

Dienogest Therapy Against the Combined Oral Contraceptive Pill in Deep Infiltrating Endometriosis Cases: A Systematic Review and Meta-Analysis

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Abstract

Objectives: Deep endometriosis (DE) is a common disease in 15%–45% of childbearing-age women. Combined oral contraceptive pill (COCP) and dienogest have been used for decades to treat many forms of endometriosis after laparoscopy surgery. This study aims to assess the latest evidence on the effect of dienogest compared with the COCP on the pain scores of dysmenorrhea, dyspareunia, and dyschezia in DE patients.

Materials and Methods: Data from 1363 samples of 9 research literature were taken. The postlaparoscopy surgical patients are divided into the dienogest group and the COCP group. The main symptoms were assessed using a visual analog scale for dysmenorrhea, dyspareunia, and dyschezia in addition to the demographic data from patients of the 2 study groups being compared.

Results: Seven studies show significant differences in dysmenorrhea scores between the dienogest group and the COCP group. Dyspareunia scores in cases of postoperative endometriosis implants showed 6 studies with lower dyspareunia scores in the dienogest group than the COCP group, while 3 other articles showed higher dyspareunia scores in the dienogest group than in the COCP group. Assessment of the risk of bias in the meta-analysis of the therapeutic effectiveness of the Egger regression test shows nonsignificant results which proves no tendency for publication bias ($t = 1.111$; $df = 7.00$; $P = 0.303$).

Conclusion: Dienogest is an effective pain treatment and it is effective for a subgroup of patients with endometriosis and pelvic pain. It is well tolerated as a pain treatment in adenomyosis patients without complications of severe uterine enlargement or severe anemia.

Keywords: Combined oral contraceptive pill, deep endometriosis, dienogest

INTRODUCTION

Deep endometriosis (DE) is a chronic pain, in which women experience the symptoms of pain, such as dysmenorrhea, chronic pelvic pain, and dyspareunia. Although medical treatment is helpful for many women and it helps to relieve the symptoms in 50%–80% of cases, 20% of patients still show the symptoms even though laparoscopic surgery has been conducted.^[1,2] In patient-seeking pregnancy,

optimal management completed endometriosis surgery is mandatory. Although laparoscopic surgery using laparoscopy three-dimensional (3D) technology has more advantages with obvious advantages in depth perception, precision, and surgical strain than laparoscopy 2D technology, there is no significant difference in previous research.^[3–7] Current guidelines and literature about endometriosis are

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mentioned on the article as an international terminology for endometriosis.^[8,9]

In this case, supportive medical treatment is a necessity to improve women's quality of life. 70% of women suffer from lower abdominal quadrant pain accompanied by severe dysmenorrhea, dysuria, dyspareunia, and even dyschezia and 48% found an endometrium such as tissue extending the peritoneal surface that invades adjacent structure and disruption of normal anatomy in patients with recurrent pelvic pain with infertility.^[1,10]

There are many medical treatments recommended to eliminate chronic pelvic pain for DE lesions. The combined oral contraceptive pill (COCP) can be well tolerated since the metabolic effect is low and it is usually used to suppress ovulation and reduce menstrual blood flow in endometriosis. Apart from that, injectable therapy in the form of anti-gonadotropin analog hormone (GnRH-A) can also be given but it triggers pharmacological menopause by suppressing ovulation and reducing ovarian steroidogenesis and its use in the long term will have a risk of decreasing bone mineral density.^[1,11]

To treat the symptoms related to DE, the administration of progestin preparations, in fact, can inhibit ovulation, so it can reduce the levels of estrogen serum resulting in endometrial atrophy. Furthermore, although they occur, they can reduce the levels of peritoneal inflammation. In addition, although progestins, such as desogestrel and medroxyprogesterone acetate can cause some androgen-related side effects; newer-generation progestins, such as dienogest which is a fourth-generation semisynthetic selective progestin, are well tolerated and it has the pharmacological features of semisynthetic selective progestins. Inside dienogest is 19-nortestosterone, which has greater specificity in binding to progesterone receptors and it offers effects on endometriotic lesions, with little androgenic, estrogenic, glucocorticoid, or mineralocorticoid activity.^[5,12,13] Recently, the efficacy of dienogest (Visanne) in the management of endometriosis has been demonstrated. Dienogest is a synthetic progestin, a 19-nortestosterone derivative, with good oral bioavailability and high selectivity for progesterone receptors.^[14-16]

It has anti-ovulatory, antiproliferative, and inhibitory effects. Dienogest has proven to be able to inhibit nerve growth factor expression induced by tumor necrosis factor-alpha or interleukin beta, a key mediator in generating pain associated with endometriosis to inhibit nerve growth factor expressions induced by tumor necrosis factor-alpha or interleukin beta, a key mediator in generating pain associated with endometriosis.^[14,15]

The previous study has reported that dienogest not only holds down the ovulation and gives the effect of antiproliferative, but also inhibits the secretion of cytokines in endometrial stromal cells, leading to a reduction in pain associated with DE and adenomyosis. Lina el taha *et al.* mentioned that 70 women with endometriosis-associated chronic pelvic pain, dysmenorrhea, or both for > 6 months were randomized to be given either dienogest (Visanne) 2 mg/day or COCP (Yasmin, 0.03 mg ethinyl estradiol and 3 mg drospirenone) for 24 weeks.^[17,18]

This study aims to assess the latest evidence of the clinical effectiveness of supportive medical treatment using the selected medication dienogest compared to contraceptive pills to control severe dysmenorrhea, dysuria, dyspareunia, and even dyschezia.

MATERIALS AND METHODS

This study is using a systematical review and meta-analysis conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and based on the Cochrane Handbook for Systematic Reviews of Interventions that involve postsurgery adult patients of reproductive age with a laparoscopic surgery followed with medical therapies for the management of endometriosis-related pain to cure the pelvic pain related to endometriosis, dysmenorrhea score, dyschezia score, and dyspareunia score from various races. This systematic study and meta-analysis are registered with the ID: CRD42023173130 on October 27, 2023.

This systematic review is prepared under the recommendations of the Extension Statement and shown in Figure 1. As this is a systematic review and meta-analysis; therefore, formal ethical approval is not required.

Research strategy

A comprehensive search in five electronic databases had been done from 2021 to 2023: PubMed, SCOPUS, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar. Besides that, clinical-registered research is conducted (<http://clinicaltrial.gov>) for a trial that is potentially unpublished. Combinations of different keywords have been used as follows: ("Endometriosis OR "Deep Infiltrating Endometriosis" OR "Severe Endometrioma" OR "DIE"), ("Laparoscopy Dissection" OR ("Laparoscopy Radical Exaction" OR Laparoscopy Deep Infiltrating Saver") OR ("Gonadotrophin Releasing Hormone") OR "(GnRH Analog)" OR ("dienogest") OR ("Visanne") OR ("Nelandoz") OR "kontrasepsi hormonal kombinasi OR ("continuous combined oral contraceptive pill (CCOCP)"/"COCP") that not only from Europe sample but also Turkey, Iran, Brazil, and

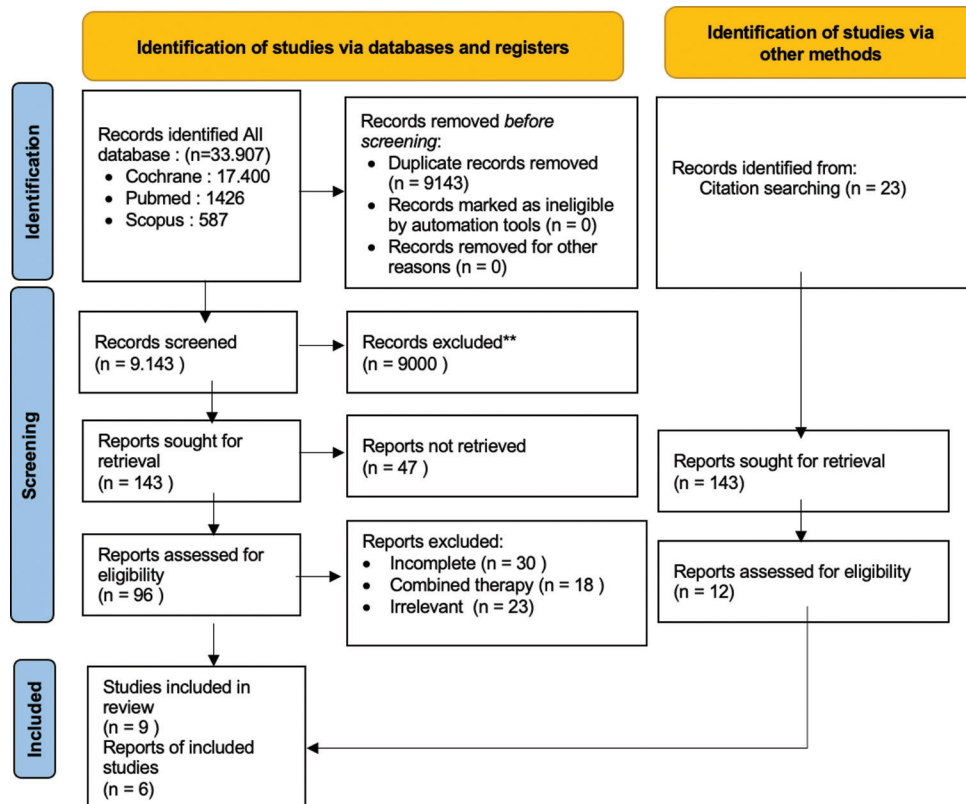


Figure 1: Shows the PRISMA graph. Network plot describing direct evidence between interventions

Indonesia. The limitation of this research is that the author did not mention the surgery that had been performed on all participants before their treatments after eliminating the duplication, a recording is done which is taken from EndNote 20, iOS version continued with the infiltration of complete text from the study which is potentially fulfilling the requirements.

Inclusion and exclusion criteria

We include a random controlled trial (RCT) which is conducted according to these criteria: (1) a study involving postsurgery adult patients of reproductive age with a laparoscopically documented diagnosis of DIE; (2) a study assessing the efficacy of any of the following medical therapies for the management of endometriosis-related pain: Combined hormonal contraceptives and dienogest; and (3) a study reporting these results: Changes on the total score of pelvic pain related to endometriosis, dysmenorrhea score, dyschezia score, and dyspareunia score and various races.

Data extraction and efficacy size

From 9143 researchers, 9 independent researchers take the data of this study, then, input the data, and every argument is solved by discussion. The domain for the data extraction involves the characteristics from the research summary attached, characteristics of the baseline population studied, domains of risk of bias, and study outcomes. The measurement

of the study result being attached is: (1) dysmenorrhea pain, dyschezia, and dyspareunia 6 months after surgery, assessed with a 10 cm visual analog scale (VAS).

Risk of bias assessment

Two independent reviewers (authors 2 and 4) assess the RCT quality completing the requirements using the tables of quality risk assessment provided by Cochrane's compliance with systematic reviews of interventions. Cochrane risks in bias assessment include the following domains: sequence generation (selection bias), concealment of sequence allocation (selection bias), participants and personnel blinding (performance bias), outcome assessment blinding (detection bias), incomplete outcome data (attrition bias), selective reporting of results (reporting bias), and other potential sources of bias. Assessments are categorized as "Low risk," "High risk," or "Unclear risk bias."

RESULTS

Results of literature research

There are 33,907 studies about the treatment of endometriosis and adenomyosis after surgery coming from Cochrane (17,400 studies), PubMed (1,426 studies), and Scopus study (587 studies); but only 9,143 studies are found in the online bibliography matching into the screening searching result. From that number, 143 are complete texts, with 96 eligible

RCTs that all participants received medication after laparoscopy surgery. However, after sorting them out, there are only 9 studies (1363 patients) included in this systematic review and meta-analysis of this network. All participants are divided into 2 groups with double-blind control trials receiving medication either dienogest or COCP.

Assessment of the risk of bias from the articles used in the meta-analysis of the effectiveness of dienogest therapy versus contraceptive pills in cases of postsurgical endometriosis implants

Assessments of the risk of bias in the studies included in the systematic review and meta-analysis of dienogest therapy against the COCP in the case of postintrasurgery endometriosis cases are shown in Table 1.

There are 9 articles related to the effectiveness of dienogest therapy against contraceptive pills in cases of postoperative endometriosis implants. In Table 1, it can be seen that from the 9 articles, 3 articles are found with a high risk of bias; they are: Antonio Maiorana 2022, BilgehanSaglikGokmen 2023, and Tolga Karacan 2020. This is because the three studies are not clinical trials but observational studies. In Table 1, it also appears that there are 2 studies by Cihan Kaya 2021 and Purwanto 2021 whose risk of bias is categorized as unclear. This is due to not providing information regarding the randomization and concealment methods of the random order of allocation to research groups. Apart from that, blinding is not carried out in these two studies. Next, there are 4 articles which have a low risk of bias; they are: GelarehNiakan 2021, Lina El Taha 2021, Ticiana A. A. Miraa 2021, and Yutaka Osuga 2017.

Meta-analysis of the effectiveness of dienogest therapy against contraceptive pills in cases of postoperative endometriosis implants

Dysmenorrhea score

The comparison of dysmenorrhea score in the group of dienogest with the group of combined oral contraceptives is shown in Table 2.

We can see from the table that there are 9 studies used in the meta-analysis of the effectiveness of dienogest therapy against contraceptive pills in cases of postoperative endometriosis implants. The dysmenorrhea score of those 6 studies (Antonio Maiorana 2022, BilgehanSaglikGokmen 2023, Cihan Kaya 2021, Lina El Taha 2021, Purwanto 2021 dan Ticiana A. A. Miraa 2021) in the dienogest group is lower than that in the COCP group. In the other 3 articles (GelarehNiakan 2021, Tolga Karacan 2020 dan Yutaka Osuga 2017), the dysmenorrhea score in the dienogest group is higher than it is in the COCP group.

Meta-analysis was carried out using a random effect model because the data are heterogeneous ($Q = 63,655$, $df = 8$; $I^2 = 87,432$). Based on the data, it is revealed that 7 studies show significant differences of dysmenorrhea scores in the dienogest group compared with the COCP group, except for 2 studies (Lina El Taha 2021 dan Ticiana A. A. Miraa 2021) due to the range of 95% interval of trust covers number 1. Overall, the whole dysmenorrheas score in the dienogest group is significantly lower than the COCP group with a mean difference of $-0,473 \pm 0.109$ ($P < 0.001$).

Table 1: Characteristics of study data

Author	Design	Population	Treatment (dosage)	Control (dosage)	Number of Patients	Age (average)	Outcome variable
Antonio Maiorana <i>et al.</i> 2023	Observasional Study	Adult with endometriosis	Dienogest 2mg	COCP (EE 35 µg plus norethisterone 1 mg)	128	31,6	Post-treatment VAS score
Bilgehan Saglik Gokmen <i>et al.</i> 2023	Prospective Observasional Study	Premenopausal women with endometriosis	Dienogest 2mg	COCP (EE 35 µg plus norethisterone 1 mg)	200	41,5	Post-treatment VAS score
Cihan Kaya <i>et al.</i> 2021	Open Label-RCT	Women with pelvic pain	Dienogest 2mg	COCP (EE 35 µg plus norethisterone 1 mg)	171	40	Post-treatment VAS score
Gelareh Niaken <i>et al.</i> 2021	Open Label-RCT	Women with symptomatic endometriosis	Dienogest 2mg	COCP (EE 35 µg plus norethisterone 1 mg)	115	29,7	Post-treatment VAS score
Lina El Taha <i>et al.</i> 2021	Double blind-RCT	Adult with endometriosis	Dienogest 2mg	COCP (EE 35 µg plus norethisterone 1 mg)	127	36,9	Post-treatment VAS score
Joko Purwanto <i>et al.</i> 2020	Open Label-RCT	Women with pelvic pain	Dienogest vs COCP	COCP (EE 35 µg plus norethisterone 1 mg)	204	44,6	Post-treatment VAS score
Triciaana AA Miraa <i>et al.</i> , 2020	Double blind-RCT	women with endometriosis	Dienogest 2mg	COCP (EE 35 µg plus norethisterone 1 mg)	126	46,5	Post-treatment VAS score
Tolga Karacan <i>et al.</i> , 2020	Retrospective Cohort	Infertile women with endometriosis	Dienogest 2mg	COCP (EE 35 µg plus norethisterone 1 mg)	154	32,8	Post-treatment VAS score
Yutaka Osuga <i>et al.</i> , 2017	Double blind-RCT	Patient with endometriosis	Dienogest 2 mg	COCP (EE 35 µg plus norethisterone 1 mg)	138	32,1	Post-treatment VAS score

Table 2: Dysmenorrhea Score in the Dienogest group and combined oral contraceptive group

Study name	Dienogest		COCP		Difference Mean±SD
	Mean±SD	n	Mean±SD	n	
Antonio Maiorana 2022	6,24±4,23	128	8,3±2,53	128	-2,0±0,44
Bilgehan Saglik Gokmen 2023	3,8±2,70	200	6,9±19,12	200	-3,1±1,37
Cihan Kaya 2021	4,9±4,10	171	6,7±3,30	171	-1,8±0,40
Gelareh Niakan 2021	4,8±0,80	115	4,5±1,20	115	+0,3±0,13
Lina El Taha 2021	5,5±3,10	127	6,1±3,40	127	-0,6±0,41
Purwanto 2021	4,6±0,80	204	4,9±0,80	204	-0,3±0,08
Ticiana A.A. Miraa 2021	1,8±x2,95	126	1,9±0,86	126	-0,2±0,27
Tolga Karacan 2020	9,0±3,90	154	6,0±1,70	154	+3,0±0,34
Yutaka Osuga 2017	5,9±1,70	138	4,4±1,10	138	+1,5±0,17

Table 3: Dyschezia score in Dienogest group and combined oral contraceptive group

Study name	Dienogest		COCP		Difference Mean±SD
	Mean±SD	n	Mean±SD	n	
Antonio Maiorana 2022	2,9±4,09	128	3,8±4,02	128	-0,9±0,51
Bilgehan Saglik Gokmen 2023	3,7±3,10	200	4,4±1,30	200	-0,7±0,24
Cihan Kaya 2021	1,1±2,80	171	1,3±2,20	171	-0,2±0,27
Gelareh Niakan 2021	7,0±3,0	115	10±3,30	115	-3,0±0,42
Lina El Taha 2021	3,8±3,50	127	3,4±3,70	127	0,4±0,45
Purwanto 2021	4,6±0,80	204	4,9±0,80	204	-0,3±0,08
Ticiana A.A. Miraa 2021	4,8±4,09	126	3,7±3,98	126	1,1±0,51
Tolga Karacan 2020	5,0±2,10	154	5,0±1,30	154	-0,0±0,20
Yutaka Osuga 2017	4,5±2,80	138	5,9±20,00	138	-1,4±0,29

Table 4: Dyspareunia Score in the Dienogest group with the combined oral contraceptive group is shown in table 4

Study name	Dienogest		COCP		Difference Mean±SD
	Mean±SD	n	Mean±SD	n	
Antonio Maiorana 2022	6,0±3,89	128	5,8±3,87	128	+0,2±0,49
Bilgehan Saglik Gokmen 2023	3,4±1,80	200	5,2±3,80	200	-1,8±0,30
Cihan Kaya 2021	1,8±3,00	171	0,4±1,30	171	+1,4±0,25
Gelareh Niakan 2021	6,0±2,20	115	7,0±2,50	115	-1,0±0,31
Lina El Taha 2021	6,1±2,20	127	5,9±2,90	127	+0,2±0,32
Purwanto 2021	4,9±0,80	204	4,9±0,80	204	0,0±0,08
Ticiana A.A. Miraa 2021	1,8±2,95	126	1,3±2,77	126	+0,5±0,36
Tolga Karacan 2020	5,0±1,60	154	7,0±1,84	154	-2,0±0,20
Yutaka Osuga 2017	3,4±2,80	138	4,5±2,90	138	-1,1±0,34

Dyschezia score

The comparison of dyschezia score in the dienogest group and the combined oral contraceptive group is shown in Table 3.

Table 3 shows the dyschezia scores from 9 studies used in the meta-analysis of the effectiveness of dienogest therapy versus contraceptive pills in cases of postoperative nometrios implants. There are 7 studies (Antonio Maiorana 2022, BilgehanSaglikGokmen 2023, Cihan Kaya 2021, Gelareh Niakan 2021 Purwanto 2021, TolgaKaracan 2020, and Yutaka Osuga 2017) with dyschezia scores in the dienogest group that were lower than those in the COCP group. Meanwhile, in 2 other articles (Lina El Taha 2021 and Ticiana A. A. Miraa

2021), the dyschezia score for the dienogest group was higher than the COCP group.

Meta-analysis was carried out with a random effect model because the data are heterogeneous ($Q = 41,278$; $df = 8$; $I^2 = 80,619$). Based on the data, it is known that 7 studies show that the difference in dyschezia scores between the dienogest group and the COCP group is significant, except for 2 articles (Cihan Kaya 2021 and Lina El Taha 2021) because the 95% confidence interval range covers the number 1. Overall, the dyschezia score in the dienogest group was significantly lower than the COCP group with a mean difference of -0.314 ± 0.089 ($P < 0.001$).

Dyspareunia score

A comparison of the dyspareunia score in the dienogest group with the combined oral contraceptive group is shown in Table 4.

Table 4 shows the dyspareunia score from 9 studies used in the meta-analysis of the effectiveness of dienogest therapy versus contraceptive pills in cases of postoperative endometriosis implants. There are 6 studies (Bilgehan Saglik Gokmen 2023, 2021, GelarehNiakan 2021, Purwanto 2021, TolgaKaracan 2020, and Yutaka Osuga 2017) of dyspareunia, in which the dienogest group's score is lower than that of the COCP group. Meanwhile, in 3 other articles (Antonio Maiorana 2022, Cihan Kaya and Lina El Taha 2021), the dyspareunia score for the dienogest group is higher than the COCP group.

The results of the meta-analysis comparing dyspareunia scores in the dienogest group with the COCP group are shown here, it is found that the meta-analysis is carried out with a random effect model because the data are heterogeneous ($Q = 79.295$; $df = 8$; $I^2 = 89.991$). Based on the data, it is known that 6 articles show that the difference in dyspareunia scores between the dienogest group and the COCP group is significant, except for 3 articles (Antonio Maiorana 2022, Lina El Taha 2021 and Ticiana A. A. Miraa 2021) because the 95% confidence interval range covers the number 1. Overall, the dyspareunia score in the dienogest group is significantly lower than in the COCP group with a mean difference of -0.384 ± 0.045 ($P < 0.001$).

Based on the results of the meta-analysis, it can be seen that the dysmenorrhea, dyschezia, and dyspareunia scores in the dienogest group are significantly lower than those in the COCP group.

Risk of publication bias

In the funnel plot, in Figure 2, it can be seen that the data are not symmetrical due to the research with the results providing a larger size of effect than other studies, but the results of the analysis using the Egger regression test show results that

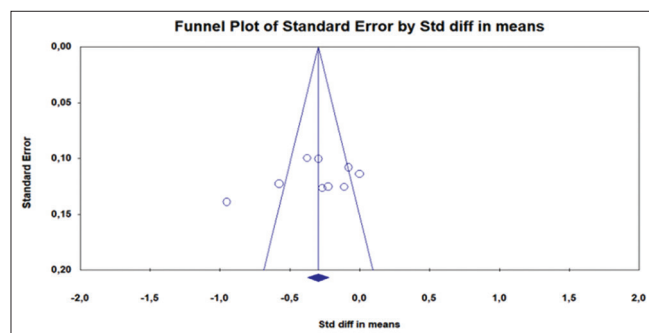


Figure 2: Funnel plot diagram to assess publication bias in meta-analysis of the effectiveness of dienogest therapy versus contraceptive pills in post-surgical cases of susuka endometriosis

are not significant. This proves that there is no potential for publication bias ($t = 1.111$; $df = 7.00$; $P = 0.303$).

Quality of evidence

The quality of evidence from the meta-analysis of the effectiveness of dienogest therapy against contraceptive pills in cases of post-surgical endometriosis implants is all moderate.

DISCUSSION

Due to the negative impacts caused by endometriosis surgery in the form of ovarium damage and the decrease of fertility level, continuous medical treatment is mandatory as postsurgical supporting therapy to prevent recurrence and chronic pelvic pain. Combined contraceptive pills, such as medroxyprogesterone acetate or norethisterone, are used as the medical treatment and known as long-term endometriosis treatment, which is cheap, effective, and can be well-tolerated.^[17,19-21] Another study compares the dienogest and the progestin norethindrone acetate (NETA) derivative 19-nortestosterone in women with endometriosis and it is found as a statistically significant difference in reducing the mean of dysmenorrhea scores favoring the dienogest group. Hence, there is no significant improvement in quality-of-life scores or sexual function scores.^[3,8]

The results from those 9 studies have evaluated long-term use of dienogest up to 52–53 weeks and reported that dienogest clinically improves pelvic pain in patients with previous laparoscopy surgery-related symptoms with a reduction in VAS scores but most patients suffer for abnormal menstrual bleeding as a side effect for dienogest.

In 6 studies conducted by Antonio Maiorana 2022, Bilgehan Saglik Gokmen 2023, Cihan Kaya 2021, Lina El Taha 2021, Purwanto 2021, and Ticiana A. A. Miraa 2021 on the therapeutic effect and the safety of dienogest 2 mg/day intake evaluated in 956 women using endometriosis-related VAS scores, it can be concluded that the decrease in the mean of VAS score is well tolerated with few side effects in favor of dienogest over combined contraceptive pills after 24 weeks of treatment. Overall, from the results of the study population and comparing them with 96 previous literatures, we observe significant differences in pain-related symptom scores of DIE in patients who revived dienogest than the COCP. And also, there is a significant difference in pain reduction in dysmenorrhea, dyspareunia, dyschezia, and pelvic pain scores in the dienogest group than the COCP group due to the effect of dienogest that reduce the secretion of inflammatory cytokines or reduce endometrial foci by suppressing the ovulation hormone despite the risk of abnormality.^[6,15,17]

Endometriosis is an estrogen-dependent disease known to be effective in controlling the symptoms of endometriosis patients, especially chronic pelvic pain symptoms. There are several hormonal drug options, such as GnRH agonists, low-dose oral contraceptives, and levonorgestrel intrauterine systems, but there are limitations to the duration of GnRH agonist treatment due to adverse effects associated with low estrogen symptoms.^[21,22] Low-dose oral contraceptives should be administered with caution in patients aged 40 years or older due to the risk of thrombosis, and the levonorgestrel intrauterine system has abnormal bleeding problems, and the risk of pelvic inflammatory disease.^[23-25] Dienogest proved that it improves pain relief in patients with endometriosis, especially for patients seeking fertility preservation, across a wide range of ages, and demonstrated safety assuming that appropriate consideration is given to irregular uterine bleeding and anemia.^[26-29] However, the results of this study are limited to 16 weeks of treatment, and data regarding longer treatment periods are needed.^[17,19,24,27,29]

CONCLUSION

These nine studies emphasize that dienogest is an effective treatment for pain symptoms caused by adenomyosis under double-blind, placebo-controlled conditions. Due to reports of the risk of irregular heavy uterine bleeding and anemia associated with dienogest, endometriosis patients with severe uterine enlargement and severe anemia are excluded from the study. These 9 studies also show that dienogest is well tolerated despite a high incidence of irregular genital bleeding. Dienogest is effective for the subgroup of patients with endometriosis and pelvic pain and is well tolerated as a symptomatic treatment of pain in DE patients, not accompanied by complications of severe uterine enlargement or severe anemia.

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Author contributions

Conceptualization, methodology, writing original draft preparation, review, and editing by IA, NS, ST, and BR. Data validation and analysis by IA. All authors have read and agreed to the final version of the manuscript.

Data availability statement

All data generated or analyzed during this study are included in this published article.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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