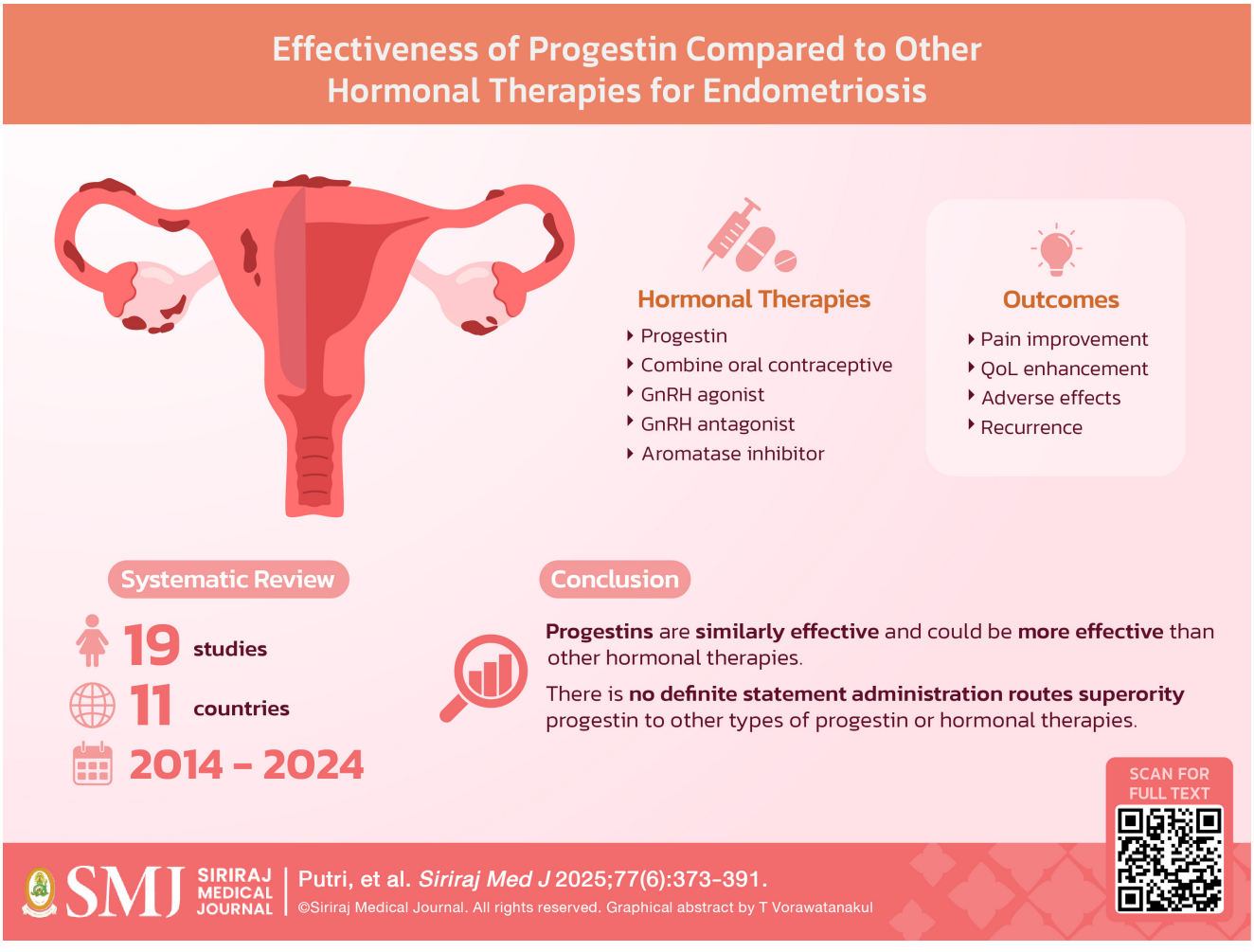
Effectiveness of Different Progestin Modalities Compared to Other Hormonal Therapies for Endometriosis: A Systematic Review

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ABSTRACT

Objective: A systematic review was conducted with a study compilation of women with endometriosis in determining the evidence of the use of various progestin modalities compared to other hormonal therapies in improving endometriosis-associated pain, enhancing quality of life (QoL) and minimizing adverse effects and recurrence of disease.

Materials and Methods: This review carried out search strategies on various searching databases to analyze all comparisons of various progestin-only therapies with each other, other types of hormonal therapies, and placebo. The primary outcome is improvement of endometriosis-associated pain. Meanwhile, the secondary outcomes are the impact on QoL or treatment satisfaction, adverse effects, and disease recurrence.

Results: Progestogen (including progestin-only contraceptives) combined oral contraceptives (COC), gonadotropin-releasing hormone (GnRH) agonists, and antagonists are the hormonal therapies that were included in this study. These hormonal therapies significantly decrease the symptoms and increase the patient's QoL, particularly dienogest, the most used progestogen in the study. The recurrence of the disease was mentioned when progestin-only contraceptives were compared to each other, GnRH agonists and antagonists, which were similar. In addition, almost all of the studies mentioned that irregular bleeding was the most commonly observed adverse effect.

Conclusion: Progestin-only contraceptives are similarly effective and could be more effective than other hormonal therapies in decreasing endometriosis-related symptoms, improving QoL, recurrence rate and minimizing adverse effects. This study also concludes that there is no definite statement on the superiority of specific kinds or administration routes of progestogen to other types of progestin or hormonal therapies.

Keywords: Endometriosis; progestin; hormonal therapy (Siriraj Med J 2025; 77: 373-391)

INTRODUCTION

Endometriosis is a chronic hormone-dependent gynaecological disorder that can be distinguished by the growth and appearance of similar histological components of endometrial glands (epithelial and stromal) outside the anatomical cavity of the uterine. This prevalence of endometriosis in women of reproductive age is approximately 10-15%, although it can rise as high as 70% among women with chronic pelvic pain (CPP).[1] The most common clinical manifestations are persistent pelvic pain and impaired fertility. Intermenstrual haemorrhage, dysmenorrhea, and dyspareunia, along with bowel and bladder symptoms such as dyschezia and dysuria, can also present as symptoms of endometriosis.[2]

Nowadays, there are specific options for treating symptomatic endometriosis, including hormonal therapies, surgical intervention, or a combination of both.[3,4] The approach to treating endometriosis requires an individualized-based therapy based on personal preference, efficacy, severity of symptoms, adverse effects, costs, and availability to determine an efficient treatment method. Therefore, hormonal therapy is one of the most frequent and recommended treatments because it suppresses menstruation and ovulation in order to control the disease and clinical manifestations. In endometriosis, hormonal therapy works by disrupting the menstruation cycle in the deactivation of the hypothalamus-pituitary ovary axis by causing a pseudo-decidual state with consequent amenorrhea, which in turn prevents the progression of the disease.[2,5]

According to the European Society of Human Reproduction and Embryology (ESHRE) guidelines, progestogen or progestin is a recommended first-line choice of hormonal therapy for endometriosis.[4] Progestin has multiple mechanisms in progesterone receptors that induce beneficial effects in reducing the progression of endometriosis and relieving pain.[5] This therapy has many options of modalities for patients, so it can be convenient for women with endometriosis who prefer not to worry about daily pill-taking or monthly injections. Also, it is suitable for women with estrogen tolerance due to its side effects and health risks. The most common adverse effects include irregular uterine bleeding, mood swings, weight gain, and decreased density of bone. However, progestin has a lower incidence of side effects than other hormonal therapies and rarely causes treatment abandonment. Approximately two-thirds of patients are satisfied as their symptomatic endometriosis improves to some extent.[4]

The available progestins that can be administered to patients include oral, intramuscular, subcutaneous, or intrauterine routes. Although there are many different types of progestin, the most frequent progestins that are utilized are dienogest (DNG), norethindrone acetate (NETA), which

is available in the oral route, and medroxyprogesterone acetate (MPA), which is administered via oral, intramuscular, and subcutaneous.[2,4] However, as time passes, the excess kinds of progestins have various outcomes in the therapy in treating endometriosis. Furthermore, the necessity of providing better evidence must be attempted. Therefore, this systematic review aims to evaluate the efficacy of various progestin modalities for treating endometriosis. It compares these treatments with other hormonal therapies in reducing symptoms, minimizing adverse effects, and preventing recurrence.

MATERIALS AND METHODS

Literature search

A systematic review of the efficacy of different progestin modalities compared to other therapies in women with endometriosis was conducted using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. The relevant articles were selected through a search in PubMed, Cochrane, Science Direct and Google Scholar. We apply keywords such as "Endometriosis OR Endometrium Ectopic" AND "Progestin OR Progestogen." The database search was made in March 2024 and included articles from 1 January 2014 to 29 February 2024.

Study selection

The inclusion requirements for this systematic review are randomized controlled trials (RCTs), clinical trials, retrospectives, and observational studies that used progestin modalities compared to other progestin therapies, hormonal therapies, placebos, or without treatment. We selected studies that involved women with surgery-based diagnosis (with or without histopathologic confirmation) and validated radiology-based diagnosis by magnetic resonance or ultrasound of endometriosis. The primary outcome is the improvement of endometriosis-associated pain or symptoms. In addition, the secondary outcomes are the impact on quality of life (QoL), adverse effects, and disease recurrence. Meanwhile, the excluded criteria for this systematic review are non-fully accessible articles, non-English articles, and other study methods not mentioned in the inclusive criteria. The results of assessing the database will be extracted into an extraction table. (Table 1)

Data extraction

The included studies will be extracted to obtain data as follows: (1) Author's name, year of study, country (2) Type of progestin therapy (3) Study design (4) Diagnosis method of endometriosis (4) Type of intervention comparator (5) Result of study (6) Included participant (7) Evaluated outcome.

Risk of Bias Analysis

The Cochrane Collaboration's Risk of Bias Assessment Tool assessed the risk of bias analysis from the included study in the Review Manager 5 application. The overall quality was moderate. The risk of bias assessment was examined by each study's risk of bias and the overall percentage of each risk of bias component judgment, as shown below.

RESULTS

The predetermined search term identified 367 references published from 1 January 2014 to 29 February 2024. After checking for duplicates, 193 references were removed so that 111 references would be screened for their eligibility. Eighty references were excluded from being included because the studies could not be accessed. These 19 studies fulfilled the inclusion criteria. Fifty-five studies were excluded for the following reasons: irrelevant population, unrelated interventions, different outcomes measured, and incomplete data. (Fig 1)

Progestin, compared to other progestin therapies

In a study conducted by Lee et al., it evaluated dienogest (DNG), levonorgestrel-releasing intrauterine system (LNG-IUS), and untreated women with laparoscopically confirmed endometriosis. Endometriosis-associated pain was significantly lower in the DNG and LNG-IUS than in the untreated group, where the VAS scores were not significantly different after 6- and 12-month interventions. The rate of endometriosis recurrence was higher in the untreated group than in the treated group. Meanwhile, the side effects of both interventions are not substantially different between DNG and LNG-IUS. The most frequent adverse reaction was vaginal bleeding, which is self-limited in most patients.[6]

Carvalho et al evaluated the efficacy of etonogestrel (ENG)-releasing contraceptive implant compared to LNG-IUS in surgical and histopathological diagnosed endometriosis. Dysmenorrhea and noncyclic pelvic pain were significantly reduced in both groups with no statistical difference from each other. There was an improvement in the patient's QoL in both groups, but the difference was not shown significantly.[7]

Meanwhile, a clinical trial that Vahid-Dastjerdi carried out compared the effectiveness of two oral progestins, DNG and medroxyprogesterone acetate (MPA), in surgically confirmed endometriosis. The reduction of pelvic pain was significantly different in contrast to dysmenorrhea

TABLE 1. Summary and results of the included study.

Author, Year, Country	Progestin Therapy	Type of Study	Type of Diagnosis	Comparator	Participants Included	Outcome Evaluated				Result
						Pain	QoL	Recurrence	Adverse Effects	
Progestin vs Progestin										
KH Lee *et al.*, 2018, South Korea.	Dienogest 2 mg / Oral	Retrospective Cohort	Surgical	52-mg 20-mg/d LNG-IUS and no treatment	130 vs 72 vs 83	Yes		Yes	Yes	- The VAS score reduction of pain in dienogest, LNG-IUS, and untreated groups significantly differed after 6 and 12 weeks ($p = 0.004$ and $p = 0.001$, respectively). - The recurrence incidence between dienogest (3.8%), LNG-IUS (9.7%) and untreated groups (32.5%) was significantly different ($p = 0.001$). - There was an unnoticeable difference ($p = 0.381$) in the side effects rate between dienogest (36.9%) and LNG-IUS (29%). - The most observed side effect was vaginal bleeding.
Carvalho, N *et al.*, 2018, Brazil.	Etonogestrel / Implant	Randomized Clinical Trial	Surgical + Histopatho-logical	52-mg 20-mg/d LNG (IUS)	52 vs 51	Yes	Yes			- The VAS score of noncyclic pain and dysmenorrhea reduced significantly in both groups after 180 days. ($p < 0.001$). - There were no significant differences in the mean VAS score of noncyclic pelvic pain and dysmenorrhea of both treatments after 180 days. ($p = 0.241$ and $p = 0.431$, respectively). - The quality of life's assessment showed substantial improvement in all the domains of the core and modular segments of the EHP-30 questionnaire in both treatment groups ($p < 0.05$), with no statistical differences between them ($p > 0.05$).

TABLE 1. Summary and results of the included study. (Continue)

Author, Year, Country	Progestin Therapy	Type of Study	Type of Diagnosis	Comparator	Participants Included	Outcome Evaluated				Result
						Pain	QoL	Recurrence	Adverse Effects	
Vahid-Dastjerdi, M *et al.*, 2023, Iran	Dienogest 2 mg / Oral	Randomized Clinical Trial	Surgical	10 mg MPA (Oral)	48 vs 53	Yes		Yes	Yes	- The measured endometriosis-related pain was significantly lower in the dienogest group than in the MPA group ($p < 0.001$). - The recurrence incidence of endometriosis between both groups was not different statistically ($p = 0.4$). - The drug-related side effects were significantly different between both groups ($p < 0.001$).
Progestin vs Combined Oral Contraceptive (COC)										
Kashi, A.M *et al.*, 2021, Iran	Dienogest 2 mg / Oral	Randomized Double-Blinded Clinical Pilot	Surgical	EE 30 µg + Levonorgestrel 0.3 mg (Oral) and Placebo	30 vs 30 vs 20	Yes	Yes		Yes	- The VAS score between dienogest and COC showed significantly lower scores for pelvic pain ($p = 0.026$) and dyspareunia ($p = 0.04$) than the placebo group. Meanwhile, there was no meaningful difference for dysuria ($p = 0.378$) and dyschezia ($p = 0.547$). - There was a consequential difference in the overall quality of life score ($p = 0.001$). - The treatment-related side effects were spotting, hair loss, headache, nausea, hot flashes, backache, hand numbness, and skin dryness, with no significant difference between the three groups

TABLE 1. Summary and results of the included study. (Continue)

Author, Year, Country	Progestin Therapy	Type of Study	Type of Diagnosis	Comparator	Participants Included	Outcome Evaluated				Result
						Pain	QoL	Recurrence	Adverse Effects	
Caruso, S *et al.*, 2022, Italy	Dienogest 2 mg / Oral	Randomized Clinical Trial	Radiological	1.5 mg 17b-estradiol / E2 and 2.5 mg Nomegestrol acetate / NOMAC (Oral)	98 vs 99	Yes	Yes			- Pain improvement was assessed by the CPP VAS score that was statistically meaningful ($p < 0.001$) until 12 months of follow-up. - The significant improvement of CPP ($p <0.01$), dysmenorrhea ($p = 0.02$), and dyspareunia ($p = 0.003$) between both groups was shown at the 6 months of follow-up. - The overall quality of life score in the dienogest group had better SF-36 somatic ($p < 0.01$) and FSFI scores ($p < 0.006$) than women on E2/NOMAC after 6 and 12 months of treatment
Niakan, G *et al.*, 2021, Iran	Dienogest 2 mg / Oral	Randomized Clinical Trial	Surgical	EE 30 µg + Levonorgestrel 0.3 mg (Oral) and Placebo	30 vs 30 vs 30	Yes	Yes		Yes	- The VAS score of dyspareunia was not substantially different after 3 months of treatment ($p =0.11$). - The pelvic pain symptoms were significantly reduced ($p =0.003$), while dysuria and dyschezia were not significantly reduced ($p = 0.81$, $p = 0.67$, respectively) after 3 months of treatment. - The overall quality of life score was statistically different between the control and dienogest ($p = 0.02$) and COC ($p = 0.001$) but not statistically different between intervention groups. - The observed drug-related side effects were spotting, hair loss, headache, nausea, hot flashes, backaches, numbness, and skin dryness, which were not statistically meaningful between the three groups ($p > 0.05$).

TABLE 1. Summary and results of the included study. (Continue)

Author, Year, Country	Progestin Therapy	Type of Study	Type of Diagnosis	Comparator	Participants Included	Outcome Evaluated				Result
						Pain	QoL	Recurrence	Adverse Effects	
Piacenti, I *et al.*, 2021, Italy	Dienogest 2 mg / Oral	Prospective Cohort Study	Surgical + Histopatho-logical or Radiological	EE 0,02 mg + Levonogestrel 0.1 mg (Oral)	43 vs 43	Yes	Yes		Yes	- Dienogest significantly reduced CPP ($p = 0.002$) and dyspareunia ($p = 0.021$). Meanwhile, COC significantly reduced dyspareunia ($p =. 0.023$). - The physical component quality of life scoring was substantially improved in the dienogest and COC groups ($p < 0.0001$, $p < 0.034$, respectively). Meanwhile, the mental component scoring was only substantially improved in the dienogest group ($p < 0.0001$). - The most common side effect in both groups was vaginal bleeding in the first 3 months of treatment ($p <0.001$).
Taha, LE *et al.*, 2021, Lebanon	Dienogest 2 mg / Oral	Randomized Clinical Trial	Surgical or Radiological	EE 0.03 mg and Drospirenone 3 mg (Oral)	25 vs 26	Yes	Yes		Yes	- Dienogest and COC significantly decreased the VAS score of endometriosis-related pelvic pain ($p <0.0001$), but there were no significant differences between both groups ($p = 0.111$). - Both groups have similar improved patient quality of life, which was statistically meaningful on the core question of pain. ($p < 0.001$). - Dienogest has fewer side effects than the COC.

TABLE 1. Summary and results of the included study. (Continue)

Author, Year, Country	Progestin Therapy	Type of Study	Type of Diagnosis	Comparator	Participants Included	Outcome Evaluated			Adverse Effects	Result
						Pain	QoL	Recurrence		
Progestin vs Gonadotropin-releasing Hormone Agonist (GnRH Agonist)										
Abdou, A M *et al.*, 2017, Egypt	Dienogest 2 mg / Oral	Randomized Clinical Trial	Surgical	Leuprolide Acetate 3.75 mg (Intra Muscular Injection)	121 vs 121	Yes			Yes	- The VAS score notably reduced pelvic pain, dyspareunia, and back pain (p = 0.000). - There was no statistically meaningful difference in VAS score reduction between both groups in pelvic pain (p = 0.170), dyspareunia (p = 0,263) and back pain (p = 0.597). - The most frequent side effect of the dienogest group was vaginal bleeding (64.5%) which was highly substantially different (p = 0.000) between the two groups. - The most frequent side effects of leuprolide acetate were hot flushes (46.3%), which was highly substantially different (p = 0.00) between the two groups. - Other observed side effects were vaginal dryness (p = 0.001), weight gain (p = 0.02), which was significantly different, and headache (p = 0.13), which was not significantly different between both groups.
Purwanto, J *et al.*, 2020, Indonesia	Dienogest 2 mg / Oral	Randomized Clinical Trial	Surgical	Leuprolide Acetate 3.75 mg (Intra Muscular Injection)	10 vs 10	Yes			Yes	- There was a significantly reduced VAS score in the dienogest and leuprolide acetate groups every four weeks of follow-up until 12 weeks (p = 0.004 and p = 0,003, respectively). However, both groups had a significant difference in VAS scores (p = 1.00). - The adverse effects of the treatment were vaginal dryness, joint pain, decreased libido, headaches, and hot flashes, which were substantially different between both groups (p = 0.238).

TABLE 1. Summary and results of the included study. (Continue)

Author, Year, Country	Progestin Therapy	Type of Study	Type of Diagnosis	Comparator	Participants Included	Outcome Evaluated				Result
						Pain	QoL	Recurrence	Adverse Effects	
Tang, M *et al.*, 2023, China	Dienogest 2 mg / Oral	Prospective Clinical Trial	Surgical	Leuprolide Acetate 3.75 mg (Intra Muscular Injection)	41 vs 40	Yes		Yes		- The VAS pain score showed improvement and was statistically meaningful between both groups after 3 and 6 months of treatment ($p < 0.05$). - The Kupperman score was statistically meaningful between both groups after 3 and 6 months of treatment ($p < 0.05$), which assessed the severity of symptoms. - The postoperative recurrence rate was eight patients in the dienogest group and two patients in the GnRH agonist group, significantly different between the two groups ($p < 0.05$).
Ceccaroni, M *et al.*, 2021, Italy	Dienogest 2 mg / Oral	Randomized Clinical Trial	Surgical	Leuprolide Acetate 3.75 mg (Intra Muscular Injection)	65 vs 81	Yes			Yes	- Dienogest and GnRH agonists reduced endometriosis-related pain significantly ($p < 0.001$). - There were several observed adverse effects, such as amenorrhea ($p = 0.05$) and hot flushes ($p < 0.001$), which were substantially different in GnRH agonist than dienogest. Meanwhile, spotting ($p < 0.001$) was substantially different in dienogest than GnRH agonist.
Ozaki, R *et al.*, 2020, Japan	Dienogest 2 mg / Oral	Prospective Clinical Trial	Surgical	Goserelin Acetate 1.8 mg (Subcutaneous Injection)	35 vs 35	Yes			Yes	- Dienogest reduced endometriosis-related pain more significantly than GnRH agonists ($p = 0.006$). - The side effect that occurred more significantly in GnRH agonists than dienogest was hot flashes ($p < 0.001$). - Breast pain and metrorrhagia were the side effects that occurred more significantly in dienogest than GnRH agonists ($p = 0.04$ and $p < 0.001$, respectively).

TABLE 1. Summary and results of the included study. (Continue)

Author, Year, Country	Progestin Therapy	Type of Study	Type of Diagnosis	Comparator	Participants Included	Outcome Evaluated				Result
						Pain	QoL	Recurrence	Adverse Effects	
Progestin vs Gonadotropin-releasing Hormone Antagonist (GnRH Antagonist)										
Carr, B *et al.,* 2014, USA.	MPA 104 mg/ 0.65 mL/ Subcutaneous Injection	Randomized Clinical Trial	Surgical	Elagolix 150 mg daily and Elagolix 75 mg twice a day	84 vs 84 vs 84	Yes			Yes	- There was a significantly reduced VAS score in the dienogest and leuprolide acetate groups every 4 weeks of follow-up until 12 weeks (p = 0.004 and p = 0,003, respectively). However, neither group had a notable VAS score difference (p = 1.00). - The adverse effects were vaginal dryness, joint pain, decreased libido, headaches, and hot flashes, which were not statistically meaningful between both groups (p = 0.238).
Progestin vs Aromatase Inhibitor										
Acien, P *et al.,* 2021, Spain.	Levonorgestrel / IUS	Randomized Clinical Trial	Radiological	Anastrozole 1 mg	15 vs 16	Yes		Yes		- Anastrazole and LNG-IUD reduce endometriosis-associated pain with a substantial difference (p = 0.048) in the first year of follow-up. - The recurrence rate between both groups was similar by the end of follow-up, but LNG-IUD tends to reoccur more rapidly than anastrozole.

TABLE 1. Summary and results of the included study. (Continue)

Author, Year, Country	Progestin Therapy	Type of Study	Type of Diagnosis	Comparator	Participants Included	Outcome Evaluated				Result
						Pain	QoL	Recurrence	Adverse Effects	
Progestin vs Placebo										
Tanmahasamut, P *et al.*, 2017. Thailand.	Desogestrel 0.075 mg / Oral	Randomized Clinical Trial	Surgical	Placebo	19 vs 19	Yes			Yes	- Desogestrel has significantly reduced the VAS score of pelvic pain, dysmenorrhea, and noncyclic pelvic pain (p = 0.005, p = 0.005, p = 0.007, respectively). However, there was no meaningful statistical difference in the VAS score of dyspareunia (p = 0.342). - The most frequent side effect of the treatment was menstrual alteration, which was consequently different in both groups (p < 0.001).
Lang, J *et al.*, 2017. China	Dienogest 2 mg / Oral	Randomized Clinical Trial	Surgical	Placebo	126 vs 129	Yes	Yes		Yes	- Dienogest has significantly reduced endometriosis-associated pelvic pain over placebo (p < 0.0001). - Diegonest has improved patients' quality of life. - The most frequent adverse effect was vaginal bleeding.
Yu, Q, *et. al.*, 2018. China	Dienogest 2 mg / Oral	Randomized Clinical Trial	Surgical	Placebo	109 vs 110	Yes	Yes		Yes	- Dienogest has significantly reduced endometriosis-associated pelvic pain over placebo (p < 0.0001). - Diegonest has improved patients' quality of life. - The most frequent adverse effect was vaginal bleeding.

Abbreviations: LNG-IUS = Levonorgestrel Intrauterine System, MPA Medroxyprogesterone Acetate, EE = Ethinyl Estradiol

and dyspareunia, which were not significantly different in both groups. The recurrence rate between both groups was not consequently different. Adverse effects were notably different between both groups, with the expected effects of DNG being headache in contrast to MPA, which was weight gain.[8]

Progestin, compared to other hormonal therapies Combined Oral Contraceptive (COC)

Kashi et al conducted a study comparing effects of dienogest, contraceptive oral contraceptive pills (COCP) containing ethinyl-estradiol (EE) and levonorgestrel and placebo. The results was a significant difference in the reduction of pelvic pain and dyspareunia between three groups but there was no significant difference between dysuria and dyschezia. Assessed QoL shows a notable difference in the mean score improvement with no statistical difference post-intervention between the three groups. There was a low adverse effect rate in the DNG and COCP groups. The most common side effects were spotting, hair loss, headache, hot flashes, and nausea, with unmeaningful difference in complications between the two groups.[9]

Caruso et al randomized women with endometriosis by confirming transvaginal sonography that received dienogest or COCP containing 17b-estradiol (E2) and nomegestrol acetate (NOMAC) to evaluate their effectiveness every 3 months within 12 months. It was reported that DNG had better improvements than E2/NOMAC, with unnoticeable differences. Both intervention groups had improvement in mental and somatic aspects with no statistical difference. However, DNG had a better somatic score than E2/NOMAC in 6 and 12 months, which is statistically meaningful.[10]

Another clinical trial performed by Niakan et al utilized comparison effects of dienogest, COCP containing EE/Levonorgestrel, and placebo within 12 weeks on

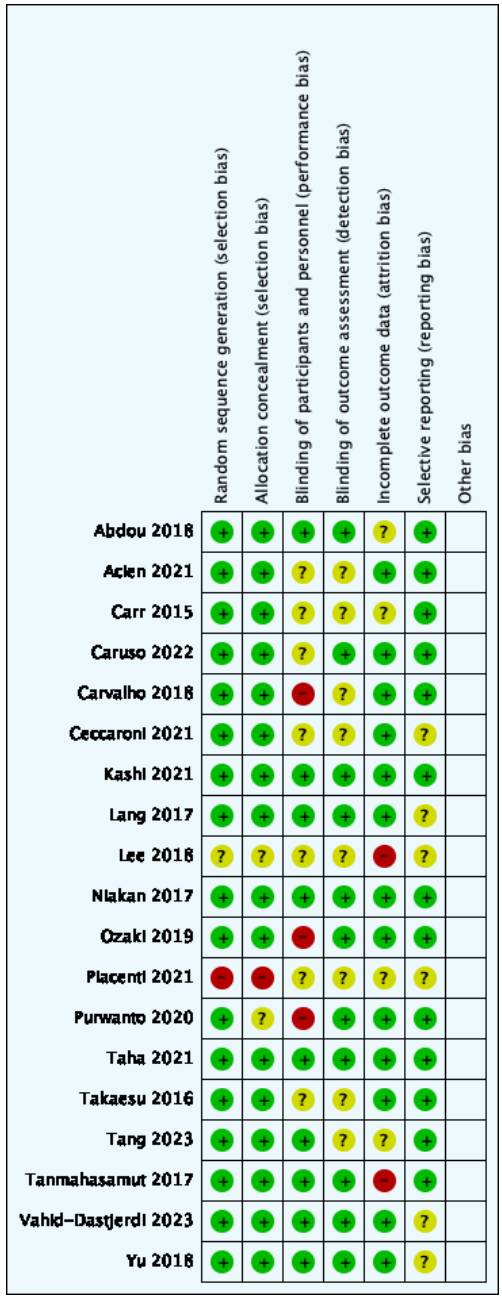


Fig 1. Risk of bias summary: Review authors' judgements about each risk of bias item for each included study.

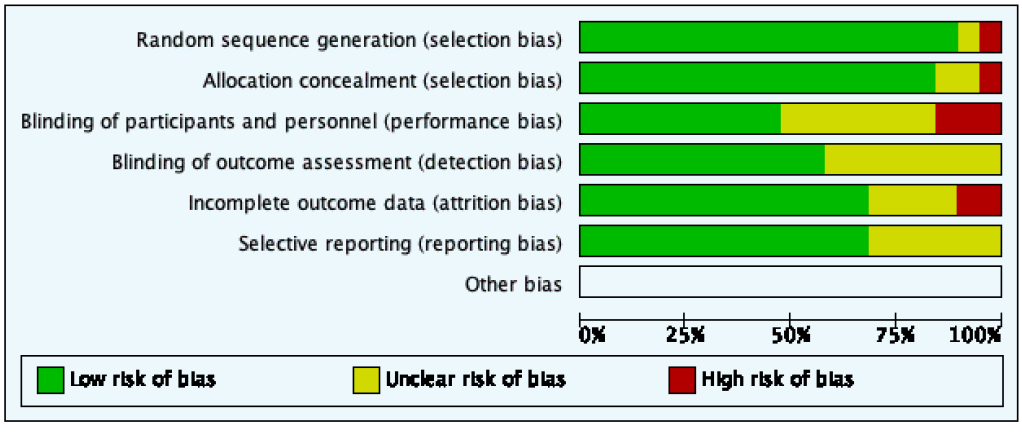


Fig 2. Risk of bias graph: Review authors' judgements about each risk of bias item presented as percentages across all included studies.

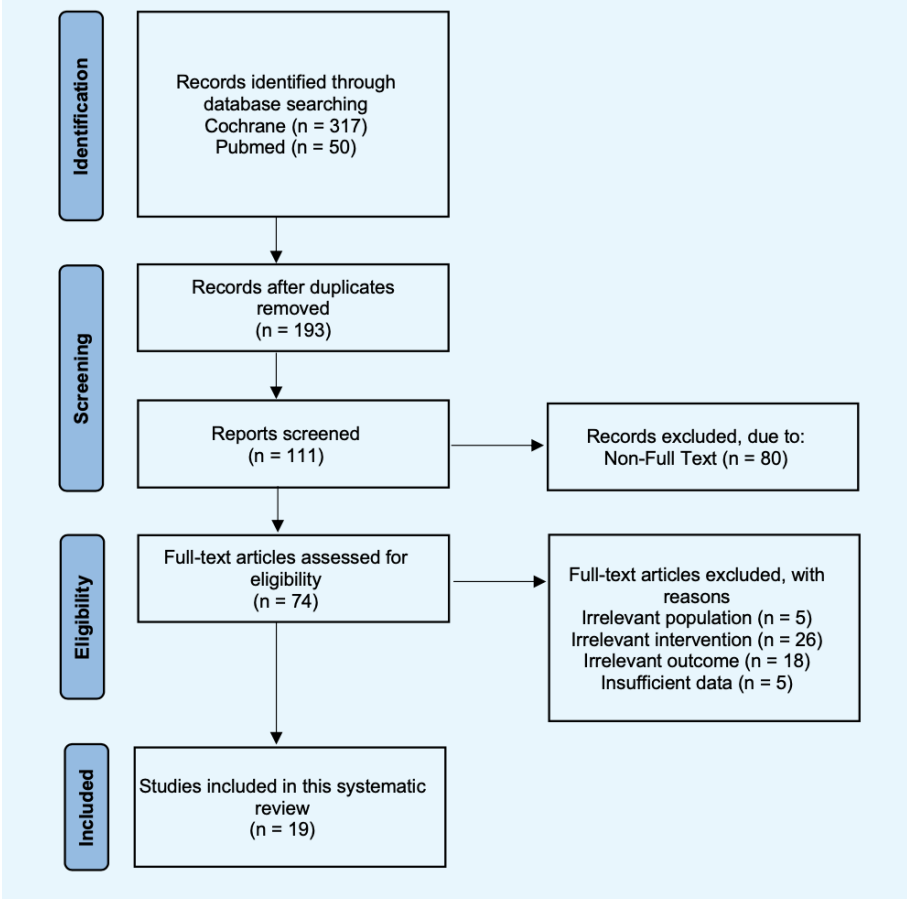


Fig 3. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria of the study.

women with surgical confirmed endometriosis. The mean VAS score of dyspareunia was reduced with no statistical difference between the three groups. Pelvic pain was reduced after 3 months post-intervention following dienogest, COCP and placebo. There is no significant effect of dienogest and COCP in treating dyschezia or dysuria. The mean overall score of QoL was substantially reduced in the three groups. Furthermore, the study discovered a low rate of adverse effects of dienogest and COCP, with the most common complications being hair loss, headache, hot flashes and nausea.[11]

Piacenti et al managed a study on surgical or radiological confirmed endometriosis with the therapy of oral dienogest or continuous EE/Levonorgestrel for 6 months. It was reported that dyspareunia and CPP significantly decreased, with no statistical difference between the two groups. QoL was improved, especially in the physical component, which decreased substantially, but there was no statistical difference between both groups. In addition, the study reported vaginal bleeding as the most frequent side effects.[12]

Taha et al. carried out a clinical trial comparing the efficacy of dienogest and COCP-containing EE/drospirenone. The study discovered that both interventions significantly improved the mean VAS score on non-cyclic pelvic pain; however, there are notable differences in statistics. Furthermore, CPP had a greater reduction of severity than dysmenorrhea and dyspareunia in both groups. The evaluation of QoL improvement was statistically meaningful, with no statistical differences in both interventions. The adverse effects encountered by patients were abnormal uterine bleeding, mood swings, headache, nausea and breast pain, which is more frequent in COCP than dienogest.[13]

Gonadotropin-releasing hormone agonist

After performing a surgical procedure to confirm endometriosis, Abdou et al. conducted a clinical trial comparing the effectiveness of dienogest consumed daily to leuprolide acetate (LA) injected monthly for 12 weeks. The alteration of the VAS score on pelvic pain, back pain and dyspareunia is significantly reduced, with no meaningful statistical difference between both interventions. The most frequent adverse effect in dienogest was vaginal bleeding and hot flushes, which were significantly higher than LA. Meanwhile, the most common adverse effect in LA is hot flushes and vaginal dryness, which were also consequently higher than the dienogest.[14]

Takaesu et al. conducted research on evaluating the efficacy of dienogest consumed daily and goserelin acetate injected monthly for 24 weeks and the group without any treatment assigned. Dysmenorrhea and CPP have significant improvement during progestin administration after 3 months of consumption, whereas it took 6 months for the non-treatment group. The study reported a gradual pain exacerbation in the three groups. The study only shows a substantial difference in recurrence rate between the dienogest and the non-treatment group. The most frequent side effect is irregular bleeding in the dienogest compared to goserelin, a hot flash.[15]

Purwanto et al. also performed a trial comparing the effect of therapy between dienogest and LA injected monthly within 12 weeks on women with laparoscopy-confirmed endometriosis. There was a decrease of VAS score in every 4 weeks of assessment in both groups with only a significant difference in the dienogest group. The side effects were found after 8 and 12 weeks of therapy. There are no statistical differences in adverse effects on both groups.[16]

Another research comparing the efficacy of dienogest and LA was conducted by Tang, Yang and Zhang on women with post-laparoscopic surgery in a 6-month observation. The average postoperative VAS score in both groups decreased; however, it only showed a statistically significant decrease in VAS score in the dienogest group. The recurrence incidence was eight patients in the dienogest with a 77.5% effectiveness rate and two patients in the LA group with an 82.9% effectiveness rate.[17]

Ceccaroni et al. compared two postoperative endometriosis treatments: oral dienogest and injection LA for 6 months for 30 months. It was found that both dienogest and GnRH agonists had noticeable reductions in dysmenorrhea, dyspareunia, dyschezia and CPP. The most frequent adverse effects of the dienogest were hot flushes in contrast to GnRH agonist, which was amenorrhea. Furthermore, there was a significantly lower incidence of amenorrhea and hot flushes in the GnRH agonist group than in the dienogest group. Meanwhile, there was a significantly higher incidence of spotting in the GnRH agonist group than in the dienogest group.18 Ozaki et al. carried out a clinical trial comparing the treatment outcome of post-laparoscopic endometriosis patients with daily oral dienogest and goserelin acetate injected monthly within 3 months. The comparison of preoperative and 4-month postoperative pain related to endometriosis was significantly lower in dienogest-administered patients than in goserelin acetate-injected patients. As for the adverse event, it showed that the incidence of hot flashes was lower in dienogest than in glycol acetate. In contrast, the incidence of breast pain and metrorrhagia was considerable higher statistically in goserelin acetate than dienogest.[19]

Gonadotropin-releasing hormone antagonist

Carr et al. conducted a randomized trial study comparing the outcome of depot medroxyprogesterone acetate (DMPA) administered subcutaneously on weeks 1 and 12 of treatment in contrast to oral GnRH agonist administered in two methods of dose (150 mg once daily and 75 mg twice daily). All treatment groups appeared to have a significant reduction of baseline VAS score in endometriosis-associated pain, with elagolix 75 mg twice a day having more pronounced effects compared to elagolix 150 mg every day and DMPA. The most frequent elagolix's side effects were headache, nausea, and nasopharyngitis, whereas DMPA were headache, nausea, and upper respiratory tract infection.[20]

Aromatase inhibitor

A clinical study performed by Acien et al. to determine the efficacy of a levonorgestrel-releasing intrauterine device (LNG-IUD) within 6 months and an aromatase inhibitor, which was anastrozole daily on patients with ultrasound-confirmed endometriosis. All endometriosis-related pain significantly improved in all groups during and after 6 months, and the most significant improvements observed were dysmenorrhea and CPP with anastrozole administered to the patient. Nevertheless, there was only a substantial difference between the anastrozole and non-anastrozole groups in the 1-year follow-up. The recurrence rate was similar between both groups (50%), but there was no consequential statistical difference.[21]

Placebo

A double-blinded, placebo-controlled, randomized study conducted by Tanmahasamut et al. assessed the efficacy of desogestrel daily in reducing endometriosis-associated pain for 6 months. Both groups significantly improved from the baseline VAS score in all types of pain. Desogestrel had a notable statistical difference in the VAS score reduction in overall pain, dysmenorrhea, and non-cyclic pelvic pain. Four patients were observed to have moderate-to-severe pain at 6 months post-treatment, which was significant statistically compared to desogestrel. Alteration of menstruation patterns was found in the desogestrel and the placebo, which was meaningful statistically.[22]

Another clinical placebo-controlled study was performed by Lang et al. to determine the effectiveness

of dienogest in endometriosis for 24 weeks. The study stated that the VAS score related to endometriosis-associated pelvic pain (EAPP) was an absolute reduction from the baseline, which was different considerably on the statistics after 24 weeks. Also, QoL shows improvement in the physical and mental health of dienogest. The most frequent adverse effect was vaginal haemorrhage.[23]

Yu et al. also conducted a placebo-controlled study to determine the efficacy of dienogest in endometriosis for 24 weeks. A mean change of VAS score from the baseline in EAPP on the dienogest group was found. On the contrary, the placebo group had a slight decrease in VAS scores. The study reported improvement in QoL in almost all physical and mental health domains. A slight decrease in mental health was observed in the placebo group, which may have affected the overall improvement. The most common adverse effect was vaginal haemorrhage.[24]

DISCUSSION

Interpretation of findings

Endometriosis is a hormone-dependent chronic inflammatory condition that needs prolonged therapy that corresponds to the efficacy of outcomes with sufficient tolerability. Hormonal therapies are necessary to be given to women with endometriosis by regulating hormones in order to prevent symptoms, progression of severity, and reoccurrence of the disease. Multiple aspects are considered when choosing the most convenient therapy, such as age, reproductive status, pain severity, economic status, possible adverse effects, incidence rate of recurrence, comorbidities, and many other considerations. Discontinuation of hormonal therapies tends to cause disease recurrence. The medication should be focused on long-term effectiveness with minimal adverse effects. Hormonal contraceptive therapies for endometriosis in this systematic review have significant outcomes in relieving endometriosis-associated pain, enhancing quality of life, preventing recurrence, and reducing the incidence of adverse effects.[2,4]

Among the proposed first-line therapies, progestogens have strong recommendations through their clinical effectiveness in treating endometriosis. In addition, progestogens have various modalities, availability, and affordable costs. Progestin is known for its indication of prolonged treatment. Dienogest is a fourth-generation high-selective progestogen, one of the first-line therapies for endometriosis. It is the first treatment choice due to its safety, efficacy, availability, tolerability, and affordable cost. The disadvantage of consuming dienogest might be the side effects, such as abnormal uterine bleeding; however, it has a lower side effect than other hormonal therapies in several studies.[25,26] Mostly, the studies included dienogest to be compared to other therapies and showed more efficacy than other hormonal treatments discussed below.

Throughout the study, progestogen showed significantly reduced endometriosis-related pain, lower recurrence incidence, minimal side effects, and improved quality of life of patients. Dienogest was compared to LNG-IUS, which both are effective. However, the comparison of efficacy was hardly known in contrast to being compared to oral medroxyprogesterone acetate, in which dienogest was more effective in relieving pain and had a lower incidence of adverse effects while the recurrence rate was similar.[6,8] LNG-IUS was also compared to another progestin-only contraceptives, an etonogestrel implant. Both were effective as long-term therapies, but both modalities have no significant difference in therapy outcomes. Therefore, LNG-IUS and etonogestrel implants are good choices for women who do not wish to consume medication daily. However, both modalities need to be administered by medical professionals due to their expensive cost and the possibility of unpredictable bleeding. Furthermore, those modalities may not overcome or control the pain.[7,25,27]

Three studies were conducted to determine the efficacy of progestogen: dienogest and desogestrel, which will be compared to placebo. Both dienogest and desogestrel were acceptable and effective as a treatment of endometriosis in reducing clinical symptoms, refining the quality of life and reducing the rate of side effects and recurrence.[22–24] Dienogest and desogestrel are selective progestins from nortestosterone derivatives which work specifically in endometrial tissues. Unlike other nortestosterone derivatives, dienogest has a lower androgenic effect with a higher anti-androgenic effect, which is beneficial in minimizing the effects of changes in fat and carbohydrate levels, while desogestrel has an androgenic effect. The selection of the type of progestin used must consider the androgenic effects, anti-mineralocorticoid effects, and glucocorticoid effects to minimise metabolic side effects.[28]

During the comparison between the progestogens and COC therapies, all of the progestogen treatments that were compared were only diengoest to various COCs. The most COC included in this study was oral ethinyl EE/levonorgestrel. It was an effective COC in treating endometriosis. However, dienogest had significantly reduced pain symptoms and higher quality of life scores than EE/levonorgestrel, but the incidence of side effects was similar in both interventions.[9,10,12] Other combinations of COC that were studied were the oral EE/ NOMAC

and EE / Drospirenone, which were also effective, but still, dienogest has a more significant impact in relieving symptoms, lower rate of side effects and better quality of patient life than both COC. COC is safe for long-term consumption, particularly for women who avoid unintended pregnancy.[10,13,29]

Another widely studied was the comparison between progestogens and GnRH agonists. Four studies used leuprolide acetate injection, which was compared to dienogest. Most of those studies mentioned that both hormonal interventions effectively treat endometriosis. However, dienogest has more advantages, such as it can be used as a long-term therapy with a lower recurrence rate and adverse effects than leuprolide acetate, which was only injected in short-term therapy.[14,16–18] Other two studies included goserelin acetate injection, which mentioned that dienogest was more effective than goserelin acetate in reducing endometriosis-associated pain. Regarding sustainability, dienogest is more sustainable than both GnRH agonist therapies.[15,19] Meanwhile, a study determined the efficacy of progestogens with GnRH antagonist and aromatase inhibitor, which can be prescribed as a second-line therapy for endometriosis. A clinical trial utilizing oral progestin-only contraceptives containing medroxyprogesterone acetate injected subcutaneously was compared to oral GnRH antagonist containing lanolin, mentioning that both hormonal interventions have a comparable efficacy on endometriosis therapy.[20] In addition, it is considered to combine hormone add-back therapy to avoid loss of bone mineral density in prescribing sole GnRH agonist and GnRH antagonists.[2,28]

This review also included one clinical trial using LNG-IUS compared to oral aromatase inhibitor anastrozole, which stated that prescribing both hormonal interventions was more effective than using LNG-IUS solely in reducing endometriosis-related symptoms. It is similar to guideline recommendations that aromatase inhibitors should be combined with other endometriosis hormonal therapies, such as progestogens, to reach their maximal efficacy.[21] In addition, long-term use of aromatase inhibitors can increase the risk of osteopenia, osteoporosis, and fracture; therefore, requires many considerations in prescribing aromatase inhibitors.[28]

Practical implications

Nowadays, the recent hormonal therapies include progestogen, combined oral contraceptive pills, aromatase GnRH agonists and antagonists in a variety of routes of administration. guidelines and expert insights have stated progestogen as an option in endometriosis.[30] Still, in choosing the suitable treatment options, it is recommended for clinicians to decide on an individual-based approach.[4] From all the proposed therapies, progestogen has appeared to be the foremost option utilized across nations. Progestogen that is prescribed by consideration of clinicians due to its side profile effects to each individual. Among the options of progestogen therapies, dienogest has emerged to be the most used progestogen.[4,30]

Dienogest, a 19-nortestosterone derivative, has been approved as an endometriosis treatment in several countries. Recently, there have been researches on investigating the safeness of dienogest to be a routine prescription on endometriosis in daily practices.[31] The Visanne Post-Approval Observation Study (VIPOS) is the largest non-interventional study conducted in six European countries in 7 years. The study mentioned that dienogest is safe as a long-term treatment for 15 months and longer with no serious side effects.[32] Meanwhile, The EffectiveNess of VISanne in Improving quality of life in Asian wOmen (ENVISIOeN), another non-interventional study carried out in six Asian countries concluded that dienogest improve patient's quality of life and endometriosis-associated pelvic pain in Asian women. The research also distinguished that dienogest can be a favorable first-line non-intervention option in a long-term treatment on alleviating endometriosis-related symptoms.[33]

Another treatment approach of endometriosis aside from hormonal therapies are non-hormonal therapies and surgery. The widely offered non-hormonal treatment on endometriosis is nonsteroidal anti-inflammatory drugs (NSAID). Although NSAID can be prescribed to patients on reducing endometriosis-associated pain solely or combined with hormonal therapy, it is incapable of reducing the progressivity of endometriosis. Also, several recent guidelines stated a weak recommendation on NSAID due to its gastrointestinal side effects especially in a long-term consumption.[4,34]

Surgery is as effective as hormonal therapy in relieving endometriosis associated-pain. Indication for surgery includes ovarian endometriomas, superficial peritoneal lesions, and deep infiltrating endometriosis that will decrease ovarian reserve by observing the measured anti-müllerian hormone (AMH) and ultrasonography measured total of the antral follicles.[35,36] In addition, undergoing surgery on endometriosis improves fertility outcomes by repairing the anatomical abnormalities caused by the ectopic endometrial implants.[37] Nowadays, one of the most common gynecological intervention, which is laparoscopy approach has been widely performed on endometriosis with its lower incidence of post surgery complications compared to laparatomy.[38,39] Aside from

its therapeutic function to endometriosis, laparoscopy approach also assists clinicians in diagnosing endometriosis along with MRI.[39,40] Hormonal therapy is suggested to be prescribed after the surgical intervention to enhance the outcome of the endometriosis-associated symptoms and prevent recurrence if the patient would not intend to get pregnant immediately. Meanwhile, in presurgical hormone treatment does not improve the surgery outcome but it is offered to reduce pain symptoms in a waiting interval as an adjunct before proceeding to surgical intervention.[4]

Limitations of study

The limitations of our systematic review are the limited number of studies carried out on each comparison of progestogens to other hormonal therapies due to our strict data inclusion requirement. The evidence of measured endometriosis-associated pain is diverse in every study included; therefore, it is challenging to compare. Furthermore, medication-related decrease in baseline parameters of pain is an important statement. However, it can be misleading to the placebo effect due to producing a high response rate, especially in a short-term study. A small-scale of populations might lead into a patient-based preference treatment and homogenous patients such as age, preference, socioeconomic status that can affect the interpretation of the investigations which also can be biased. Meanwhile, a brief follow-up research, could also influence the final interpretation mainly by only focusing on symptom improvement which might overshadow symptoms relapse, adverse effects and quality of life in the time ahead. A diverse and long-term follow-up could improve the conclusion more than previous.

Despite the various kinds of hormonal therapies that were compared, the distinct number of studies in every comparison of hormonal therapies made it challenging to assume the superiority of a specific, especially the lack of comparison of progestogen with progestogen itself, GnRH antagonist, and aromatase inhibitor. In addition, the progestogen that is compared to the placebo is only dienogest, which is now currently the most widely used progestogen in most countries. This made other progestogen effects to treat endometriosis unexplained well in comparison to placebo.

In terms of future research, identifying more studies in comparing progestin-only therapies to other hormonal therapies that might be used as endometriosis treatment with flexible criterias. By using more adjustable requirements of study such as a confined measured outcome could gain more studies than before that can be beneficial in concluding the findings. Furthermore, more investigations can be conducted regarding comparing progestins to other hormonal medications. It is also acceptable to any other aspect that could be analyzed to know the distinct superiority of hormonal contraception in endometriosis treatment, such as laboratory findings (hormone levels), radiological findings (endometrioma size), bone mineral density and others.

CONCLUSION

Based on the systematic review, progestogens are similarly effective or could be more effective than other hormonal treatments in decreasing endometriosis-associated pain, improving patients' life qualities, restraint relapse, and reducing adverse effects of endometriosis. There is no well-defined evidence of specific administration routes of progestogens that are more effective than another method of administration.

Data Availability Statement

This article review has provided all relevant publications.

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All authors acknowledge that there is no conflict of interest.

Registration Number of Clinical Trial

None.

Author Contributions

Conceptualization and methodology, S.A.P., R.N., and I.A.L. ; Investigation, S.A.P., R.N., I.A.L. ; Formal analysis, S.A.P., R.N., and I.A.L. ; Validation, R.N., I.A.L. ; Visualization and writing – original draft, S.A.P; Writing – review and editing, S.A.P. ; Supervision, R.N., I.A.L. ; All authors have read and agreed to the final version of the manuscript.

Use of Artificial Intelligence

There is no involvement of the artificial intelligence usage.

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