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Research Article

Mifepristone versus Dienogest in Medical Management of Endometrioma Up to 6 Cm Diameter: A Prospective Observational Study

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ABSTRACT
Background: Endometriosis, the presence of endometrial tissue outside the uterus, is a chronic estrogen-dependent condition affecting ~10% of reproductive-age women, peaking at 25–30 years. It accounts for ~60% of pelvic pain and 50% of infertility cases. Lesions may occur on pelvic peritoneum, ovaries, recto vaginal septum, ureter, and rarely elsewhere. Ovarian endometriosis, often associated with endometriomas (55% of cases), can cause adhesion and symptoms such as dysmenorrhea, premenstrual pain, dyspareunia, and fatigue.
Objective: To compare Dienogest and Mifepristone in reducing pain and endometrioma .size in endometriosis.
Materials & Methods: This randomized clinical trial was conducted in the G&O OPD, Medical College Kolkata (June 2020–May 2021). Women with dysmenorrhea, diagnosed with endometrioma ≤6 cm, and not seeking conception were included. Those with severe pain needing hospitalization or requiring surgery were excluded. A total of 236 patients were randomized equally: Group 1 received Dienogest 2 mg/day; Group 2, Mifepristone 25 mg/day. Follow-up at 3 and 6 months assessed endometrioma size and pain using the Visual Analogue Scale (VAS).
Results: Reduction in endometrioma size showed no statistical significance between groups at 3 or 6 months (p=0.2024, p=0.0522). Pain reduction at 3 months was greater with Dienogest (VAS 3.92±1.65) vs Mifepristone (4.69±1.45), p<0.0001. At 6 months, scores further declined (0.53±0.64 vs 0.82±0.71), p=0.0012. Overall pain reduction was greater with Dienogest (8.10±0.99 vs 7.82±1.03), p=0.0342.
Conclusion: Dienogest was more effective than Mifepristone in relieving endometriosis-associated pain, with no significant difference in endometrioma size reduction.

Keywords: Endometriosis, Dysmenorrhea, Dyspareunia, Dienogest, Mifepristone, Endometrioma.

INTRODUCTION

Endometriosis is defined as the presence of estrogen-dependent endometrial-like glands and stroma outside the uterine cavity, affecting approximately 10% of women in the reproductive age group.[1] It is diagnosed in nearly 60% of females presenting with chronic pelvic pain and in about 50% of women with infertility.[2,3] The condition manifests as dysmenorrhea, dyspareunia, dyschezia, chronic pelvic pain, and infertility, with ovarian involvement being one of the most common presentations. Ovarian endometriosis frequently results in the formation of endometrioma, accounting for up to 55% of ovarian endometriosis cases. [4]

Endometriomas are thought to develop when hormonally active ectopic endometrial tissue on the ovary undergoes cyclic bleeding, forming a hematoma. [5, 6] These lesions contain dense endometrial stroma and fibrotic adhesions, leading to persistent pain and complicating surgical management. Endometriosis is a chronic, relapsing disorder without a definitive cure; hence, the American Society for Reproductive Medicine (ASRM) emphasizes long-term medical management to control symptoms, preserve fertility, and reduce surgical frequency. [7]

Treatment aims include alleviating pain, suppressing lesion progression, and improving quality of life. Options range from hormonal therapy—such as combined oral contraceptives,

progestins, GnRH agonists, and androgens—to surgical interventions. [8] While GnRH agonists can reduce cyst size, their efficacy in long-term pain relief is inconsistent and side effects often limit their use.[9] According to the European Society of Human Reproduction and Embryology (ESHRE) guidelines, surgery is recommended for ovarian endometriomas larger than 3 cm, with laparoscopic cystectomy being the gold standard.[10] However, surgical intervention carries the risk of reducing ovarian reserve, especially in women desiring future fertility. This makes medical therapy a vital consideration, particularly for smaller endometriomas (≤6 cm).

Among medical options, Mifepristone and Dienogest have gained attention for their role in endometriosis management.

Mifepristone (RU-486) is a selective progesterone receptor modulator (SPRM) with tissue-specific agonist/antagonist activity. [11] While FDA-approved for pregnancy termination and Cushing syndrome, it has demonstrated off-label potential for endometriosis by alleviating pelvic pain and reducing lesion activity in early trials and animal models. [12, 13] However, clinical evidence in endometriomas is still limited.

Dienogest is an oral progestin with pronounced endometrial activity and additional anti androgenic properties. [14] It induces endometrial atrophy, suppresses estradiol production, and promotes decidualization of ectopic endometrium. [15] Large randomized trials have confirmed its efficacy in reducing both the size of endometriotic lesions and associated pain, with good tolerability. [16]

Given the lack of head-to-head comparisons between mifepristone and dienogest in managing smaller endometriomas (≤6 cm), this study aims to evaluate and compare their effectiveness in symptom control, lesion size reduction, and tolerability in a prospective observational setting.

MATERIALS AND METHODS

This was an institutional based prospective observational study conducted in the Department of Obstetrics & Gynaecology, Medical College Kolkata from June 2020 to May 2021 after receiving the clearance from institutional ethical committee (Ref No: MC/KOL|/IEC/NON SPON 681/03/2020, dated12/03/20. Patients who were diagnosed (by USG and/or Laparoscopy) with endometrioma up to 6 cm in diameter, and those who did not desire to conceive for the time being are included in this study. Patients with severe pain abdomen requiring hospitalization and injectable analgesics, severe menorrhagia needing blood transfusion and complications of endometrioma like torsion, intracystic hemorrhage, intra-abdominal hemorrhage that need surgical management were excluded from the study.

Sample size calculation: - Based on the previous paper comparing these two drugs the main outcome of the group for Mifepristone and Dienogest were 55% and 72.5% respectively. The required sample size came out to be 118 for each group (including 10% dropouts). **C**onsecutive sampling method was applied – all eligible patients who meet the inclusion criteria and present during the study period are enrolled until the desired sample size is reached. Group 1 received Dienogest 2 mg/day, while Group 2 received Mifepristone 25 mg/day. Follow-ups occurred at 3 and 6 months post-treatment, assessing reduction in endometrioma size and associated pain using the Visual Analogue Scale (VAS).

Statistical analysis: - For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS (version 27.0; SPSS Inc., Chicago, IL, USA) and Graph Pad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables, and count and percentages for categorical variables. P-value ≤ 0.05 was considered as statistically significant.

RESULTS

The mean age (mean ± SD) was 25.3983 ± 4.1120 years in the Dienogest group (Group 1) and 25.4068 ± 4.1659 years in the Mifepristone group (Group 2). The difference in mean age between the two groups was not statistically significant (p = 0.9875). (Table 1)

Table 1. Distribution of Mean Age (Years)

Gruop	Mean Age	SD	Minimum	Maximum	Median	P value
1(n=118)	25.3983	4.1120	19.0000	35.0000	25.0000	0.9875
2(n=118)	25.4068	4.1659	19.0000	35.0000	25.0000	

The baseline mean endometrioma size was 4.2890 ± 0.9467 cm in the Dienogest group and 4.4636 ± 0.9150 cm in the Mifepristone group (p = 0.1511). At 3-month follow-up, the mean

size had decreased to 3.6297 ± 0.9711 cm and 3.7898 ± 0.9535 cm, respectively (p = 0.2024). After 6 months of treatment, the size further reduced to 1.9144 ± 0.6594 cm in the Dienogest group and 2.0864 ± 0.6943 cm in the Mifepristone group; this difference approached but did not reach statistical significance (p = 0.0522). (Table 2)

Table 2. Size of Endometrioma at Baseline, 3, And 6 Months (Cm)

Size	Group	Mean	SD	Minimum	Maximum	Median	P value
0 Month	1(n=118)	4.2890	0.9467	2.6000	6.000	4.1000	0.1511
	2(n=118)	4.4636	0.9150	2.6000	6.000	4.5000	
3 Months	1(n=118)	3.6297	0.9711	2.0000	5.6000	3.6000	0.2024
	2(n=118)	3.7898	0.9535	2.0000	5.6000	3.7500	
6 Months	1(n=118)	1.9144	0.6594	0.0000	3.4000	2.0000	0.0522
	2(n=118)	2.0864	0.6943	1.0000	3.4000	2.0000	

The mean reduction in endometrioma size was 2.3746 ± 0.7623 cm in the Dienogest group and 2.3771 ± 0.5930 cm in the Mifepristone group, with no statistically significant difference (p = 0.9772). (Table 3)

Table 3. Mean Reduction in Size of Endometrioma (Cm)

Group	Mean	SD	Minimum	Maximum	Median	P value
1(n=118)	2.3746	0.7623	0.6000	4.2000	2.3000	0.9772
2(n=118)	2.3771	0.5930	1.1000	3.8000	2.4000	

At baseline, the mean Visual Analogue Scale (VAS) pain score was 8.6356 ± 0.7357 in the Dienogest group and 8.6441 ± 0.7456 in the Mifepristone group (p = 0.9300). After 3 months of treatment, scores decreased to 3.9153 ± 1.6464 and 4.6949 ± 1.4471, respectively, with the difference being statistically significant (p < 0.0001). At 6 months, scores further declined to 0.5339 ± 0.6363 in the Dienogest group and 0.8220 ± 0.7117 in the Mifepristone group, again showing a significant difference (p = 0.0012). (Table 4)

Table 4. VAS Pain Score at Baseline, 3, And 6 Months

VAS	Group	Mean	SD	Minimum	Maximum	Median	P value
0 Month	1(n=118)	8.6356	0.7357	8.0000	10.0000	8.0000	0.9300
	2(n=118)	8.6441	0.7456	8.0000	10.0000	8.0000	
3 Months	1(n=118)	3.9153	1.6464	1.0000	8.0000	4.0000	<0.0001
	2(n=118)	4.6949	1.4471	2.0000	8.0000	4.0000	
6 Months	1(n=118)	0.5339	0.6363	0.0000	2.0000	0.0000	0.0012
	2(n=118)	0.8220	0.7117	0.0000	2.0000	1.0000	

The mean reduction in VAS score from baseline to 6 months was 8.1017 ± 0.9905 in the Dienogest group and 7.8220 ± 1.0264 in the Mifepristone group, the difference being statistically significant (p = 0.0342). (Table 5)

Table 5. Mean reduction of VAS pain score

Group	Mean	SD	Minimum	Maximum	Median	P value
1(n=118)	8.1017	0.9905	6.0000	10.0000	8.0000	0.0342
2(n=118)	7.8220	1.0264	6.0000	10.0000	8.0000	

DISCUSSION

The present study compared the efficacy of Dienogest and Mifepristone in reducing the size of ovarian endometriomas and alleviating associated pelvic pain over a six-month treatment period. Both treatment groups were comparable at baseline in terms of mean age, initial endometrioma size, and baseline pain scores, with no statistically significant differences.

Our findings indicate that both Dienogest and Mifepristone resulted in progressive reduction in endometrioma size at 3 and 6 months;

however, the difference in size reduction between the two groups was not statistically significant at any time point.

Carbonell JL et al. (2016) conducted a double-blind, placebo-controlled trial in 360 women with laparoscopically confirmed endometriosis, comparing Mifepristone (2.5, 5, or 10 mg daily for six months) with placebo. All Mifepristone doses significantly improved AFS scores, with 5 mg showing the best safety–efficacy profile.[17] In our study, a 25 mg dose of mifepristone was used, as lower-dose formulations were not available in the Indian market, and this dosage effectively reduced both endometrioma size and associated pain.

Momoeda M et al. (2009) evaluated the long-term safety and efficacy of Dienogest (2 mg daily for 52 weeks) in 135 women with endometriosis. No significant changes in adverse event incidence or severity occurred, and bone mineral density loss was minimal. Symptom improvement was marked, reported in 72.5% of patients at 24 weeks and 90.6% at 52 weeks.[18]

Vignali M et al. (2020) assessed 2 mg daily Dienogest in 70 patients, with mean endometrioma volume reduced by 66.71% at six months and 76.19% at twelve months. Dysmenorrhea improved by 74.05% and 96.55%, while dyspareunia and chronic pelvic pain showed respective reductions of 42.71% and 48.91% at six months, and 51.93% and 59.96% at twelve months, confirming its role in reducing both lesion size and pain.[19]

Similarly, Petraglia F et al. (2005) found significant pelvic pain reduction ($p < 0.001$) with long-term Dienogest, a favorable safety profile, and persistence of symptom relief for at least 24 weeks after stopping treatment. [20]

Lee JH et al. (2018) reported a decrease in VAS pain scores from 5.03 ± 1.73 at baseline to 2.46 ± 1.32 at 24 weeks, with sustained improvement in both recurrent symptom-only and recurrent endometrioma groups. [21]

In our study, the mean percentage reduction in VAS scores was higher in the Dienogest group, supporting its efficacy for symptom control. The therapeutic outcomes were consistent with earlier reports, although adverse effects were not assessed.

A review of the literature revealed no studies directly comparing the effectiveness of Dienogest and Mifepristone in the treatment of endometrioma; hence, a direct comparison of our findings in a similar context was not possible. However, the lack of significant difference in cyst size reduction between groups suggests that both agents act primarily by suppressing ectopic endometrial activity rather than physically resolving cysts completely. [22]

Limitation: - Our study has certain limitations, including a relatively small sample size and short follow-up, which may reduce the ability to detect long-term differences in recurrence or lesion regression. The limited sample may not adequately represent the general population. Being a single-centre study conducted in a tertiary care hospital, the possibility of hospital-based bias cannot be excluded. Additionally, as an open-label design was used, subjective bias in pain score reporting is possible. Despite these constraints, the results offer clinically relevant evidence supporting both agents as effective and well-tolerated medical options for endometrioma management.

CONCLUSION

Both Dienogest and Mifepristone are effective in reducing endometrioma-associated pain and lesion size, with Dienogest showing a slight advantage in pain relief at six months. However, the reduction in endometrioma size did not differ significantly between the Dienogest and Mifepristone groups. Larger, multicentric randomized trials with longer follow-up are warranted to confirm these findings and evaluate recurrence rates.

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Conflicts of interest: Nil

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