scientific reports

Check for updates

OPEN

Long-term clinical outcomes of dienogest for perimenopausal women with symptomatic adenomyosis

Chi-Hau Chen[1], Yi-Heng Lin[1], Chia-Yi Lee[2], Hung Shen[2], Ya-Ting Hsu[1] & Pei-Chi Wu[1,2]✉

We aimed to evaluate the successful long-term use of dienogest for the management of pelvic pain and bleeding control in perimenopausal women with symptomatic adenomyosis using real-world data. All women aged ≥ 40 years with adenomyosis who complained of dysmenorrhea and/or menorrhagia and received dienogest between September 2018 and December 2021 were retrospectively recruited. The primary outcome was successful long-term use of dienogest for pelvic pain and/or bleeding control. A total of 87 women were analyzed. Overall, forty-nine (56%) patients had excellent pain control, but 17 (20%) eventually underwent hysterectomy, while 21 (24%) received dienogest for over 24 months (mean 33.5 ± 8.5 months). According to subgroup analysis by age (≥ 45 vs. <45), older women easily discontinued dienogest due to side effects (51% vs. 30%, $p = 0.047$) but less frequently changed to surgery (11% vs. 30%, $p = 0.012$) than younger women. Older age, higher CA-125 value, and larger uterine size before treatment were linked to poorer long-term responses to dienogest. As risk factor, uterine volume > 352.7 cm^3 reflects easier treatment failure (sensitivity = 65.4%, specificity = 66.7%, area = 0.68, $p = 0.032$). In perimenopausal women with symptomatic adenomyosis, nearly half of the treated patients benefitted from dienogest. Our informative findings can assist clinicians in pre-treatment counseling and identifying factors correlated with treatment effectiveness.

Keywords Dysmenorrhea, Adenomyosis, Medical treatment, Uterine size, Dienogest

Adenomyosis is a benign gynecological disease caused by invasion of the endometrium into the myometrium[1]. It has been reported that the prevalence is 5–70%, and approximately 70–80% of patients with adenomyosis are 40 to 50 years old[2–4], i.e., in the perimenopausal stage. During perimenopause, patients with adenomyosis often experience the most severe symptoms, including progressive dysmenorrhea and hypermenorrhea, which can significantly impact their quality of life. Although hysterectomy has traditionally been the definitive treatment for patients with adenomyosis, medical management, as an alternative, should always be provided before invasive treatment[1,5].

The rationale for medical treatment is based on the biological similarity of adenomyosis to endometriosis. Several nonhormonal and hormonal therapies, including progestins, oral contraceptives, and gonadotropin-releasing hormone (GnRH) analogues, are currently used in adenomyosis[5]. Dienogest (DNG), a 19-nortestosterone derivative, is a progestin with high selectivity for progesterone receptors[6]. It is approved for the medical treatment of endometriosis, and several studies have supported its use in treating pain associated with adenomyosis[7–12]. While DNG is generally well tolerated[4], massive metrorrhagia remains a significant reason for discontinuing treatment[11].

Although some perimenopausal patients with severe adenomyosis do not have child-bearing plans, they still prefer conservative management for uterine preservation. This highlights the need for effective long-term treatment options for symptomatic adenomyosis to manage symptoms until menopause. While there have been several studies on the long-term use of DNG for endometriosis, only one study has examined the effects of DNG use for adenomyosis beyond two years[10]. Furthermore, no studies have specifically explored the use of DNG in perimenopausal women. In this study, we investigated the clinical outcomes of real-world cases of DNG use in perimenopausal women over 40 with symptomatic adenomyosis. Specifically, we aimed to evaluate the efficacy

[1]Department of Obstetrics and Gynecology, National Taiwan University College of Medicine and Hospital, No. 8, Zhongshan S. Rd., Zhongzheng Dist, 100225 Taipei City, Taiwan (R.O.C.). [2]Department of Obstetrics and Gynecology, National Taiwan University Hospital, Hsin-Chu Branch, No. 25, Ln. 442, Sec. 1, Jingguo Rd., North Dist, 300195 Hsinchu City, Taiwan (R.O.C.). ✉email: peggywu0707@hotmail.com

of DNG in the long-term management of pelvic pain and bleeding and to identify predictors associated with successful long-term use of DNG in this population. According to previous studies, menstrual cycles were noted to become increasingly irregular with age, particularly after age 45[13,14]. Based on this, our cohort was further allocated into a younger group (more or equal to 40 years old and less than 45 years old) and an older group (more or equal to 45 years old to menopause).

Results

A. Baseline characteristics

A total of 87 women were included in this study. The mean age when they first took DNG was 45.8 years, the mean drug duration was 12.9 (range 1–50) months, and the mean follow-up was 20.9 months. Their demographics and disease characteristics are summarized in Table 1. The major indication for DNG treatment was dysmenorrhea. Thirty-seven women (43%) had pretreatment anemia with a hemoglobin (Hb) value < 11 g/dL. Over half (52%) of the treated women maintained DNG treatment for more than six months. An excellent treatment response for dysmenorrhea was reported in 49/87 (56%) patients.

Among the 87 women, 40 were younger than 45 years old and had significantly lower parity (0.8 [range 0–2] vs. 1.6 [range 0–5], $p < 0.001$), and the other 47 were older than 45 but had not yet reached menopause (Table 1). There was no difference in the dominant clinical symptoms between the younger and older groups, nor in the VAS scores and Hb levels. After comparing the treatment duration between subgroups, the symptom improvement or drop-out rate for DNG treatment was not significantly different. However, the older women more easily discontinued DNG due to side effects than the younger women (51% vs. 30%, $p = 0.047$). On the other hand, the younger group was more likely to choose surgery when encountering side effects or ineffective treatment, leading to a significantly higher surgical rate than in the older group (33% vs. 11%, $p = 0.012$).

Variables	All ($n = 87$)	≥40–<45y/o ($n = 40$)	≥45–<54 y/o ($n = 47$)	p[b]
Age (years)	45.8 ± 3.6	42.5 ± 1.6	48.5 ± 2.4	-
Parity [a]	1.2 (0–5)	0.8 (0–2)	1.6 (0–5)	0.001*
Body mass index (kg/m^2)	23.0 ± 4.0	23.6 ± 5.0	22.5 ± 2.7	0.228
Cesarean section	20 (23)	10 (25)	10 (21)	0.685
Dominant symptom				
Dysmenorrhea	79 (91)	38 (95)	41 (87)	0.279
Hypermenorrhea	8 (9)	2 (5)	6 (13)	
Other sonographic finding				
Ovarian cyst	8 (9)	7(18)	1 (2)	0.053
myoma	30 (35)	14 (35)	16 (34)	
Cyst and myoma	7 (8)	4 (10)	3 (6)	
Previous medication				
Oral pills (≥ 3 months)	12 (14)	3 (8)	9 (19)	0.134
LNG-IUS	9 (10)	2 (5)	7 (15)	0.170
GnRH-a	10 (12)	2 (5)	8 (17)	0.100
Pretreatment baseline				
VAS (cm)	7.0 ± 2.0	7.1 ± 1.9	6.9 ± 2.0	0.748
CA-125 (U/mL)	91.3 ± 81.1	98.6 ± 95.1	85.2 ± 67.7	0.463
Hb (g/dL)	10.6 ± 2.3	10.6 ± 2.3	10.6 ± 2.4	0.973
E2 (pg/mL)	134.4 ± 89.2	151.2 ± 100.7	127.4 ± 85.3	0.487
FSH (mIU/mL)	8.9 ± 8.0	7.0 ± 2.3	9.7 ± 9.3	0.376
Treatment duration (months)				
≤ 6	42 (48)	17 (43)	25 (53)	0.391
> 6	45 (52)	23 (57)	22 (47)	
Follow-up duration (months)	20.9 ± 13.5	21.3 ± 14.5	20.5 ± 12.7	0.788
Pain improved sufficiently	49 (56)	25 (63)	24 (51)	0.194
Stop due to side effects	36 (41)	12 (30)	24 (51)	0.047*
Change to surgery	18 (21)	13 (33)	5 (11)	0.012*

Table 1. Baseline characteristics of women aged more than 40-year-old, receiving dienogest for adenomyosis-related dysmenorrhea and/or hypermenorrhea ($n = 87$). Note: Data presented as mean ± standard deviation, or number (percentage). DNG: dienogest; LNG-IUS: levonorgestrel-releasing intrauterine system; GnRH-a: gonadotropin-releasing hormone agonist; CA-125: cancer antigen 125; Hb: hemoglobulin; E2: estradiol; FSH: follicle stimulating hormone; VAS: visual analogue scale. [a] Data presented as mean (range). [b] Subgroup comparison: ≥40–<45y/o vs. ≥45–<54 y/o. * Statistically significant difference.

B. **Dominant reason for stopping DNG treatment**

Discontinuation of DNG was observed in 14 (16%) women due to ineffectiveness and 22 (25%) due to side effects, including uncontrolled bleeding, headache, and depression. 41% (12/29) of patients with ineffective treatment or uncontrolled bleeding eventually shifted to surgical management. The dominant reasons for discontinuing DNG treatment for adenomyosis in different treatment windows among the perimenopausal women are shown in Table 2. Forty-two (48%) women chose to drop out from treatment by six months. Of the 87 women, 42 (48%) discontinued DNG within 6 months, primarily due to ineffective treatment ($n = 10$, 11%) or intolerable side effects ($n = 18$, 22%). In contrast, among those who discontinued DNG after more than 6 months ($n = 6$, 7% of the total population and 32% of this subgroup), the main reasons were symptomatic improvement or reaching menopause.

C. **Comparison between successful and failed long-term use of DNG**

Among the 45 women who continued treatment for more than six months, the mean duration of DNG treatment was 22.2 ± 12.4 (range 7–50) months, and the mean VAS score decreased from 7.2 ± 2.1 cm at baseline to 1.6 ± 1.8 cm at 6 months of treatment. Twenty-five women were still undergoing DNG treatment when this study began its analysis, indicating that they were highly satisfied with the efficacy of DNG. Furthermore, 28 women continued with DNG treatment for more than one year; of them, 21 women indicated good control of their symptoms and used the treatment for more than two years (mean 33.5 ± 8.5 months). On the other hand, 26 patients discontinued DNG less than 12 months due to ineffective pain control ($n = 11$) or uncontrolled bleeding ($n = 15$). To determine the risk factors affecting the continuation of DNG treatment for symptomatic adenomyosis, we compared the 21 patients who had successful long-term use of DNG for symptomatic adenomyosis with the 26 patients who failed to maintain treatment because of pain or bleeding. As shown in Table 3, the women whose symptoms were not controlled well with DNG were older (47.1 ± 4.0 vs. 44.4 ± 3.1 years, $p = 0.008$). Both groups had significant VAS score decreases after treatment; however, the reduction was more prominent in the successful group (-2.1 ± 2.7 vs. -5.8 ± 2.4, $p < 0.001$). The pretreatment CA-125 level was significantly higher in the failed group than in the successful group (109.9 ± 90.6 vs. 61.2 ± 37.4 U/mL, $p = 0.029$), as was the uterine volume (353.1 ± 209.0 vs. 1241.7 ± 123.0 cm^3, $p = 0.036$).

D. Predictors for successful long-term use of DNG

Univariate logistic regression identified younger age (odds ratio [OR] 0.80, 95% confidence interval [CI] 0.66–0.95, $p = 0.013$), lower pretreatment CA-125 levels (OR 0.99, 95% CI 0.98–1.00, $p = 0.042$), and smaller uterine size (OR 0.99, 95% CI 0.99–1.00, $p = 0.044$) as predictors for the successful long-term use of DNG. Notably, there was a moderate correlation between pretreatment CA-125 levels and uterine size (Pearson correlation coefficient = 0.52, $p < 0.001$). Thus, a larger sample size may be required for a definitive multivariate analysis. Receiver operating characteristic (ROC) curve analysis using the pretreatment uterine size as a predictor revealed that 352.7 cm^3 was an optimal cut-off value (sensitivity = 65.4%, specificity = 66.7 area = 0.68. As shown in Tables 3 and 19 (90.5%) women who successfully used long-term DNG had a uterine volume of less than 352.7 cm^3.

	All ($n = 87$)	≤ 6 m	> 6 m
Stopping treatment	**61 (70)**	**42 (48)**	**19 (21)**
Reasons			
Ineffective treatment	14 (16)	10 (11)	4 (5)
Side effect	22 (26)	18 (22)	4 (5)
Uncontrolled bleeding	15 (17)	12 (14)	3 (3)
Headache	6 (7)	5 (6)	1 (1)
Depression	1 (1)	1 (1)	0
Others	17 (20)	12 (14)	5 (6)
Medical diseases	4 (5)	3 (4)	1 (1)
Breast cancer	1 (1)	1 (1)	0
Ovarian cyst or myoma enlarging	5 (6)	1 (1)	4 (5)
Give up or worry about long-term side effects	7 (8)	7 (8)	0
Improvement of symptoms or till menopause	8 (9)	2 (2)	6 (7)
Changing to surgery	**18 (21)**	**12 (14)**	**6 (7)**
Reasons			
Ineffective treatment or massive bleeding	12 (14)	10 (11)	2 (2)
Enlarging ovarian cyst or myoma	5 (6)	1 (1)	4 (5)
Other reason	1 (1)	1 (1)	0

Table 2. Dominant reason for stopping dienogest treatment and surgery in different treatment windows for women aged more than 40-year-old ($n = 87$). Note: Data are presented as number (percentage). m: month.

	Failed long-term use ($n=26$)	Successful long-term use ($n=21$)	p
Age (years)	47.1 ± 4.0	44.4 ± 3.1	0.008 *
Parity	1.4 ± 1.1	1.2 ± 0.9	0.607
Body mass index (kg/m^2)	23.6 ± 5.2	23.1 ± 2.9	0.670
Duration (months)	4.2 ± 3.1	33.5 ± 8.5	< 0.001 *
Dominant symptom			
Dysmenorrhea	21 (80.8)	19 (90.5)	0.307
Hypermenorrhea	5 (19.2)	2 (9.5)	
Sonographic figures of adenomyosis			
Main lesion in posterior uterine wall	8 (30.8)	8 (38.1)	0.758
Diffuse type	8 (30.8)	4 (19.0)	0.505
Other sonographic finding			
Ovarian cyst	1 (3.8)	5 (23.8)	0.138
Myoma	11 (44.3)	5 (23.8)	
Cyst and myoma	1 (3.8)	2 (9.5)	
VAS (cm)			
Baseline	6.6 ± 1.9	7.1 ± 2.2	0.508
DNG-treated	4.5 ± 2.7	1.3 ± 1.4	< 0.001 *
Change from baseline	-2.1 ± 2.7 *	-5.8 ± 2.4 *	< 0.001 *
Hb (g/dL)			
Basal	10.5 ± 2.3	10.2 ± 2.5	0.707
DNG-treated	10.2 ± 2.6	12.3 ± 1.4	0.017 *
Change from basal	0.9 ± 2.6	2.8 ± 2.4 *	0.088
Pretreatment			
CA-125 (U/mL)	109.9 ± 90.6	61.2 ± 37.4	0.029 *
E2 (pg/mL)	125.8 ± 95.5	133.9 ± 132.9	0.894
FSH (mIU/mL)	10.6 ± 11.2	6.1 ± 2.3	0.447
Uterine volume (cm^3)	353.1 ± 209.0	241.7 ± 123.0	0.036 *
Predictor of failure			
Uterine volume > 352.7 (cm^3)	19 (73.1)	2 (9.5)	0.032 *

Table 3. Comparison between successful and failed long-term use of dienogest for dysmenorrhea and/or hypermenorrhea control in women aged more than 40-year-old with adenomyosis ($n=47$). Note: Data presented as mean ± standard deviation, or number (percentage). DNG: dienogest; LNG-IUS: levonorgestrel-releasing intrauterine system; GnRH-a: gonadotropin-releasing hormone agonist; CA-125: cancer antigen 125; Hb: hemoglobulin; E2: estradiol; FSH: follicle stimulating hormone; VAS: visual analogue scale. * Statistically significant difference.

Discussion

Although some perimenopausal patients with severe adenomyosis do not have child-bearing plans, they still prefer conservative management for uterine preservation. The primary treatment goals for them are adequate symptom relief and improved quality of life. In our real-world data study, we found that over half (45/87) of women continued DNG treatment for more than 6 months, with 33% (29/87) maintained the treatment for more than 12 months. Overall, 56% (49/87) of patients achieved excellent pain control. Most importantly, when evaluating pretreatment factors, larger uterine size (uterine volume > 352.7 cm^3) was a predictor of treatment discontinuation.

Emerging data suggest that DNG is well-tolerated in the systemic treatment of adenomyosis[7–12], though massive metrorrhagia remains a major reason for discontinuation[11]. While these studies have provided promising data, most were conducted over shorter durations and on highly selective patient populations, often excluding those with uterine or ovarian neoplasms, severe anemia, or significantly enlarged uteri. However, adenomyosis frequently coexists with these comorbidities, and these conditions should be considered in the management plan[15]. Our case series included 10 women with severe anemia, 45 with uterine myoma or ovarian cysts, and 31 with a maximum uterine dimension > 10.0 cm, which may be the reason for the lower treatment response rate and higher discontinuation rate in our study than in previous studies. Importantly, by not excluding these patients, our findings more accurately reflect real-world clinical practice.

Our study showed thirteen women (15%) discontinued DNG due to ineffective treatment for dysmenorrhea or even aggravated pain. Similarly, in a safety cohort of 122 women with endometriosis, 14 (11.5%) participants discontinued DNG due to ineffectiveness[16]. In our study, DNG could maintain low VAS scores during drug use in women who achieved successful long-term treatment. Even among those who eventually discontinued treatment, DNG was effective in reducing VAS scores. The degree of VAS score reduction in both groups

underscores DNG's efficacy for dysmenorrhea management. However, patients who discontinued the medication may not have achieved their desired level of pain relief and often proceeded with surgical interventions.

Irregular uterine bleeding is the most common side effect, while the other frequently reported adverse effects of DNG, such as headache, acne, nausea, weight gain, breast tenderness, depressed mood, and flatulence, are generally mild-to-moderate and have minimal impact on treatment discontinuation rates[17]. In our study, the most common adverse effect of DNG was vaginal spotting, which was often self-limited and did not require additional treatment. However, there were 16 (18%) women with uncontrolled bleeding who needed to stop DNG, which may be due to the perimenopausal period as a risk factor for abnormal bleeding[18], as well as extremely enlarged uteri[12]. A variety of symptoms in the perimenopausal period present with not only irregular bleeding but also psychological symptoms and vasomotor symptoms[19]. The fluctuation in estrogen levels in perimenopause may cause hormonal headaches, which may become more severe during DNG treatment. In our perimenopausal population, women over 45 years old who experienced increased headaches or migraines were more likely to discontinue DNG.

In the post marketing surveillance of the efficacy of DNG for treating adenomyosis, severe metrorrhagia frequently occurred in women with extremely enlarged uteri. Therefore, a length of the corpus uteri of 10 cm or more was set as an exclusion criterion for using DNG in previous studies[8,12]. However, this criterion has not been statistically examined. Our study found that a uterine volume > 352.7 cm^3 was a predictor for early treatment failure, consistent with previous studies that have indicated that a larger uterine volume is an unfavorable factor for treatment outcomes[8,12,20]. However, the sonographic types of adenomyosis, including posterior uterine lesion or diffuse type, did not differ significantly between our successful and failed long-term treatment groups. Our study also revealed that once a woman could continue the treatment for more than 6 months, there was a greater possibility of maintaining long-term treatment for symptom control. Since intolerable bleeding was the most common side effect, premedication or adjuvant therapy, such as GnRH agonists, can be applied along with DNG to decrease uterine size, control bleeding, and achieve long-term DNG treatment.

In addition to uterine size, other reported risk factors for metrorrhagia during DNG treatment include younger age, severe anemia before treatment, elevated CA-125 levels, and high pain scores[11,21]. The women in our study were all in perimenopause, with a median age of 45.8 years, suggesting that excessive bleeding and prolonged periods are more likely to exacerbate DNG's side effects in perimenopausal period. Interestingly, we found that a pretreatment CA-125 level less than or equal to 98.8 U/mL was a low-sensitivity (46.2%) but high-specificity (90.0%) predictor of successful long-term DNG treatment without abnormal bleeding. This suggests that patients with lower CA-125 levels may be more likely to tolerate the treatment successfully. In our study, univariate analysis identified older age, elevated CA-125 levels, and larger uterine size as risk factors for the failure of long-term DNG use. Although these factors did not achieve significance in multivariate analysis due to the limited sample size, our real-world data still provide valuable insights. Further validation in larger cohorts is required.

DNG does not suppress the basic secretion of gonadotropins, such as FSH and luteinizing hormone (LH), and has a moderate effect on the suppression of estrogen secretion[22]. A study of patients in Japan who were taking DNG (2 mg/day) recorded estradiol (E2) levels of 42.1 ± 50.7 pg/mL after 16 weeks[8]. However, the existing data on hormonal changes in women taking DNG are from relatively young, regularly menstruating women. In contrast, the post-treatment E2 levels in our study were notably higher than those reported in previous studies. In the failed long-term treatment group, the E2 levels were 82.9 ± 32.7 pg/mL, while in the successful long-term treatment group, they were 87.3 ± 114.4 pg/mL. This suggests that the inhibitory effect of DNG on estrogen levels may vary with age, particularly in perimenopausal women. Given the fluctuating estrogen levels, estrogen-dependent lesions such as uterine myomas and ovarian endometriomas may grow. In fact, five women in our study experienced tumor enlargement during DNG treatment, including 2 cases of myoma, 2 ovarian cysts, and 1 ovarian cancer, which necessitated a shift to surgical intervention. These findings highlight the importance of follow-up sonography during DNG treatment to monitor for potential tumor growth.

This study was designed in a setting where both DNG treatment and surgeries for adenomyosis were financially supported by the National Health Insurance (NHI). This allowed patients to freely choose between conservative management and surgery, based on tolerance and treatment success, without financial constraints. Consequently, the data from this study more accurately reflect real-world clinical conditions and patient preferences, offering reliable insights into the use of DNG for adenomyosis in perimenopausal women.

The retrospective and single-center design of this study are its major limitations. However, the relatively large sample size lends reliability to our findings, providing valuable insights for treatment counseling. To strengthen the evidence further, external validation with a prospectively designed study would be essential for a deeper understanding of symptom control, adverse effects, and reasons for treatment discontinuation.

Conclusions

Half of the perimenopausal women (≥ 40 years) with symptomatic adenomyosis benefited from DNG treatment. Older women tended to discontinue DNG more frequently due to side effects, although they transitioned to surgery less often compared to younger women. Specifically, smaller pretreatment uterine sizes were associated with better symptom control and longer-term use of DNG. This study supports the use of DNG as a viable alternative treatment for symptomatic adenomyosis and provides valuable insights for treatment counseling, particularly in identifying factors that correlate with treatment effectiveness.

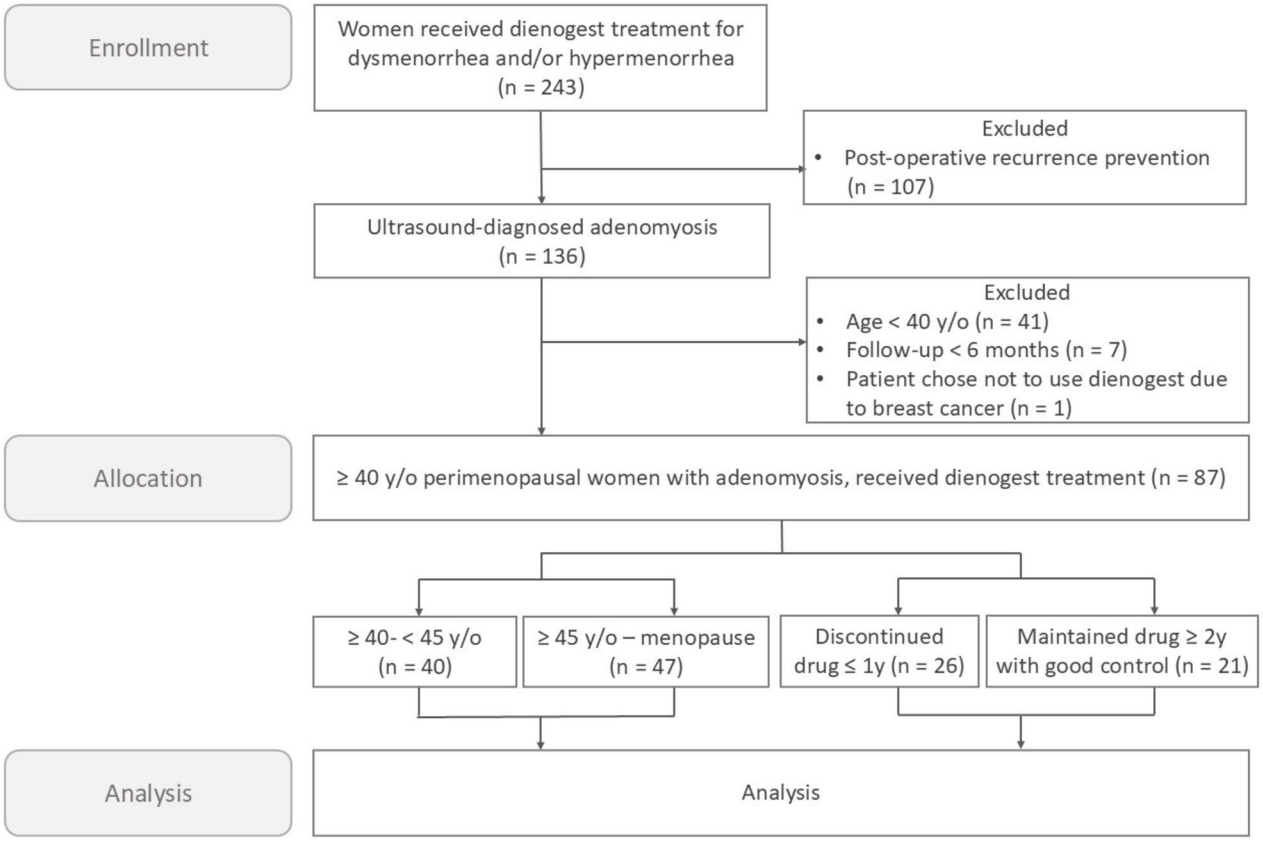

Fig. 1. Flowchart of patient selection and analysis. The flowchart illustrates the selection process for patients included in the study. Patients were analyzed based on age groups (younger group: 40–44 years old, and older group: ≥45 years old to menopause) and categorized according to their treatment outcomes (those who either "successfully maintained long-term DNG treatment ≥ 2 years for bleeding and pain control" or "discontinued drug ≤ 1 year due to abnormal bleeding or poor pain control").

Materials and methods

A retrospective chart review of women who did not want further childbearing and were newly prescribed DNG treatment for dysmenorrhea and/or hypermenorrhea between September 2018 and December 2021 was conducted in a tertiary referral center in Taiwan.

A total of 243 women were included. The study flow chart is shown in Fig. 1. Indications for DNG treatment were analyzed, and 107 women prescribed DNG for short-term preoperative control or postoperative prevention of endometriosis recurrence were excluded[23]. Women younger than 40, those with a posttreatment follow-up duration of fewer than six months, and those with conditions unsuitable for DNG treatment, such as known breast cancer, high thromboembolic effects, and smoking, were also excluded. Finally, this cohort study was conducted on 87 available subjects. According to previous studies, menstrual cycles were noted to become increasingly irregular with age, particularly after 45[13,14]. Thus, our cohort was further allocated into a younger group (more or equal to 40 years old and less than 45 years old) and an older group (more or equal to 45 years old to menopause). For the specific sub-analysis comparing the risk factors for long-term treatment success versus treatment failure due to pain or bleeding, only the 47 patients who met the inclusion criteria (those who either "successfully maintained long-term DNG treatment ≥ 2 years for bleeding and pain control" or "discontinued drug ≤ 1 year due to abnormal bleeding or poor pain control") were included. The remaining 40 cases that did not meet these criteria were excluded from this sub-analysis (Fig. 1). The baseline demographic data included age, parity, method of delivery, and body mass index. Sonographic findings of adenomyosis, uterine size, and other gynecological lesions were recorded. A detailed history, examination, and transvaginal sonography (TVS) evaluation were carried out on the first visit. Diagnosis of adenomyosis using TVS based on the Morphological Uterus Sonographic Assessment (MUSA) statement included globular uterine enlargement in the absence of leiomyoma, asymmetric enlargement of the anterior or posterior wall, cystic anechoic lakes or spaces in the myometrium, irregular junctional zone between myometrium and endometrium and subendometrial echogenic linear striations[24]. **Supplement 1** is an example of ultrasound features of adenomyosis. After identifying adenomyosis, the uterine volume was assessed using the formula for an ovoid (length × width × depth × 0.52).

The primary outcome was the successful long-term (i.e., more than 2 years) use of dienogest for the control of pelvic pain and/or bleeding. For women with symptomatic adenomyosis, the pain scales and pretreatment data, including hormonal status, complete blood cell counts, liver function tests, and cancer antigen 125 (CA-125)

level as an indicator of endometriosis, were recorded. Pain was assessed by using a visual analogue scale (VAS), where the pain scale is subdivided into ten grades; "no pain" is indicated on the left side of the scale, and "the maximum pain you could imagine" is designated on the right side of the scale. Previous conservative treatment for adenomyosis was also reviewed. DNG 2 mg (Visanne, Bayer, Leverkusen, Germany) was prescribed orally once per day after completing the abovementioned exam. The patient returned to our clinic in the 1st, 3rd, and 6th months of the treatment course and then every three months for a prescription. During the treatment, blood tests and pelvic sonography were performed every six months. In addition, a personal interview was conducted for treatment effect evaluation and adverse effect management. Once the patient decided to discontinue the treatment, the follow-up started. The posttreatment follow-up interval was defined as the time frame between the day the patient stopped DNG treatment and her last visit on the medical record. If necessary, the follow-up included clinical symptoms of adenomyosis and laboratory or sonographic data. Menopause was defined when the follicle-stimulating hormone (FSH) level was more than 30 mIU/mL in the presence of menopausal symptoms, such as hot flashes, and no menstrual bleeding occurred after stopping dienogest for a year.

SPSS Software (version 22, IBM, Armonk, NY, USA) was used for statistical analyses. The independent t-test and ANOVA were applied for normally distributed data, while the Mann–Whitney U test and Kruskal–Wallis test were used for non-normally distributed data, as appropriate for baseline characteristic comparisons. Chi-Square and Fisher's Exact Test were used to evaluate the association between two categorical variables. A value of less than 0.05 was considered statistically significant. The binary logistic regression analysis was performed for predictors of long-term DNG use. Missing data was excluded from the analysis.

This study received approval from the Research Ethics Committee (ID NO.202207140RINB) of the National Taiwan University Hospital and was performed in accordance with relevant guidelines and regulations. Additionally, this study was registered at ClinicalTrials.gov with the identifier NCT05751876, URL: https://classic.clinicaltrials.gov/ct2/show/NCT05751876. Because of a retrospective study, there were only verbal inform consents before the examinations and medications. Due to the retrospective nature of the study, the Research Ethics Committee of the National Taiwan University Hospital waived the need of obtaining informed consent.

Data availability

All the raw datasets generated during the current study are available from the corresponding author on reasonable request.

Received: 25 December 2023; Accepted: 5 March 2025
Published online: 10 March 2025

References

1. Vercellini, P., Viganò, P., Somigliana, E. & Fedele, L. Endometriosis: pathogenesis and treatment. *Nat. Rev. Endocrinol.* **10**, 261–275 (2014).
2. Graziano, A. et al. Diagnostic findings in adenomyosis: a pictorial review on the major concerns. *Eur. Rev. Med. Pharmacol. Sci.* **19**, 1146–1154 (2015).
3. Harada, T. et al. The impact of adenomyosis on women's fertility. *Obstet. Gynecol. Surv.* **71**, 557–568 (2016).
4. Naftalin, J. et al. How common is adenomyosis? A prospective study of prevalence using transvaginal ultrasound in a gynaecology clinic. *Hum. Reprod.* **27**, 3432–3439 (2012).
5. Vannuccini, S., Luisi, S., Tosti, C., Sorbi, F. & Petraglia, F. Role of medical therapy in the management of uterine adenomyosis. *Fertil. Steril.* **109**, 398–405 (2018).
6. Sasagawa, S. et al. Dienogest is a selective progesterone receptor agonist in transactivation analysis with potent oral endometrial activity due to its efficient Pharmacokinetic profile. *Steroids* **73**, 222–231 (2008).
7. Hirata, T. et al. Efficacy of dienogest in the treatment of symptomatic adenomyosis: a pilot study. *Gynecol. Endocrinol.* **30**, 726–729 (2014).
8. Osuga, Y., Fujimoto-Okabe, H. & Hagino, A. 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. *Fertil. Steril.* **108**, 673–678 (2017).
9. Osuga, Y., Watanabe, M. & Hagino, A. Long-term use of dienogest in the treatment of painful symptoms in adenomyosis. *J. Obstet. Gynaecol. Res.* **43**, 1441–1448 (2017).
10. Neriishi, K. et al. Long-term dienogest administration in patients with symptomatic adenomyosis. *J. Obstet. Gynaecol. Res.* **44**, 1439–1444 (2018).
11. Nagata, C. et al. Risk factors of treatment discontinuation due to uterine bleeding in adenomyosis patients treated with dienogest. *J. Obstet. Gynaecol. Res.* **38**, 639–644 (2012).
12. Miao, J., Lu, J., Tang, J. & Lu, P. Long-term treatment of dienogest with symptomatic adenomyosis: retrospective analysis of efficacy and safety in clinical practice. *Gynecol. Endocrinol.* **38**, 656–660 (2022).
13. Kaufert, P. A., Gilbert, P., Tate, R. & P., & Defining menopausal status: the impact of longitudinal data. *Maturitas* **9**, 217–226 (1987).
14. Gracia, C. R. & Freeman, E. W. Onset of the menopause transition: the earliest signs and symptoms. *Obstet. Gynecol. Clin. North. Am.* **45**, 585–597 (2018).
15. Taran, F. A., Weaver, A. L., Coddington, C. C. & Stewart, E. A. Characteristics indicating adenomyosis coexisting with leiomyomas: a case-control study. *Hum. Reprod.* **25**, 1177–1182 (2010).
16. Nirgianakis, K. et al. Risk factors for non-response and discontinuation of dienogest in endometriosis patients: A cohort study. *Acta Obstet. Gynecol. Scand.* **100**, 30–40 (2021).
17. Strowitzki, T. et al. Safety and tolerability of dienogest in endometriosis: pooled analysis from the European clinical study program. *Int. J. Womens Health.* **7**, 393–401 (2015).
18. Delamater, L. & Santoro, N. Management of the perimenopause. *Clin. Obstet. Gynecol.* **61**, 419–432 (2018).
19. Guerin, J., Engelmann, A., Mattamana, M. & Borgelt, L. M. Use of hormonal contraceptives in perimenopause: A systematic review. *Pharmacotherapy* **42**, 154–164 (2022).
20. Ono, N. et al. Evaluating the safety of dienogest in women with adenomyosis: A retrospective analysis. *J. Obstet. Gynaecol. Res.* **47**, 1433–1440 (2021).
21. Kobayashi, H. & Imanaka, S. Proposal for developing treatment algorithms of women with symptomatic adenomyosis: A single-center experience. *J. Obstet. Gynaecol. Res.* **47**, 3257–3268 (2021).

22. Sasagawa, S. et al. Dienogest, a selective progestin, reduces plasma estradiol level through induction of apoptosis of granulosa cells in the ovarian dominant follicle without follicle-stimulating hormone suppression in monkeys. *J. Endocrinol. Invest.* **31**, 636–641 (2008).
23. Chiu, C. C. et al. Maintenance therapy for preventing endometrioma recurrence after endometriosis resection surgery - A systematic review and network meta-analysis. *J. Minim. Invasive Gynecol.* **29**, 602–612 (2022).
24. Van den Bosch, T. et al. Terms, definitions and measurements to describe sonographic features of myometrium and uterine masses: a consensus opinion from the morphological uterus sonographic assessment (MUSA) group. *Ultrasound Obstet. Gynecol.* **46**, 284–298 (2015).

Author contributions

CH Chen: Study design, Data collection, and Manuscript editing. YH Lin: Data collection.CY Lee: Data collection.H Shen: Data collection. YT Hsu: Data collection. PC Wu: Manuscript writing, Statistical analysis. All authors reviewed the manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-93156-5.

Correspondence and requests for materials should be addressed to P.-C.W.