Role of mifepristone in conservative management of fibroid uterus

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ABSTRACT

Women aged between 30's and 40's years facing several gynaecological problems. Uterine leiomyomas or fibroids are common gynaecological problems among women with a variable prevalence. The main symptoms are accompanied with pain, bleeding, uterine abnormalities leading to deterioration in the quality of life of patients. Mainly surgical and medical treatments of fibroids are used effectively in clinical practice. However, its role in reduction of fibroid volume is under debate and discrepancies in claims have been reported in various studies using different protocols. 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.

Key-Words: leiomyomas, fibroids, gynaecological problems, Mifepristone-50, quality of life

INTRODUCTION

Uterine leiomyomas or fibroids are common gynaecological problems among women in their 30's and 40's with a variable prevalence. However, symptomatic fibroids are accompanied with pain, bleeding, uterine abnormalities leading to deterioration in the quality of life of a patient. Both surgical and medical treatments of fibroids are used effectively in clinical practice. Among surgical modes of treatment, hysterectomy has a limitation that it cannot be a universal treatment of choice for all the women given the reservation that women who wish to conceive and wish to preserve their uterus would not like to undergo hysterectomy [1].

Myomectomy is another surgical treatment of choice which offers preservation of uterus and low rates of recurrence. With the advent of new surgical modalities such as hysteroscopic myomectomy, laparoscopic myomectomy and laparoscopic myoma coagulation, the surgical treatment has gained more acceptability with shorter hospitalization, more rapid recovery and cost savings per patient. However, despite improvements in surgical treatment techniques and their increasing success rates, surgical treatments are preferred as a last resort by the patients given the fact that apart from hysterectomy, none of the surgical treatments offer a recurrence free survival. Owing to these limitations, surgical treatments are less popular among women not in advanced age and those who want to preserve their uterus. That is why medical management is the treatment of choice and is generally preferred as a primary treatment modality both by treating gynaecologist as well as the patient. Mifepristone has been shown to be effective for treatment of fibroids. Mifepristone has been shown to decrease fibroid size. It also reduces heavy menstrual bleeding and improves fibroid-specific quality of life [2-5].

However, its role in reduction of fibroid volume is under debate and discrepancies in claims have been reported in various studies using different protocols [6-7]. With this background, 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.

MATERIAL AND METHODS

The present study was carried out as a prospective longitudinal study among patients presenting with confirmed diagnosis of uterine fibroids from May, 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-2.5cm & above
- Those giving consent
- Reproductive age or premenopausal
- Accepting the use of non-hormonal contraceptive
- Agreeing to have ultrasound examination in every follow up or evaluation visit
- Agreeing to 2 endometrial biopsies-one before starting treatment & after treatment termination.

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

Permission from Institutional Ethical Committee was obtained. An informed consent was obtained from all the participants enrolled in the study. After enrolment, relevant medical history was taken and thorough physical examination was done. All the patients were subjected to pelvic USG examination to know the exact size and volume of uterus, number, size, volume and location of myomas and endometrial thickness at the start of treatment. Three largest diameters (A, B and C) were measured in two planes in approximately perpendicular axis in all myomas. As most of myomas were cuboidal therefore volume was calculated using formula A x B x C. In case of multiple myomas, largest one (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 haemoglobin, blood counts, baseline liver and renal function tests, bleeding time, clotting time, and an Endometrial Biopsy was done before starting and after the termination of treatment.

Sonography was performed at 12 weeks and 24 weeks intervals. Subsidisation of clinical signs and symptoms / complaints and haematological assessment was done at final follow up on 24th week. The outcome measures analysed were change in volume and number of myomas, and diminution of symptoms. The results of these 50 patients were collected, tabulated and analyzed.

**RESULTS**

**Age wise distribution of cases:** As shown in Figure-1, maximum number of cases (n=18; 36%) belonged to the age group of 36-40 years followed by those aged 41-45 yrs (n=16; 32%) and 30-35 yrs (n=12; 24%). Only 4 (8%) cases were aged 46-50 years. Age of patients ranged from 30 to 49 years with a mean age of 39.40 ± 4.92 years.

**Distribution of cases according to presenting signs and symptoms:** Figure-2, shows that majority of women had menorrhagia (n=43; 86%) followed by those having polymenorrhoea (n=25; 50%), intermenstrual bleeding (n=19; 38%), polymenorrhagia (n=18; 36%), abdominal pain (n=14; 28%) and dysmenorrhoea (n=9; 18%) respectively. There were 4 (8%) women with complaints of dyspareunia.
Fig.-2: Distribution of cases according to presenting signs and symptoms

Distribution of patients according to size of tumors (cumm): Size of tumor ranged from 2400 to 205920 cumm respectively. Maximum number of patients (n=16; 32%) had tumor size 20,000-50,000 cumm followed by those having tumor size 10,000-20,000 cumm (n=12; 24%), 11 (22%) had tumor size 50,000-100,000 cumm, 4 (8%) had tumor size >100,000 cumm respectively. There were 7 (14%) cases with tumor size <10,000 cumm. Mean tumor size was 42599±43690 cumm (Figure-3).

Distribution of patients according to type of myoma: Submucosal myoma was the most common type (n=22; 44%) followed by subserosal type (n=15; 30%). Intramural type was present in 10 (20%) cases and cervical type in 3 (6%) cases (Figure-4).

Fig.-3: Distribution of patients according to size of tumors (cumm)
Final Follow Up: Change in clinical profile of the patients: Complete resolution of complaints such as menorrhagia, polymenorrhagia, polymenorrhoea, intermenstrual bleeding and dysmenorrhoea was observed, which was significant statistically too (p<0.05). Abdominal pain was present in 14 (28%) patients at enrolment and was residual in 1 (2%) patient only at follow up, thus showing this change to be statistically significant too (p=0.002) (Figure-5).

Comparison of change in number of tumours and tumour size between enrolment and final follow up assessment: At enrolment, there were 49 (98%) patients with one tumor and 1 (2%) with two tumors while at final follow up, complete resolution of tumor was observed in 17 (34%) patient and reduction in number of tumors in 1 (2%) patient, thus leaving remaining 33 (66%) patients with one tumor only. Statistically, there was a significant reduction in number of tumors (p<0.001) (Figure-6).

As seen in Figure-7, at enrolment, majority of patients had tumor size >20,000 cumm (62%), however, at final follow up, majority of patients (66%) had tumor size <20,000 cumm. Mean tumor size at enrolment was 42599±43690 (2400-205920) cumm, however at final follow up this size reduced to 17057±24243 (range 0-88768) cumm, thus showing a reduction of 60% in tumor size. Statistically, this change was significant too (p<0.001).

Outcome of Therapy at the end of six months: At the end of study, a total of 15 (30%) cases showed complete resolution of myoma. There were 32 (64%) cases showed partial resolution while remaining 3 (6%) cases showed deterioration in myoma (Fig.8).
Fig. 6: Comparison of change in number and size of tumour in enrolment and follow up

Fig. 7: Comparison of change in enrolment and follow up

Fig. 8: Outcome of Therapy at the end of six months

- Complete resolution: 30.0%
- Partial resolution: 64.0%
- Deterioration: 6.0%
DISCUSSION

Symptomatic fibroids are accompanied with pain, bleeding, uterine abnormalities leading to deterioration in quality of life of patient affected by them. Both surgical and medical treatments of fibroids are used effectively in clinical practice. Despite improvements in surgical treatment techniques, surgical treatments are preferred as a last resort by the patients given the fact that apart from hysterectomy, none of the surgical treatments offer a recurrence free survival [1,8]. Owing to these limitations, surgical treatments are less popular among women not in advanced age and those who want to preserve their uterus. That is why medical management is the treatment of choice and is generally preferred as a primary treatment modality both by treating gynaecologist as well as the patient [3,4,9].

Mifepristone has been shown to be effective for treatment of fibroids. Mifepristone has been shown to decrease fibroid size. It also reduces heavy menstrual bleeding and improves fibroid-specific quality of life. 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 [10].

In 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 this incidence to 40% by age 35, and almost 70% by age 50 In present study, only a total of 4 (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%), occurrence of disease and diagnosis was made by the age of 40 [1,11].

In present study, all the women enrolled were symptomatic with majority of women having menorrhagia (n=43; 86%) as the most common complaint followed by those having polymenorrhoea (n=25; 50%), intermenstrual bleeding (n=19; 38%), polymenorrhagia (n=18; 36%), abdominal pain (n=14; 28%) and dysmenorrhoea (n=9; 18%) respectively. There were 4 (8%) women with complaints of dyspareunia. 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 hypothesized to be secondary to the loss of symmetric uterine contractions owing to change in uterus size [3,4,6,12].

Except for 1 patient who had two tumors, all the remaining patients had only one tumors. With respect to size of myoma, majority of patients in present study had myoma size >20,000 cumm (n=31; 62%) and mean size of myomas was observed to be 42599±43690 cumm. Seth et al. (2012) have reported a much higher volume of myoma (143958±17670 cumm). Kulshreshtha et al. (2013) has also reported the myoma volume to be 176800 cumm at enrolment. The high standard deviation values in all the studies indicate a great variability in myoma sizes and hence the variability in size could be justified. One of the other reasons for differences in size of myoma across different studies could be the fact that there is no consensus regarding definitive landmarks to identify the boundaries of myoma 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 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, hence despite variability in adopting the method of measurement of size of myoma 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 myoma [13].

In present study, depending upon the location of the myoma, they were identified as cervical, intramural, submucosal or subserosal. Intramural and subserosal types comprised half the myomas while submucosal type was the most common (n=22; 44%). Similar results were observed by Saraveloset al. (2011) and Sue and Sarah (2009) [14,15]. One of the reasons for selection of a 50 mg weekly protocol as used in 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 [16].

As a result, in present study, no significant side effect requiring intervention was observed over a period of 6 months of protocol [7,9]. Only side
The results of 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 to 60% reduction in myoma 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 myoma size (60%) obtained in 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 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 who showed improvement at first follow up but deterioration in subsequent follow up.

REFERENCES