REVIEW ARTICLE

EFFICACY, EFFECTIVENESS, AND SAFETY OF DIENOGEST FOR THE TREATMENT OF ENDOMETRIOSIS: A SYSTEMATIC REVIEW

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Highlights: (1) Dienogest showed superior efficacy to placebo in reducing overall pain. (2) Evidence indicates non-inferiority of dienogest compared to leuprorelin. (3) No significant differences in adverse events between dienogest and comparators.

PRE-PROOF
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EFFICACY, EFFECTIVENESS, AND SAFETY OF DIENOGEST FOR THE TREATMENT OF ENDOMETRIOSIS: A SYSTEMATIC REVIEW

ABSTRACT

Endometriosis is a chronic and benign inflammatory disease that affects women of reproductive age and impairs their quality of life. Objective: To investigate the efficacy, effectiveness, and safety of using dienogest in the treatment of endometriosis compared to placebo and medications offered within the Brazilian Unified Health System (SUS). Method: A systematic review was conducted through searches in four scientific databases, following the recommendations of the Cochrane Handbook and reporting according to The PRISMA 2020 statement checklist (PROSPERO: CRD42023388774). Results: Nine studies were included, totaling 1,625 participants. For overall and pelvic pain, the results may favor dienogest over placebo and goserelin. There was no difference between dienogest and triptorelin for overall pain, and dienogest appears to be superior to triptorelin for pelvic pain. Dienogest was non-inferior to leuprorelin. Between dienogest and the other comparators, there was no difference in lower back pain, dyspareunia, pregnancy rate, treatment discontinuation, and total adverse events. Conclusion: Dienogest may be safe when compared to placebo and the drugs available in the SUS. Regarding efficacy and effectiveness, the results suggest the superiority of dienogest compared to placebo and goserelin; non-inferiority compared to leuprorelin, and no difference between dienogest and triptorelin and ethinylestradiol+levonorgestrel; however, the confidence in the evidence is uncertain.

Keywords: Endometriosis; Dienogest; Estradiol; Systematic Review

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INTRODUCTION

Endometriosis is a chronic and benign inflammatory disease, dependent on estrogen, that primarily affects women of childbearing age, despite reports in pre-menarcheal patients and an incidence of 2 to 5% among post-menopausal women[1]. It is characterized by the presence of functional tissue similar to the endometrium located outside the uterine cavity[2,3] and, although not malignant, shares characteristics similar to cancer, such as

resistance to apoptosis, development of local and distant foci, invasion of other tissues, and a chronic inflammatory environment[4]. It is estimated that approximately 10% of women of reproductive age and 50% of infertile women worldwide live with endometriosis[3,5,6]. Menstrual irregularities, chronic pelvic pain, dysmenorrhea, dyspareunia, and infertility are signs and symptoms that can decrease a patient's quality of life[3,6,7].

Hormonal therapy is generally initiated when endometriosis is suspected in young women before surgical confirmation of the lesions and when symptoms persist or return after surgical intervention. Treatment includes medications that modify the hormonal environment, either by suppressing ovarian activity or by acting directly on steroid receptors and enzymes found in the lesions[4]. Combined oral contraceptives (estrogen and progesterone) are the first-line treatment for most women with endometriosis-related pain. Those treatments can be used long-term, are well-tolerated, relatively inexpensive and easy to use, and provide contraception and additional benefits, including reducing the risk of ovarian and endometrial cancer. However, their use carries a thromboembolic risk related to estrogen, which does not occur with the use of progestins. Treatment with high doses of progestins is cheaper and not associated with bone loss, unlike gonadotropin-releasing hormone (GnRH) analogs, in addition to being better tolerated, having no androgenic side effects, and having a less detrimental impact on lipids than danazol[8].

Dienogest is part of the progestin class, exhibiting high specificity for the progesterone receptor, insignificant binding affinities for estrogen, androgen, glucocorticoid, and mineralocorticoid receptors, and high tolerability by patients[9]. It also possesses progestogenic and antiestrogenic effects on eutopic and ectopic endometrium, without the androgenic effects of other 19-norprogestin derivatives. On the other hand, it maintains the typical antiandrogenic effect of progesterone derivatives and does not cause metabolic imbalances.

Dienogest-only therapy has contraindications similar to other progestins. According to the Clinical Protocol and Therapeutic Guidelines (PCDT) for Endometriosis, published in 2016 by Brazilian Ministry of Health, in addition to surgical treatment, the following

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medications are available in the SUS: combined oral contraceptives (ethinylestradiol+levonorgestrel); medroxyprogesterone; danazol; and GnRH analogs (goserelin, leuprorelin, and triptorelin)[10].

Thus, despite being the only medication with an indication approved in the package insert by the National Health Surveillance Agency (Anvisa) for the treatment of endometriosis in Brazil[11], dienogest is not incorporated into the Unified Health System (SUS).

Considering the possibility of making a therapeutic alternative with greater efficacy available in the SUS, this study investigated the efficacy, effectiveness, and safety of using dienogest in the treatment of endometriosis in women, compared to placebo and the medications currently available in the SUS.

METHODS

A systematic review was conducted based on the Brazilian methodological guidelines for systematic review development[12], following the recommendations of the Cochrane Handbook[13] and reporting according to The PRISMA 2020 statement checklist[14]. The review protocol was previously developed and registered on the PROSPERO platform: CRD42023388774.

All supplementary material related to this systematic review can be found at:

https://osf.io/pkwu9/?view_only=e94073d21ac743dda33f7e453f26c768.

Based on the research question "*Is the use of dienogest effective and safe for the treatment of endometriosis, compared to placebo and the medications currently available in the SUS (ethinylestradiol+levonorgestrel; medroxyprogesterone acetate; danazol; goserelin; leuprorelin or triptorelin)?*", the PICOS acronym was developed, with: P (population): women diagnosed with endometriosis; I (intervention): dienogest; C (comparators): placebo; ethinylestradiol+levonorgestrel; medroxyprogesterone acetate; danazol; goserelin; leuprorelin; triptorelin; O (Outcomes): pain (change in total endometriosis-associated pelvic pain score, non-menstrual pelvic pain score, dyspareunia score,

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dysmenorrhea score, lower back pain, overall pain); endometriosis recurrence; total and severe adverse events (AEs), symptom improvement; quality of life; pregnancy rate; treatment discontinuation due to AE; S (Study design): Randomized Controlled Trials (RCTs), observational studies (cohort), cohort studies with a comparator group.

RCTs and cohort studies that evaluated the efficacy, effectiveness, and safety of dienogest use in the treatment of endometriosis were included, regardless of the patient's age or prior surgical procedure.

Excluded were conference abstracts, tertiary studies, studies evaluating dienogest combined with other pharmacological therapy, studies that did not compare dienogest to one of the medications available in the SUS, studies without a comparator, studies that identified only the drug class without specifying the medication, studies evaluating the intervention in the context of in vitro fertilization, and studies evaluating dose-response, pharmacodynamics, or pharmacokinetics of the medication.

Searches were conducted in September 2022, in five scientific literature databases: PubMed Central and MEDLINE (Medical Literature Analysis and Retrieval System Online/via PubMed), EMBASE (Elsevier), Cochrane Library, and LILACS (Latin American and Caribbean Health Sciences Literature/via VHL – Virtual Health Library). Additionally, references from systematic reviews found in the databases and primary studies included in the eligibility process were consulted.

Search strategies were developed based on the combination of keywords, structured from the PICOS acronym, using MeSH terms in PubMed and Cochrane, DeCS in Lilacs, and Emtree in Embase, combined by appropriate Boolean operators. There were no restrictions regarding the year and language of publication. The complete search strategy is described in the supplementary material.

Evidence selection was performed in duplicate by five independent reviewers, and any disagreements were resolved by consensus. Duplicate publications were identified using Rayyan software[15]. In the screening stage, studies were selected by reading the title and abstract, using Rayyan software[15], keeping those studies that met the eligibility criteria (according to the research question).

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Subsequently, a full reading of the initially selected studies was performed, keeping those studies that met the eligibility criteria, and reporting the reasons for exclusion. Data extraction was performed in duplicate by five reviewers, independently, and any disagreements were resolved by consensus. Extraction was carried out in a single Microsoft Office Excel® spreadsheet, validated by two other methodologists.

Regarding study characteristics, data were extracted on: author/year, study design, countries, participants (total and per group), mean age, endometriosis severity, measurement instruments used for outcomes. In the absence of information, the term "not reported" was used.

Data were extracted regarding the primary outcomes: pain (overall pain, pelvic pain, dyspareunia, dysmenorrhea, lower back pain, and Biberoglu and Behrman pain scale - B&B), endometriosis recurrence, total and severe adverse events (AEs); and secondary outcomes: symptom improvement; quality of life; pregnancy rate; treatment discontinuation due to AE.

Pain and quality of life data were extracted in mean and standard deviation format, except for dyspareunia and B&B scale results which had a specific score. For the outcome of treatment discontinuation due to adverse events, data were extracted by absolute number. For studies that did not report total adverse events, the data for the adverse event with the highest prevalence among those reported in the studies was considered. All follow-up times (standardized in weeks) for the outcomes reported in the studies were extracted.

The methodological quality of the studies was assessed by five reviewers, independently. The Rob 2.0 (Revised Cochrane risk-of-bias tool for randomized trials) was used for assessing the risk of bias in RCTs[16] and the ROBINS-I (Risk of Bias of Non-randomised Studies of Interventions) tool for non-randomized trials and observational studies[17]. Disagreements in each methodological assessment were resolved by consensus.

A narrative analysis was performed with mean and proportion results for studies that could not be statistically pooled. Where meta-analyses were possible, for dichotomous data, results were presented as risk ratios (RR) with a 95% confidence interval (95% CI),

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and for continuous outcome data, results were presented as mean differences (MD) or standardized mean differences (SMD) and 95% CI.

The analysis was performed by intention-to-treat, to measure the impact in case of participant losses before study completion. When possible, data from different studies were summarized through meta-analysis, observing the clinical and methodological characteristics of the included studies. Statistical heterogeneity was tested in each meta-analysis using Cochrane's Q, I^2, and Chi^2 statistics calculated internally in the Review Manager – RevMan software[18].

Available data were used to perform statistical analyses using RevMan software[18] for standardized mean difference, mean difference, and risk ratio, and a forest plot was generated in this software. When there was no high heterogeneity, data from individual trial results were pooled in a meta-analysis. Analyses were performed using random-effects models. In cases where data could not be pooled or only one study was included in the comparison, results were presented in narrative form.

The review protocol considered the assessment of publication bias, using Egger's test and funnel plot, in which a weighted estimate of the linear regression of the intervention effect is performed and asymmetry is an indication of bias graphically, if more than 10 studies were included in the meta-analysis.

The overall quality of evidence for the most relevant primary outcomes (overall pain, pelvic pain, dysmenorrhea, dyspareunia) and important outcomes (adverse events) was assessed using the GRADE system - Grading of Recommendation, Assessment, Development and Evaluation[19], using Gradepro software. The importance of the outcomes was classified according to Hirsch et al.[20], a study identified through the Core Outcome Measures in Effectiveness Trials (COMET)[21].

It was verified that the empirically validated minimal clinically important difference (MCID) for endometriosis-associated pelvic pain, measured on a 0 to 100 VAS, is 10 points[22]. Therefore, on a 0 to 10 VAS, a difference of one point was considered significant. For the other outcomes, no relevant MCID was found. Thus, for pain-related outcomes, an MD greater than 10 points on a 100-point scale was considered an MCID, analogous

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to pelvic pain. For the others, the line of no effect was used as an MCID for risk ratios and risk difference.

RESULTS

From 686 publications identified in the databases, after removing duplicates, 613 titles and abstracts were evaluated after duplicate exclusion. Sixty-nine eligible reports were read in full, of which 57 were excluded because they did not meet the criteria of this systematic review. The excluded publications and the reason for exclusion are presented in the Supplementary Material. Thus, 12 publications were included[23-34], referring to nine studies.

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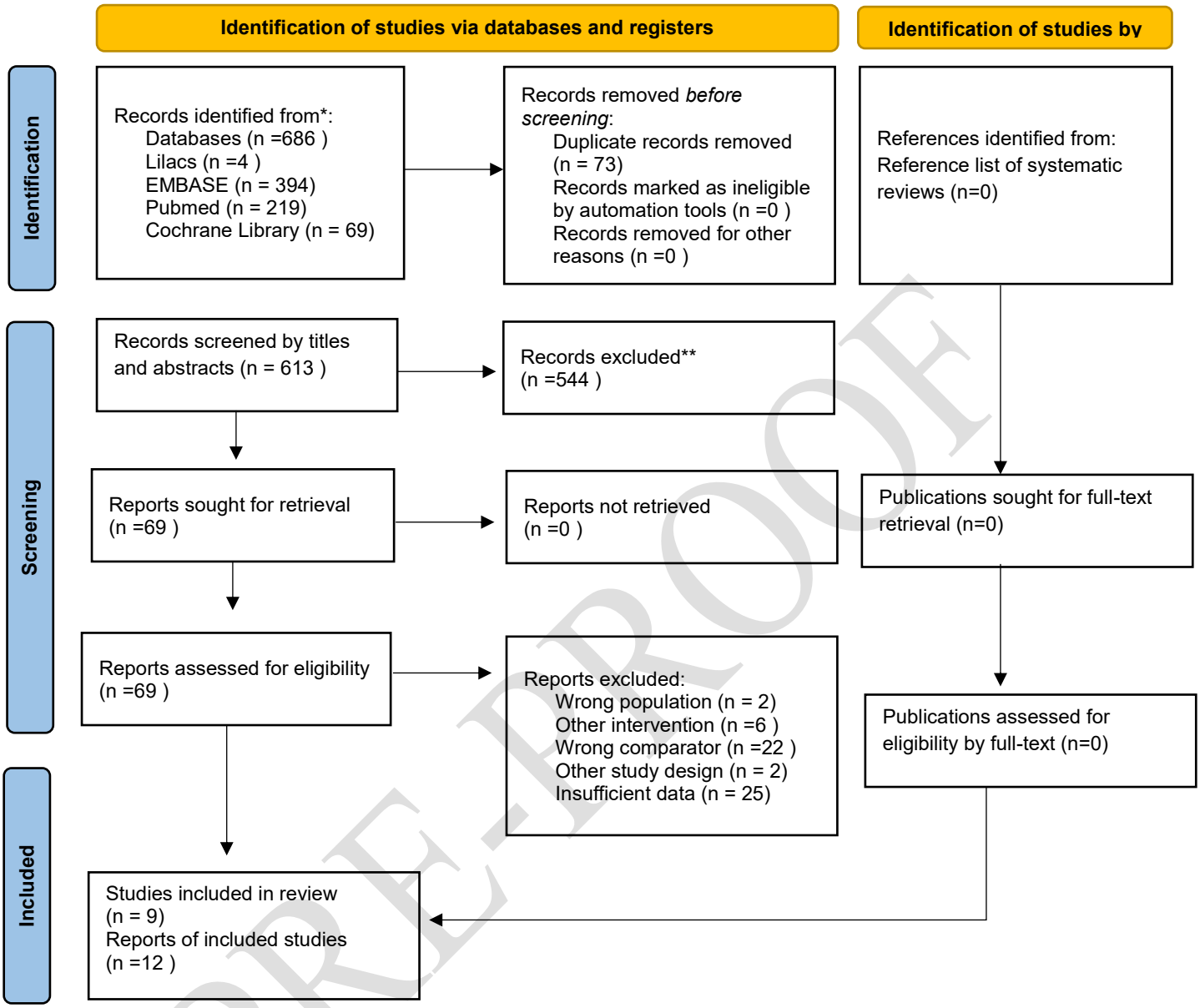

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Figure 1. Flowchart of study selection.

Source: Authors' own elaboration, adapted from the PRISMA 2020 recommendation.[14]

Detailed characteristics of the included studies are in the supplementary material. Regarding study designs, eight RCTs[23-26,28,30,32,33] and 2 prospective cohorts[29,34] were included. Although Takenaka et al.[34] reported it as a naturalistic study, in accordance with

the described method, the study design was categorized by the reviewers as a cohort. Similarly, Takaesu et al.[33] reported that the study consisted of a randomized cohort, and the authors of this review classified it as an RCT. The studies were conducted mainly in European countries such as Germany, Austria, Spain, France, Italy, Poland, Portugal, and Ukraine[24,29,30,32], followed by countries located in East Asia such as China and Japan[25,28,33,34], the Middle East, represented by Iran26, and Africa, represented by Egypt[23]. Four studies were reported as multicenter[24,25,30,32]. In total, 1625 participants were included, with an average of around 159 per study, ranging from 3034 to 262 women[25]. The dienogest group had an average of 73 participants, ranging from 1534 to 126 participants[25]. The control group had an average of 70 participants, ranging from 1534 to 129 participants[30]. All studies used 2 mg of dienogest daily, in a single dose, with the exception of one study[34], where the administration form was 1 mg, twice daily. The identified comparators were placebo (once daily)[25,26,30], leuprorelin (1.88 mg or 3.75 mg, every 28 days)[23,32,34], ethinylestradiol + levonorgestrel (daily dose of 30 μg + 0.3 mg or 0.1 mg + 0.02 mg)[26,29], goserelin (1.8 mg every 28 days)[28,33], and triptorelin (3.75 mg every 28 days)[24]. Follow-up time ranged from 12 to 24 weeks, with 24 weeks being the most frequent follow-up period[25,26,29,32,33].

Fifteen outcomes were found: overall pain[24,25,28,30,32], pelvic pain[23,24,26,30,32-34], lower back pain[23], dyspareunia[24], dysmenorrhea[24], dyspareunia score[24,26], B&B pain scale[30,32], quality of life[25,26,30,32], patient-reported improvement[25,30], endometrioma recurrence[28], total adverse events[24–26,32,33], severe adverse events[23–26,32,33], pregnancy rate[24,25], and treatment discontinuation[26,32]. Due to the number of outcomes found, this article presents only the results related to overall pain, pelvic pain, and total adverse events. All results generated from the analysis of the other outcomes are available in the supplementary material. The authors reported no conflicts of interest in six studies[23,26,28,29,33,34]. Most studies were funded. Only one reported not having received funding[23], and three studies did not provide this information[28,29,34].

Women aged 18 to 45 years were included, with a mean age of 32 years. Participants had endometriosis of stages I to IV severity, classified by the revised American Society for Reproductive Medicine (r-ASRM) or the revised American Fertility Society (r-AFS)

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score. Only four studies[28,29,33,34] did not report the severity of endometriosis or did not limit the inclusion of women by severity.

Five studies indicated that dienogest was used after laparoscopic surgery[23-26,33], while two studies[28,34] indicated that use occurred before surgery. The other studies did not report whether use occurred before or after surgery[29,30,32].

For the evaluation of pain-related outcomes, studies used the visual analog pain scale, with some differences in its measurement. Adverse events were identified through self-report, the Hoechst Adverse Reaction Terminology System (HARTS), and unspecified questionnaires.

Due to the heterogeneity of study reports, it was only possible to perform a meta-analysis of studies that reported total adverse events in the dienogest versus placebo comparison. The other results of the included studies were described narratively.

The risk of bias judgment for some outcomes is described in Figure 2. Penalties involved: study protocol not identified[24,28]; randomization list generated by the funding company[31]; absence of information on the method of data collection[24,26]; absence of information on the pain scale used[24]; absence of allocation concealment[29]; absence of information on patient blinding[28,34] and assessor blinding[31-33]; absence of information on baseline[33] and on the method of drug administration[34]; information on allocation concealment not presented[28], follow-up losses[25], and on the criteria for outcome analysis[30]. The evaluation of other secondary outcomes is presented in the supplementary material.

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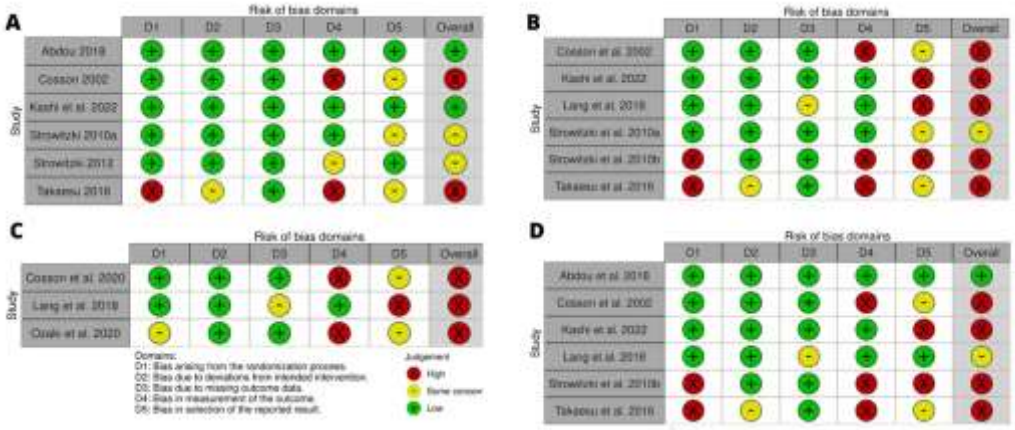

Figure 2. Assessment of the risk of bias in RCTs, according to the Rob2.0 tool for the outcomes: (A) pelvic pain; (B) total adverse events; (C) general pain; (D) serious adverse events.

Source: Authors' own elaboration, using RobVis.

As studies comparing dienogest to four different medications and placebo were included, they were presented by outcome and comparison to facilitate understanding. Differences were found in study designs, scales used for outcome measurement, and follow-up times used in the studies, and in some situations, data were not presented in a consolidated manner. A more in-depth description of baselines and results of other outcomes is in the supplementary material.

Overall pain was reported for comparisons of dienogest with placebo, triptorelin, and goserelin, at two follow-up times (16 and 24 weeks). The results favored dienogest over placebo and goserelin, while there was no difference between dienogest and triptorelin (Table 1).

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Table 1. Results for general pain and pelvic pain between dienogest and different comparators.

General pain				
Comparator	**Author (year)**	**Follow-up time**	**Results**	**GRADE (Certainty of evidence)**
Placebo	Lang et al. (2018)	24 weeks	Favors dienogest (MD: -25.80, 95% CI -31.33 to -20.27; p<0.00001).	⊕⊕⊕◯ Moderate
Triptorelin	Cosson et al. (2002)	16 weeks	There was no difference in effect (RR: 0.97, 95% CI 0.83 to 1.14; p=0.74).	⊕⊕◯◯ Low
Goserelin	Ozaki et al. (2020)	16 weeks	Favors dienogest (MD: -2.60, 95% CI -4.83 to -0.37; p=0.02).	⊕⊕◯◯ Low
Pelvic pain				
Comparator	**Author (year)**	**Follow-up time**	**Results**	**GRADE (Certainty of evidence)**
Placebo	Niakan et al. (2021)	12 weeks	Favors dienogest (MD -1.96, 95% CI -3.46 to -0.46; p=0.01).	⊕⊕◯◯ Low
	Strowitzki et al. (2010a)	24 weeks	Favors dienogest (DM: dienogest -27.4 mm, placebo -15.1 mm).	⊕⊕◯◯ Low
Triptorelin	Cosson et al. (2002)	16 weeks	Favors dienogest (RR: 0.71, 95% CI 0.51 to 0.97; p=0.03).	⊕⊕◯◯ Low

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	Ozaki et al. (2020)	16 weeks	Favors dienogest (The authors reported that the pain score was significantly lower in the dienogest group than in the goserelin group [p=0.04]).	⊕⊕◯◯ Low
Goserelin	Takaesu et al. (2016)	24 weeks	It is not possible to state (The authors did not report the standard deviation. Average pelvic pain: dienogest 1.36, goserelin 1.2).	⊕⊕◯◯ Low
		24 months	It is not possible to state (The authors did not report the standard deviation. Average pelvic pain: dienogest 2.92, goserelin 3.32).	⊕◯◯◯ Very low
Leuprorelin	Abdou et al. (2018)	12 weeks	There was no difference in effect (MD: -1.92, 95%CI -4.63 to 0.79; p=0.17).	⊕⊕⊕◯ Moderate

Source: prepared by the authors. Note: MD - mean difference; CI - confidence interval; RR - relative risk.

Lang et al.[25] measured pain using the EAPP instrument (endometriosis-associated pelvic pain score). According to the authors, the least squares mean test of the pain difference between treatments at baseline and week 24 was -24.54 mm (95% CI -29.93; -19.15), representing a clinically important difference and favoring the use of dienogest.

The pelvic pain outcome was reported for comparisons of dienogest with placebo, triptorelin, goserelin, leuprorelin, and ethinylestradiol+levonorgestrel, at follow-up times

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of 12, 16, and 24 weeks, as well as 24 months. The results favored dienogest over placebo, goserelin, and triptorelin. In comparison with leuprorelin, studies indicated the non-inferiority of dienogest and the absence of difference. It should be noted that in one of them, it was not possible to evaluate the difference between the technologies due to the fragility of reporting by the authors, while there was no difference between dienogest and triptorelin. Regarding ethinylestradiol+levonorgestrel, two studies indicated no difference compared to dienogest, and one favored dienogest.

The meta-analysis for total adverse events indicated no statistically significant difference between dienogest and placebo regarding the risk of total adverse events at 12 and 24 weeks (RR 1.46; 95% CI 0.90-2.37).

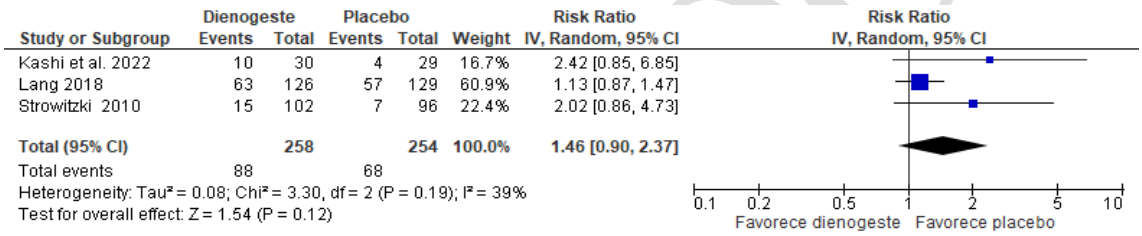

Figure 3. Forest plot of the total adverse event outcome in the dienogest versus placebo comparison.

Source: Authors' own elaboration

Total adverse events were reported for comparisons of dienogest with placebo, triptorelin, goserelin, leuprorelin, and ethinylestradiol+levonorgestrel, at follow-up times of 12, 16, and 24 weeks, as well as 12 and 24 months. In the comparison of dienogest with placebo, three studies indicated no difference. It should be noted that in one of them, it was not possible to evaluate the difference between the technologies as the proportion of adverse events in the placebo group was not reported. There was also no difference between dienogest and triptorelin (Table 2).

Between dienogest and leuprorelin, one study indicated the absence of difference between the technologies, and one study did not present consolidated data, making comparison impossible. The same occurred in the comparison with goserelin. Regarding

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ethinylestradiol+levonorgestrel, two studies indicated no difference compared to dienogest, both with two distinct follow-up times.

Table 2. Results for total adverse events between dienogest and different comparators.

Total adverse events				
Comparator	**Author (year)**	**Follow-up time**	**Results**	**GRADE (certainty of evidence)**
Placebo	Niakan et al. (2021)	12 weeks	There was no difference in effect (RR: 2.50, 95%CI 0.88 to 7.10; p=0.09).	⊕⊕⊕◯ Moderate
	Strowitzki et al. (2010a)	12 weeks	There was no difference in effect (RR: 2.02, 95%CI 0.86 to 4.73; p=0.11).	⊕⊕⊕◯ Moderate
	Niakan et al. (2021)	24 weeks	It is not possible to state (dienogest: 46.7% (14/30). The placebo group data were not presented).	NA
	Lang et al. (2018)	24 weeks	There was no difference in effect (RR: 1.13, 95%CI 0.87 to 1.47; p=0.35).	⊕⊕⊕◯ Moderate
Triptorelin	Cosson et al. (2002)	16 weeks	There was no difference (RR: 1.03, 95%CI 0.90 to 1.19; p=0.64).	⊕⊕⊕◯ Moderate
Goserelin	Ozaki et al. (2020)	12 months	It is not possible to state (Consolidated data were not presented).	NA

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	Takaesu et al. (2016)	24 months	There was no difference (RR: 1.06, 95%CI 0.98 to 1.15; p=0.12).	⊕⊕◯◯ Low
Leuprorelin	Abdou et al. (2018)	12 weeks	It is not possible to state (Consolidated data were not presented).	NA
	Strowitzki al. (2012)	24 weeks	There was no difference (RR: 0.64, 95%CI 0.35 to 1.15; p=0.14).	⊕⊕◯◯ Low
Ethinylestradiol + levonorgestrel	Niakan et al. (2021)	12 weeks	There was no difference (RR: 1.67, 95%CI 0.69 to 4.00; p=0.25).	⊕⊕⊕◯ Moderate
		24 weeks	There was no difference (RR: 0.93, 95%CI 0.55 to 1.58; p=0.80).	⊕◯◯◯ Very low
	Piacenti et al. (2021)	12 weeks	There was no difference (OR: 1.10, 95%CI 0.47 to 2.56; p=0.83).	⊕◯◯◯ Very low
	Piacenti et al. (2021)	24 weeks	There was no difference (OR: 1.11, 95%CI 0.45 to 2.71; p=0.82).	⊕◯◯◯ Very low

Source: prepared by the author. Note: NA - not applicable; CI - confidence interval; OR: odds ratio; RR - relative risk.

Ozaki et al.[28], who compared dienogest and goserelin, reported that hot flashes were significantly less frequent in the dienogest group (p<0.001). However, breast pain and metrorrhagia scores were significantly higher in the dienogest group (p=0.04 and p<0.001, respectively).

In the comparison between dienogest and leuprorelin, Abdou et al.[23] reported no statistically significant difference for the headache event (p=0.13). Weight gain (p=0.020) and vaginal bleeding (p=0.000) were significantly more frequent in the dienogest group,

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while vaginal dryness (p=0.001) and hot flashes (p=0.00) were significantly more frequent in the leuprorelin group.

Niakan et al.[27], who compared dienogest, placebo, and ethinylestradiol+levonorgestrel, reported no statistically significant difference between the groups for adverse effects at both follow-up times. Although this review included nine studies, they compared dienogest to placebo or four different medications. Thus, it was not possible to assess publication bias.

Due to the number of outcomes considered in the study, only those considered critical (overall pain, pelvic pain, dysmenorrhea, dyspareunia) and important (adverse events) were evaluated, considering the different comparators, follow-up times, and study designs. All these analyses are described in the supplementary material.

Regarding the overall pain outcome, the certainty of evidence was considered low in the comparisons of dienogest to placebo and goserelin. The assessments were penalized by the high risk of bias in the studies and by indirect evidence.

Pelvic pain was evaluated for two comparisons. In the comparison of dienogest and placebo, low certainty of evidence was demonstrated for the outcome at all follow-up times. When dienogest was compared to goserelin, the certainty of evidence was considered very low at the 24-week follow-up time.

For the total adverse events outcome, the confidence in the evidence was low in two comparisons: dienogest and placebo, due to penalty for risk of bias and indirect evidence; and dienogest and leuprorelin, due to very serious risk of bias. In the comparison of dienogest and triptorelin, the certainty of evidence was classified as moderate, with penalty for risk of bias (serious). The comparison of dienogest and goserelin was reported by an observational study, with low certainty of evidence, penalized for risk of bias (very serious). When dienogest was compared to ethinylestradiol+levonorgestrel, the certainty of evidence was low, with penalties for risk of bias (serious). At the 12 and 24-week follow-up times, the certainty of evidence for this comparison was very low, due to judgments on risk of bias (very serious) and indirect evidence (serious).

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DISCUSSION

This systematic review included 12 publications from 9 studies that evaluated the efficacy, effectiveness, and safety of dienogest in the treatment of endometriosis compared to placebo and the options available in the SUS.

For the overall pain outcome, dienogest may be superior to placebo (moderate certainty of evidence) and goserelin (low certainty of evidence), and there appears to be no difference between dienogest and triptorelin (low certainty of evidence). Two systematic reviews that compared dienogest to GnRH analogs did not identify a statistically significant difference in pain reduction[40,41]. The results also indicated that dienogest was superior to placebo in pain control[40]. Considering the MCID of 10 points on a 100-point scale, it can be stated that the mean difference in overall pain in the dienogest versus placebo comparison (-25.80) represented a clinically significant improvement in patients' pain. Some studies suggested that dienogest could be more effective than placebo in reducing pain, although the certainty of this evidence was very low[42]. Another review showed that leuprorelin is as effective as dienogest in relieving endometriosis-related pain[43].

Regarding pelvic pain, dienogest was superior to placebo (low certainty of evidence) and triptorelin (low certainty of evidence). However, regarding goserelin, it was not possible to confirm its superiority (very low certainty of evidence). Studies indicated the non-inferiority of dienogest to leuprorelin (very low certainty of evidence) in terms of efficacy, and regarding effectiveness, it was not possible to confirm due to lack of data. There was no difference between the efficacy and effectiveness of dienogest and ethinylestradiol+levonorgestrel (low certainty of evidence). Corroborating this finding, a systematic review with meta-analysis[44] classified medications by the greatest reduction in pelvic pain severity after 3 months of use and observed no significant difference in the effects of dienogest and GnRH analogs.

As for total adverse events, there was no difference in the comparisons of dienogest to placebo (moderate certainty of evidence) and triptorelin (moderate certainty of evidence).

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For both leuprorelin and goserelin, one study indicated the absence of difference between the technologies, and one study did not present consolidated data, making comparison impossible (low certainty of evidence for both). In contrast, another study found adverse events to be more frequent in women in the GnRH analog group than in the dienogest group[45].

In Brazil, dienogest is the only medication with an indication approved in the package insert by Anvisa for the treatment of endometriosis11. However, it is not part of the list of medications provided by the SUS for the treatment of endometriosis and has not been evaluated by the National Commission for the Incorporation of Technologies in the SUS (Conitec) for this indication. Nevertheless, the medication is considered an option among oral and continuous progestogens by national and international guidelines to reduce overall and pelvic pain associated with endometriosis, due to its good tolerability profile. However, the assessment of the certainty of evidence in these guidelines is considered low to moderate[4,46-50].

Specifically, the Japanese Clinical Guideline for endometriosis states that pain reduction using low-dose estrogen oral contraceptives, GnRH analogs, and progestins is equivalent (evidence level I, recommendation strength B)[49]. In contrast, the French agency (HAS - Haute Autorité de Santé) points out that no real clinical benefit was found with the use of dienogest in the treatment of endometriosis, recommending its use as a second-line option after failure and/or as a relay for GnRH analogs. The HAS opinion considered the effect of dienogest modest but was favorable to the reimbursement of the medication's use in hospital and municipal settings[51,52.]

Finally, it is worth noting that most comparators (GnRH analogs) are administered via deep intramuscular injection in the gluteus in single monthly/quarterly doses, while dienogest is for daily oral use, which could represent a convenience in the use of dienogest or ethinylestradiol+levonorgestrel.

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Limitations

The summarization of evidence was limited by the variability of: outcomes used by the studies to measure pain; instruments for measuring outcomes; follow-up times considered in the studies. Furthermore, in some situations, data were not presented in a consolidated manner, limiting the comparison of studies. A non-inferiority study and a study that included only women with severe endometriosis were also included.

Searches in grey literature sources were not included. However, other systematic reviews were consulted to identify eligible primary studies. Only studies in English, Spanish, and Portuguese were included, although little evidence was found in other languages. It was not possible to summarize the data through meta-analysis due to the different study designs, distinct comparator medications, the use of different instruments for outcome measurement, in addition to the different follow-up times.

Due to data heterogeneity, it was not possible to evaluate the difference in dienogest use before and after laparoscopic surgery.

Final Considerations

The results of this review suggest the superiority of dienogest when compared to placebo and goserelin, and no difference between dienogest and triptorelin and ethinylestradiol+levonorgestrel, and non-inferiority in the comparison of dienogest and leuprorelin for the treatment of endometriosis, considering different pain-related outcomes. Dienogest likely resulted in pain reduction when compared to placebo and may have reduced pelvic pain relative to placebo, leuprorelin, and ethinylestradiol+levonorgestrel. For total adverse events, there was likely no difference between dienogest and placebo, triptorelin, and ethinylestradiol+levonorgestrel.

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It is observed that there is evidence for the medication to be considered for the treatment of endometriosis within healthcare systems, provided that economic evidence and its budgetary impact are also considered.

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EFFICACY, EFFECTIVENESS, AND SAFETY OF DIENOGEST FOR THE TREATMENT OF ENDOMETRIOSIS: A SYSTEMATIC REVIEW

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