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MIFEPRISTONE A THERAPEUTIC OPTION IN MEDICAL MANAGEMENT OF SYMPTOMATIC UTERINE LEIOMYOMA

Obstetrics & Gynaecology

Dr. Rajni Priyanka* Senior Resident, Dept. of Obst & Gynae, P.M.C.H, Patna *Corresponding Author

Dr. Chitra Sinha Associate Professor, Dept. of Obst & Gynae, P.M.C.H, Patna

ABSTRACT

Background – Fibroid is the commonest benign tumor of uterus and one of the important indication for hysterectomy . Medical management of fibroids in perimenopausal women are effective as myoma regress after menopause .Various drugs are available for medical management including mifepristone ,an antiprogestine.

Objectives –to evaluate the effect of mifepristone on symptomatic myoma in perimenopausal women.

Variables to evaluate efficacy – changes in fibroid and uterine volumes, heoglobin level, endometrial thickness, side effects.

Design – prospective study

Material and method – this was a prospective study done at Department of Obstetrics and Gynecology of Patna Medical College and Hospital, Patna from October 2017 to March 2019 (over a period of 18mths. A total 45women attending outdoor, who were diagnosed with uterine fibroids were selected according to the inclusion criteria. 10 mg mifepristone was given to perimenopausal women with symptomatic myoma for three month. Changes in fibroid and uterine volumes, hemoglobin level was compared pre and post treatment. Improvement in symptoms and side effects of mifepristone were noted.

Result –Immediate reduction in amount of heavy bleeding were noted in 100%, and 38((84.44%) women become amenorrhoeic after treatment . Mean PBAC score was 80.36±71.96 initially and it was decreased by 70.22% after one month of treatment and significantly to 91.42% after completion of treatment. Volume of leiomyoma decreased by 26.45%.there is 2.3% rise in haemoglobin level noted after completion of treatment. The drug did not have major side effect. In follow up after 6 month ie after 3 month of completion of treatment 45% patients were asymptomatic and no further change in myoma volume were noted.

Conclusion - Mifepristone can be useful in treating symptomatic myoma in premenopausal women

KEYWORDS

Fibroid, Mifepristone, Leiomyoma, Medical Treatment

INTRODUCTION -

Uterine leiomyoma are very slow growing, common benign tumor of uterus. Its incidence varies between 20 -to 25% among reproductive age group women and typically found during the middle and later reproductive years. Most women with leiomyoma are asymptomatic initially, however affected women commonly present with heavy bleeding, increased menstrual pain, pressure in lower abdomen, infertility and miscarriage. The severity of symptoms mainly depends upon the number of fibroids, size and the site[1]. The treatment options depends on the severity of symptoms. Although hysterectomy is the main definitive operative treatment for symptomatic women with fibroid and accounts for 40% of all hysterectomy[2]. Other invasive treatment options like myolysis, myomectomy cryoablation, percutaneous laser ablation, MRI-guided focused ultrasound, uterine artery embolization, transvaginal uterine artery ablation are also available.

Various new drugs are available for long term medical management of symptomatic fibroid uterus[3]. In medical management, Danazol, GnRH analogue (Gonadotrophin releasing hormone agonist and antagonist), selective estrogen receptor modulators(SERM), Antiprogestogens and progesterone receptor modulators are used. But medical treatment has its own limitations and none of the drug is approved by FDA for the treatment of myoma. The most commonly Long term GnRH agonist reduces leiomyoma size to about 50% in three month[4], but it is costly, and associated with antiestrogenic side effects like hot flushes, vaginal dryness and bone loss[5]. It cannot be used for a long time and regrowth of myoma and recurrence of symptoms occur after stopping treatment[6].

Mifepristone is a progesterone antagonist also known as RU-486. It is a synthetic steroid with antiprogesterone and antiglucocorticoid properties. It is a progesterone receptor modulator and bind strongly to endometrial progesterone receptor, minimally to estrogen receptors and upregulates androgen receptors .Mifepristone decreases the number of progesterone receptors in the myometrium and leiomyoma, maintaining the hormonal milieu as in the follicular phase, thus inhibiting the growth of steroid- dependent myoma. It also causes an alteration in the blood flow to the leiomyoma by a direct vascular effect. Mifepristone decreases leiomyoma volume as well as effective in improving menorrhagia and other myoma related symptoms[7]. Mifepristone is less expensive, minimal side effects and very easy to administer.

MATERIAL AND METHODS

This study was done from October2017 to March 2019 over a period of eighteen month at the department of obstetrics and gynecology, PMCH, Patna, Bihar. Informed consent were taken from all patients.

Inclusion criteria-Women between 35- 50 year of age with symptomatic fibroids (menorrhagia, dysmenorrhoea, pressure symptoms) were included in this study.

Exclusion criteria - Uterine size >20 Week, Fibroids >10 cm size, Endometrial hyperplasia, Renal or hepatic dysfunction, Women desiring pregnancy, pregnancy or lactation, suspected uterine, cervical or ovarian malignancy. Women who used any type of hormonal medicine during previous three month were also excluded from the study.

In this study 45 patients were selected after fulfilling exclusion and inclusion criteria. An elaborate history was taken from all the patients regarding menstrual cycle, The amount of bleeding, duration of bleeding, passage of clots were asked. Menstrual blood loss was assessed using pictorial blood assessment chart.. Complete general and gynaecological examination was done, blood samples were taken for haemoglobin level, liver and renal function test. Ultrasound was done to confirm the diagnosis of leiomyoma, to see the number, size and volume, to measure endometrial thickness and to rule out any pelvic pathology. Volume of each myoma was calculated and added in cases with multiple myoma. Volume was calculated by measuring longitudinal (D1), transverse(D2) and cross-sectional(D3) diameters of the fibroid by the ellipsoid method by the (formula $V = 0.523 \times D1 \times D2 \times D3$).

10 mg mifepristone was given once daily, orally in empty stomach for good absorption, for three month starting from 5th day of period. Patients were called for follow up at 1month and 3 month during the therapy and again at 6 month ie 3 month after stopping treatment to see any recurrence of symptoms .In This study uterine size, myoma volume , haemoglobin level were compared with pretreatment level. Improvement in symptoms like menorrhagia and pain lower abdomen were noted. Change in fibroid volume were noted by ultrasound after three month and compared with pretreatment level. Side effects of mifepristone was also noted.

RESULT

The mean age of patients in this study was 39.63± 3.8 years and median

parity is 3. Mean BMI of patients were 26.23 kg/m2±3.2.Fifty five percent women were educated..

Table – 1 Demographic Features

Parameters	
Mean age	39.63 years ± 3.8
Median parity	3(2-5)
Mean BMI	26.23kg /m2 ± 3.21
Education Illiterate Primary Matriculation Graduation	 20 10 11 4

The commonest presenting symptoms of the patients were menorrhagia(84.44%) associated with dysmenorrhoea and pelvic pain. six patients initially presented with infertility but after taking a detailed history they reported associated menorrhagia and dysmenorrhoea.

Table 2: Patient distribution according to symptoms

Symptoms	Number of patients	Percentage(%)
Menorrhagia	38	84.44%
Pelvic pain	23	51.11%
Dysmenorrhoea	38	84.44%
Backache	7	15.55%
Urinary problem	3	6.66%
Infertility	6	13.33%

In present study 100% improvement seen in women with menorrhagia immediately. All the 38 patients with with heavy menstrual bleeding become amenorroeic after three month of treatment. PBAC reduced significantly and the effect started at the very first cycle. Reduction in mean PBAC score was significant. In this study mean PBAC score was 80.36±71.96 initially and it was decreased by 70.22% after one month of treatment and significantly to 91.42% after completion of treatment.

The mean haemoglobin improved from 9.58 to 11.76 gm/dl with p-value =0.001,which was statistically significant. There was 1.3% rise seen in endometrial thickness which is stastically nonsignificant. It was observed that after 3 month of treatment with mifepristone ,the mean fibroid volume reduced from 236.80 to 112.76 cm3 (p value-<0.001) which is statistically significant and the percentage mean volume reduction was 47.45%. In follow up after 3 month of completion of treatment, 45% patients were asymptomatic and no change in myoma volume were noted.

Table 3: pre and post treatment comparison of haemoglobin level, endometrial thickness, myoma volume, PBAC score

Parameters	Pre-treatment	At 1month	At 3 month	Mean change at 3 month
Haemoglobin (%)	9.58± 1.6	10.2±1.5	11.67±1.3 (Pvalue <0.05)	2.1±1.7 rise
Endometrial thickness(mm)	6.9	7.0	7.8	1.3% rise
Myoma volume(cm3)	236.80±167.8	142.9±152.6	112.76±142.9	26.45% decrease
Mean PBAC SCORE	80.36±71.96	24.76± 32.13% value-	10.23±16.34 (P-value<0.001)	91.42% decrease

Most common side effect of mifepristone in present study was weakness and fatigue in 26.6% women seen during the treatment. 15.5% women complains of leg cramps. Hot flushes seen in 17.7% and mood swings were seen in 4.4% .Other side effects were gastrointestinal symptoms and headache. One patient complained of palpitation.

Table 4: Side effects

Side effects	No of patients	Percentage
Weakness and fatigue	12	26.66%
Hot flush	8	17.77%
Leg cramps	7	15.55%
GI symptoms	5	11.11%
palpitation	1	2.22%
Headache	3	6.66%
Mood swings	2	4.445

In follow up after 6 month ie after 3 month of completion of treatment 45% patients were asymptomatic and no change in myoma volume were noted.18(40%) patients complained of menorrhagia requiring intervention .In those patients mifepristone were restarted in 22.2% and rest opted for other medical or surgical treatment.

DISCUSSION –

Mifepristone is effective in decreasing the severity of fibroid specific symptoms and thus helps in improving the quality of life .Different studies evaluated the different doses of mifepristone varying from 5 to 50 mg /day for 3 to 9 month and low doses were also effective in improving menorrhagia ,dysmenorrhoea and pelvic pressure ,and in reducing fibroid volume by 26-57% and inducing amenorrhoea in 41-100% .[1,8,9,10,11,12]

In present study, menorrhagia was the most common presenting symptoms seen in 84.44% cases associated with dysmenorrhoea .In a study by Seth et al, 93.96 % cases presented with heavy uterine bleeding followed by heaviness in lower abdomen in 26.83%.[12] In the present study there was a great improvement in the symptoms as all 38 patients become amenorrhoic at the end of 3 month treatment with mifepristone. Women were counselled about this effect of mifepristone and were assured that their menstrual function would resume after stoppage of treatment. So in this study 100% amenorrhoea was seen which corresponds with the study done done by Yang H Zen et al.[11]

In present study, there was a significant reduction in mean PBAC score and it was decreased by 70.22% after one month of treatment and significantly to 91.42% after completion of treatment at 3 month. In a study by Kulshrestha et al, 10 mg mifepristone was given for 3 month and reduction in mean PBAC score was 96.4%[1]. In a study by Sabita et al, mean blood loss was corrected in 100% of the patients[13].

In this study, at the time of enrolment all the patients had normal endometrial thickness, at the end of 3 month there was 1.3% rise in thickness. Only 6 patient had endometrial thickness >8 mm which decreased again at 3 month after stopping therapy which is comparable with a study done by Kulshrestha et al[1].The decrease in myoma volume was 26.45% in this study it matches with study done by Kulshrestha et al in which the reduction with 10 mg dose was 22.5% although size reduction was more with 25 mg dose for 3 month [9,11,12] . Weakness and fatigue was the main side effect seen in 26.6% cases followed by hot flushes in 17.7% which is comparable to other studies[1,8,9 12.] no serious complication were seen in study done by Spitz IM[14]. .

CONCLUSION-

Heavy menstrual bleeding is the main problem with fibroid, mifepristone is very effective in reducing heavy menstrual bleeding and pelvic pain thus leads to improved quality of life of women. Hemoglobin levels are significantly increased. Amenorrhoea developed in more than 90% cases which is reversible. Endometrial changes were seen but no evidence of atypia, other side effects were minimal and non significant. Mifepristone can be a safe and effective choice for treating fibroid uterus especially in perimenopausal women in whom myomas would regress after menopause. But its use is limited due to recurrence of symptoms after stopping treatment and further studies are required to see the long term outcome.

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