The Journal of Obstetrics and Gynecology of India (September–October 2021) 71(5):522–529
https://doi.org/10.1007/s13224-021-01483-0

ORIGINAL ARTICLE

Role of Dienogest in Endometriosis in Young Women

Renuka Malik[1] · **Manmeet Kaur Mann**[1]

Received: 4 September 2020 / Accepted: 13 April 2021 / Published online: 3 May 2021

Abstract

Introduction Endometriosis associated pelvic pain (EAPP) is the most common complaint of patients with endometriosis. Nearly, 70% of females with endometriosis present with EAPP while endometriomas are found in 17–44% of patients.

Material and Methods A short-term single centre study was carried out in 56 patients in the age group of 15–35 years with complaints of pain and diagnosed as endometriosis either by imaging studies and/or by laparoscopy was given dienogest 2 mg OD, and effect of treatment was seen as improvement of pain score over a period of 3 months. The effect of dienogest was also seen on size of endometrioma. Patients were followed up at 1 and 3 months.

Results and Discussion Out of 56 patients, 38 (67.8%) patients reported their pain relief within 2–5 days after starting dienogest. Out of 41 patients (73%) who had severe pain at enrollment, only 1 patient (1.79%) complained of severe pain at the end of 1 month with dienogest. Successful reduction in endometriotic cyst size (>50%) was seen in 3 patients (5.3%) at the end of 1 month with dienogest. Out of 56 patients, 41 patients (73.2%) had significant pain relief (>30%) at three months of treatment. At the end of 3 months, seven patients (12.5%) had significant cyst size reduction (>50%) with dienogest. No major side effects were noted.

Conclusion Dienogest is well tolerated drug for endometriosis showing significant relief of pain. However, it was seen that though endometriomas did not grow during treatment, significant regression was uncommon.

Keywords Endometriosis in young women · Dienogest · Pelvic pain · Cyst regression

Introduction

Endometriosis is an estrogen-dependent disease with ectopic growth of proliferative endometrial tissue outside the uterine cavity characterized by pelvic pain, dysmenorrhea, dyspareunia and/or sub fertility. Prevalence of endometriosis varies widely, 10% in females of reproductive age group, 20–50% among the infertile women and nearly 90% in women with pelvic pain. Endometriosis-associated pelvic pain (EAPP) is the most common complaint of patients with endometriosis. About 70% of females with endometriosis present with EAPP while endometriomas are found in 17–44% of patients [1]. Definitive diagnosis of endometriosis can be made by laparoscopic guided biopsy which is an invasive modality not easily accessible. Endometriomas can be detected by non-invasive imaging using ultrasound with sensitivity of about 80% and specificity of 90%. B-mode ultrasound has 80% sensitivity and 91% specificity rate in diagnosing endometriomas in premenopausal women [2]. Sensitivity of magnetic resonance imaging (MRI) is same as ultrasonography in detecting endometriomas [3–5]. As endometriosis is a chronic disease medical treatment to relieve pain and other symptoms is often needed before resorting to surgical excision. Medical treatment available in India includes dienogest, progesterone, oral contraceptives, Danazol and gonadotrophins. Dienogest binds to the progesterone receptor and, when taken continuously, inhibits systemic gonadotropin secretion and has local antiproliferative and anti-inflammatory effects on endometriotic lesions.

Aim and Objectives of Study

To see pain relief and reduction in size of endometrioma at 1 and 3 months of dienogest treatment. Side effects of dienogest at 1 and 3 months were also noted.

✉ Renuka Malik
renucam@yahoo.co.in

Manmeet Kaur Mann
manmeetmann1234@gmail.com

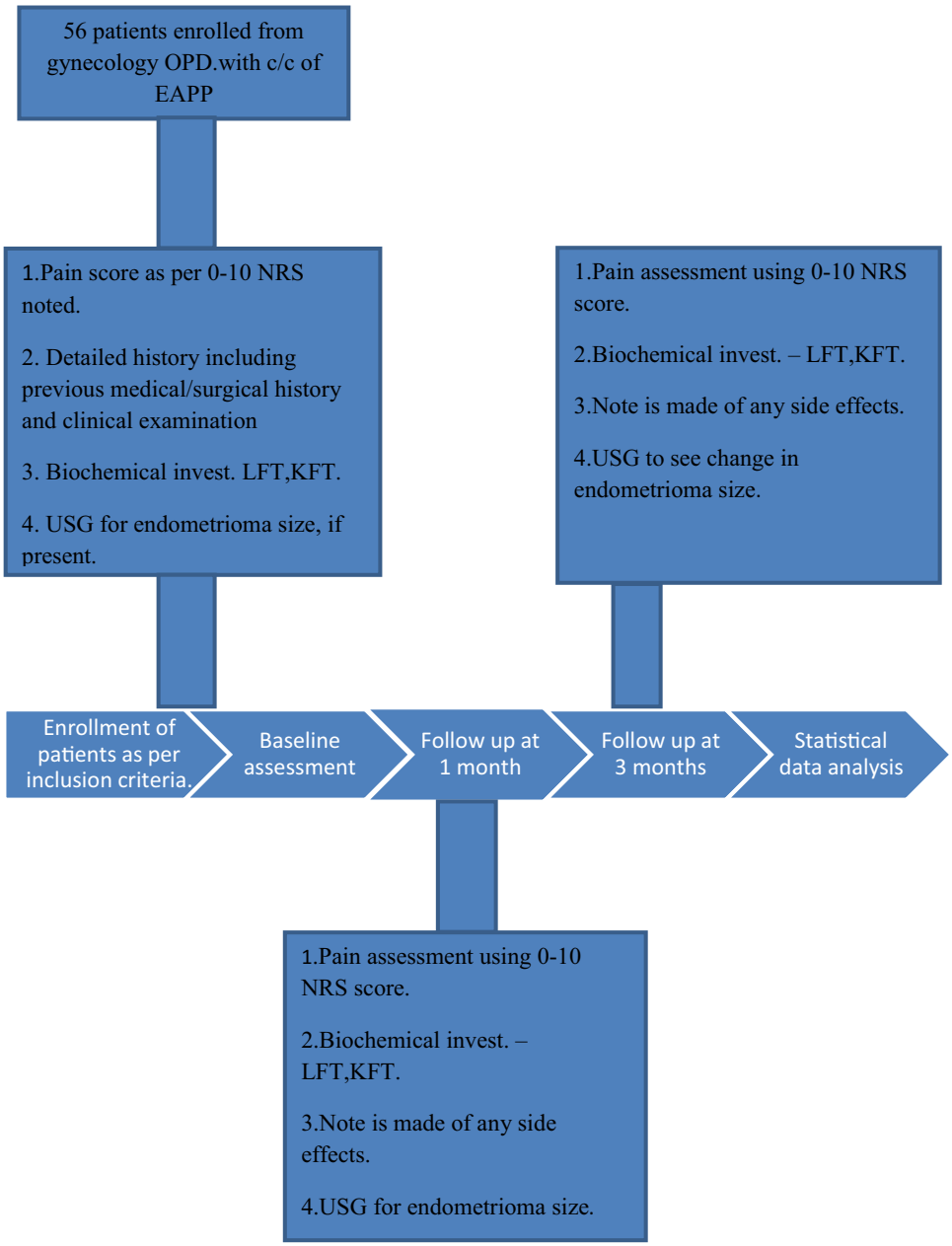
[1] Department of OB-GYN, ABVIMS & DR RML Hospital, Delhi, India

Material and Methods

This study on effectiveness of dienogest in endometriosis in young women was carried out in Department of Gynecology A.B.V.I.M.S & Dr. R.M.L Hospital from November 2018 to December 2019. It was a prospective observational study. A total of 56 patients attending the gynae OPD during the study period, in the age group of 15–35 years with complaints of pain and diagnosed as endometriosis either by imaging studies and/or by laparoscopy were recruited. Patients meeting the inclusion criteria were given dienogest 2 mg OD and effect of treatment seen in resolution of pain over a period of 3 months. The effect of dienogest was also seen on size of endometrioma. Patients were followed up at 1 and 3 months. Patients of endometrioma > 8 cm were excluded from the study. Baseline kidney function tests (KFT), liver function tests and pelvic USG was done and repeated at 1 and 3 months.

Significant pain relief on treatment was defined as >30% pain reduction. Significant reduction in endometrioma was taken as >50% regression in largest dimension of cyst. Side effects both minor and major were looked into at each follow up visit. Effect on LFT and KFT was noted separately at 1 and 3 months.

Flow Chart showing Follow Up of Patients in the Study



Statistical Analysis

Categorical variables were presented in number and percentage (%), and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov–Smirnov test. If the normality was rejected then non-parametric test was used. Statistical tests were applied. Quantitative variables were compared using Wilcoxon signed rank Test (as the data sets were not normally distributed) between the pre- and post-treatment. Qualitative variables were compared using Chi-Square test. p value of 0.05 was considered as statistically significant. The data were entered in MS EXCEL spreadsheet, and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Sample Size Calculation

The study by So Yun Park et al. was taken as reference to calculate sample size [6]. Endometriosis occurs in 6 to 10% of women as per ACOG Updates Guideline 2010. Taking this value as reference, the minimum required sample size with 10% margin of error and 5% level of significance was 35 patients. To increase power of study, we took 60 patients which had four drop outs.

Formula used.

1. For comparing Pre with post

$$N >= \frac{(\text{standard deviation})^2}{(\text{mean difference})^2} * \left(Z_\alpha + Z_\beta\right)^2,$$

where Z_α is value of Z at two sided alpha error of 5% and Z_β is value of Z at power of 90% and mean difference is difference in mean values of pre and post.

2. $N \geq ((p(1-p))/(\text{ME}/Z_\alpha)2$, Where Z_α is value of Z at two sided alpha error of 5%, ME is margin of error and p is prevalence rate.

Calculations:-

1. Pooled standard deviation = square root (28.6*28.6 + 14.6*14.6)/2) = 22.71

$$n >= \left((22.71 * 22.71) * (1.96 + 1.28)^2\right) / (40.8 - 7.3)^2 = 4.82 = 5(\text{approx.})$$

2. $N >= (.1 * (1 - .1))/(.1/1.96)^2 = 34.57 = 35(\text{approx.})$

Observation and Results

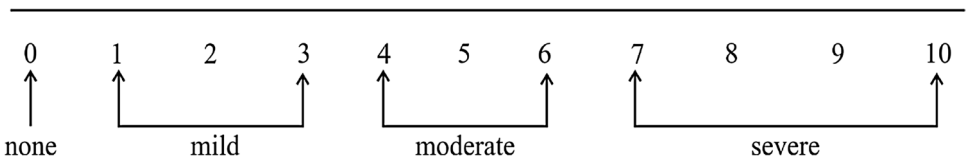
Characteristics of Study Population

This study comprised of 56 young women in the age group of 15–35 years. Out of 56 patients, 42 (75%) were in the age group of 21–30 years. 8 (14.2%) patients were in age group of 15–20 years. In our study, Adolescents (less than 19 years) were 5 (8.9%). In total, 33 (59%) women in our study population were unmarried. Among the 56 study subjects, 40 patients (71%) were nulligravida, 6 (11%) were primiparous and 10 (18%) were multiparous. Out of 40 nulligravida patients, seven patients had primary infertility.

Diagnosis of endometriosis: Patients were enrolled on basis of history, clinical examination and ultrasound/MRI or laparoscopic findings of endometriosis. Endometriosis was diagnosed in 54 (96.4%) of study subjects by ultrasound findings of endometriomas. Two patients (3.5%) had preceding laparoscopy for endometriosis. At enrollment, all the patients (100%) had EAPP as well as endometriomas. Both laparoscopy and imaging modalities as ultrasonography (USG) and magnetic resonance imaging (MRI) were used to diagnose endometriosis. Transabdominal ultrasonography was done in 33 patients (59%), and transvaginal ultrasonography was done in 23 patients (41%) to diagnose endometriomas. Out of 56 patients, 52 patients (92.8%) had endometriomas diagnosed on ultrasonography alone, two patients (3.5%) were diagnosed by MRI and USG both while in two patients (3.5%) laparoscopy and USG both were done to diagnose endometriosis. Patients diagnosed by laparoscopy also had endometrioma excision and were put on dienogest in postoperative period.

Symptom of Pain

As per inclusion criteria of this study all the enrolled subjects had chief complaint of pain although of varying intensities. Intensity of pain was assessed using numerical rating pain scale (NRS) as mild, moderate and severe.



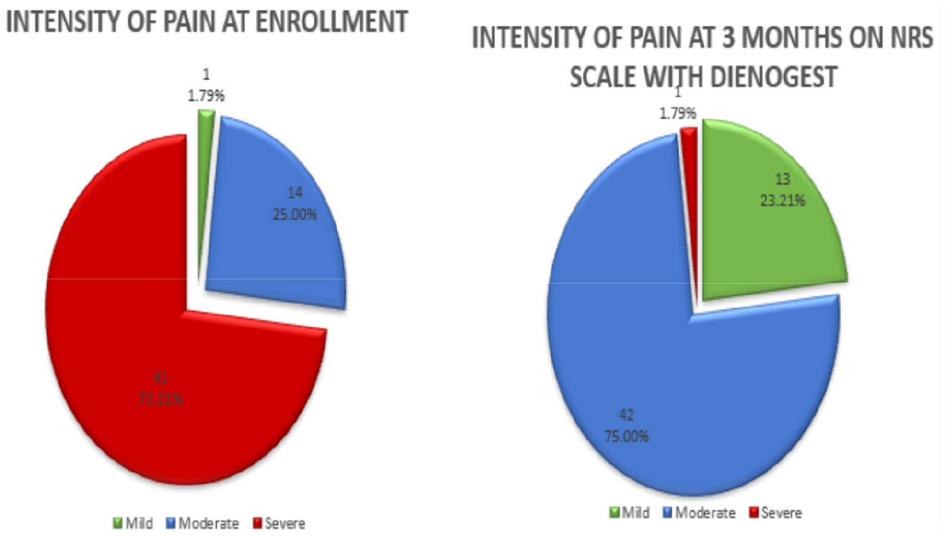


Fig. 1 Intensity of pain at enrollment and 3 months with dienogest on NRS scale

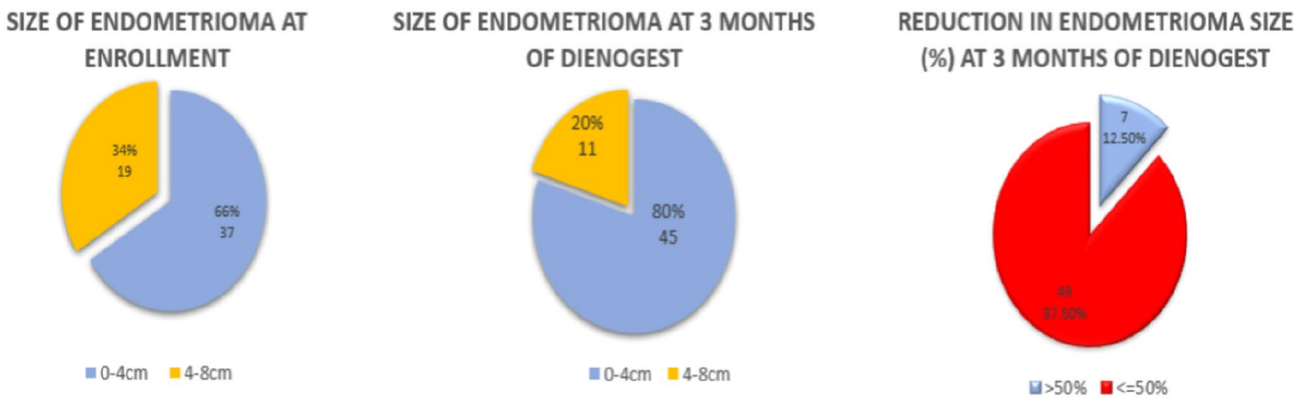


Fig. 2 Size of endometrioma at enrollment, 3 months of dienogest and %reduction in size at 3 months

At enrollment out of 56 patients, 41 (73.2%) had severe pain, 14 (25%) had moderate and 1 (1.7%) had mild pain as per numerical rating scale (Fig. 1). A total of 43 patients (77%) had history of dysmenorrhea while five patients (10%) had dyspareunia. Two patients (3.5%) had history of dyschezia.

Presence of Endometrioma

All the patients enrolled in the study had endometriomas of varying sizes. 37 (66%) patients had endometriomas ˂ 4 cm in size while 19 (34%) patients had endometrioma between

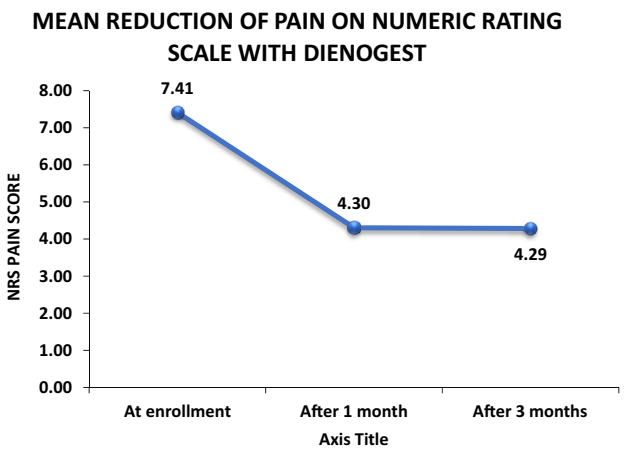


Fig. 3 Mean reduction of pain on numerical rating pain scale from enrollment, at 1 month and 3 months with dienogest

Table1 Assessment of pain on numerical rating pain scale at enrollment, 1 and 3 months

Numerical rating pain scale	Assessment at enrollment ($n=56$)	Assessment at 1 month ($n=56$)	Assessment at 3 months ($n=56$)	Total	*P* value	Test performed
Mild	1 (1.79%)	13 (23.21%)	13 (23.21%)	27 (16.07%)	*p*-value < .0001	Chi square test
Moderate	14 (25%)	42 (75%)	42 (75%)	98 (58.33%)		
Severe	41 (73.21%)	1 (1.79%)	1 (1.79%)	43 (25.60%)		
Mean ± SD	7.41 ± 1.67	4.3 ± 1.19	4.29 ± 1.17	5.33 ± 2	*p*-value < .0001	Wilcoxon Signed Ranks Test
Median	8 (6–9)	4 (4–5)	4 (4–5)	5 (4–7)		
Range	3–9	2–7	2–7	2–9		

4–8 cm (Fig. 2). Endometriomas of >8 cm were excluded as per our study.

Follow Up of Patients

Patients were followed up, and the following variables were assessed at the end of one and three months of treatment.

1. Relief of pain at end of 1 and 3 months.
2. Regression of endometrioma at 1 and 3 months.
3. Side effects at 1 and 3 months.

Pain relief

Out of 56 patients, 38 (67.8%) patients reported their pain relief within 2–5 days after starting dienogest. 10 (17.8%) patients had pain relief within 6–10 days and 8 (14.2%) had pain relief after 10 days.

After 1 month of treatment with dienogest, out of 56, 41 patients (73.2%) had significant pain relief (>30%)]. Mean reduction of pain on NRS scale from enrollment till 1 month was from 7.4 to 4.3 (*p*-value ˂0.0001) (Fig. 3). Out of 41 patients (73%) who had severe pain at enrollment, only one patient (1.79%) was left with severe pain at the end of 1 month with dienogest. This patient had pain relief of 22.3%. She was prescribed additional opioid analgesic for adequate pain relief but was willing to continue dienogest. Out of 56 patients, 41 patients (73.2%) had significant (taken as >30%) pain relief. Mean reduction in pain on numerical rating pain scale was from 7.3 to 4.29 (*p*-value ˂0.0001) at the end of 3 months with dienogest (Table 1). Out of 56 patients only one patient (1.79%) was left with severe pain, 42 (72%) had moderate and 13 (23.2%) had mild pain as per NRS scale at end of 3 months with dienogest. This patient who complaint of severe pain had NRS score of 9 at enrollment and had reduced to 7 at 3 months of dienogest. She needed additional analgesics at the time of pain intermittently.

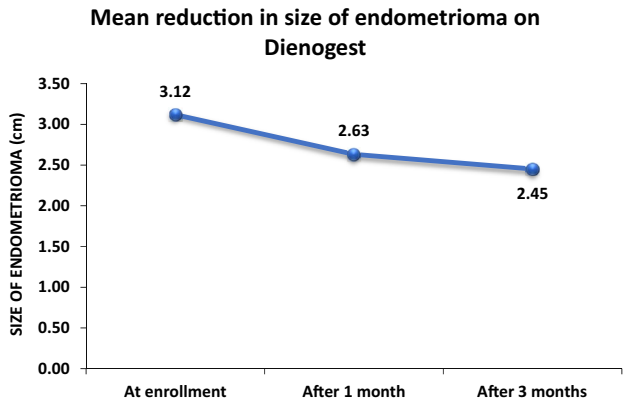


Fig. 4 Mean reduction in size of endometrioma from enrollment, at 1 and 3 months

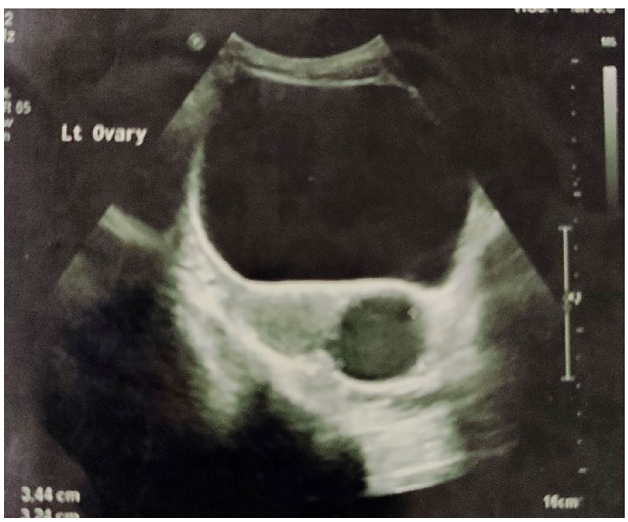


Fig. 5 Showing endometrioma Size 3.44 × 3.41 at enrolment

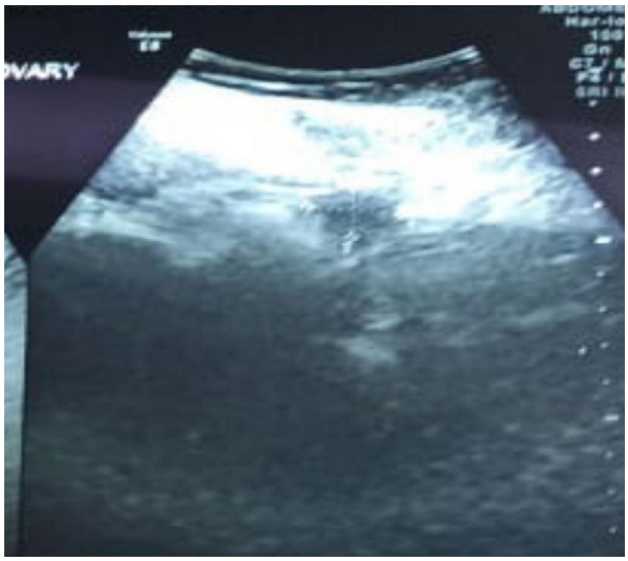


Fig. 6 Showing regression of endometrioma at 3 months

Reduction in Size of Endometrioma With dienogest

A total of 37 patients (66%) had endometrioma < 4 cm and 19 (34%) had endometrioma 4–8 cm. Successful reduction in endometriotic cyst size (>50%) was seen in three patients (5.3%) at the end of 1 month with dienogest. Mean reduction in endometrioma size on dienogest was from 3.1 cm to 2.6 cm and 2.4 cm at 1 and 3 months, respectively (p-value $^{<}$0.0001) (Fig. 4). At the end of 3 months out of 56 patients, 7 patients (12.5%) had significant cyst size reduction (>50%) with dienogest, 24 patients (42.8%) of them showed no reduction in size at 3 months of dienogest. 25(44.64%) patients had less than 50% reduction.]. Only five patients (8.9%) had complete disappearance of endometriomas (all with size ≤ 4 cm). Patients with small endometrioma had better response to dienogest (Figs. 5 and 6).

Side Effects

Side effects were noted at the end of one and three months. Minor included spotting P/V), amenorrhea, headache, breast pain, acne and bowel disturbances while major side effects included any thromboembolic events, deranged liver functions or renal functions. At 1 month of dienogest, 14 patients (25%) had abnormal uterine bleeding (AUB), 8 (14.2%) had breast pain, 3 (5.36%) had headache and 3 (5.36%) had acne. At 3 months of dienogest, 14 patients (25%) had spotting, 2 (3.5%) had amenorrhea, 8 (14.2%) had breast pain, 3 (5.36%) had headache and 3 (5.36%) had acne (Table 2). None of the patient had any major side effects.

Discussion

In our study, at enrollment mean NRS score was 7.4 which reduced to 4.3 and 4.29 at 1 and 3 months of dienogest, respectively. Another study found marked decrease in pain with dienogest, EAPP score decreased from 6.3 at enrollment to 0.9 at end of 6 months with dienogest [7]. A long-term study reported pain score (VAS) decrease from 20 to 9 mm over treatment period of 65 weeks [8]. Pain relief was also assessed by measuring percentage reduction in NRS score at 1 and 3 months, respectively. We took 30% reduction in pain as significant. Our study concluded significant pain relief (>30%) in 41 patients (73.2%) at 1 and 3 months of dienogest. Other studies too show a beneficial effect in pain reduction by dienogest. The VISanne Study to Assess Safety in ADOlescents (VISADO) in 2011–2014 found that 81% of the patients had ≥ 30% of pain relief from baseline over 24-week period [9]. A long-term 52-week study of dienogest showed improvement in pain score in 72.5% of patients after 24 weeks and in 90.6% patients after 52 weeks [10]. Another study reported dienogest effective in improving quality of life by decreasing EAPP in 78.4% subjects [11].

Table2 Side effects of dienogest in study subjects at 1 and 3 months

	At 1 month		At 3 months	
Side effects	Frequency	Percentage (%)	Frequency	Percentage (%)
AUB	14	25	14	25
Amenorrhea	0	0	2	3.5
Breast pain	8	14.29	8	14.29
Headache	3	5.36	3	5.36
Acne	3	5.36	3	5.36
Bowel disturbances	0	0	0	0
Thromboembolic episodes	0	0	0	0
Deranged LFT	0	0	0	0
Deranged KFT	0	0	0	0

Not many studies have been done till date to see effect of dienogest in reducing endometrioma size. In our study, five patients (8.9%) had complete disappearance of endometriomas at end of 3 months. We had taken significant reduction as more than 50%regression in largest dimension. Using those criteria, there was not much reduction in size of endometrioma in our study but on dienogest no further growth in size of endometrioma was seen in any of the patients. We found that 5.3% ($n=3$) and 12.5% ($n=7$) of the patients had >50% reduction in cyst size at 1 and 3 months, respectively. Mean reduction in cyst size was from 3.1 cm at enrollment to 2.63 and 2.45 cm at 1 and 3 months of dienogest. Similar to our study, Ludovico Muzii et al. found reduction in mean cyst diameter from 4.0 to 2.4 cm at 6 months of dienogest [7]. Some studies showed a very good effect in reducing cyst size.One study found 75% volume reduction with dienogest in 6 month period Another study showed cyst disappearance in 76.5% of the patients at end of 6 months of dienogest use. It was seen that dienogest is effective in reducing smaller endometriomas (≤4 cm). Five patients (8.9%) had complete disappearance of endometriomas (all of size ≤4 cm) while 24 patients (42.8%) showed no reduction in endometrioma size at the end of 3 months of dienogest. Smaller endometrial lesions respond better to medical treatment than the larger ones. Some studies have reported regression of endometrioma on prolonged use [6, 12–14].

Dienogest has minimal side effects among all the agents used for endometriosis. In our study, side effects were noted as minor and major. In minor side effects, at 1 month of dienogest 14 patients (25%) had spotting, 8 (14.2%) had breast pain, 3 (5.3%) had headache and 3 (5.3%) had acne. No patient had bowel disturbance as side effect. No major side effects were noted. At 3 months of dienogest, 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. No patient discontinued dienogest because of side effects. A study found the commonest side effect was abnormal uterine bleeding and slight reduction of bone mineral density [15]. A similar clinical trial-Visanne study to assess safety in adolescents (VISADO), at the end of 52 weeks, found decrease in BMD of—1.2% (SD = 2.3%) with partial recovery after treatment discontinuation. A long-term 65-week study found that dienogest was well tolerated with side effects like headache, breast discomfort, depressed mood, acne and each of them occurring in less than 10% of the total women [16]. Ours being a short-term study, effect on BMD was not measured.

A systematic review in 2015 compared dienogest with other medical therapies. Nine randomized trials were included. Dienogest in the dose of 2 mg/day had similar results with Buserelin, leuprolide and Triptorelin in reducing EAPP [17]. Other studies have found that dienogest has lesser side effects with almost equal efficacy as GnRH agonists in relieving endometriotic symptoms. Long-term studies conducted till date have reported that its efficacy increases cumulatively with minimal side effects [18, 19]. Dienogest has been approved by European Union in 2009 for endometriosis and was approved by DCGI, India in 2017 for treatment of endometriosis. As seen in our study, there was reduction of pain but the effect on endometrioma regression is not much, it is more effective in small endometrioma. At present, oral dienogest can be considered as a safe and first-line medical option of treatment in endometriosis especially in young women desirous of preserving their future fertility.

Strength and Limitation of Our Study

We had 100% acceptability rate. Limitation of our study was the short term study duration and effect of dienogest on prolonged use could not be studied.

Conclusion

Dienogest is an effective and safe drug in relieving pain in patients of endometriosis. It is not very effective in reducing larger endometriomas so clinicians treating young females should be aware about this especially treating larger endometriomas without pain.

Funding None required.

Declarations

Conflict of interest The author declare that they have no conflict of interest.

Ethical Approval Ethical clearance for the study was taken from hospital ethics committee with number- TP (MD/MS) (97/2018)/IEC/PGIMER/RMLH 1930. (Attached as supplementary file).

Informed Consent Written informed consent of all study subjects was taken.

References

1. Foti PV, Farina R, Palmucci S et al. Endometriosis: clinical features, MR imaging findings and pathologic correlation. Insights Imaging. 2018;9(2):149–72.
2. Alcázar JL, García-Manero M. Ovarian endometrioma vascularization in women with pelvic pain. Fertil Steril. 2007;87(6):1271–6.
3. Noventa M, Scioscia M, Schincariol M et al. Imaging modalities for diagnosis of deep pelvic endometriosis: comparison between trans-vaginal sonography, rectal endoscopy sonography and

magnetic resonance imaging. A Head-to-Head Meta-Anal Diagn. 2019;9(4):225.
4. Moura AP, Ribeiro HS, Bernardo WM et al. Accuracy of transvaginal sonography versus magnetic resonance imaging in the diagnosis of rectosigmoid endometriosis: systematic review and meta-analysis. PLoS ONE. 2019;14(4):e0214842.
5. Guerriero S, Saba L, Pascual MA et al. Transvaginal ultrasound vs magnetic resonance imaging for diagnosing deep infiltrating endometriosis: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2018;51(5):586–95.
6. Park SY, Kim SH, Chae HD et al. Efficacy and safety of dienogest in patients with endometriosis: a single-center observational study over 12 months. Clin Exp Reprod Med. 2016;43(4):215.
7. Muzii L, Galati G, Di Tucci C et al. Medical treatment of ovarian endometriomas: a prospective evaluation of the effect of dienogest on ovarian reserve, cyst diameter, and associated pain. Gynecol Endocrinol. 2020;36(1):81–3.
8. Petraglia F, Hornung D, Seitz C et al. Reduced pelvic pain in women with endometriosis: efficacy of long-term dienogest treatment. Arch Gynecol Obstet. 2012;285(1):167–73.
9. Ebert AD, Dong L, Merz M et al. Dienogest 2 mg daily in the treatment of adolescents with clinically suspected endometriosis: the VISanne study to assess safety in ADOlescents. J Pediatr Adolesc Gynecol. 2017;30(5):560–7.
10. Schindler AE. Dienogest in long-term treatment of endometriosis. Int J Women's Health. 2011;3:175.
11. Techatraisak K, Hestiantoro A, Ruey S et al. Effectiveness of dienogest in improving quality of life in Asian women with endometriosis (ENVISIOeN): interim results from a prospective cohort study under real-life clinical practice. BMC Womens Health. 2019;19(1):68.
12. Angioni S, Pontis A, Malune ME et al. Is dienogest the best medical treatment for ovarian endometriomas? Results of a multicentric case control study. Gynecol Endocrinol. 2020;36(1):84–6.
13. Xholli A, Filip G, Previtera F et al. Modification of endometrioma size during hormone therapy containing dienogest. Gynecol Endocrinol. 2020;36(6):545–49.
14. Andres MP, Mendes RF, Hernandes C et al. Hormone treatment as first line therapy is safe and relieves pelvic pain in women with bowel endometriosis. Einstein (São Paulo). 2019;17(2):1–6.
15. Momoeda M, Harada T, Terakawa N et al. Long-term use of dienogest for the treatment of endometriosis. J Obstet Gynaecol Res. 2009;35(6):1069–76.
16. Strowitzki T, Faustmann T, Gerlinger C et al. Safety and tolerability of dienogest in endometriosis: pooled analysis from the European clinical study program. Int J Women's Health. 2015;7:393.
17. De Paula AM, Lopes LA, Baracat EC et al. Dienogest in the treatment of endometriosis: systematic review. Arch Gynecol Obstet. 2015;292(3):523–9.
18. Takaesu Y, Nishi H, Kojima J et al. Dienogest compared with gonadotropin-releasing hormone agonist after conservative surgery for endometriosis. J Obstet Gynaecol Res. 2016;42(9):1152–8.
19. Lee SR, Yi KW, Song JY et al. Efficacy and safety of long-term use of Dienogest in women with ovarian Endometrioma. Reprod Sci. 2018;25(3):341–6.

About the Author

Renuka Malik Dr Renuka Malik is working as a Professor and Consultant in ABVIMS & DR RML Hospital, a tertiary level Central Government teaching hospital. She is an alumni of Lady Hardinge Medical College .Her areas of interest include laproscopy, menopause and high risk obstetrics.