Original Article

The Role of Dienogest in the Short-Term Treatment of Endometriosis in Young Women

Arzoo S[1], Akter MS[2], Begum NJ[3], Jannat F[4], Naher K[5], Alam MB[6]

Abstract

Background: *Endometriosis is a long-term, benign, recurrent, debilitating disease experienced by women. Endometriosis associated pelvic pain (EAPP) is the most common complaint reported by patients with the condition. Nearly 70% of females with endometriosis present with EAPP while endometrioma are found in 17-44% of patients. The purpose of the study is to investigate the efficacy and safety of Dienogest as medical therapy to these patients.* ***Materials and Methods:*** *This prospective observational study was carried out in the department of Obstetrics & Gynecology of Eastern Medical College & Hospital from January to December 2023. A total of 96 patients with the age range of 15–35 years with complaints of pain and diagnosed as endometriosis by ultrasonogram were included. All the patients were treated by Dienogest 2 mg orally. The effects of treatment were determined by seeing the resolution of pain and decreasing the size of endometrioma. Patients were followed up in the 1st and 3rd months.* ***Results:*** *Out of 96 patients 72 reported their pain relief within 10-15 days after starting Dienogest. Out of 71 patients who had severe pain at enrollment only 3% had severe pain after 1 month and 1% had severe pain after 3 months of treatment with Dienogest. Successful reduction in endometriotic cyst size (>50%) was seen in 18 (18.75%) at the end of 1 month with Dienogest. At the end of 3 months 24 patients (25.0%) had significant cyst size reduction (>50%) with Dienogest. Complete disappearance of endometriomas was seen in 10 patients (10.41%). No major side effects after 3 months of treatment.* ***Conclusion:*** *Dienogest is a well-tolerated drug for endometriosis. It shows significant relief of pain. However, it was observed that the endometrioma did not grow further, but it did not show significant regression either. It is well tolerated with favorable safety profile.*

Keywords: Endometriosis, Dienogest, Short-term treatment.
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Introduction

Endometriosis is a chronic, recurring and debilitating condition that affects around 5–10% of women. Although the exact cause of endometriosis is still unknown, its hallmark characteristic is the growth of functional endometrial tissue outside the uterus. The most common symptom of endometriosis is pain, which can manifest in various forms, such as dysmenorrhea, dyspareunia, and lower back pain and this pain is the primary reason why women seek medical help[1]. Endometriosis is a benign disease-causing symptoms of pelvic pain, dysmenorrhea and dyspareunia that often relapse after surgical therapy[2]. The aim of most medical therapies is to decrease the symptoms to improve the quality of life. Approved medical treatments for managing endometriosis symptoms include gonadotropin-releasing hormone (GnRH) analogs and the androgen danazol. However, both treatment options are linked to safety and tolerability concerns, which restrict their long-term use[3]. Various progestins provide long-lasting effectiveness, but depending on their pharmacological characteristics, they may lead to weight gain or androgenic side effects when used at the higher doses necessary for optimal effectiveness[4].

Norethisterone acetate, a potent progestin derivative of 19-norethisterone, is also effective for use in patients with endometriosis[5]. However, its primary side effects include breast tenderness, weight gain, acne, hirsutism, and breakthrough bleeding. Levonorgestrel (LNG) has also been used for treating women with symptomatic minimal-to-moderate endometriosis[6], leading to improvements in the severity and frequency of pain and menstrual symptoms. The levonorgestrel intrauterine device (LNG-IUD) is an effective treatment for recto

[1]Shabera Arzoo, Professor, Dept. of Gynaecology & Obstetrics, Eastern Medical College & Hospital, Cumilla, Bangladesh.
[2]Musammat Shamima Akter, Professor, Dept. of Gynaecology & Obstetrics, Eastern Medical College & Hospital, Cumilla, Bangladesh.
[3]Nur Jahan Begum, Professor, Dept. of Gynaecology & Obstetrics, Eastern Medical College & Hospital, Cumilla, Bangladesh.
[4]Fatematul Jannat, Assistant Professor, Dept. of Gynaecology & Obstetrics, Eastern Medical College & Hospital, Cumilla, Bangladesh.
[5]Kamrun Naher, Assistant Professor, Dept. of Obstetrics and Gynaecology, Eastern Medical College & Hospital, Cumilla, Bangladesh.
[6]Mohammed Badrul Alam, Assistant Professor, Dept. of Anaesthesiology, Bangladesh Medical University, Dhaka, Bangladesh.

Address of Correspondence: Prof. Dr. Shabera Arzoo, Professor, Department of Gynaecology & Obstetrics, Eastern Medical College & Hospital, Cumilla, Bangladesh. Mobile: +8801711385778, Email: arzooshabera@gmail.com

vaginal endometriosis in women who have previously undergone conservative surgery without excision of deep lesions[7]. Dienogest is an oral progestin approved for the treatment of endometriosis at a daily dose of 2 mg in regions such as Europe, Japan, Canada, South Africa, Australia and various countries in Asia. It provides distinct pharmacological advantages for treating endometriosis, including strong progestogenic effects that effectively reduce endometrial lesions. Additionally, it offers moderate suppression of estrogen levels while having minimal androgenic, mineralocorticoid or glucocorticoid activity[8].

Endometriosis is associated with pelvic pain (EAPP) is the most prevalent symptom among patients with endometriosis. Around 70% of women with endometriosis experience EAPP, while endometriomas are found in 17-44% of cases[9]. The definitive diagnosis of endometriosis is typically made through laparoscopic-guided biopsy, which is an invasive procedure and not easily accessible. Endometriomas, however, can be detected by non-invasive imaging, such as ultrasound, which has a sensitivity of approximately 80% and a specificity of 90%. B-mode ultrasound demonstrates 80% sensitivity and 91% specificity in diagnosing endometriomas in premenopausal women[10]. Sensitivity of magnetic resonance imaging (MRI) is same as ultrasonography in detecting endometrioamas[11]. The purpose of the study is to investigate the efficacy (pain relief with reduction in size of endometrium) and side effects at 1st and 3rd months of Dienogest treatment.

Materials and Methods

This prospective observational study was carried out in the department of Obstetrics & Gynecology of Eastern Medical College & Hospital from January to December 2023. A total of 96 patients attending the outpatient department of Obstetrics & Gynecology with the age range of 15–35 years with the complaints of pelvic pain and diagnosed as endometriosis by ultrasonogram (64 patients by abdominal ultrasound and 32 patients by trans-vaginal sonography) were included. Those who have the size of endometrioma >8 cm and known case of liver and renal failure were excluded from the study. Patients meeting the inclusion criteria were given Dienogest 2 mg orally. Before giving the drug details history, clinical examinations, relative investigations and proper counselling with informed consent were obtained. The effects of treatment were determined by seeing the resolution of pain and decreasing the size of endometrioma. Patients were monitored at the 1st and 3rd months. Significant pain relief was defined as a decrease of more than 30% in pain. Pain intensity was evaluated using the numerical rating scale (NRS), categorized as mild, moderate, or severe. A significant reduction in endometriomas was considered when there was more than a 50% decrease in the largest cyst dimension. Side effects, both minor and major, were noted at each follow-up visit. Effects on the liver function test (LFT) and renal function test (RFT) were also noted separately at 1 and 3 months.

Results

This study comprised of 96 young women in which 78 (81.2%) were in the age group of 21–30 years, 18 (18.7%) patients were in the age group of 15–20 years. In our study 53 (55.2%) women were unmarried. Besides, 68 (70.8%) patients were nulligravida, 16 (16.6%) were primiparous and 12 (12.5%) were multiparous. Out of 68 nulligravida patients, 18 (26.5%) patients had primary infertility. At enrollment out of 96 patients, 71 (73.9%) had severe pain, 23 (23.9%) had moderate and 2 (2.2%) had mild pain as per NRS (figure-1). A total of 43 (77%) patients had a history of dysmenorrhea while 5 (10%) patients had dyspareunia. Two (3.5%) patients had a history of dyschezia. All the patients included in the study had endometriomas of different sizes. 57 (59.37%) patients had endomewasmas <4 cm in size, while 39 (40.62%) patients had endometrioma between 4–8 cm. Endometriomas of >8 cm were excluded as per our exclusion criteria. Patients were monitored, and the following variables were evaluated at the end of one and three months of treatment: a) pain relief, b) regression of endometriomas, and c) side effects.

Pain relief: Out of 96 patients, 72 (75%) reported experiencing pain relief within 2-5 days of starting Dienogest. 18 (18.75%) patients had pain relief within 6-10 days and 6 (6.25%) had pain relief after 10 days. After 1 month of treatment, 71 patients (73.9%) had significant pain relief (>30%). Mean reduction of pain on NRS (Numeric Rating Scale) scale from enrollment till 1 month was from 7.6 to 4.2 (p <0.0001) (Figure 2). Out of 71 patients (73.9%) who had severe pain at enrollment, only 3 patients (3.l1%) were left with severe pain at the end of 1 month with Dienogest. They were given an additional opioid analgesic for sufficient pain relief but chose to continue using Dienogest. Dienogest. Besides, 41 patients (73.2%) had significant (taken as >30%) pain relief. Mean reduction in pain on NRS scale was from 7.6 to 3.1 (p-value <0.0001) at the end of 3 months with Dienogest. (figure 2). Out of 96 patients only one patient (1.01%) was left with severe pain, 68 (70.83%) had moderate pain and 27 (28.12%) had mild pain as per NRS scale at the end of 3 months with Dienogest (Table-I).

Regression: A total of 47 patients (48.95%) had endometrioma <4 cm and 49 (51.04 %) had endometrioma 4-8 cm. Successful reduction in endometriotic cyst size (>50%) was seen in 18 (18.75%) at the end of 1 month with Dienogest.

Mean reduction in endometrioma size on Dienogest was from 5.6 cm to 4.1 cm and 3.2 cm at 1 and 3 months, respectively (Figure 3). At the end of 3 months out of 96 patients, 24 patients (25.0%) had significant cyst size reduction (>50%) with Dienogest, 14 patients (14.58%) showed no reduction in size at 3 months of Dienogest and 48 patients (50.0%) had <50% reduction. Only 10 patients (10.41%) had complete disappearance of endometriomas. Patients with smaller endometriomas showed a better response to Dienogest.

Side Effects: Side effects were noted at the end of 1 and 3 months. Minor side effects included spotting, amenorrhea, headache, breast pain, acne, and bowel disturbances, while major side effects involved thromboembolic events, as well as abnormal liver or renal functions. At 1 month of Dienogest, 26 patients (27.08%) had abnormal uterine bleeding (AUB), 14 (14.58%) had breast pain, 5 (5.2%) had headache and 3 (3.12%) had acne. At 3 months of Dienogest, 21 patients (21.87%) had spotting, 4 (4.16%) had amenorrhea, 16 (16.6%) had breast pain, 6 (6.25%) had headache and 5 (5.20%) had acne. None of the patients had any major side effects (Table II).

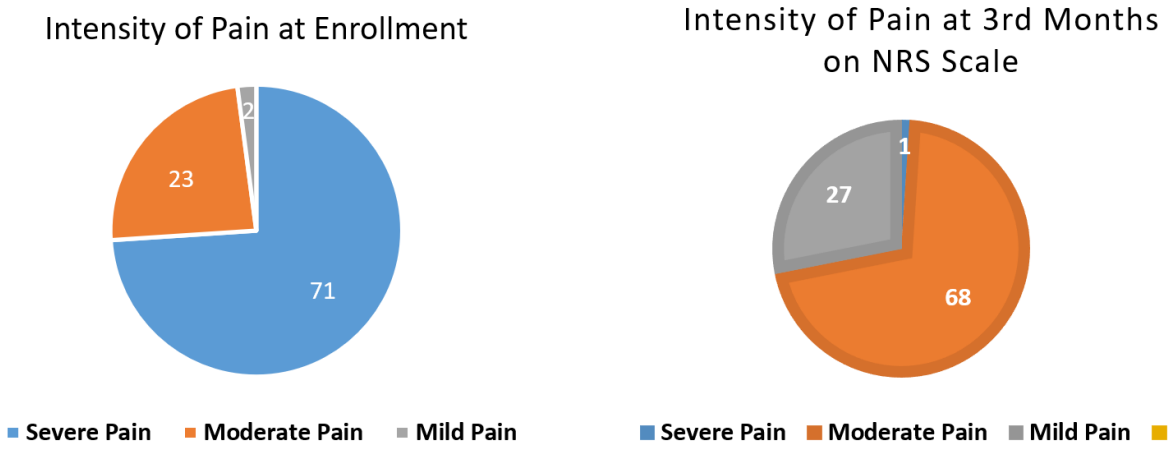

Figure-1: Intensity of pain at enrollment and at 3rd months on NRS scale

Table-I: Reduction in size of endometrioma with Dienogest

Numerical rating pain scale	Assessment at Enrollment (n = 56)	Assessment at 1 month (n = 56)	Assessment at 3 months (n = 56)	Total	P value
Mild	2 (2.08%)	24 (25%)	27 (28.12%)	53 (18.4%)	p <0 .0001*
Moderate	23 (23.9%)	69 (71.8%)	68 (70.83%)	160 (55.5%)	
Severe	71 (73.9%)	3 (3.12%)	1 (1.0%)	75 (26.04%)	
Mean ± SD	7.61 ± 1.67	4.8 ± 1.19	4.1 ± 1.17	5.5 ± 2	p<0.0001**
Median	8 (6-9)	4 (4-5)	4 (4-5)	5 (4-7)	

p value obtained from χ2 test* and Wilcoxon Signed Ranks Test**

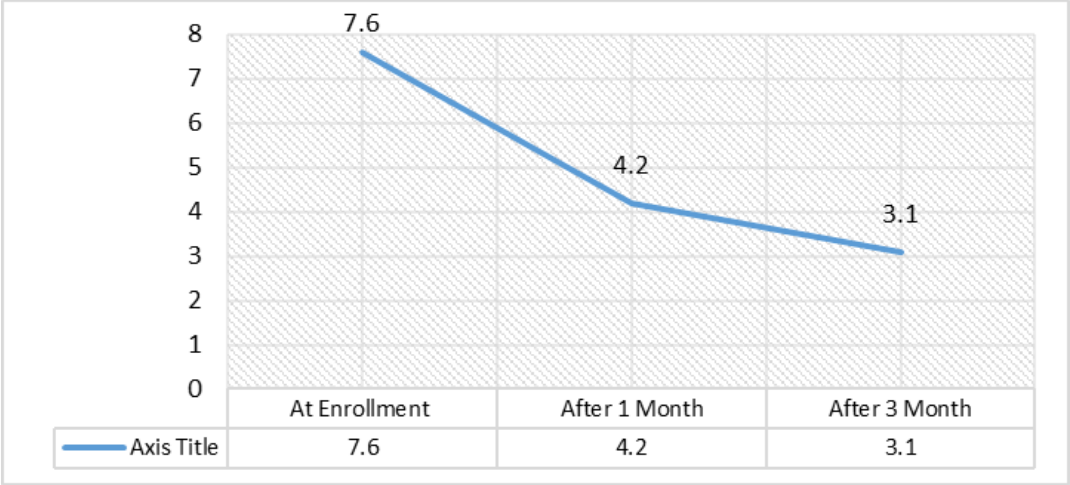

Figure-2: Mean reduction of pain on NRS scale with Dienogest at enrollment, 1 and 3 months

Table-II: Side effects of Dienogest in the study subjects at 1 and 3 months

	At 1 month		At 3 months	
Side effects	**Frequency**	**Percentage (%)**	**Frequency**	**Percentage (%)**
AUB	26	27.08	21	21.87
Amenorrhea	0	0	4	4.16
Breast pain	14	14.58	16	16.6
Headache	5	5.20	6	6.25
Acne	3	3.12	5	5.20
Bowel disturbances	0	0	0	0
Thromboembolism	0	0	0	0
Deranged LFT	0	0	0	0
Deranged KFT	0	0	0	0

AUB= Abnormal Uterine Bleeding, LFT=Liver Function Tests, KFT= Kidney Function Tests

Discussion

In our study at enrollment the mean NRS (Numeric Rating Scale) score was 7.6 which reduced to 4.2 and 3.1 at one and 3 months of Dienogest. An almost similar result was observed in another study where at enrollment mean NRS score was 7.4 which reduced to 4.3 and 4.29 at 1 and 3 months of Dienogest, respectively[12]. But in another study found a marked decrease in pain with Dienogest, EAPP (endometriosis-associated pelvic pain) score decreased from 6.3 at enrollment to 0.9 at end of 6 months with Dienogest[13].

Pain relief was also evaluated by measuring the percentage reduction in the NRS score at 1 and 3 months. A 30% reduction in pain was considered significant. Our study found a significant pain relief (>30%) in patients. Out of 96 patients, 71 (73.95%) experienced significant pain relief at 3 months of Dienogest treatment. In another study pain relief pattern is almost similar to our result where 41 patients (73.2%) had decreased pain at 3 months of Dienogest[12]. The Visanne Study to Assess Safety in Adolescents (VISADO), conducted between 2011 and 2014, found that 81% of participants experienced at least a 30% reduction in pain from baseline over a 24-week period[14]. A separate long-term study (52 weeks) on Dienogest showed a pain score improvement in 72.5% of patients after 24 weeks and in 90.6% of patients after 52 weeks[15]. Another study indicated that Dienogest effectively enhanced quality of life by reducing Endometriosis-Associated Pelvic Pain (EAPP) in 78.4% of participants[16].

There have been few studies conducted so far to evaluate the impact of Dienogest on reducing the size of endometriomas. In our study, 10 patients (10.41%) showed a complete resolution of endometriomas after 3 months. Another study showed five patients (8.9%) had complete disappearance of endometriomas at the end of 3 months which is less than our study[12]. A significant reduction was defined as a decrease of more than 50% in the largest dimension, which was observed in 24 patients (25%). Although there was a limited reduction in the size of endometriomas based on these criteria, no further growth in the size of the endometriomas was observed in any of the study participants receiving Dienogest. We found that 48 (50%) patients had <50% reduction in cyst size at 3 months. The mean reduction in cyst size was from 5.6 cm at enrollment to 4.1 cm after 1 month and 3.2 cm after 3 months of Dienogest treatment. Muzii, et al. reported a reduction in the mean cyst diameter from 4.0 cm to 2.4 cm after 6 months of Dienogest treatment[13]. It was seen that Dienogest is effective in reducing smaller endometriomas (≤ 4 cm). A total of 10 patients (8%) experienced complete disappearance of their endometriomas, all of which were ≤ 4 cm in size. Their findings suggested that Dienogest is especially effective in reducing smaller endometriomas (≤ 4 cm). Smaller endometrial lesions tend to respond better to medical treatments compared to larger ones[17].

Dienogest has minimal side effects compared to other treatments for endometriosis. In our study, we observed both minor and major side effects. In minor side effects, at 1 month of Dienogest 26 patients (27.08%) had spotting, 14 (14.58%) had breast pain, 5 (5.2%) had headache and 3 (3.12%) had acne. No patient had bowel disturbance and any major side effects. At 3 months of Dienogest, 21 patients (21.81%) had spotting, 4 (4.16%) had amenorrhea, 16 (16.6%) had breast pain, 6 (6.25%) had headache and 5 (5.20%) had acne. After 3 months, the results indicate a reduction in the frequency of spotting, although a new symptom, amenorrhea, develops. In another study, some minor side effects were observed at 1 month of Dienogest. In our study, 4 patients (25%) experienced spotting, 8 patients (14.2%) had breast pain, 3 patients (5.3%) reported headaches, and 3 patients (5.3%) developed acne. There were no bowel disorders and major side effects of that study. At 3 months of Dienogest in that study, 14 patients (25%) had spotting, 2 (3.5%) had amenorrhea, 8 (14.2%) had breast pain, 3 (5.3%) had headache and 3 (5.3%) had acne. No major side

effects were noted at 3 months as well[12]. No patient discontinued Dienogest due to side effects. Most studies suggested that the most common side effects of Dienogest was abnormal uterine bleeding[18].

This favorable profile of Dienogest 2 mg is combined with an efficacy equivalent to the highest current treatment standards, providing a progressive improvement in pain with continued use[19]. Continued use of Dienogest induces a hypoestrogenic, hypergestagenic local endocrine environment, causing a decidualization of endometrial tissue followed by atrophy of the endometriotic lesions[20]. Reflecting these observations, the guidelines from the World Endometriosis Society have recommended Dienogest as an empirical treatment option for women without laparoscopic confirmation and as a suitable adjuvant therapy following endometriosis surgery[21].

Conclusion

Short-term use of Dienogest 2 mg showed a favorable safety and tolerability profile. It also showed significant relief of pain and decreased the size of the endometrioma. Minor side effects occur which are tolerable but no major side effects during the treatment period. Predictable changes in the bleeding pattern, especially at the beginning of Dienogest treatment, require proper counseling to ensure patient adherence. The pooling of data from well-controlled trials of Dienogest contributes to evidence-based medicine in the management of endometriosis, offering outcomes that could be highly relevant to daily practice.

Conflict of Interest

The authors declared that they have no conflicts of interest.

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