Original Article

Efficacy and Safety of Long-Term Use of Dienogest in Women With Ovarian Endometrioma

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Abstract

Dienogest (DNG) is a progestin with highly selective progesterone activity and minimal androgenic activity and is helpful in reducing endometriosis-related pain. This study assessed the long-term efficacy and safety and recurrence rate of endometrioma with DNG use beyond 12 months of treatment. A retrospective cohort study was conducted with data collected from 7 university-affiliated hospitals and included a total of 514 women with ovarian endometrioma. All patients received 2 mg of oral DNG daily for at least 48 weeks postoperatively. During continuation of DNG, the recurrence rate of ovarian endometrioma on ultrasound, adverse events, changes in menstrual pattern, and pain score (visual analogue scale) were analyzed. The average period of DNG administration in this study was 72.2 $\pm$ 5.2 weeks (range: 48-164). The recurrence rate of endometrioma was 1.8% (9 of 514), and the median duration to recurrence was 58 weeks (range: 24-76). Pain was described as overall improved by 82.2% of patients; 61.6% stated the pain was "improved" and 20.6% reported "much improved." The mean VAS score was 4.9 at baseline and significantly decreased to 2.68, 2.2, 1.6, and 2.6 at 12, 24, 48, and 96 weeks. Amenorrhea rate was 58.3% in the first 12 weeks and increased to 86.4% at 72 weeks. Prolonged daily administration of 2 mg DNG followed by surgery was associated with a lower recurrence rate of ovarian endometrioma and a reduced pain score and symptoms.

Keywords
endometriosis, progestin, Dienogest

Introduction

Endometriosis, defined as the implantation of endometrial stroma and gland outside the uterus, is prevalent up to 10% in reproductive-age women.[1] This condition often causes chronic pelvic pain, dysmenorrhea, and infertility and may negatively affect the quality of life in severe cases.[2,3]

Surgery is generally recommended for the diagnosis and treatment of endometriosis, but medical treatment is also essential for managing endometriosis-related pain and preventing recurrence. The current options for medical treatment of endometriosis include gonadotropin-releasing hormone (GnRH) agonists, progestins, or combined oral contraceptives (OCs).

Among these, progestins have been widely used as first-line drug treatments for symptomatic endometriosis. These induce decidualization of endometrial tissues and suppress ovulation[4] and reduce inflammation in endometriotic cells or the microenvironment.[5,6] The accumulated evidence for the efficacy of progestins on endometriosis-related symptoms has led to their approval for the treatment of endometriosis by the US Food and Drug Administration. However, progestins may cause hormone-related systemic side effects, such as abnormal

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uterine bleeding, weight gain, breast tenderness, and mood change, and these adverse events can lead to discontinuation of this medication.

Dienogest (DNG) is a derivative of 19-nortestosterone, but its chemical structure differs from that of other 19-nortestesterone-derived progestins owing to the attachment of a cyanomethyl group to an ethinyl estradiol group.[7,8] Dienogest provides some pharmacological benefits with its high selectivity for progesterone receptors and progestogenic effects on the endometrium while it exerts minimal androgenic, mineralocorticoid, and glucocorticoid activities.[7,9,10] Gonadotropin-releasing hormone agonists are also well-established, effective treatments for relieving endometriosis-related pain.[7,11] The mechanism involves downregulation of the GnRH receptors, which lead to a hypoestrogenic state. Several randomized clinical trials have compared the efficacy of oral DNG and various types of GnRH agonist and found that DNG is as effective as GnRH agonists in the reduction of pain and dysmenorrhea.[12-14]

Convincing evidence for the efficacy of DNG for symptomatic endometriosis has been reported, in addition to favorable outcomes with fewer side effects related to hypoestrogenism. The discontinuation rate of DNG therapy in the early period due to side effects was reported to be low.[12-14] Therefore, we aimed to investigate the clinical efficacy and safety profile of DNG and the recurrence of ovarian endometrioma in patients after long-term postoperative administration of oral DNG.

Materials and Methods

This retrospective cohort study included a total of 514 women who underwent laparoscopic ovarian cystectomy for ovarian endometrioma, followed by postoperative DNG 2 mg once daily for at least 12 months for the prevention of recurrence; patient medical record data and operative reports were collected from 7 university-affiliated hospitals in South Korea for August 2010 and January 2015.

Patient characteristics included age, parity, height, weight, body mass index (BMI), and laterality of endometrioma (unilateral or bilateral). Patients with pathological diagnoses other than endometrioma were excluded. Duration of administration of DNG and use of OCs, progestins, or GnRH analogues within 6 months before DNG were recorded. Pelvic pain and symptom changes after DNG use were expressed in visual analogue scale (VAS) score or categorized into 4 groups: much improved, improved, no change, or worsened.

Data on menstrual changes after DNG use, current status of use, reasons for discontinuation, serum cancer antigen 125 (CA-125) levels prior to and during DNG use, and bone mineral density (BMD) at the lumbar spine (L1-L4) and femur (neck and total) by dual-energy X-ray absorptiometry (DXA) were also collected. Adverse events during DNG use were also analyzed.

Recurrence of pain was defined as newly developed pelvic pain during DNG use, and recurrence of endometrioma was defined as newly developed endometrioma on pelvic ultrasonography (USG). Ovarian endometrioma was mainly diagnosed by typical findings of a hypoechoic, homogeneous, and semi-solid ovarian cystic mass on transvaginal or transrectal pelvic ultrasonography.

Statistics

All continuous variables were summarized as mean (standard deviation). Categorical variables were summarized in tabular form according to the number of factors. The Wilcoxon-signed rank test was applied to compare baseline and follow-up BMD values. The differences in recurrence rates according to the type of medications used before DNG administration were assessed using the χ^2 test. All analysis was performed with the R statistical program (R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/]./).

Results

The mean age of patients was 33.9 $\pm$ 7.1 years (range: 20-49), and the mean BMI was 21.0 $\pm$ 3.0 kg/m^2 (range: 15.2-37.5). The overall average period of DNG administration was 72.2 $\pm$ 5.2 weeks (range: 48-164). About one-third (32.5%) of patients had bilateral endometriomas. About half (48.6%) of patients received injections of GnRH agonists immediately after surgery, and about 43.6% did not take any medications before DNG administration (Table 1). Over 59% (305 of 514) of patients remained on DNG, with a mean duration of 67.4 weeks, and the longest duration of continued use was 152 weeks. The mean duration of administration was 76.4 weeks even in patients who discontinued DNG (Table 2). Of the patients included in the study, 209 (40.6%) discontinued DNG therapy. The most common reason for physicians' decision to discontinue prescribing DNG was the clinical data printed on the drug information sheet that DNG should be used only for approximately 18 months. Physicians also decided to stop prescribing DNG when no recurrence was observed after 15 to 20 months of DNG use postoperatively. Patients wanted to discontinue DNG therapy because of abnormal uterine bleeding (n = 3), edema (n = 1), sweating (n = 1), depressed mood (n = 1), and aggravation of symptoms of underlying medical disease—ankylosing spondylitis (n = 1; Table 2).Endometrioma recurred during continuation of DNG in 1.8% (9 of 514), and the median duration to recurrence was 58 weeks (24-76).

The mean VAS score was 4.9 at baseline and significantly decreased to 2.6 (n = 170), 2.2 (n = 91), 1.6 (n = 95), and 2.6 (n = 48) at 24, 48, 72, and 96 weeks, respectively (Figure 1). The lowest VAS score was reported at 72 weeks. Among 180 patients who reported pain status at 6 months of DNG use, 61.6% (n = 111) stated that the pain was "improved" and 20.6% (n = 37) reported pain "much improved" in comparison to the baseline level. Only 17.8% of the patients reported "no change" (n = 29) or "worse" (n = 3; Figure 2).

The mean serum CA-125 level at baseline was 4.9 U/mL (n = 170); at 6 months, the level decreased by 50% (2.6 U/mL,

Table. 1. Clinical Characteristics of Study Patients.

Patients (n = 514)			
Age, years	33.8 ± 7.1 (20-49)	Duration of DNG (weeks)	72.2 ± 5.2 (48-164)
Parity	0.36 ± 0.78 (0-3)	Type of endometrioma	
Height, cm	162.1 ± 65.5 (133.0-179.7)	unilateral	343
Weight, kg	55.1 ± 8.1 (37.0-100.5)	bilateral	171
BMI, kg/m^2	21.0 ± 3.0 (15.2-37.5)		
Preceding Medication	No. of Patients	Duration of Preceding Medication, Weeks	Duration of DNG Use, Weeks
Oral contraceptive	23	49.8 (4-180)	70.2 (48-120)
GnRH agonist	250	19.5 (4-32)	74.2 (48-164)
Levonorgestrel IUS	3	34.0 (40-240)	70.6 (48-108)
Other progestin	5	27.2 (8-64)	63.2 (48-120)
NSAIDs	2	NA	84.2 (72-96)
None	224		69.9 (48-152)
No data	7		88.0 (56-108)

Abbreviations: BMI, body mass index; DNG, dienogest; IUS, intrauterine system; NA, no available data; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 2. Reasons for Discontinuation of DNG Other Than Pregnancy Planning.

Reasons for Discontinuation	Number of Patients (%), n = 209	Duration of DNG Use, Mean (Weeks)
Due to adverse events	24 (11.4%)	65.2 (48 ~ 120)
Follow-up loss	18 (8.6%)	57.8 (48 ~ 100)
Patient's wants	10 (4.8%)	62.2 (48 ~ 96)
Physician decision	139 (66.5%)	69.0 (48 ~ 128)
Switch to other medication	15 (7.2%)	69.3 (48 ~ 136)
No data	3 (1.43%)	67.8 (48 ~ 60)

Abbreviation: DNG, Dienogest.

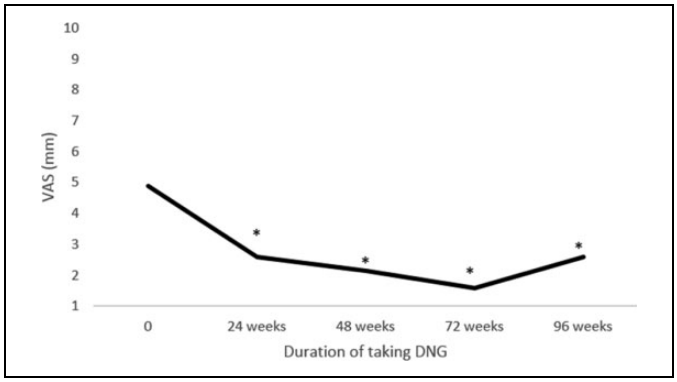

Figure 1. Pain during Dienogest (DNG) use, mean Visual Analogue Scale (VAS) score.

n = 91). The CA-125 levels steadily decreased to 1.6 U/mL (n = 48) until 72 weeks and remained at a low level (2.6 U/mL, n = 12) until 24 months of follow-up.

A total of 225 (43.7%) patients reported adverse events (AEs; Table 3). The most common AEs were amenorrhea (66.2%, 149 of 225) and abnormal uterine bleeding (14.6%, 33 of 225). The menstrual pattern during DNG administration is shown in Figure 3. We categorized amenorrhea as an AE

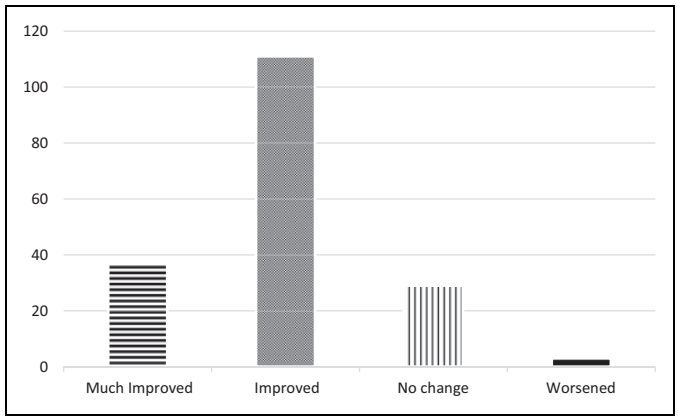

Figure 2. Pain change at 6 months of Dienogest (DNG) use, 4 descriptive categories.

because the purpose of DNG administration after endometrioma surgery was treatment and prevention of endometriosis and not induction of amenorrhea. The prevalence rates of amenorrhea among the patients who evaluated their menstrual pattern at each follow-up were 58.3% (119 of 204), 72.6% (151 of 208), 78.3% (163 of 208), and 86.4% (83 of 96) at 12, 24, 48, and 72 weeks of DNG use, respectively.

The rate reached over 50% just 12 weeks after DNG administration began and steadily increased. The prevalence of abnormal uterine bleeding, including frequent bleeding, prolonged bleeding, and spotting, among 347 patients who evaluated their menstrual pattern at each follow-up was 16.7% (58 of 347), which decreased thereafter to only 10.1% (31 of 208) after 1 year and 4.2% (4 of 96) after 18 months.

Any bleeding that continued 1 year after the start of administration was mostly described as spotting. Abdominal pain was reported by 3.1% (7 of 225) and weight gain by 1.9% (6 of 225). Depressed mood was reported by 2.2% (5 of 225). However, AE symptoms were moderate and resolved with discontinuation of DNG, without the need for additional intervention. Other AEs reported by fewer than 5 patients are shown

Table 3. Adverse Events During Dienogest Use.[a,b].

Adverse Events	n (%)
Amenorrhea	149 (29.0)
Abnormal uterine bleeding	33 (6.4)
Abdominal pain	9 (1.8)
Weight gain	6 (1.2)
Depressed mood	5 (1.0)
Insomnia	5 (1.0)
Acne	4 (0.8)
Headache	3 (0.6)
Hot flush, sweating	2 (0.4)
Breast tenderness	2 (0.4)
Oily skin	1 (0.2)
Others[a]	5 (1.0)

Abbreviations: DNG, Dienogest.
[a]n = 514.
[b]Others refers to adverse events such as a change in the amount of menstruation (n = 1), itching (n = 1), palpitation (n = 1), dizziness (n = 1), and nausea (n = 1).

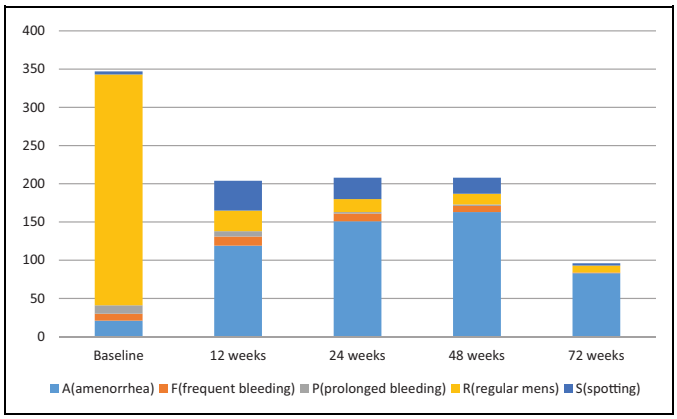

Figure 3. Menstrual patterns during Dienogest (DNG) use.

in Table 3. All the symptoms were charted in accordance with the patient's report.

Only 12 of 514 patients underwent BMD testing after DNG administration. BMD testing was performed based on each physician's decision. The mean interval at which BMD was measured was 74 weeks (48-128 weeks). A significant decrease in BMD (g/cm^2) was observed at the lumbar spine (from 0.91 to 0.88 g/cm^2; Wilcoxon-signed rank test, $P < .05$) but not at the femur neck (from 0.71 to 0.71 g/cm^2; Wilcoxon-signed rank test, $P > .05$) and total femur (from 0.82 to 0.80 g/cm^2; Wilcoxon-signed rank test, $P > .05$). Patients who demonstrated a decrease in lumbar spine BMD discontinued DNG and were administrated OCs due to concern about further bone loss.

Discussion

This study evaluated the efficacy and safety of long-term postoperative DNG for the prevention of endometrioma recurrence; the cumulative recurrence rate was 1.8% during the 41 months' follow-up, and the median duration to recurrence was 18.0 months (range, 12-41 months). This result was comparable with those in other reports that describe the recurrence rate of 0% to 1.7% during 18 to 24 months' use of DNG as a postoperative medical treatment.[15-17]

In addition, DNG was effective for the prevention of endometriosis pain recurrence after about 6 months of use, and efficacy was sustained for at least 18 months, with a reduction in serum CA-125 levels.

The present study evaluated the efficacy of postoperative long-term DNG use for the prevention of endometrioma recurrence; DNG was administered for over 1 year, with a median duration of 17.5 months and a maximum follow-up of 41 months. During long-term follow-up, the efficacy for prevention of endometrioma recurrence was very high, with a cumulative recurrence rate of 1.8%; this rate is much lower than that reported for other postoperative medical treatments, such as levonorgestrel-releasing intrauterine system or combined OCs.[18-20] Most previous studies addressed the recurrence of endometriosis from the aspect of pain, and the effects of DNG for the prevention of endometrioma recurrence have seldom been reported. Although a recent study reported DNG use for an average of 87 weeks, the number of patients included in the study was relatively small, and the primary modality of diagnosis was imaging without the assessment of clinical symptoms. Moreover, half of the patients had coexistence of adenomyosis.[21] In contrast, all patients in the current study underwent laparoscopy for pathologic confirmation, and those with other conditions were excluded. It is not clear why DNG showed superior efficacy in preventing endometrioma recurrence in comparison with other medical treatment options. One explanation is that prevention of recurrence may be due to complete inhibition of ovulation by DNG at a dose ≥ 2 mg.[22] In addition, this efficacy may be due to the both 19-norprogestins and progesterone derivatives properties of DNG, which have a pronounced progestogenic effect on the endometrium, without being androgenic, and which induce moderate suppression of ovarian activity, manifested as moderate hypoestrogenic effects.[12,23] In addition, DNG may have distinct molecular effects on endometriotic cells. It has been shown that DNG comprehensively inhibits abnormal estrogen production through inhibition of aromatase and 17β-hydroxysteroid dehydrogenase 1, and its therapeutic effects on endometriosis through induction of autophagy and promotion of apoptosis with suppression of phosphoinositide 3/protein kinase B and extracellular signal-regulated kinase 1/2 activity have been also suggested.[24,25]

Endometriosis-related pain was effectively suppressed during treatment in the current study. The most dramatic decrease in pain was observed in the first 6 months, and the effect was sustained for at least 18 months of DNG use. Our results are consistent with those of previous studies that demonstrated the efficacy and safety of DNG treatment for the management of endometriosis-associated pain.[26,27] In a randomized trial, DNG at a dose of 2 mg daily for 12 weeks reduced endometriosis-related pain with greater efficacy than placebo after diagnostic

laparoscopy.[28] In a 24-week noninferiority trial, the efficacy for endometriosis pain was equivalent to that of leuprolide acetate, with less hypoestrogenic effect and more favorable effects on BMD.[12] When the total duration of use was extended to 65 weeks in an open-label study, favorable efficacy and safety profiles were also reported.29 Although previous reports seem very promising for symptomatic management of endometriosis, data regarding long-term efficacy and safety of DNG beyond 1 year of treatment are still limited. Since endometriosis is a chronic disease that requires long-term management, and relief of pain seems to be related to medication status,[17] more data on long-term efficacy, safety, and tolerability of DNG are needed.

In our study, the most common AEs related to DNG treatment were bleeding-related, consistent with previous reports. As expected, the frequency and amount of irregular bleeding decreased as treatment progressed, and only a small fraction of patients discontinued medication. However, in contrast with previous reports,[29,30] the rate of those experiencing amenorrhea was much higher in our study, reaching 60% at 3 months and over 90% at 18 months. The reason is not clear, but it may be related to differences in study populations and ethnicity. Moreover, since more than half of the patients received 3 to 6 cycles of postoperative GnRH analogues before DNG use, these patients may have experienced more favorable bleeding profiles. It is notable that the most common cause of discontinuation of medication was not related to AEs but was due to physician discretion (more than 60%). Many physicians are aware that a previous study extended the use of DNG up to 65 weeks and may have hesitated to prescribe medication beyond that time point. However, this and previous studies support the efficacy and safety of long-term DNG.

One of the concerns for long-term use of DNG is the effect on bone health. A previous study showed significant superiority of DNG over GnRH analogues with regard to changes in BMD.[12] Another study showed no cumulative decrease in BMD for up to 52 weeks of treatment and no significant changes in bone metabolic markers.[30] However, our data, based on a small sample size (11 patients), demonstrated significant reduction in BMD at the lumbar spine after 1 year of treatment with DNG, which is in agreement with the results of studies in a Japanese population.[14,30] Nonetheless, based on the current evidence, the long-term effects of DNG on bone health seem to be minimal and superior to those of GnRH analogues.[31] Asian women have a lower natural BMD than Caucasians, and ethnic differences in physiological estrogen levels warrant further research on the long-term effects of DNG on bone metabolism in Asian populations.[32,33] Asian women with estrogen deficiency are more likely to have BMD below the expected range for age than Caucasian women.[34]

This study has several strengths. First, the sample size with ovarian endometrioma was the largest among studies regarding DNG use for endometriosis. Second, the duration of DNG use was longer than in previous studies,[21,29] and only 1 study evaluated the long-term effect for 24 months.[17]

However, this retrospective study had several additional limitations. First, the medication used before DNG treatment was heterogeneous. More than half of the patients received GnRH analogues or OCs before changing to DNG, which may have influenced the results. In fact, our study showed significantly higher rate of recurrence of endometrioma or pain in patients who took OCs before DNG administration. Another limitation is that endometrioma recurrence was evaluated using ultrasonography instead of laparoscopy with histologic confirmation. However, previous studies of transvaginal ultrasonography in diagnosing ovarian endometrioma reported a 77% to 89% sensitivity rate and an 89% to 98% specificity rate.[35,36]

In conclusion, postoperative long-term use of DNG is highly effective in preventing endometrioma recurrence, with symptomatic relief and a relatively low discontinuation rate due to AEs. Because of high efficacy for the prevention of endometriosis recurrence and acceptable safety profiles, physicians should consider using long-term DNG beyond 1 year for endometriosis.

Authors' Note

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: All authors have been symposium speakers and advisory board members of, and received honoraria and consulting fees from, Bayer HealthCare.

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