

Efficacy and Safety of Low Dose Mifepristone in Adenomyosis: A Retrospective Cohort Study

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Abstract:

Objectives: The present study was to assess the efficacy and safety of low dose mifepristone in treatment of adenomyosis and evaluate the effect of mifepristone on dysmenorrhea, dyspareunia, menstrual bleeding and the adverse effect of mifepristone.

Methods: Group A (n=20) received 5 mg mifepristone daily and group B (n=20) received 5 mg mifepristone daily with a poor-effect levonorgestrel-releasing intrauterine device for 12 months. Pain severity was scored using a Visual Analogue Scale (VAS). The treatment was judged effective in improving dysmenorrhea when the VAS score decreased by more than 2 points. Uterine size was measured using transvaginal ultrasound (uterine volume = length × width × depth × 0.52). The thickness (in cm) of the endometrium (2 layers) was recorded using ultrasound. The level of serum CA125 was determined using ELISA. Haemoglobin, and estradiol level were routinely measured.

Results: In group A, the menorrhagia of patients receiving mifepristone were markedly decreased after 6 months compared with the baseline ($P < 0.001$). At 12 months of treatment, haemoglobin levels were remarkably different in group A compared with the group B (38.24 ± 21.01 , $n = 20$; 5.80 ± 5.96 , $n = 20$; $P = 0.037$). The effective rates of improvement in dysmenorrhea in group A patients were 100% (20/20) and 100% (20/20) after treatment at 6 and 12 months, respectively.

Conclusions: A 5 mg/day mifepristone regimen has demonstrated high efficacy in the treatment of adenomyosis, particularly in patients experiencing dysmenorrhea and/or menorrhagia, with a favorable safety profile and minimal adverse effects.

Keywords: Adenomyosis, Mifepristone, dysmenorrhea, Adverse effects.

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Introduction

Adenomyosis is defined as the presence of ectopic endometrial glands and stroma in the myometrium. Also known as internal endometriosis.[1] The prevalence of adenomyosis has been estimated to range from 5% to 70%, and approximately 20% of reproductive-aged people with a uterus are diagnosed with adenomyosis. [2,3] In India Isolated adenomyosis is estimated to be prevalent in about 10% women with subfertility and about 1% overall. The most common symptoms include heavy menstrual bleeding, painful menses and infertility. Risk factors for adenomyosis include conditions leading to increased estrogen exposure (increased parity, early menarche, short menstrual cycles,

elevated body mass index, oral contraceptive pill use, tamoxifen use) and prior uterine surgery (dilation and curettage, caesarean section, myomectomy, etc.) The traditional hysterectomy is generally unaccepted by women with adenomyosis, and conservative surgical resection of adenomyotic lesions often results in recurrence due to the residual lesions and the risk of uterine rupture during pregnancy is there. Uterine artery embolization (UAE) and high-intensity focused ultrasound (HIFU) can also be used to treat adenomyosis, but still there is delima regarding its efficacy and safety. Therefore, medical treatment is the lifelong management plan for adenomyosis. Medical treatment for adenomyosis, including

gonadotropin-releasing hormone agonist (GnRH-a), oral contraceptives, LNG IUS, and progestins, are limited in terms of effectiveness, tolerability, and costs.^[4] Therefore, it is necessary to look for a better drug that are inexpensive, with less side effects, and are suitable for long-term use. In 1982, mifepristone was reported as the first selective progesterone receptor modulator.^[5] Mifepristone works by antagonism of glucocorticoid and progesterone receptors. At low doses, mifepristone works by being a selective antagonist of progesterone. The drug does so by binding to the intracellular progesterone receptor. At high doses, mifepristone blocks cortisol at the glucocorticoid receptor. Short-term clinical use of mifepristone has demonstrated that it is well tolerated and its side effects are usually mild. In addition, the cost of mifepristone for long-term treatment is very low.^[7] Mifepristone has been used potentially in gynecological conditions like endometriosis and uterine fibroids.^[6] But the limited data available on its use in adenomyosis. Objectives of our study was to assess the efficacy and safety of low dose mifepristone in treatment of adenomyosis and evaluate the effect of mifepristone on dysmenorrhea, dyspareunia, menstrual bleeding and the adverse effect of mifepristone.

Material & Methods

The present study was conducted in the Department of Obstetrics and Gynaecology, Rohilkhand Medical College, Bareilly, Uttar Pradesh, India during a period from June 2024 to June 2025.

A total of 40 adenomyosis cases were enrolled in the present study. All the cases were categorized into two groups (group A & group B). Each group had 20 cases. Group A (n=20) received 5 mg mifepristone daily and group B (n=20) received 5 mg mifepristone daily with a poor-effect levonorgestrel-releasing intrauterine device for 12 months.

Pain severity was scored using a Visual Analogue Scale (VAS). The scale ranged from zero to ten; the extreme left side of the scale denoted "no pain," and the extreme right side indicated "maximum pain." A score of more than 6 was considered severe pain. The treatment was judged effective in improving dysmenorrhea when the VAS score decreased by more than 2 points.

In this study, quantitative measurement of menorrhagia was done by pictorial blood loss assessment chart.

We defined "ineffective LNG-IUD" as no change or a worsening in either the pain score or amount of menstrual loss 6 month after using LNG-IUDs in the adenomyosis patients.

Uterine size was measured using transvaginal ultrasound (uterine volume = length $\times$ width $\times$ depth $\times$ 0.52). The thickness (in cm) of the endometrium (2 layers) was recorded using ultrasound. The level of serum CA125 was determined using ELISA. Haemoglobin, and estradiol level were routinely measured in accordance with the manufacturers' instructions, and adverse reactions caused by mifepristone, were closely observed.

Uterine size, serum CA125 levels, estradiol levels, Visual Analogue Scale (VAS) score, menstrual blood loss, endometrial thickness, and haemoglobin levels were compared before and 6 month and 12 months after treatment and investigated again.

Statistical Analysis: Data was analysed with the help of latest version of SPSS software. Mean $\pm$ Standard deviations were observed. P-value was taken less than or equal to 0.05 ($p \leq 0.05$) for significant differences.

Results

In group A, and group B were followed up at 6 and 12 months of treatment. Among group A, 16 of 20 (80%), and group B, 4 of 20 (20%) women had the symptom of menorrhagia. There were no significant differences between the mifepristone group (group A) and mifepristone with LNG-IUD group (group B) in age, uterine size, VAS score, serum CA125 levels, and endometrial thickness at baseline ($P > 0.05$) (Table 1). However, the haemoglobin levels were significantly lower, and the menstrual volume was greater in group A than those in group B ($P < 0.01$).

As shown in Table 2, In group A, the menorrhagia of patients receiving mifepristone were markedly decreased after 6 months compared with the baseline ($P < 0.001$). Furthermore, at 12 months of treatment, haemoglobin levels were remarkably different in group A compared with the group B (38.24 ± 21.01 , $n = 20$; 5.80 ± 5.96 , $n = 20$; $P = 0.037$).

After 6 and 12 months, the levels of serum CA125, uterine size, and estradiol level in group A and B were not significantly difference ($P > 0.05$). The effective rates of improvement in dysmenorrhea in group A patients were 100% (20/20) and 100% (20/20) after treatment at 6 and 12 months, respectively.

Table 1: Patient demographics and clinical characteristics before treatment

Parameters	Group A (n = 20) (receiving 5mg/d Mifepristone)	Group B (n = 20) (Receiving 5mg/d Mifepristone with ineffective LNG-IUD)	P
Age (year)	40.73 ± 4.13	40.61 ± 4.57	0.581
Parity	1.22 ± 0.58	0.78 ± 0.62	0.057
Gravity	2.71 ± 1.13	3.17 ± 1.03	0.573
Abortion	1.38 ± 1.06	2.27 ± 1.64	0.180
Body mass index	20.56 ± 2.41	21.08 ± 2.04	0.531
VAS score	7.78 ± 2.15	7.10 ± 2.34	0.367
Menorrhagia (pad)	7.05 ± 3.20	3.52 ± 3.05	0.001*
Uterine size (cm ³)	238.20 ± 121.54	176.62 ± 101.11	0.166
Serum CA125 (U/mL)	170.55 ± 153.88	129.41 ± 203.72	0.066
Hemoglobin (g/L)	102.70 ± 21.99	124.56 ± 21.27	0.002*
Endometrial thickness (cm)	0.21 ± 0.08	0.19 ± 0.04	0.759
Estradiol (pg/L)	325.91 ± 216.10	292.29 ± 161.96	0.648

Table 2: Change of efficacy and safety variables after Mifepristone treatment

Items	Group A	Group B	P value
VAS score change			
At 6 months	-6.05 ± 1.25	-5.69 ± 2.56	0.448
At 12 months	-6.02 ± 1.94	-5.02 ± 1.89	0.267
Menorrhagia change (pad)			
At 6 months	-7.05 ± 3.10	-3.22 ± 3.10	0.001
At 12 months	-6.10 ± 3.58	-1.49 ± 1.59	0.305
Serum CA125 change (U/mL)			
At 6 months	-48.02 ± 140.56	-24.89 ± 94.13	0.821
At 12 months	-16.20 ± 105.65	-14.64 ± 84.13	0.897
Uterine size change (cm ³)			
At 6 months	-27.05 ± 91.39	-16.89 ± 70.19	0.815
At 12 months	-37.756 ± 99.89	-25.89 ± 91.90	0.452
HB change (g/L)			
At 6 months	23.44 ± 16.88	8.30 ± 12.78	0.278
At 12 months	38.24 ± 21.01	5.80 ± 5.96	0.035
ET change (cm) (2 layers)			
At 6 months	0.07 ± 0.28	0.11 ± 0.17	0.673
At 12 months	0.30 ± 0.20	0.14 ± 0.10	0.003
E ₂ change (pg/L) At 6 months	41.30 ± 244.20	-12.93 ± 143.75	0.789
At 12 months	-236.79 ± 279.67	-176.78 ± 160.45	0.651
Efficacy, n/n (%)			
At 6 months	20/20 (100%)	20/20 (100%)	-
At 12 months	20/20 (100%)	20/20 (100%)	-
Amenorrhea, n/n (%)			
At 6 months	20/20 (100%)	20/20 (100%)	-
At 12 months	15/20 (75%)	8/20 (40%)	0.212

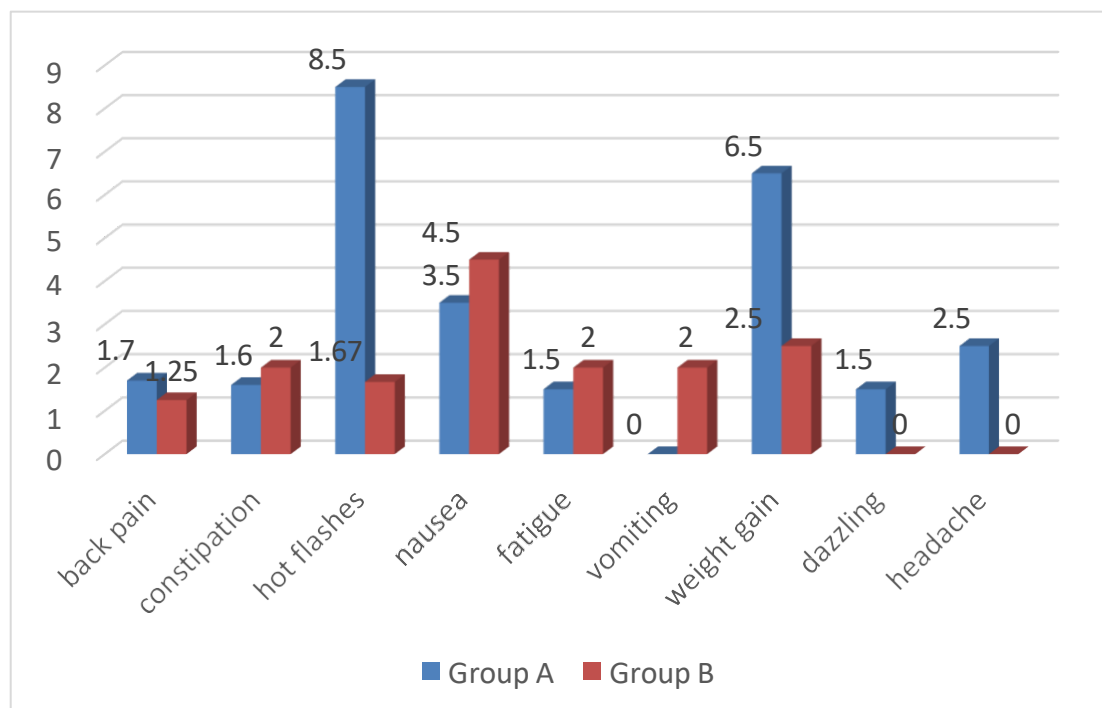


Figure 1: Comparison of adverse events between two groups Table.

3: Comparison of variables between at 6 months and at 12 months

Variables	Group A (N=20)		P-value	Group B (N=20)		P-value
	At 6 months	At 12 months		At 6 months	At 12 months	
VAS score	-6.05± 1.25	-6.02 ± 1.94	0.953	-5.69± 2.56	- 5.02± 1.89	0.352
Menorrhagia change (pad)	-7.05 ± 3.10	-6.10 ± 3.58	0.375	-3.22± 3.10	-1.49 ± 1.59	0.032
Serum CA125 change (U/mL)	-48.02 ± 140.56	-16.20± 105.65	0.423	-24.89± 94.13	-14.64± 84.13	0.718
Uterine size change (cm3)	-27.05 ± 91.39	-37.75± 99.89	0.725	-16.89± 70.19	-25.89± 91.90	0.729
HB change (g/L)	23.44 ± 16.88	38.24 ± 21.01	0.018	8.30± 12.78	5.80 ± 5.96	0.432
ET change (cm) (2 layers)	0.07 ± 0.28	0.30 ± 0.20	0.004	0.11± 0.17	0.14 ± 0.10	0.500
E ₂ change (pg/L)	41.30 ± 244.20	-236.79± 279.67	0.001	-12.93± 143.75	-176.78± 160.45	0.001
Efficacy, n/n (%)	20/20(100%)	20/20 (100%)	--	20/20 (100%)	20/20 (100%)	--
Amenorrhea, n/n (%)	20/20 (100%)	15/20 (75%)	0.018	20/20 (100%)	8/20 (40%)	<0.0001

When intra group comparison was performed between variables at 6 months and 12 months (Table.3). Hb change ($p=0.018$), ET change ($p=0.004$), E₂ change ($p=0.001$) and amenorrhea ($p=0.018$) was highly significant difference in group A patients. While in group B patients, Menorrhagia change (pad) ($p=0.032$), E₂ change (pg/L) ($p=0.001$) and amenorrhea ($p<0.0001$) was highly significant difference. Others variables in both group cases between at 6 months and at 12 months were not significantly differenced ($p>0.05$).

Discussion

Recent clinical studies on adenomyosis have demonstrated that mifepristone can inhibit ovulation and directly influence the progesterone receptor, thereby preventing the proliferation and differentiation of ectopic endometrium, reducing its growth potential and facilitating its regression. [8]

The results of our study suggested that the various indicators were significantly improved in patients with adenomyosis after 6 and 12 months of low-dose mifepristone treatment. Low-dose mifepristone

therapy may effectively manage the clinical manifestations of adenomyosis in individuals experiencing dysmenorrhea and hyper menorrhea, aligning with findings documented in recent research about high dosages of mifepristone.[9]

In the present study, in group B who underwent the treatment of 5 mg mifepristone daily with ineffective LNG-IUD, they did not present with an apparent decrease in uterine volume or CA 125 levels.

Furthermore, our data indicated that the symptoms of dysmenorrhea and hypermenorrhea progressively reemerged following the cessation of mifepristone treatment, ultimately returning to their initial pretreatment intensities. Notably, six months post-discontinuation, a substantial rise in uterine size and blood CA125 levels was seen compared to pretreatment data, differing from the outcomes associated with mifepristone for uterine myoma.[10] A 2022 study by Chen SY et al evaluated the 12-month effects and mechanisms of low-dose mifepristone (5 mg/day) in adenomyosis. Patients received mifepristone alone (n = 45) or with a poor-effect LNG-IUD (n = 13), while a surgical control group (n = 8) was used for immunohistochemical analysis. VAS scores, uterine size, endometrial thickness, serum CA125, estradiol, and hemoglobin levels were assessed before, during, and after treatment. Mifepristone significantly reduced pain ($P < 0.001$), decreased uterine size, and thickened the endometrium. Immunohistochemical analysis showed downregulation of NGF and COX-2 and a transient increase in Ki-67 expression, which normalized post-treatment. No hyperplasia or malignancy was observed. The study concluded that 5 mg/day mifepristone effectively alleviates painful adenomyosis with minimal side effects. [6]

A multicenter, placebo-controlled, double-blind RCT by Che X et al (China) in year 2023 evaluated mifepristone (10 mg/day) for 12 weeks in 134 adenomyosis patients. The primary endpoint was VAS score reduction, with secondary measures including menstrual blood loss, hemoglobin, CA125, platelet count, and uterine volume. Mifepristone significantly reduced pain (mean VAS change: -6.63 vs. -0.95; $P < 0.001$) compared to placebo, with no significant safety concerns or serious adverse events. The study concluded that mifepristone is an effective and well-tolerated treatment option for adenomyosis.[11]

In the present study, when we compared the variables between at 6 months and 12 months. Hb change ($p=0.018$), ET change ($p=0.004$), E2 change ($p=0.001$) and amenorrhea ($p=0.018$) was highly significantly difference in group A patients. While in group B patients, Menorrhagia change (pad) ($p=0.032$), E2 change (pmol/L) ($p=0.001$) and amenorrhea ($p<0.0001$) significantly difference.

According to the study of Bagaria M, et al. In a six months study with 2.5 mg daily mifepristone, there was no further reduction in uterine volume or relief in menorrhagia after 3 months. Amenorrhoea rates reduced from 65 per cent at three months to 32 per cent at six months. [12] In another study of 12 months duration, no further volume reduction was seen after six months and increased rates of breakthrough bleeding or spotting was reported. [13] Besides, intermittent administration has been suggested for long term mifepristone use, with treatment duration of 3-4 months followed by an off-drug interval till menstruation occurred.[14] Though it is now known that endometrial thickening with more than three months treatment is due to cystic dilatation and not due to hyperplasia, yet intermittent therapy would be more reassuring to the treating clinicians. [14]

Conclusion

A 5 mg/day mifepristone regimen has demonstrated high efficacy in the treatment of adenomyosis, particularly in patients experiencing dysmenorrhea and/or menorrhagia, with a favorable safety profile and minimal adverse effects. The findings suggest that this low-dose regimen can effectively alleviate symptoms and improve quality of life for affected individuals. Additionally, the occasional co-administration of low-dose mifepristone with an oral progestin may serve as a promising approach to further reduce endometrial thickness while mitigating the risk of excessive breakthrough bleeding. This combined strategy could also contribute to ensuring endometrial safety, thus enhancing the long-term feasibility of mifepristone therapy for adenomyosis. Furthermore, to comprehensively assess the long-term efficacy and safety profile of this treatment, an extended follow-up period is warranted, allowing for a thorough evaluation of symptom recurrence, hormonal changes, and potential late onset adverse effects after treatment discontinuation.

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