Original Article

Efficacy and Safety of Dienogest in the Management of Women with Endometriosis; Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Endometriosis is a sex hormone-dependent disease in which the uterine glands are out of the endometrial cavity. It affects about 10.8%–18.6% of women in the childbearing period.

Methods: We searched PubMed, Cochrane CENTRAL, SCOPUS, and Web of Science for randomized, double-blind, placebo-controlled studies. Quality assessment was evaluated according to GRADE. Clinical trials were assessed according to Cochrane's risk of bias tool. We included the following outcomes: Vas score for Pelvic pain, Bleeding or spotting, Adverse events, Physical health, Number of bleeding or spotting episodes, and Duration of bleeding or spotting episodes. We analyzed continuous data using mean difference (MD) and 95% confidence interval (CI), while dichotomous data were analyzed using odds ratio (OR) and 95% CI

Results: Five studies met the eligibility criteria for our meta-analysis. We found that dienogest was statistically better than placebo in terms of Vas score for Pelvic pain (MD=-26.68 [-40.74, -12.61], (P = 0.002), and physical health (MD=3.68 [2.40, 4.96], ($P < 0.001$), While placebo was better than dienogest regarding bleeding (RR=2.46 [1.65, 3.68], ($P < 0.001$), and adverse events (RR=1.19 [1.00, 1.42], (P = 0.04). There was no significant difference between both groups regarding number of bleeding or spotting episodes (MD=-0.51 [-1.10, 0.07], (P = 0.09), and duration of bleeding or spotting episodes (MD=8.69 [-0.84, 18.22], (P = 0.07).

Conclusions: Our results prove that dienogest is well tolerated and effective in the management of pelvic pain related to endometriosis.

Key Words: Dienogest; endometriosis; pelvic pain; placebo.

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INTRODUCTION

Endometriosis is a chronic inflammatory disease in which the uterine glands are out of the endometrial cavity[1]. It is a sex hormone-dependent disease that affects about 10.8%–18.6% of women in the childbearing period. This percentage may increase in infecund women from 20% to 50%[2]. Endometriosis may present with many unsteady symptoms like pelvic pain, Dysmenhorrea, dyspareunia, dysuria, dyschezia, and lower back pain[3,4]. Many patients who suffer from endometriosis had to take analgesics, especially NSAIDs to relieve the pain but do not improve the other symptoms in addition to their side effects on GIT[5].

There are several ways to treat endometriosis such as hormonal therapy, and surgical removal of the lesion whether open or laparoscopic. However, surgical removal has a high tendency of recurrence reaching 50% over 5 years[6]. Therefore, hormonal therapy is a good alternative to surgery although few drugs have been accepted for use in the management of endometriosis[4,7]. The accepted drugs for management include androgens (i.e., danazol), progestins, and gonadotropin-releasing hormone (GnRH) agonists[8]. Now, the most frequent method for treatment of endometriosis is by adding hormonal therapy pre and\ or post-surgical removal of the endometriotic lesion[9]. Each one of these drugs has adverse effects that limit its long-term use. GnRH agonists may affect the bone mineral density and decrease the level of estrogen[7,10]. Progestins also have some side effects such as weight gain, breast tenderness, and irregularity of the menstrual cycle[11,12].

Dienogest is one of these progestins which has magnificent effects as it combines the effect of estrogen and progestin on the endometrial wall besides its anti-inflammatory, and antiangiogenic effects[13–17]. Old trials proved that dienogest has a great effect on the reduction of pelvic pain associated with endometriosis with an optimal dose of 2 mg/day[18–20].

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This study is performed to assess the efficacy of dienogest on endometriosis-associated pelvic pain and quality of life in women with endometriosis

METHODS

Our study was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[21].

Search strategy

We searched the different electronic databases using the following strategy: (dienogest OR visanne OR dinagest) and (endometriosis).

Study Selection

We did the screening in the subsequent steps: Firstly, we imported the data from research databases to a Microsoft Excel[22] sheet by EndNote Software[23]. Then we performed titles and abstract screening of the articles presented in our Excel sheet. Finally, we performed a full-text screening of the included studies from the second step.

Eligibility Criteria

The inclusion criteria for study selection were:

- Study design: We included only randomized, double-blind, placebo-controlled studies and we excluded the other study designs, observational studies, conference abstracts, meta-analyses, all animal studies, and reviews.
- Participants: women suffering from endometriosis with pelvic pain.
- Intervention: Dienogest.
- Comparator: Placebo.

Outcomes: Vas score for Pelvic pain, Bleeding or spotting, Adverse events, Physical health, Number of bleeding or spotting episodes, and Duration of bleeding or spotting episodes.

Data Collection

We searched Scopus, PubMed, Cochrane library, and Web of Science databases till April 2022 for articles that matched our inclusion criteria. We collected three categories of data from included studies: the first category is the baseline and demographic characteristics of the included participants, such as the author, year, age, sample size, BMI, number of abortions, VAS (mm), and follow up (weeks). The second category included the main outcomes for analysis such as Vas score for Pelvic pain, Bleeding or spotting, Adverse events, Physical health, Number of bleeding or spotting episodes, and Duration of bleeding or spotting episodes. The third category was data of quality assessment. The process of data collection was done using Microsoft Excel[22].

Risk of bias Assessment

We followed The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Guidelines for assessing the quality of this study. We assessed the risk of bias in our included trials using Cochrane's risk of bias tool[19]. The tool assesses adequate randomization of patients, allocation concealment, and adequate blinding through seven domains. Each domain is put to either "low", "unclear", or "high" risk of bias.

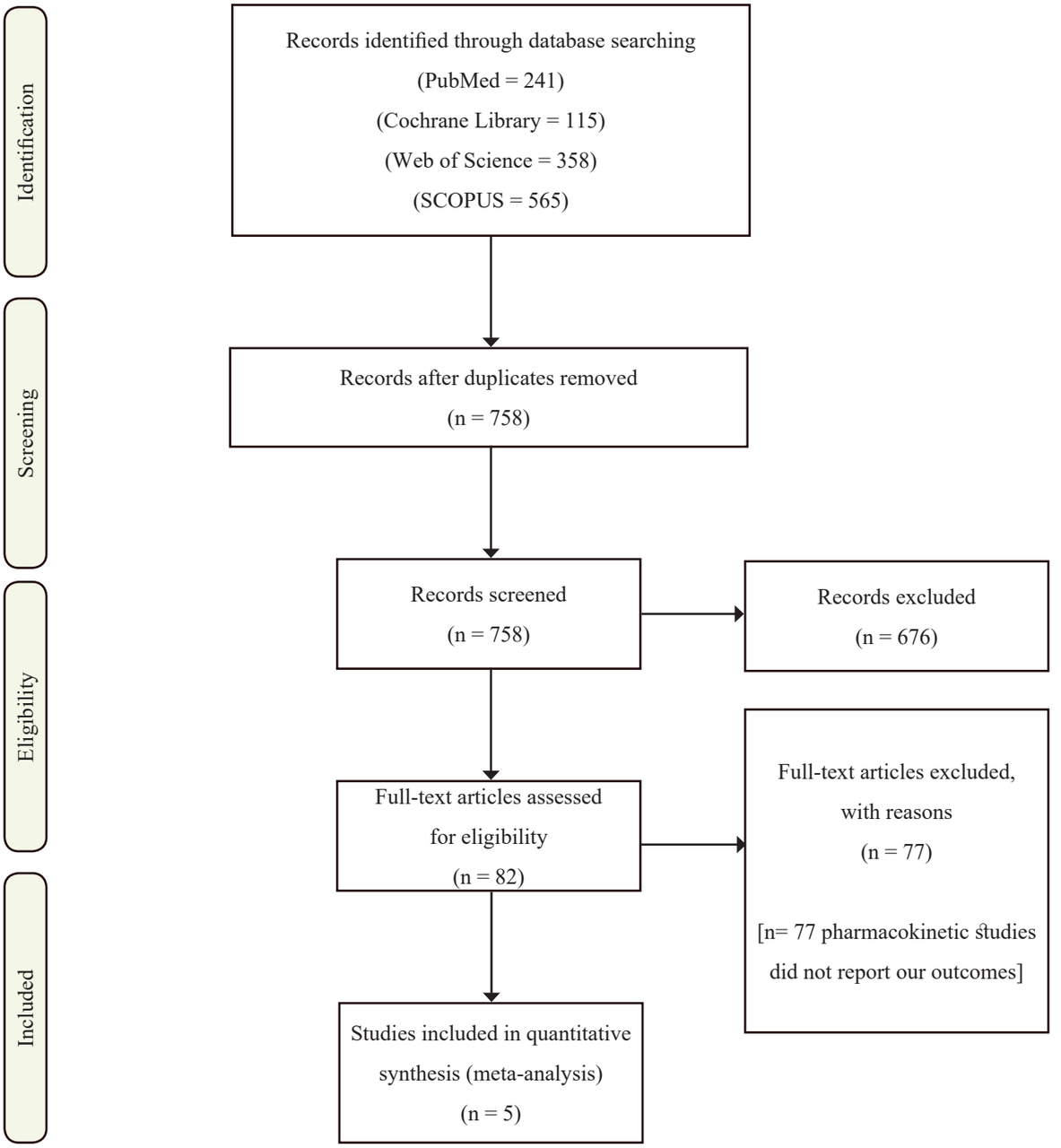
Statistical Analysis

We used Review Manager for the analysis of our outcomes. Our study included continuous and dichotomous outcomes. We analyzed continuous data using mean difference (MD) and 95% confidence interval (CI) by Review Manager software, while dichotomous data were analyzed using risk ratio (RR) and 95% confidence interval (CI). The homogeneous data were analyzed using a fixed-effects model, while heterogeneous data were analyzed under a random-effects model. To measure heterogeneity among the studies, we used the I2 and the *p-value* of the Chi-square tests[24]. Values of $P < 0.1$ or $I2 > 50\%$ were significant indicators of the presence of heterogeneity.

RESULTS

Summary of included studies

We described the results of our search in The PRISMA diagram (Figure 1). We included five RCTs (25–29) in our study. We analyzed 762 women with endometriosis in our study. A total of 345 patients received dienogest while 417 patients received placebo. The mean age of patients was 35.63 and 33.6 years in the dienogest and placebo groups, respectively. (Table 1) summarizes the included studies, the demographic data of patients, number of abortions, baseline VAS score for pain, and follow-up duration of patients.



ig. 1: shows a PRISMA flow diagram of our literature search.

Table 1: Shows summary of the included studies and baseline data of patients

STUDY ID	Sample Size		Age (years) mean(SD)		BMI, mean(SD)		Number of abortions ,mean(SD)		VAS mm, mean (SD)		follow up (weeks)
	DNG	Placebo	DNG	Placebo	DNG	Placebo	DNG	Placebo	DNG	Placebo	
Harada 2017	53	129	NR	NR	NR	NR	NR	NR	76.3(16.5)	77.7(15)	12,16,24
Lang 2017	126	129	35.5(5.02)	35.1(5.05)	21.7(2.81)	22.02(3.4)	NR	NR	57.1(20.4)	60.4(22.1)	12,16,24
Niakan 2021	30	30	34.22(6.54)	30.55(6.78)	NR	NR	0.05(0.22	0.44±0.80	NR	NR	12
Osuga 2017	34	33	37.3(7.9)	37.4(6.6)	22.2(3.2)	21.4(2.4)	1.2(1.2)	1.2(1.1)	66.3(19.1)	69.0(20.6)	12,16
Strowitzki 2010	102	96	31.5(6.7)	31.4(6.0)	22.7(3.5)	22.5(3.5)	NR	NR	56.8(18.0)	57.0(17.8)	12

N= number, SD= standard deviation, BMI= body mass index, and NR= not reported

Results of risk of bias

The quality assessment of the included RCTs yielded an overall low risk of bias. All studies reported proper randomization, allocation concealment, and blinding of participants and personnel therefore they were categorized as low risk of bias. Regarding the attrition bias, all studies were at low risk except Osuga *et al*[27] which did not report sufficient data so it was categorized as unclear risk. Other domains are illustrated in (Figure 2).

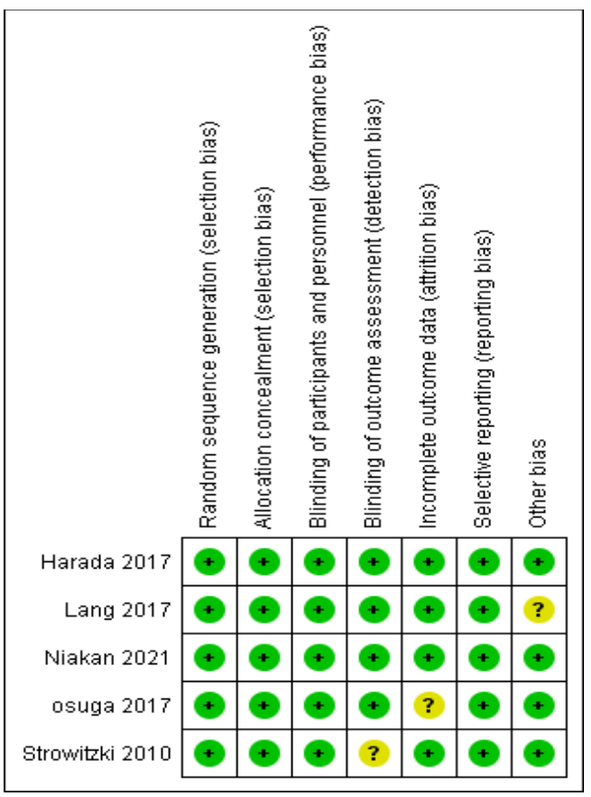


Fig. 2: shows risk of bias graph

Analysis of outcomes

1. Vas score for Pelvic pain

We performed a subgroup analysis of the Vas score for pelvic pain outcome according to the follow-up duration of the patients. Regarding 12 weeks follow-up duration, Three studies[26,27,29] reported the Vas score for pain. The overall analysis favored the dienogest group over the placebo group significantly (MD=-26.68 [-40.74, -12.61], (P = 0.002)). Data were heterogeneous ($P < 0.001$); I^2 = 90% (Figure 3a).

As for 16 weeks duration, two studies (27,29) assessed the Vas score at this duration. The combined mean difference favored the dienogest group (MD=-32.73 [-46.64, -18.82], ($P < 0.001$)). Pooled analysis was heterogeneous (P = 0.02); I^2 = 81%) (Figure 3b).

Two studies[25,29] evaluated the pain outcome at 24 weeks. The overall mean difference showed that dienogest significantly reduced the pain compared to placebo (MD=-32.94 [-47.34, -18.54], ($P < 0.001$)). Data were heterogeneous (P = 0.002); I^2 = 90% (Figure 3c).

2. Bleeding or spotting

Three studies assessed the spotting or bleeding outcome[27–29]. Bleeding was significantly lower in the placebo group than in the dienogest group (RR=2.46 [1.65, 3.68], ($P < 0.001$)). The overall analysis was homogeneous (P = 0.74); I^2 = 0% (Figure 4).

3. Adverse events

Four studies reported adverse events[26–29]. The combined risk ratio demonstrated that the dienogest group was associated with more adverse events than the placebo group (RR=1.19 [1.00, 1.42], (P = 0.04)). Data were homogenous (P = 0.24); I^2 = 29% (Figure 5).

4. Physical health

Physical health was reported by two studies[28,29]. Values of physical health were significantly higher in the dienogest group (MD=3.68 [2.40, 4.96], ($P < 0.001$). The analysis was homogenous (P = 0.29); $I^2 = 10\%$ (Figure 6).

5. Number of bleeding or spotting episodes

Two studies (26,29) reported this outcome. The overall mean difference showed no variation between both groups (MD=-0.51 [-1.10, 0.07], (P = 0.09)). The combined analysis was heterogeneous (P = 0.01); $I^2 = 84\%$. We could not solve the heterogeneity by either the leave-one-out method or performing subgroup analysis. (Figure 7).

6. Duration of bleeding or spotting episodes

This outcome was measured by three studies[25,26,29]. We found no difference between both groups (MD=8.69 [-0.84, 18.22], (P = 0.07)). Data were heterogeneous ($P < 0.001$); $I^2 = 97\%$ (Figure 8).

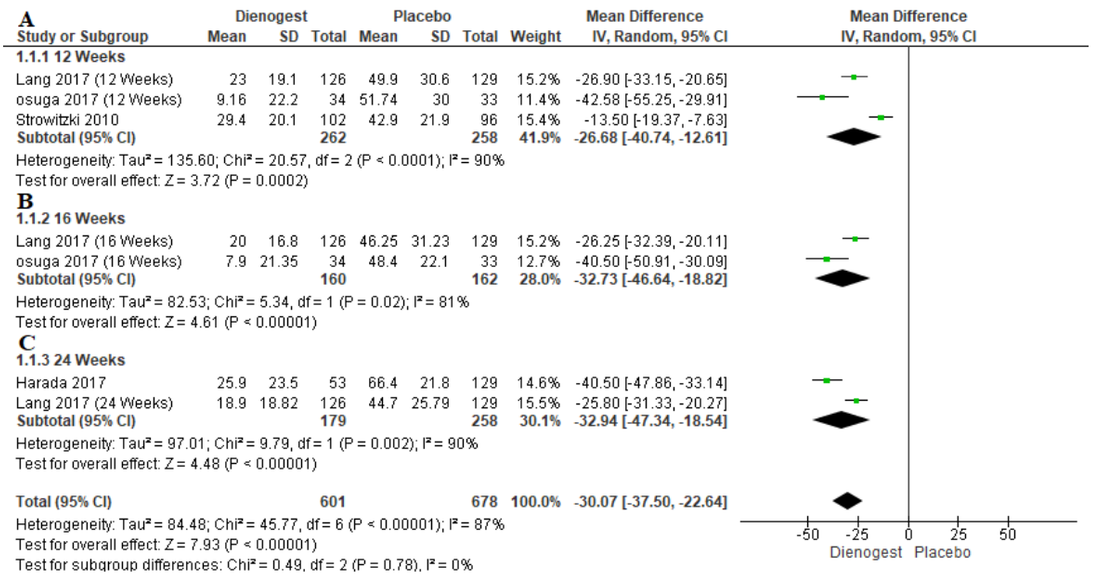


Fig. 3: Vas score for Pelvic pain

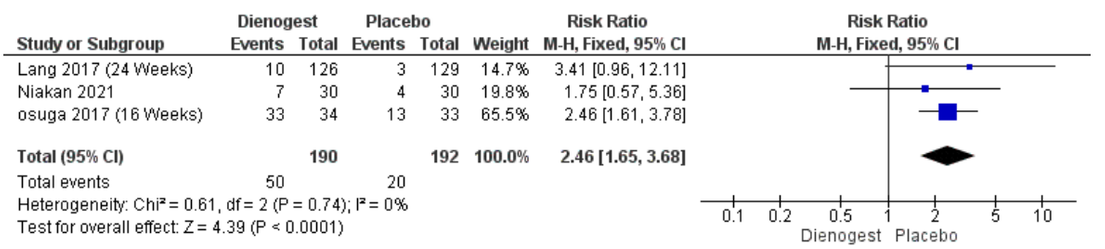


Fig. 4: Bleeding or spotting

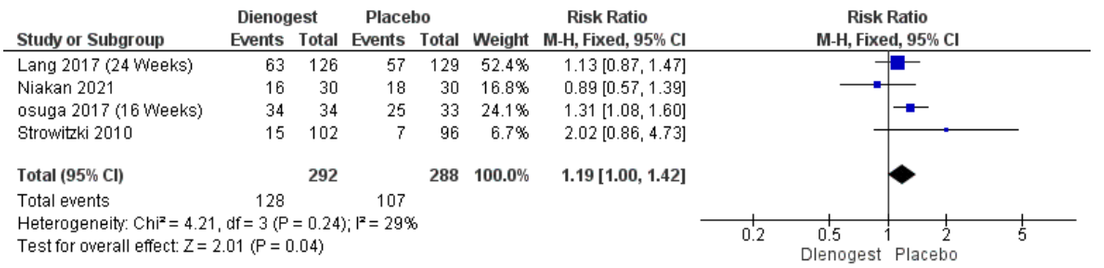


Fig. 5: Adverse events

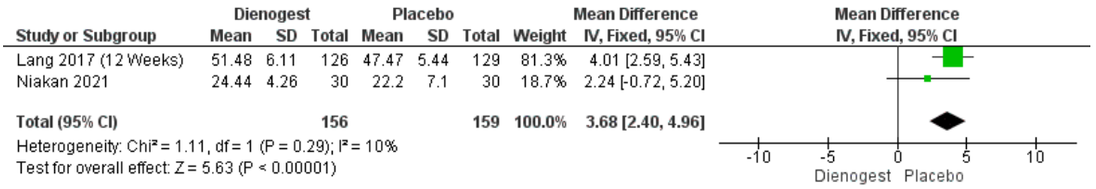


Fig. 6: Physical health

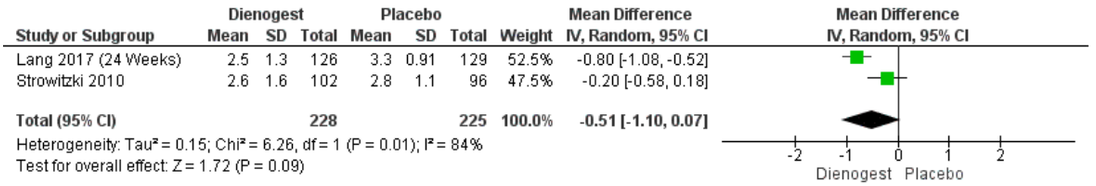


Fig. 7: Number of bleeding or spotting episodes

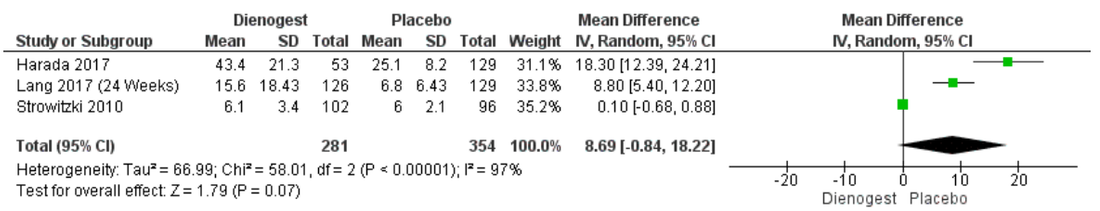


Fig. 8: Duration of bleeding or spotting episodes

DISCUSSION

Endometriosis is considered a widespread disease as it affects about 15% of women in their childbearing period. Endometriosis may cause a reduction in the quality of life of these women as it causes chronic pelvic pain[30–32].

Many physicians believe that the endometriosis treatment has to be empirical even without a confirmed diagnosis of the disease by laparoscope. The surgical management showed a risk of morbidity and might cause temporary effectiveness. Compared to medical treatment, surgical treatment is more expensive and more invasive[33]. Anti-inflammatory, analgesics, progestins, and combined contraceptive pills are the first line of medical treatment for endometriosis[33–35]. The long-term treatment of endometriosis using estrogen-progestogen combination and progestins was revealed to be effective, safe, inexpensive, and well-tolerated[36].

The second line of the medical treatment for women who showed no improvement with the first line of the treatment is the levonorgestrel-releasing intrauterine system (LNG-IUS), gonadotropin-releasing hormones agonists (GnRH-a)[37,38]. Utilization of GnRH analogs is effective for endometriosis but may cause symptoms of hypoestrogenism. Long-term therapy of GnRH is associated with a reduction in bone density[39].

Dienogest is a highly selective progestin, which belongs to the fourth generation of progestin. It does its action by binding to progesterone receptors with a small mineralocorticoid, androgenic, glucocorticoid, or estrogenic effects[19]. Dienogest shows a combination of progestogenic, anti-inflammatory, antiproliferative, and antiangiogenic effects that lead to a decrease in the growth of endometrial tissue[16,40,41]. One of the features of endometriosis is chronic inflammation. Dienogest can inhibit the expression of toll-like receptor 4 (TLR4) and the proinflammatory function of human endometrial epithelial cells (hEEC)[16].

There are two studies[32,42] that evaluate the efficacy of long-term therapy, 52-53 weeks, using dienogest for endometriosis. Their results show the ability of dienogest to improve the symptoms such as chronic pelvic pain with manageable side effects. Most patients treated with dienogest complained of abnormal menstruation. However, these patients tolerated this symptom and continued taking the drug. Long-term therapy is associated with a reduction of the intensity and frequency of this bleeding[32,42].

In our systematic review and meta-analysis, we evaluate the efficacy and safety of dienogest in women suffering from endometriosis. Our result showed that dienogest was associated with more reduction of pain than the placebo however dienogest was associated with more bleeding and

adverse events than the placebo. Regarding the number of bleeding times and duration of bleeding, there was no significant difference between the dienogest group and the placebo group.

Andres *et al*[43] conducted a meta-analysis that included nine studies and evaluated the efficacy and safety of dienogest. Regarding the conclusion of this meta-analysis, a dose of two mg/day of dienogest showed good tolerability and efficacy in the management of endometriosis similar to the effect of GnRH analogs.

In 2020 Samy *et al*[44] performed a network meta-analysis of 36 randomized controlled trials. The results of this network proved that combined hormonal contraceptives, dienogest, GnRH analogs, elagolix, and progesterone were the best options for management of the pelvic pain related to endometriosis. There were some limitations like the significant heterogeneity between some outcomes and the lack of studies in some treatment arms.

Lin *et al*[45] conducted a systematic review and meta-analysis of the safety and efficacy of dienogest in the management of endometriosis. Lin *et al* performed an analysis of 1493 patients from seven clinical trials. The results revealed that the dienogest was better than the placebo and GnRH placebo for the management of pain related to endometriosis. However, the included studies had many differences like the treatment duration, the route of administration, the category of endometriosis, the types of GnRH analogs, and the participants' ethnicity. All of these differences explain the heterogeneous data extracted from the included trials.

Osuga *et al*, Strowitzki *et al*, Lang *et al*, and Niakan *et al*[26–29] performed randomized double-blind placebo trials that compare the dienogest and the placebo for management of endometriosis. All of them had the same conclusion that dienogest showed a significant improvement in the pain related to endometriosis. Yu *et al*[46] performed a 28-week open-label extension study of women who completed 24 weeks in a double-blind controlled trial[26]. Its result proved that long-term therapy with dienogest has significant efficacy in relieving endometriosis-associated pelvic pain (EAPP).

LIMITATIONS

The interpretation of our results is limited by the small sample size of patients and the small number of studies. Also, there was a lack of evidence on different important outcomes that may affect the choice of the assessment tool. Also, the heterogeneity in some outcomes is another limitation.

CONCLUSION

Dienogest shows a significant improvement in endometriosis-associated pelvic pain (EAPP) and the physical health of the patients. Dienogest is considered a well-tolerated and effective treatment for EAPP.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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