ABSTRACT

Aims and objectives: The present study was carried out to study the reduction in size of fibroids and change in symptomatic profile following treatment with mifepristone 50 mg per week for 6 months.

Materials and methods: A prospective longitudinal study was conducted to evaluate the role of mifepristone in conservative management of fibroids between Jan 2012 and July 2013. Fifty women were enrolled in the study and 50 mg of mifepristone was given weekly for 6 months.

Results: This sustained effect model without side effects helped us to reduce the size of myoma by 60%. It is a significant and important landmark that shows that a long-term use of 50 mg dosage could be continued without any associated side effect using a weekly protocol instead of a daily protocol. The success of the treatment protocol could be implied from the fact that in the present study complete resolution was observed in 15 (30%) cases, while partial resolution was observed in 64% cases. Deterioration in myoma size was observed in three cases (6%) only. Two of these cases were subserosal type and did not respond to treatment at either of two intervals, while another was intramural type that showed improvement at first follow-up but deterioration in subsequent follow-up.

Conclusion: Weekly protocol of mifepristone with variable dosages is recommended for further assessment as a viable choice of treatment for uterine fibroids.

Keywords: Fibroid, Mifepristone, Ultrasound.

INTRODUCTION

Uterine fibroids are very common gynecological pathology. They are mostly seen in middle-aged woman with a variable prevalence.1 Symptomatic fibroids present with pain, bleeding, and pressure symptoms leading to decrease in the quality of life of a patient. There are various surgical and medical modalities of treatment of fibroids, which are found to be very effective. Among surgical modes of treatment, hysterectomy cannot be offered to younger women who wish to conceive and wish to preserve their uterus. Myomectomy offers preservation of uterus and low rates of recurrence and is usually the surgical treatment of choice for young patients. With recent and novel advances, new surgical modalities, such as hysteroscopic myomectomy and laparoscopic myomectomy, the surgical treatment is more acceptable with less duration of hospital stay, quick recovery, and is more economical for patient.2 However, even though surgical treatment techniques have more success rates, they are usually chosen as a ultimate resort by the patients given the fact that apart from hysterectomy, none of the surgical treatments offer a recurrence-free survival. Due to these limitations, surgical treatments are less popular among younger women and those women who want to retain their uterus. That is why medical management is the preferred choice and is generally preferred as a primary mode of treatment both by treating gynecologist and the patient. Mifepristone has been shown to be effective for treatment of fibroids by decreasing size of fibroids.3-5 It also reduces heavy menstrual bleeding and improves fibroid-specific quality of life. Dissimilarity in claims has been reported in various studies using different protocols. With this backdrop, the present study was carried out to study the reduction in size of fibroids and change in symptomatic profile following treatment with mifepristone 50 mg per week for 6 months.

MATERIALS AND METHODS

The study was executed as a prospective cohort study among patients presenting with confirmed diagnosis of uterine fibroids from January 2012 to July 2013. A total of 50 patients were enrolled in the study.

Inclusion criteria

The following inclusion criteria were used:
• Diagnosed fibroid cases
• Fibroid size—2.5 cm and above
• Those giving consent
• Reproductive age or premenopausal
• Accepting the use of nonhormonal contraceptive
• Accepting to have ultrasound examination in every follow-up
• Agreeing to two endometrial biopsies: one before starting treatment and after treatment termination.

Exclusion criteria
The following exclusion criteria were used:
• Those who desire to conceive
• Breastfeeding
• Hormonal contraception or any hormonal therapy received in the last 3 months
• Any contraindications to receiving antiprogestins
• Those who are not consenting

Permission from the Institutional Ethical Committee was obtained. A written and informed consent was taken from all the participants enlisted in the study.

After enrolment, relevant medical and surgical history was taken and thorough physical examination was done. All the patients were subjected to pelvic ultrasonographic examination to know the volume of uterus; number, size, volume, and location of fibroid; and thickness of endometrium at the start of treatment. Most of the fibroids were cuboidal; therefore, volume was calculated using the formula $A \times B \times C$, which are three largest diameters measured in two planes in approximately perpendicular axis. In case of multiple fibroids, largest (dominant) was used for volume calculations and follow-up. Uterine size was also measured in two different axial planes and volume calculated using formula for a cone.

Blood samples were collected for hemoglobin, blood counts, baseline liver and renal function tests, bleeding time, clotting time, and an endometrial biopsy was done before starting and after the end of treatment.

A total of 50 mg of mifepristone was given weekly. Ultrasound was done for the participants 12 weeks after the commencement of treatment and again at 24 weeks. Subsidization of clinical signs and symptoms/complaints and hematological assessment was done at final follow-up on 24th week. The results were analyzed in terms of change in volume and number of fibroids and abatement of symptoms.

The results obtained from participants were brought together, tabulated, and analyzed.

RESULTS
Age-wise Distribution of Cases
As shown in Graph 1, maximum number of cases ($n = 18$; 36%) were of age group 36 to 40 years. Cases in age group 41 to 45 years were 16 (32%) followed by 30 to 35 years ($n = 12$; 24%). Only four (8%) cases were aged 46 to 50 years. Age of patients ranged from 30 to 49 years with a mean age of $39.40 \pm 4.92$ years

Distribution of Cases According to Presenting Signs and Symptoms
Graph 2 shows that majority of women had menorrhagia ($n = 43$; 86%). Another common symptom was polymenorrhagia ($n = 25$; 50%) followed by intermenstrual bleeding ($n = 19$; 38%), polymenorrhagia ($n = 18$; 36%), abdominal pain ($n = 14$; 28%), and dysmenorrhagia ($n = 9$; 18%). Complaint of dyspareunia was seen in four women, which is 8% of all symptoms.

Distribution of Patients According to Size of Fibroid (cu mm)
Size of fibroid ranged from 2400 to 205,920 cu mm. In most of the patients ($n = 16$; 32%) the fibroid size was 20,000 to 50,000 cu mm, next were those having fibroid

Graph 1: Age-wise distribution of cases
Graph 2: Distribution of cases according to presenting signs and symptoms
size 10,000 to 20,000 cu mm (n = 12; 24%), 11 participants (22%) had fibroid size 50,000 to 100,000 cu mm, 4 (8%) had fibroid size >100,000 cu mm. There were seven (14%) cases with fibroid size <10,000 cu mm. Mean fibroid size was 42,599 ± 43,690 cu mm. This is shown in Graph 3.

Distribution of Patients According to Type of Fibroid

Submucous fibroid was found to be the most common type (n = 22; 44%). Subserosal fibroid was found in 15 cases (30%). Intramural type was seen in 10 (20%) cases and cervical type in 3 (6%) cases. This is illustrated in Graph 4.

Final Follow-up—Change in Clinical Profile of the Patients

Complete resolution of complaints, such as menorrhagia, polymenorrhea, polymenorrhagia, intermenstrual bleeding, and dysmenorrhea was observed, which was significant statistically too (p < 0.05). Abdominal pain was present in 14 (28%) patients at enrolment and at the end of study was present in 1 participant (2%) only, thus showing this change to be statistically significant too (p = 0.002).

This is shown in Graph 5.

Comparison of Change in Number of Fibroids and Fibroid Size Between Enrolment and Final Follow-up Assessment

At enrolment, there were 49 (98%) patients with one fibroid and 1 (2%) with two fibroids while at final follow-up, complete resolution of fibroid was observed in 17 (34%) patients and reduction in number of fibroids in 1 (2%) patient, thus leaving remaining 33 (66%) patients with one fibroid only. There was a remarkable reduction in number of fibroids, which is significant (p < 0.001). This is seen in Graph 6.

As seen in Graph 7, at enrolment, majority of patients had fibroid size >20,000 cu mm (62%), however, at final follow-up, majority of patients (66%) had fibroid size <20,000 cu mm. Mean fibroid size at enrolment was 42,599 ± 43,690 (2,400–205,920) cu mm; however, at final follow-up it was reduced to 17,057 ± 24,243 (0–88,768) cu mm,
Results at the End of 6 Months

When the study concluded, a total of 15 (30%) cases showed complete resolution of fibroid; 32 cases which were 64% of total cases showed partial resolution, while remaining 3 (6%) cases showed deterioration in fibroid. This is shown in Graph 8.

DISCUSSION

Symptomatic fibroids usually present with abdominal pain, menstrual irregularities, and pressure symptoms if they are big, leading to poor quality of life of patient affected by them. Medical management is the preferred treatment modality both by treating gynecologist and by the patients who do not want to get exposed to surgical methods and desire a conservative approach.

Mifepristone has proven to be effective for treatment of fibroids. It does not only diminish the size of fibroid but also cures menstrual irregularities and improves quality of life of women initially deteriorated by symptomatic fibroid. The present study was conducted to analyze the reduction in size of fibroids and to assess the symptomatic relief in participants who took once-weekly mifepristone 50 mg week for duration of half of year (6 months).

In the present study, age of patients ranged from 30 to 49 years with a mean age of 39.40 ± 4.92 years. Majority of patients were above 35 years of age. It has been shown that the incidence of uterine fibroids by age 35 is 60% among African-American women, increasing to >80% by age 50, whereas in Caucasian women the reported incidence is 40% by age 35, and almost 70% by age 50. In the present study, only a total of four (8%) cases were aged between 46 and 50 years, while 16 (32%) were aged 41 to 45 years. The findings suggest that in majority of cases (60%), disease and diagnosis occurred by the age of 40.

In the present study, all the women enrolled were symptomatic, with majority of women having menorrhagia (n = 43; 86%) as the most common complaint. Polymenorrhea was the second most common complaint (n = 25; 50%) followed by bleeding in between periods (n = 19; 38%), polymenorrhagia (n = 18; 36%), abdominal pain (n = 14; 28%), and dysmenorrhea (n = 9; 18%). Dyspareunia was seen in four patients. Menstrual problems and abnormal uterine bleeding have been cited to be the most common symptoms among women seeking health services intervention in India. Menstrual irregularities are found to occur because of the absence of proportional uterine contractions due to modification in size of the uterus.

Except for one patient who had two fibroids all the remaining patients had only one tumor. With respect to size of fibroid, majority of patients in the present study...
Role of Mifepristone in Conservative Management of Fibroids

had fibroid size >20,000 cu mm (n = 31; 62%) and mean size of myoma was observed to be 42,599 ± 43,690 cu mm. Seth et al have reported a much higher volume of myoma (143,958 ± 17,670 cu mm). Kulshrestha et al have also reported the myoma volume to be 176,800 cu mm at enrolment. The high standard deviation values in all the studies indicate a great variability in fibroid sizes and hence the variability in size could be justified. One of the other reasons for differences in size of fibroid across different studies could be the fact that there is no consensus regarding definitive landmarks to identify the boundaries of fibroid and allocation of shape characteristic. Some workers have considered myomas to be elliptical in shape and thus calculated the volume of an ellipsoid while others have treated it to be cylindrical or spherical in nature. In the present study, we treated it to be cuboidal in shape. As most of the studies report the effect of treatment in terms of % change in size, despite variability in adopting the method of measurement of size of fibroid used in a study, there is no problem in keeping the effect of treatment to be reported as a uniform standard % change, if the same method is used for calculation of size of fibroid.

In the present study, depending upon the location of the fibroid they were identified as cervical, intramural, submucosal, or subserosal. Intramural and subserosal types comprised half of the fibroids, while submucosal type was the most common (n = 22; 44%). Similar results were observed by Saravelos et al and Sue and Sarah. One of the reasons for selection of a 50 mg weekly protocol as used in the present study was to control the side effects which are quite frequently reported in protocols using a 50 mg or above daily protocol. Keeping in view an almost equal efficacy of low daily dosage protocols (5 and 10 mg) reported in literature, which was equivalent to high daily dosage protocols (50 and 100 mg), it seemed that there is still controversy in selecting the optimum daily dosage. It was conceived that a relatively mid-dose (50 mg) at a relatively lower frequency (weekly instead of daily) might provide equal efficacy but a better control over side effects.

As a result, in the present study, no significant side effect requiring intervention was observed over a period of 6 months of protocol. Only side effect found to be was amenorrhea, which was present invariably in all the patients. At the end of study, a significant improvement in symptoms affecting the quality of life of patients was observed and except for one patient complaining of abdominal pain no other complication was reported. It is well documented that mifepristone, in low dosages, improves the quality of life of patients and given the fact that in present study no side effect was reported even after using a 50 mg protocol, the significance of results assumes more importance that weekly administration of oral mifepristone improves the quality of life of patients and keeps the side effects under check comparable to those for low-dose protocols (5 to 10 mg).

The results of the present study provide a new insight for deciding the optimum management protocol to achieve long-term continuation of treatment with low or no side effects. This sustained effect model without side effects helped us in 60% reduction in fibroid size. It is a significant and important landmark that shows that a long-term use of 50 mg dosage could be continued without any associated side effect using a weekly protocol instead of a daily protocol. Moreover, this protocol helps in getting significant improvement over time too. The extent of reduction in fibroid size (60%) obtained in the present study is in the higher ranges reported in literature and absence of any side effect justifies the use of this protocol with adequate safety. The success of the treatment protocol could be implied from the fact that in the present study complete resolution was observed in 15 (30%) cases, while partial resolution was observed in 64% cases. Deterioration in fibroid size was observed in three cases (6%) only. Two of these cases were subserosal type and did not respond to treatment at either of two intervals, while another was intramural type who showed improvement at first follow-up but deterioration in subsequent follow-up.

REFERENCES