

Observational Study for Adverse Effects and Discontinuation with Long-Term Post-Operative Hormonal Treatment for Endometriosis in Real-World Practice

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Objectives: To evaluate the side effects and causes of discontinuation of either combined oral contraceptives or dienogest (DNG) used to prevent recurrence in patients with surgically confirmed endometriosis.

Methods: We retrospectively analyzed the medical records of 213 women with endometriosis who had been treated with combined oral contraceptives (ethinyl estradiol 0.02 mg/drospirenone 3 mg [EE/DRSP]) or DNG 2 mg for 12 months or more. The side effects reported by the patients, laboratory parameters, causes of discontinuation of medication, and recurrence rates were evaluated one, two, three, four, and five years after starting medication (Y1, Y2, Y3, Y4, and Y5).

Results: EE/DRSP were administered to 59 patients, while DNG was administered to 154 patients. The mean durations of postoperative use of EE/DRSP and DNG were 44.5 ± 22.6 months and 23.6 ± 13.5 months, respectively. The prevalence of side effects was 27.1%, 19.0%, 10.0%, 10.5%, and 7.4% in the EE/DRSP group and 29.2%, 15.7%, 14.0%, 23.1%, and 0.0% in the DNG group at Y1, Y2, Y3, Y4, and Y5, respectively. The discontinuation rates were 1.7%, 1.7%, 4.0%, 0.0%, and 7.4% at Y1, Y2, Y3, Y4, and Y5, respectively, in the EE/DRSP group and 10.4%, 3.3%, 4.0%, 3.8%, and 0.0% at the same times in the DNG group. The recurrence rates were less than 4% in both the groups.

Conclusions: The side effects of commonly prescribed postoperative hormone treatments were relatively mild, and the occurrence of side effects decreased with continuous administration. Further, the long-term use of postoperative hormone treatments is likely to prevent recurrence of endometriosis after surgery.

Key Words: Adverse effects, Dienogest, Endometriosis, Oral contraceptives, Recurrences

Endometriosis is a chronic, inflammatory, estrogen-dependent disease characterized by the abnormal proliferation of endometrial tissue outside the uterine cavity.¹ Surgery and the subsequent histological confirmation of endometrial glands and/or stromal lesions are still considered the gold standard for the diagnosis

of endometriosis.² Thus, the goal of indicated surgery is the histological verification of endometriosis and resection of all visible endometriotic lesions. However, despite the meticulous surgical intervention, the recurrence rate of endometriosis has been estimated as 21.5% at two years and between 40% and 50%

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at five years after the initial surgery.^{3,4} Therefore, effective and long-standing prevention of recurrence is fundamental to the achievement of therapeutic success.^{3,4}

Various medical treatments in postoperative settings have been studied, including the administration of combined oral contraceptives (COCs), gonadotropin-releasing hormone agonist (GnRHa), danazol, and progestins and levonorgestrel intrauterine system placement.⁵ In most cases, the adverse effects (AEs) of these medications limit their long-term application for the recommended durations.^{6,7} The recently introduced synthetic progestin dienogest (DNG) is known to have good tolerability and effective along with a lower adverse effect profile than GnRHa, although it is associated with some bleeding problems.⁸⁻¹¹ Further, COCs are proven, effective, and safe drugs for use in long-term endometriosis treatment.¹²⁻¹⁵

For the successful extended use of hormonal treatment, guidance and management regarding AEs are crucial. However, most of the clinical data on AEs only cover a medication duration within one year of initiation, and clear details of the long-term follow-up data beyond a year are lacking.

Therefore, we aimed to analyze the occurrence rates of AEs and causes of discontinuation of medication in women who had been treated with either COCs or DNG postoperatively for at least one year and up to five years.

MATERIALS AND METHODS

Patients

The clinical data of 213 women with pathologically confirmed endometriosis were analyzed retrospectively. After the initial surgery, all the patients had been treated with either COCs (EE 0.02 mg/DRSP 3 mg) or DNG 2 mg daily for 12 months or more from May 2013 to July 2020 at the Pusan National University Hospital, Busan, Republic of Korea.

Clinical follow up and medical record review

Baseline characteristics of the patients, such as age, body mass index, parity, duration of postoperative medical therapy, and initial type and stage of endometriosis were analyzed. After the surgery, scheduled assessments were performed at intervals of every 3-6 months including ultrasound evaluation and history taking of AE profiles. Recurrence was defined as newly developed endometrioma observed through transvaginal or transrectal ultrasound imaging. AEs and the reasons for discontinuation were investigated one, two, three, four, and five years after starting medication (Y1, Y2, Y3, Y4, and Y5) by directly interviewing the clinicians.

Statistical analysis

Continuous variables were compared using the paired t-test or the Student's t-test if the data were normally distributed. The Wilcoxon signed rank test or the Mann-Whitney U test was used to compare continuous variables if the data were not normally distributed. Categorical variables were compared using the chi-square test. All statistical analyses were conducted

using IBM SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, N.Y., USA), and $P < 0.05$ indicated statistical significance.

The strengths and weaknesses of each treatment option were explained in detail to each of the participants after which they selected the type of medication. This study was approved by the Institutional Review Board (IRB) of the Pusan National University Hospital (IRB Number 2106-009-103).

RESULTS

Of 213 patients, 59 were treated using COCs (27.6%) and 154 were treated by administering DNG (74.6%). Baseline characteristics of pa-

tients were evaluated (Table 1). The DNG group included a greater number of patients with stage 4 and/or deep infiltrating endometriosis than the COC group. The mean duration for which medication was administered was 44.5 ± 22.6 months in the COC group and 23.6 ± 13.5 months in the DNG group.

The incidence rates of AEs in the DNG group were 29.2%, 15.7%, 14.0%, 19.2%, and 0% at Y1, Y2, Y3, Y4, and Y5, respectively. The most frequent AEs were lower abdominal pain (7.2%, $n = 11/154$) and frequent bleeding (6.5%, $n = 10/154$) after one year of DNG use. Lower abdominal pain decreased after two years; however, frequent bleeding was observed continually up to the fourth year of medication. The patients also gained weight up to the third year, though it

Table 1. Patient characteristics.

	Total (n = 213)	COCs group (n = 59)	DNG group (n = 159)	Pvalue
Age (years)	33.8 ± 8.6	33.5 ± 9.0	34.0 ± 8.5	0.700
BMI (kg/m ²)	21.8 ± 3.7	21.2 ± 2.6	22.1 ± 4.0	0.069
Parity nulliparous	145	41	105	0.628
parous	68	18	49	
Duration of postoperative medication (months)	29.4 ± 19.0	44.5 ± 22.6	23.6 ± 13.5	< 0.000
Stage 2	33	19	14	< 0.000
3	84	24	60	
4	96	16	80	
Types of endometriosis				0.025
Unilateral	136	35	101	
Bilateral	53	17	36	
Peritoneal	21	4	17	
Others	3	3	0	< 0.000
With DIE	22	0	22	

Values, mean \pm SD or number of patients. COCs, combined oral contraceptives; DNG, dienogest; BMI, body mass index; DIE, deep infiltrating endometriosis.

was not reported afterward.

The incidence rates of AEs in the COC group were 27.1%, 20.1%, 10.0%, 10.5% and 7.4% at Y1, Y2, Y3, Y4, and Y5, respectively. The most common AEs after one year of COC use were lower abdominal pain (11.9%, n = 7/59), frequent bleeding (5.1%, n = 3/59), and mood change (5.1%, n = 3/59). Most AEs decreased with time, although frequent lower abdominal pain was reported even after the second year.

Further, each AE and the reason for discontinuation of COCs and DNG were analyzed (Table 2, 3). In the COC group, lower abdominal pain was the most frequently observed AE, while frequent bleeding, weight gain, and lower abdomi-

nal pain were the common AEs among patients in the DNG group. Patients in both the groups exhibited discontinuation rates that were much lower than the AE occurrence rates. The discontinuation rates by AEs were 11.7%, 4.1%, 4.0%, 3.8%, and 0% at Y1, Y2, Y3, Y4, and Y5, respectively in the DNG group, while they were 3.4%, 3.8%, 4.0%, 0%, and 3.7% in the COC group at the same times.

Reasons for patient drop-out per year in the study included follow-up loss, intolerable AEs and immediate plan for pregnancy. In the COC group, the numbers of follow-up-loss patients were 3, 1, 12 and 11 per year. In DNG group, they were 11, 62, 21 and 13 per year.

Table 2. Adverse effects and reason for discontinuation of COCs group for 5 year follow-up periods.

Parameters	At 1 year (n = 59)	At 2 year (n = 53)	At 3 year (n = 50)	At 4 year (n = 38)	At 5 year (n = 27)
Adverse effects occurrence	16	11	5	4	2
Frequent bleeding	3	1	1	1	
Weight gain	2				
Lower abdominal pain	7	6	2	3	
Headache	1	1			1
Mood change	3	1			
Epigastric pain		1			
Alopecia			1		
Insomnia					1
Discontinuation	3	2	2	0	1
Wants childbearing	1			-	-
Due to adverse effects	2	2	2	0	1
Frequent bleeding	1	1	1		
Epigastric pain		1			
Alopecia			1		
Headache					1
Recurrence	1				
Recurrence	2	1	-	-	-

Values, number of patients.

Table 3. Adverse effects and reason for discontinuation of DNG group for 5 years follow-up periods.

Parameters	At 1 year (n = 154)	At 2 year (n = 121)	At 3 year (n = 50)	At 4 year (n = 26)	At 5 year (n = 12)
Adverse effects occurrence	45	19	7	5	0
Frequent bleeding	10	8	2	2	
Weight gain	9	1	3		
Lower abdominal Pain	11	7	2	1	
Headache	2	1			
Mood change	2			1	
Epigastric pain	1				
Alopecia	1				
Nausea	1				
Breast discomfort	3	1		1	
Amenorrhea	1				
Hot flush	2				
Paresthesia	1	1			
Discontinuation	22	9	3	1	2
Wants childbearing	2	2	1		
Wants contraception	1	2			2
Menopause	1				
Due to adverse effects	18	5	2	1	0
Frequent bleeding	3	2			
Weight gain	5		1		
Lower abdominal Pain	2	1	1		
Mood change	2			1	
Breast discomfort	1				
Amenorrhea	1				
Hot flush	2				
Headache		1			
Recurrence	3	3	2	1	

Values, number of patients.

Recurrence rates observed through sonography were 3.4% and 1.9% at one year in the DNG and COC groups, respectively. After two years, there was no recurrence among patients in the COC group. In the DNG group, the recurrence rates were 1.9%, 2.5%, 4.0%, 3.8%, and 0% at Y1, Y2, Y3, Y4, and Y5, respectively.

DISCUSSION

Endometriosis is a complex clinical condition, and despite extensive research over the past 160 years, several controversies and dilemmas related to its pathogenesis, diagnosis, clinical management, prognosis, and epidemiology remain.¹⁶ However, what is certain is that endometriosis is

a chronic disease with a 50% chance of recurrence five years after surgery, and therefore, long-term surveillance and management of the condition are required.⁴ Considering that hormone therapy is the mainstream treatment indicated for successful long-term patient care for endometriosis, it is important for physicians to understand its efficacy and possible complications.

In this study, the incidence rates of AEs were relatively higher than those in previous studies. For instance, Park et al. discussed the incidence of AEs after one year of DNG use in Korean women; the incidence rate was 18.1%, and the most frequently observed AEs were frequent or prolonged uterine bleeding (3.2%), insomnia (2.7%), nausea (2.1%), weight gain (2.1%), and acne (2.1%).¹⁷ Further, according to the study of Kim et al., the incidences of headache, breast discomfort, nausea, and weight gain were 6.0%, 8.0%, 5.3%, and 24.0%, respectively, after 18 months of DNG use.¹⁸

It is widely known that frequent bleeding is an adverse effect of DNG; however, its dramatically higher incidence rates in the current study might have been because of the time at which DNG was initiated. To reduce instances of irregular bleeding, patients are advised to start medication on the second or third day of their menstruation.^{8,10} However, in this study, most patients experienced altered periods because of recent ovarian surgeries; thus, there was no strict control over the initiation timing of DNG. Further, the higher incidences of lower abdominal pain might have been due to discomfort at the operation site after

surgery, inflammatory changes during the post-surgical healing process, and/or altered menstrual periods and related dysmenorrhea. These AEs may be reduced by adjusting the initiation time of medication. Additionally, it has been recently reported that cyclic DNG administration or the preceding administration of GnRHa could reduce the symptoms of abnormal vaginal bleeding.^{19,20}

According to the official product information of COCs, during their administration, the incidence of pelvic pain is less than 10%, that of genital tract bleeding is 14%, and that of premenstrual syndrome is 13.2%.

Moreover, we found that the discontinuation rates were lower than the incidence rates, which suggests that most AEs were negligible. Nevertheless, severe AEs, such as thromboembolism and possible bone loss, are clinically important factors that have to be considered when deciding whether to continue medication. However, considering that the occurrence of such severe AEs is rare, managing negligible AEs is one of the major factors in determining a patient's compliance with long-term application of medical therapy.

A comparison between the incidence rates of AEs and medication discontinuation rates between the two groups for five years were not statistically significant (data not shown). Such results require careful interpretations; the current study did not intend to compare the two drugs, and its study groups are distinctively composed of patients with different characteristics. Therefore, it is hard to state that the two study groups have no significant differences; rather, well-de-

signed prospective studies regarding such issue are warranted.

This study has several limitations. First, it was a simple observational study wherein direct evaluation of the patients was limited. Second, some of the AEs might not have been related to hormonal treatment. Third, the number of patients included in this study was relatively small; especially in the DNG group, the number of patients rapidly decreased after two years of medication. This may have been due to the initial approval of DNG use only for 18 to 24 months in pivotal studies.

Despite these limitations, this study provides important practical information on endometriosis management in real-world clinical settings and presents relatively long-term data of up to five years. Our findings showed that most AEs were not severe, and the medication discontinuation rates were much lower than the incidence rates of AEs in patients treated with DNG and COCs for secondary prevention of endometriosis. Although the AEs were very diverse, the incidence rates were relatively high. These results could serve as a guide for patients to decide when to start medical treatment. When considering long-term hormonal treatment for endometriosis patients, timely, detailed explanation of the expected AEs and options to control them is essential.

In conclusion, through our clinical experience, the present study findings present valuable information on long-term hormonal therapy to prevent the recurrence of endometriosis, which could consequently aid physicians in coming up

with personalized treatment plans for patients. Furthermore, we found that the associated AEs were not severe enough to warrant discontinuation of medication. It is important that clinicians provide information regarding minor AEs to patients in advance to effectively increase their compliance and thus successfully control the recurrence of endometriosis.

CONFLICT OF INTEREST

There are no potential conflicts of interest to declare.

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