ORIGINAL ARTICLE: ENDOMETRIOSIS

Evaluation of the efficacy and safety of dienogest in the treatment of painful symptoms in patients with adenomyosis: a randomized, double-blind, multicenter, placebo-controlled study

Yutaka Osuga, M.D.,[a] Haruka Fujimoto-Okabe,[b] and Atsushi Hagino[b]

[a] Department of Obstetrics and Gynecology, Faculty of Medicine, The University of Tokyo; and [b] Clinical Development Department, Mochida Pharmaceutical Co., Ltd., Tokyo, Japan

Objective: To evaluate the efficacy and safety of dienogest (DNG), a progestational 19-norsteroid, in patients with symptomatic adenomyosis.
Design: Phase III, randomized, double-blind, multicenter, placebo-controlled study.
Setting: Clinical study sites in Japan.
Patient(s): Sixty-seven patients with adenomyosis.
Intervention(s): Patients were randomly assigned to receive DNG (2 mg/d, orally) or placebo for 16 weeks. In cases of complicated anemia, patients were treated for anemia before randomization.
Main Outcome Measure(s): The primary end point was the change from baseline to after treatment pain score, using zero- to three-point verbal rating scales that defined pain severity according to limited ability to work and need for analgesics. The visual analogue scale was used as another pain parameter.
Result(s): Decreases from baseline in the pain score and the visual analogue scale at the end of treatment were significantly more in the DNG group than in the placebo group ($P<.001$). During the treatment period, almost all of the patients treated with DNG experienced irregular uterine bleeding and one patient had mild anemia. No severe cases of anemia were observed.
Conclusion(s): These results suggest that DNG is effective and well tolerated in the treatment for painful symptoms associated with adenomyosis not complicated by severe uterine enlargement or severe anemia.
Clinical Trial Registration Number: JapicCTI-142642(en). (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Dienogest, adenomyosis, placebo-controlled study, double-blind, randomized study

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Adenomyosis is a common gynecological disease in women of reproductive age. Adenomyosis is an estrogen (E)-dependent disease characterized by the proliferation of ectopic endometrial-like tissue within the myometrium. It significantly reduces quality of life (QOL) due to severe painful symptoms such as dysmenorrhea and pelvic pain. Based on the biological similarity of adenomyosis to endometriosis, GnRH agonists, low-dose oral contraceptives (OCs), or levonorgestrel intrauterine system are primarily used according to hormonal therapies for endometriosis. However, none of them have been clearly validated for the therapeutic effect in adenomyosis, and there are no drugs indicated for adenomyosis in Japan and overseas. Therefore, an

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Reprint requests: Yutaka Osuga, M.D., Department of Obstetrics and Gynecology, Faculty of Medicine, The University of Tokyo, Tokyo 113-8655, Japan (E-mail: yutakaos-tky@umin.ac.jp).

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effective and well-tolerated option for the treatment of adenomyosis symptoms is highly desirable.

Dienogest (DNG), a progestational 19-norsteroid derivative, is a synthetic oral progestin with highly selective binding to P receptors (PR) (1). It exerts antiovulatory (2) and mild hypoestrogenic (3) effects, as well as antiproliferative activity in human endometrial cells (4). Based on this hormonal profile, DNG is used as a treatment for painful symptoms in patients with endometriosis, without causing any severe hypoestrogenic adverse effects (3, 5). It is also expected to be an effective treatment for painful symptoms associated with adenomyosis. On the other hand, irregular genital bleeding due to the progestational action of DNG on the endometrium is a well-known adverse effect in patients with endometriosis (6). It occasionally results in severe anemia in patients with adenomyosis (7).

The aim of this study was to elucidate the efficacy and safety of DNG in patients with adenomyosis with pelvic pain. Randomized controlled conditions were the goals of this study.

MATERIALS AND METHODS

Patients and Study Design

This study was a randomized, double-blind, multicenter, placebo-controlled phase III study of DNG. It was conducted between August 2014 and June 2015 at 20 clinical study sites in Japan. The protocol was approved by the institutional review boards of all of the participating sites.

Inclusion criteria were as follows: [1] aged 20 years or older; [2] regular menstrual cycles of 38 days or less; [3] adenomyosis diagnosed by imaging analysis (both magnetic resonance imaging [MRI] and transvaginal sonography) (8); and [4] pain symptoms (lower abdominal pain and/or lumbago) scoring three points or more on the verbal pain rating scale developed by Harada et al. (9, 10; Table 1) during the menstrual cycle.

Exclusion criteria were as follows: [1] endometriosis or uterine leiomyoma diagnosed by imaging analysis (both MRI and transvaginal sonography); [2] severe anemia (hemoglobin concentrations <8.0 g/dL); and [3] marked uterine enlargement (maximum dimension, >100.0 mm or myometrial thickness, >40.0 mm). In cases of mild or moderate anemia (hemoglobin levels between 8.0 and 11.0 g/dL), patients were given anemia treatment for the hemoglobin concentrations reached at least 11.0 g/dL before randomization. Written informed consent was obtained from all of the patients.

Gynecologists with ample experience of image diagnosis were selected as investigators in this study. No specific criteria for adenomyosis based on transvaginal ultrasonography and MRI were selected. Adenomyosis was diagnosed by investigators, and no central determination was made by image specialists.

Study Treatments and Measurements

Patients who met all of the inclusion criteria and did not have any of the exclusion criteria were randomly assigned by the permuted-block method in a 1:1 ratio to receive a 1-mg DNG tablet (the DNG group) or an identical placebo tablet (the placebo group) twice daily for 16 weeks, starting between the second and fifth day of the menstrual cycle. Allocation concealment was accomplished centrally by an independent organization and maintained blindness for patients, investigators, and sponsor until after all data were collected. For the duration of the study, the use of reliable contraception other than hormonal agents was required and patients were allowed to take analgesics.

Patients were assessed for their pain score, visual analogue scale (VAS), uterine size, and serum E_2 concentration at baseline menstrual cycle before randomization and every 4 weeks during the treatment period. The QOL was rated using the MOS 36-Item Short-Form Health Survey (11) at baseline and at the end of treatment (EOT: 16 weeks or when discontinued).

Laboratory hematology was measured at baseline, every 4 weeks during the treatment period, 4 weeks after EOT, and after resuming menstruation. Laboratory biochemical and urinalysis tests were conducted at baseline and every 8 weeks during the treatment period. Monitoring and auditing procedures confirmed that the clinical study was conducted in accordance with the Helsinki Declaration and Good Clinical Practice.

Efficacy and Safety End Points

The primary efficacy end point was the change in the pain score from baseline to after treatment. The other efficacy end points were the change in the pain score during the course of treatment and change in the VAS and uterine size from baseline to after treatment. Uterine size was determined based on the diameters of three angles (D1, D2, D3, in millimeters) including the maximum diameter of the uterus by transvaginal ultrasonography. The uterus was evaluated as a spheroid. The maximum diameter of the uterine corpus (from the internal cervical os to the fundus serosa) was measured for the maximum diameter of the uterus.

The primary safety end point was adverse effects (AEs). The secondary safety end point was adverse drug reactions (ADRs). The number of days and severity of genital bleeding were assessed using a patient diary form.

Statistical Analysis

The primary analysis set for the efficacy analysis was the full analysis set (FAS). Sensitivity was analyzed by comparing the

TABLE 1

Grading, scoring, and definitions for components of the pain score.

Grade	Score	Definition
Pain severity score (lower abdominal pain and/or lumbago)		
None	0	None
Mild	1	Low efficiency for work and/or study
Moderate	2	Needing to rest in bed and/or loss of work
Severe	3	In bed for ≥1 da
Analgesics usage score		
None	0	None
Mild	1	Taking analgesics for 1 d
Moderate	2	Taking analgesics for 2 d
Severe	3	Taking analgesics for ≥3 d

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results from the FAS with the results from the per protocol set. The primary analysis set for the safety analysis was the safety analysis set. The FAS consisted of randomized patients who received the study drug at least once during the treatment period and were assessed for their pain score after the start of the treatment period. The primary analysis set consisted of patients in the FAS who satisfied the inclusion criteria; did not have any exclusion criteria; did not use prohibited concomitant drugs or receive prohibited concomitant therapy during the observation period or the treatment period; received the study drug for at least 56 days (during the period from the start to the end of the treatment); whose drug compliance was at least 75% from the start to the end of the treatment period; and whose nonmedication duration was within 14 times in succession. The safety analysis set consisted of patients who received the study drug at least once during the treatment period and had safety data collected after the treatment period.

The primary efficacy analysis was an analysis of covariance (ANCOVA) of the change in the pain score (FAS) from baseline to after treatment, with treatment as a fixed factor and the baseline pain score as a covariate, using last observation carried forward (two-sided significance level of 5%). Imbalances in patient characteristics were analyzed using the Wilcoxon two-sample test (two-sided significance level of 15%). The AEs were summarized by preferred term using the Medical Dictionary for Regulatory Activities Version 18.0.

The SAS Release 9.2 (SAS Institute) was used for statistical analysis. Based on a previous DNG study in adenomyosis (Late Phase II Study), with a mean difference of −1.7 from placebo in the change from baseline in the pain score at 16 weeks, and an SD of 2.2, calculations showed that with a power of ≥80%, a total of 60 patients should be randomized to verify superiority of DNG to placebo, using a 5% significance level and a standard *t*-test.

RESULTS

Demographic Characteristics and Disposition

Consent was obtained from 87 patients and 68 patients were randomized into the DNG (n = 35) or placebo (n = 33) group. Of these patients, 67 (34 in the DNG group and 33 in the placebo group) received at least one dose of study medication and were included in the FAS and safety analysis sets. In the DNG group, two patients discontinued the study medication. One discontinuation was due to ADRs (hot flush and menopausal symptoms) and consent withdrawal for personal reasons; and the other was due to failed contraception. In the placebo group, three patients discontinued the study medication. One discontinuation was due to an ADR (irregular uterine bleeding); another was due to consent withdrawal for personal reasons; and the third was due to consent withdrawal for personal reasons as well as drug noncompliance. In the FAS, as shown in Table 2, no differences other than weight (P=.132) were observed in the baseline characteristics and baseline values between the treatment groups.

Efficacy

Table 2 shows that the mean value of the pain score and its components, the pain severity score and analgesics usage score, decreased at 16 weeks of treatment in both the DNG and placebo groups. The decrease in the pain score, as assessed by the pain severity score and the analgesics usage score, was significantly more in the DNG group than in the placebo group (−3.8 vs. −1.4; P<.001).

The mean VAS values also decreased in both groups at 16 weeks of treatment. The decrease in VAS values was significantly more in the DNG group than in the placebo group (−58.4 vs. −20.6; P<.001) (Table 2). Figure 1 shows that the changes in the pain score, pain severity score, analgesics usage score, and VAS during the treatment period were more pronounced in the DNG group than in the placebo group at all the evaluation points.

The MOS 36-Item Short-Form Health Survey showed a typical change in the bodily pain subscale. The mean ± SD in the baseline value of the bodily pain score for the DNG and placebo groups was 35.8 ± 19.9 and 35.2 ± 17.8, respectively. Both of these outcomes were markedly worse than the standard value for age-matched Japanese women (76.1 ± 21.3 years) (12). The improvement in the mean bodily pain score at EOT was significantly more in the DNG group than in the placebo group (38.1 vs. 11.7; P<.001) (Table 3), whereas the value in the DNG group was almost comparable with the aforementioned standard value.

The ranges of baseline uterine sizes were from a maximum of 326.4 cm^3 to a minimum of 41.7 cm^3, with a

TABLE 2

Demographic and efficacy data (full analysis set).

Characteristic	Dienogest (n = 34)	Placebo (n = 33)	*P* value
Age (y)[a]	37.3 ± 7.9	37.4 ± 6.6	.816
Weight (kg)[a]	56.9 ± 7.7	54.2 ± 7.1	.132
BMI (kg/m^2)[a]	22.2 ± 3.2	21.4 ± 2.4	.415
Menstrual cycle length (d)[a]	28.4 ± 4.1	28.1 ± 4.7	.835
Hemoglobin level (g/dL)			
Baseline[a]	12.8 ± 1.3	12.3 ± 1.6	.177
At EOT	13.2 ± 0.7	12.8 ± 1.4	
Number of partus[a]	1.2 ± 1.2	1.2 ± 1.1	.845
Pain score			
Baseline[a]	4.6 ± 1.1	4.8 ± 1.0	.298
Change at 16 wk[b]	−3.8 ± 1.9	−1.4 ± 1.8	<.001
Pain severity score			
Baseline[a]	2.4 ± 0.5	2.5 ± 0.5	.397
Change at 16 wk[b]	−1.9 ± 1.0	−0.6 ± 0.8	<.001
Analgesics usage score			
Baseline[a]	2.1 ± 1.0	2.3 ± 0.8	.470
Change at 16 wk[b]	−1.9 ± 1.2	−0.8 ± 1.3	<.001
Visual analogue scale (mm)			
Baseline[a]	66.3 ± 19.1	69.0 ± 20.6	.518
Change at 16 wk[b]	−58.4 ± 23.6	−20.6 ± 23.6	<.001
Uterine size			
Baseline (cm^3)[a]	96.5 ± 60.3	93.3 ± 68.3	.749
Reduction at EOT (%)[b]	20.0 ± 28.8	9.6 ± 23.0	.103

Note: Data presented as mean ± standard deviation. BMI = body mass index; EOT = end of treatment.

[a] Difference between groups analyzed by Wilcoxon two-sample test.

[b] Difference between groups analyzed by an analysis of covariance (ANCOVA), with the treatment group a fixed factor and the baseline score as a covariate.

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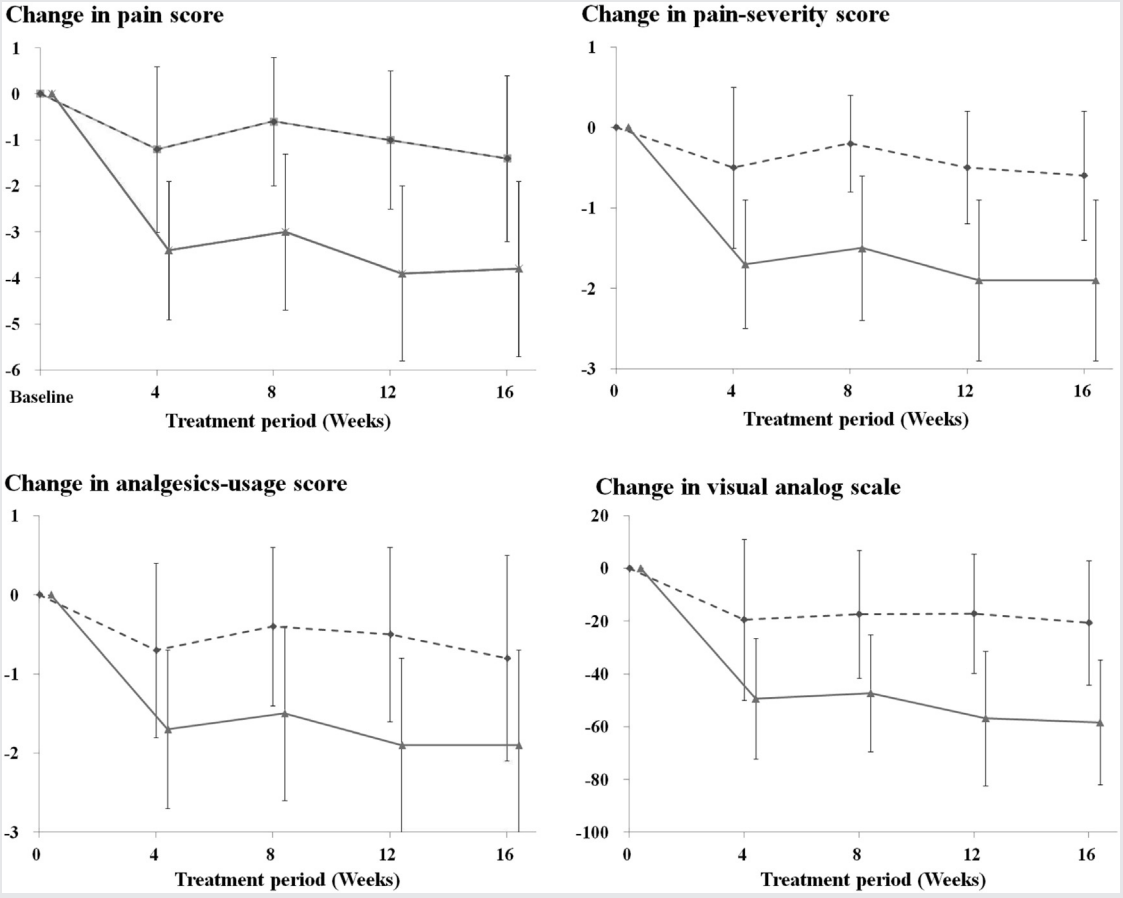
FIGURE 1



Changes in pain score, pain severity score, analgesics usage score, and visual analogue scale during the treatment period. The *solid line* shows the dienogest group, and the *dotted line* shows the placebo group. Each point represents the mean ± SD.

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median of 79.7 cm^3, in the DNG group and from a maximum of 429.9 cm^3 to a minimum of 25.4 cm^3, with a median of 92.4 cm^3, in the placebo group. The mean reduction in uterine size was somewhat greater in the DNG group than in the placebo group, but there was no significant difference (20.0 vs. 9.6; P=.103) (Table 2). Serum E_2 concentrations (mean ± SD [median]) at baseline and at 16 weeks of treatment were 124.8 ± 103.8 pg/mL (99.5) and 42.1 ± 50.7 pg/mL (24.0) in the DNG group, and 158.2 ± 119.6 pg/mL (113.0) and 107.3 ± 114.6 pg/mL (65.0) in the placebo group, respectively.

Safety

The incidences of AEs and ADRs were 100% (34/34 patients) and 100% (34/34 patients) in the DNG group, and 76% (25/33 patients) and 46% (15/33 patients) in the placebo group, respectively. No serious AEs or severe cases were observed in either group.

The most frequent ADRs in the DNG group and the placebo group were irregular uterine bleeding (97% [33/34 patients] vs. 39% [13/33 patients], respectively), followed by hot flush (6% [2/34 patients] vs. 0, respectively). More patients reported irregular genital bleeding in the DNG group. Two patients discontinued treatment due to ADRs: in one patient, hot flush and menopausal symptoms (in the DNG group); and in the other patient, irregular uterine bleeding (in the placebo group). None of the patients in the DNG group discontinued treatment due to genital bleeding. The proportion of days (mean ± SD) on which genital bleeding occurred during the treatment period in both the DNG and placebo groups were tabulated by severity. In the DNG group, the proportion of days with no bleeding was 52.8% ± 27.0%, the proportion of days with spotting was 28.9% ± 21.5%, the proportion of days with breakthrough bleeding was 16.4% ± 17.7%, the proportion of days with bleeding equivalent to normal menstruation was 1.6% ± 3.1%, and the proportion of days with bleeding more than normal menstruation was 0.3% ± 0.9%. In the placebo group, the proportion of days with no bleeding was 75.0% ± 8.9%, the proportion of days with spotting was 10.4% ± 6.5%, the proportion of days with breakthrough bleeding was 7.8% ± 4.1%,

TABLE 3

Changes in the MOS 36-Item Short-Form Health Survey SF-36 QOL score from baseline to the end of treatment (full analysis set).

Scale	Dienogest (n = 34)	Placebo (n = 33)	*P* value[a]
Physical functioning	2.4 ± 7.9	5.0 ± 14.0	.085
Role physical	12.5 ± 36.0	6.8 ± 41.1	.038
Bodily pain	38.1 ± 29.7	11.7 ± 31.6	< .001
General health	2.3 ± 9.9	−0.7 ± 14.1	.351
Vitality	6.5 ± 16.7	2.0 ± 13.3	.234
Social functioning	8.5 ± 17.1	4.9 ± 22.3	.094
Role emotional	4.9 ± 33.0	7.1 ± 28.6	.275
Mental health	4.0 ± 14.5	−1.5 ± 17.0	.214

Note: Data presented as mean ± standard deviation.
[a] Difference between groups analyzed by an analysis of covariance (ANCOVA), with the treatment group as a fixed factor and the baseline score as a covariate.

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the proportion of days with bleeding equivalent to normal menstruation was 4.5% ± 2.2%, and the proportion of days with bleeding more than normal menstruation was 2.2% ± 2.7%. Compared with the placebo group, there was a lower proportion of days with no bleeding in the DNG group, but most of the cases of genital bleeding that occurred in the DNG group were spotting or breakthrough bleeding, which resolved either during the treatment period or after EOT. It seems like numbers of days with heavy bleeding in the DNG group is reduced. Resumption of menses after EOT was confirmed in all 34 patients in the DNG group, with 28.3 ± 9.3 days from EOT to the first day of menstruation.

The abnormal changes in laboratory tests were assessed as AEs in two patients in the placebo group, hemoglobin increased and CA-125 increased, whereas no such cases were seen in the DNG group. The mean ± SD of the hemoglobin concentrations at baseline and at EOT were 12.8 ± 1.3 g/dL and 13.2 ± 0.7 g/dL in the DNG group, and 12.3 ± 1.6 g/dL and 12.8 ± 1.4 g/dL in the placebo group, respectively. There were 10 patients who required treatment for anemia before randomization. Although one patient in the DNG group complained of feeling anemic during irregular uterine bleeding, no decrease in hemoglobin level was observed, and the ADR resolved after the patient was given an iron preparation during the treatment period.

DISCUSSION

This study confirmed that DNG is an effective treatment for painful symptoms due to adenomyosis with double-blind, placebo-controlled conditions. Due to the reports of the risks for severe irregular uterine bleeding and anemia associated with DNG, adenomyosis patients with severe uterine enlargement and severe anemia were excluded from the study. The study also demonstrated that DNG was well-tolerated despite a high incidence of irregular genital bleeding.

After 16 weeks of treatment with DNG, the mean decrease in the pain score was significantly more than that for placebo, as measured by more than two rating scales (−3.8 vs. −1.4), thereby showing a clinically identifiable effect of DNG. Another pain parameter, the VAS, produced almost the same results as the pain score. Both the pain score and the VAS showed that the effect of DNG was stable throughout the treatment period.

The QOL score also demonstrated the effect of DNG on pain symptoms. Among the eight QOL subscales, the baseline bodily pain subscale score was markedly lower than the standard value for Japanese women, whereas the score after treatment with DNG increased markedly to a level almost comparable with the standard value. These scores demonstrated that DNG significantly improved QOL in patients with adenomyosis with respect to pain symptoms.

Uterine enlargement is a typical symptom of adenomyosis. The reduction in uterine size after treatment with DNG was somewhat more pronounced than that for placebo, but without reaching significance. Consequently, it seems that DNG has an effect on symptoms control and not on the disease process.

The hypoestrogenic effect of DNG is reported to be less frequent than with GnRH agonists, delivering a therapeutic effect with minimal changes to bone metabolism in patients with E-dependent diseases (3). In the present study, the mean serum E_2 concentration was 42.1 pg/mL in the DNG group, comparable to the level seen in the aforementioned report.

Irregular bleeding is common with progestins (6, 13) and most of the genital bleeding in the DNG group in this study was spotting or breakthrough bleeding. However, mean hemoglobin concentrations in the DNG group maintained a normal range throughout the treatment period and there were no cases of severe genital bleeding that required emergency intervention, such as blood transfusions, or resulted in the discontinuation of DNG treatment.

Hirata et al. (14) reported that administration of DNG for 24 weeks to patients with adenomyosis improved pain and showed no change in the uterine size, and that changes in serum E_2 concentrations were minimal and DNG was well tolerated. These results coincided with the results of the present study.

Adenomyosis is an E-dependent disease, like endometriosis, and conservative medical therapy with hormonal drugs used for the treatment of endometriosis is known to be effective also in controlling the symptoms of adenomyosis, especially painful symptoms. There are several hormonal drug options, such as GnRH agonists, low-dose OCs, and levonorgestrel intrauterine systems (15). However, there are restrictions on the treatment period of GnRH agonists due to the adverse effect associated with low E symptoms, low-dose OCs should be administered with care to patients aged 40 years or older due to the risk for thrombosis, and a levonorgestrel intrauterine system has the problems of perforation and expulsion, and the risk of pelvic inflammatory diseases. Adenomyosis frequently develops from the sexual maturation period to menopause, peaking in 40s. The radical treatment for adenomyosis is hysterectomy, and medical therapy for patients who wish to get pregnant or preserve the uterus has challenges. The DNG improves pain in patients with adenomyosis who wish fertility preservation, at various ages, and showed its safety on the premise that appropriate consideration will be given to irregular uterine bleeding and anemia. However, the results of the present study are limited to 16-week treatment, and data on a longer treatment period are necessary.

This study has several limitations. Diagnosis of adenomyosis was conducted by transvaginal sonography and MRI. Histologic diagnosis is considered to be the principal method for diagnosis of adenomyosis. However, it has been reported that diagnosis by transvaginal sonography and MRI is highly precise (8, 16). In the present study, detailed standards for transvaginal sonography or MRI were not defined, but in general, the characteristic findings for adenomyosis from transvaginal sonography are diffuse myometrial thickening and small cyst-like myometrial opacities, and the characteristic findings for adenomyosis from MRI are low signal areas with unclear boundaries, containing scattered bright spots on T_2-weighted imaging. In the present study, image diagnosis using transvaginal sonography and MRI were performed by a gynecologist with ample experience, and therefore it is likely that the diagnosis was highly precise. In addition, laparoscopy to rule out endometriosis was not performed in this study, out of consideration of the invasive nature of this procedure. Accordingly, we consider that there are limitations to the certainty with which an initial stage endometriosis lesion can be ruled out. It also might be preferable to consider ruling out chronic pelvic infection.

In conclusion, DNG was effective and well tolerated as a treatment for painful symptoms in patients with adenomyosis, not complicated by severe uterine enlargement or severe anemia. These findings suggest that DNG may be a new therapeutic alternative for the subgroup of patients with adenomyosis and pelvic pain.

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