

A Study on the Systematic Review & Meta-Analysis of the Effectiveness of Dienogest Therapy against the Combined Oral Contraceptive Pill on Patient with Endometriosis Surgery Cases:

A Study of VAS Scores for Dysmenorrhea, Dyschesia and Dysparenia.

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Abstract

Introduction: DIE is a common disease of women of childbearing age. After laparoscopy, combined oral Contraceptive Pill (COCP) and Dienogest have been used for endometriosis. This study aims to evaluate the effect of dienogest compared with the combined oral contraceptive pill on the pain scores of dysmenorrhea, dyspareunia, and dyschezia in patients with deep infiltrating endometriosis.

Method: The data was taken from 1363 samples of 9 research literature, divided into 2 groups: the dienogest group and the group receiving the combination of contraceptive pills. The main symptoms assessed were using a visual analog scale (VAS) for dysmenorrhea, dyspareunia, and dyschezia

Result: 7 studies showed significant differences in dysmenorrhea scores between the Dienogest and CCOCP groups, except for 2 articles. For Dyspareunia Score there were 6 studies with the dyspareunia score in the Dienogest group being lower than in the combination of contraceptive pill group. In contrast, in 3 other articles, the dyspareunia score in the Dienogest group was higher than in the combination of contraceptive pill group. There were no significant differences among the study groups in terms of patient demographics. Assessment of the risk of bias in the meta-analysis of the therapeutic effectiveness of the Egger regression test showed non-significant results. This shows that there is no potential for publication bias ($t=1.111$; $df=7.00$; $p=0.303$)

Conclusion: These 9 studies firmly stated that dienogest was the effective treatment in a double-blind, placebo-controlled condition and showed that dienogest was effective and was well tolerated as a treatment for pain symptoms

Keywords: Dienogest, CCOCP, Deep Infiltrating Endometriosis.

Introduction

DIE (stadium 4-endometriosis) 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 helps to relieve the symptoms in 50-80% of cases, 20% of patients still show the symptoms even though laparoscopic surgery has been conducted. In this case, supportive medical treatment is a necessity to improve women's quality of life. 70% of women with lower abdominal quadrant pain accompanied by severe dysmenorrhea, dysuria, dyspareunia, and even dyschezia and 48% of DIE are patients with infertility.¹⁻³

There are many medical treatments recommended to eliminate chronic pelvic pain for deep implant endometriotic lesions. The Combination Oral Contraceptive Pill (CCOCP/COCP) can be well tolerated since the metabolic effect is low and it is usually used to suppress the 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 (BMD).^{4,5}

To treat the symptoms related to DIE, the administration of progestin preparations can inhibit ovulation, and reduce the levels of serum estrogen resulting in endometrial atrophy, and even though this occurs, it reduces the levels of peritoneal inflammation. 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 have the pharmacological features of semisynthetic selective progestins. The content of dienogest is 19-nortestosterone has greater specificity in binding to progesterone receptors and offers effects on endometriotic lesions, with little androgenic, estrogenic, glucocorticoid, or mineralocorticoid activity.^{2,3,6}

Recently, the efficacy of dienogest (Visanne) in the management of endometriosis has been demonstrated. Dienogest is a synthetic progestin, 19-nortestosterone derivative, with good oral bioavailability and high selectivity for progesterone receptors. It has anti-ovulatory, antiproliferative, and inhibitory effects. Dienogest has been shown to inhibit nerve growth factor expression induced by tumor necrosis factor-alpha or interleukin beta, a key mediator in generating pain associated with endometriosis by to inhibit nerve growth factor expression induced by tumor necrosis factor-alpha or interleukin beta, a key mediator in generating pain associated with endometriosis

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 deep infiltrating endometriosis and adenomiosis. Lina el taha et al mention that Seventy women with endometriosis-associated chronic pelvic pain, dysmenorrhoea, or both for >6 months were randomized to either dienogest (Visanne) 2 mg/day or CCOCP (Yasmin, 0.03 mg ethinyl estradiol and 3 mg drospirenone) for 24 weeks. ⁶⁻⁸

This study aims to evaluate 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.

Method of Material

This study is a systematical review and meta-analysis according to the standard recommended by Cochrane Handbook of Systematic Reviews of Interventions that involves post-surgery adult patients of reproductive age with a laparoscopic surgery that following 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 review is prepared under the recommendations of the Extension Statement because this study is a systematic review and meta-analysis, formal ethical approval is not required.

Searching Strategy

A comprehensive search in these five electronic databases has been done from 2021 to 2023: PubMed, SCOPUS, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar. Besides that, a clinical-registered search 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 (“CCOCP”/”COCP”) that not only from Europe sample but also Turkey, Iran, Brasil and Indonesia. The limitation of this research is that the author didn’t mention the surgery that has had all participants done before their medication.

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. This systematic study and meta-analysis are registered with the ID: CRD42023173130 on 27 October 2023.

Inclusion and exclusion criteria

We include a random controlled trial (RCT) which is conducted according to these criteria: (1) a study involving post-surgery 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 (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 which is then input, 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

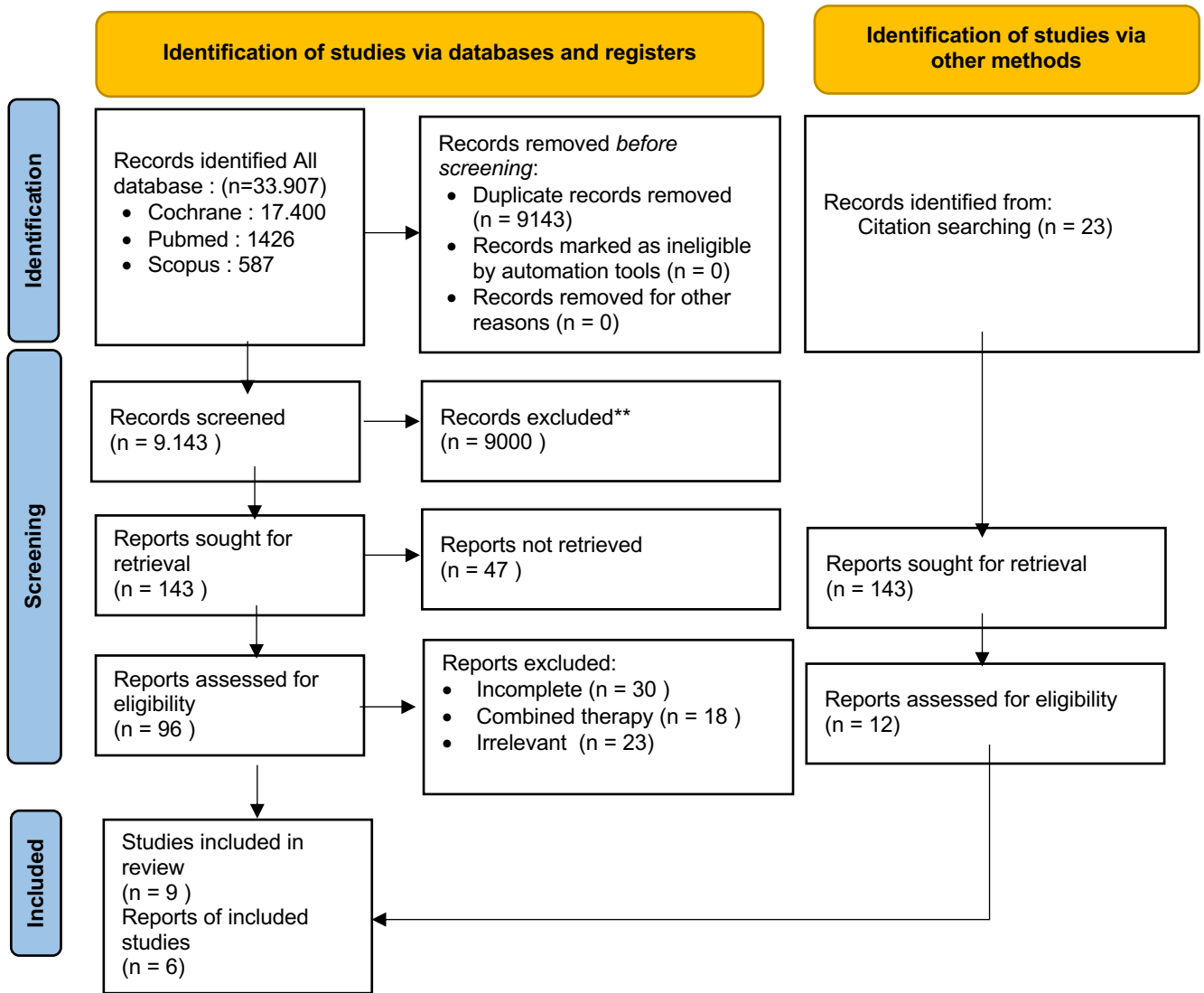
Two independent reviewers (authors 2 and 4) assessed the RCT quality completing the requirements using the tables of quality risk assessment provided by Cochrane's compliance with systematic reviews of interventions. Cochrane risks in bias assessment include the following domains: sequence generation (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

A. Results of Literature Research

There are 33.907 studies about the treatment endometriosis and adenomyosis after surgery that came from Cochran (17.400 studies), PubMed (1426 studies) and Scopus study (587 studies), but only 9143 studies were found in the online bibliography match 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 conducting selection, there are only 9 studies (1363 patients) included in this systematic review and meta-analysis of this network all participant divided into 2 groups with double blind control trials received medication either dienogest or COCCP.



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

Table 1. Characteristics of study data

No	Author	Design	Population	Treatment (dosage)	Control (dosage)	Number of Patients	Age (average)	Outcome variable
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1	Antonio Maiorana et al 2023	Observasional Study	Adult with endometriosis	Dienogest 2mg	CCOCP (EE 35 µg plus norethister one 1 mg)	128	31,6	Post-treatment VAS score
2	Bilgehan Saglik Gokmen et al 2023	Prospective Observasional Study	Premenopausal women with endometriosis	Dienogest 2mg	CCOCP (EE 35 µg plus norethister one 1 mg)	200	41,5	Post-treatment VAS score
3	Cihan Kaya et al 2021	Open Label-RCT	Women with pelvic pain	Dienogest 2mg	CCOCP (EE 35 µg plus norethister one 1 mg)	171	40	Post-treatment VAS score
4	Gelareh Niaken et al 2021	Open Label-RCT	Women with symptomatic endometriosis	Dienogest 2mg	CCOCP (EE 35 µg plus norethister one 1 mg)	115	29,7	Post-treatment VAS score
5	Lina El Taha et al 2021	Double blind-RCT	Adult with endometriosis	Dienogest 2mg	CCOCP (EE 35 µg plus norethister one 1 mg)	127	36,9	Post-treatment VAS score
6	Joko Purwanto et al 2020	Open Label-RCT	Women with pelvic pain	Dienogest vs COCP	CCOCP (EE 35 µg plus norethister one 1 mg)	204	44,6	Post-treatment VAS score
7	Triciaana AA Miraa et al, 2020	Double blind-RCT	women with endometriosis	Dienogest 2mg	CCOCP (EE 35 µg plus norethister one 1 mg)	126	46,5	Post-treatment VAS score
8	Tolga Karacan et al, 2020	Retrospective Cohort	Infertile women with endometriosis	Dienogest 2mg	CCOCP (EE 35 µg plus norethister one 1 mg)	154	32,8	Post-treatment VAS score
9	Yutaka Osaga et al, 2017	Double blind-RCT	Patient with endometriosis	Dienogest 2 mg	CCOCP (EE 35 µg plus norethister one 1 mg)	138	32,1	Post-treatment VAS score

A. 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 post-surgical endometriosis implants

Assessments of the risk of bias in the studies included in the systematic review and meta-analysis of dienogest therapy against the CCOCP in the case of Post-Intrasurgery Endometriosis Cases are shown in table 1.

		Risk of bias							
		D1	D2	D3	D4	D5	D6	D7	Overall
Meta analysis	Antonio Maiorana 2022	⊗	⊗	⊗	⊗	⊗	⊕	⊕	⊗
	Bilgehan Saglik Gokmen 2023	⊗	⊗	⊗	⊗	⊗	⊕	⊕	⊗
	Cihan Kaya 2021	⊖	⊖	⊗	⊗	⊖	⊕	⊕	⊖
	Gelareh Niakan 2021	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕
	Lina El Taha 2021	⊕	⊕	⊖	⊖	⊕	⊕	⊕	⊕
	Purwanto 2021	⊖	⊖	⊗	⊗	⊕	⊕	⊕	⊖
	Ticiana A.A. Miraa 2021	⊕	⊕	⊖	⊖	⊕	⊕	⊕	⊕
	Tolga Karacan 2020	⊗	⊗	⊗	⊗	⊖	⊕	⊕	⊗
	Yutaka Osuga 2017	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕

D1: Random sequence generation
 D2: Allocation concealment
 D3: Blinding of participants and personnel
 D4: Blinding of outcome assessment
 D5: Incomplete outcome data
 D6: Selective reporting
 D7: Other sources of bias

Judgement
 ⊗ High
 ⊖ Unclear
 ⊕ Low

Figure 1. Assessment of the risk of bias in articles used in the meta-analysis of the effectiveness of dienogest therapy against oral contraceptives in cases of post-surgical endometriosis implants

There are 9 articles related to the effectiveness of dienogest therapy against contraceptive pills in cases of post-operative endometriosis implants. In table 1, it can be seen that from the 9 articles, 3 articles are found; they are: Antonio Maiorana 2022, Bilgehan Saglik Gokmen 2023 and Tolga Karacan 2020 with a high risk of bias. 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; they are: Gelareh Niakan 2021, Lina El Taha 2021, Ticiana A.A. Miraa 2021 and Yutaka Osuga 2017 which have a low risk of bias.

A. Meta-analysis of the effectiveness of dienogest therapy against contraceptive pills in cases of post-operative endometriosis implants

B.1. Dysmenorrhea Score

The comparison of dysmenorrhea score in the group of Dienogest with the group of combined oral contraceptive is shown in table 2.

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

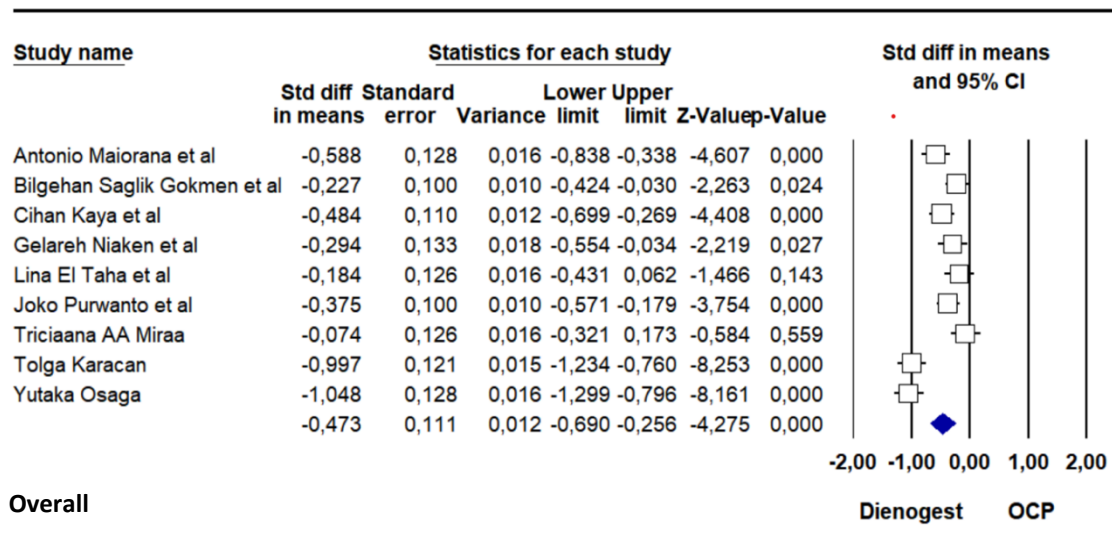
We can see from table to that there are 9 studies used in meta-analysis of the effectiveness of dienogest therapy against contraceptive pills in cases of post-operative endometriosis implants, there are 6 studies (Antonio Maiorana 2022, Bilgehan Saglik Gokmen 2023, Cihan Kaya 2021, Lina El Taha 2021,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

The results of the meta-analysis comparing dysmenorrhea scores in the dienogest group with the COCP group are shown in Figure 1. Figure 2 shows meta-analysis carried out with a random effect model because the data is heterogeneous ($Q=63,655$, $df=8$; $I^2=87,432$). Based on the data in picture 1, it is revealed that 7 studies show the significant differences of dysmenorrhea score in Dienogest group with COCP group, except in 2 articles (Lina El Taha 2021 dan Ticiana A.A. Miraa 2021) caused by the range of 95% interval of trust covers number 1. Overall, the whole

dysmenorrheas score in Dienogest group is significantly lower than COCP group with the mean difference $-0,473 \pm 0,109$ ($p < 0,001$).

B.2. Dyschezia score

The Comparison of Dyschezia score in Dienogest group and the combined oral contraceptive group is shown in table 3



Random-effect model

Heterogeneity: Q value=63,655; $df=8$; $p < 0,001$, $I^2=87,432$

Test for overall effect: z value= -4,275; $p < 0,001$

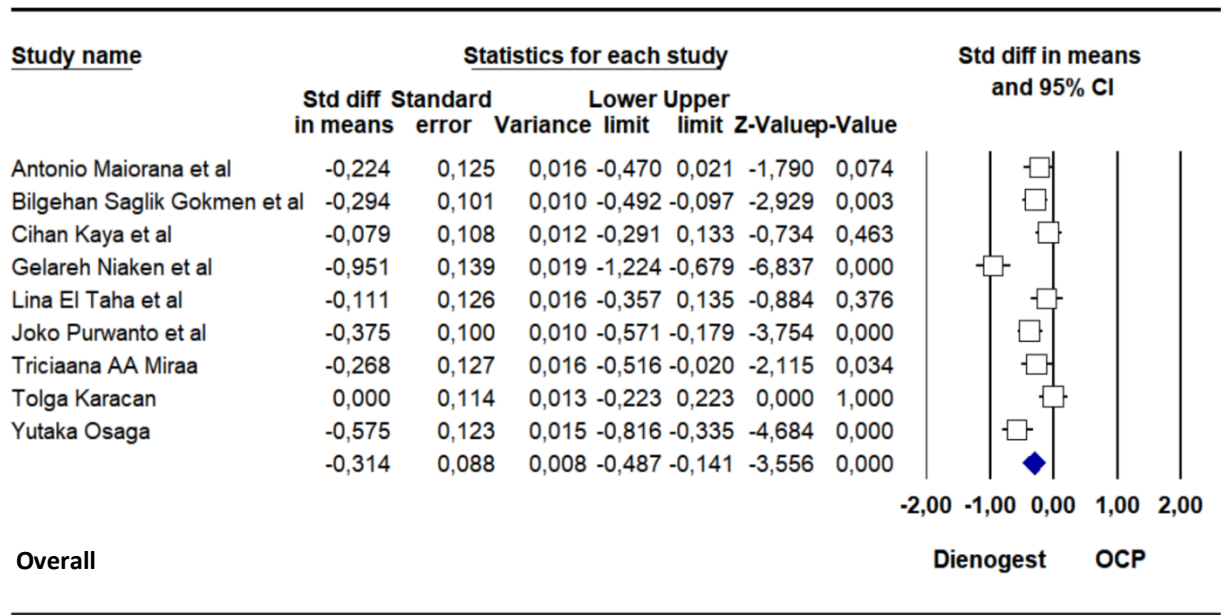
Figure 2. Meta-analysis results comparing dysmenorrhea scores in the dienogest group with the COCP group

Table 3. Dyschezia score in Dienogest group and combined oral contraceptive group
Dyschezia sasoFunnel PlotFunnl

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 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 post-operative nometriosis implants, there are 7 studies (Antonio Maiorana 2022, Bilgehan Saglik Gokmen 2023, Cihan Kaya 2021, Gelareh Niakan 2021 Purwanto 2021, Tolga Karacan 2020 and Yutaka Osuga 2017) with dyschezia scores in the Dienogest group 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



Random-effect model

Heterogeneity: Q value=41,278; df=8; p<0,001, I2= 80,619

Test for overall effect: z value= -3,556; p<0,001

Figure 3. Meta-analysis results comparing dyschezia scores in the dienogest group with the COCP group

Dienogest group was higher than the COCP group. The results of the meta-analysis comparing dyschezia scores in the dienogest group with the COCP group are shown in Figure 2.

Figure 3 shows meta-analysis carried out with a random effect model because the data is heterogeneous (Q=41,278; df=8; I2=80,619). Based on the data in Figure 2, 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 ($p < 0.001$).

B.3. Dyspareunia Score

Comparison of the Dyspareunia Score in the Dienogest group with the combined oral contraceptive group is shown in table 4.

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
Ticians 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

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 post-operative endometriosis implants, there are 6 studies (Bilgehan Saglik Gokmen 2023, 2021, Gelareh Niakan 2021, Purwanto 2021, Tolga Karacan 2020 and Yutaka Osuga 2017) with dyspareunia, the Dienogest group's score was 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 was higher than the COCP group.

The results of the meta-analysis comparing dyspareunia scores in the dienogest group with the COCP group are shown in Figure 4, where it was found that the meta-analysis was carried out with a random effect model because the data was heterogeneous ($Q=79.295$; $df=8$; $I^2=89.991$). Based on the data in Figure 3, 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 was significantly lower than in the COCP group with a mean difference of -0.384 ± 0.045 ($p < 0.001$).

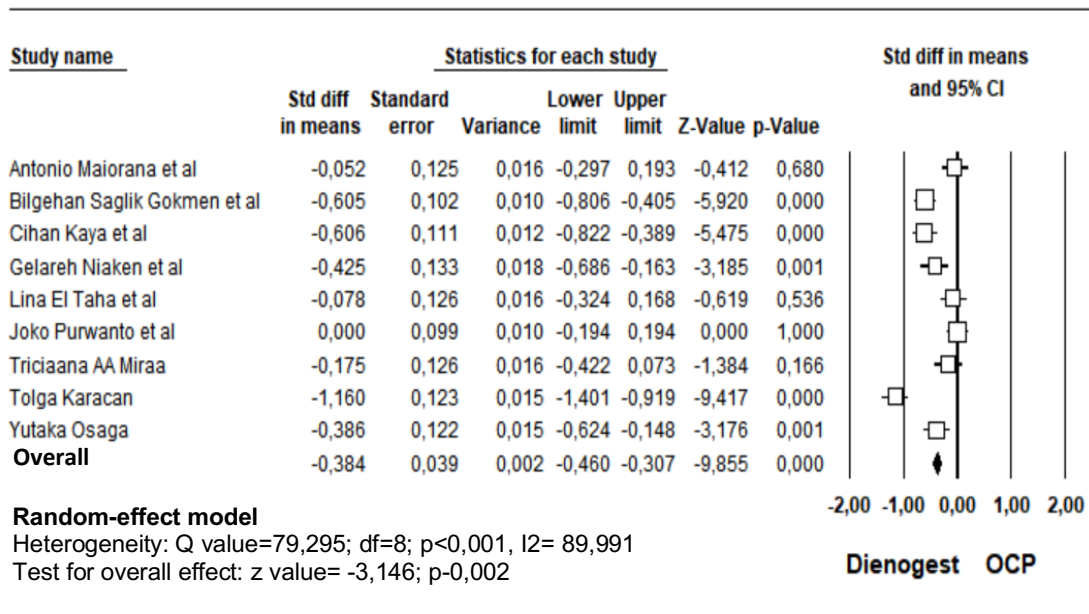


Figure 4. Meta-analysis results comparing dyspareunia scores in the dienogest group with the COCP group

Based on the results of the meta-analysis in Figures 1, 2 and 3, it can be seen that the dysmenorrhoea, dyschezia and dyspareunia scores in the Dienogest group were significantly lower than those in the COCP group.

B. Risk of publication bias

In the funnel plot, in figure 5, it can be seen that the data is not symmetrical due to research with the results providing a larger effect size than other studies, but the results of the analysis using the Egger regression test show results that are not significant. This shows there is no potential for publication bias ($t = 1.111$; $df = 7.00$; $p = 0.303$)

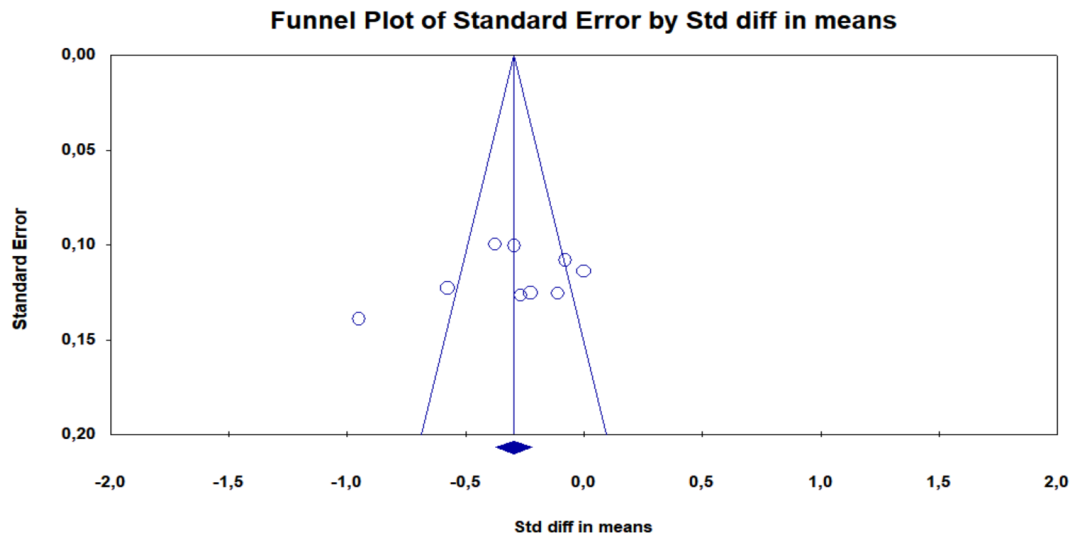


Figure 5. Funnel plot diagram to assess publication bias in meta-analysis of the effectiveness of dienogest therapy versus contraceptive pills in post-surgical cases of susuka endometriosis

C. Quality of evidence

Quality of evidence meta-analysis of the effectiveness of dienogest therapy against contraceptive

Tabel 5. Quality of evidence meta-analysis of the effectiveness of dienogest therapy versus contraceptive pills in cases of post-surgical endometriosis implants

Studies	Number of studies (number of subjects)	Quality Assessment					Summary of findings	
		Bias Risk	Inconsistency	Indirectness	Impresion	Publication bias	Effect size mean different \pm SD (95% CI)	Quality of evidence
Comparison of dysmenorrhea score	9 (n= 2726)	Not serious	Nothing	Direct	No impresion	Nothing	-0,473 \pm 0,109 (p<0,001)	+++ (moderate)
Comparison of dyschezia score	9 (n= 2726)	Not serious	Nothing	Direct	No impresion	Nothing	-0,314 \pm 0,089 (p<0,001)	+++ (moderate)
Comparison of dyspareunia score	9 (n= 2726)	Not serious	Nithing	Direct	No impresion	Nothing	-0,384 \pm 0,045 (p<0,001)	+++ (moderate)

pills in cases of post-surgical endometriosis implants is shown in table 5. The quality of evidence

from the meta-analysis of the effectiveness of dienogest therapy versus contraceptive pills in cases of post-surgical endometriosis implants shown in table 5 is all moderate.

Discussion

Due the negative impacts from the endometriosis surgery in the form of ovarium damage and the decrease of fertility level, continuous medical treatment is mandatory as the post-surgical supporting therapy to prevent recurrence and chronic pelvic pain. The combined contraceptive pills, such as medroxyprogesterone acetate or norethisterone, is used as the medical treatment and known as long-term endometriosis treatment, which is cheap, effective and can be well-tolerated.^{10,13,15} Another study that compared dienogest and the progestin norethindrone acetate (NETA) derivative 19-nortestosterone in women with endometriosis and found a statistically significant difference in reducing the mean of dysmenorrhea scores favoring the dienogest group, but there was no significant improvement in quality-of-life scores or sexual function scores.^{14,18}

The results from 9 studies have evaluated long-term use of dienogest up to 52-53 weeks and reported that dienogest clinically improves pelvic pain in patient 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 Ticiania A.A. Miraa 2021 on the therapeutic effect and 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 VAS score is well tolerated with few side effects in favor of dienogest over combined contraceptive pills after 24 weeks of treatment. Overall, the results of the study population and compared them with 96 previous literatures, we observed significant differences in pain-related symptom scores of DIE in patient who received dienogest than the combined oral contraceptive pill. And also there is a significant different pain reduction in dysmenorrhea, dyspareunia, dyschezia, and pelvic pain scores in dienogest group than COCP group due the effect of dienogest that reduce the secretion of inflammatory cytokines or reduce endometrial foci by suppressing the ovulation hormone. despite the risk of abnormal.^{17,18,20} Endometriosis is an Estrogen-dependent disease is known to be effective in controlling the symptoms of Endometriosis patient, 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, 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 the abnormal bleeding problem, and the risk of pelvic inflammatory disease. Dienogest proved that it improves pain relief in patients with endometriosis especially for patient who seeking fertility preservation, across a wide range of ages, and demonstrated safety assuming that appropriate consideration is given to irregular uterine bleeding and anemia. However, the results of this study were limited to 16 weeks of treatment, and data regarding longer treatment periods are needed.^{17,19}

Conclusion

These 9 studies emphasize that dienogest is an effective treatment for pain symptom 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 were 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 adenomyosis patients, not accompanied by complications of severe uterine enlargement or severe anemia.

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