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ORIGINAL ARTICLE

A controlled clinical trial comparing potent progestins, LNG-IUS and dienogest, for the treatment of women with adenomyosis

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Abstract

Purpose: To evaluate the efficacy of two progestins, levonorgestrel intrauterine system (LNG-IUS) and dienogest (DNG), for adenomyosis.

Methods: This study enrolled 157 women with adenomyosis, randomized to either LNG-IUS (n = 76) or DNG (n = 81) groups as a controlled clinical trial for 72 months. Participants were classified by three different localizations of adenomyosis: diffuse, focal, and extrinsic. VAS (Visual analog scale) score, days, and amount of uterine bleeding were assessed. Uterine volume or bone mineral density (BMD) were measured by three-dimensional ultrasonography or dual-energy X-ray absorptiometry.

Results: LNG-IUS and DNG comparably reduced pain scores in patients with adenomyosis. With regard to pain control, DNG offered greater efficacy than LNG-IUS in 3 months of treatment. In all types of adenomyosis, the days of bleeding after 12 months with DNG were significantly decreased compared to those with LNG-IUS. The decrease of whole uterine body was transient in any subtypes. A comparable decrease in BMD due to age-related changes in both groups was observed.

Conclusions: LNG-IUS and DNG could be useful for long-term management of adenomyosis. In terms of durations of uterine bleeding, DNG was superior to LNG-IUS for 6 years.

KEYWORDS
adenomyosis, dienogest, LNG-IUS, pelvic pain, uterine bleeding

1 | INTRODUCTION

Adenomyosis is a commonly encountered gynecological disease, affecting women of reproductive age. Although the prevalence of adenomyosis remains unknown, the diagnosis is more often made in multiparous patients, in their fourth and fifth decade of life.[1] Clinical problems caused by adenomyosis include the impaired quality of life due to severe painful symptoms, abnormal uterine bleeding (AUB), and infertility, demanding appropriate treatment.[2] Despite its prevalence and the severity of the symptoms, the pathogenesis and etiology of adenomyosis have yet to be elucidated. Epidemiological data suggest that a large number of births, spontaneous and induced abortions, and endometrial hyperplasia are associated with increased risks of adenomyosis.[3] Other risk factors associated with

adenomyosis include endometriosis, surgical trauma, cesarean section or curettage, and smoking.[3]

Recently, the development and increasing use of diagnostic modalities, including ultrasonography (US) and magnetic resonance imaging (MRI) in women with chronic pelvic pain or infertility have contributed to the detection of adenomyosis in younger women, indicating several etiopathogenic conditions and different subtypes.[4] Primarily, the developments in MRI have led to elucidation of diversity in the localization of adenomyosis. We categorized adenomyosis patients who desired conservative management into three subtypes of adenomyosis according to MRI findings: (a) diffuse type; (b) focal type; and (c) extrinsic type. Ectopic endometrial implants shown in adenomyotic tissues are known to follow different distribution patterns in the myometrium. As the diffuse type, the endometriotic glands and stroma are distributed throughout the myometrium. The adenomyotic lesion of the uterus occupies more than 50% area in sagittal-section MRI. In contrast, as the focal type, the lesion is confined to the myometrium. The area of adenomyosis in the uterus is localized to less than 50% area in the sagittal section on MRI circumscribing the identified nodules. As the extrinsic type, we classified patients with adenomyotic lesions in the posterior wall adhesive to the rectum as well as in the outer shell of the uterus disrupting the serosa, and a preserved junctional zone in the uterus representing the inner myometrium beneath the endometrium.[5]

Pharmacological management with hormonal drugs for symptomatic adenomyosis, such as oral contraceptive/low-dose estrogen–progestin (OC/LEP), progestins, gonadotropin-releasing hormone (GnRH) agonist is controversial. The present study evaluated the efficacy of two progestins, levonorgestrel intrauterine system (LNG-IUS) and dienogest (DNG), for women with adenomyosis.

LNG-IUS treatment is generally effective for pain and heavy uterine bleeding, attributed to the following mechanisms: (a) progestogenic influences on adenomyosis foci; (b) atrophy of the eutopic endometrium; and (c) control of endometrial factors that changed during adenomyosis. Decreased expression of growth factor and the related receptors has been found in women with heavy bleeding and adenomyosis following LNG-IUS treatment.[6] Another randomized study showed a positive effect of LNG-IUS in around 100 women with adenomyosis suffering from heavy menstrual bleeding.[7] On the other hand, DNG, a 19-nortestosterone derivative, is an antiandrogenic drug with high selectivity for progesterone receptors (PRs), and has been used to treat adenomyosis. DNG suppresses ovarian function, and proves highly effective in the treatment of chronic pelvic pain.[8] In addition, DNG directly inhibited cellular proliferation and induced apoptosis in human adenomyotic cells.[9]

While both LNG-IUS and DNG have been shown to be effective in relieving dysmenorrhea and menorrhagia in patients with adenomyosis, data clarifying which agent should be the first choice remain insufficient. Therefore, as a first controlled clinical trial, the present investigation was conducted to evaluate the efficacy of these two progestins for the women of adenomyosis with pelvic pain and/or AUB.

2 | MATERIALS AND METHODS

This study was conducted among women who visited Kurashiki Heisei Hospital for a health checkup, and was approved by the ethics committee at Kurashiki Heisei Hospital (approval no. H25-015) as an open-label study. One hundred fifty-seven patients were enrolled from January 2013 to December 2020. All participants provided signed informed consent prior to enrolment, and were treated for 72 months. Inclusion criteria were as follows: (a) first diagnosis of adenomyosis by US and/or MRI; (b) intolerable dysmenorrhea or abnormal uterine bleeding; (c) no history of moderate-dose hormonal pills, GnRH agonist (GnRHa), testosterone derivatives, estrogen antagonists, aromatase inhibitors, DNG or other progestins, or surgical treatment before enrollment; (d) no complications of uterine fibroids, including submucosal fibroids; (e) age <45 years and premenopausal status (follicle-stimulating hormone <11 mIU/ml); (f) maximum thickness of myometrium in adenomyosis lesions ≤35 mm; and (g) no history of disease or treatments that affect bone density, such as hypophosphatemia or steroid hormone therapy. We categorized adenomyosis patients who desired conservative management into three subtypes of adenomyosis according to MRI findings: (a) diffuse type; (b) focal type; and (c) extrinsic type. Exclusion criteria were as follows: (a) more than 2-cm ovarian endometrioma in diameter; (b) the thick adenomyosis with width of more than 35 mm; (c) the invasive endometriotic lesions to the rectum diagnosed by MRI.

One hundred and fifty-seven women with adenomyosis were enrolled and randomized to either an LNG-IUS (Mirena® 52 mg; Bayer Yakuhin) ($n = 76$) or a DNG group (Mochida Pharmaceutical) ($n = 81$; 2 mg/day). When the last digit of the patient ID was an even number, the patient was to receive LNG-IUS, and when the last digit was an odd number, the patient was to receive DNG. Visual analog scale (VAS) scores were used to assess pain (from 0 mm = no pain to 100 mm = worst pain possible). For this efficacy analysis, VAS, number of days of uterine bleeding and volume of bleeding for the last month before continued progestin treatment were assessed in the first, second, and third months in addition to every 6 months. Uterine volume or bone mineral density (BMD) of lumbar and femoral bone were measured every year by three-dimensional (3D) transvaginal US (Voluson E8 or E10; General Electric Co.) or dual-energy X-ray absorptiometry. No patients had any pathologies or had received any treatments affecting bone density, such as hypophosphatemia or hormonal drugs. Five years later, we surveyed clinical outcomes.

Values of $p < 0.05$ were considered indicative of a significant difference for all data, and data are shown as mean ±standard deviation. Data were analyzed using Wilcoxon rank sum test, Mann–Whitney *U*-test or One-way ANOVA using SAS version 9.4 (SAS Institute Inc.,).

3 | RESULTS

Clinical background characteristics for the 157 patients with adenomyosis are presented in Table 1. Previous cesarean section was

TABLE 1 Clinical data for 157 patients treated with LNG-IUS or DNG for adenomyosis

	LNG-IUS			DNG		
	Focal	Diffuse	Extrinsic	Focal	Diffuse	Extrinsic
Number of patients	21	27	28	23	28	30
Age (years)	42.3 ± 4.2	43.1 ± 3.6	41.5 ± 5.3	41.4 ± 3.5	43.6 ± 4.1	40.2 ± 4.5
BMI (kg/m^2)	24.6 ± 3.1	25.4 ± 2.3	23.4 ± 5.1	24.2 ± 3.4	25.1 ± 3.1	24.9 ± 4.0
Past pregnancies	1.8 ± 0.4	2.1 ± 0.6	1.2 ± 0.6	1.7 ± 0.8	2.2 ± 0.8	1.5 ± 0.7
Previous cesarean section (%)	11 (52.4%)*	3 (11.1%)	5 (17.9%)	12 (52.2%)*	4 (14.3%)	7 (23.3)
Ovarian endometrioma (%)	3 (14.3%)	3 (11.1%)	11 (39.3%)*	4 (17.4%)	5 (17.9)	14 (46.7)*

*$p < 0.05$ vs. other adenomyosis subtypes in each treatment.

significantly more common in the focal group (52.4% in LNG-IUS and 52.2% in DNG) than in the diffuse and extrinsic groups. A higher association with ovarian endometrioma was observed in the extrinsic type (39.3% in LNG-IUS and 46.7% in DNG). In terms of age, body mass index, and number of previous pregnancies, no significant differences were seen among the three subtypes in either progestin group.

Figure 1 shows the changes of VAS for 78 months. Both LNG-IUS and DNG treatments reduced VAS scores in patients with

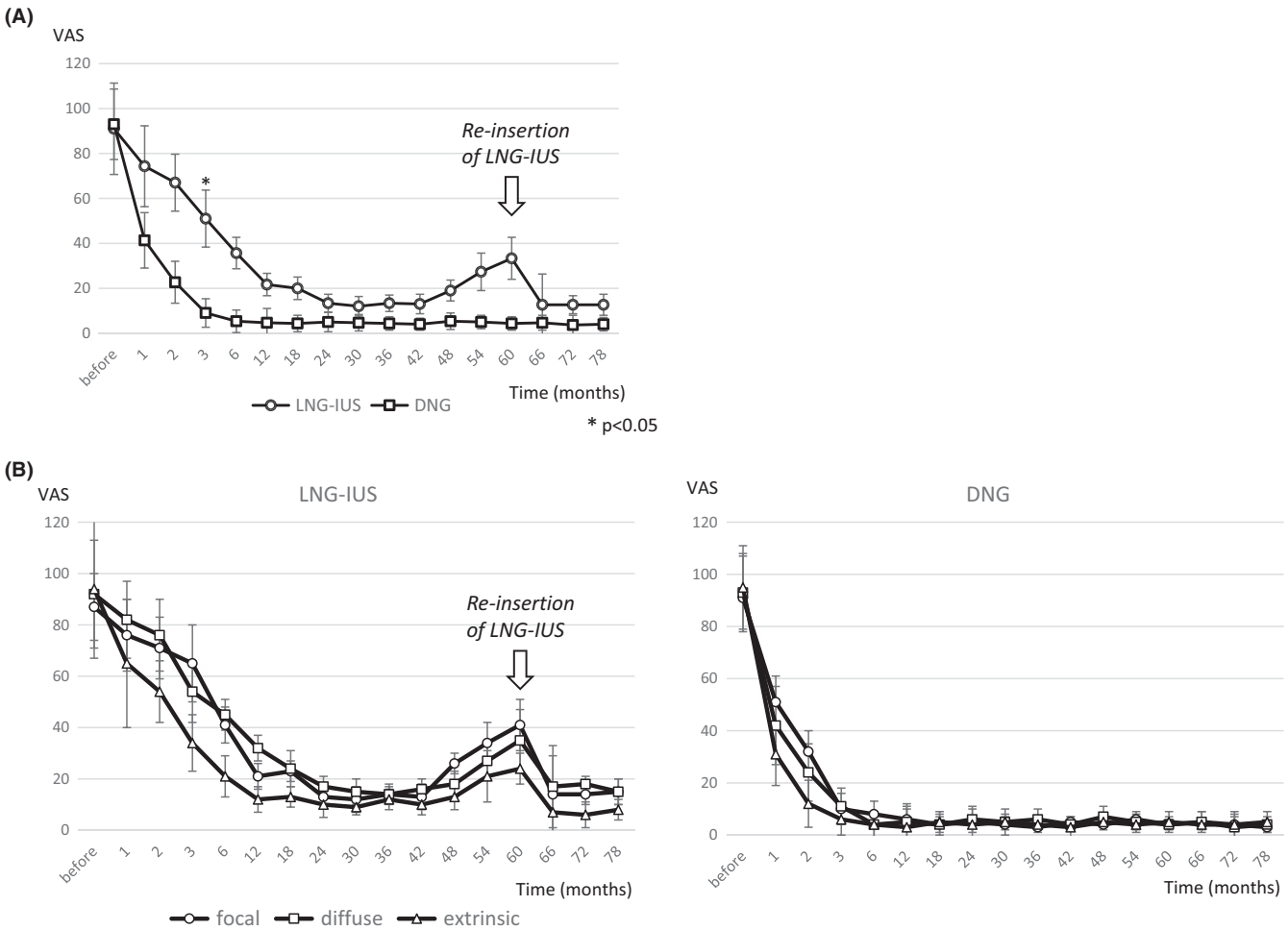


FIGURE 1 Changes in visual analog scale (VAS) score by treatment with levonorgestrel intrauterine system (LNG-IUS) and dienogest (DNG) for 78 months. (A) total, (B) three different subtypes (focal, diffuse, and extrinsic) of adenomyosis. Secondary LNG-IUS was re-inserted at the treatment for 60 months. Pain score was assessed using the VAS (0–100). (A) Open circles or squares indicate LNG-IUS or DNG treatment; *$p < 0.05$: LNG/IUS vs. DNG at the same point of time. (B) Open circles, squares, and triangles indicate focal, diffuse, and extrinsic types of adenomyosis, respectively

adenomyosis. In terms of pain reduction, DNG exerted the significant effects than LNG-IUS in 3-month treatment (Figure 1A). Within each LNG-IUS and DNG group, no differences in pain reduction were seen among the three subtypes of adenomyosis (Figure 1B).

A common adverse effect of both LNG-IUS and DNG is uterine bleeding. Figure 2 shows days (Figure 2A and C) and volume of uterine bleeding (Figure 2B and D) for the last month before the continued progestin treatment. Days of uterine bleeding with LNG-IUS were more frequent than those with DNG, particularly from 6 to 24 months of treatment (Figure 2A). Especially DNG treatment, the days of bleeding in the diffuse subtype were more frequent than for other subtypes within 6 months (Figure 2C). In addition, days of bleeding after 12 months of DNG administration were decreased in all types of adenomyosis (Figure 2C). Heavy uterine bleeding within 6 months was observed with LNG-IUS in diffuse and focal subtypes, although the significant differences were not found (Figure 2D).

At 12 months after starting LNG-IUS treatment, the volume of whole uterine body in the diffuse subtype was significantly decreased than that before treatment. In DNG treatment for the diffuse and focal subtypes, similar decrease was observed from 12 to 24 months after treatment. However, this effect appeared transient, with no changes from baseline apparent in any subtypes after 36 months of treatment (Figure 3).

Drug-induced bone loss was evaluated as decreases in BMD from the young adult mean (ΔYAM) at the lumbar spine and femur (Figure 4). At 12 months, DNG treatment showed a transient decrease in BMD compared to LNG-IUS, but after 24 months of treatment, no significant difference in bone loss was evident between the two groups (Figure 4A). Concerning cumulative changes in ΔYAM, the extent of decrease was similar between LNG-IUS and DNG groups. In contrast, bone loss was significantly reduced after 72 months of treatment compared with that after 6 months of treatment, suggesting that a comparable decrease in BMD due to age-related changes in both groups (Figure 4B).

Care is required regarding causes of discontinuation, and cases with adverse effects of treatment were as follows: (a) symptoms of severe irritable bowel syndrome (IBS) were uncontrollable in seven cases (LNG-IUS, $n = 3$; DNG, $n = 4$) of extrinsic subtype (12.1%; 7/58), all eventually treated by surgery (total laparoscopic hysterectomy [TLH] and/or adhesiolysis); (b) heavy uterine bleeding was found in nine cases (LNG-IUS, $n = 4$; DNG, $n = 5$) of diffuse type (16.4%; 9/55), all requiring TLH; (c) progression of adenomyosis or ovarian endometrioma was identified in nine cases with LNG-IUS (11.8%; 9/76), treated by TLH and/or cystectomy; and (d) decreased libido was recognized only in four patients treated with DNG (4.9%; 4/81) (Table 2).

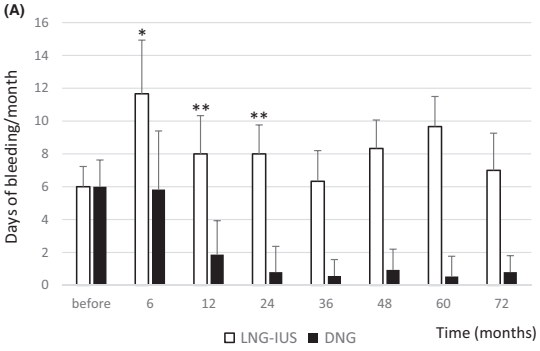
4 | DISCUSSION

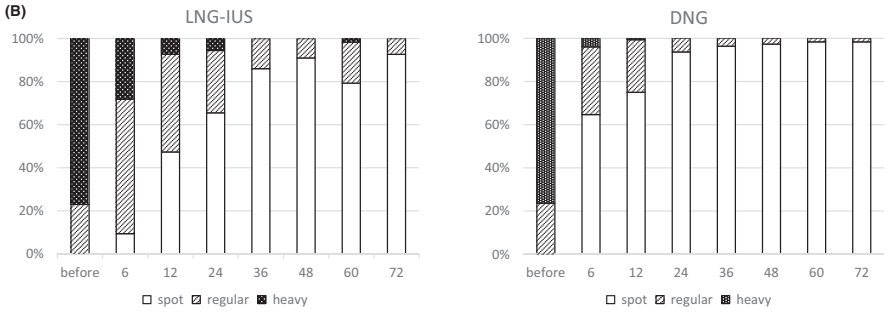
Depending on the age, clinical symptoms, and reproductive status of the woman, patients suffering from adenomyosis may require a life-long management plan, where medical, surgical, and infertility treatments may play roles, alone or in combination.[10] However, no specific guidelines have been defined regarding management, and few clinical trials focusing on medical treatment for adenomyosis have been conducted. Medical treatments, including non-steroidal anti-inflammatory drugs, progestins, OC/LEP, and GnRHa may improve symptoms due to adenomyosis, but optimal management of patients with adenomyosis remains controversial. Potent progestins, such as LNG-IUS and DNG, appear similarly beneficial in resolving AUB and pelvic pain in the long-term treatment of adenomyosis. We, therefore, sought to evaluate the efficacy of these progestins in patients with adenomyosis in a controlled clinical trial. In the present study, we found that the BMD loss induced low estrogen state as seen with GnRH agonist treatment was not observed, and the age-related BMD loss was comparable in LNG-IUS and DNG groups (Figure 4B).

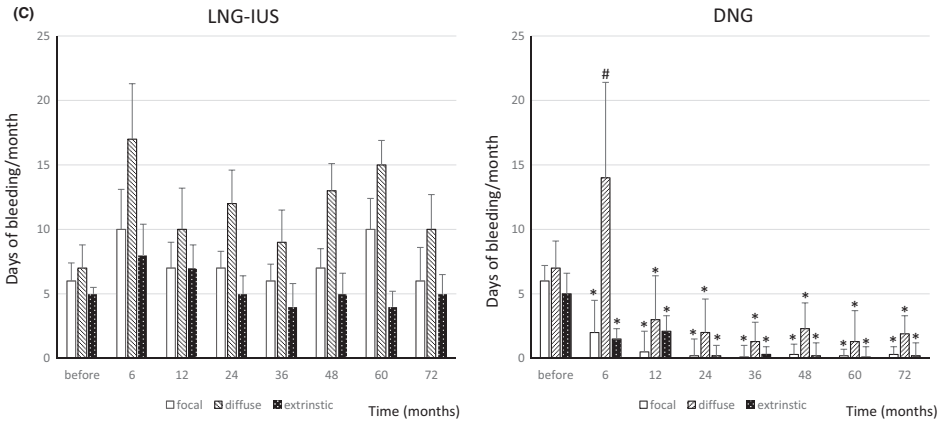
The most widespread hypothesis is that adenomyosis originates from invagination of the basalis level of the endometrium into the myometrium. An alternative theory maintains that adenomyotic lesions result from metaplasia of displaced embryonic pluripotent Müllerian remnants or differentiation of adult stem cells. Kishi et al.[5] showed that adenomyosis appears to consist of four distinct subtypes, that is, intrinsic, extrinsic, intramural, and indeterminate. The intrinsic adenomyosis could predict the risk of serious unpredictable bleeding during DNG treatment.[11] In addition, the patients with adenomyosis also frequently show endometriosis. Deep endometriosis is recognized as deeper lesions with a microscopic appearance resembling external adenomyosis.[12] Extrinsic type is defined as a direct infiltration into the outer shell of the uterus from pelvic endometriosis.[11] According to these theories and lesion morphology, we classified cases according to three different localizations of the adenomyosis: diffuse, focal, or extrinsic type (Table 1).

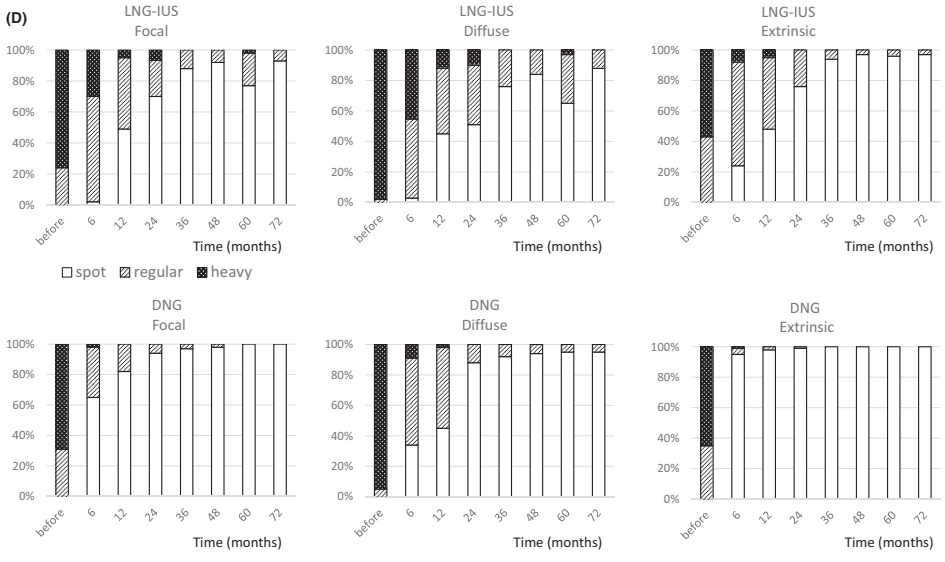
As shown in Figure 1, both progestins were similarly effective even after 60 months. With regard to pain relief, DNG was more stable than LNG-IUS, whereas DNG has the occurrence of uterine bleeding on account of forgetting to take the medicine. In terms of the days and extent of uterine bleeding (Figure 2), the efficacy of DNG was evident compared with LNG-IUS in all subtypes after 12 months of treatment. However, median number of days of bleeding in diffuse-type cases was 14 days a month after 6 months (Figure 2C). Statistical analysis showed that both LNG-IUS and DNG treatments for 12 months could reduce the size of the uterine body. Nevertheless, this effect appeared transient or

FIGURE 2 Comparison of (A) days or (B) volume of uterine bleeding since a month prior to treatment with LNG-IUS or DNG until 72 months. (C) days and (D) volume of bleeding were assessed by three different subtypes (focal, diffuse, and extrinsic) of adenomyosis. (A): open or closed squares indicate LNG-IUS or DNG treatment. (B) and (D): open, gray-shaded, and closed-dot bars indicate spotting, regular, and heavy amounts of bleeding, (C): focal, diffuse, and extrinsic types of adenomyosis, respectively. $^{*}p < 0.05$, $^{**}p < 0.01$: LNG/IUS vs. DNG at same point of time. $\#p < 0.05$: in each medicine among other two subtypes at same point of time


(A)
Days of bleeding/month
Time (months)
before
6
12
24
36
48
60
72
LNG-IUS
DNG
* p<0.05
** p<0.01


(B)
LNG-IUS
DNG
spot
regular
heavy


(C)
LNG-IUS
DNG
Days of bleeding/month
Time (months)
focal
diffuse
extrinstic
* P<0.05
# P<0.05


(D)
LNG-IUS Focal
LNG-IUS Diffuse
LNG-IUS Extrinsic
DNG Focal
DNG Diffuse
DNG Extrinsic
Time (months)
spot
regular
heavy

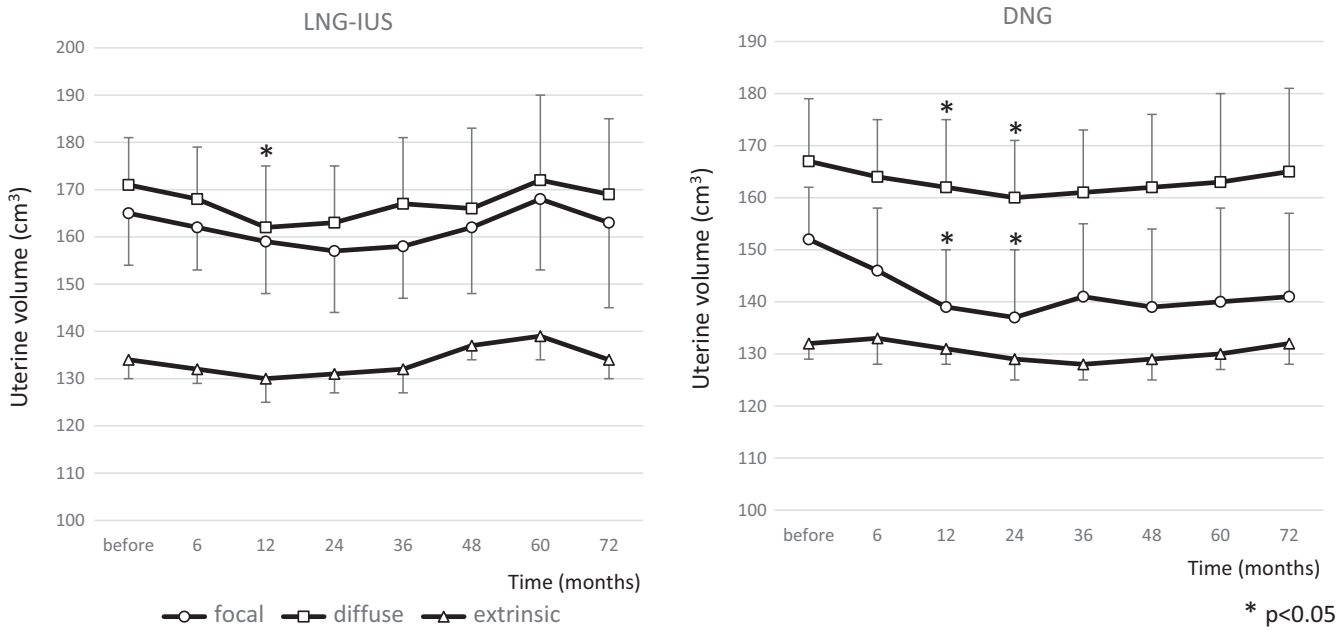


FIGURE 3 Volume of the uterine body treated with LNG-IUS or DNG in focal, diffuse, and extrinsic subtypes of adenomyosis for 72 months using three-dimensional transvaginal ultrasonography. *$p < 0.05$ vs. before treatment with LNG/IUS or DNG

insufficient compared with GnRHa (Figure 3). Of note, the cumulative decrease in bone mass, particularly at the lumbar spine, was not severe, and was considered to be an age-related change for 6 years (Figure 4B). Indeed, the cost for LNG-IUS is superior to that for DNG. After 5-year treatment, 17% of patients treated with DNG chose LNG-IUS for its low cost. On the contrary, 88% of patients treated with LNG-IUS selected DNG because of its effectiveness for next 5 years.

With regard to DNG administration for adenomyosis, a previous randomized, double-blinded, placebo-controlled trial for 16 weeks found significant decreases in pain and VAS scores.[8] Other studies from the same group evaluated the safety and efficacy of long-term DNG administration for 52 weeks or 2 years (especially, extrinsic type).[13,14] In particular, DNG could be effective for peri-menopausal or obese patients for whom OC/LEP use is unfavorable. Irregular uterine bleeding is a major problem in the treatment with DNG, but its frequency can be reduced with continuous administration.

On the other hand, LNG/IUS has been successfully used to treat adenomyosis to reduce menstrual blood loss and pain via reductions in thickness of the myometrial junctional zone and total uterine volume.[15,16] LNG-IUS guarantees a reduction in side effects caused by other oral treatments, in contrast with low serum hormonal levels, and locally high concentrations of LNG in the endometrium and adjacent tissues. In the current study, cases with worsening symptoms or enlargement of adenomyosis (mainly in diffuse type) required hysterectomy. Of note, patients showing the diffuse type warrant careful observation.

In case of large diffuse type, both LNG-IUS and DNG would not be suitable for the management. In this type, there is the possibility of atypical heavy uterine bleeding, because the uterus has no the sufficient normal myometrium. Hence, this large diffuse type should be treated with the surgical or other medical treatment. When the patients desire for the pregnancy, we should choose adenomyomectomy or GnRHa.

Several other therapies have been approved for treating adenomyosis. Although no randomized controlled trials have confirmed its efficacy for adenomyosis, OC/LEP is expected to decrease excessive menstrual bleeding and relieve pain in patients with adenomyosis by causing endometrial desquamation and atrophy. Due to coagulation and reactivation of the fibrinolytic system during menstruation in adenomyosis, the use of OC/LEP should be avoided in patients at risk of thrombosis, such as those who are obese, those who smoke, and the elderly.

Some limitations to this study must be considered. First, the present findings are limited by the controlled clinical trial, not the randomized controlled trial. Although the patients were randomized by the patient ID, this allocation method is not accurately recognized as a randomized controlled trial. Second, sample sizes in each group of cases were small, and the clinical data originated from a single hospital, not multiple centers. Larger, randomized clinical studies are needed to evaluate the clinical usefulness of medical treatment and to identify the most suitable targets.

In summary, we want to believe that the novel findings from this study classified into three different subtypes may provide worthwhile information for drug selection in controlled clinical trials investigating the treatment of adenomyosis. DNG and LNG-IUS could also provide cost-effective, reversible, long-term treatment for patients with adenomyosis, reducing the need for surgical intervention. To maintain the quality of life of women with adenomyosis at each stage of life, especially with the diffuse subtype, clinicians must select the most effective treatment.

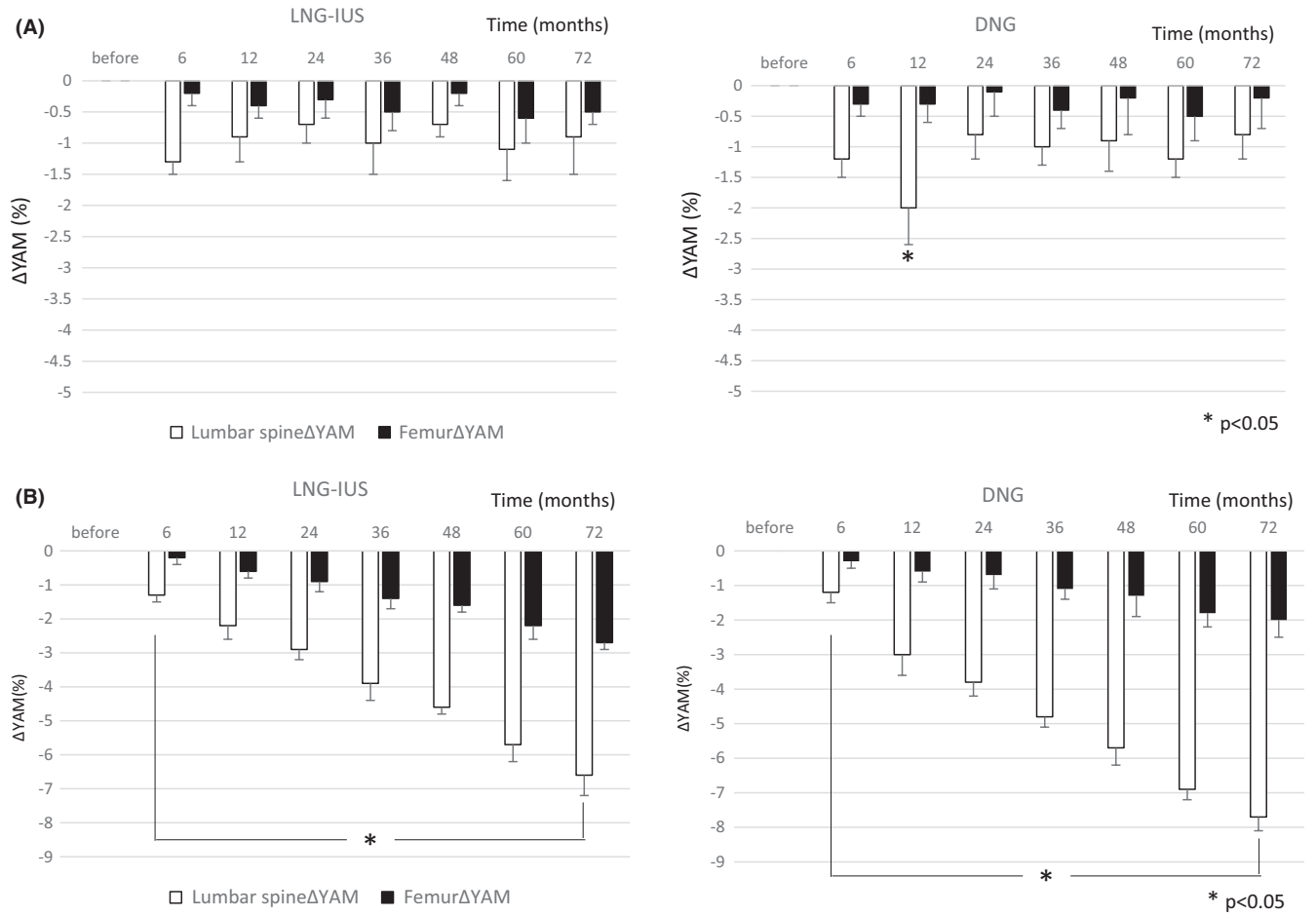


FIGURE 4 Assessment of bone mineral density (BMD) in the lumbar spine and femur by dual-energy X-ray absorptiometry. Values of BMD are determined as the percentage of the young adult mean (YAM). (A) annual reduction rates and (B) cumulative reduction rates of ΔYAM for 72 months were shown. *$p < 0.05$: (A) between LNG/IUS and DNG groups at same point of time, and (B) between 6 and 72 months of treatment in each group

TABLE 2 The number of cases interrupted the treatment with LNG-IUS or Dienogest

	LNG-IUS			Dienogest		
Cause of interruption	**focal**	**diffuse**	**extrinsic**	**focal**	**diffuse**	**extrinsic**
Severe IBS symptoms	0	0	3	0	0	4
Heavy uterine bleeding	2	4	0	1	5	0
Progression of adenomyosis	2	3	0	0	0	0
Progression of endometrioma	1	0	3	0	0	0
Expulsion of IUS	2	5	0	-	-	-
Decreased libido	0	0	0	1	2	1

Abbreviations: IBS, irritable bowel syndrome.

CONFLICTS OF INTEREST

Ikuko Ota, Fuminori Taniguchi, Yoshiaki Ota, Hiroki Nagata, Ikumi Wada, Takaya Nakaso, Ai Ikebuchi, Eri Sato, Yukihiro Azuma, and Tasuku Harada declare that they have no conflicts of interest.

HUMAN SUBJECTS

This study was approved by the Ethics Committee at Kurashiki Heisei Hospital (approval no. H25-015). The protocol for the research project including human subjects has been approved by a suitably constituted Ethics Committee.

ANIMAL SUBJECTS

This article does not contain any studies with animal subjects performed by any of the authors.

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