Original Article

Effectiveness of Dienogest for Treatment of Recurrent Endometriosis: Multicenter Data

Reproductive Sciences
1-8

DOI: 10.1177/1933719118779733
journals.sagepub.com/home/rsx
SAGE

Jae Hoon Lee, MD[1,2], Jae Yen Song, MD, PhD[3], Kyong Wook Yi, MD, PhD[4], Sa Ra Lee, MD, PhD[5], Dong-Yun Lee, MD, PhD[6], Jung-Ho Shin, MD, PhD[4], SiHyun Cho, MD, PhD[2,7], Seok Kyo Seo, MD, PhD[1,2], and Sung Hoon Kim, MD, PhD[8]

Abstract

This study aimed to assess whether dienogest (DNG) is also effective in patients with recurrent endometriosis based on multicenter data of 121 women who were clinically diagnosed as having recurrent endometriosis and treated for more than 24 weeks with DNG (2 mg daily). We evaluated the changes in endometriosis-associated pain scores (visual analog scale [VAS]), serum cancer antigen 125 (CA-125) levels, and endometrioma sizes following DNG medication in these women along with adverse events associated with DNG medication. The mean duration of DNG treatment was 57.80 (24.08) weeks, and during continuation of DNG, the mean VAS score was 5.03 (1.73) at baseline and significantly decreased to 2.46 (1.32) at 24 weeks after taking DNG. In subgroup analysis, the trend of pain-related symptoms was compared between the symptom-only recurrence group and the recurrent endometrioma group. In both groups, the pain scores decreased significantly during the first 24 weeks but remained relatively unchanged thereafter. Moreover, the size of recurrent endometriomas and CA-125 levels also decreased significantly compared to baseline. The mean size of recurrent endometriomas was 3.77 (1.59) cm in diameter and decreased to 2.74 (1.53) cm after 24 weeks of DNG treatment (P for trend < .001). The mean CA-125 level was 80.04 U/mL at baseline and significantly decreased to 33.11 U/mL after taking DNG for 24 weeks and lasted until 72 weeks (P for trend = .0288). Overall, 51 (42.15%) patients reported adverse events, and the most common one was irregular bleeding pattern (29.75%, 36/121). In conclusion, DNG was found to be effective in reducing the size of endometriomas and provided symptomatic relief in this cohort of women with recurrent endometriosis.

Keywords

dienogest, endometriosis, endometrioma, recurrence

Introduction

Endometriosis, defined as the implantation of endometrial stroma and gland outside the uterus, is a benign disease prevalent in up to 10% of reproductive-age women.[1] This condition is associated with both pelvic pain and infertility and may negatively affect the quality of life in severe cases. In patients with endometriosis, surgical treatment is often performed to improve pain and rate of spontaneous pregnancy.

[1] Department of Obstetrics and Gynecology, Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea
[2] Institute of Women's Life Medical Science, Yonsei University College of Medicine, Seoul, South Korea
[3] Department of Obstetrics and Gynecology, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea
[4] Department of Obstetrics and Gynecology, College of Medicine, Korea University, Seoul, South Korea
[5] Department of Obstetrics and Gynecology, College of Medicine, Ewha Womans University, Seoul, South Korea
[6] Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea
[7] Department of Obstetrics and Gynecology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea
[8] Department of Obstetrics and Gynecology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Corresponding Authors:
Sung Hoon Kim, Department of Obstetrics & Gynecology, Asan Medical Center, University of Ulsan College of Medicine, Olympic-ro 43 Gil 88 Songpa-gu Seoul 05505, Korea.
Email: kimsung@amc.seoul.kr
Seok Kyo Seo, Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
Email: tudeolseo@yuhs.ac

However, even after excising all visible disease and restoring normal anatomic relationships of pelvic organs, symptoms recur in at least 10% to 20% of treated women per year.[2,3] Without postoperative medication, 45% to 55% of patients who had been treated surgically require further surgery by 5 to 7 years because of recurrent endometriosis.[4] Recent reports suggest that second surgery for recurrent endometrioma is associated with a higher loss of ovarian tissue and ovarian reserve evaluated by antimüllerian hormone, antral follicle count, and ovarian volume compared to first surgery.[5,6] Therefore, preventing recurrence after surgical treatment is becoming routine management in patients with endometriosis.

Once the recurrence is diagnosed, an alternative option other than the second surgery is medical treatment for recurrent disease. Current options for medical treatment include gonadotropin-releasing hormone (GnRH) agonists, progestins, levonorgestrel-releasing intrauterine system, or combined oral contraceptives (OCs). Although OCs are the most commonly prescribed medication for endometriosis for decades, OCs have been criticized for lack of evidence for therapeutic efficacy and for increasing the risk of thromboembolism,[7,8] and progestin-only pill is suggested as a better first-line treatment option for endometriosis by some investigators.[7,9] In particular, dienogest (DNG) has received spotlight as a targeted progestin for endometriosis for its unique characteristics.[10-13] Dienogest is a derivative of 19-nortestosterone, providing some pharmacological benefits relevant to the treatment of endometriosis, including high selectivity for progesterone receptors and progestogenic effects on the endometrium that lead to effective disease reduction. It exerts minimal androgenic, mineralocorticoid, and glucocorticoid activities with only moderate suppression of estrogen levels.[11,14,15] In a randomized, multicenter trial of 252 participants, DNG showed equivalent efficacy to depot leuprolide in relieving the pain associated with endometriosis.[13] In contrast to GnRH agonist that have risk of bone loss following long-term use, DNG also showed favorable safety profile in a study of 151 participants with a mean follow-up of 61 weeks.[12]

Although DNG has improved endometriosis-related symptoms and reduced recurrence after surgical treatment of endometriosis in previous studies,[11-13,16] efficacy of DNG on recurrent endometriosis is not well established. Considering that endometriosis is known to be a chronic disease with epigenetic characteristics,[17] we assumed that recurrent endometriosis might have different responses to DNG. This study aimed to assess whether DNG is also effective in patients with recurrent endometriosis based on multicenter data of 121 women who were clinically diagnosed as having recurrent endometriosis and treated for more than 24 weeks with DNG (2 mg daily).

Materials and Methods

Study Population

This retrospective cohort study included 121 women with a clinical diagnosis of recurrent endometriosis who had been confirmed as having endometriosis histologically at the time of the previous surgery. Only patients who previously underwent conservative cystectomy were eligible, and all participants were treated with DNG (2 mg daily) as the initial treatment once recurrence was detected. Women who had taken any hormonal medication in the preceding 6 months were excluded from this study. The patients' medical record data and operative reports were collected from 7 university-affiliated hospitals in South Korea from July 2005 through June 2016. While receiving DNG, the patients' pain-related symptoms, serum cancer antigen-125 (CA-125) levels, pelvic ultrasonography findings, and adverse events were monitored at 6 monthly intervals. This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System (4-2017-0234).

Criteria and Definitions

In this study, recurrence of endometriosis was defined as newly developed dysmenorrhea or pelvic pain regardless of ultrasound findings or newly developed endometriomas with a minimum diameter of 2.0 cm on pelvic ultrasonography.[18,19] Treatment with DNG was considered to have had no effect if the diameter of the ovarian endometrioma did not decrease or if, regardless of ultrasound findings, the pain symptoms were aggravated. For patients in whom the endometrioma size fluctuated over time, if the most recent cyst size was smaller than that at baseline, DNG was regarded as being effective.

Adverse events were defined as any unfavorable and unintended sign, symptom, or disease occurring with the use of DNG. Amenorrhea was defined as no menses for a time period equivalent to a total of 3 menstrual cycles or 6 months. For patients with regular menstrual periods, if the pattern of bleeding that deviated from the original pattern—such as prolonged menstruation, metrorrhagia, or oligomenorrhea—this was defined as an irregular bleeding pattern. Although this definition is broad, it has an advantage of representing the discomfort that patients feel directly.

Variable Measurements

The primary outcome measure was the changes in the symptoms of dysmenorrhea and nonmenstrual pelvic pain assessed by a visual analog scale (VAS). The VAS is a well-established tool for the measurement of pelvic pain associated with endometriosis and is known to be superior to fixed interval scales, relative pain scales, and verbal reports of pain.[20,21]

The diagnosis of an ovarian endometrioma was based on transvaginal or transrectal ultrasonography, fulfilling the following ultrasonographic criteria a round mass with a thick wall, a minimum diameter of 2 cm, regular margins, and homogenous low echogenic fluid content with scattered internal echoes, without papillary projection.[18,22,23] Previous studies of transvaginal ultrasonography findings reported a sensitivity of 77% to 89% and a specificity of 89% to 98% in diagnosing endometriomas using these criteria.[24,25] The size of an endometrioma was defined as its maximum diameter in any

dimension[18,26] as measured by ultrasonography; the maximum diameter was used to assess changes in the size of the endometrioma after DNG administration.

CA-125 level was compared between baseline and following DNG medication when data were available. The extent of endometriosis present at the time of undergoing previous surgical intervention was staged according to the classification system of the American Society for Reproductive Medicine[27] based on the patients' medical records. Adverse events were assessed by directly questioning women on incidences of side effects commonly associated with endometriosis and hormonal therapy, including irregular bleeding pattern, breast discomfort, bloated feeling, headache, depressive mood, hot flushes, acne, and hirsutism. Additional adverse events were documented from spontaneous reports.

Statistical Analysis

The demographic characteristics of the participants were analyzed using descriptive statistics. All data were assessed by the Kolmogorov-Smirnov test to evaluate whether they were normally distributed. Since all data were normally distributed, continuous variables were analyzed using Student t tests and are reported as the mean (standard deviation; SD). Categorical variables were analyzed using the χ^2 test and are expressed as frequencies and percentages.

Analyses of pain scores and size of endometriomas were performed by paired t tests, Wilcoxon signed rank test, and linear mixed model for random and fixed effects. To evaluate the ability of DNG to reduce pain symptoms over time, the patients were divided into 2 subgroups according to the type of recurrence: a symptom-only recurrence group and a recurrent endometrioma group. Post hoc analyses were also performed for multiple comparisons.

Although this study was a retrospective study, the authors confirmed whether the sample size was sufficient to examine the effect of DNG. The sample size for paired t test was calculated on the assumption that DNG has an equal efficacy for recurrent endometriosis as reported in previous studies: δ (difference) = 4.75 and σ (SD) of 2.42 for the primary outcome.[13] A total of 6 evaluable patients were required to yield a power $(1-\beta)$ of 90% to demonstrate the efficacy of DNG treatment. The data analysis was performed using SAS (version 9.4; SAS Inc, Cary, North Carolina) and PASS (version 12; NCSS, LLC, Kaysville, Utah), with a P value <.05 considered statistically significant.

Results

General Characteristics of the Study Population

The general characteristics of the study population are shown in the Table 1. Dienogest was administered to 121 participants diagnosed as having recurrent endometriosis for 57.80 (24.08) weeks. Patients with recurrent endometriomas accounted for 72.73% (88/121) of the total recurrences observed. The mean interval from the most recent surgery for endometriosis to the latest episode of recurrence was 52.07 (37.11) months, and 53.72% (61/121) of patients had history of medical treatment to prevent recurrence immediately after the previous surgery.

Table 1. Demographic Characteristics of Patients With Recurrent Endometriosis.

	Recurrent Endometriosis, n = 121	Number of Participants
Age, years	34.82 (6.83)	121
Parity	0.44 (0.76)	121
BMI, kg/m^2	21.07 (3.53)	109
Period after surgery to relapse, months	52.07 (37.11)	113
Mean duration of DNG intake, weeks	57.80 (24.08)	121
Type of recurrence, %		121
Symptom-only	27.3	33
Rt. endometrioma	31.4	38
Lt. endometrioma	27.3	33
Bilateral endometrioma	14.0	17
Dysmenorrhea pain scale (VAS)	5.03 (1.73)	68
CA-125, U/mL	80.04 (104.54)	73
Size of endometrioma in diameter, cm	3.77 (1.59)	105
Rt. endometrioma	3.79 (1.61)	55
Lt. endometrioma	3.76 (1.58)	50
Type of previous surgery, %		
Open ovarian cystectomy	7.4	9
Laparoscope guided ovarian cystectomy	92.6	112
ASRM stage of endometriosis in previous surgery		64
I	0.0%	0
II	12.5%	8
III	42.2%	27
IV	45.3%	29
Previous medication after surgery	Mean duration, months	65
GnRH agonist	5.76 (0.80)	41
Oral contraceptives	13.79 (13.10)	20
Progestins	12.7 (6.80)	3
Levonorgestrel-releasing IUS	55	1

Abbreviations: ASRM, American Society for Reproductive Medicine; BMI, body mass index; CA-125, cancer antigen-125; DNG, dienogest; GnRH, gonadotropin-releasing hormone; IUS, intrauterine system; VAS, visual analog scale.

Effect of DNG on Pain Symptoms

Overall, the pain score decreased significantly from before to 24 weeks and 48 weeks after taking DNG (Table 2). To investigate the effect of DNG according to the form of recurrence, we compared the trend of pain-related symptoms between the symptom-only recurrence group and recurrent endometrioma group (Table 2). The trend of pain-related symptoms over time was not significantly different between the 2 groups: The response to DNG in recurrent endometrioma group was similar to that of symptom only recurrence group (P = .7441). In both

Table 2. Pain-Related Symptoms During Dienogest Treatment According to Form of Recurrence, Mean VAS Score.

	Before Treatment, n = 68	24 Weeks After Treatment, n = 61	48 Weeks After Treatment, n = 17	
All groups (VAS)	5.03 (1.73)	2.46 (1.32)[a]	2.24 (1.09)[a]	
	Recurrent Endometrioma Group	Symptom-Only Recurrence Group	*P* Value[b]	$P_{group \times time}$[c]
Baseline	5.09 (1.72) (n = 43)	5.04 (1.71) (n = 24)	.9070	.7441
24 Weeks after treatment	2.58 (1.50) (n = 38)[a]	2.32 (0.95) (n = 22)[a]	.4660	
48 Weeks after treatment	2.60 (1.27) (n = 10)[a]	1.83 (0.41) (n = 6)[d]	.1770	

Abbreviations: VAS, visual analog scale.
[a]*P* < .001 compared with baseline.
[b]*P* value compared pain symptoms between recurrent endometrioma group and symptom-only recurrence group at each time point.
[c]*P* value for difference of pain score between recurrent endometrioma group and symptom-only recurrence group at 3 time points, calculated by multivariable linear mixed model.
[d]*P* < .01 compared with baseline.

Table 3. Size of Recurrent Endometriomas After Dienogest Treatment.

	Before Treatment	24 Weeks After	48 Weeks After	72 Weeks After	96 Weeks After	*P* for Trend
Overall, cm[a]	3.77 (1.59) (n = 105)	2.74 (1.53) (n = 86)[b]	2.26 (1.68) (n = 65)[b,c]	1.81 (1.58) (n = 44)[b,c,d]	2.04 (1.58) (n = 29)[b,e,f]	<.0001
Rt.	3.79 (1.61) (n = 55)	2.69 (1.74) (n = 43)[b]	2.34 (1.90) (n = 32)[b,e]	1.66 (1.61) (n = 22)[b,c,f]	2.48 (1.43) (n = 12)[b]	<.0001
Lt.	3.76 (1.58) (n = 50)	2.79 (1.32) (n = 43)[b]	2.18 (1.46) (n = 33)[b,e]	1.96 (1.57) (n = 22)[b,c,g]	1.74 (1.65) (n = 17)[b,e,f]	<.0001
Unilateral[a]						
Rt.	3.64 (1.30) (n = 38)	2.60 (1.69) (n = 27)[b]	2.17 (1.82) (n = 20)[b,h]	1.08 (1.56) (n = 12)[b,e,g]	1.18 (1.56) (n = 4)	.0001
Lt.	3.48 (1.29) (n = 33)	2.77 (1.36) (n = 27)[b]	2.14 (1.59) (n = 22)[b,c]	1.77 (1.87) (n = 12)[b,c,g]	1.29 (1.89) (n = 9)[b,c,f]	<.0001
Bilateral[i]						
Rt.	4.11 (2.18) (n = 17)	2.85 (1.85) (n = 16)[j]	2.63 (2.06) (n = 12)[j]	2.35 (1.44) (n = 10)[j,h]	3.13 (0.85) (n = 8)[j]	<.0001
Lt.	4.29 (1.96) (n = 17)	2.83 (1.29) (n = 16)[j]	2.25 (1.23) (n = 11)[j]	2.19 (1.18) (n = 10)[j]	2.25 (1.26) (n = 8)[j]	<.0001

[a]Post hoc analyses for multiple comparison in overall and unilateral group were performed using paired *t* test.
[b]*P* < .001 compared with baseline.
[c]*P* < .001 compared with 6 months after DNG treatment.
[d]*P* < .001 compared with 12 months after DNG treatment.
[e]*P* < .01 compared with 6 months after DNG treatment.
[f]*P* < .01 compared with 12 months after DNG treatment
[g]*P* < .05 compared with 12 months after DNG treatment.
[h]*P* < .05 compared with 6 months after DNG treatment.
[i]Post hoc analyses for multiple comparison in bilateral group were performed using Wilcoxon signed rank test.
[j]*P* < .01 compared with baseline.

groups, the pain scores decreased significantly during the first 24 weeks but remained relatively unchanged thereafter. Dienogest lacked any therapeutic effects on pain symptoms in 2 patients.

Effects of DNG on the Size of Endometriomas and CA-125

A total of 105 endometriomas of 88 patients were analyzed (Table 3). The mean size of recurrent endometriomas was 3.77 (1.59) cm in diameter and decreased significantly after DNG treatment (*P for trend* < .001). The endometrioma size constantly decreased until 72 weeks. After 72 weeks, the endometrioma size increased slightly, but this was not statistically significant. To investigate the effect of DNG according to the baseline size of the endometrioma, we compared groups with a baseline endometrioma size < 4 cm and ≥ 4 cm (data not shown). Large endometriomas(≥ 4 cm) tended to show better response to DNG, but the difference was not statistically significant ($P = .0685$). The CA-125 also decreased significantly from baseline after taking DNG for 12 months and lasted until 18 months (Figure 1).

Amenorrhea and the Lack of Drug Efficacy

The rate of amenorrhea steadily increased as the duration of medication was prolonged: 25.62% (31/121), 28.05% (23/82), 56.0% (28/50), and 77.27% (17/22) at 24, 48, 72, and 96 weeks, respectively. For 16 (13.22%) patients, DNG lacked any therapeutic effect; the size of the endometrioma increased ($n = 9$), the pain symptoms were aggravated despite a decrease in endometrioma size ($n = 3$), or new endometriomas developed in those who had symptom-only recurrence at baseline (n = 4). The median duration of DNG administration

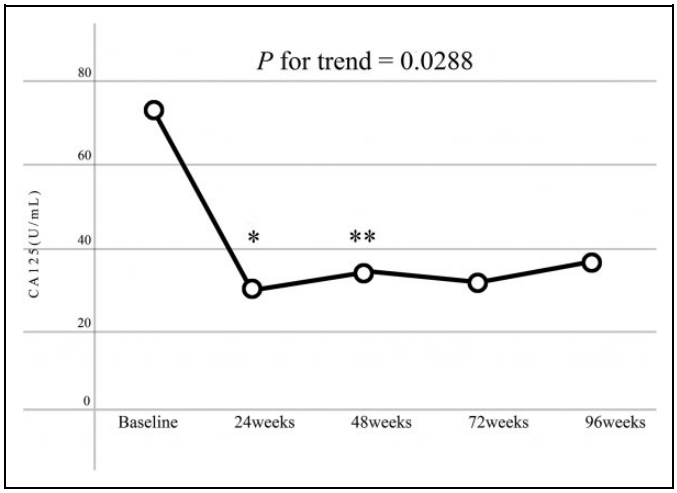

Figure 1. Effect of dienogest on cancer antigen-125. * $P < .01$ compared with baseline ** $P < .05$ compared with baseline. CA-125 indicates cancer antigen-125.

Table 4. Adverse Events of Dienogest During Follow-Up Period.

Adverse Events	Occurrence Rate, %
Irregular bleeding pattern[a]	28.8 (n = 36)
Weight gain	4.1 (n = 5)
Acne	2.5 (n = 3)
Headache	1.7 (n = 2)
Hot flush	1.7 (n = 2)
Mood change	1.7 (n = 2)
Breast discomfort	0.8 (n = 1)

[a] Bleeding events that deviated from the original pattern in patients with a regular menstrual pattern: prolonged menstruation, intermenstrual vaginal bleeding, oligomenorrhea, and so on.

for those who did not benefit from DNG was 48 weeks (range, 24-104 weeks).

Adverse Events of DNG

Overall, 51 (42.15%) patients reported adverse events. Irregular bleeding pattern was the most common side effect during the whole period. (29.75%, 36/121; Table 4). The rate of irregular bleeding patterns was 29.75% (36/121), 19.51% (16/82), 12.0% (6/50), and 9.10% (2/22) at 24, 28, 72, and 96 weeks, respectively. Other adverse events reported by patients are shown in Table 4. Adverse events were mild to moderate, and only 6 (4.96%, 6/121) patients discontinued DNG because of side effects. After discontinuation of DNG, side effects were resolved without need for additional intervention.

Discussion

In this study, DNG was found to be effective in improving pain-related symptoms of recurrent endometriosis and reducing the size of recurrent endometriomas as well as serum CA-125 levels. The results of the present study indicate DNG reduce pain-related symptoms effectively also in patients with recurrent endometriosis. Overall, the pain scores decreased significantly from 6 months after taking the medication, and this effect persisted even after 48 weeks. The efficacy of DNG in terms of pain-related symptoms was also assessed according to the form of recurrence: a symptom-only recurrence group versus a recurrent endometrioma group. We postulated that patients with diffuse invisible peritoneal involvement may experience a different degree of pain relief from the use of DNG compared to patients with recurrent endometriomas. In this study, only pain scores up to 48 weeks after initiation of DNG were included because of the small number of participants. One reason for the low number of participants is that many patients developed amenorrhea, especially after 48 weeks of taking DNG. Patients with amenorrhea often did not respond appropriately when asked about the degree of dysmenorrhea or pain-related symptoms.

Dienogest also reduced the size of recurrent endometriomas effectively. In fact, many large endometriomas showed good response to DNG in this study. These findings are quite consistent with the recent Japanese study showing that DNG treatment led to a significant reduction in the size of the chocolate cyst.[26] The largest endometrioma in this study had a maximum diameter of 10 cm. After 96 weeks of DNG administration, it was decreased to diameter of 4.1 cm. The mechanism of action how DNG led to a significant reduction in the endometriotic cyst is not clear. According to a recent cell culture study, in vitro DNG treatment suppressed extracellular signal regulated kinase 1/2 pathways, inhibited mammalian target of rapamycin, induced autophagy, and promoted the apoptosis of endometriotic cells.[28] Another study has also shown that DNG could improve the responsiveness to progestin treatment in endometriotic tissue by increasing the progesterone receptor isoform B/A ratio.[29]

However, for 16 (13.22%) patients, DNG at a dose of 2 mg daily had no obvious treatment effect, which seems to be higher than the rate reported in the previous studies: Only 1 (0.3%) case lacking efficacy of DNG was reported in pooled analysis including 4 phase II and phase III trials performed in Europe that investigated 514 women with confirmed endometriosis.[10,13,16,30,31] Direct comparison with previous studies is difficult because participants of previous studies are composed of patients with the first surgical diagnosis as well as recurrent disease, while this study targeted only recurrent endometriosis. In addition, the primary outcome of other studies was improvement in pain-related symptoms, whereas the change in size of recurrent endometriomas was also one of the primary efficacy variables, suggesting that lack of the efficacy of DNG was defined differently from previous studies.

Even if the differences are taken into account, there is an absolute gap in the rate of lacking efficacy between the present study and previous studies. Based on results of this study, it can be speculated carefully that the rate of resistance to DNG might be higher in recurrent endometriosis. Expression

of progesterone receptor is known to be extremely low in endometriotic tissues, which results in progesterone resistance.[32,33] For this reason, progestins were thought to reduce pain by suppressing or attenuating ovulation in patients with endometriosis. However, DNG has been reported to directly reduce endometriotic lesion through inducing hypoestrogenic, hypergestagenic local endocrine environment.[15,34] Nevertheless, considering DNG is also a kind of progestin, there may be participants who do not exhibit tissue-direct effects by DNG, and the prevalence of DNG resistance may be higher in recurrent disease. It is very difficult to differentiate the recurrent endometriosis into either of a newly developed lesion or a regrown lesion from remnant disease. Considering that the average interval between the previous surgery and DNG treatment in patients with recurrent endometriosis was 53.9 months, it can be presumed that there would have been epigenetic changes over time in the endometriotic lesion.

It is also noteworthy that DNG treatment caused a significant decrease in serum CA-125 levels in this study. CA-125 has high specificity but low sensitivity which is the disadvantage as a biomarker for the diagnosis of endometriosis.[35] However, since all patients included in this study has a history of histologically diagnosed endometriosis, increase in serum CA-125 concentration is more likely to be the result of endometriosis. Moreover, recent meta-analysis found that the serum CA-125 level was associated with endometriosis in Caucasian, Asian, and overall populations, and with both early and advanced stage disease.[36] Considering this study was aimed at Korean women with various stages of recurrent endometriosis, CA-125 has value as an indicator of DNG treatment in this study.

The mechanism of CA-125 elevation in endometriosis is not known exactly; however, a few studies suggested elevation in serum CA-125 level correlates well with the extent and severity of endometriosis.[37-40] Moreover, results of one study postulated that alteration of endothelial permeability induced by inflammatory reactions of endometriosis allows CA-125 to reach the circulation,[41] implying that CA-125 reflects the bioactivity of endometriosis. In another in vitro study, CA-125 from human peritoneal fluid was shown to enhance the invasiveness of a benign endometriotic cell line, [42]raising the possibility that CA-125 itself plays a role in disease activity of endometriosis. Either way, the decrease in serum CA-125 level following DNG treatment in this study may be due to effect of DNG on the unknown endometriosis-related activity.

The proportion of patients who experienced amenorrhea at 24 weeks follow-up in this study was lower than with the previous study in European population (25.62% vs 38.9%).[13] However, the proportion of those with amenorrhea was increased as the duration of medication was prolonged, and the rate of amenorrhea was 77.27% at 96 weeks follow-up. Compared to the recent Korean data on long-term DNG treatment, this rate seems to be lower than in those treated with DNG immediately after first surgery (78.3%).[43] Despite no data, it might be also due to progesterone resistance in those with recurrent endometriosis, which might cause higher failure rate in treatment as well as higher rate of uterine bleeding. The other adverse events observed in this study also differed from those reported in previous studies. Pooled data from European trials revealed that headache was the most common adverse event (9.0%), followed by breast discomfort (5.4%).[10] In contrast, in the present study, only 2 (1.7%) women complained of headache and only 1 (0.8%) experienced breast discomfort. Instead, weight gain (4.1%) was a relatively common side effect.

Since the present study was based on retrospective medical record review, it has several limitations. The duration and choice of medication used immediately after primary surgery was heterogeneous, and the diagnosis of recurrence was solely based on pain-related symptoms and ultrasonography findings instead of laparoscopy with histologic confirmation. In addition, although the incidence of amenorrhea after DNG treatment was high in the participants, CA-125 was measured without considering the menstrual cycle.

However, to the best of our knowledge, this is the first study that evaluated the therapeutic effect of DNG on recurrent endometriosis as a primary end point. The sample size of this study was relatively large compared to the previous other studies, and the mean follow-up was over 12 months. To overcome the shortcoming that resulted from a lot of missing values, linear mixed-effects models were chosen for analyses, which is powerful in handling missing values, especially in the context of longitudinal designs.[44] In conclusion, the present retrospective study has shown that DNG is effective in reducing the size of endometriomas, and the serum CA-125 levels along with symptomatic relief and tolerable safety profiles in women with recurrent endometriosis. Further prospective studies are necessary to confirm the findings of the present study.

Authors' Note

This article was written on the basis of the results of an advisory board meeting by Bayer HealthCare.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Bulun SE. Endometriosis. *N Engl J Med*. 2009;360(3):268-279.
2. Candiani GB, Fedele L, Vercellini P, Bianchi S, Di Nola G. Repetitive conservative surgery for recurrence of endometriosis. *Obstet Gynecol*. 1991;77(3):421-424.
3. Sutton CJ, Pooley AS, Ewen SP, Haines P. Follow-up report on a randomized controlled trial of laser laparoscopy in the treatment of pelvic pain associated with minimal to moderate endometriosis. *Fertil Steril*. 1997;68(6):1070-1074.

4. Shakiba K, Bena JF, McGill KM, Minger J, Falcone T. Surgical treatment of endometriosis: a 7-year follow-up on the requirement for further surgery. *Obstet Gynecol*. 2008;111(6):1285-1292.
5. Muzii L, Achilli C, Lecce F, et al. Second surgery for recurrent endometriomas is more harmful to healthy ovarian tissue and ovarian reserve than first surgery. *Fertil Steril*. 2015;103(3): 738-743.
6. Ferrero S, Scala C, Racca A, et al. Second surgery for recurrent unilateral endometriomas and impact on ovarian reserve: a case-control study. *Fertil Steril*. 2015;103(5):1236-1243.
7. Casper RF. Progestin-only pills may be a better first-line treatment for endometriosis than combined estrogen-progestin contraceptive pills. *Fertil Steril*. 2017;107(3):533-536.
8. Vercellini P, Eskenazi B, Consonni D, et al. Oral contraceptives and risk of endometriosis: a systematic review and meta-analysis. *Hum Reprod Update*. 2011;17(2):159-170.
9. Berlanda N, Somigliana E, Vigano P, Vercellini P. Safety of medical treatments for endometriosis. *Expert Opin Drug Saf*. 2016;15(1):21-30.
10. Strowitzki T, Faustmann T, Gerlinger C, Schumacher U, Ahlers C, Seitz C. Safety and tolerability of dienogest in endometriosis: pooled analysis from the European clinical study program. *Int J Womens Health*. 2015;7:393.
11. Harada T, Taniguchi F. Dienogest: a new therapeutic agent for the treatment of endometriosis. *Womens Health (Lond)*. 2010;6(1): 27-35.
12. Ota Y, Andou M, Yanai S, et al. Long-term administration of dienogest reduces recurrence after excision of endometrioma. *J Endometr Pelvic Pain Disord*. 2015;7(2):63-67.
13. Strowitzki T, Marr J, Gerlinger C, Faustmann T, Seitz C. Dienogest is as effective as leuprolide acetate in treating the painful symptoms of endometriosis: a 24-week, randomized, multicentre, open-label trial. *Hum Reprod*. 2010;25(3):633-641.
14. Oettel M, Breitbarth H, Elger W, et al. The pharmacological profile of dienogest. *Eur J Contracept Reprod Health Care*. 1999;4(suppl 1):2-13.
15. Sasagawa S, Shimizu Y, Kami H, et al. Dienogest is a selective progesterone receptor agonist in transactivation analysis with potent oral endometrial activity due to its efficient pharmacokinetic profile. *Steroids*. 2008;73(2):222-231.
16. Strowitzki T, Faustmann T, Gerlinger C, Seitz C. Dienogest in the treatment of endometriosis-associated pelvic pain: a 12-week, randomized, double-blind, placebo-controlled study. *Eur J Obstet Gynecol Reprod Biol*. 2010;151(2):193-198.
17. Guo SW. Epigenetics of endometriosis. *Mol Hum Reprod*. 2009; 15(10):587-607.
18. Lee DY, Bae DS, Yoon BK, Choi D. Post-operative cyclic oral contraceptive use after gonadotrophin-releasing hormone agonist treatment effectively prevents endometrioma recurrence. *Hum Reprod*. 2010;25(12):3050-3054.
19. Seracchioli R, Mabrouk M, Frasca C, et al. Long-term cyclic and continuous oral contraceptive therapy and endometrioma recurrence: a randomized controlled trial. *Fertil Steril*. 2010;93(1):52-56.
20. Jensen MP, McFarland CA. Increasing the reliability and validity of pain intensity measurement in chronic pain patients. *Pain*. 1993;55(2):195-203.
21. DeLoach L, Higgins M, Caplan A, Stiff J. The visual analog scale in the immediate postoperative period. *Anesth Analg*. 1998;86(1): 102-106.
22. Exacoustos C, Zupi E, Carusotti C, et al. Staging of pelvic endometriosis: role of sonographic appearance in determining extension of disease and modulating surgical approach. *J Am Assoc Gynecol Laparosc*. 2003;10(3):378-382.
23. Van Holsbeke C, Van Calster B, Guerriero S, et al. Endometriomas: their ultrasound characteristics. *Ultrasound Obstet Gynecol*. 2010;35(6):730-740.
24. Mais V, Guerriero S, Ajossa S, Angiolucci M, Paoletti AM, Melis GB. The efficiency of transvaginal ultrasonography in the diagnosis of endometrioma. *Fertil Steril*. 1993;60(5):776-780.
25. Kurjak A, Kupesic S. Scoring system for prediction of ovarian endometriosis based on transvaginal color and pulsed Doppler sonography. *Fertil Steril*. 1994;62(1):81-88.
26. Sugimoto K, Nagata C, Hayashi H, Yanagida S, Okamoto A. Use of dienogest over 53 weeks for the treatment of endometriosis. *J Obstet Gynaecol Res*. 2015;41(12):1921-1926.
27. Canis M, Donnez J, Guzick D, et al. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. *Fertil Steril*. 1997;67(5):817-821.
28. Choi J, Jo M, Lee E, Lee DY, Choi D. Dienogest enhances autophagy induction in endometriotic cells by impairing activation of AKT, ERK1/2, and mTOR. *Fertil Steril*. 2015;104(3):655-664.e651.
29. Hayashi A, Tanabe A, Kawabe S, et al. Dienogest increases the progesterone receptor isoform B/A ratio in patients with ovarian endometriosis. *J Ovarian Res*. 2012;5(1):31.
30. Kohler G, Faustmann TA, Gerlinger C, Seitz C, Mueck AO. A dose-ranging study to determine the efficacy and safety of 1, 2, and 4 mg of dienogest daily for endometriosis. *Int J Gynaecol Obstet*. 2010;108(1):21-25.
31. Petraglia F, Hornung D, Seitz C, et al. Reduced pelvic pain in women with endometriosis: efficacy of long-term dienogest treatment. *Arch Gynecol Obstet*. 2012;285(1):167-173.
32. Attia GR, Zeitoun K, Edwards D, Johns A, Carr BR, Bulun SE. Progesterone receptor isoform A but not B is expressed in endometriosis. *J Clin Endocrinol Metab*. 2000;85(8):2897-2902.
33. Cheng YH, Imir A, Fenkci V, Yilmaz MB, Bulun SE. Stromal cells of endometriosis fail to produce paracrine factors that induce epithelial 17beta-hydroxysteroid dehydrogenase type 2 gene and its transcriptional regulator Sp1: a mechanism for defective estradiol metabolism. *Am J Obstet Gynecol*. 2007;196(4):391. e391-397; discussion 391.e397-398.
34. Klipping C, Duijkers I, Remmers A, et al. Ovulation-inhibiting effects of dienogest in a randomized, dose-controlled pharmacodynamic trial of healthy women. *J Clin Pharmacol*. 2012;52(11): 1704-1713.
35. Wild RA, Hirisave V, Bianco A, Podczaski ES, Demers LM. Endometrial antibodies versus CA-125 for the detection of endometriosis. *Fertil Steril*. 1991;55(1):90-94.
36. Shen A, Xu S, Ma Y, et al. Diagnostic value of serum CA125, CA19-9 and CA15-3 in endometriosis: a meta-analysis. *J Int Med Res*. 2015;43(5):599-609.
37. Barbieri RL, Niloff JM, Bast RC Jr, Scaetzl E, Kistner RW, Knapp RC. Elevated serum concentrations of CA-125 in

patients with advanced endometriosis. *Fertil Steril*. 1986; 45(5):630-634.
38. Matalliotakis IM, Goumenou AG, Mulayim N, Karkavitsas N, Koumantakis EE. High concentrations of the CA-125, CA 19-9 and CA 15-3 in the peritoneal fluid between patients with and without endometriosis. *Arch Gynecol Obstet*. 2005;271(1):40-45.
39. O'Shaughnessy A, Check JH, Nowroozi K, Lurie D. CA 125 levels measured in different phases of the menstrual cycle in screening for endometriosis. *Obstet Gynecol*. 1993;81(1):99-103.
40. Mol BW, Bayram N, Lijmer JG, et al. The performance of CA-125 measurement in the detection of endometriosis: a meta-analysis. *Fertil Steril*. 1998;70(6):1101-1108.
41. Seeber B, Sammel MD, Fan X, et al. Panel of markers can accurately predict endometriosis in a subset of patients. *Fertil Steril*. 2008;89(5):1073-1081.
42. Gaetje R, Winnekendonk DW, Scharl A, Kaufmann M. Ovarian cancer antigen CA 125 enhances the invasiveness of the endometriotic cell line EEC 145. *J Soc Gynecol Investig*. 1999;6(5): 278-281.
43. Lee SR, Yi KW, Song JY, et al. Efficacy and safety of long-term use of dienogest in women with ovarian endometrioma. *Reprod Sci*. 2018;25(3):341-346. doi:10.1177/1933719117725820.
44. McLean RA, Sanders WL, Stroup WW. A unified approach to mixed linear models. *Am Stat*. 1991;45(1):54-64.