

Research Article

Is Long-Term Dienogest Treatment Tolerable in Korea?

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Introduction

Endometriosis is defined as the presence of endometrial glands and stroma outside the uterine cavity. The prevalence rate of endometriosis is approximately 5-10% of all women of reproductive age, it reduces the patient's quality of life through the occurrence of pain, including dysmenorrhea, dyspareunia, and lower back pain [1-3].

It is known that the primary treatment of endometriosis is surgery. The European Society of Human Reproduction and Embryology (ESHRE) guidelines state that surgical treatment is warranted for an ovarian endometrioma of larger than 3 cm, and that laparoscopic stripping of the cyst wall is considered the gold standard for treatment [4]. Because the surgical excision of lesions has shown to improve the level of pain and enhance fertility, ovarian cystectomy is preferable to oophorectomy, and most women who undergo endometriosis are of childbearing age. However, a pooled analysis of 23 studies estimated the recurrence rates as 40% to 50% 5 years after the primary surgery [5].

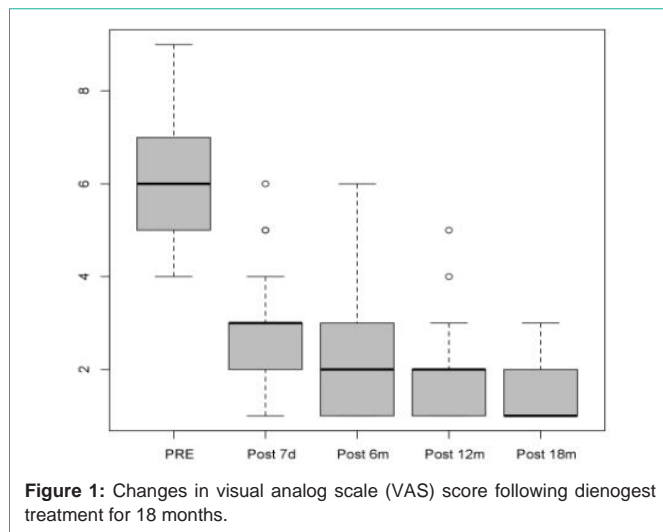
Medical treatment for the relief of symptoms and the prevention of recurrence after surgery include Gonadotropin-Releasing Hormone (GnRH) analogs, progestin, danazol, and estrogen/progestin combinations. However, these treatments have adverse

effects including impaired hepatic function associated with danazol, as well as a decrease in bone mineral density, which may be caused by GnRH analogs. Thus, their long-term use is limited [6,7].

Dienogest (Visanne, Bayer HealthCare, Berlin, Germany) is a selective progestin that has been approved for treating endometriosis at a low oral dose of 2 mg/day. Dienogest has many beneficial pharmacological uses, such as a potential progestogenic effect, moderate suppression of estrogen, and low concern for increased androgen and corticoid levels. Progestogenic effects lead to an effective reduction in endometrial lesions, and no significant androgenic, mineralocorticoid, or glucocorticoid activity. Dienogest has been developed to reduce side effects, such as a decreasing estradiol (E2) concentration, along with an elongation of the tolerable dose period [8-10].

Recent studies have reported that repeated surgeries for recurrent endometriomas mark a decrease in ovarian reserve and the success rate of in vitro fertilization [11,12].

Dienogest is able to prevent the recurrence of endometriosis after surgery for more than 15 months. However, most of the clinical data reflect follow-up durations of up to 6 months, and few data have been published beyond 12 months. To determine the tolerability of long-term treatment using dienogest, we evaluated patients who had



undergone ovarian cystectomy for endometriosis.

Methods

Data were collected retrospectively from a chart review of 150 patients treated with 2 mg of dienogest over an 18-month period after a conservative surgery at Yangsan Hospital of Pusan National University. The subjects included 150 patients, 103 of whom had undergone laparoscopic unilateral cystectomy, 35 had undergone a laparoscopic bilateral cystectomy, and 12 had undergone a laparoscopic unilateral adnexectomy. Oral administration of dienogest was initiated on day 3 of the first menstruation following surgery. The primary modality of the diagnosis was through imaging (magnetic resonance or transvaginal ultrasonography). The Institutional Review Board of Pusan National University's Yangsan Hospital approved this study, although written informed consent was not obtained because the present study was based only on a retrospective review of medical records. Transvaginal ultrasonography was used to measure the largest diameter of an endometriotic cyst. These measurements were repeated every 6 months after surgery. The serum cancer antigen 125 (CA125), cancer antigen 19-9 (CA19-9), and estradiol (E2) and Anti-Mullerian Hormone (AMH) concentrations were determined at baseline before treatment, and were repeatedly measured every 6 months to assist in assessing the clinical states of the patients.

The adverse event profile and patient satisfaction regarding dienogest treatment was determined through a questionnaire. Menstrual pain was determined before surgery, after surgery, before dienogest treatment, and after dienogest treatment. The severity of pain was measured on a 10-point visual analog scale (VAS; 0 mm, absence of pain; 100 mm, unbearable pain) during the outpatient visits.

Transvaginal ultrasonography was conducted on the patients every 6 months to assess the presence of endometrioma. Recurrent endometriosis was diagnosed when a round mass was identified with a thick wall, having a diameter of 2 cm or more, regular margins, and a homogenous low echogenic fluid content with scattered internal echoes. The patients were also evaluated according to the r-ASRM stage classification.

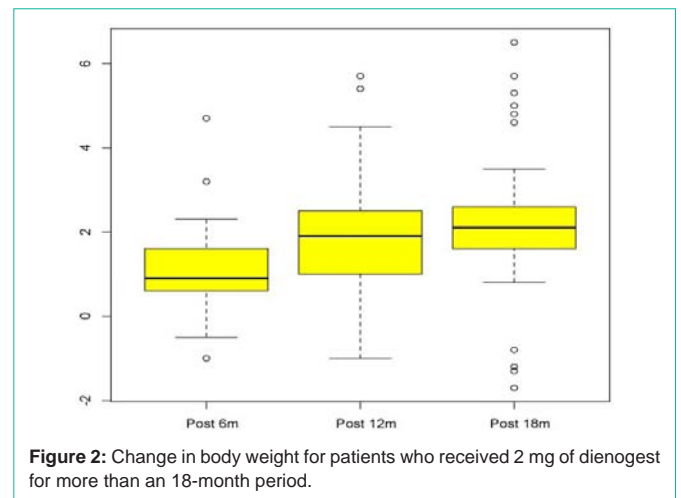


Table 1: Clinical characteristics.

Characteristics	Patients (n = 150)
Age (yr)	39.4 ± 8.1
Body mass index (kg/m ²)	19.8 ± 2.5
Previous pregnancy	68 (45)
Previous surgery for endometriosis	12 (8)
r-ASRM stage of endometriosis	
Stage I-II	39 (26)
Stage III-IV	111 (74)
Type of endometriosis	
Deep infiltrating	11 (7.3)
Unilateral	115 (76.7)
Bilateral	35 (23.3)
Presence of Other diseases	
Leiomyoma	56 (37.3)
Adenomyosis	28 (18.7)
Ovarian cyst	19 (12.7)
Paratubal cyst	11 (7.3)

Values are presented as mean ± standard deviation or number (%).

Adverse events were defined as any unfavorable or unintended signs or symptoms occurring with the use of dienogest. Serious adverse events were defined and documented according to the international standards.

Body weight was measured (at minimum) during the initial visit, and then repeatedly measured every 6 months. Weight gain was defined as an increase of over 1 kg.

The patients were instructed to record bleeding events daily on a diary card to provide information on the mean number of days, number of episodes, and duration of episodes of bleeding. Uterine bleeding was defined as bleeding for more than 10 days.

Continuous variables were analyzed using a paired t-test or Student's t-test. A Wilcoxon signed rank test was used to compare the continuous variables if the data were not normally distributed. Categorical variables were presented as percentages and compared

Table 2: Laboratory parameters in 2 mg dienogest administered group: categorized based on treatment period.

Blood test	Pre-treatment	Post-treatment			P-value
		6 months	12 months	18 months	
CA125 (U/mL)	90.65±18.99	32.7±12.42	27.3±15.42	18.7±13.52	0.042
CA19-9 (U/mL)	63.20±16.64	28.7±17.32	21.3±9.26	18.6±11.29	0.025
E2 (pmol/L)	231.82±98.13	89.83±28.17	56.82±30.81	27.56±53.29	0.019

Value are presented as mean ± SE.

CA125, cancer antigen 125; CA19-9, cancer antigen 19-9; E2, estradiol.

using a chi-square test. All statistical analyses were conducted using SPSS ver. 21.0 (IBM Co., Armonk, NY, USA), and p-values <0.05 were considered to indicate a statistical significance.

Results

Demographic characteristics of the participants who received 2 mg of dienogest are shown in Table 1. The average age of the patients was 39.4±8.1 years (range of 18-47 years in age), and the median duration of dienogest administration was 24 months (range of 18–60 months). All patients were diagnosed with endometriosis through a laparoscopy. A total of 111 patients (74%) were classified with stage III (moderate) or higher endometriosis, and 39 (26%) with stage I-II. However, the pain and staging were not correlated. The most common type of endometriosis was unilateral endometrioma (76.7%), followed by bilateral endometrioma (23.3%).

Serum cancer antigen 125 (CA 125), cancer antigen 19-9 (CA 19-9), and estradiol (E2) were determined at baseline prior to treatment, and were repeatedly measured every 6 months to assist in assessing the clinical state (Table 2). The mean serum cancer antigen CA 125, CA 19-9, and E2 levels before surgery were measured as 90.65±18.99 U/mL, 63.20±16.64 U/mL, and 231.82±98.13 pmol/L, respectively. During treatment of dienogest, the CA 125, CA 19-9, and E2 levels gradually decreased to 18.7±13.52 U/mL, 18.6±11.29 U/mL, and 27.56±53.29 pmol/L after 18 months.

The effects of dienogest on endometriosis-associated pain were determined by measuring pain-using VAS before surgery, after surgery, and after the dienogest treatment. The pain was significantly reduced after 18 months of medication as compared to pre-treatment (40.8±28.6 mm versus 7.3±14.6 mm, p<0.01) (Figure 1). Eleven patients showed no changes in their VAS scores after dienogest treatment during the 18-month period, whereas 139 patients showed decreased VAS scores. We observed that 92.7% of the patients demonstrated an improvement in terms of pain after surgery and long-term dienogest administration.

Because the goal of the study was to determine the effects of dienogest treatment for an 18-month period or longer, we analyzed the adverse events 18 months after dienogest administration. The most common adverse drug reaction was weight gain (24.0%), followed by headaches (6.0%), breast discomfort (5.3%), depression (2.0%), acne (1.3%), nausea (5.3%), and abdominal pain (3.3%) (Table 3). All adverse events except weight gain were generally mild to moderate, and only two women (1.3%) reported bleeding events as the primary reason for their discontinuation. However, the rate of discontinuation of treatment from weight gain was very high. The mean value of weight change during dienogest treatment was 2.8 kg, but 36 patients showed weight gain of over 4 kg during the 18-month period. Among

Table 3: Adverse drug reactions for patients who received 2 mg of dienogest for more than an 18-month period.

Adverse drug reactions	No (%) patients (n = 150)
Headache	9 (6.0%)
Breast discomfort	8 (5.3%)
Depressed mood	3 (2.0%)
Acne	2 (1.3%)
Nausea	8 (5.3%)
Weight gain	36 (24.0%)
Abdominal pain	5 (3.3%)

Note: Mean treatment duration: 21 months. Values are presented as number (%) of patients.

the 36 patients, 12 women (8%) discontinued dienogest treatment on their own despite its effectiveness and an adequate explanation. A body weight analysis includes patients who provided both the baseline and highest end of the treatment data (Figure 2).

Discussion

Because of an increased post-operative recurrence rate of endometrium and its related complications, secondary prevention is necessary to enhance the quality of life and fertility of those suffering from chronic endometriosis [13-16]. In the current retrospective analysis, we analyzed the efficacy and safety of long-term oral dienogest therapy for 150 patients under treatment in a single institution. In addition, we found the following effects of dienogest after 18 months or more of use.

Our study showed that, in patients who had taken dienogest treatment for at least 18 months after laparoscopic endometriosis surgery, the pain was decreased compared to the preoperative status, and the pain was relieved gradually with the use of dienogest. Our data indicate that dienogest was helpful in relieving endometriosis-associated pain based on a VAS. Laboratory findings also suggested noticeable therapeutic effects. CA125 and CA19-9 were slightly decreased after surgery, and gradually decreased with dienogest treatment during 6 months of interval follow-ups. Elevated serum CA 125 and CA 19-9 concentrations were significantly associated with endometriosis, and CA 19-9 is increased further in the more advanced stages of disease. The decrease in CA125 and CA19-9 suggest that dienogest treatment is effective in preventing the recurrence of endometriosis. Though the mechanism is not evident, dienogest treatment is suggested to inhibit extracellular signal-regulated kinase pathways, suppress the mammalian target of rapamycin, induce autophagy, and accelerate the apoptosis of endometriotic cells [17]. It is also possible that dienogest creates a high progesterone receptor ratio, and therefore enhances the responsiveness to progestin

treatment in endometriotic tissue [18].

The adverse effects were mild to moderate in intensity, and were associated with low discontinuation rates. The most common adverse effects were atypical genital bleeding. It is known that the cause of atypical genital bleeding was a breakthrough of pseudodecidualized endometrium [19]. The initial increase in bleeding with dienogest treatment was followed by a progressive reduction during the continued treatment, accompanied by an increase in the amenorrhea rate. These observations suggest that the amount of atypical genital bleeding may depend on the space of the endometrium or the volume of the pseudodecidual. Thus, we can conclude that the patients in the dienogest treatment group showed irregular bleeding, but they all experienced only mild symptoms and none developed anemia. Furthermore, atypical genital bleeding rarely resulted in a discontinuation of treatment. In our cases, only two patients stopped treatment. In addition, headaches (6.0%), breast discomfort (8.7%), depression (2.0%), acne (4.7%), nausea (5.3%), weight gain (12.0%), and abdominal pain (3.3%) were also noted, but the symptoms were negligible. Weight gain turned out to be a common adverse effect of progestins [20-23]. The mean value of the weight change during dienogest treatment was 2.8 kg, but 36 of the patients showed a weight gain of over 4 kg during the 18-month period. Among the 36 patients, 12 women discontinued Progestin treatment despite the advantages of the treatment being mentioned again. Concern regarding weight gain in Korean women seems particularly high.

In other studies, the recurrence rate of ovarian endometriotic cysts was reported to be 25% for patients who underwent an operation within a 24-month period. The rate increases to 40–50% after 36 months post-operation [24]. Patients who received GnRHa as a post-operative treatment showed a 5.3% recurrence within 24 months [25]. In contrast, others have reported that GnRHa has no effect on the recurrence rate [26,27]. In contrast, a previous study with a smaller pool reported the effectiveness of administering 2 mg of dienogest for a 13-month period after an operation, suggesting its potential effectiveness as a treatment for endometriosis [28,29]. In our study, the recurrence rate after dienogest therapy was merely 4.5%. Among the group studied, 89.7% of the patients who were given dienogest continuously for 18.0±7.1 months described no complaints of any intolerable side effects, whereas 10.3% patients stopped at 2.4±1.0 months. The cause of discontinuation was weight gain for all cases, and other adverse effects were moderate.

The serum E2 levels decreased steadily until reaching lower than 60 pg/ml at 18 months. However, the E2 range was relatively broad, and reached approximately 280 pg/ml in certain cases. These elevated E2 levels were regarded as a result of follicle growth without ovulation under dienogest treatment. In this regard, dienogest appears to be a good candidate for the long-term treatment of endometriosis because it does not reduce the serum estradiol to the postmenopausal level, as does GnRH agonist. Long-term use of dienogest could be beneficial for patients who want to preserve their fertility. Dienogest prohibits an exacerbation of endometriosis, and may preserve the ovarian function. Therefore, dienogest can be considered effective for not only short-term but also long-term treatment in patients suffering from infertility. In accordance with our findings, the guidelines from the World Endometriosis Society recommends dienogest as an empirical treatment option for patients without a laparoscopic diagnosis, and as

a suitable post-endometriosis surgery treatment [4].

Owing to its retrospective nature, the present study has several limitations. A large amount of data on certain important clinical outcomes in a few of the patients was missing. Because the data were solely based on a review of medical records written by clinicians, it was possible that the adverse events, such as uterine bleeding, could have been underestimated. In spite of these limitations, the present study shows that dienogest administration over an 18-month period is highly effective in preventing the recurrence of endometriosis after surgery, weakening endometriosis-associated pain, and reducing the size of recurrent endometriomas. Further prospective studies will be needed to evaluate the effects of long-term dienogest medication on the bone quality, the future risk of osteoporosis, and the ultimate reproductive outcomes in women with endometriosis.

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