

EFFICACY OF MIFEPRISTONE IN REDUCING THE SIZE OF FIBROIDS

Rajat Kumar Ray¹, Sunita Sama²

¹Director, Department of Obstetrics and Gynaecology, Ray Hospital and Test Tube Baby Centre, Rourkela, Odisha.

²Consultant, Department of Obstetrics and Gynaecology, Ray Hospital and Test Tube Baby Centre, Rourkela, Odisha.

ABSTRACT

BACKGROUND

Uterine leiomyomata are the commonest benign gynaecological tumours occurring in up to 25 per cent of women in reproductive age. There are various surgical and medical modalities of treatment of fibroids which are found to be very effective. Recent evidence suggests that progesterone is essential for maintenance and growth of uterine leiomyoma and that oestrogen is required only for upregulation of progesterone receptors. Mifepristone (RU 486) is a progesterone receptor modulator with primarily antagonistic properties. Dissimilarity in claims has been reported in various studies using different protocols.

The aim of the present study was to evaluate the efficacy of treatment with mifepristone 25 mg daily for 3 months for reduction in size of fibroids.

MATERIALS AND METHODS

Ultrasound was done to confirm the diagnosis of leiomyomas as well as to ascertain number, location and volume of myomas. Volume of each myoma was calculated. Mifepristone was administered in a dose of 25 mg/day orally till 3 months. Patients were followed up every month till 3 months. Repeat ultrasound was done to assess the size of fibroids.

Settings and Design- Prospective Cohort Study.

Statistical Analysis- Statistical analysis was done using MedCalc software. Proportions were analysed using a chi-square test. Unpaired student's t-test was used for mean values. Results were expressed as mean & standard deviation. P<0.05 was considered as significant.

RESULTS

The age range of patients was 24 to 45 years. There was a significant reduction in the volume of the fibroids after 3 months (38.54±42.42 cc to 20.38±25.42 cc). In 9 women, the fibroid volume did not change, but there was symptomatic relief.

CONCLUSION

Mifepristone in a dose of 25 mg daily for 3 months can be used as an effective drug in the medical management of fibroids. Mifepristone can be a good choice especially in perimenopausal women in whom myomas would regress after menopause and patients who want to avoid surgery.

KEYWORDS

Mifepristone, Fibroids, Progesterone.

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BACKGROUND

Uterine fibroids are very common gynaecological pathology. Symptomatic fibroids present with pain, bleeding, and pressure symptoms leading to decrease in the quality of life of a patient. About 40 percent present with severe symptoms requiring therapy.¹ There are various surgical and medical modalities of treatment of fibroids, which are found to be very effective. Myomas account for up to 40 per cent of all hysterectomies in premenopausal women.² 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. Though minimal invasive methods like uterine artery embolization, high intensity focused ultrasound, and magnetic resonance-guided focused ultrasound are available, still they are beyond the reach of most women due to high expertise required and cost. Several medical treatments are advocated for the treatment of fibroids. Danazol reduces uterine volume by 18-23 percent,³ but it is not preferred due to its marked androgenic side-effects and liver dysfunction. Gonadotrophin releasing hormone agonist (GnRH) reduces leiomyoma size to about 50 per cent in three months. But it is expensive and also associated with hypoestrogenism leading to hot flushes, vaginal dryness and bone loss.⁴ There is a regrowth of myoma after variable periods following cessation of treatment.

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Corresponding Author:

Dr. Rajat Kumar Ray,

Director, Department of Obstetrics and Gynaecology,

Ray Hospital and Test Tube Baby Centre,

N-18, Civil Township, Rourkela- 769004, Odisha.

E-mail: rajatkuray@gmail.com

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Recent evidence suggests that progesterone is essential for maintenance and growth of uterine leiomyoma and that oestrogen is required only for upregulation of progesterone receptors.⁵ Hence, there was a surge of studies evaluating effect of antiprogestogens like ulipristal & asoprisnil in non-surgical treatment of uterine myomas. The most commonly used progesterone receptor modulator is mifepristone (RU 486). It binds strongly to endometrial progesterone receptors, minimally to oestrogen receptors and upregulates androgen receptors. It has been shown to decrease myoma size as well as symptoms.⁶ Reduction in size with mifepristone might be due to the direct effect in reducing number of progesterone receptors. It has been observed that ovarian acyclicity is present with use of mifepristone leading to hormonal milieu similar to early follicular phase, which also inhibit steroid dependent growth of myoma. Mifepristone also delays or inhibits ovulation, which may produce amenorrhoea. It has got a direct suppressive effect on endometrial vasculature which accounts for reducing menstrual blood loss.⁷

Dissimilarity in claims has been reported in various studies using different protocols.

Objective

The present study was carried out to study the efficacy of treatment with mifepristone 25 mg daily for 3 months for reduction in size of fibroids.

MATERIALS AND METHODS

The study was executed as a prospective cohort study among patients presenting with confirmed diagnosis of uterine fibroids from January 2016 to December 2017 at Ray Hospital & Test Tube Baby Centre, Rourkela, India. We enrolled 50 patients fulfilling the inclusion criteria in our study.

Inclusion Criteria

The following inclusion criteria were used-

- Diagnosed fibroid cases.
- Fibroid size- 2.5 cm and above.
- Age 20 years to 45 years.
- Accepting to have regular follow up ultrasound examination.

Exclusion Criteria

The following exclusion criteria were used-

- Fibroids of size >10 cms.
- Those who desire to conceive.
- Breastfeeding.
- Diagnosed or suspected ovarian, cervical, or uterine malignancy.
- Presence of medical ailments like liver disorders, renal disorders, heart disease, or adrenal disorders.
- Pelvic inflammatory disease or other adnexal pathologies.
- Sickle cell anaemia.
- Bleeding disorders.

- Woman necessitating early surgical intervention.
- Any contraindications to receiving antiprogestins.

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

A complete general and gynaecological examination was done. Blood testing was done for haemoglobin, liver and kidney function tests and serum oestradiol levels. Ultrasound was done to confirm the diagnosis of leiomyomas as well as to ascertain number, location, volume of myomas and to rule out any other pelvic pathology like adenomyosis, endometriosis & adnexal mass. Volume of each myoma was calculated by the ellipsoid method and the formula $V=0.5233 (D1 \times D2 \times D3)$ was used, where D1, D2 and D3 represented three orthogonal diameters of the fibroid. Hysteroscopy was performed when endometrial polyp or sub mucosal myomas were suspected. Endometrial aspiration was performed to rule out any abnormal histopathology in married women and in unmarried women when required on the basis of increased endometrial thickness on ultrasound.

Mifepristone was administered in a dose of 25 mg/day orally till 3 months.

Patients were followed up every month till 3 months. Repeat ultrasound was done to assess the size of fibroids.

Main Outcome Measure

Change in volume of fibroids.

Statistical Analysis

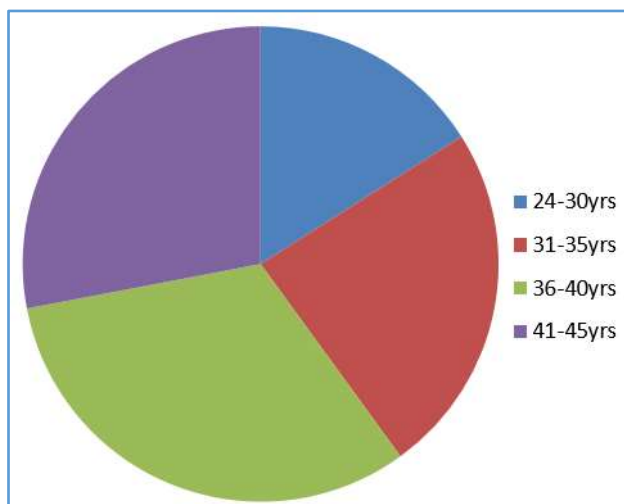
Statistical analysis was done using MEDCALC software. Proportions were analysed using a Chi-square test. Unpaired Student's t-test was used for mean values. Results were expressed as mean & standard deviations of mean. $P < 0.05$ was considered as significant.

RESULTS

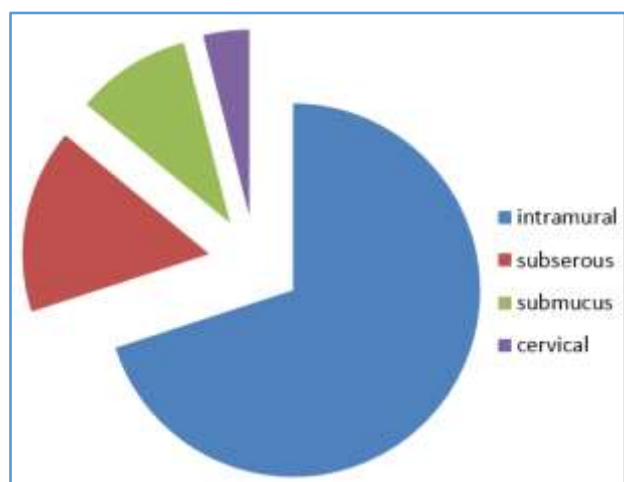
All the women came for regular checkup. The age range of patients was 24 to 45 years. When the patients were divided according to age, maximum number of patients were of 36 to 40 years (16 in number). Cases in age group 41 to 45 were 14 in number followed by 31 to 35 years age group (12 in number). Rest 8 cases were of age group 24 to 30 years. (Graph 1). Maximum number of cases had a intramural type of fibroid (35 in number). 8 cases were sub serous type. 5 cases were of submucous type. Cervical fibroid was seen in 2 cases (Graph 2). There was a significant reduction in volume of the fibroids after 3 months (38.54 ± 42.42 cc to 20.38 ± 25.42 cc). (Table 1) In 9 women the fibroid volume did not change, but there was symptomatic relief.

Parameters	Baseline (Mean±SD)	After 3 Months (Mean±SD)	P value
Volume of fibroids (in cc)	38.54±42.42	20.38±25.42	0.01

Table 1. Change in Ultrasound Parameters



Graph 1. Age Wise Distribution



Graph 2. Types of Fibroids

DISCUSSION

Fibroid is a tumor of hyper-estrogenic environment. Therefore, medical treatment targets lowering oestrogen levels. The drugs used for the purpose are GnRH agonists and antagonists, Danazol, Gestrinone, Cabergoline, Aromatase inhibitors or Selective oestrogen receptor modulators like Raloxifene.⁸ Current studies support that growth of myoma in humans is progesterone dependent also and therefore antiprogestins (Mifepristone) and selective progesterone receptor modulators (SPRMs-Asoprisnil) can be effective in treatment. Hormonal treatment reduces size, improves haemoglobin by controlling bleeding and avoids surgery as patient reaches menopause. Usually the fibroid stops to grow after menopause, as it is a hormone dependent tumour. Mifepristone has both ant progesterone and ant glucocorticoid properties in dose dependent manner. Mechanism of reduced bleeding and myoma size is likely to be due to structural, functional and micro vascular effects of Mifepristone on the endometrium and uterine musculature in dose and duration dependent manner.

Eisinger, et al reported fall of 48% in mean uterine volume while amenorrhoea in 61% only after 6 months of 10 mg mifepristone.⁹ Another study by Kettle et al., reported amenorrhoea in 40-70% over one year at 5-10 mg dose, while 100 mg led to 100% amenorrhoea.¹⁰

Abnormal uterine bleeding affects the daily routines, work efficiency and health status of a woman. So most of them opt for hysterectomy as one-time management. With higher doses speedy and better control of bleeding is achieved, this improves the general condition of women and haemoglobin levels, relieves anxiety and provides women a sense of wellbeing and effectivity of treatment. Higher dose also produces hot flushes and other anti-glucocorticoid side-effects. In our study we used 25 mg daily to achieve symptomatic improvement with minimal side effects. There was a significant reduction on volume of the fibroids after 3 months (38.54 ± 42.42 cc to 20.38 ± 25.42 cc) in our study. Our study correlates with the study by Engman et al.,⁶ who had a 28% decline in size after three months. More number of receptors is there in fibroids compared to rest of normal myometrium therefore steadier fall is seen in it.

Mifepristone is well tolerated drug with no serious adverse effects.¹¹ Common side effects reported are mild hot flushes seen in 10-38 per cent patients with no correlation to dose, fatigue in 8-12 per cent, and increase in liver transaminases in 4-7 per cent. In our study, few patients had mild hot flushes.

Mifepristone can best be used in women with anaemia and those who want to avoid surgery. It also can be used in preoperative cases to reduce size and build up haemoglobin level to have better surgical outcome.

CONCLUSION

Mifepristone in a dose of 25 mg daily for 3 months can be used as an effective drug in the medical management of fibroids. Mifepristone can be a good choice especially in perimenopausal women in whom myomas would regress after menopause and in patients who want to avoid surgery.

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