DOI: 10.21276/sjams.2016.4.10.24

Scholars Journal of Applied Medical Sciences (SJAMS) **ISSN 2320-6691 (Online)**
Sch. J. App. Med. Sci., 2016; 4(10B):3669-3675 **ISSN 2347-954X (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublisher.com

Original Research Article

Efficacy of Selective Estrogen Receptor Modulators in the Management of Abnormal Uterine Bleeding In Women of Early Reproductive Age Group

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Abstract: Study was aimed to compare the therapeutic efficacy of SERMs (ormeloxifene) to Norethisterone in the medical management of Abnormal Uterine Bleeding (AUB)**.**It was Prospective, comparative, interventional randomized study. A total of 60 women who attended Outpatient Gynaecology Department ,Guwahati with complain of AUB in reproductive age group were randomly allocated to 2 equal groups, Group-O, which received 60mg ormeloxifene twice weekly for 3 months then once weekly for next 3 months and Group N which received 5 mg Norethisterone twice daily for 21 days for 6 months. The reduction in mean PBAC score with ormeloxifene (176.8 to 29.13) was significantly more than that seen with Norethisterone (179.73 to 86.87) after 6 months of therapy ($p<0.0035$). The increase in haemoglobin level and reduction in endometrial thickness was significantly more with ormeloxifene than Norethisterone (8.8gm/dl to 10.1gm/dl vs 8.7gm/dl to 9.2gm/dl(p value 0.0031) ,8.9 mm to 2.4mm vs 7.8mm to 5.9mm (p value0.0035) respectively. No major side effects were reported in any group. Ormeloxifene was found to be more effective than Norethisterone in reducing PBAC score and endometrial thickness.
Keywords: Abnormal uterine bleeding, early reproductive age, Ormeloxifene, Norethisterone, Pictorial blood loss assessment chart score (PBAC).

INTRODUCTION

Abnormal uterine bleeding may be defined as any variation from the normal menstrual cycles, and include changes in regularity and frequency of menses, in duration of flow or in amount of blood loss [1]. Abnormal uterine bleeding affects 10 to 30 percent of reproductive-aged women and up to 50 percent of perimenopausal women [2, 3]. Factors that impact the incidence most greatly are age and reproductive status. For example, uterine bleeding is uncommon in prepubertal girls and menopausal women, whereas rates of abnormal bleeding increase significantly in adolescent, perimenopausal, and reproductive-age groups. Approximately 5% of women in 30 – 49 age groups consult gynaecologists for AUB. Most women with menorrhagia have no pelvic pathology [4]. This is the most common cause of iron deficiency anaemia in healthy fertile women.

Over the year abnormal uterine bleeding has become quite common presenting complain. Today the total span of menstruating years has increased due to early menarche and late menopause. A wide range of treatment modalities are available which include medical therapy and surgical interventions. The ultimate cure is hysterectomy. Though the option is relatively safe with low mortality one cannot deny the long term complication of hysterectomy like premature ovarian failure, cardiovascular disease and intestinal or urinary dysfunction. Thus more and more women are looking forward to an effective medical therapy. Pharmacological management should be the first line of management. It can be hormonal or non-hormonal. Hormonal agents include estrogen, progesterones, combination of the two, androgens, danazol, GnRH agonists and the latest SERMS (Selective estrogen Receptor Modulators).

Non-hormonal drugs like NSAIDs, ethamsylate and anti-fibrinolytics have also been found to be highly effective. Medical management has always been the first therapeutic option to be tried and if it fails to show results, one can resort to surgical interventions. Hysterectomy should be the last resort in the management. Because of the morbidity associated with the surgical procedures, the RCOG recommends

beginning with medical management before resorting to surgical interventions. The latest of the pharmacological agents that have become available for the treatment are selective estrogen receptor modulators. These are designer drugs which have an affinity to the estrogen receptor and act like oestrogens in some tissues and have antiestrogenic effects in others.

Ormeloxifene is one such SERM which has shown anti-estrogenic effect in the uterus that forms the pharmacological basis of using it in abnormal uterine bleeding. The SERMs are unique compounds that have attracted great interest because of their potential for the prevention and treatment of bone loss and menorrhagia, although apparently being estrogen antagonists in breast [5].

MATERIALS AND METHODS

Present study has been conducted from 2015 – 2016, in 60 patients attending the outpatient department of Obstetrics and Gynaecology, Gauhati medical college and Hospital., within the early reproductive age group with the complain of abnormal uterine bleeding. Study is aimed at determining the therapeutic efficacy of SERMS on abnormal uterine bleeding. Approval from the Hospital ethical committee has been taken before commencing the study.

Aims and objectives

1. Therapeutic efficacy of SERMS
2. Compare the efficacy of SERMS with other medical treatment modalities
3. Patient compliance and satisfaction
4. Side effects of SERMs

EXCLUSION CRITERIA:

(1) Postmenopausal bleeding
(2)Endometrial biopsy suggestive of atypical hyperplasia or malignancy
(3) Cervical dysplasia
(4) Fibroid uterus
(5) Bleeding dyscrasia
(6) Clinical evidence of jaundice or hepatic dysfunction
(7) Hypersensitivity to the drug
(8) Uterine size >6 weeks gestational pregnant uterus.
(9) Women desirous of fertility.
(10) History of abortion within 3 month or childbirth within 1 year
(11) Endometrial polyp
(12) Adenomyosis

Informed consent was taken from all the patients. A detailed history and clinical examination was done. As DUB is a diagnosis of exclusion investigations were done to rule out any other possible cause for abnormal uterine bleeding. These included complete blood cell count, thyroid stimulating hormone, coagulation profile, Pap smear, pelvic ultrasound to measure endometrial thickness and rule out any pelvic pathology and endometrial sampling

The cases were advised to maintain a menstrual diary to record the total number of days of bleeding, number of sanitary pads used, degree of soaking of each pad, number and size of clots passed, and if dysmenorrhoea experienced. The Pictorial Blood loss Assessment Chart (PBAC) Scoring was then done accordingly to assess menstrual blood loss. PBAC is a simple procedure for objective assessment of menstrual blood loss. A PBAC score $\geq$ 100 indicates a menstrual blood loss $\geq$ 80 ml and is considered diagnostic for menorrhagia (Table – 1) [6].

Table 1: PBAC scoring

Pads	
Lightly soiled pads	1
Moderately soiled pads	5
Severely soiled pads	20
Clots	
Small clots	1
Large clots	5
Flooding	20

The patients were divided randomly into 2 groups (N and O group) and treated accordingly as shown in table 2

Table 2 showing Treatment groups

GROP	Drug	Dose	Duration
N	NORETHISTERONE	5 mg BD	21 days for 6 cycles
O	ORMELOXIFENE	60 mg twice weekly	3 months
		Then 60 mg weekly	3 months

After drug administration, patient has been advised to come for follow up after one month for first follow up. Rest of the follow up is scheduled at 3rd and 6th month. During each visit a detailed menstrual history was taken, PBAC score was calculated. Haemoglobin concentration and endometrial thickness were measured after 3 and 6 months of the treatment. Any side effects if experienced were also noted.

Statistical Analysis

Data were compared using Mann–Whitney U-test for numerical variables and Fischer's exact test for categorical variables. A $P < 0.05$ was considered significant. Friedman's ANOVA followed by Dunn's posthoc test was used for multiple comparisons in

PBAC scores, Hb level and endometrial thickness between the groups.

RESULTS AND OBSERVATIONS

In the present study, out of 60 patients 30 received treatment with ormeloxifene and 30 with norethisterone. All the cases in both the groups were matched well with respect to age & parity. Majority of the cases are in the age group of 31-35 years in both the groups i.e. 15 patients (50%) in O group and 17 patients (56.6%) in N group not showing any significant statistical difference. Maximum no. of patients i.e. 20 patients (66.6%) in both the groups were multipara. The pre-treatment mean Hb level, mean PBAC score and Mean endometrial thickness were comparable in both the groups. 62 % of cases in O group and 57% in group were having Hb level <9 gm/dl.

Table 3: showing clinical profile of women

Sl. No	Clinical Parameter	Ormeloxifene group	Norethisterone Group
1	Age group (31-35 years)	15(50%)	17(56.6%)
2	Parity (multipara)	20(66.6%)	20(66.6%)

It was seen that Pre-treatment mean PBAC score in both groups were comparable i.e. 179.7 & 176.8 (p value 0.6194) .Both the groups showed statistically significant fall in PBAC score following treatment. Mean reduction in PBAC score after 3 and 6 months was more in group O than group N respectively (83.5% reduction vs 51.6%) as per table 4. and this difference was statistically significant. (P value is 0.0001 and < 0.0001 respectively.

Table 4: showing reduction in PBAC score

	PBAC score before treatment	PBAC score after 3 months	P value	PBAC score after 6 months	P value
Ormeloxifene	176.80± 14.608	65.767 ± 51.800	*** P<0.001	29.133 ± 54.528	*** P<0.001
Norethisterone	179.73± 0.593	88.83 ± 45.996	*** P<0.001	86.87± 44.015	*** P<0.001

Pre-treatment mean ET in both groups was comparable i.e. 7.8mm & 8.9mm (p value 0.3992). The decrease in mean ET after 3 and 6 months was more in group O (3.2mm, 2.47mm) than group N (6.4mm, 5.9mm) respectively as per table 5 and this difference was statistically significant.(p value is 0.0036 and .0035 respectively).

Table 5: showing reduction in endometrial thickness

	ET before treatment	ET after 3 months	P value	ET after 6 months	P value
Ormeloxifene	8.987± 4.186	3.223± 2.489	P<0.001	2.476 ± 1.918	*** P<0.001
Norethisterone	7.858 ± 3.454	6.432 ± 3.401	*** P<0.001	5.901 ± 3.331	*** P<0.001

Pre-treatment mean Hb level in both groups were comparable i.e. 8.7 gm/dl & 8.8 gm/dl (p value 0.911) .Mean Hb in group O after 3 & 6 months was 10.1gm/dl & 10.3 gm/dl respectively and that in group N was 9.2gm/dl & 9.27gm/dl after 3 & 6 months respectively as per table 6.Three patients in both group were given 1 unit blood transfusion for correction of severe anaemia .4 cases in O group and 3 cases in N group were given 3 doses of inj. Iron sucrose on alternate days. Rest all patients were given tablet iron one tab daily The mean rise in Hb level after 3 and 6 months was more in group O than group N and this difference was statistically significant. (p value is 0.0069 and .0031 respectively).

Table 6: showing rise in Hb following treatment

	Hb before Treatment	Hb after 3 months	P value	Hb after 6 months	P value
Ormeloxifene	8.837± 1.117	10.117± 1.254	*** P<0.001	10.383 ± 1.445	*** P<0.001
Norethisterone	8.783 ± 1.025	9.200 ± 1.035	** P<0.01	9.277± 1.453	<0.05

It was found that 19 patients (63%) in O group and 15 patients (50%) were suffering from dysmenorrhoea which was comparable to each other. After 6 months dysmenorrhoea persisted in 5 patients (17%) in O group and 6 patients (20%) in N group as per table 7 suggesting that both ormeloxifene and Norethisterone are effective in reducing dysmenorrhoea up to 83% in O group and 80% in N group (p value <.0005 , <.0292 respectively). However there was no statistically significant difference in between the two groups in relieving dysmenorrhoea.(p value 1).

Table 7: Showing effects on dysmenorrhea

	dysmenorrhea before treatment	dysmenorrhea after treatment	P value
Ormeloxifene	19(63.3%)	15(50%)	0.0005
Norethisterone	5(17.25%)	6(20%)	0.0292

It was observed that ormeloxifene is effective in reducing PBAC score in both proliferative endometrium from 175 to 51(p value < 0.0001) and 12 (p value < 0.0001) after 3 months and 6 months respectively and secretory endometrium from 179 to 48(p value 0.0002) and 15 (p value 0.0002) after 3 & 6 months respectively as shown in table 8. However in patients with atrophic endometrium mean PBAC score was 176 before treatment which reduced to 144 after 3 months(p value 0.2492) but again increased to 187 after 6 months(p value 0.785) suggesting that ormeloxifene is not effective in reducing PBAC score in patients with atrophic endometrium.

Table 8: showing relation between D&C findings & PBAC score in Ormeloxifene group

D & C endometrium	Pre-treatment PBAC SCORE	PBAC SCORE at 3rd month	P value	PBAC SCORE at 6rd month	P value
Proliferative (15)	175.3	51.2	<0.0001	11.71	<0.0001
Secretory (10)	179.20	48.4	0.0002	14.8	0.0002
Atrophic (5)	176.4	144.2	0.2492	187.33	0.7857

It was seen that Norethisterone is effective in reducing PBAC score in proliferative endometrium from 178 to 97.6(p value < 0.0001) and 95.2 (p value .0002) after 3 months and 6 months, in secretory endometrium from 178 to 95.7(p value 0.0006) and 94.3 (p value 0.0002) after 3 & 6 months respectively. Even in patients with atrophic endometrium mean PBAC score was 182 before treatment which reduced to 67.5 after 3 months(p value 0.009) & to 64.5 after 6 months(p value 0.0009) suggesting that Norethisterone is more effective in reducing PBAC score in patients with atrophic endometrium than ormeloxifene.

Table 9: showing relation between D&C findings & PBAC score in Norethisterone group

D&C endometrium	Pre-treatment PBAC SCORE	PBAC SCORE at 3rd month	P value	PBAC SCORE at 6rd month	P value
Proliferative (13)	178	97.61	<0.0001	95.23	0.0002
Secretory(9)	178	95.77	0.0006	94.33	0.0022
Atrophic(8)	182.25	67.5	0.0009	64.5	0.0009

There were no major side effects in both the groups as per table 10 . Amenorrhea was seen in 4 (13%) cases while 7 patients (23%) had oligomenorrhea after 6 months therapy of ormeloxifene. However, only 2 (7%) cases were complaining of oligomenorrhea in N group and none had amenorrhea. The incidence of functional ovarian cyst was 20% in O group as compared to 10% in N group (p value 0.476) suggesting insignificant data.

Table 10: showing adverse effects in both groups

S.no	O group	N group	Two-sided P value
WEIGHT GAIN	1	4	0.1945
OVARIAN CYST	6	3	0.4716
AMENORRHEA	4	0	
OLIGOMENORRHEA	7	2	
HEADACHE	2	2	1.0000
DIZZINESS	0	0	
GI DISTURBANCE	2	1	1.0000

The satisfaction level in the present study was 24 (80%) patients in O group and 17 patients (56%) in N group. Subjects having PBAC score > 100 and who underwent hysterectomy were considered as treatment failure.6 patients (20%) in O group were not satisfied and they underwent hysterectomy. In N group 13 patients (44%) were not satisfied. Among these 4 patients (13%) still had menorrhagia with PBAC > 100, while 9 patients (30%) in N group underwent hysterectomy.

Table 11: showing level of satisfaction in both groups

S no	O Group (n=30)(%)	N group (n=30)(%)	P value
Satisfied	24(80)	17(56)	0.0946
unsatisfied	6(20)	13(44)	

DISCUSSION

Present Study is a prospective study to evaluate the effects of ormeloxifene on menstrual blood loss, change in Hb concentration, and change in endometrial thickness and side effects. The aim of the study is to compare the therapeutic efficacy of ormeloxifene to Norethisterone in AUB in women of early reproductive age group.

Maximum no. of patients i.e. 20 (66%) were multipara. Bleeding was more common in multipara. This may be due to altered pituitary ovarian function following delivery. Biswas *et al.;* [7], S fayyaz *et al.;* [8], Bellad Girija *et al.;* [9], Grover S *et al.;* [10], Tapan Kumar *et al.;* [11] and Agarwal and Singh *et al.;* [12] all took study group 100% multiparous.

The mean rise of Hb in O group is 1.3 gm/dl after 3 months of therapy and 1.5 gm/dl after 6 months of therapy. Both findings are statistically significant. Also mean rise of Hb in N group i.e 0.5gm/dl and 0.57 gm/dl after 3 and 6 months respectively is statistically significant. Biswas *et al.;* [7] found mean increase of 1.3 gm/dl in Hb concentration in their respective studies. A significant increase in mean hemoglobin concentration of 1.82 gm% after 6 months was found by Neha Agarwal [12] & 1.3gm/dl by Ravibandu and Palla [13].

Ormeloxifene was found to cause significant reduction in endometrial thickness (3.2 mm and 2.4 mm) compared to group N (6.4mm,5.9 mm)after 3 and 6 months (Two tailed p value 0.0036 and 0.0035 respectively). Reduction in endometrial thickness is a definitive objective evidence showing reduction in menstrual blood loss .While both ormeloxifene and norethisterone exhibit antiestrogenic activity in the endometrium preventing endometrial proliferation, ormeloxifene is more efficacious as it directly blocks the estrogen receptors and thereby prevents mitogenic activity exhibited by estrogen.

Biswas *et al.;* [7] found that mean endometrial thickness decrease from 11.4 mm to 7.8mm after 6 months of therapy(p value <0.005 , t score = 21).M Tripura *et al.;* [14] found that mean endometrial thickness decrease from8 mm to 6 mm after 36 months of therapy. Jacob KJ *et al.;* [15] also found that ormeloxifene causes significant reduction in ET of 2.47 mm from 7.8mm to 5.3mm(p value <0.001,t score 4.7) compared to Norethisterone which was 0.8 mm from 6.7mm to 5.9mm (p value 0.109 , t score=1.7). Bellad Girija *et al.;* [9] found that 74 out of 85 subjects (87.05%) showed a reduction in endometrial thickness from 11.4mm to 7.3mm.

Ormeloxifene competes with estradiol for binding with cytosol receptors. It not only blocks cytosol receptors but also causes their prolonged depletion and has long lasting post withdrawal effect. Thus efficacy of the drug improves with time which is depicted by increasing reduction in menstrual blood loss with prolonged use.

The mean PBAC scores at the end of the study period were 29.13 and 86.87 in groups O and N respectively reporting an overall reduction in menstrual blood loss (MBL) by 83.5% and 52.2 % in groups O and N respectively after 6 months. Ormeloxifene was thus, found to be more efficacious in reducing menstrual blood loss in AUB compared to cyclical progesterone.

The results in our study with respect to efficacy of ormeloxifene in reducing MBL were comparable with majority of the other similar studies. Evidence states that when oral progesterone is given cyclically from D5 – D26 of menstrual cycle, reduction in MBL is seen. Biswas *et al.;* [7] found a decrease in mean PBAC score from 272 to 107.8 after 6 months of treatment (p value<0.001, t score = 20.20) in 72 % of the patients. This decrease was more in women with age >40 years i.e. 82 %. Tapan kumar *et al.;* [11] found mean decrease in PBAC score in Ormeloxifene group from 108 to 62(p value <0.05) compared to progesterone group in which mean decrease in PBAC score from 113 to 94 occurred (p value <0.05).

In the present study it was found that ormeloxifene is ineffective in reducing PBAC score in patients with atrophic endometrium (ET<5mm) in 100% of cases. The finding is similar to Shravage *et al.;* [16] in which 80 % of the patients who failed to respond to ormeloxifene had ET< 5mm (atrophic endometrium). The cut-off value of less than 5mm to diagnose atrophic endometrium by TVS was taken as per criteria of Shia Salen". Though in theory, ormeloxifene is supposed to improve mean blood loss even in hypo estrogenic state by virtue of exerting a mild estrogenic effect by means of agonist action of ER-b receptors; such an effect has not been seen in the present study

Ormeloxifene in the present study reduce dysmenorrhoea by 73% which is similar to Ravibandu and Palla[119]. Ravibandu and Palla *et al.;* [13] found that

there was significant improvement, 84% of patients had relief from dysmenorrhoea (p<0.001)

Biswas *et al.;* [7] found that dysmenorrhoea reduced from 23 patients (27%) to only 5 patients (5.8%) after 6 months of therapy (p value < 0.005 and z=3.68). Grover S *et al.;* [10] found that dysmenorrhoea was relieved in 62.5% patients who initially had the complaint of dysmenorrhoea. Bellad Girija *et al.;* [9] found that dysmenorrhoea was relieved in 78.26 % patients.

One of the major side effects of use of ormeloxifene was amenorrhoea. This is due to hypo estrogenic effects causing delay in ovulation thereby lengthening the follicular phase .In the present study amenorrhea following treatment was seen in 13.3% of patients (4 out of 30). M Tripura *et al.;* [14] found that during a 6 month follow up period 46 % patients developed amenorrhoea which increased to 86% in 3 year follow up. Jacob KJ *et al.;* [15] found that 20% of patients had amenorrhoea at the end of 3 months. In various studies conducted, in majority of the subjects menstrual cyclicity returned to normalcy after 3 months. The limitation of our study was lack of follow up after 6 months of study as a result of which it is not possible to comment on whether the menstrual cyclicity returned to normal or not. Long term follow up is required to observe the efficacy of these drugs and to note the recurrence of symptomatology.

Ormeloxifene has got an excellent safety profile and has been found to have very few side effects. In the present study no major side effects were noted in any of the treatment group. Patient's compliance was good in both the treatment groups. Ovarian cysts were seen in 6(20%) patients in O group while 3 patients (10%) in N group were found to have ovarian cyst. These were asymptomatic and functional. None had required any intervention till the end of the study. In the present study none of the patients has other side effects like abnormal vaginal discharge, pelvic pain, breast tenderness etc.

Grover S *et al.;* [10] reported 27.3% ovarian cysts in their study which were painless and they regress spontaneously in follow up .On histopathology all cysts were found to be serous cysts. Subjects who opted for surgical treatment and whose PBAC score was >100 were taken as failure of treatment. In this study 20% of the patients failed to respond to ormeloxifene and ended up in hysterectomy, while 80% were satisfied with ormeloxifene which is statistically significant and comparable to above similar studies. Only 56.6% were satisfied with norethisterone. The two sided p value is 0.0946 suggesting no statistically significant difference between two groups for level of satisfaction.

Mandal *et al.;* [17] found that 11.11% of patients in Ormeloxifene group and 14.71% of patients in OCP group were poorly satisfied .Incidence of hysterectomy in poor responders in ORM group is 5.56% and in OCP group it is 11.76%. Ormeloxifene has been evaluated for management of menorrhagia in various studies since the year 2000. It is associated with a number of advantages. It can be started at any time during the cycle. It is an effective endometrial haemostat controlling bleeding within 48 hours. It is economical compared to any drug. While preventing DUB it is a concurrent contraceptive. It also offers perimenopausal bone and cardiovascular protection which is not seen with any other drug treating DUB.

Limitations of the study

It is a small sample size and short duration study with the absence of double blinded placebo controlled trial to control information bias. There was failure to allocate the subjects evenly in two treatment groups of different age composition. Large RCT are needed to compare the efficacy of these drugs with other medical therapies such as progestins, tranexamic acid, and levonorgestrel-releasing intrauterine system. Long-term follow-up is required to observe the efficacy of these drugs and to note the recurrence of symptomatology.

CONCLUSION

Abnormal uterine bleeding is a common problem that is encountered in the gynecology outpatient department. The main mode of management is pharmacological therapy. Both ormeloxifene and progesterone (norethisterone) were found to be effective in treating these cases as assessed by reduction in PBAC score, rise in hemoglobin level and reduction in endometrial thickness. But the effect was seen more with ormeloxifene. Hence, ormeloxifene was found to be superior to norethisterone in the management of AUB.

Apart from its efficacy, it has shown its superiority by good compliance due to convenient dose schedule and cost benefit for total therapy. Besides it does not increase the risks of breast cancer because of its anti-estrogenic action on the breast tissues. No major side effects were seen with either of the drugs. One of the major limitations of the study was that the 13% of the patients became amenorrhoeic after onset of the treatment in Ormeloxifene group who were not followed up later to know whether the menstrual cyclicity returned to normal or not. Thus, Ormeloxifene may be considered for the medical management of idiopathic menorrhagia, especially for patients who prefer the nonsteroidal treatment & those women who wish to preserve their fertility.

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