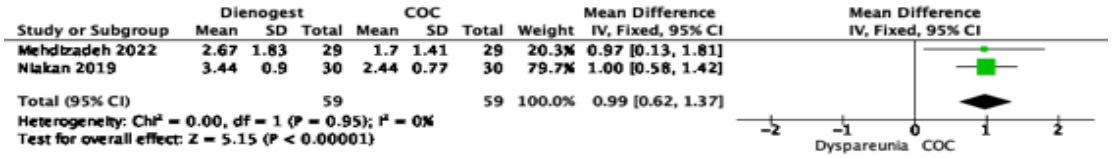


Fig 5. Summary SMD of dienogest for dyspareunia improvement in endometriosis of dienogest and COC group

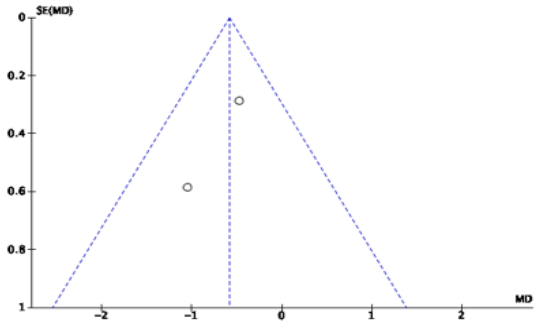


Fig. 6. Funnel plot dienogest and pelvic pain improvement in dyspareunia of dienogest and placebo group

1.09, 0.08; p=0.02) (Fig.4). When compared to combined oral contraceptive, dienogest also didn't improve dyspareunia. Combined oral contraceptives had substantially better dyspareunia improvement than the dienogest treatment, with a mean difference of 0.99 (95% CI 0.62, 1.37; p<0.00001), which is COC treatment gives a better improvement in dyspareunia with a mean difference of 0.99 (95% CI 0.62, 1.37; p<0.00001) than dienogest group significantly (Fig.5). The funnel plot was created that demonstrated symmetry, indicating that publication bias was acceptable and unlikely to impact findings (Fig.6).

DISCUSSION

Endometriosis is a common condition that affects 5-15% of women of reproductive age. It lowers their quality of life by causing symptoms like pelvic pain and frequent recurrence of symptoms following discontinuation of treatment with conservative therapy [21]. Chronic pelvic pain, dysmenorrhea, dyspareunia, dysuria, and dyschezia are all symptoms of endometriosis-related discomfort. Detailed counselling and a trial of appropriate analgesics, progestogens, or combined oral contraceptive tablets should be part of the empirical therapy of symptoms presumed to be brought on by endometriosis without a confirmed diagnosis.

Numerous practitioners believe that endometriosis should be treated empirically before or after laparoscopic confirmation of the condition. Compared to medical therapy, surgery is intrusive and costly, involves a risk of morbidity, and may prove to be only partially or temporarily successful [11,22–25]. Analgesic and anti-inflammatory medications, combination contraceptive tablets, and progestins such as medroxyprogesterone acetate or norethisterone are included in first-line therapy. Dienogest, a synthetic oral progestin with no androgenic, glucocorticoid, or mineralocorticoid action. It has high progestational and mild anti-gonadotrophic effects [26–29]. A previous randomized clinical study shows that oral dienogest reduces pelvic discomfort in women with endometriosis better than in a placebo [6,30–32]. Dienogest was shown to be similarly effective in reducing pelvic pain in clinical studies that compared oral dienogest with gonadotropin-releasing hormone (GnRH) agonists for 16 weeks or 24 weeks in women with endometriosis [13].

This study revealed conclusively that dienogest is an effective treatment for pelvic discomfort and dyspareunia associated with endometriosis. Dienogest treatment gives a better improvement in pelvic pain with a mean difference of 1.01 (95% CI 1.2, 0.82; p<0.00001) and dyspareunia with a mean difference of 0.58 (95% CI 1.09, 0.08; p<0.02) than placebo group significantly. It is relevant with study between week 12 and week 12, the dienogest and control groups experienced mean VAS score decreases of 27.4 mm and 15.1 mm, respectively. This represents a significant score difference of 12.3 mm in favor of dienogest (P<0.0001) [33–36]. Moreover, DNG treatment significantly improve dyspareunia 0.58 (95% CI 1.09, 0.08; p < 0.02) than placebo. It is relevant with study at three months (p<0.05). The research group showed a slight improvement in chronic pelvic discomfort, dysmenorrhea, and dyspareunia; this change increased from six to twenty-four months (p<0.001) [37–40].

However, when compared with a combined oral contraceptive, COC treatment significantly improve pelvic pain and dyspareunia, with a mean difference of 0.99 (95% CI 0.62, 1.37; p<0.00001) and 0.99 (95% CI 0.62, 1.37; p<0.00001), respectively, than the dienogest group. This study is a crucial component of evidence-based medical therapy prescription for treating the pain associated with endometriosis.

CONCLUSION

In summary, endometriosis is a chronic medical condition that not only negatively affects a woman's quality of life but has a huge economic impact, often due to delay in diagnosis, the need for ongoing treatment, and high recurrence rates. In double-blind research, DNG efficacy was compared to placebo. Dienogest should be considered as an alternate treatment for endometriosis-related symptoms.

ACKNOWLEDGMENT

The authors thank all the authors of the articles reviewed in this paper.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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