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Dienogest in endometriosis treatment: A narrative literature review

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Endometriosis is characterized by the implantation of endometrial cells outside the uterus. This hormone-dependent disease is highly prevalent among women of reproductive age. Clinical symptoms of endometriosis include dysmenorrhea, pelvic pain, and infertility, which can negatively impact the overall quality of life of those affected. The medical treatment of endometriosis serves as an important therapeutic option, aimed at alleviating pain associated with the condition and suppressing the growth of endometriotic lesions. As such, it is employed as an adjuvant therapy following surgery or an empirical treatment after the clinical diagnosis of endometriosis. Dienogest, a fourth-generation progestin, has received approval for the treatment of endometriosis in many countries. A growing body of evidence has demonstrated its efficacy in managing endometriosis-associated pain, preventing symptoms, and reducing lesion recurrence. In this review, we examine the clinical efficacy, safety, and tolerability of dienogest in treating endometriosis. We also provide updated findings, drawing from clinical studies that focus on the long-term use of this medication in patients with endometriosis.

Keywords: Dienogest; Endometriosis; Medical therapy; Progestins

Introduction

Endometriosis, defined as the ectopic implantation of endometrial cells, is a common gynecological disease affecting 10% to 15% of women of reproductive age [1]. This condition often results in painful symptoms such as dysmenorrhea, noncyclic chronic pelvic pain, and dyspareunia, and it is frequently linked with infertility. Studies report that the prevalence of endometriosis ranges from 25% to 50% among women with infertility [2].

The etiopathogenesis of endometriosis continues to be a subject of debate and is not fully understood. Several theories have been proposed to explain its origin, including retrograde menstruation, lymphatic spread, coelomic metaplasia, Müllerian remnants, and stem cell recruitment [3-8]. However, none of these theories fully account for the various types of endometriosis. Endometriosis is known for its high recurrence rate and often follows a chronic clinical course, even after surgical intervention. As a result, medical treatment is typically employed as an adjuvant therapy following surgery. In recent years, a consensus has emerged that medical therapy can be proposed as a primary empirical treatment following a clinical diagnosis of endometriosis. Furthermore, long-term medical treatment is widely considered necessary for managing endometriosis-associated pain and preventing recurrence [9-13].

Currently, the medical treatment options for endometriosis include progestins, oral contraceptive pills, gonadotropin-releasing hormone (GnRH) agonists, hormone-releasing intrauterine devices, and subdermal implants. Among these, progestins have emerged as one of the most important options worldwide [11,14,15]. Dienogest (DNG) is a fourth-generation progestin that is orally active and exhibits highly selective binding to the progesterone receptor [16]. It has received approval for the treatment of endometriosis in numerous countries [14,17-19]. In this literature review, we discuss the clinical efficacy, safety profile, and tolerability of DNG in patients with endometriosis, as well as recent evidence regarding its long-term use.

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Mechanisms of action of DNG in endometriosis

DNG is a derivative of 19-nortestosterone, distinguished from other progestins of the same derivation by the presence of a cyanomethyl group rather than an ethynyl group at position 17α [20]. Pharmacologically, DNG primarily exerts a localized effect on endometriotic lesions, demonstrating minimal angiogenic, estrogenic, glucocorticoid, or mineralocorticoid activity. It also exhibits both anovulatory and antiproliferative effects [9,21,22]. Studies have shown that DNG moderately inhibits the secretion of gonadotropins, leading to a reduction in the endogenous production of estradiol. This suppression induces decidualization of the ectopic endometrium, with subsequent atrophy [20,23]. Furthermore, DNG inhibits the proliferation of endometrial cells by modulating the expression of matrix metalloproteinases and aromatase, which are involved in the ectopic endometrial response to endogenous estrogen [24,25]. The anti-angiogenic and anti-inflammatory properties of DNG, which are relevant to the reduction of endometriotic lesions, have been observed in both *in vivo* and *in vitro* studies involving eutopic or ectopic endometrial cells [26-28].

Therapeutic efficacy of DNG in placebo-controlled trials

The therapeutic efficacy, safety, and tolerability of oral DNG in the treatment of endometriosis have been studied in clinical trials (Table 1). In a phase 3, placebo-controlled, randomized, double-blind, multicenter study, the efficacy and safety of DNG were assessed within a Chinese population [29]. DNG (2 mg) was administered once daily to 255 women, aged 18 to 45 years, who had been laparoscopically diagnosed with endometriosis and had an endometriosis-associated pelvic pain (EAPP) score of at least 30 mm on a 0- to 100-mm visual analog scale (VAS). The primary efficacy variable was the absolute change in EAPP score from baseline to week 24, while secondary efficacy variables included the intake of supportive analgesic medication (SAM). After 24 weeks of treatment, the mean reduction in EAPP score was significantly greater in the women treated with DNG compared to those who had received the placebo. Women in the DNG group also reported a decrease in SAM intake (specifically, in the number of 200 mg ibuprofen tablets taken in the previous 4 weeks), from an average of 1.5 at the start of the study to 0.5 at week 24. The women in the placebo group reported a slight increase in SAM intake, from a mean of 1.7 to 1.9.

In another randomized, double-blind, multicenter study, the effectiveness of oral DNG (2 mg once daily) over a 12-week period was compared to that of a placebo [30]. This study enrolled 198 patients (aged 18 to 45 years) with laparoscopically confirmed endometriosis, approximately 70% of whom had stage III or IV disease. EAPP was evaluated using the VAS score. The mean reductions in VAS score from baseline to week 12 in the full analysis set were 27.4 mm for the DNG group and 15.1 mm for the placebo group. This constituted a significant score difference of 12.3 mm, favoring DNG. In terms of numerical data, a higher percentage of patients receiving DNG were rated as "much improved/very much improved" on the clinician-rated Clinical Global Impressions improvement scale (52.9% vs. 22.9%). Similarly, a greater proportion of patients gave responses of "highly satisfied/very highly satisfied" on a patient-rated overall satisfaction scale (43.1% vs. 20.8%) compared to those receiving the placebo.

In a 12-week placebo-controlled trial [30], an open-label extension study was conducted to assess the long-term efficacy and safety of DNG. This study recruited 168 women, of whom 91% completed the 53-week extension, resulting in a total study duration of 65 weeks. This research was conducted in parallel with two other studies [31]. Over the course of DNG treatment, the EAPP score decreased steadily, dropping from 57±17 at the baseline of the placebo-controlled study to 12±11 at the conclusion of treatment. Abnormal bleeding profiles were observed, including irregular bleeding (22%), infrequent bleeding (24%), and amenorrhea (28%). Despite these findings, only two patients discontinued treatment due to bleeding irregularities.

Therapeutic efficacy of DNG compared with GnRH agonists

Several studies have been conducted to compare the therapeutic efficacy of DNG with that of GnRH agonists, such as leuprorelin, buserelin, and triptorelin. One randomized parallel clinical trial involved 59 patients with endometriosis who were administered DNG (1 mg twice daily), along with 61 patients who were given decapeptyl (3.75 mg via intramuscular injection every 28 days), for a period of 16 weeks. The results showed comparable efficacy between the two treatments [32]. In another randomized, open-label, multicenter study, oral DNG (2 mg once daily; n=90) was administered for 24 weeks and was found to be noninferior to intramuscular leuprorelin (3.75 mg every 4 weeks; n=96) in reducing EAPP score from baseline. This was assessed using VAS scores in the per-protocol set [33]. The proportions of patients in the DNG and leuprorelin groups who experienced an improvement in pelvic pain from baseline were 97% and 96%, respectively.

In a separate randomized, double-blind, multicenter study conducted in Japan, oral DNG (1 mg twice daily; n=129) and intranasal buserelin acetate spray (300 mg three times daily; n=125) were administered for 24 weeks. Both treatments demonstrated broadly comparable efficacies for all symptoms, including lower abdominal

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Table 1. Included randomized clinical studies on the efficacy and safety of DNG compared with placebo or GnRH agonists

Study	Design	Participants	Duration (wk)	Intervention	Main outcomes
Placebo-controlled study					
Lang et al. (2018) [29]	Placebo-controlled, randomized, double-blind, multicenter phase 3 study	255 Chinese women (aged 18–45 years) who reported VAS score ≥ 30 mm	24	129 Women with placebo and 126 with DNG 2 mg/day	DNG was superior to placebo in reducing EAPP and was safe and well tolerated in Chinese women with endometriosis.
Strowitzki et al. (2010) [30]	Randomized, double-blind, placebo-controlled, multicenter trial	198 Women (aged 18–45 years) who reported VAS score ≥ 30 mm	12	96 Women with placebo and 102 with DNG 2 mg/day	In the full analysis set, the mean reductions in VAS score between baseline and week 12 were 27.4 mm and 15.1 mm in the DNG and placebo groups, respectively; a significant score difference of 12.3 mm was observed in favor of DNG ($p < 0.0001$).
DNG vs. GnRH agonist					
Cosson et al. (2002) [32]	Multicenter, open, randomized, parallel-group clinical trial	142 Women (aged 18–40 years) with grade 2, 3, or 4 endometriosis at initial laparoscopy	16	59 Women with DNG 1 mg/day and 61 with decapeptyl 3.75 mg IM every 4 weeks	VAS scores were comparable in both groups, and efficacy was not significantly different between the two groups.
Strowitzki et al. (2010) [33]	Randomized, multicenter, open-label trial	Women (aged 18–45 years) with histologically proven endometriosis	24	124 Women with DNG 2 mg/day and 128 with leuprolide acetate 3.75 mg IM every 4 weeks	DNG demonstrated equivalent efficacy to leuprolide at the standard dose in relieving the pain associated with endometriosis, while offering advantages in terms of safety and tolerability.
Harada et al. (2009) [22]	Phase III, randomized, double-blind, multicenter, controlled trial	271 Patients (aged ≥ 20 years) with endometriosis diagnosed via surgery or imaging analysis	24	137 Women with DNG 2 mg/day and 134 with intranasal buserelin acetate 900 μg/day	Pre- to post-treatment changes in the scores of five subjective symptoms during non-menstruation (lower abdominal pain, lumbago, defecation pain, dyspareunia, and pain on internal examination) and two objective findings (induration in the pouch of Douglas and limited uterine mobility) were measured. DNG reduced the scores of all symptoms and findings at the end of treatment. The mean changes in the scores of all symptoms and findings, except induration in the pouch of Douglas, were comparable to those obtained with buserelin acetate. The reduction in BMD during DNG treatment was significantly lower than that during buserelin acetate treatment.
Ceccaroni et al. (2021) [34]	Prospective randomized controlled trial	146 Women (aged 18–45 years), laparoscopic eradication of rASRM stage III–IV DIE with bowel and parametrial surgery	24	65 Women with DNG 2 mg/day and 81 with triptorelin or leuprorelin 3.75 mg IM every 4 weeks	Both DNG and GnRH agonists were associated with a highly significant reduction of pain at 6 and 30 months, without any significant difference ($p < 0.001$). Regarding treatment tolerability, a more satisfactory profile was reported with DNG ($p = 0.026$). No difference was found in terms of clinical relapse, imaging relapse, or live births.

DNG, dienogest; GnRH, gonadotropin-releasing hormone; VAS, visual analog scale; EAPP, endometriosis-associated pelvic pain; IM, intramuscular; BMD, bone mineral density; rASRM, revised American Society for Reproductive Medicine; DIE, deep infiltrating endometriosis.

pain, lumbago, dyschezia, and dyspareunia, from baseline to the end of the treatment period [22]. However, the DNG group reported a higher frequency of irregular genital bleeding and a lower loss of bone mineral density (BMD) compared to the buserelin acetate group. In a separate prospective randomized controlled trial, 146 patients who had undergone laparoscopic surgery for deep infiltrating endometriosis were enrolled. These participants were randomized to receive either 2 mg/day of DNG or either triptorelin or leuprorelin every 4 weeks for a duration of 6 months [34]. Both groups exhibited a significant reduction in pain at the 6- and 30-month marks. No differences were observed in clinical relapse, imaging relapse, or live births between the two treatment regimens. However, the DNG group reported a more satisfactory profile.

Efficacy of postoperative DNG on recurrence of endometriosis

A meta-analysis of 10 studies evaluated the risk of endometriosis recurrence in women who received DNG following surgery [35]. Recurrence in this study was defined based on radiographic evidence of endometrioma via ultrasound or magnetic resonance imaging; patient-reported recurrence of symptoms such as pelvic pain, dysmenorrhea, dyspareunia, or noncyclic pelvic pain after conservative endometriosis surgery with DNG treatment; and findings from second-look laparoscopy. The recurrence rate was then compared to that of control participants. The use of DNG postoperatively was found to reduce the risk of endometriosis recurrence. The incidence rate of endometriosis recurrence in patients treated with DNG was 2 per 100 women over an average follow-up period of 29 months (95% confidence interval [CI], 1.43 to 3.11). This was in contrast to the recurrence rate of 29 per 100 women who were under expectant management over an average follow-up period of 36 months (95% CI, 25.66 to 31.74). The likelihood of recurrence was significantly reduced with the postoperative administration of DNG (log odds, −1.96; 95% CI, −2.53 to −1.38; $p<0.001$).

Another recent meta-analysis of 11 studies examined disease recurrence in patients who received DNG maintenance treatment compared with those who received other medications, including the levonorgestrel-releasing intrauterine system and GnRH analogs, as well as those who did not receive any treatment [36]. The recurrence rate for patients on DNG maintenance was found to be lower than that for patients who received no treatment, while demonstrating comparable efficacy to other treatments in preventing disease recurrence. Therefore, DNG is suggested as a viable maintenance treatment for patients with endometriosis, with the aim of reducing the rate of disease recurrence following conservative surgery [36].

Long-term use of DNG and adverse effects

Several studies have reported a broad range of systemic adverse effects (AEs) during DNG treatment. A pooled analysis of four randomized clinical trials evaluated the safety and tolerability of DNG in treating endometriosis. This analysis involved 332 women who were administered 2 mg of DNG for a period of 12 to 65 weeks [37]. The most frequently reported AEs were headaches (9%), breast discomfort (5.4%), depressive mood (5.1%), and acne (5.1%). In another study that examined DNG treatment over a duration of up to 65 weeks, the most common AEs (occurring in more than 5% of cases) were headache, nasopharyngitis, and breast discomfort. Despite these AEs, DNG was generally well tolerated and exhibited an overall favorable safety profile [31].

A retrospective multicenter study conducted in Korea analyzed the long-term efficacy and safety of postoperative DNG (2 mg) in 514 women. The average duration of DNG administration was 72.2±5.2 weeks, with a range of 48 to 164 weeks [38]. The most frequently observed AEs were bleeding-related events such as amenorrhea (29%; 149/514 cases) and abnormal uterine bleeding (AUB) (6.4%; 33/514 cases). Notably, the most common reason for DNG discontinuation in this study was not related to AEs, but to physician discretion (>60%). This may be attributed to many physicians' awareness of a previous study that extended the use of DNG to 65 weeks, leading to hesitation in prescribing the medication beyond this period. Cycle irregularity, or AUB, is one of the most common AEs during DNG treatment. This is typically more frequent during the first few weeks of medication, after which it tends to decrease with continued use [19,29,39-42]. Changes in bleeding patterns associated with DNG are generally well tolerated and are unlikely to be the primary reason for DNG discontinuation [14,37].

The Visanne Post-approval Observational Study, the largest real-world, non-interventional study on this topic, investigated the safety of DNG and other hormonal treatments for endometriosis in routine clinical practice [43]. This study included more than 25,000 women who were initiating new treatments for endometriosis, including DNG (2 mg) and other hormonal medications. These women were recruited from 1,000 centers across six European countries and were monitored for 7 years. The primary outcomes evaluated were anemia and either *de novo* or clinically worsening depression. The findings indicated that the hazard ratio for anemia was 1.1 (95% CI, 0.4 to 2.6) for DNG in comparison to "other approved endometriosis treatment (OAED)," and 1.3 (95% CI, 0.7 to 2.4) for DNG when compared with options "not approved but frequently used for endometriosis treatment (NAED)" [44]. The adjusted hazard ratios for new or worsening depression were 1.8 (95% CI, 0.3 to 9.4) for DNG compared to OAED and 1.5 (95% CI, 0.8 to 2.8) for DNG

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compared to NAED. The study identified no safety concerns related to anemia for DNG users. Although a slight increase in the risk of depression cannot be excluded, this may be attributable to the baseline severity of endometriosis or unidentified country-specific confounding variables.

The EffectiveNess of VISanne in Improving quality of life in Asian wOmen with eNdometriosis (ENVISIOeN) study, a prospective non-interventional study conducted in six Asian countries, evaluated health-related quality of life in a real-world setting [40]. This study included 887 patients who received DNG following a clinical or surgical diagnosis of endometriosis. Data were gathered for up to 24 months after initiation of DNG. The study findings indicated that DNG consistently enhanced EAPP from 6 to 24 months and improved health-related quality of life. This improvement was measured using the Endometriosis Health Profile-3 tool in women who had received either a clinical or a surgical diagnosis of endometriosis.

DNG has been found to inhibit ovulation and moderately suppress the production of estradiol, with the average systemic E2 concentration remaining at 39 pg/mL following treatment with 2 mg of DNG [45]. This raises potential concerns about the long-term use of DNG and its potential negative impact on bone health. In a 52-week trial involving 135 patients who were administered 2 mg of DNG daily, the BMD at the lumbar spine decreased by −1.6% at 24 weeks and −1.7% at 52 weeks [41]. However, no cumulative decrease was observed. A separate study investigated changes in BMD in 60 patients who were given DNG (2 mg/day) following surgery for endometrioma (mean duration of DNG treatment, 18.6 months) [46]. The BMD at the lumbar spine significantly decreased after the first 6 months (−2.2%) and 1 year (−2.7%) compared to baseline measurements. Similarly, the BMD at the femoral neck also significantly decreased after 1 year (−2.8%). For the 24 women who were administered DNG for 2 years or more, the BMD values after 2 years were comparable to those recorded after 1 year at both the lumbar spine and femoral neck sites.

In a retrospective study, researchers examined changes in BMD among 44 patients who used DNG for 3 years. The study found that BMD in the lumbar spine and femur decreased by −4.4% and −3.6%, respectively, compared to baseline measurements [47]. The researchers found that bone loss primarily occurred in the lumbar spine during the 1st year of treatment, and this loss gradually lessened over the course of the treatment period. These findings should be considered when advising patients on appropriate preventive measures [47]. Another study noted that bone loss associated with DNG had partially recovered by 6 months after the cessation of treatment [48]. Current evidence indicates a reduction in BMD during DNG treatment in adolescents and women of reproductive age. However, the clinical significance of this finding—specifically, whether this decrease in BMD is progressive and accumulates over the duration of DNG treatment, as well as whether it increases the risk of fractures later in life—requires further investigation.

Conclusion

For many years, the primary use of medical therapy for endometriosis has been as an adjunct or maintenance treatment following surgical diagnosis and intervention. The surgical management of endometriosis offers several benefits, including the removal of lesions with histological confirmation and anatomical restoration, and it can alleviate pain symptoms associated with endometriosis. However, a potential risk exists of diminished ovarian function due to surgical trauma, which could adversely impact fertility, especially in women planning to conceive. Consequently, a patient-tailored therapeutic approach, involving either surgical or medical treatment for endometriosis, should be meticulously evaluated. This evaluation should take into account various factors including age, the nature and severity of symptoms, future plans for pregnancy, and the condition of the ovarian reserve.

A recent paradigm shift has occurred towards considering empirical medical treatment following the clinical diagnosis of endometriosis [10,11,49]. Current guidelines, along with expert opinions, endorse progestin as the first-line medical option for the treatment of endometriosis. DNG offers benefits including comparable efficacy to GnRH agonists in reducing endometriosis-related pain and fewer side effects due to hypoestrogenism. Therefore, its long-term use is feasible and supported by accumulated data [11,49-51].

Endometriosis is a chronic condition that can cause persistent symptoms, such as pelvic pain, disease progression, or recurrence throughout a person's lifetime. Consequently, emphasis has been placed on the necessity for long-term medical treatment to alleviate endometriosis-related symptoms and prevent recurrence. During treatment with DNG, some AEs may occur, including changes in bleeding patterns and various hormone-related symptoms (such as weight gain, mood changes, and androgenic effects). However, these are generally well tolerated and are not primary causes of treatment discontinuation. More importantly, DNG-related AEs do not overshadow the established benefits of DNG in managing endometriosis symptoms and reducing the risk of recurrence.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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