Original Article

Mifepristone Therapy in Symptomatic Leiomyomata Using a Variable Dose Pattern with a Favourable Outcome

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Background: Leiomyomata causing symptoms have a deleterious effect on the health of women during reproductive age. Mifepristone, a progesterone antagonist was studied for reduction of symptoms in leiomyomata in perimenopausal women.

Material and Methods: Mifepristone was administered to 7 women aged 47-50 years. Another 3 women less than 47 years were taken up for comparison of benefit of Mifepristone on leiomyomata related symptoms. Mifepristone was given in a stepwise declining dose for a period of 9 months to 1 year. The treatment was begun with 25 mg and the dose was reduced every 3 months. Every 3 months, the size of myomas, bleeding pattern, location of myomas, endometrial thickness, haemoglobin, and any side effects were all recorded. Results: There was considerable amelioration in the symptoms in both premenopausal as well as perimenopausal women, while mifepristone was continued. The reduction in myoma size was found to be statistically significant. After stoppage of drug in women aged 40-45 years, i.e. premenopausal group, the symptoms returned. However, in perimenopausal women, in 6 out of 7 women the symptoms abated completely and they had a smooth transition to menopause. Conclusion: Mifepristone is a very promising drug for conservative management of leiomyomata, especially in perimenopausal age (47 years or more), where hysterectomy was averted in all 7 women.

Keywords: Endometrial thickness, leiomyoma, mifepristone, perimenopausal

INTRODUCTION

Hysterectomy and myomectomy are the most common surgical procedures used to treat leiomyomas. Even with total hysterectomy where ovaries are conserved, in due course of time, owing to interference in the vascular supply, the ovarian function starts declining. Estrogen deprivation results in morbidity in terms of vasomotor symptoms, bone loss, and genitourinary atrophy. Myomectomy also carries risk of surgical complications and can be useful only with a single large or few myomas.

A medical method of treatment for leiomyomas is of definite advantage. GnRH analogs, ulipristal acetate, aromatase inhibitors, levonorgestrel intrauterine system, and antiprogesterones are all being tried for medical treatment of myomas. Mifepristone has been evaluated in the present study to ameliorate the symptoms due to myomas, such as menorrhagia, dysmenorrhea, pressure effects, anemia, and hence avert a surgical procedure.

MATERIALS AND METHODS

A prospective study was carried out on women with leiomyomas who presented in the premenopausal and perimenopausal age. Initially, women who were high risk for surgery such as one with coronary artery disease on antiplatelet therapy, and a woman operated for colonic cancer with leiomyomas were treated. However, as good response was observed, more women were recruited as and when they presented in the outpatient.

Inclusion criteria considered were women more than 35 years of age, with myoma related symptoms (menorrhagia, dysmenorrhea, pressure symptoms), with single or multiple myomas, willing to continue a medical treatment of myomas. Myomectomy was avoided in all the women.

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medical therapy for at least 6 months. Exclusion criteria decided on were women who desired future fertility, had received GnRH analogs at least 3 months before the study, with hepatic or renal insufficiency, and endometrial tissue showing hyperplasia with or without atypia. Group A consisted of seven women in perimenopause, that is, >47 years of age. Group B comprised three premenopausal women between 40 and 45 years, for comparison with women, who were in the perimenopausal group. All women in both the Groups A and B were still menstruating.

The symptoms for which treatment was begun were heavy blood flow during menstruation, dysmenorrhea, and pressure symptoms [Table 1].

All women were subjected to a general physical examination. A per speculum checkup was done to rule out local causes of bleeding such as cervical polyp or myomatous polyp. Pap smear with liquid-based cytology was done on all patients. A minimum investigation workup included measurement of

- Hemoglobin
- Blood sugar
- Thyroid status
- Lipid profile
- Renal function tests
- Hepatic function tests.

A pelvic ultrasonogram was obtained to know about the size of uterus, number and size of leiomyomas, location of myomas, adnexal disease, and endometrial thickness. Endometrial sampling was done in all patients. A minimum investigation workup included measurement of

1. Pattern of menstrual bleeding and amount of blood flow
2. Change in size of leiomyoma. The surface area of the largest myoma was derived by measuring the two maximum diameters of the largest myoma with transvaginal sonography. Surface area was used as a parameter for size of myoma. In some studies, the volume of myoma was has been used as a study parameter, measured with magnetic resonance imaging. However, as magnetic imaging was not available in the vicinity of our hospital and the patients would not have complied because of the distance and expense involved, surface area had to be considered to judge the change in size of myoma
3. Hemoglobin
4. Endometrial thickness
5. Change in the location of leiomyomas
6. Formation of ovarian cysts or change in the size of existing cysts
7. Any side effects of the drug.

**RESULTS**

**Bleeding pattern**

All women were amenorrheic at the end of 1 month and remained so till 10 mg dose. However, in two women, a slight bleeding episode occurred at 5 mg dose. After mifepristone therapy was stopped at 1 year, two patients from Group B reported with scanty blood flow, one at 3 months and in the second at 1 year after mifepristone was stopped.

**Size of leiomyomas**

Considering surface area of the largest leiomyoma, there was a significant reduction in the size of myoma at 3 months. In one woman of Group A, there was small submucous leiomyoma which completely disappeared at 3 months, suggesting a 100% decrement. For calculation of percentage change in size of myomas, this patient was excluded, as it would have caused a wide variation

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**Table 1: Symptoms related to leiomyomas**

| Symptoms            | Number of patients |
|---------------------|--------------------|
| Menorrhagia         | 10                 |
| Dysmenorrhea        | 7                  |
| Pressure symptoms   | 5                  |

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12.5 mg once daily for next 3 months. At 6 months, the dose of mifepristone was further reduced to 10 mg and patients who continued after 9 months were given 5 mg dose for the last 3 months. We planned to use mifepristone for 9 months to 1 year, considering an earlier study where patients were put on 10 mg and 5 mg dose in two groups and were followed up for 1 year. This study had revealed shrinkage of myomas, amelioration of symptoms, and endometrial hyperplasia, but no premalignant change in endometrium. A jeweller's scale was used to measure the exact quantity of daily dose from the available 200 mg tablet and 25 mg tablet.

Variables studied were:

1. Pattern of menstrual bleeding and amount of blood flow
2. Change in size of leiomyoma. The surface area of the largest myoma was derived by measuring the two maximum diameters of the largest myoma with transvaginal sonography. Surface area was used as a parameter for size of myoma. In some studies, the volume of myoma was has been used as a study parameter, measured with magnetic resonance imaging. However, as magnetic imaging was not available in the vicinity of our hospital and the patients would not have complied because of the distance and expense involved, surface area had to be considered to judge the change in size of myoma
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7. Any side effects of the drug.
in the standard deviation and thus the statistical calculation. The statistical significance for percentage decrease was calculated for remaining 9 patients. The mean decrease in size was 49.65% ± 23.65% from 0 to 3 months, 11.95% ± 28.84% from 3 to 6 months, and 33.59% ± 18.86% from 6 to 9 months. The \( P \) value was significant for change in size for 0–3 months, 3–6 months, and 6–9 months. \( P \) value was also significant for change in myoma size between 0 and 6 months and 0–9 months [Figure 1 and Tables 2-4].

**Statistical analysis**

- 0 versus 6 months: \( P = 0.007 \) (<0.01 significant)
- 0 versus 9 months: \( P = 0.007 \) (<0.01 significant).

**Effects of mifepristone on hemoglobin**

The hemoglobin at the start of therapy ranged between 7.8 gm% and 12.5 gm%. Four women had hemoglobin <10 gm%. The mean HB at 0 months was 10.2 ± 1.56 gm%. However, all women showed a rise in hemoglobin and at 3 months the mean hemoglobin was 11.2 ± 0.67 gm%. The increase in hemoglobin was statistically significant, \( P \) value being 0.03 (\( P < 0.05 \) is considered statistically significant) [Figure 2 and Table 5].

**Change in endometrial thickness**

Mean endometrial thickness in women of both Group A and Group B at 0 month was 5.71 ± 2.25 mm. At the end of 3 months of 25 mg daily dose, the endometrial thickness showed an increase. In patient no. 3, the thickness increased to 12 mm at 3 months and was 15 mm at 9 months, and hence, mifepristone had to be stopped for fear of further endometrial hyperplasia [Table 6].

Table 6, is showing endometrial thickness at 3, 6, 9, and 12 months and mean endometrial thickness. In the present study, we found endometrial thickness at 0 month 5.71 ± 2.25 mm which increased after 3 months, that is, 8.74 ± 3.50 mm and then decreased slightly to 8.51 ± 2.80 mm at 6 months and 5.57 ± 2.29 at 9 months [Figure 3].

The change in endometrial thickness was analyzed statistically and is shown below:

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**Table 2: Surface area of largest leiomyoma in mm²**

| Patient number | Group | Age (years) | 0 month | 3 months | 6 months | 9 months |
|----------------|-------|-------------|---------|----------|----------|----------|
| 1              | Group B | 40          | 200     | 120      | Stopped mifepristone | Stopped mifepristone |
| 2              | Group B | 42          | 49      | 1260     | 396      | 783      |
| 3              | Group B | 44          | 1598    | 1260     | 990      | 357      |
| 4              | Group A | >47         | 2346    | 1332     | 1152     | 783      |
| 5              | Group A | >47         | 5934    | 1280     | 990      | 357      |
| 6              | Group A | >47         | 1295    | 1295     | 1271     | 899      |
| 7              | Group A | >47         | 5264    | 3750     | 3380     | 2980     |
| 8              | Group A | >47         | 480     | 650      | Stopped mifepristone | Stoped mifepristone |
| 9              | Group A | >47         | 1184    | 528      | 450.6    | 311.4    |
| 10             | Group A | >47         | 500     | 500      | Stopped mifepristone | Stoped mifepristone |
| **Total number (n)** |       |             | 10      | 9        | 8        | 5        |
| **Mean±SD**    |       |             | 2059.5±2020.35 | 1171.66±1069.93 | 1098.7±979.96 | 1066.0±1100.39 |
| **Range**      |       |             | 49-5934 | 120-3750 | 396-3380 | 311.4-2980 |

SD: Standard deviation
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0 month versus 3 months: $P = 0.044$; $t = 2.16$ (significant <0.05).

0 month versus 6 months: $P = 0.038$; $t = 2.22$ (significant <0.05).

0 month versus 9 months: $P = 0.903$; $t = 0.122$ (not significant [NS] >0.05).

3 months versus 6 months: $P = 0.881$; $t = 0.151$ (NS > 0.05).

6 months versus 9 months: $P = 0.044$; $t = 2.22$ (significant <0.05).

The increase in endometrial thickness, hence between 0 and 9 months was not significant.

**Adnexal masses**

None of the 10 women studied had ovarian cysts at the start of therapy. The adnexae were examined by

| Patient number | Age in years and group | 0 month | 3 months | 6 months | 9 months |
|----------------|------------------------|---------|----------|----------|----------|
| 1              | 40, Group B            | 200     | 120      | Stopped mifepristone | Stopped mifepristone |
| 2              | 42, Group B            | 49      | 0        | Stopped mifepristone | Stopped mifepristone |
| 3              | 44, Group B            | 1598    | 1260     | 396      | Stopped mifepristone |
| 4              | >47, Group A           | 2346    | 1332     | 1152     | 783      |
| 5              | >47, Group B           | 5934    | 1280     | 990      | 357      |
| 6              | >47, Group B           | 2280    | 1295     | 1271     | 899      |
| 7              | >47, Group B           | 5264    | 3750     | 3380     | 2980     |
| 8              | >47, Group B           | 780     | 480      | 650      | Stopped mifepristone |
| 9              | >47, Group B           | 1184    | 528      | 450.6    | 311.4    |
| 10             | >47, Group B           | 960     | 500      | 500      | Stopped mifepristone |

Overall mean percentage decrease±SD $= -49.65±23.45$ $-11.95±28.84$ $-33.59±18.86$

SD: Standard deviation

| Patient number | Age in years and group | 0 month | 6 months | 9 months |
|----------------|------------------------|---------|----------|----------|
| 3              | 44, Group B            | 1598    | 396      | Stopped mifepristone |
| 4              | >47, Group A           | 2346    | 1152     | 783      |
| 5              | >47, Group A           | 5934    | 990      | 357      |
| 6              | >47, Group A           | 2280    | 1271     | 899      |
| 7              | >47, Group A           | 5264    | 3380     | 2980     |
| 8              | >47, Group A           | 780     | 650      | Stopped mifepristone |
| 9              | >47, Group A           | 1184    | 450.6    | 311.4    |
| 10             | >47, Group B           | 960     | 500      | Stopped mifepristone |

Overall percentage decrease mean±SD $= -52.0±21.41$ $-67.65±18.51$

SD: Standard deviation
ultrasonography every 3 months. No new cyst formation occurred in any of the women that were treated with mifepristone.

Location of myomas
The location of all the myomas in women with multiple myomas was studied and noted at the first visit. Mifepristone had a favorable effect on the location of myomas. In six women with submucous myomas, one small myoma disappeared at 3 months. In five women with submucous myomas, the myomas became intramyometrial, hence less symptomatic and more patient-friendly.

Side effects
Some women complained of weakness, however, side effects such as nausea, vomiting, rash, and fever were not reported by any of the 10 women enrolled in the study. Endometrium showed an increase in thickness at the end of 3 months, in this study on 25 mg mifepristone dose.

Comparison between Group A and Group B
In Group A comprising perimenopausal women >47 years of age, mifepristone was stopped in 3 women at 9 months when menopause had occurred as judged by a follicle stimulating level >40mIU/ml. In four patients, 5 mg dose was continued till 12 months and of these four women of Group A, all were asymptomatic at 12 months with a considerable reduction in the myoma size as well. The patients in Group A are being followed up till date, for 6 months to 2 years after completion of 1-year mifepristone therapy. Of the seven women in Group A, six have attained menopause and are between 1 and 2 years postmenopausal. In one patient, 18 months after stoppage of mifepristone, she had an episode of bleeding with reduced myoma size and endometrial thickness 7 mm. She was now 50 years, was put on anastrozole, and is now amenorrheic with endometrial thickness reduced to 4 mm after 2 months therapy of anastrozole.

In Group B consisting of premenopausal women of age between 40 and 45 years, in two patients, mifepristone was stopped at 3 months and 6 months when myoma had reduced considerably in size and was asymptomatic. In patient no 3, the myoma had decreased in size, but as there was a marked increase in endometrial thickness, mifepristone was stopped at 6 months. On follow-up in patient no. 1 and 2 of Group B, after 6 months

Table 5: Hemoglobin (g%)

| Patient number | Age and group 0 month | 3 months | 6 months | 9 months |
|----------------|-----------------------|----------|----------|----------|
| 1              | 40, Group B           | 10       | 11       |          |
| 2              | 42, Group B           | 9        | 11       |          |
| 3              | 44, Group B           | 11       | 11.5     |          |
| 4              | >47, Group A          | 12.5     | 12.5     |          |
| 5              | >47, Group A          | 9        | 10       |          |
| 6              | >47, Group A          | 12.5     | 11.5     |          |
| 7              | >47, Group A          | 7.8      | 11.5     |          |
| 8              | >47, Group A          | 11       | 11.5     |          |
| 9              | >47, Group A          | 9        | 10.5     |          |
| 10             | >47, Group A          | 10.2     | 11       |          |

Total number (n): 10
Mean±SD: 10.2±1.56
Range: 7.8-12.5

SD: Standard deviation

Table 6: Endometrial thickness (mm)

| Patient number | Age and group 0 month | 3 months | 6 months | 9 months |
|----------------|-----------------------|----------|----------|----------|
| 1              | 40 years, Group B     | 6        | 6.5      | X        |
| 2              | 42 years, Group B     | 5        | 0        | X        |
| 3              | 44 years, Group B     | 9.6      | 12       | 15       |
| 4              | >47 years, Group A    | 6.6      | 7        | 7.5      | 6        |
| 5              | >47 years, Group A    | 3        | 7        | 6        | 4        |
| 6              | >47 years, Group A    | 9        | 14       | 7        | 10       |
| 7              | >47 years, Group A    | 6        | 6.2      | 7.5      | 7        |
| 8              | >47 years, Group A    | 3.9      | 14       | 9.6      | 4        |
| 9              | >47 years, Group A    | 5        | 6        | 7.5      | 4        |
| 10             | >47 years, Group A    | 3        | 6        | 8        | 4        |

Total number (n): 10
Mean±SD: 5.71±2.25
Range: 3.96-14

SD: Standard deviation

Figure 3: Mean endometrial thickness

In Group A comprising perimenopausal women >47 years of age, mifepristone was stopped in 3 women at 9 months when menopause had occurred as judged by a follicle stimulating level >40mIU/ml. In four patients, 5 mg dose was continued till 12 months and of these four women of Group A, all were asymptomatic at 12 months with a considerable reduction in the myoma size as well. The patients in Group A are being followed up till date, for 6 months to 2 years after completion of 1-year mifepristone therapy. Of the seven women in Group A, six have attained menopause and are between 1 and 2 years postmenopausal. In one patient, 18 months after stoppage of mifepristone, she had an episode of bleeding with reduced myoma size and endometrial thickness 7 mm. She was now 50 years, was put on anastrozole, and is now amenorrheic with endometrial thickness reduced to 4 mm after 2 months therapy of anastrozole.

In Group B consisting of premenopausal women of age between 40 and 45 years, in two patients, mifepristone was stopped at 3 months and 6 months when myoma had reduced considerably in size and was asymptomatic. In patient no 3, the myoma had decreased in size, but as there was a marked increase in endometrial thickness, mifepristone was stopped at 6 months. On follow-up in patient no. 1 and 2 of Group B, after 6 months
of cessation of therapy, the women started having menorrhagia, and it was found on ultrasound that the myomas had regained the original size, as was before starting mifepristone.

**DISCUSSION**

Mifepristone or RU486 is a synthetic steroid with antiprogesterone and antiglucocorticoid activity. Mifepristone decreases the number of progesterone receptors in the myometrium and leiomyoma, maintaining the hormonal **milieu** as in the follicular phase; thereby inhibiting the growth of steroid-dependent myoma. Mifepristone also causes an alteration in the blood flow to the leiomyoma by a direct vascular effect. In a study, it was found that mifepristone reduces the uterine size by decreasing the myoma volume and does not affect the nonmyomatous tissue. They observed that reduction in uterine volume (26%) was parallel to reduction in leiomyoma volume (32%).

Mifepristone has been tried in varying doses ranging from 5 to 50 mg in different studies. In a recent study, 25 mg mifepristone was administered for 3 months and the myoma volume was found to have reduced by 53.62%. In this study, 92.68% women had attained amenorrhea at 3 months. In a study from India, 25 to 10 mg were used in two groups for comparison of dose-dependent effect on size of myomas. It was seen that in 25 mg group after 3 months of therapy, the reduction in volume of myoma was more than in 10 mg group. In one study, mifepristone was administered in a single dose of 50 mg orally, given every week and patients were observed for 6 months. The study showed that after 6 months of therapy, the fibroid volume reduced by 44.57% and bleeding per vaginam decreased by 100%.

In another trial, 10 mg tablet was given orally daily for 3 months to women with leiomyoma-related symptoms. They found that at the end of 3 months, menstrual blood loss declined by 94.8% and the largest leiomyoma volume decreased by 26%–32%.

In yet another study, 5 mg daily oral mifepristone was administered to 42 women with symptomatic uterine leiomyomata and uterine volume >160 ml for 6 months. After 6 months of treatment 41% women had achieved amenorrhea and uterine size decreased by 47%. Recently, in one trial, 2.5 mg mifepristone was given orally for 6 months. After 6 months of therapy, uterine volume decreased by 11% and myoma-related symptoms such as pain and bleeding showed improvement.

Vaginal mifepristone used in a 10 mg daily dose was tried in a recent study for 3 months. The leiomyoma showed a decrease in size by 39.7% and bleeding days reduced by 3–5 days. Amenorrhea was not observed in this study.

In our study, we gave 25 mg orally daily, as starting dose for first 3 months and size of leiomyoma decreased by about 44.05%. The patients were given 12.5 mg for the next 3 months and decrease in myoma size was 11.75% between 3 and 6 months. All women had achieved amenorrhea at the end of 3 months in the present study.

A comparison of studies where 2.5–25 mg was given for 3–6 months, it was seen that maximum reduction in myoma and uterine size at the end of 3 months was seen with 25 mg dose. In studies where assessment has been done at 6 months, the decrease in myoma size/uterine size was least with 2.5 mg dose among 4 studies (50 mg weekly, 5 mg daily, 2.5 mg daily, 25 mg daily for 3 months followed by 12.5 mg for 3 months). In these four studies that have been compared at 6 months including ours, the decrease in myoma size/uterine size, was almost similar at 6 months, except in the ultra-low-dose 2.5 mg trial [Table 7].

Endometrial hyperplasia has been reported in few studies at the end of 3 months with mifepristone administration. In our study, endometrial hyperplasia was seen in 1 women where endometrial thickness increased to 15 mm, but no atypia was found on histopathology.

Side effects such as nausea, vomiting, and bloating have been reported in a few studies. In one study, mild

| Study number | Mifepristone dose | Decrease in size of leiomyoma/uterine volume at different duration of therapy |
|--------------|------------------|--------------------------------------------------------------------------------|
|              |                  | 3 months | 6 months |
| 1            | 25 mg orally daily | 47.38%/37.31% | 44.57% (myoma size) |
| 2            | 50 mg orally weekly | 44.57% (uterine size) | 44.57% (myoma size) |
| 3            | 10 mg orally daily | 26%-32% (myoma size) | 47% (uterine size) |
| 4            | 5 mg orally daily | 26%-32% (myoma size) | 11% (uterine size) |
| 5            | 2.5 mg orally daily | 39.7% (myoma size) | 47.91% (myoma size) |
| 6            | 10 mg vaginally | 39.7% (myoma size) | 47.91% (myoma size) |

7. Present study: 25 mg orally daily for 3 months, 12.5 mg daily orally next 3 months.
rise in transaminase levels was seen at 6 months which however became normal at 9 months.\textsuperscript{[6]} However, no patient complained of gastrointestinal side effects in the present study.

The present study comprised fewer women because it was done in a secondary care center, where patients were drawn from the outpatient of a single gynecologist. This trial using a step-down pattern of dose decrement has not been used in many studies. Although the number of patients studied in our study was less, it has the advantage of patients being examined by the same observer at every visit, resulting in better consistency in observations. Moreover, longer follow-up has been provided in the present study and some of the patients have been observed for as long as 3 years.

Favorable outcome has been detected in all women who were perimenopausal (>47 years) at 1 year of treatment, with complete cessation of bleeding, barring one episode of scant bleeding in two women, significant reduction in myoma size, improvement in hemoglobin, and no endometrial hyperplasia at 9 months of therapy. In the premenopausal women <45 years, the myoma-related symptoms ameliorated considerably till when mifepristone was continued. However, a permanent resolution of myoma-related symptoms was not evident in this group, and the symptoms recurred after about 6 months of stoppage of the drug, when ultrasonic imaging revealed that myomas had again started increasing in size.

**Conclusion**

Therapy with mifepristone is a very safe, inexpensive modality for treatment of leiomyomas in women. In the perimenopausal age group, it averted hysterectomy in all women, with reduction in size of leiomyomas and smooth transition to menopause in six out of seven women. The step-down pattern of mifepristone dose administration has been found to be very useful as compared to other studies where a fixed dose regimen was used. In premenopausal women, mifepristone can be used to buy time, while surgery is being planned, to improve the hemoglobin and reduce myoma size so that myomectomy (hysteroscopic or laparoscopic) can be performed with ease and with lesser blood loss.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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