



## ROLE OF ORMELOXIFENE IN MANAGEMENT OF SYMPTOMATIC UTERINE LEIOMYOMA IN REPRODUCTIVE AGE GROUP

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### ABSTRACT

**Introduction:** Abnormal uterine bleeding due to leiomyoma is common problem in the reproductive age group and was found to be third most common cause of hysterectomies in teaching hospital of India<sup>1</sup>. The search for ideal

drug for medical management of fibroid is still on so that we can avoid operative interventions in symptomatic women of reproductive age group. Ormeloxifene is Selective Estrogen Receptor Modulator developed at CDRI, Lucknow. It has proven to be an important drug in treatment of AUB, but its utility in fibroid is yet to be defined. Through this study, we have explored its role in AUB due to leiomyoma.

**Aim and objective:** To assess decrease in menstrual blood loss (MBL) by pictorial blood loss assessment chart to assess increase in hemoglobin level, to assess change in endometrial thickness, to assess change in fibroid size in patients of AUB with leiomyoma treated with Ormiloxifene.

**Materials and Methods:** Subjects were given tablet ormeloxifene 60 mg biweekly for 3 months, followed by 60mg weekly for next 3 months. Subjects were assessed after 3 months and 6 months for MBL, endometrial thickness, fibroid volume and hemoglobin level.

**Observation:** There was statistically significant decrease in MBL, endometrial thickness, (p=0.0334 and p=0.0096), increase in hemoglobin (p=0.0001) and no change in fibroid volume. after 3 months and 6 months respectively

**Conclusion:** SERM such as ormeloxifene in standard biweekly dosage is effective in providing symptomatic relief in a patient of AUB-L when prescribed for a short period of 6 months

**KEYWORDS :** AUB (abnormal uterine bleeding), HMB (heavy menstrual bleeding), ET (endometrial thickness), AUB-L (abnormal uterine bleeding due to leiomyoma).

### INTRODUCTION:

Abnormal Uterine Bleeding (AUB) is a common problem amongst women in reproductive age. AUB can occur at any age. It may be accompanied by pain, discomfort, significant social embarrassment, and have substantial effect on health. AUB leads to loss of productivity, affect quality of life and may result in surgical intervention including hysterectomy<sup>1</sup>. In India, the reported prevalence of AUB is around 17.9%<sup>2</sup>. A large portion of women with menorrhagia will subsequently undergo a hysterectomy, which is a definitive cure for AUB, but operative procedure requires hospitalisation and anaesthesia and the procedure is not suitable for women who want to preserve their fertility or for women nearing menopause because menorrhagia will rectify itself with onset of menopause. Although conservative surgery (i.e. endometrial ablation) is an alternative to hysterectomy, it is invasive, and not without complication. Long-term daily oral drug treatment is restricted by poor compliance. The search for ideal drug for medical management of fibroid is still on so that we can avoid operative interventions in symptomatic women of reproductive and perimenopausal age group. Ormeloxifene (centchroman or 3,4-trans-2,2-dimethyl-3-phenyl-4-p-(b pyrrolidinoethoxy)-phenyl-7-methoxy chroman) is a non-steroidal, selective estrogen receptor modulator (SERM) and has been in use as a weekly oral contraceptive for approximately last 20 years, particularly in India, where it was originally developed<sup>3,4</sup>. Like any SERM, ormeloxifene interacts with estrogen receptors, eliciting tissue specific responses. When it was used as a contraceptive, its beneficial effect on dysfunctional uterine bleeding and endometriosis was observed, which led to controlled trials for the management of dysfunctional uterine bleeding after approval was given by the Indian Drug Regulatory Authorities for this indication. In this study we have tried to find out the role of ormeloxifene in AUB due to leiomyoma.

### AIMS AND OBJECTIVES:

#### Aims:

To study the role of ormeloxifene in management of symptomatic uterine fibroid in reproductive age group

#### Objectives:

Primary objective: To assess decrease in menstrual blood loss by pictorial blood loss assessment chart

#### Secondary objectives:

To assess increase in hemoglobin level  
To assess change in endometrial thickness  
To assess change in fibroid volume

#### MATERIAL AND METHODS:

This is prospective, Interventional study over a period of one and half year from March 2017 to July 2018 and conducted at Department of OBGY at GMCH Nagpur. Data was collected and analysed in statistical software, STATA Version 10.1 2011. Detailed history was obtained from selected subjects fulfilling the inclusion criteria. Menstrual blood loss was assessed with PBAC score by asking about number of soakage of pads and passage of clots. The patients were educated to calculate PBAC score. A thorough clinical examination was done, written consent was taken of subjects selected. Endometrial biopsy was taken on OPD basis with help of endometrial biopsy curette and send for HPE. After HPE report, patients were started with tab ormeloxifene 60 mg biweekly for 3 months, followed by 60mg weekly for next 3 months. Subjects were assessed after 3 months. PBAC score, hemoglobin level, fibroid volume and endometrial thickness (ET) by TVS were noted. Subjects were evaluated for any side effects, improvement in symptoms, Repeat investigations like CBC were carried out. If patient is compliant and ready to continue the treatment, they were allowed to continue the tab ormeloxifene 60 mg once a week for next 3 months. All subjects were followed up for period of 6 months. If endometrial thickness was to be found more than 13 mm, subjects were reassured and repeat endometrial biopsy was taken at OPD basis with endometrial curette and send for HPE. At the end of 6 months, subjects were analyzed for blood loss by PBAC score, hemoglobin, endometrial thickness and fibroid volume. Women with dysmenorrhea was assessed with VAS score before and after treatment

**OBSERVATIONS:**

Amongst 50 subjects enrolled in the study ,42 subject completed the treatment. Out of 8 subjects who didn't complete the treatment 2 were lost to follow-up and 6 subject opted for surgical treatment.

Out of 50 subjects,42 subjects were having single fibroid. Subjects having two numbers of fibroid were 7 and one subject has four numbers of fibroids. Endometrial thickness, PBAC score, Hemoglobin and visual analogue scale compared during treatment course. Mean Endometrial thickness of study subjects before starting the treatment was 9.42 cm which reduced to 8.75 cm and 8.27 cm respectively after 3 and 6 months of treatment. The reduction in endometrial thickness was significant with p values 0.0334 and 0.009 respectively. Mean PBAC score before starting of treatment were calculated to be 133.45. With treatment it improved to 99.0 and 70.02 at the end of 3 and 6 months with p values 0.009 and 0.0001 respectively. Hemoglobin was also found to be increased significantly (p=0.009 and 0.0001 after 3 and 6 months of treatment). It was 9.25 gm% before treatment and increased to 9.69 gm% and 10.121 gm% at 3 and 6 months of treatment. VAS score were calculated for patients with dysmenorrhea at the start and end of treatment (51.66 and 26.66 respectively) and found to be improved with p value 0.037.

**Table no.1: comparison of various parameters before and after treatment.**

Parameters	Value at start of the treatment	Value after 3 months of atment	P value a after 3 months of vation	Value after 6 months of tment	P value after 6 months of vations
Mean endometrial thickness(cm)	9.42 (SD=2.48)	8.75 (SD=2.42)	0.0334	8.27(SD=3.63)	0.009
Mean PBAC score	133.45 (SD=32.44)	99.72 (SD=25.13)	0.009	70.02(SD=15.91)	0.0001
Mean Hemoglobin(gm%)	9.25 (SD=0.760)	9.69SD=0.684	0.009	10.121 (SD=)	0.0001
Mean VAS	51.66 (SD=10.4)	-	-	26.66(SD=15.27)	0.0377

Comparison between uterine fibroid volume before and after treatment of 6 months was statistically not significant, details of which are given below.

**Table no.2: comparison of uterine fibroid volume before and after treatment.**

Fibroids	Mean of fibroid volume before treatment	Mean of fibroid volume after treatment	P value
Fbroid volume 1 (n=38)	68.22 ± 115.15	63.66 ± 111.12	0.1928
Fibroid volume 2 (n=6)	18.38 ± 25.89	15.61 ± 19.92	0.4761
Fibroid volume 3 (n=1)	3.9	3.5	-----
Fibroid volume 4 (n=1)	0.33	0.33	-----
Mean of all fibroids (n=33)	76.46 ± 121.39	70.97 ± 117.34	0.1719

Fibroid volume 1= volume of first fibroid  
 Fibroid volume 2=volume of 2nd fibroid  
 Fibroid volume 3=volume of 3 rd fibroid  
 Fibroid volume 4=volume of 4th fibroid

Mean of solitary and multiple fibroids are compared in this table. 3rd and 4th fibroids were sole in number hence SD and P value could not obtained. At the end of 6 months of treatment mean of volume of all fibroids was compared and found to be not significant.(P= 0.1719).

**DISCUSSION AND CONCLUSION:**

There is a higher content of oestrogen and progesterone receptors in leiomyoma than in myometrium. Oestrogens play a crucial role in promoting leiomyoma growth. Recent evidence suggests that although progesterone is essential for maintenance and growth of leiomyoma, oestrogen is required for up regulation of progesterone receptors<sup>5</sup>. In studies with the other SERM raloxifene, leiomyoma size decreased in postmenopausal women while it increased in the premenopausal women, and it was postulated that doses were too low to reverse the proliferative effect of serum estradiol in premenopausal women, unlike postmenopausal women who have much lower serum estrogen. Therefore, although 60-mg twice weekly ormeloxifene may suffice for AUB- O and AUB-E, it may be inadequate in AUB-L, with the associated higher local oestrogen content in the leiomyoma tissue especially in premenopausal women. Mean age in the present study was 38.96 years . Hence, no reduction in leiomyoma size may reflect inadequate efficacy in reducing size and no role in stimulation of growth. Hence ormeloxifene may be given in AUB-L for symptom relief to subject and not for size reduction per se in either group. Ormeloxifene may be an option for the medical management of AUB-L in subject in whom steroidal treatment is not desired, especially in young subject who also request contraception

In a study conducted by Mandira et al concluded the significant reduction of endometrial thickness from pretreatment value of 7.99±1.16 mm to post treatment values of 7.12±1.15 mm. This was probably the explanation for achieving lower blood loss and hence lower PBAC score as mean PBAC score before treatment was 184.41 which reduces to 83.77 post treatment with statistically significant (P<0.001) . There was statistically significant increase in mean hemoglobin level from 9.2 g/dl to 10.5 g/dl after 6 months (P<0.001). The mean pretreatment fibroid volume was 22.81±36.03 cc. And the mean post treatment fibroid volume was 25.69±42.44 cc. The P value being 0.074 was not significant. The volume of fibroids remained unchanged in 90.9% women at the end of treatment <sup>6</sup>. A similar study conducted by Vijaya et al, the mean pretreatment endometrial thickness was 11.067 mm and the mean posttreatment endometrial thickness was 8.956 mm after 6 months. Based on the estimated marginal means, the mean difference is significant at the 0.5 level<sup>7</sup>. In another study conducted by Agrawal et al, the mean pretreatment endometrial thickness was 11.35 mm with a range of 8- 17mm. It was reduced to 9.4 mm after 3 months of therapy (range 6-13mm; p<0.0001) and to 8.13 mm after 6 months (range 4-11mm; p<0.0001) and median PBAC score was 334 and 322 pre and post treatment which was statistically significant. The mean pretreatment Hemoglobin concentration was 9.04 gm% (range 7.3-11gm%). It was significantly increased to 10.01 gm% at 3 months (range 8.4-11.7gm%; p<0.0001) and further increased to 10.86 gm% at 6 months (range 9.3- 12.4gm%; p<0.0001). Thus there was significant increase in mean hemoglobin concentration of 1.82 gm% after 6 months <sup>8</sup>. Sweta et al in their study had a mean endometrial thickness reduction of about 30.87% and mean PBAC (ml) before treatment was 343.13 and post treatment it was 68.84 and was statistically significant<sup>8</sup>. Thus findings in our study is consistent with other studies conducted, only few of them are discussed above.

**CONCLUSION:**

Oral medical treatments have been shown to provide partial relief from heavy menstrual blood loss. Medical treatment of menorrhagia should aim to relieve symptoms, improve quality of life and avoid the operative morbidity. Despite a decrease in MBL by 50%, many women remain menorrhagic when treated with tranexamic acid, mefenemic acid, flurbiprofen, norethisterone or ethamsylate and many are noncompliant due to daily dosing. Ormeloxifene, like other triphenylethylene SERM, has a long-lasting oestrogen antagonist action. The long half-life of ormeloxifene provides a basis for a weekly dosing schedule. It has virtually no side-effects which is commonly associated other hormonal regimens. No effect on hypothalamic-pituitary axis and has a large margin of safety. In addition, in our study, none of the side-effects

were severe enough to warrant intervention. It may be used as an interim treatment to delay operation especially in patients who need improvement in general condition. The drug is also cost effective. It is also a good option for adolescents and women in the perimenopausal age group. For young females who desire contraception, this is definitely a better choice. However, its role as the sole medical method in fibroid management needs to be assessed by more studies in future.

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