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Dr. Bharti Maheshwari
Professor and Head of Department of Obs and Gynae, Muzaffarnagar Medical College, Bahadarpur, Uttar Pradesh, India

Dr. Sakshi Mittal
PG JR, Obs and Gynae, Muzaffarnagar Medical College, Bahadarpur, Uttar Pradesh, India

Dr. Manju Prabhakar
Associate Professor Obs and Gynae, Muzaffarnagar Medical College, Bahadarpur, Uttar Pradesh, India

Dr. Preeti Sharma
Assistant Professor Obs and Gynae, Muzaffarnagar Medical College, Bahadarpur, Uttar Pradesh, India

Corresponding Author:
Dr. Bharti Maheshwari
Professor and Head of Department of Obs and Gynae, Muzaffarnagar Medical College, Bahadarpur, Uttar Pradesh, India

Role of low dose mifepristone in management of uterine fibroid

Dr. Bharti Maheshwari, Dr. Sakshi Mittal, Dr. Manju Prabhakar and Dr. Preeti Sharma

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Abstract
Background: Fibroid is the most common benign tumour of the uterus affecting 20% of women of reproductive age group. The symptoms include menstrual disturbances, commonly menorrhagia and dysmenorrhea. Mifepristone on the other hand is a progesterone receptor modulator with mainly antagonistic properties.This study was done to study the effect of 25 mg Mifepristone daily for 3 months on improvement of fibroid related symptoms and on the size of uterine fibroid and evaluate the side-effects of Mifepristone.
Materials and Method: This clinical study compared the role of low dose mifepristone in the management of uterine fibroid. The total sample size was determined to be 100 patients of age 18-49 years. Uterine volume, volume of the fibroid, their number and size was assessed by performing abdominal or transvaginal sonography at baseline, one month and 3 months.
Results: The mean age of the study population was 39.17±6.67 (18-49) years. Menorrhagia was the predominant symptom among 54.0%. Majority (63.0%) of the subjects had Intra-mural fibroid. The mean PBAC score and Numeric Pain Rating Scale score decreased significantly from baseline to 1 month to 3 months. The mean uterine volume, Volume of the fibroid decreased and endometrial thickness increased significantly from baseline to 1 month to 3 months. The mean Hb level increased significantly from baseline to 1 month to 3 months.
Conclusion: It can be concluded that at the end of 3 months, there was significant reduction in the amount of menorrhagia, dysmenorrhea, abdominal pain, uterine and fibroid volume and improvement in haemoglobin level.

Keywords: endometrial thickness, uterine volume, uterine fibroid, volume of fibroid

Introduction

Fibroid is the most common benign tumour of the uterus affecting 20% of women of reproductive age group [1]. It is responsible for 1/3rdof all gynaecological admissions in hospitals [2] and is the most common indication for hysterectomy accounting for about 40% of all hysterectomies in premenopausal women [3].

The etiology of uterine fibroid is not clearly known

Approximately 20-40% of these uterine tumours are symptomatic in premenopausal women accounting for 20-80% of hysterectomies in these women [4-5].

The 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 they may interfere with reproduction by causing infertility or preterm birth depending upon the location of fibroid [6].

Anterior wall fibroids can cause pressure symptoms on the bladder and increased frequency of micturition. Posterior wall fibroids lead to spontaneous abortions, infertility etc. The severity of symptoms typically depends on size, number of fibroids, and their location [10].

New medications have been introduced, for practical and long-term medical therapy for symptomatic fibroids [9]. Medical management is especially given to minimize the symptoms and signs. This includes drugs under the following classes-antifibrinolytic, tranexamic acid, danazol, GnRH analogs, progestogens and the antiprogesterone mifepristone [9, 10].

Mifepristone (RU 486) on the other hand is a progesterone receptor modulator with mainly antagonistic properties. It is synthesized from its precursor norethindrone and competitively binds and inhibits the progesterone receptors [9].

Its mechanism of action is binding strongly to the endometrial progesterone receptors, and minimally to estrogen receptors and up regulates the androgen receptors [10, 11, 12]. It also delays or inhibits ovulation, and produce amenorrhea.

Mifepristone reduces the fibroid volume consistently, by around 50%

This study was done to study the effect of Mifepristone daily for 3 months on improvement of fibroid related symptoms and on the size of uterine fibroid and evaluate the side-effects of Mifepristone.

Aim and Objective

1. To study the effect of Mifepristone daily for 3 months on improvement of fibroid related symptoms and on the size of uterine fibroid.

Materials and method

This Clinical study compared the role of low dose mifepristone in the management of uterine fibroid after clearance from board of studies and ethical committee in the Department of Obstetrics & Gynecology, Muzaffarnagar Medical College, Muzaffarnagar, Uttar Pradesh.

Sample Size: Total 100 females with uterine fibroid were evaluated for 1 year duration.

Inclusion criteria

Women of reproductive age group (18-49 years) with-

1. Symptomatic fibroids.
2. Asymptomatic patients showing fibroid of size >2.5cm on ultrasonography.

Exclusion criteria

1. Presence of pregnancy or lactation.
2. Women desirous of pregnancy.
3. Suspicious of uterine, ovarian or endometrial malignancies.
4. H/o hormonal treatment over past 3 months.
5. Presence of any renal, respiratory or heart disease, PID or any other adnexal pathology.
6. Uterine fibroid >20weeks size.
7. Atypical endometrial hyperplasia.
8. Those having contraindication for use of mifepristone.

Study procedure

All women finally included in the study were given 25mg mifepristone daily for 3 months. The details of menstrual cycle, symptoms and their severity were noted. Menstrual blood loss was assessed according to the PBAC score, which is a semi-quantitative assessment that takes into account the number of pads soaked, their degree of soakage, passage of clots and episode of flooding. A score of more than 100 accounts for menorrhagia.

Monthly assessment of presence and intensity of pelvic pain, pain during menses, dyspareunia, pressure symptoms, low backache was done according to the Numeric Pain Rating Scale. Each questionnaire was asked at baseline, 1 month and 3 months interval.

Uterine volume, volume of the fibroid, their number and size was assessed by performing abdominal or transvaginal sonography at baseline, one month and 3 months. Endometrial biopsy was taken for subjects present with abnormal bleeding pattern or endometrial thickness on ultrasound >8 mm on registration and from all subjects at the end of 3 months to rule out any histopathological abnormality. The drug side effects like nausea, vomiting, diarrhoea, hot flushes, headache, mood swings, weakness, fatigue, weight gain, loss of libido were assessed.

Results

The mean age of the study population was 39.17±6.67 (24-60) years.

Table 1: Age distribution of the study population

	Minimum	Maximum	Mean	Std. Deviation
Age (years)	24.00	60.00	39.17	6.67

Menorrhagia was the predominant symptom among 54.0% followed by Dysmenorrhoea (20.0%), Post-menopausal bleeding (11.0%), Metrorrhagia (10.0%), Polymenorrhea (8.0%) and Polymenorrhea (3.0%). Majority (63.0%) of the subjects had Intra-mucosal fibroid whereas 3.0% had ligament fibroid, 6.0% had cervical fibroid, 12.0% Submucosal and 10.0% had Subserosal fibroid.

Table 2: Distribution of symptoms among study population

		Frequency	Percent
Symptoms	Menorrhagia	54	54.0%
	Polymenorrhea	8	8.0%
	Poly menorrhoea	3	3.0%
	Metrorrhagia	10	10.0%
	Post-menopausal bleeding	11	11.0%
	Dysmenorrhoea	20	20.0%
Type of fibroid	Intra-mucosal	69	69.0%
	Submucous	12	12.0%
	Subserous	10	10.0%
	Broad ligament fibroid	3	3.0%
	Cervical fibroid	6	6.0%

The mean PBAC score decreased significantly from baseline to 1 month to 3 months. The mean Numeric Pain Rating Scale score decreased significantly from baseline to 1 month to 3 months.

Table 3: Comparison of mean PBAC score between baseline, 1 month and 3 months

		Mean ± S.D.	p-value
PBAC score	Baseline	237.69±8.89	< 0.001*
	1 month	53.83±15.22	
	3 months	14.42±6.83	
	Baseline vs. 1 month		< 0.001*
	Baseline vs. 3 months		< 0.001*
	1 month vs. 3 months		< 0.001*
Numeric Pain Rating Scale score	Baseline	5.17±1.21	< 0.001*
	1 month	3.86±1.02	
	3 months	1.40±0.92	
	Baseline vs. 1 month		< 0.001*
	Baseline vs. 3 months		< 0.001*
	1 month vs. 3 months		< 0.001*

Repeated-measures ANOVA test
*Significant difference

The mean uterine volume, Volume of the fibroid and endometrial thickness increased significantly from baseline to 1 month to 3 months.

Table 4: Comparison of mean uterine volume between baseline, 1 month and 3 months

		Mean ± S.D		p-value
Uterine volume	Baseline	193.06±6.80		< 0.001*
	1 month	191.15±5.19		
	3 months	170.45±10.66		
	Baseline vs. 1 month			< 0.001*
	Baseline vs. 3 months			< 0.001*
	1 month vs. 3 months			< 0.001*
Volume of the fibroid	Baseline	66.13±6.75		< 0.001*
	1 month	57.42±6.60		
	3 months	38.32±6.48		
	Baseline vs. 1 month			< 0.001*
	Baseline vs. 3 months			< 0.001*
	1 month vs. 3 months			< 0.001*
Endometrial thickness	Baseline	6.33±0.81		< 0.001*
	1 month	7.19±0.78		
	3 months	8.17±0.71		
	Baseline vs. 1 month			< 0.001*
	Baseline vs. 3 months			< 0.001*
	1 month vs. 3 months			< 0.001*

Repeated-measures ANOVA test
*Significant difference

The mean Hb level increased significantly from baseline to 1 month to 3 months.

Table 5: Comparison of mean Hb level between baseline, 1 month and 3 months

Hb	Mean ± S.D		p-value
Baseline	9.39±0.88		< 0.001*
1 month	10.27±0.88		
3 months	11.06±0.82		
Baseline vs. 1 month			< 0.001*
Baseline vs. 3 months			< 0.001*
1 month vs. 3 months			< 0.001*

Repeated-measures ANOVA test
* Significant difference

Discussion

Most uterine fibroids appear during the reproductive stage and gradually atrophy after menopause [13, 14]. The therapeutic approach to uterine fibroids varies, and the final treatment plan is usually designed according to the patient's age, fertility demands, symptoms, fibroid characteristics, and other factors [15].

Current studies support that growth of fibroids in humans is progesterone dependent also and therefore antiprogestins can be effective in treatment [20]. One such drug is Mifepristone which controls bleeding, decreases dysmenorrhea, reduces uterine volume and fibroid size, improves hemoglobin percentage.

Symptoms

Hari et al., [11] reported that the most common presenting symptom was menorrhagia which was seen in 84% of patients followed by dysmenorrhea in 78%.

Type of fibroid

Intramural was the most common type of fibroid in the present study which was in similarity to the findings by *Hari et al*. [11].

PBAC score

In ours study, there was an improvement of the pictorial blood assessment chart (PBAC) score over 3 months with an improvement of 93.9%. *Arora et al*. reported that the percentage reduction in pictorial blood assessment chart during six months treatment course was 100% because all women in the test group achieved amenorrhoea. Whereas, in the control group tranexamic acid and mefenamic acid led to approximately 50% reduction in the PBAC score with a statistically significant difference.

Numeric pain rating scale score

In current study, the mean Numeric Pain Rating Scale score decreased significantly from baseline to 1 month to 3 months with a reduction of 77.2%. Study conducted by *Hari et al.* [11] showed a maximum decrease in VAS percentage that is 87.5%.

Endometrial thickness and histopathology

In our study, the mean endometrial thickness increased significantly from baseline to 1 month to 3 months. *Alakananda et al.* showed that 34% patients showed endometrial hyperplasia after treatment and most common type was proliferative endometrium [21].

In an early comparative trial, Mifepristone and leuprolide acetate were equally effective in decreasing uterine volume and blood flow to the uterus [25].

Uterine volume

In our study, the mean uterine volume decreased significantly from baseline to 1 month to 3 months with 11.64% improvement in the uterine volume. This coincided with the study by *Alaknanda et al.*, [21] there was decrease of 16.54% in uterine volume compared to the pre-treatment volume.

In the study by *Engman et al.*, [20] with 50 mg mifepristone on alternate days, there was no change in uterine volume. In the study by *Carbonell et al.*, [25] 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.

Fibroid volume

The decrease in fibroid volume occurred by 42.5% which was similar to the studies by *Hari et al*.

Similar findings were published in *Kirsty et al*. [26] where with the dose of 5 mg or 10 mg Mifepristone for 6 months, size reduction of 50% was observed.

Although the exact mechanism for leiomyoma size reduction with mifepristone remains to be determined, one study reported that mifepristone could directly decrease the number of P receptors in the myometrium and leiomyoma. Mifepristone may change the blood flow to the leiomyoma by a direct vascular effect [27].

Hb level

In current study, the mean Hb level increased significantly from baseline (9.39±0.88) to 1 month (10.27±0.88) to 3 months (11.06±0.82).Our study value had similar results when compared to *Engman et al.* [20] and *Carbonell et al.* [28] whose values were 12.1±5 and 11.0±2 respectively

A systematic Cochrane review of 2012 [30] found only three truly RCTs of MFP vs other medical therapies or placebo, involving 112 participants with different dosages, concluding that MFP use relieves heavy menstrual bleeding [31].

Summary and conclusion

From the present study, it can be concluded that at the end of 3 months, there was significant reduction in the amount of menorrhagia, dysmenorrhea, abdominal pain, uterine and fibroid

volume and improvement in haemoglobin level.

There were minimal tolerable side effects like nausea, backache, hot flushes and increased liver transaminases, which was the major reason for good patient compliance.

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