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Meta-Analysis

Dienogest versus gonadotropin-releasing hormone analogues for the clinical treatment of endometriosis: an updated meta-analysis

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ABSTRACT

Endometriosis is a chronic gynecological condition where endometrial-like tissue grows outside the uterus, leading to persistent pelvic pain, dysmenorrhea, dyspareunia, and infertility. The objective of the systematic review was to examine the efficacy and safety of Dienogest, which is a synthetic, orally active 19-nortestosterone derivative, in the treatment of women with endometriosis compared to GnRH-a, which is commonly used to treat conditions like endometriosis. We conducted a search of PubMed, Google Scholar, and Cochrane Library databases from inception until August 2024 for clinical studies, using the following keywords: ("Dienogest") and ("gonadotropin-releasing hormone analogue" or GnRH analogues OR GnRH agonist) and (Endometriosis). Relevant randomized control trials were identified. Pooled effect estimates were calculated using a random effect model. This meta-analysis included eight randomized controlled trials (RCTs) with 1,219 patients, 602 in the dienogest group and 617 in the GnRH analogue group. Both treatments were equally effective in controlling pain, dysmenorrhea, and dyspareunia, but dienogest offered advantages. Dienogest significantly reduced the recurrence rate (RR: 0.37, 95% CI [0.15, 0.91]; p=0.03) and hot flushes (RR: 0.24, 95% CI [0.10, 0.59]; p=0.002) and protected against bone mineral density (BMD) loss. However, it increased the risk of irregular vaginal bleeding (RR: 3.61, 95% CI [1.09, 11.97]; p=0.04). Other side effects, such as headache, vaginal dryness, spotting, and alopecia, were not statistically significant. It concluded that Dienogest has comparatively fewer side effects than GnRH analogue, making it a considerably safer option for treating endometriosis.

Keywords: Dienogest, GnRH analogue, GnRH agonist and endometriosis

INTRODUCTION

Endometriosis is a chronic inflammatory disease that refers to forming of endometrial-like tissue outside uterus. It can cause adhesions, scar tissue, and a persistent inflammatory response that can change a woman's pelvic anatomy.[1] It is a common hormone-dependent illness among women, and it regresses after menopause. It is estimated that this disease affects 10-15% of women of reproductive age.[2] This disorder is commonly associated with infertility and causes painful symptoms which include dysmenorrhea, non-cyclic persistent pelvic discomfort, and dyspareunia. According to studies, infertile women have a prevalence that varies from 25% to 50%.[3]

Endometriosis, including many chronic inflammatory conditions, requires a long-term treatment regimen to regulate and suppress endometriotic lesions.[4] The most frequent hormonal therapies are progestins, combination oral contraceptives (COCs), and gonadotropin-releasing hormone analogues (GnRH-a) which includes buserelin, leuprolide acetate, and triptorelin. Although these treatments are effective, they frequently have side effects that limit long-term use and patient compliance.[5] GnRH-a, the most commonly used medicinal treatment for

endometriosis, operates by suppressing ovarian activity and altering the endometrium and endometriosis tissue. However, it produces a hypoestrogenic state, which leads to menopausal symptoms such as hot flushes, mood swings, sleep issues, irregular menstruation cycles, vaginal burning, decreased libido, and decreased BMD.[6] As a result, GnRH-a is often given for up to 6 months.[7]

A selective 4th-generation progestin, dienogest (DNG) when taken consistently, dienogest binds to the progesterone receptor, suppresses the secretion of gonadotropin systemically, and exhibits anti-inflammatory, antiproliferative, and antiangiogenic properties that effectively reduce growth of endometriosis lesions by creating a local progestogenic environment, suppressing the systemic estrogen level moderately.[8] Comparative studies on GnRH-a and DNG for endometriosis have yielded inconsistent results, highlighting need for further investigation. Although a prior meta-analysis by Oliveira et al offered valuable insights into their efficacy and safety profiles, its findings were constrained by a limited scope of outcomes and a small sample size.[9]

We conducted an updated meta-analysis incorporating a more comprehensive set of clinical endpoints, providing a clearer understanding of effectiveness and safety of treatments for endometriosis. With an expanded sample size and additional studies, analysis strengthens validity of findings. This comprehensive analysis provides detailed head-to-head comparison of dienogest and GnRH-a to inform treatment decisions for endometriosis.

METHODS

This meta-analysis was performed in compliance with the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines.[10] Summary of literature search is represented by PRISMA flowchart (Figure 1).

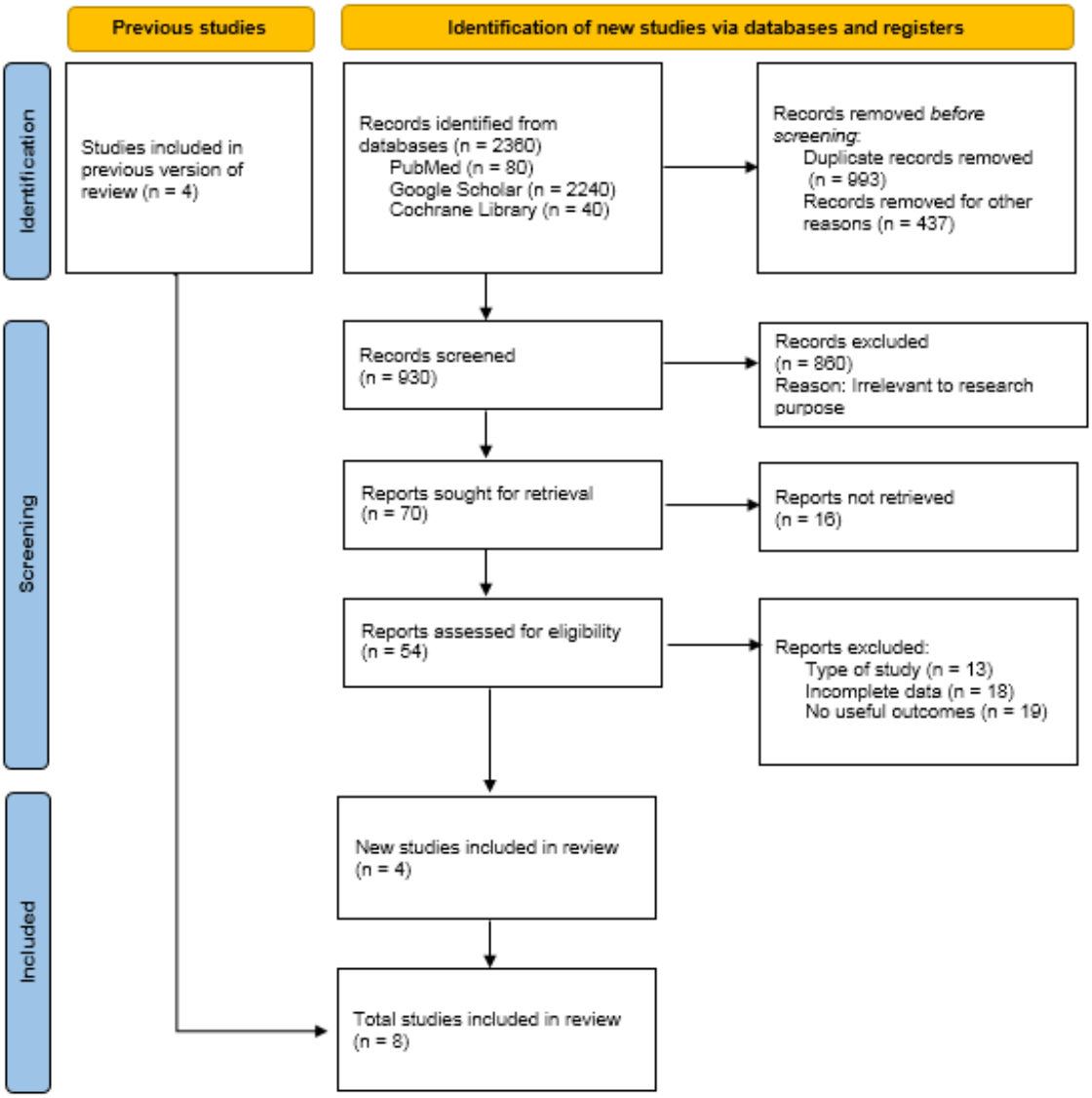

Figure 1: PRISMA flow diagram of literature search.

Search strategy

We conducted a search of PubMed, Google Scholar, and Cochrane Library databases from inception until August 2024 for clinical studies, using the following keywords and relevant MeSH terms used in the comprehensive literature search: ("Dienogest") AND ("gonadotropin-releasing hormone analogue" OR GnRH Analogues OR GnRH Agonist) AND (Endometriosis). Language apart from English was excluded. No restrictions of age, time, or sample size were applied. We also skimmed through the references to every article we could find.

Study selection

After the systematic search produced all of the articles, they were exported to EndNote X9 Reference Manager (Clarivate analytics, Philadelphia, Pennsylvania), where duplicates from other web databases were eliminated. After evaluating the titles and abstracts of the remaining papers, two separate authors assessed the full texts. A third reviewer was consulted in the event of an argument. The objective of the systematic review was to search the literature for an answer to the question we presented, which was "to examine the efficacy and safety of the DNG in the treatment of women with endometriosis compared to GnRH-a." The format of the systematic review was "PICOS," which stands for population, intervention, comparator, outcome and study design. P: Women with endometriosis diagnosed, I: Dienogest, C: GnRH-a, O: Efficacy and S: Randomized Studies

Inclusion criteria

Patients of 18 years or older with a clear pathology, clinical diagnosis of endometriosis; intervention measures: use of dienogest comparing GnRH-a therapy; type of literature: clinical trials, dienogest and GnRH-a treatment groups have higher comparability, and feasibility of the experimental scheme is strong; outcome indicators: the control of pelvic pain, dysmenorrhea, dyspareunia and the incidence of adverse reactions as secondary outcomes were inlcuded.

Exclusion criteria

Non-clinical research; non-dienogest or GnRH-a treatment; studies that were published as abstracts, letters to the editor, comments, or "grey literature" or those included secondary outcomes (meta-analysis) or systematic reviews were not included; any other medication comparison, besides dienogest and GnRH-a, was compared; studies in a language other than English; repeated published literature and studies that did not report any outcome of interest were excluded.

Data and outcomes

Primary outcomes efficacy of pelvic pain, dyspareunia, dysmenorrhea control, and recurrence rate. Secondary end-points included: irregular vaginal bleeding, vaginal dryness, spotting, alopecia, headache, hot flushes and BMD. Efficacy will be evaluated by analysis of our primary outcomes, and safety will be evaluated by analysis of secondary outcome as adverse effects.

Data extraction and quality assessment

Two investigators (Z.M.H and K.M) independently abstracted data from the articles that were included. Baseline characteristics of the included studies were extracted onto the Microsoft excel sheet that was created by authors. In each study, following data was extracted: study name and year; study design; sample size; patient population in each group; general baseline characteristics (age, BMI, and weight); GnRH-a used, dosage of GnRH analogue and DNG; all outcomes of interest.

Two independent reviewers (H.S and A.B) performed quality assessments of the studies that were included in the analysis. The quality assessment tool for randomized controlled trials was Cochrane risk of bias (RoB 2.0).[11] Any disagreement was resolved by 3rd reviewer (K.M).

Statistical analysis

For statistical analysis, review manager (RevMan version 5.4.1) provided by Cochrane collaboration network was used. Dichotomous data was used to derive the Risk Ratio (RR) and corresponding 95% confidence intervals (95% Cls), and similarly, for continuous outcomes, mean difference (MD) was obtained and their 95% Cls using the random-effects model.

Higgins I^2 was used to measure heterogeneity. The value of I^2=25-50% was considered mild heterogeneity, 50-75% was considered moderate, and greater than 75% was considered severe heterogeneity. A $p<0.05$ was considered statistically significant.

RESULTS

Study selection and characteristics

A systematic search of the literature was conducted and has yielded 2,360 articles. After screening, duplicates and ineligible articles were removed. Eight studies were included in this meta-analysis. All of them are RCTs with number of patients 1,219 (602 in dienogest group and 617 in GnRH analogue group).[12-19] Mean age of the patients in dienogest group is 33.0 years and in GnRH analogue group is 34.1 years.

Baseline characteristics of the included studies are summarized in (Table 1).

Table 1: General characteristics of the included studies.

Author	Study design	Study duration	Country	Patient population		GnRH analogue	Dosage	
				Dienogest	GnRH analogue		Dienogest	GnRH analogue
Abdou et al[19]	RCT	May 2014-December 2016	Egypt	121	121	Leuprolide acetate	2 mg/day oral	3.75 mg/4 weeks IM
Cosson et al[13]	RCT	June 1994-July 1998	France	59	61	Decapeptyl	1 mg/day oral	3.75 mg/4 weeks IM
Harada et al[12]	RCT	June 2003-February 2005	Japan	128	125	Buserelin acetate	2 mg/day oral	900 ug/day IN
Ceccaroni et al[17]	RCT	January 2016-July 2017	Italy	65	81	Triptorelin/ leuprorelin	2 mg/day oral	3.75 mg/4 weeks IM
Purwanto et al[18]	RCT	July- February 2019	Indonesia	10	10	Leuprolide acetate	2 mg/day oral	2 mg/4 weeks depot injection
Strowitzki et al[14]	RCT	December 1998-April 2001	Germany	124	128	Leuprolide acetate	2 mg/day oral	3.75 mg/4 weeks IM
Takaesu et al[15]	RCT	April 2009-June 2013	Japan	54	51	Goserelin	2 mg/day oral	1.8 mg/4 weeks SC
Tang et al[16]	RCT	December 2020- March 2022	China	41	40	GnRH a	4 mg/day oral	3.75 mg/4 weeks IM

Quality assessment

Quality assessment of 8 RCTs was done using the RoB-2 tool respectively and all the included RCTs have score low risk of bias (Figure 2).

Primary outcome

Efficacy of pelvic pain control

The efficacy of pelvic pain control was reported by two out of eight studies including 372 patients (183 in dienogest group while 189 in GnRH analogue). The analysis of this outcome showed statistically insignificant results revealing that there was no difference between the two treatments in controlling pain (RR: 0.82, 95% CI [0.61, 1.09]; p=0.17, I^2=38%) (Figure 3 A).

Dysmenorrhea

A total of two studies (Crosson et al and Strowitzki et al) were included in the outcome of dysmenorrhea which reported it. Pooled results of these studies showed insignificant results revealing that there was no difference between the 2 drugs in controlling dysmenorrhea (RR: 1.26, 95% CI [0.46, 3.46]; p=0.65, I^2=89%).[14,17]

However, the results displayed significant heterogeneity (Figure 3 B).

Dyspareunia

For the effectiveness of dienogest and GnRH analogues in reducing dyspareunia, four studies were included in the analysis which resulted in statistically insignificant results (RR: 0.96, 95% CI [0.81, 1.14]; P=0.64, I^2=0%),

This indicates that dienogest and GnRH analogue do not differ in their effectiveness in reducing dyspareunia (Figure 3 C).

Recurrence rate

Recurrence of endometriosis was reported by only two studies including 186 patients (95 in dienogest group and 91 in GnRH analogue group). Their pooled results showed that dienogest significantly lowers the recurrence as compared to GnRH analogues (RR: 0.37, 95% CI [0.15, 0.91]; p=0.03, I^2=0%) (Figure 4 A).

Change in visual analog scale score for pelvic pain

Three of the included studies evaluated pelvic pain by VAS Score at 3 months while three of them reported it at 6 months. Analysis of this outcome in both cases revealed statistically insignificant results indicating that there is no difference in VAS Score of pain among the patients taking dienogest or GnRH anaologue. VAS score at 3 months (MD: -0.32, 95% CI [-0.67, 0.03]; p=0.07, I^2=0%), VAS Score at 6 months (MD: -0.08, 95% CI [-0.49, 0.33]; p=0.70, I^2=0%) (Figure 4 B).

Secondary outcomes

The results for all the secondary outcomes, incidence of adverse events taking place during treatment comparing the safety of dienogest and GnRH-a have been reported in tabular form in (Table 2) and the forest plots have been presented in (Figure 5 and 6).

Table 2: Results of secondary outcomes; incidence of irregular vaginal bleeding, hot flushes, headache, vaginal dryness, spotting, alopecia and change in BMD during treatment.

Outcome	Study (n)	Effect size (RR/MD)	95% CI	P value	I^2 (%)	Conclusion
Irregular vaginal bleeding	3	RR: 3.61	[1.09, 11.97]	0.04	97	Higher in Dienogest group
Hot flushes	5	RR: 0.24	[0.10, 0.59]	0.002	94	Lower in Dienogest group
Headache	4	RR: 0.92	[0.58, 1.46];	0.73	51	No significant difference
Vaginal dryness	2	RR: 0.53	[0.09, 3.18]	0.49	88	No significant difference
Spotting	2	RR: 6.26	[0.58, 67.71]	0.13	82	No significant difference
Alopecia	2	RR: 0.70	[0.35, 1.41]	0.32	0	No significant difference
Change in BMD	2	MD: 2.77	[0.16, 5.39]	0.04	80	Lower in Dienogest group

RR-Relative risk; MD-Mean difference; CI-Confidence interval; I^2-Measure of heterogeneity.

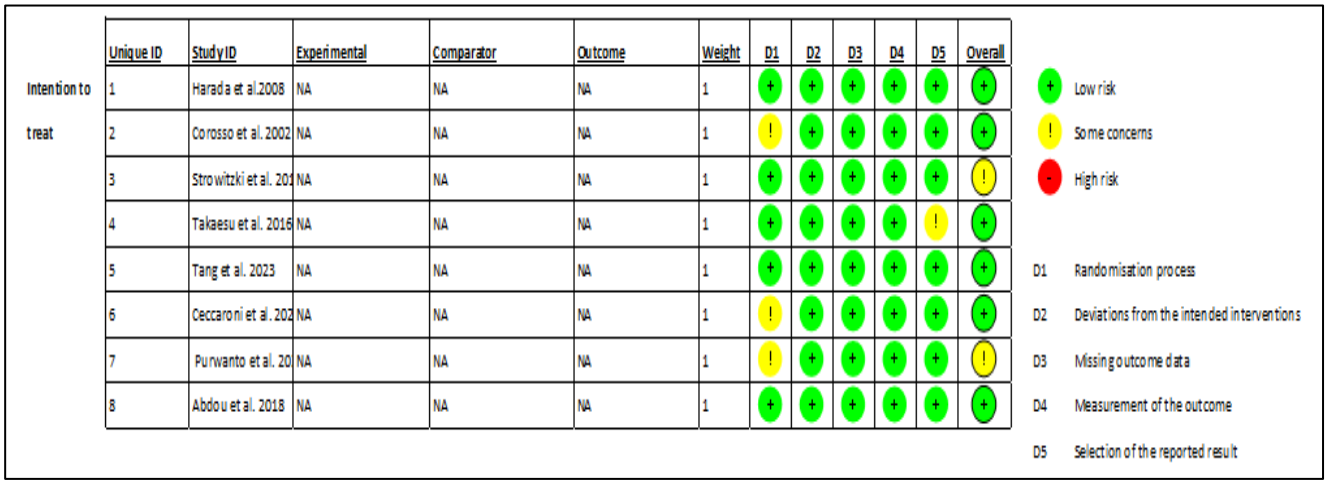

Figure 2: Quality assessment for randomized controlled trials.

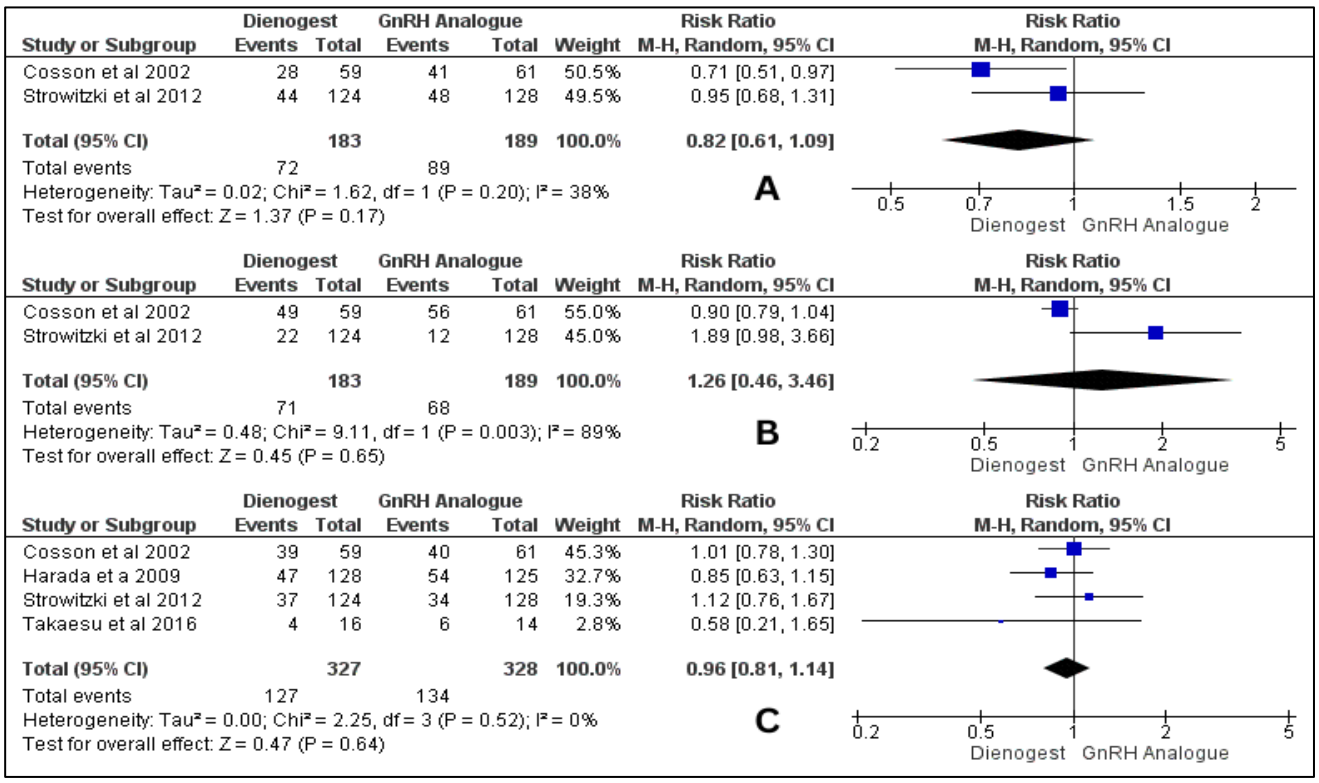

Figure 3 (A-C): Forest-plot for the incidence of pelvic pain after treatment, forest-plot for the incidence of dysmenorrhea after treatment and forest-plot for the incidence of dyspareunia after treatment.

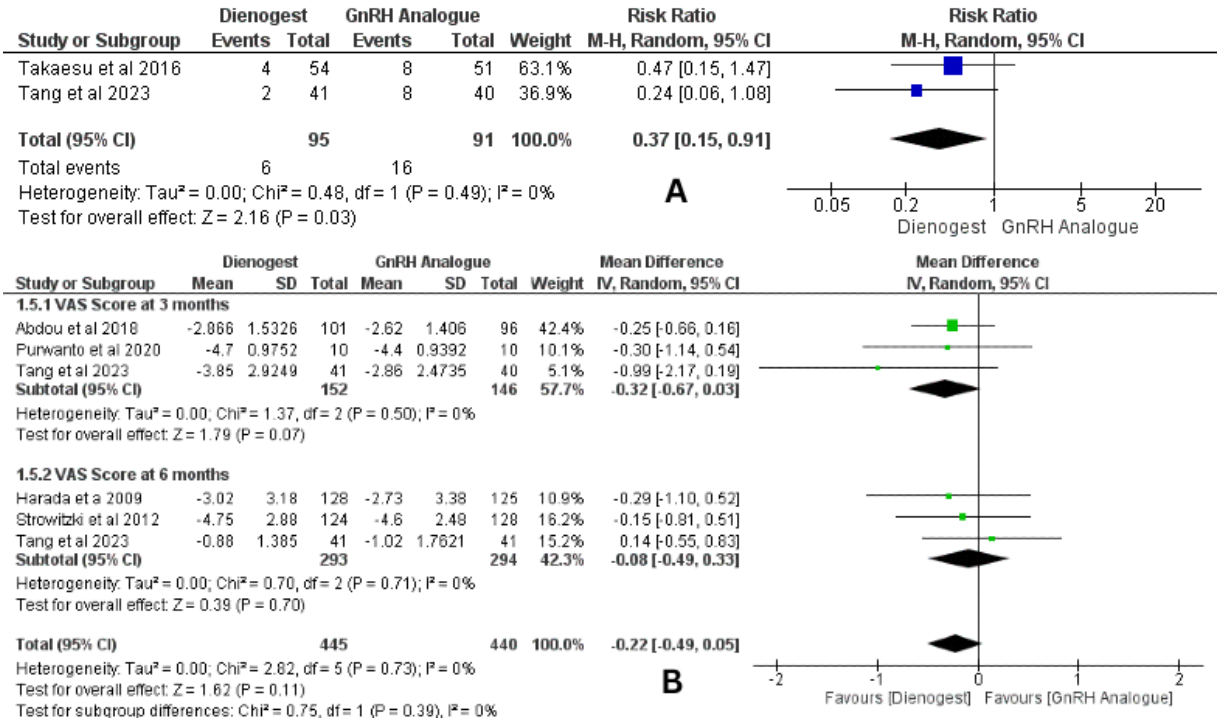

Figure 4 (A and B): Forest-plot for the recurrence rate and forest-plot for the change in VAS score for pelvic pain.

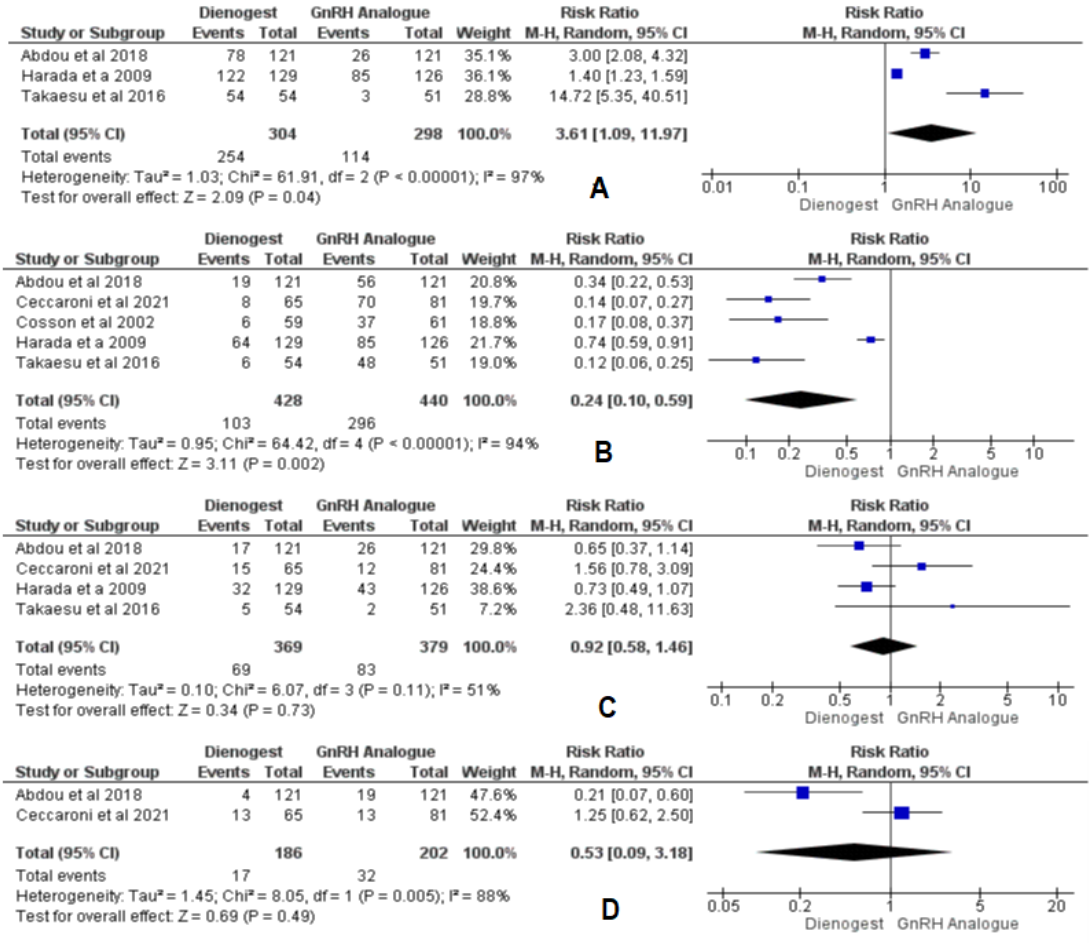

Figure 5 (A-D): Forest of irregular vaginal bleeding, forest of hot flushes, forest of headache and forest of vaginal dryness.

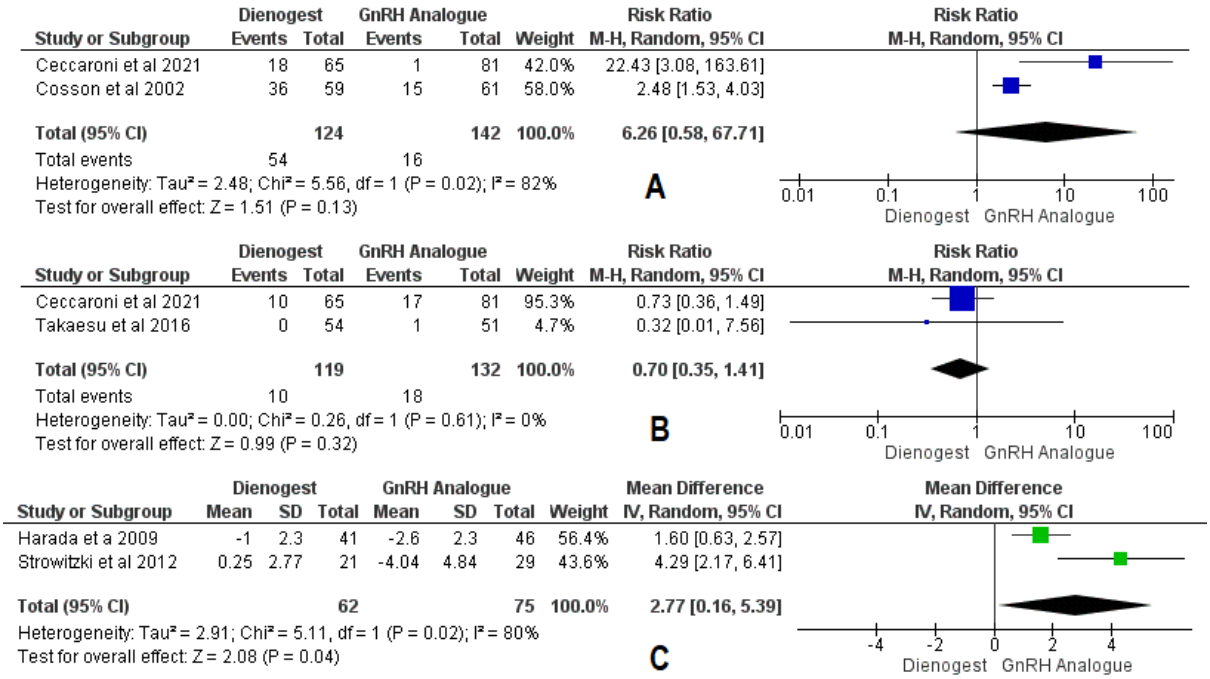

Figure 6 (A-C): Forest of spotting, forest of alopecia and forest of change in BMD.

DISCUSSION

Our systematic evaluation and meta-analysis of 8 articles aimed to compare the effectiveness and safety of dienogest versus gonadotropin-releasing hormone (GnRH) analogues for treating endometriosis. Our findings indicate that dienogest is as much effective for clinical treatment of endometriosis as GnRH analogue; we found no statistically significant difference between both groups in controlling pelvic pain, dysmenorrhea, and dyspareunia. Our analysis also indicated that dienogest is much safer in treating endometriosis than GnRH analogue, as it is associated with relatively fewer adverse effects. Adverse effects like hot flushes and loss in BMD are significantly lower in patients taking dienogest. Moreover, outcomes like headache, alopecia, spotting, and vaginal dryness did not reach statistical significance. Besides its high efficacy and fewer adverse effects profile, we found that irregular vaginal bleeding is significantly higher in patients taking dienogest. However, recurrence rate is significantly lower in patients treated with dienogest.

The results of our meta-analysis correspond with those of the previous meta-analysis conducted by Oliveira et al in 2017, which comprised 4 trials with 753 participants.[9] In the mentioned study, both treatments effectively controlled lower abdominal pain and dyspareunia, but dienogest caused less bone mass density loss than GnRH analogs, our finding confirmed it with a larger sample size. The earlier study reported fewer headaches with dienogest, but our larger sample size found no significant difference in headache frequency between the two groups. Contrary to the previous study, our analysis found that hot flushes were significantly less common with dienogest treatment. Compared to previous studies, our research also evaluated outcomes like dysmenorrhea, irregular vaginal bleeding, vaginal dryness, spotting, alopecia, and recurrence rates, providing stronger evidence for the effectiveness and safety of dienogest in endometriosis.

Pelvic pain is the most prevalent symptom of endometriosis.[20] A particular way that dienogest, a progestin, functions, by inhibiting the generation of ovarian estrogen and the growth of endometrial cells. Dienogest lessens inflammation and pain by causing a hypoestrogenic condition that shrinks the size and activity of endometrial lesions. Research indicates that dienogest's direct action on endometrial lesions and its anti-inflammatory properties play a major role in pain reduction.[21,22] Malik et al found that 67.8% of patients experienced pain reduction within two to five days of starting dienogest, highlighting its effectiveness in promptly alleviating endometriosis-related symptoms. This timely relief is likely due to dienogest's efficient suppression of estrogen levels and stabilization of endometrial lesions.[8] Furthermore, dienogest may offer sustained analgesic effects by maintaining a steady progestin level without significant fluctuations. According to Vincent's research in 2018, elevated progesterone levels are linked to a dissociation between unpleasantness and pain intensity as well as a decrease in the emotive aspect of the pain experience.[23]

An additional line of treatment for endometriosis is the use of GnRH analogues. By suppressing the hypothalamic-pituitary-gonadal axis, they prevent ovulation and reduce estrogen levels, which in turn suppresses endometriosis lesions. Pain and inflammation

can be greatly reduced by this inhibition.[7] According to A.M.A.'s study, pelvic pain in endometriosis is managed equally by both therapy groups.[19] GnRH analogues are suggested as second-line treatments in Russian guidelines, after progestogens as the first line of treatment.[24]

An Italian multicenter study found that dienogest plus estradiol valerate and GnRH analogues had similar VAS scores and equally improved quality of life after laparoscopic endometriosis surgery, with similar success during the first nine months in reducing recurrence of pain.[5] Our findings showed no significant difference in the two treatment group's VAS scores for pelvic pain, suggesting that both therapies are equally successful in treating pain associated with endometriosis. It adds attention to the idea that variables other than pain reduction, like patient preferences and side effect profiles, might affect treatment decisions.[7,25]

Our research revealed that both medications are similarly effective at managing dysmenorrhea and dyspareunia. Both medications have the potential to regulate dysmenorrhea due to their anovulatory and hypoestrogenic properties, as well as their antiproliferative activity in human endometrial cells, which all contribute to the reduction of pain and inflammation.[26-28] Menstrual pain may be lessened by dienogest by the reduction of uterine size and reduction of uterine artery blood flow during treatment.[29]

About half of women who have endometriosis experience pelvic pain during sexual activity, which has a substantial negative influence on their quality of life.[30] In people with endometriosis, sexual activity can be painful because of deep endometriotic nodules in the retrocervical area, which can irritate or stretch delicate tissue when they penetrate.[31] It is hypothesized that patients with endometriosis may have dyspareunia due to an increased level of nerve growth factor (NGF). A possible explanation for the increased pain and sensitivity felt during sexual activity is this overexpression of NGF.[32] Estrogen levels are markedly lowered by dienogest and GnRH analogs.[33,34] Reduced estrogen levels minimize endometriotic lesions' inflammatory reactions and nerve irritation, which lessens pain during sexual activity.[35]

Our research finds that dienogest is more effective than GnRH analogs for endometriosis due to its significantly lower recurrence rate. Despite the fact that GnRH analogues are useful in the treatment of endometriosis, their usage is restricted to a six-month period because of potential side effects, which sometimes necessitate extra add-back hormone therapy. Compared to medications like dienogest, which do not require such add-back treatments, this additional complication may exacerbate long-term disease control and raise the rate of recurrence.[36,37] Tang's study demonstrates that dienogest enhances patient tolerance and compliance. Hot flushes and bone loss are common side effects of GnRH analogue use, which reduces adherence and leads to inconsistent disease management. Despite the effectiveness of GnRH analogue, this decreased adherence may lead to increased rates of postoperative recurrence.[38]

Our analysis reveals that hot flushes were significantly more frequent with GnRH analogues compared to dienogest, while other adverse effects such as headache, alopecia, and vaginal dryness were similar between the two treatments. Hot flushes are a frequent adverse effect of GnRH analogues, mainly because of a large decrease in estrogen levels that interferes with the body's normal thermoregulatory processes.[39] Other experts speculate that a change in neurotransmitters that impacts the thermoregulation center could be the reason behind hot flushes.[40] Due to their ability to affect estrogen levels, headaches related to endometriosis treatment occur similarly with GnRH analogues and dienogest. Similar to Raffaelli's work demonstrating that estrogen withdrawal is a major factor in menstrual migraines, both treatments reduce estrogen, which can cause headaches.[41] Lowered estrogen levels caused by hormonal changes following endometriosis treatment cause vaginal dryness. Since estrogen is necessary for vaginal lubrication, therapies like GnRH analogs and progestins like dienogest that lower estrogen can cause dryness, therefore resulting in painful intercourse.[42] Endometriosis treatments with dienogest and GnRH analogs can cause alopecia due to hormone-induced hypoestrogenism. According to Brough, who discovered that lower estrogen levels during menopause or with specific treatments are connected to greater female pattern hair loss as estrogen is thought to protect against hair loss.[43]

Our investigations show that GnRH analogs significantly reduce BMD more than dienogest. By inhibiting ovarian activity, dienogest and GnRH analogues both significantly lower estrogen levels, resulting in hypoestrogenism.[31,35] Bone health is largely dependent on estrogen. Severe estrogen suppression causes a reduction in bone formation and an acceleration of bone resorption, which worsens the loss of BMD.[39] Sagsveen has highlighted that GnRH analogues induce significant BMD loss, increasing fracture risk due to their severe suppression of estrogen, which accelerates bone mass loss.[40] Surrey indicates that GnRH analogs are usually limited to six months due to hypoestrogenic side effects, including BMD reduction. However, with appropriate add-back therapy, treatment can be extended to a year while minimizing these effects and maintaining effectiveness.[41]

We discovered that patients on dienogest had more irregular vaginal bleeding than those on GnRH analogs, though both treatments caused similar spotting. Dienogest causes irregular bleeding due to progesterone-induced endometrial thinning and pseudodecidua formation, affecting 70%-90% of patients.[42] In contrast, GnRH analogues induce hypoestrogenism, leading to predictable amenorrhea or light bleeding, with up to 90%

efficacy in achieving amenorrhea.[43] Thus, increased bleeding irregularities are frequently the consequence of dienogest's effect on the endometrial lining.

Future directions

Future studies should assess the long-term effects of GnRH analogs and dienogest on bone health, fertility, mental health, and quality of life, explore mitigation strategies, compare cost-effectiveness, and include diverse populations for better generalizability.

Limitations

Our meta-analysis of dienogest versus GnRH analogs for endometriosis offers valuable insights but is limited by study heterogeneity, a limited number of RCTs, potential publication bias, and gaps in follow-up, long-term outcomes, and cost-effectiveness data. The lack of detailed baseline characteristics underscores the need for more diverse and comprehensive future research. Moreover, variability in treatment protocols, with the majority of studies comparing GnRH analogs and dienogest post-surgery and two studies (Harada et al, Strowitzkii et al) evaluating these therapies without prior surgery, introduces heterogeneity and potential bias into the meta-analysis.[12,14]

CONCLUSION

Our meta-analysis indicates that dienogest is as effective as GnRH analogues in managing endometriosis, offering comparable relief from pelvic pain, dysmenorrhea, and dyspareunia. Dienogest demonstrates a notably better safety profile, with significantly fewer adverse effects such as hot flushes and BMD loss. Although irregular vaginal bleeding is more common with dienogest, its lower recurrence rate and reduced risk of severe side effects highlight its advantage as a preferable option for long-term endometriosis treatment.

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