

A prospective interventional study to evaluate the effects of medical therapy (Mifepristone 25 mg) on the management of uterine fibroids

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ABSTRACT

Background and Objectives: In India, the uterine fibroid is a common indication of hysterectomy. An effective option for medical treatment may decrease the morbidity associated with hysterectomy. We aimed to evaluate the effect of mifepristone (25 mg), progesterone antagonist, on uterine fibroids in perimenopausal women. **Methods:** Fifty-four perimenopausal women of age ≥ 18 years having symptomatic uterine fibroids were selected from Gynecology OPD and given 25 mg mifepristone once daily continuously for 2–4 cycles of 3 months each. Variables such as baseline fibroid size, position, and hemoglobin were measured and followed at 3, 6, 9, and 12 months. The data were entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0. A *P* value of <0.05 was considered statistically significant. **Results:** Majority were intramural fibroids (70.37%) followed by submucosal in 16.67%. Size of fibroids ranged from <3 to >7 cm; the majority of fibroids were in 5–7 cm size. No significant association of location with the size of fibroid was found. Out of 54 cases included in the study, change in size in uterine fibroids was observed in 98.14% cases. There was an increase in hemoglobin, from 8.6 g% at baseline to 9.7 g% at 12 months. **Conclusion:** Mifepristone resulted in a reduction in uterine fibroids size and an increase in hemoglobin at the end of 12 months. It may be an option for uterine leiomyoma treatment, as it is given orally, cost-effective and has minimal side effects.

Keywords: Fibroid, leiomyoma, medical management, mifepristone, uterine

Background

Uterine fibroids (UFs), known as uterine leiomyomas, are benign smooth muscle neoplasms of the uterus affecting women of reproductive age.^[1] UF occur in 70% of women by the onset of menopause.^[2] They are estimated to be clinically apparent in 25% of women of reproductive age.^[3] Although they are often asymptomatic, UF can cause symptoms such as menorrhagia, abnormal uterine bleeding, pelvic pain or pressure, infertility, and recurrent pregnancy loss.^[4] Larger fibroids sometimes push

the bladder or bowel and cause an increased urge to urinate or digestion problems (constipation, pain), and cause obstruction of the ureters impending to the immediate treatment.^[5]

In clinical practice, for the treatment of fibroids, surgical treatments are used effectively. Surgical treatments are preferred as the last resort by the patients because none of the surgical treatments, other than hysterectomy, offer a recurrence-free survival.^[5] However, during the current practice, the authors themselves have been consulted by many patients who are afraid of surgery and want a medical treatment for the fibroids. Medical treatment seems easier to be adopted, inculcates less fear, and is on a cheaper side. This has led to the practicing physicians to prescribe certain drugs for selective treatment of fibroids. It

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becomes essential to know the indications and the appropriate dose to treat the patients with minimal side effects.

Such attempts to find the nonsurgical alternate to treat fibroids has been searched for decades, which involved the use of both progestins and estrogen-progestin combinations; however, their evidence of good response is lacking. Subsequently the use of GnRH agonists and antagonists were found to be efficacious but caused side effects with prolonged use of more than 6 months restricting their use as an adjuvant treatment before surgery with overall good results. Another benchmark development is the use of steroidal drug which may function as antiprogestins—Mifepristone.^[6]

Mifepristone is a steroid drug that can inhibit the secretion of progesterone through noncompetitive inhibition. It also reduces the level of epidermal growth factor receptors in fibroid tissue, inhibits the proliferation of tumor cells, thus inhibiting the growth of fibroids.^[7,8] Its effects on the endometrium as selective progesterone receptor modulators are reversible and without any serious changes. Studies evaluated the efficacy of mifepristone in doses varying from 2.5 to 50 mg/day,^[9-12] and it was observed that doses <10 mg had lesser efficacy, whereas a higher dose of 25 mg daily was an effective dose for causing a clinically significant (50%) reduction in leiomyoma volume.^[10,11,13] It showed that long-term medical treatment of uterine fibroids is feasible today and more studies are needed to adjudicate on its dosage, use, efficacy, and safety in the clinical practice.

Thus, we did this study to evaluate the effects of medical therapy (mifepristone 25 mg) on the management of uterine fibroids among perimenopausal women.

Methods

A prospective interventional study was conducted in the department of Obstetrics and Gynecology over a period of 1 year (31st January 2019 to 30th January 2020) where women with uterine fibroids were enrolled for medical management after informed medical consent. The study was approved from the institutional ethical committee of the hospital (ASCOMS/IEC/2018/316). A written informed consent was taken from all the patients enrolled in the study as per the inclusion and exclusion criteria.

Sample size

The study of Engman *et al.*^[14] observed that median (IQR) of total myoma volume at baseline was 161 (111–209) and at the end of the study was 106 (52–205). Taking these values as a reference, the minimum required sample size with 95% power of study and 5% level of significance is 39 patients. Taking lost to follow-up as 20%, the total sample size to be taken is 49. To reduce the margin of error, the sample size taken is 54.

Inclusion criteria

- 1) Patients with the age of 18 years and above
- 2) Diagnosed fibroid cases

- 3) Fibroid size ≥ 2.5 cm
- 4) Patients who accepted the use of nonhormonal contraceptive
- 5) Patients who agreed to have an ultrasound examination in every follow-up or evaluation visit

Exclusion criteria

1. Pregnancy
2. Undiagnosed cause of irregular bleeding PV
3. Underlying any other metabolic, hepatic, or renal complication

All included participants underwent Pap smear (excluding unmarried women), endometrial evaluation by Pipelle or aspiration in all married women >35 years, Hb levels, CBC, S. ferritin levels, TSH, serum prolactin levels, and TVS/USG for fibroid size and location and the endometrial thickness <5 mm on the day of start of therapy. The intervention included mifepristone 25 mg, which was started from 5th day of the periods continuously for 3 months. A break was given until the subject has had her periods (for the endometrium to shed). Again, it was started from the 5th day of next periods for the next 3 months. Likewise, the therapy was given for a total of 4 cycles maximum if required (12 months), according to the size of the fibroid. Data pertaining to the demography, investigation findings, and the fibroid were recorded and analyzed.

The outcome measure was the reduction in the size of the uterine fibroids during the course of the treatment from 3 months to 12 months, depending upon the individual and the size of the fibroid.

Statistical analysis

Categorical variables were presented in number and percentage (%), and continuous variables were presented as mean \pm SD and range. Qualitative variables were compared using Chi-Square test. A *P* value of <0.05 was considered statistically significant. The data were entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

Mean age of the patients in the study was 45.26 years. Most of the patients (35.19%) were of >45 years age, followed by 31.48% patients in 36–45 years age group. Total 85.19% of patients were married [Table 1].

Chief complaints of the study subjects were menorrhagia in 79.63% and heaviness in 5.56% of patients. Total 14.81% of patients were asymptomatic [Figure 1].

The intramural fibroid was the most common (70.37%) followed by submucosal (16.67%) and subserosal (12.96%) fibroids. Size of most of the fibroids (33.33%) was 5–7 cm, followed by 29.63% having tumor size 3–5 cm and 20.37% having size <3 cm [Table 2].

There was no significant association of the location of different types of fibroids with the size of the fibroid ($P = 0.714$) [Table 3].

At 3 months, there was no change in size in 11.11% patients. At 12 months, one patient (1.85%) had no change in tumor size. At 3 months, 0.5–0.9 mm change was noted in 29.63% patients; total 24.07% patients had 0.5–0.9 mm change at 12 months. A change of 1–1.4 mm in size was noted in 38.89% patients at 3 months, which increased to 42.59% patients at 12 months. Change in size of 1.5–1.9 mm was in 14.81% patients at 3 months and in 16.67% patients at 12 months. More than 2 mm change was present in 5.56% patients at 3 months and 14.81% patients at 12 months [Table 4].

At presentation, mean hemoglobin was 8.6 (g%) that increased to 9.7 (g%) at 12 months after the medical treatment [Figure 2].

Discussion

Although curative treatment for UF relies on surgical therapies, medical treatments are considered as the first-line treatment to preserve fertility and avoid or delay surgery.^[15,16]

In the index study, we found that medical management (mifepristone 25 mg) was effective in reducing the size of the small to medium fibroids. Our findings are supported by a recent analysis in the treatment of UF over a period of 2004–2018 by data mining technology and the medication rule which showed that among the common clinical drugs including leuporelin (GnRH-a), danazol (androgen), gestrinone (progestin), mifepristone (progesterone receptor antagonist), and some cases of combination therapy, the clinical use of mifepristone was the commonest with mild drug reactions and thus was worthy of clinical use and application.^[11]

The substantial effects of mifepristone are based on the combination effects on the estrogen, progesterone, and androgen regulators. The reduction in size of fibroids with mifepristone can be attributed to the direct effect in decreasing the number of progesterone receptors, and creating an early

follicular like hormonal environment, thus leading to inhibition of steroid-dependent growth of myoma. Mifepristone also results in delay or inhibition of ovulation; causing amenorrhea and reduction of blood loss. It also causes direct suppressive effects on the endometrial vasculature by suppressing the stromal vascular endothelial growth factor (VEGF) release.^[10,15]

Fibroids is a growing problem among women after 35 years of age. The mean age of the patients in our study was 45.26 years with chief complaints of menorrhagia and heaviness. Among other studies, the mean age of the patients was 40.8 years in the study by Engman *et al.*; main symptoms reported were pelvic pain, bladder pressure, micturition problem, and low back pain.^[14] In a study by Jain, patients >35 years of age were included in the study; the main symptoms were menorrhagia, dysmenorrhea, and

Table 1: Distribution of demographic characteristics n (%)

Age in years		
18-25	6	11.11%
26-35	12	22.22%
36-45	17	31.48%
>45	19	35.19%
Mean±SD		45.26±10.93
Range		19-55
Marital status		
Married	46	85.19%
Unmarried	8	14.81%

Table 2: Distribution of location and size of fibroid n (%)

Location		
Subserosal	7	12.96%
Intramural	38	70.37%
Submucosal	9	16.67%
Size (in cm)		
<3	11	20.37%
3-5	16	29.63%
5-7	18	33.33%
>7	9	16.67%

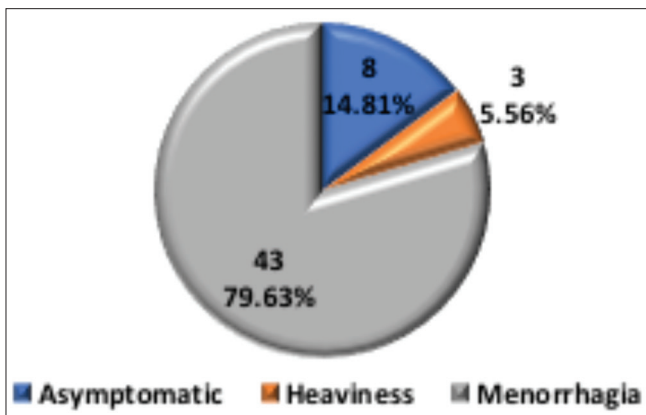


Figure 1: Distribution of chief complaints of study subjects

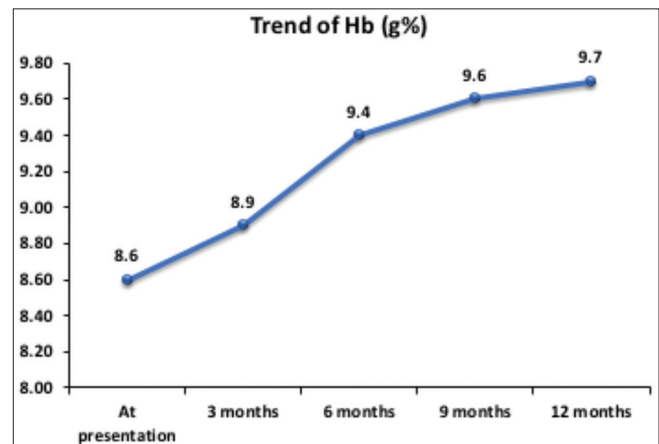


Figure 2: Trend of hemoglobin of study subjects

Table 3: Association of location with size of fibroid

Location	Size				Total	P	Test performed
	<3 (n=9)	3-5 (n=18)	5-7 (n=13)	>7 (n=14)			
Subserosal	2 (22.22%)	2 (11.11%)	1 (7.69%)	2 (14.29%)	7 (12.96%)	0.714	Chi-square test, 3.724
Intramural	6 (66.67%)	13 (72.22%)	8 (61.54%)	11 (78.57%)	38 (70.37%)		
Submucosal	1 (11.11%)	3 (16.67%)	4 (30.77%)	1 (7.14%)	9 (16.67%)		
Total	9 (100.00%)	18 (100.00%)	13 (100.00%)	14 (100.00%)	54 (100.00%)		

Table 4: Change in size of fibroid at different time intervals

	3 months (n=54)	6 months (n=54)	9 months (n=54)	12 months (n=54)
No change in size	6 (11.11%)	3 (5.56%)	2 (3.70%)	1 (1.85%)
0.5-0.9 mm	16 (29.63%)	12 (22.22%)	12 (22.22%)	13 (24.07%)
1-1.4 mm	21 (38.89%)	27 (50.00%)	27 (50.00%)	23 (42.59%)
1.5-1.9 mm	8 (14.81%)	6 (11.11%)	7 (12.96%)	9 (16.67%)
>2 mm	3 (5.56%)	6 (11.11%)	6 (11.11%)	8 (14.81%)

pressure symptoms.^[15] Mean age was 38.47 years in the study by Seth *et al.*; abnormal and excessive uterine bleeding (AUB) was the commonest problem reported, followed by heaviness in lower abdomen and pain for which they came to the hospital.^[17] Raghav *et al.* reported that the mean age of the patients was 39.40 years with main symptoms being menorrhagia followed by those having polymenorrhagia, intermenstrual bleeding, polymenorrhagia, abdominal pain, and dysmenorrhagia.^[7]

The fibroids ranged in size from <3 cm to >7 cm. As compared to our study, Raghav *et al.* reported that mean size was 42,599 mm³, in the range of 2,400–205,920 mm³.^[7] In a study by Kulshrestha *et al.*,^[9] at enrolment, myoma volume was 176,800 mm³. Seth *et al.* reported a much higher volume of myoma (143,958 mm³).

On advocating treatment with mifepristone 25 mg, no reduction in size was seen in one of the fibroids in the duration of 12 months. The increased duration of the medical treatment led to an increased reduction in the size of the fibroid. At 12 months after treatment, >2 cm reduction in size was found to be increased as compared to 3-month, 6-month, and 9-month duration. As compared in Saxena *et al.* (2019), there was 85.08% reduction in multiple myomas and 79.11% reduction in single myomas.^[10]

An increase in hemoglobin was found after 12 months of treatment as compared to baseline. Our results are comparable to that of previous studies. Kulshrestha *et al.* and Jain reported that there was a significant rise in hemoglobin levels with a dose of 25 mg ($P < 0.05$).^[9,15]

The duration of treatment with mifepristone has been a variable factor depending upon the dose of mifepristone. Two doses have been tried 10 mg and 25 mg. The previous studies with mifepristone reported lesser efficacy with doses of 10 mg. It was concluded that for causing a clinically significant (50%) reduction in leiomyoma volume, an effective dose was 25 mg

daily.^[13] Saxena *et al.* (2019) found both doses to be effective in the reduction of myoma size, with 25 mg showing better pain reduction and overall symptoms improvement in case of failure in response with 10 mg.^[10]

Jain studied the effect of mifepristone in the reduction of symptoms in leiomyomata in perimenopausal women. When mifepristone was continued, symptoms in both premenopausal and perimenopausal women were considerably improved.^[15] The decrease in myoma size was statistically significant. Mukherjee and Chakraborty evaluated the efficacy of daily administration of 25 mg mifepristone in treating uterine leiomyoma. A 47% reduction in the leiomyoma volume and a 53% reduction in the uterine volume were found. Improvement in symptoms was also found. After treatment, 75.7% of patients became amenorrhoeic.^[18]

Overall, mifepristone 25 mg seems better among the various doses in the effective management of fibroids without significant side effects. Some of the prior studies examined and validated the effectiveness of mifepristone 25 mg dose in ameliorating the symptoms and reduction in the size of uterine fibroids.^[9,14,18,19]

Among the alternative treatments of uterine fibroids, uterine arterial embolization (UAE) has shown good clinical results in the treatment of uterine bleeding, uterine cancer as well as adenomyosis, and other uterine diseases. In a recent published case-control study (2019),^[20] it was found that mifepristone and surgery and better options as compared to UAE. The authors found that the reduction in fibroid volume, average blood flow, peak systolic velocity, and thickest artery diameter were more with mifepristone as compared to UAE. The limitations of UAE procedure stem from the fact that ischemia concurrent to embolization results in further secretion of vascular growth factors in the local area resulting in increased growth of the fibroids.

Because of the increasing demands for postoperative quality of life and reproductive function, the majority of the patients select approaches that can maintain the uterus while achieving therapeutic effects.^[21] Thus, the role of medicinal drugs becomes important in this regard.

Why there is a current need of alternate medical treatment?

Although fibroids are benign, the associated complications may vary from intermittent bleedings to continuous bleedings, from

single pain episodes to severe pain, dysuria, constipation, chronic bladder, and bowel spasms with rare occurrence of peritonitis. Metro- and menorrhagia also cause infertility.^[22] Thus, it needs to be judiciously managed on an individual symptomatic basis. The present surgical treatments are expensive and approximately one-third of the hysterectomies are due to fibroids. Removal of a uterus negatively affects a woman in terms of her mental and physical well-being even after treatment of the pathology. This makes it vital to develop and effectively use medical alternatives with the goals of fibroid reduction and fertility preservation.^[23]

Sometimes, the decision to operate and medically manage may complicate the situation from the patient's point of view. However, studies such as ours may help to clarify the individual dilemma in quite a few cases and help the doctor and the patient choose the best treatment for themselves.

Limitations of the study

The study has limitations. The outcomes of the medical management were not compared with the surgery outcomes. Even variable doses of mifepristone were not compared during the study.

However, the main strength of the study was the long follow-up (12 months) of the patients to monitor the size of the fibroids. And above all, the results showed that fibroids can be medically managed with 25 mg of mifepristone with minimal side effects.

Conclusion

Mifepristone caused a reduction in the size of uterine fibroids in 98.14% cases and a simultaneous increase in hemoglobin levels till the end of 12 months. Thus, mifepristone 25 mg is effective in reducing the size or complete curing of the fibroids and can be used as a surgical substitute in patients who have fibroid associated anemia, small to medium fibroids, women who want to preserve uterus and in cases where leiomyoma are unresectable, or surgery is difficult.

Key points

1. Mifepristone is a safe medical alternative to the surgical management of uterine fibroids.
2. The dosage of 25 mg is appropriate for the significant reduction in the size of the fibroids in the follow-up period of 1 year.
3. The routine use of medical management of fibroids shall make women fearless in addressing their complaints related to fibroids and beginning an early intervention.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials

will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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