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A Prospective and Interventional Study of the Role of Low Dose Mifepristone in the Management of Uterine Leiomyoma in Perimenopausal Women

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Original Research Article

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Abstract: The objective of this study is to determine the effect of progesterone antagonist, Mifepristone in perimenopausal women in decreasing the severity of symptoms like menorrhagia, dysmenorrhea, abdominal pain and urinary symptoms, in decreasing the fibroid volume and uterine volume, in improving the hemoglobin percentage, in increasing the endometrial thickness, to look for the side effects profile and to look for the effects which were present at the end of treatment persisted during post treatment follow up. It is a prospective and interventional study done among the perimenopausal women with symptomatic fibroid uterus who came to the Gynecological OPD in Gandhi Hospital, Secunderabad for a period of one and half year in a sample size of 50 patients. After taking a detailed menstrual history and calculating Pictorial Blood loss Assessment Chart (PBAC) score for menorrhagia and Visual Analogue Scale (VAS) score for dysmenorrhea and abdominal pain, baseline fibroid and uterine volumes, haemoglobin percentage and endometrial thickness were noted and endometrial biopsy was done when endometrial thickness crossed≥8mm. The drug mifepristone 25 mg was given orally for a period of 3 months. The same parameters were measured after completion of 3 months of treatment and at another 3 months post treatment follow up. The values were compared with the values before treatment. Statistical analysis was done with paired t test and found whether the change in the variables before treatment, at the end of treatment and during post treatment follow up was significant or not. Menorrhagia was the most common symptom which made the patients to report to the hospital. After completing 3 months of treatment, menorrhagia, dysmenorrhea and abdominal pain decreased by 95.3%, 91.5% and 78.2% respectively. Fibroid volume and uterine volume decreased by 51.2% and 34.3% respectively, haemoglobin % increased by 13.9% and endometrial thickness by 24.8%. There were minimal tolerable side effects. At 3 months post treatment follow up also, there was improvement in symptomatology compared to before treatment. 25 mg oral mifepristone for 3 months effectively decreased menorrhagia, dysmenorrhea, abdnominal pain, decreased fibroid volume, uterine volume, improved haemoglobin % there by avoiding unnecessary surgery in perimenopausal women.
Keywords: Mifepristone, fibroid, dysmenorrhoea.

INTRODUCTION

Leiomyoma of the uterus is a benign tumor essentially composed of smooth muscle tissue and a variable amount of fibrous connective tissue. It is the most common tumor of the uterus and is found in 20 % of women in the reproductive age group [1]. In the age group between 35 and 49 years about 50% of the women have fibroids, out of which about half of them present with heavy bleeding leading to severe anaemia [2, 3]. Leiomyomas are the reason behind one third of all hospital admissions to gynecology services and one of the commonest indications for hysterectomy [4]. Leiomyomas are the most cited indication for more than 600,000 hysterectomies performed in the US annually, a procedure which is associated with morbidity, mortality and huge economic burden estimated to be approximately 34.4 billion/year [5]. Symptoms include menstrual disturbances, commonly menorrhagia and dysmenorrhea that can lead to iron deficiency anemia, pressure symptoms such as increased urinary frequency, pelvic pain and constipation, and they may interfere with reproduction [6] by causing subfertility or preterm

birth depending upon the location of fibroid. It has been said that these symptoms and signs may decrease the health – related quality of life, with 30% symptoms severe enough to miss work [7].

As recently as 15 – 20 years ago, the choices for women with symptomatic fibroids were confined to abdominal hysterectomy and conventional abdominal myomectomy. The former constituted a cure, for all symptoms were eradicated without a possibility of recurrence of fibroids, but hysterectomy is unacceptable to women wishing to retain fertility potential. Myomectomy is a major operation with associated morbidity risks. It may compromise the very same fertility that it seeks to preserve, due to potential for adhesion formation and there is a significant risk of recurrence of the disease. As such there is clearly a need for medical therapy that eliminates the need for surgery, is relatively cheap, and has efficacy that is equivalent or superior to surgery. While it has long been established that estrogen promotes fibroid growth, recent biochemical and clinical studies have suggested that progesterone, progestins and progesterone receptors (PR) may also enhance proliferative activity in fibroids. Estrogens are required only for up regulation of progesterone receptors [8]. These progestins have therefore raised the possibility that antiprogestins and PR agonists and antagonists could be useful in the medical management of fibroid uterus.

One such drug which has an effect as an antiprogestin is Mifepristone or RU 486. It is a 19 -nor steroid with antiprogesterone and antiglucocorticoid activity [9]. It is a high PR affinity antiprogestin [6]. Recently several reports showed that Mifepristone in lower doses ranging from 5mg/day to 50mg/day for duration between 3 to 6 months was useful in providing symptomatic relief by decreasing dysmenorrhea and menorrhagia in the case of women with fibroid uterus and decreasing the fibroid and uterine volume.

The other drugs are gonadotropin antagonists which are of higher cost and are associated with major side effects like osteoporosis and vasomotor symptoms[1]. The next generation Progesterone antagonist Ulipristal acetate is also evaluated its effectiveness in curing the fibroids but it is also a costly drug and long term safety is yet to be known.

The present study aims to study the effect of the dose of 25 mg Mifepristone for the management of symptomatic uterine fibroids in perimenopausal women attending the OPD, Gandhi Hospital, Secunderabad.

PATIENTS AND METHODS

Source of data: Perimenopausal women with symptomatic fibroid uterus who came to the Gynecological OPD in Gandhi Hospital, Secunderabad.

Study Design: Prospective and Interventional study

Duration of Study: One and half year, from January 2015 to July 2016

Sample size: 50 patients

Inclusion criteria

1. Women more than 40 years of age
2. Women with symptomatic fibroids
3. Size of the fibroid in between 2.5cms and 7cms
4. Without any endometrial hyperplasia with atypia
5. Non – pregnant
6. Women with single fibroid
7. In case of multiple fibroids, the dimensions of the largest fibroid were taken

Exclusion criteria

1. Women presenting with severe anemia and with acute symptoms
2. On hormonal medication within 3 months of starting the treatment or on corticosteroids
3. History of breast cancer or other genital malignancies
4. Myoma size more than 7cms
5. Cervical or tubal associated lesions
6. Current genital infections
7. Pregnancy
8. Suspicion of leiomyosarcoma on ultrasound examination
9. Severe renal dysfunction
10. Mild to moderate hepatic dysfunction
11. Associated with adenomyosis or endometriosis
12. Dilatation & Curettage report showing endometrial hyperplasia with atypia
13. History of porphyrias

Details of the work done

Informed consent was taken from all the patients before including them in the study. Detailed history was taken regarding the socio-demographic profile including age, socio–economic status and parity, detailed menstrual history regarding regularity of the cycles, duration of flow in each cycle, number of pads used per day, history of passage of clots, size of clots passed and number of flooding episodes. By using this information, average blood loss was estimated using Pictorial Blood loss Assessment Chart (PBAC). The degree of dysmenorrhea and abdominal pain was estimated using Visual Analogue Scale (VAS) score. Medical problems like hypertension and diabetes, history of usage of hormonal treatment 3 months prior to the administration of this drug, dietary habits, bowel and bladder habits, family history of breast or genital malignancies were taken note of.

Clinical examination: The height and weight were measured and BMI calculated. General health was evaluated by the presence, absence and degree of pallor, icterus, cyanosis, clubbing, generalized lymphadenopathy and pedal edema. Vitals were checked. CVS, respiratory system, CNS, GIT were examined. Detailed gynecological examination by per abdominal examination and uterine and adnexal evaluation by per speculum and bimanual examination were done.

Investigations: Hematological investigation included Complete Blood Picture, Random Blood Sugar, Blood Urea, Serum creatinine, Liver Function Tests, Coagulation Profile and Thyroid Profile. Ultrasound scan was done transabdominally with Esaote My lab machine using 5 MHz probe to look for the uterine volume, fibroid volume, type of fibroid, endometrial thickness and any other adnexal pathology. If the endometrial thickness was found to be ≥8mm in USG, endometrial biopsy was done and the sample sent for histopathological examination to look for any hyperplasia, atypia or malignancy. All the above investigations were done free of cost in Gandhi Hospital. Viscosmi formula was used for the measurement of uterine volume that is $4/3\pi \times W/2 \times L/2 \times T/2$ where W is uterine width on transverse section passing through the uterine fundus, L is the uterine length measured on sagittal section from the internal os to the fundus, T is the uterine thickness measured on sagittal section between the anterior and posterior walls. Measurement of fibroid volume was done by the formula $4/3\pi abc$, where a, b and c represent radii of the sphere in three dimensions. In case of multiple fibroids, dimension of the largest fibroid was taken for volume calculation and follow up.

After ruling out all the excluding criteria, Mifepristone 25mgper day was given orally to all the subjects for a duration of 3 months. As Mifepristone is available in the market as 200mg tablet, it was broken into 1/8th part. Electronic Digital Weight Balance Pocket Scale was used to make it to exactly 25 mg and supplied by us to the patients. During this 3 months period all the subjects were asked to report if they have any of the following symptoms: excessive nausea, vomiting, diarrhoea, pain abdomen, excessive bleeding, fever, or any hypersensitivity reactions. They were asked to maintain a proper menstrual calendar during this entire study period.

Follow up: Patients were asked to come after the completion of 3 months of treatment. At that visit, patient's menstrual flow during these 3 months was assessed using PBAC score. Dysmenorrhea and abdominal pain were assessed using VAS score. Any urinary complaints and any significant side effects like nausea, vomiting, diarrhea, hot flushes, backache etc were assessed. Hematological investigations like CBP and LFT were done. Trans-abdominal ultrasound scan was done to assess the uterine volume, fibroid volume and endometrial thickness and if endometrial thickness crossed ≥8mm, endometrial biopsy was done. All these variables were compared before treatment and after treatment to find out any significant change.

Mifepristone was stopped after 3 months of treatment and post treatment follow up was done at the end of another 3 months. At the post treatment follow up also a detailed menstrual history was taken using the menstrual calendar and the blood loss was assessed using PBAC score, dysmenorrhea and abdominal pain were assessed using VAS score, urinary symptoms were evaluated. Hematological investigations like CBP and LFT were repeated. USG was done to assess the uterine and fibroid volumes and endometrial thickness. All these variables were compared with the values before treatment to find out if the effects of mifepristone lasted for another 3 months after stopping the drug.

Ethical issues

The Institutional Ethical Committee of Gandhi Medical College has approved the study.

Informed consent was taken from all the subjects in their own language.

Statistical analysis methods

All the data obtained was analysed statistically using the Paired t test. The results were compared between:

1. Variables before treatment and after completion of 3 months of treatment
2. Variables before treatment and 3 months after stopping the treatment (post treatment follow up).

P value was calculated to determine whether the change was significant or not.

OBSERVATION AND RESULTS

Out of 50 patients who were included in the study, majority was in between 40 and 45 years of age which was 72%. The mean age was 42.1 ±4.52. Majority of the patients were in the lower middle socio-economic class. Only 2 patients were nulliparous. Most common symptom was menorrhagia (84%), followed by dysmenorrhoea (78%) and both together were present in 64% of study population. Family history of fibroid was present in 8% of patients. About 62% of study population was over-weight. The mean BMI was 27±3.66. Before starting treatment, 92% of the patients had Hb<12gm/dl/. 12 out of 50 patients had endometrial thickness ≥8mm for whom endometrial biopsy was done before starting treatment and most common HPE finding was secretory endometrium seen in 8 patients followed by proliferative endometrium seen in 4 patients.

After using 25 mg mifepristone for a period of 3 months, menorrhagia, dysmenorrhea and abdominal pain decreased by 95.6%, 91.5% and 78.2% respectively. Haemoglobin and endometrial thickness increased by 13.9% and 24.8% respectively. Uterine volume and fibroid volume decreased by 34.3% and 51.2% respectively. About 86% of patients were amenorrhoeic and about 94% of patients showed more than 80% decrease in PBAC score at the end of 3 months of treatment. After following the patients for another 3 months of stopping mifepristone, compared to the values before treatment, the decrease in the menorrhagia, dysmenorrhea and abdominal pain was 71.8%, 50.4% and 51% respectively i.e., though there was recurrence of symptoms after stopping the drug, the intensity was less than the pretreatment level. Increase in the haemoglobin was maintained at 13.8%. Endometrial thickness drastically decreased after stopping the drug. There was a little increase in the uterine volume and fibroid volume but it was always less than the pretreatment value.

Table 1: Table showing percentage change in the following variables at the end of 3 months of treatment with Mifepristone and at another 3 months post treatment follow up compared to before treatment

Parameter	% change at the end of 3 months of treatment with mifepristone	% change at the end of another 3 months post treatment follow up
Dysmenorrhoea (VAS)	↓ 91.5%	↓ 50.4%
Menorrhagia (PBAC)	↓ 95.6%	↓ 71.8%
Abdominal pain (VAS)	↓ 78.2%	↓ 51%
Haemoglobin	↑ 13.9%	↑ 13.8%
Endometrial thickness	↑ 24.8%	↑ 3.4%
Uterine volume	↓ 34.3%	↓ 29.4%
Fibroid volume	↓ 51.2%	↓ 47.7%

Table 2: Change in the following parameters at 3 months of treatment and at another 3 months post treatment follow up compared to before treatment with P value

Parameter	Mean Value before treatment	Mean Value at 3 months of treatment	p value	Mean value at another 3 months post treatment follow up	p value
Menorrhagia (PBAC)	322.7 ± 221.5	14 ± 58.58	<0.001	90.76 ± 66.76	<0.001
Dysmenorrhoea (VAS)	4.28 ± 2.46	0.36 ± 1.19	<0.001	2.12 ± 1.73	<0.001
Abdominal pain (VAS)	1.84 ± 2.45	0.4 ± 1.21	<0.001	0.9 ± 1.49	<0.001
Haemoglobin	9.96 ± 1.15	11.35 ± 0.99	<0.001	11.27 ± 1.06	<0.001
Fibroid volume	25.08 ± 29.58	12.24 ± 13.02	<0.001	13.11 ± 14.03	<0.001
Uterine volume	156.87 ± 63.65	103.038 ± 36.33	<0.001	110.762 ± 40.04	<0.001

Among 50 patients, none of them had any major side effects. In 14 patients, there were minor side effects out of which nausea and abdominal pain are common, seen in 4 patients each. 3 patients had hot flushes, in 2 LFT's were raised but not more than two times the upper limit of normal and 1 patient had backache. In the present study, after completing 3 months of treatment, menstruation regained in a mean duration of 29.92 days. 5 patients out of 50 (10%) decided to undergo hysterectomy at the end of 3 months post treatment follow up. Among them, in 2 patients, there was no significant difference in symptoms before starting treatment and at the 3 months post treatment follow up, though during treatment they were asymptomatic. In 2 patients, menorrhagia increased significantly from the period before treatment to the 3 months post treatment follow up, though symptoms decreased during the treatment period. In 1 patient, though menorrhagia decreased compared to the period before treatment, she was still having menorrhagic cycles with PBAC score more than 100 and she opted for hysterectomy.

Follow up

In the present study, follow up was 100% which was due to the very minimal side effects and significant improvement in symptoms.

DISCUSSION

Fibroids being a tumour of hyper-estrogenic environment, medical management that lowers estrogen levels such as GnRH agonists and antagonists,

aromatase inhibitors, SERMs were used for symptomatic relief and decreasing the size of fibroids. But GnRh analogues will cause higher financial burden to the patients. Their side effects are very significant as the users suffer from hot flushes and osteoporosis. Also there will be recurrence of symptoms after stopping the drug.

Current studies support that growth of fibroids in humans is progesterone dependent also and therefore antiprogestins can be effective in treatment [10]. One such drug is Mifepristone. It controls bleeding, decreases dysmenorrhea, reduces uterine volume and fibroid size, improves hemoglobin percentage and renders surgery unnecessary as patient reaches menopause because, fibroid being a hormone dependent tumor stops to grow after menopause [11]. Clinical trials using different doses of Mifepristone 5 – 50 mg were conducted for varying periods of 3 to 12 months, in various studies and its usefulness was proved. But the exact dose and duration of treatment are yet to be determined. In the present study, Oral Mifepristone 25 mg daily for a period of 3 months was administered, with 3 months post treatment follow-up. We have chosen perimenopausal age group as there is decrease in ovarian activity and once when therapy is stopped, there is less likely to increase in size of fibroids unlike in reproductive age period.In the present study, the mean age of study population was 42.1±4.52. 30% were of socio – economic class 3 compared to Shikha Seth *at al* [12] where majority were of the socio – economic class 4. Majority of the women were parous in the present study, most being para 2 (54%).Mean parity was 1 ± 1. Mean parity was 2.28±1.48 in the Seema Saharan *et al* [10] study. According to Aamir T Khan *et al* [13] parity is inversely associated with risk of fibroid development. During post-partum uterine remodeling there could be selective apoptosis of smaller lesions. Ischemia during parturition is also a proposed mechanism. Pregnancies early in the reproductive years, before age 25, may occur before the formation of myomas, and pregnancies after age 30 may occur when myomas are too large to regress. In this study majority of the women were pregnant before the age of 25 years because of which protection may not have occurred.

Majority of the patients in this study were overweight which accounted to 62%. The mean BMI in the present study and in the study done by Seema Saharan *et al* [10] was 27±3.66 and 26.64 respectively. Both showed that fibroids are more common in overweight and obese patients. In a study by Ukwenya *et al* [14] regarding prevalence of fibroids, they found that the risk of myoma increased 21% with every 10kg increase in body weight and increasing BMI. Adipose tissue converts adrenal and ovarian androgens into estrogens, whereas several mechanisms associated with obesity lead to decreased synthesis of sex hormone binding globulin. It is thus possible that the increase of biologically available estrogens could be responsible for an increase in myoma prevalence and/or growth in overweight and obese women.

In the present study, the most common presenting symptom was menorrhagia which was seen in 84% of patients followed by dysmenorrhea in 78%. In majority of the studies including the present study, the most common symptom was abnormal uterine bleeding. Intensity of menorrhagia was more in the present study compared to other studies [15].

In the present study, the mean fibroid volume was less when compared to other studies. This could be because here fibroids of size 2.5cms to 7cms were included where as in other studies the size of the fibroid included was of the higher range. Similarly the mean uterine volume was also less in the present study compared to other studies. Intramural was the most common type of fibroid in the present study similar to Joseph LluisCarbonell *et al* [16]. In the study by Raghav *et al* [17] the most common type of fibroid was sub mucous.

Patients requiring endometrial biopsy

In the present study, only in those patients in whom endometrial thickness was ≥8mm, (24% of patients) endometrial biopsy was done. In contrast, in the studies by Engman *et al.* [11] Rita Lal *et al*. [9] and Vidushi Kulshrestha *et al.*, [8] endometrial biopsy was done irrespective of endometrial thickness in all patients before treatment. In the Joseph LluisCarbonell *et al*., [16] study, endometrial biopsy was done only when endometrial thickness was ≥ 8mm, similar to the present study, and endometrial biopsy was required in 17.3% of patients before starting treatment in their study.

The most common HPE finding was secretory endometrium followed by proliferative endometrium. In the present study, hemoglobin ≤12 gm/dl was taken as anemia similar to the study of Seema Saharan *et al* [10], as considered by WHO. Accordingly, 92% of people were anemic in the present study

Improvement in symptomatology, change in uterine volume, fibroid volume, endometrial thickness and haemoglobin percentage at the end of 3 months of treatment

In the present study, the decrease in PBAC score at the end of 3 months was 95.6% which was comparable to other similar studies at same dose and duration of treatment. With increase in the duration of treatment, the percentage of patients who were amenorrhoeic had decreased. This might be because of increased rates of breakthrough bleeding or spotting. In the present study, the percentage of improvement in

VAS score was greater (87.5%) when compared to other studies.

The decrease in fibroid volume was 51.2% comparable to the study of Shikha Seth *et al*., [12] where the dose and duration of mifepristone was similar to the present study. In the present study, maximum decrease in volume of fibroid was seen with intramural type which was 54.1%, followed by sub mucous type. In the study by Shikha Seth *et al* [13] with 25 mg mifepristone for 3 months the maximum decrease in volume of fibroids was seen with intramural and subserous type. In the present study, the decrease in uterine volume at 3 months of treatment was 34.3% comparable to Shikha Seth *et al* [13] (36.3%). In the study by Engman *et al* [11], with 50 mg mifepristone on alternate days, there was no change in uterine volume. In the study by Carbonell *et al* [16], the decrease in the uterine volume was less than the present study which might be due to the lower dose of mifepristone used in these studies and also larger number of sub serous fibroids compared to the present study.

Shikha Seth *et al* [13] showed increase in hemoglobin by nearly 3 times and Seema Saharan *et al* [12] by 2 times compared to the present study. This could be because, the mean hemoglobin at the start of treatment was 9.96±1.15gm/dl in the present study, higher than that of Shikha Seth *et al* [13] (8.9±2.1gm/dl) and Seema Saharan *et al* [12] (8.7±0.37gm/dl). Also, the percentage of people who were amenorrhoeic at the end of treatment was 92.68% and 88% in the studies of Shikha Seth *et al* [13] and Seema Saharan *et al* [12] respectively which was more than the present study (86%).

Table 3: Percentage decrease in the PBAC scores and percentage of people amenorrhoeic at the end of treatment when compared to other studies

Study	Dose	Duration of treatment	% decrease in PBAC score	% of people amenorrhoeic at the end of treatment
Present study	25 mg / day	3 months	95.60%	86%
Seema Saharan *et al* [10]	10 mg / day	3 months	98%	88%
Engman *et al* [11]	50 mg alternate day	3 months	100%	100%
VidushiKulshrestha *et al* [8]	25 mg / day	3 months	96.40%	95.7%
VidushiKulshrestha *et al* [8]	10 mg / day	3 months	92.40%	90.40%

Table 4: Percentage decrease in the VAS score at the end of 3 months of treatment when compared to other studies

Study	Dose	Duration of treatment	% decrease in VAS score
Present study	25 mg / day	3 months	87.50%
Seema Saharan *et al* [10]	10 mg / day	3 months	79%
CarbonellEsteve *et al* [16]	2.5 mg / day	3 months	70%
CarbonellEsteve *et al* [16]	5 mg / day	3 months	85.70%

Table 5: Percentage decrease in the fibroid volume and uterine volume at the end of treatment compared to other studies

Study	Dose	Duration of treatment	% decrease in fibroid volume	% decrease in uterine volume
Present study	25 mg / day	3 months	51.20%	34.30%
Seema Saharan *et al* [10]	10 mg / day	3 months	58%	
Shikha Seth *et al* [12]	25 mg / day	3 months	46.38%	36.30%
Engman *et al* [11]	50 mg alternate day	3 months	27%	0%
VidushiKulshrestha et al [8]	25 mg / day	3 months	35.70%	
VidushiKulshrestha *et al* [8]	10 mg / day	3 months	22.50%	
Rita lal *et al* [9]	20 mg	3 months	29.80%	
Joseph LluisCarbonell *et al* [16]	2.5 mg	3 months	27.90%	18.20%
Joseph Lluis Carbonell *et al* [16]	5 mg	3 months	46.40%	22.10%
Bagaria *et al* [20]	10 mg/ day	3 months		26.60%

Increase in endometrial thickness in the present study at the end of treatment was less when compared to other studies. In the present study, endometrial biopsy was done only when endometrial thickness was ≥8mm before and after treatment similar to Carbonell *et al* [16] study. In other studies endometrial biopsy was done in all patients. At the end of 3 months of treatment, the most common HPE finding was secretory endometrium (50%) followed by cystic glandular dilatation (31%). Progesterone associated endometrial change was seen in 1 patient. This was in contrast to Engman *et al* [11] and Kulshrestha *et al* [8] studies where cystic glandular dilatation and proliferative endometrium were the most common HPE findings respectively.

Side effects

There were minimal tolerable side effects as the dose used in the present study was lower and the duration of treatment was shorter. The most common side effects were nausea (8%) and pain abdomen (8%), followed by hot flushes (6%). In 2 patients LFTs were raised but the rise was not more than 2 times the upper limit of normal and it reverted back to normal at 3 months following stoppage of mifepristone. In the study by Seema Saharan *et al*, [10] hot flushes, fatigue, headache were seen in 4% of patients each and LFTs were not affected. In the study by Shikha Seth *et al*, [2] liver enzymes were raised in 31.7% of patients, but not twice the upper limit of normal. Headache was seen in 12% at the end of 1st month and hot flushes were seen in 3.65% at the end of 2nd month. Engman *et al* [11] study also reported hot flushes as a significant side effect. There was no significant difference in LFTs except for a slight increase in ALT. Kulshrestha *et al* [8] reported leg cramps, hot flushes, weakness and palpitations more commonly in 25 mg group compared to 10 mg group. Similar to the other studies, transient rise in LFTs were also seen in 2.8% and 2.7% of patients in 25 mg group and 10 mg group respectively. In the study by Rita lal *et al* [9] at the end of 3 months of treatment, nausea and hot flushes were seen in 8% of patients. In the study by Carbonell *et al* [16] at lower doses of 2.5 mg and 5 mg, side effects like hot flushes, nausea, vomiting and fatigue were seen. LFTs were also raised but not twice the normal.

In none of the above studies, there were major side effects and so the compliance to drug treatment was good in almost all studies including the present study.

Change in menstruation, fibroid volume, uterine volume, endometrial thickness, haemoglobin percentage at 3 months post treatment follow up period compared to other studies

In the present study, mean PBAC score at 3 months post treatment follow up decreased by 71.8% compared to the pretreatment value. None of the patients were amenorrhoeic at 3 months post treatment follow up. Menstruation resumed in a mean duration of 29.92 days. In the study by Shikha Seth *et al*, [12] during 3 months post treatment follow up, 1 subject was amenorrhoeic, menstruation regained in a mean duration of 34.7±17.48 days. In Kulshrestha *et al*, [8] study during 9 months post treatment follow up with 25 mg and 10 mg dose of mifepristone, 35% and 28% were asymptomatic with a median PBAC score of 85 (26-1117) and 74 (32-210) respectively.

The decrease in fibroid volume remained almost stable at the end of 3 months of treatment and during post treatment follow up period in the present study similar tostudies of Rita lal *et al* [9] and Esenger [18] where25 mg dose of mifepristone was used. Carbonell *et al* [16] concluded that where lower doses of mifepristone of 2.5 mg and 5 mg were used the decrease in fibroid volume at the end of 3 months of treatment did not sustain for the next 3 months (post treatment follow up). In the present study, during the post treatment follow up period for 3 months, there was a marginal increase in uterine volume compared to the end of treatment. In Carbonell *et al* [16], (mifepristone of 2.5 mg and 5 mg), uterine volume had almost doubled at 3 months post treatment follow up compared to the end of treatment though it was less than the pretreatment value.

In the present study, there was a drastic decrease in endometrial thickness, during 3 months post treatment follow up period which was up to 8 times when compared to the thickness at the end of treatment. In Carbonell *et al* [16] study (low dose of 2.5 mg and 5 mg), endometrial thickness had come to nearly half during the post treatment follow up compared to the end of treatment.

In the present study, increase in hemoglobin of 13.9% at the end of 3 months of treatment sustained during the post treatment follow up period of 3 months which might be because in majority of patients the decrease in the menstrual flow sustained during the post treatment follow up period. In Rita lal *et al* [9] study the increase in hemoglobin did not sustain during the post treatment follow up.

Table 6: Percentage change in the fibroid volume and uterine volume at the end of post treatment follow up period

Study	Dose	% change in the fibroid volume at the end of treatment	% change in the uterine volume at the end of treatment	Duration of post treatment follow up period	% change in fibroid volume at post treatment follow up period	% change in uterine volume at post treatment follow up period
Present study	25 mg / day	51.20%	34.3%	3 months	47.70%	29.40%
Rita lal *et al*[9]	20 mg / day	29.80%		6 months	24.98%	
Carbonell *et al*[16]	2.5 mg / day	27.90%	18.2%	3 months	15.40%	8.10%
Carbonell *et al*[16]	5 mg / day	46.40%	22.1%	3 months	28.60%	11%

Requirement of Hysterectomy

In the present study, 5 patients out of 50 (10%) decided to undergo hysterectomy after completion of 3 months post treatment follow up due to recurrence of symptoms. In the study by Shikha Seth *et a*l, [12] 12.1% of patients underwent hysterectomy, (more than the present study) due to increase in fibroid volume and menorrhagia. In Carbonell *et al*, [16] prior to the termination of 3 months of treatment, in 5 mg group out of 110 patients, 1 patient underwent hysterectomy due to heavy bleeding. In 2.5 mg group, out of 110 patients, 3 patients underwent hysterectomy (due to heavy bleeding, increase in size of fibroid and no reason respectively).

Strength of the study

The study was done in an outpatient basis so no inconvenience was caused to the patients. The drug Mifepristone was available free of cost in this study so that there was no financial burden on the patients. Investigations done in the present study were done free of cost in our institution. Follow up was 100% indicating very minimal side effects and good compliance.

RECOMMENDATIONS

The drug Mifepristone which is cost effective can be used safely in the management of uterine fibroids especially in the perimenopausal age group, as the volume of the fibroids regress after the onset of menopause and hence surgery can be avoided. Even in cases where surgery was required, when mifepristone was used before surgery, due to shrinkage of fibroid size, a more conservative mode of surgery can be planned, haemoglobin improves pre-operatively, blood loss can be minimal during surgery and blood transfusions can be avoided. Endometrial biopsy has to be done when there is thickened endometrium on ultra sound to exclude endometrial hyperplasia with atypia.

CONCLUSION

Most of the women with fibroid uterus are obese (70%). The most common symptom is menorrhagia. About 50% of patients with uterine leiomyoma are symptomatic which result in significant compromise in the quality of life, leading many women to opt for surgical methods like myomectomy and hysterectomy previously. Now uterine fibroids are being medically managed. Among them, mifepristone, a progesterone antagonist is becoming a promising drug in recent years. It is a good alternative to GnRH analogues. Different doses of the drug in different combinations have been used in various studies. Among them a dose of 25 mg/day was found to be effective in alleviating the symptoms and in decreasing the fibroid and uterine volume with only minimal side effects. Especially in peri-menopausal age group, where myomas regress after menopause, use of mifepristone eliminates the need for hysterectomy. It reduces the amount of bleeding and improves hemoglobin percent, decreasing the need for blood transfusions. In patients who require surgery, preoperative mifepristone use decreases the size of the fibroid making surgery technically easier.

In the present study, Mifepristone at a dose of 25 mg for a period of 3 months significantly reduced the amount of bleeding, dysmenorrhea, abdominal pain and urinary symptoms. There was also significant decrease in uterine and fibroid volume. There was a little increase in endometrial thickness at the end of treatment where endometrial biopsy did not show any evidence of atypia or malignancy and during next 3 months post treatment, follow up endometrial thickness decreased or returned to normal. There were minimal side effects which were tolerable. About 86% of the study population was amenorrhoeic at the end of 3 months of treatment. The use of mifepristone in the present study eliminated hysterectomy in 90% of

patients. The follow up rate in the current study was 100%.

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