International Journal of Clinical Obstetrics and Gynaecology

ISSN (P): 2522-6614
ISSN (E): 2522-6622

www.gynaecologyjournal.com
2020; 4(6): 72-76
Received: 19-07-2020
Accepted: 15-09-2020

Dr. V Jayashree
Professor, Department of Obstetrics and Gynaecology, Rajah Muthiah Medical College, Annamalai University, Chidambaram, Tamil Nadu, India

Dr. A Mallika
Professor, Department of Obstetrics and Gynaecology, Rajah Muthiah Medical College, Annamalai University, Chidambaram, Tamil Nadu, India

Dr. K Roopa
Final Year Post Graduate, Department of Obstetrics and Gynaecology, Rajah Muthiah Medical College, Annamalai University, Chidambaram, Tamil Nadu, India

Corresponding Author:
Dr. V Jayashree
Professor, Department of Obstetrics and Gynaecology, Rajah Muthiah Medical College, Annamalai University, Chidambaram, Tamil Nadu, India

Mifepristone for medical management of leiomyomata uteri: A prospective study

Dr. V Jayashree, Dr. A Mallika and Dr. K Roopa

DOI: https://doi.org/10.33545/gynae.2020.v4.i6b.734

Abstract
Aim: To evaluate the effect of Mifepristone for the treatment of leiomyomata uteri.
Materials and Methods: A total of 50 women who attended gynaecological outpatient department with various symptoms associated with leiomyoma uteri were taken up for the study. Routine blood investigations including complete blood count, renal function tests, liver function tests were done. Pelvic ultra sound and Endometrial sampling were performed. The women were administered 25 mg of Mifepristone daily starting from D1-D3 of menstrual cycle for a period of 3 months. The women were followed up at the end of 3 months and after 6 months for betterment of their symptoms, improvement in their haemoglobin status, alteration in their biochemical tests like LFT, RFT. Endometrial sampling was performed at the end of 3 months of treatment. Efficacy was estimated by the reduction in the volume of fibroids, size of uterus on follow up ultra sound scans at 3 and 6 months, and improvement in quality of life.
Results: There was a significant decrease in size of uterus in 68% of women and the volume of fibroids decreased on an average to 54.8% following treatment. There was a reduction in the amount of menstrual flow in 84% of women. 22% of women reported hypomenorrhoea, 26% of women reported oligomenorrhoea, 8% reported amenorrhoea during the course of the treatment which was reversible after the completion of treatment. Almost all of them resumed regular menstruation by 6 months. Women also had significant improvement in quality of life as there was symptomatic relief and improvement of their haemoglobin levels.
Conclusion: Mifepristone in the dosage of 25mg on a short course produced significant reduction in leiomyoma volume, uterine size and produced symptomatic improvement in women with fibroids.

Keywords: Leiomyoma, fibroid, mifepristone

Introduction
Uterine leiomyomas are the most common benign uterine tumors among women of reproductive age group. They are benign hormone dependent tumors which arise from the myometrium. Among women aged over forty years, the prevalence is 30-40%. About 40% of women with myomas are symptomatic and warrant therapy [3]. They can present with variety of symptoms like menstrual abnormalities, pelvic pain, pressure, dysmenorrhoea and mass abdomen. Severity of symptoms depend on the size, site and number of myomas as well as the presence of degenerative changes [1, 2]. These were the common indications for hysterectomy and account for a large number of admission to hospitals [6]. Availability of a safe and effective nonsurgical treatment of symptomatic leiomyomata would be of considerable clinical and public health importance.
A number of antiprogestins like Ulipristal, Asoprisnil and Mifepristone (RU 486) have been used for medical management of uterine myomas. Mifepristone is a progesterone receptor modulator with primarily antagonistic properties [8, 10]. Mifepristone is administered orally, has few side effects and less expensive. So it can be used extensively for medical management of uterine leiomyoma [7].

Materials and Methods
This prospective randomised clinical trial was conducted from November 2018 to October 2020, at the Department of Obstetrics and Gynaecology, Rajah Muthiah Medical College, Annamalai University, Chidambaram, Tamil Nadu, India, after obtaining ethical clearance from the Institute's ethical committee. Patient's consent was obtained before being taken up for study. The study included 50 women of reproductive and perimenopausal age group who were

diagnosed to have fibroid uterus and presented with various symptoms caused by fibroid uterus.

Women with symptomatic myoma, atleast one myoma >2.5 cm diameter were included in the study. These women were willing to undergo medical management with Mifepristone and consented to have regular followup visits.

Women who had huge myoma (myoma size >15 cm, uterus size >20 weeks), Grade 0 submucous fibroid were excluded from the study. Women desirous of having children, users of hormonal contraceptives, women with pre-existing hepatic, renal, thyroid disorders or abnormal uterine bleeding and women who opted for surgical management were also excluded. Women who develop allergic reaction to the drug were also excluded from participating in the study.

At the initial visit, women had a questionnaire regarding the symptoms they were suffering from, the intensity and the duration. VAS scoring was used to assess the severity of the symptoms especially pain related and were plotted on a scale from 0 to 10[5]. Women were also inquired about the duration and the amount of menstrual blood loss. Pictorial blood loss assessment chart (PBAC scores) were used for the objective assessment of the quantity of menstrual blood loss. It takes into account the number of pads soaked, degree of soakage, passage of clots and episodes of flooding. A score of 100 or above denotes menorrhagia [4].

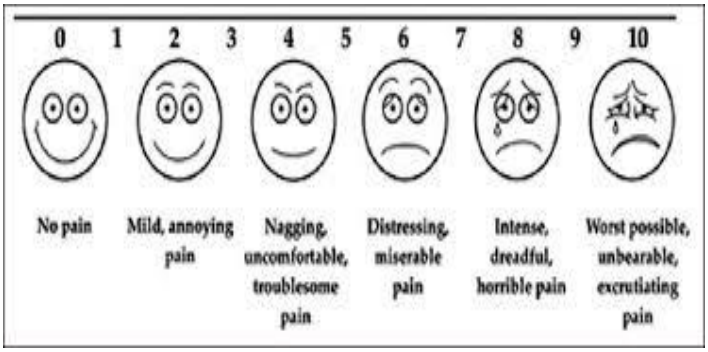


Fig 1: Visual Analogue Scale

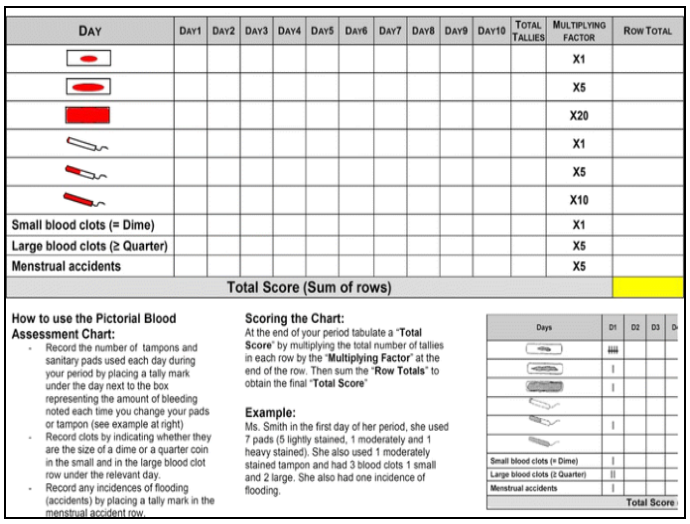


Fig 2: Pictorial blood loss assessment chart

Women had a thorough general and gynaecological examination. Per abdomen, per speculum and bimanual pelvic examination were done to assess the size of uterus clinically and to rule out any pelvic pathology. Blood investigation including complete blood count, liver and renal function tests and thyroid function tests were done. Ultrasound was performed to confirm the diagnosis of leiomyoma and to note the number, size, site of myoma, endometrial thickness and to rule out any adnexal pathology. The volume of the fibroid was calculated by the ellipsoid method using the formula, V=0.5233(D1×D2×D3), where D1, D2 and D3 were the longitudinal, transverse and cross-sectional diameters of the fibroid, respectively. In cases with multiple myomas the volumes were summed up. Endometrial sampling was performed as an outpatient procedure by aspiration method using a pipelle and sent for histopathological examination. This was done to rule out any abnormal endometrial pathology before the commencement of treatment [12].

Mifepristone is currently available in the pharmacy shops in India, in the dosage of 25 mg and 10 mg for the purpose of medical management of leiomyomata. Women were prescribed tablet Mifepristone in the dosage of 25 mg from D1-D3 of menstrual cycle for a continuous period of 3 months. They were advised to report in cases of any allergic reaction or sideeffects to the above drug. Women who were anaemic were also prescribed oral iron preparation [13].

These women were followed up at the end of 3 months of treatment, and after 6 months (ie. 3 months after completion of treatment) to assess the symptoms, menstrual blood loss, blood parameters including complete blood count, liver and renal function tests, thyroid function tests, gynaecological examination to note the size of uterus. Ultrasound scan was performed to note the change in size of fibroids and change in endometrial thickness[8]. Endometrial sampling was performed at the end of 3 months of treatment to look for any abnormalities like complex endometrial hyperplasia, atypia and malignant changes.

Results

Out of the 50 women enrolled for the study, all of them completed the course of treatment and had regular followup. There were no dropouts.

Their age ranged between 29-55 years. The mean age of the study population was 42.3 ± 5.9 years. Majority (21%) of the women belonged to the age group of 35 to 40 years. Very few (4%) were below 35 years and (5%) were above 50 years.

Body mass index (BMI) of the study population was between 17 kg/m^2 and 32 kg/m^2 with a mean of 27.5 ± 2.8 kg/m^2. Many of the women were overweight.

Mostly the women were multiparae (76%) with 2 or 3 live children. Few (12%) were primiparae and (10%) grandmultiparae. 2% were nulliparae. About 22% of women had a prior history of abortion during their childbearing period. Majority (68%) had already adopted sterilisation.

About 60% of women had other medical disorders and comorbities. The most common were diabetes mellitus (14%) and hypertension (10%). Others included hypothyroidism (8%), gall stones (4%), renal calculus (2%), rheumatoid arthritis (2%), bronchial asthma (2%), fibroadenoma breast (2%), PCOS (2%), thrombocytopenia (2%).

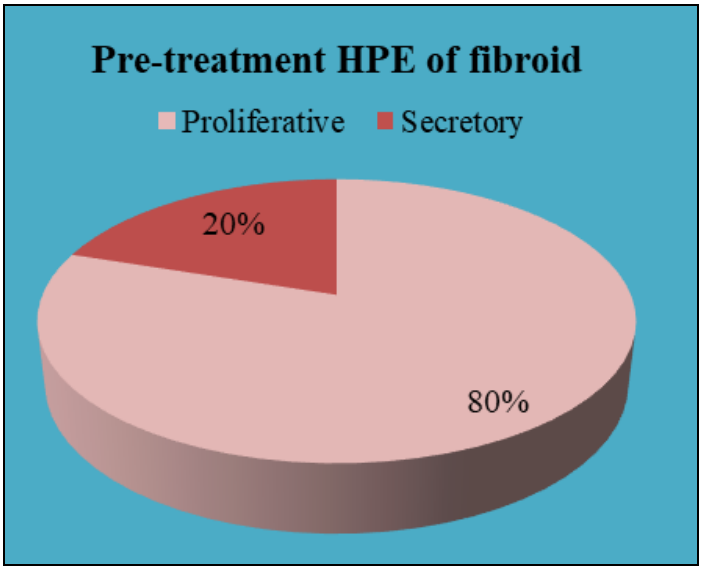
Abdominal pain, dysmenorrhea and menorrhagia were found in 68%, 40%, 25% of women respectively and were the common symptoms associated with fibroid uterus for which women sought medical care. Other associated symptoms with varying frequency of occurrence were bladder disturbances in the form of increased frequency of micturition (14%), burning micturition (14%), bowel disturbances in the form of painful defecation (2%), irregular menstrual cycles (2%), intermenstrual spotting (2%), leucorrhoea (6%), giddiness (2%), breathlessness (2%),

nausea (2%), fever (2%).

In the majority (74%) the myomas were intramuscular type and in few others submucosal (12%) and subserosal (16%). Majority (90%) of these were solitary, and few (10%) were multiple. The most common site was in the posterior wall (42%), others were in the anterior wall (36%), fundus (12%), body (4%), broad ligament (4%) and cervix (2%). The size of the uterus varied from bulky (6-8 weeks) to 14 weeks. The diameter of the myoma varied between 2 to 6 cm. The volume of the myoma varied between 2.21 cm^3 to 256.6 cm^3 and on an average 58.8 cm^3. The average haemoglobin level before treatment was 8.8g/dl. The average pain score as assessed by VAS scale was 5 ± 1.4. Endometrial pattern was predominantly proliferative in majority of women (80%) and secretory in few of them (20%).

Table 1: Pre-treatment HPE of endometrial samples (n=50)

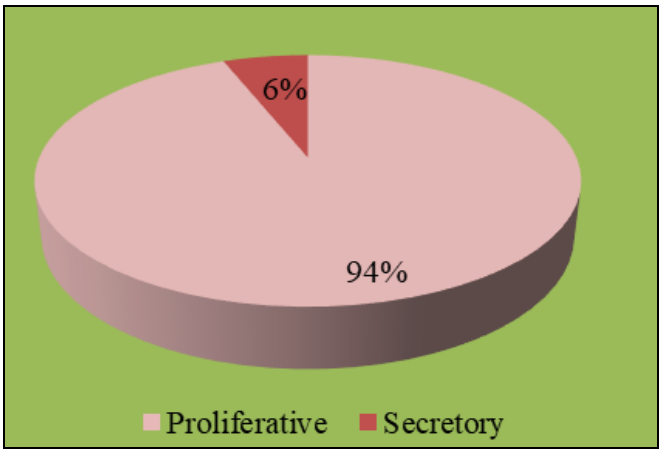
HPE	Frequency	Percentage
Proliferative	40	80.0
Secretory	10	20.0



Graph 1: Pre-treatment HPE of endometrial samples

Table 2: Post-treatment HPE of endometrial samples (n=50)

HPE	Frequency	Percentage
Proliferative	47	94.0
Secretory	3	6.0



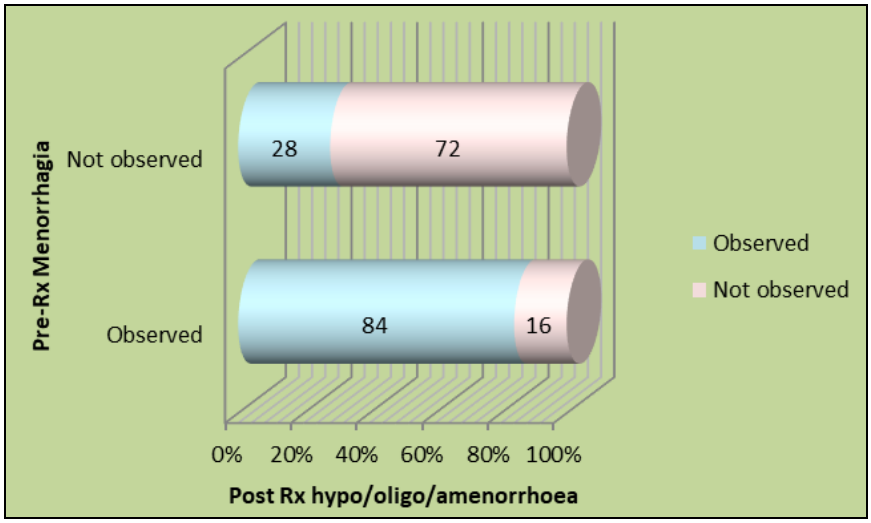
Graph 2: Post-treatment HPE of endometrial samples

Table 3: Effects on menstrual cycle (n=50)

Effects	Frequency	Percentage
Hypomenorrhoea	11	22.0
Oligomenorrhoea	13	26.0
Amenorrhoea	8	16.0

Table 4: Post-treatment alleviation of menorrhagia

Menorrhagia pre-treatment	Post-treatment hypo/oligo/amenorrhoea				$\chi 2$	p-value
	Observed (n=28)		Not observed (n=22)			
	No	%	No	%		
Observed (n=25)	21	84.0	4	16.0	15.9	<0.001
Not observed (n=25)	7	28.0	18	72.0		
McNemar Bowker Chi-square test used; The % denotes row percentage. p-value <.05 is significant						

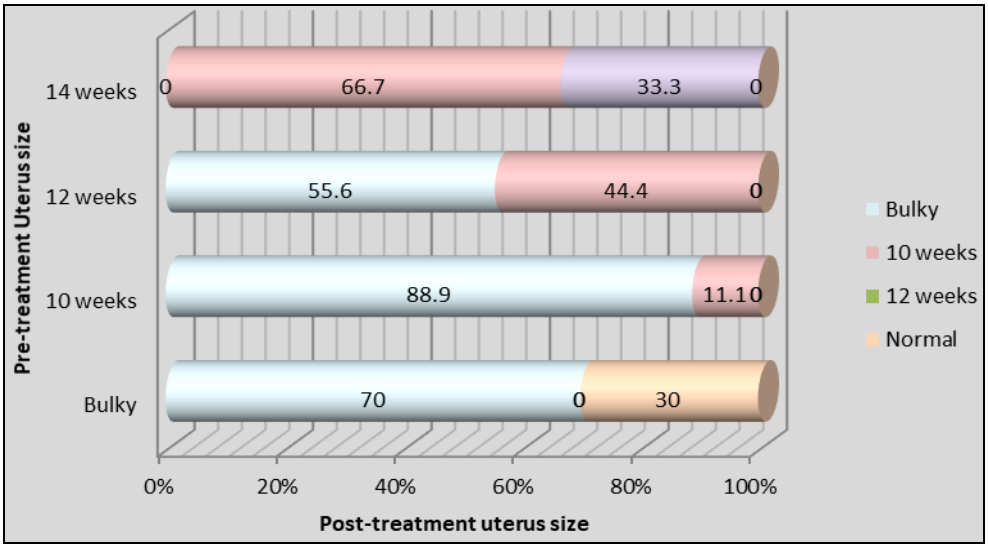


Graph 3: Alleviation of menorrhagia post-treatment (%)

Following treatment, the menstrual blood loss decreased in 84% of women who presented with menorrhagia before initiation of treatment. None of them had menorrhagia during the course of treatment or during the follow up period. About 64% had alteration in their menstrual flow pattern, in the form of hypomenorrhoea in 22% of women, oligomenorrhoea in 26% of women and amenorrhoea in 16% of women.

Table 5: Pre- and Post-treatment Uterus size comparison

Uterus pre-treatment	Post-treatment uterus								$\chi 2$	p-value
	Bulky (n=35)		10 weeks (n=8)		12 weeks (n=1)		Normal (n=6)			
	No	%	No	%	No	%	No	%		
Bulky (n=20)	14	70.0	0	0.0	0	0.0	6	30.0	27.6	**<0.001**
10 weeks (n=18)	16	88.9	2	11.1	0	0.0	0	0.0		
12 weeks (n=9)	5	55.6	4	44.4	0	0.0	0	0.0		
14 weeks (n=3)	0	0.0	2	66.7	1	33.3	0	0.0		
McNemarBowker Chi-square test used; The % denotes row percentage. p-value <.05 is significant										



Graph 4: Pre vs Post treatment comparison of uterus size (%)

The size of uterus decreased in 68% of women following treatment and continued to remain the same in 32% of women. The size of the uterus did not increase in any of the women during the treatment and followup.

Table 6: Pre and Post treatment comparison of fibroid volume (cubic cm)

	Minimum	Maximum	Mean	SD	Median	IQ Range	p-value
Pre-Rx	2.21	256.6	58.8	64.7	36.0	13.3, 66.0	**<0.001**
Post-Rx	0	125.0	29.8	33.4	16.8	4.2, 37.5	
Wilcoxon signed rank test used; p-value <0.05 is significant							

Table 7: Pre and Post treatment comparison of Hb (g/dl)

	Minimum	Maximum	Mean	SD	Median	IQ Range	p-value
Pre-Rx	6.8	12.4	8.8	1.3	8.8	8.0, 9.1	**<0.001**
Post-Rx	8.5	9.5	9.2	1.1	9.0	8.5, 9.5	
Wilcoxon signed rank test used; p-value <0.05 is significant							

Table 8: Pre and Post treatment comparison of VAS score

	Minimum	Maximum	Mean	SD	Median	IQ Range	p-value
Pre-Rx	2	8	5	1.4	4	4, 6	**<0.001**
Post-Rx	0	4	0.6	1.0	0	0, 2	
Wilcoxon signed rank test used; p-value <0.05 is significant							

The average volume of fibroid was 29.8 cm^3. There was on an average 54.8% reduction in the volume of fibroid following treatment which was statistically significant ($p< 0.05$). The mean haemoglobin level was 9.2 g/dl. There was on an average increase in haemoglobin level of 0.43 ± 0.42 g/dl and the difference was found to be statistically significant ($p< 0.05$). The average pain score was 0.6 ± 1.0. There was on an average improvement in VAS score of 4.4 ± 1.4 in these women which was also statistically significant ($p< 0.05$). The endometrial pattern was predominantly proliferative (94%) and secretory (6%) in few of them. There was no abnormal endometrial pattern like complex endometrial hyperplasia or atypia or malignant changes following treatment. There was no abnormality in the biochemical parameters like renal or liver function tests following treatment. There was no adverse effect to the drug during treatment except for nausea found in 4% of women.

Table 9: Average improvement in outcome parameters and Percentage improvement in outcome parameters

Difference in	Minimum	Maximum	Mean	SD	Median	IQ Range	Difference in	Minimum	Maximum	Mean	SD	Median	IQ Range
Fibroid volume (in cm^3)	1.7	133	29.0	33.6	15.7	5.9, 35.4	**Fibroid volume** (in%)	20.0%	100.0%	54.8%	20.1%	52.0%	42.7%, 64.9%
Hb (g/dl)	0.3	1.3	0.43	0.42	0.30	0.08, 0.73	Hb (in%)	2.0%	18.0%	5.5%	5.7%	3.6%	0.7%, 8.7%
VAS	2	8	4.4	1.4	4.0	4.0, 6.0	VAS (in%)	33.0%	100.0%	89.0%	18.9%	100.0%	72.9%, 100.0%

Discussion

Mifepristone can be considered as the drug of choice for medical management of leiomyomata uteri in women who have completed their families. Mifepristone can be a reasonable choice in perimenopausal women in whom myomas would regress after menopause. Mifepristone is also useful in unmarried women who want to avoid surgery.

In women of reproductive age, Mifepristone can be used with caution. Because of its action as a contraceptive, interceptive, contragestive and abortifacient, women generally donot conceive during the course of treatment. Nevertheless, they should be counselled to adopt a non-hormonal method of contraception which does not interfere with the action of Mifepristone during the course of treatment [11].

The dose of Mifepristone used for this purpose has reduced over the decade from 50 mg to 25 mg. With the 25 mg dosage used for a period of 3 months, there is a substantial reduction in the volume of fibroid, size of uterus and improvement of symptoms and menstrual disorders with minimal side effects[14]. The effects were evident as early as a month after starting therapy and continued to persist till 6 months.

Further studies are recommended regarding the safety and efficacy of lower doses of Mifepristone such as 10mg, 5mg and 2.5mg. The optimal dosage effective for medical management of leiomyomata is yet to be established. Further studies are required to evaluate if intermittent administration, with treatment duration of 3-4months followed by an off-drug interval till menstruation occurs would be useful for long-term usage of Mifepristone. Long term trials are needed to evaluate if there was recurrence of symptoms or regrowth of fibroids after stopping treatment in these women who underwent medical management [15].

There was a transition from secretory to proliferative type of endometrium following treatment in 14% of women which could be due to unopposed action of oestrogen on the endometrium antagonising the effect of progesterone. None of the women reported increase in endometrial thickness on ultrasound or complex or atypical endometrial hyperplasia or malignant changes in the endometrial samples on histopathological examination following treatment. Recent studies suggest that the 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. Though some of the earlier studies had reported Progesterone receptor modulator associated endometrial changes (PAEC) which include cystic dilatation of glands with mixed oestrogen and progesterone features, non-synchronous endometrium, pseudo-stratification of epithelium, pseudo-decidualised stroma, abnormal and dilated thin blood vessels with no evidence of atypical hyperplasia, such features were not reported in our study.

Mifepristone can also be used as a pre-operative adjuvant, especially in patients with pre-operative severe anaemia to improve the haemoglobin level and in large fibroids to shrink the size of fibroids and make the surgery less invasive vaginal procedure and technically easier one.

Conclusion

Mifepristone in the dosage of 25mg for a short course period of 3 months was effective for medical management of leiomyomata uteri. There was no adverse effect to the drug when used for a continuous period of 3 months. There was a significant reduction in leiomyoma volume and uterine size. Patient had significant improvement in their quality of life in the form of decrease in menstrual flow, betterment of their symptoms and improvement in their haemoglobin levels. Mifepristone can also be used as an effective pre-operative adjuvant.

References

1. Buttram VC, Reiter RC. Uterine leiomyomata: etiology, symptomatology and management. Fertil Steril 1981;36:433-445
2. Stewart EA. Uterine fibroids. Lancet 2001;357:293-298
3. Day BD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: Ultrasound evidence. Am J ObstetGynaecol 2003;188:100-7.
4. Wegeinke G, Bavid DD, Hertz Picciotto J, Harlow SD, Steege JF, Hill MC *et al*. self reported heavy bleeding associated with uterine leiomyomata. ObstetGynaecol. 2003;101:431-7.
5. Lippman SA, Warner M, Samuels S, Olive D, Vercellini P, Eskenazi B. Uterine fibroids and gynecologic pain symptoms in a population based study. FertilSteril 2003:80:1488-94.
6. Becker ER, Spalding J, Duchane J, Horowitz IR. Inpatient surgical treatment patterns for patients with uterine fibroids in the United states, 1998-2002. J Nat Med Assoc 2005;97:1336-42.
7. Murphy AA, Castellano P. RU 486: Pharmacology and potential use in the treatment of endometriosis and leiomyomata uteri. CurrOpinObstet Gynaecol 1994;6:269-78.
8. Fiscella K, Eisinger SH, Meldrum S, Feng C, Fisher SG, Guzick DS. Effect of mifepristone for symptomatic leiomyomata on quality of life and uterine size: A randomized control trial. Obstet Gynecol 2006;108:1381-7.
9. Wilson EA, Yang F, Rees ED. Estriadol and progesterone binding in uterine leiomyomata and in normal uterine tissue. Obstet Gynecol 1980;55:20-4.
10. Soules MR, McCasty KS. Leiomyomatas: Steroid Receptor content. Am J Obstet Gynecol 1982;143:6-11.
11. Malartic C, Morel O, Allerman G, Tulpin L, Desfeux P, Barranger E. Role of mifepristone for the treatment of uterine Fibroid. Gynecol Obstet Fertil 2008;36:668-74.
12. Engman M, Granberg S, Williams AR, Meng CX, Lalitkumar PG, Gemzell-Danielsson K. Mifepristone for treatment of uterine leiomyoma. A prospective randomized placebo controlled trial. Hum Reprod 2009;24:1870-9.
13. Steinauerer J, Pritts EA, Jackson R, Jacoby AF. Systematic Review of mifepristone for the treatment of uterine Leiomyomata. Obstet Gynecol 2004;103:1331-6.
14. Murphy AA, Kettel LM, Morale AJ, Roberts NJ, Yen SS. Regression of uterine leiomyomata in response to the antiprogesterone RU486. J ClinEndocrinol Metab 1993; 76:313-7.
15. Eisenger SH, Bonfiglio T, Fiscella K, Meldrum S, Guzick DS. Twelve month safety and efficiency of low dose Mifepristone for uterine myomas. J Minim Invasive Gynecol 2005;12:227-33.