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Role of Ormeloxifene in Treatment of Abnormal Uterine Bleeding (AUB) In Comparison with Other Hormanal Treatment Modalities

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Abstract

Introduction: Abnormal uterine bleeding (AUB) is state of abnormal bleeding from uterus without any clinically detectable organic, systemic and iatrogenic causes. AUB is major and one of the most distressing gynaecological problems for both patient and clinician.

Aims and objective- To compare the effect of ormeloxifene for treatment of AUB and its comparison with Norethisterone and oral contraceptives in different age groups in view of efficacy, compliance, complication and follow-up in terms of avoiding hysterectomies.

Material and Methods: 300 cases of AUB were divided into three groups during study period September 2016 to September 2017. Group A (n=100) were given ormeloxifene to received 60 mg twice weekly for 12 week followed by once weekly for 3 months. Group B (n=100) were given Norethisterone 10 mg bd in every cycle from day 5 to day 25 for 6 month and Group C were given oral contraceptive pills (OCP) from day 1 to day 21 of menstrual cycle for six cycle.

Results: There is significant reduction of PBAC score from 127 to 36 after six month of treatment in group A, 127 to 77 in group B whereas 128 to 96 in group C. Mean pre-treatment endometrial thickness decreased markedly in ormeloxifene group from 9.8 mm to 5.8 mm as compared to norethisterone (9.7-6.4mm) and OCP group (9.7-7.7mm).Complications such as hypo amenorrhea 73% patient and about 15% develop amenorrhea.

Conclusion: Ormeloxifene has better compliance and acceptability with marked relief of symptoms. Women who underwent hysterectomy after treatment were also significantly less in ormeloxifene group. Hence, ormeloxifene should be considered the first choice in management of AUB especially in perimenopausal age group where amenorrhea is acceptable.

Keywords: Abnormal uterine bleeding (AUB), Ormeloxifene, PBAC, Hysterectomy.

Introduction

Menorrhagia (menstrual blood flow >80 ml) affects 33 % of women at some stage in their lives. [1] Over 75000 hysterectomies are conducted out every year with 30% of their being done for menstrual blood loss.[2] It can affect women from menarche to menopause occurring more commonly at extremes of age.[3]A medical management is the first line of therapy for chronic menorrhagia. The agents that have been used to treat menorrhagia include iron, cyclooxygenase inhibitors, desmopressin, antifibrinolytics, gonadotropin-releasing hormone agonists, androgens, combined oral contraceptives, and progestins. Progestins can be administered systemically or

locally and they may be given cyclically or continuously. The increased use of effective medical therapies has the potential to reduce the number of surgical procedures, such as endometrial ablation and hysterectomy. [4]LNG - IUCD was found to reduce blood loss by 86% after 3 months of use and up to 97% by 12 months of use due to progestin induced decidualization of the endometrium .Patient satisfaction with the LNG IUS also compares favourably to that of ablation or hysterectomy. [5]Even though a number of treatment modalities are available, reliable drug for management of AUB should meet the requirement like drug should be effective, convenient to take; cost of drug must be low, with minimal side effects.

AUB is major cause of hospital referral as well as for hysterectomy. Hysterectomy should be the last resort in the management of AUB. Because of the morbidity associated with the surgical procedures, the RCOG recommends beginning with medical management before resorting to surgical interventions.

Ormeloxifene is a SERM, a selective estrogen receptor modulator. In some parts of the body, its action is oestrogenic (e.g., in the bones). In other parts of the body, its action is anti-oestrogenic (e.g., in the uterus and the breasts). [6, 7] It causes an asynchrony in the menstrual cycle between the ovulation and the development of the uterine lining, although its exact mode of action has not been well defined. Ormeloxifene is the ideal therapy in perimenopausal women as it does not causes uterine stimulation, prevents bone loss, has no risk of breast cancer, has a positive effect on lipids and cardiovascular system and maintains cognitive function of brain.[8]It is best known as a non-hormonal, nonsteroidal oral contraceptive which is taken once per week.[9,10]

Material and Methods

This descriptive study was conducted in J.L N Medical College, AJMER on patients attending out patients' clinic over a period of one year. 342 women presenting with abnormal uterine bleeding without any organic, systemic or iatrogenic cause were included in the study. A detailed history was taken and thorough clinical examination was done. The investigations which were carried out included complete blood count, coagulation profile, thyroid profile, blood sugar, liver function test, kidney function test, ultrasound of the abdomen and pelvis and endometrial thickness measurement.

Exclusion criteria were pelvic pathologies like uterine fibroid, endometriosis, malignancies of genital tract, medical disease like liver dysfunction, heart disease, coagulopathies, renal disease, pregnancy, IUCD or pill users, lactating women in the first 6 months of postnatal period, thyroid disorder, history of abortion within last 3 months and hypersensitivity to drug, post menopausal bleeding and those having atypical endometrial hyperplasia.

Written informed consent was taken from all the patients selected for study. 342 cases of AUB were divided into three groups during study period September 2016 to September 2017.Out of these 342, 20 patients lost in follow up and 22 patients left the study due to side effects. Group A (n=100) were given ormeloxifene to received 60 mg twice weekly for 12 week followed by once weekly for 3 months. Group B (n=100) were given Norethisterone 10 mg bd in every cycle from day 5 to day 25 for 6 month and Group C were given oral contraceptive pills (OCP) from day 1 to day 21 of menstrual cycle for six cycle. Patients were asked to maintain menstrual calendar and were called at monthly interval. At each visit, a detailed menstrual history was taken and physical examination was done. Pictorial blood loss assessment chart (PBAC) was used to measure the menstrual blood loss (MBL). The women were asked to use certain sanitary napkins which have similar absorbent capacities. They recorded the

number of napkins used each day and the degree of soiling of each pad used. Number and sizes of clots passed were also noted. Scores were assigned to different degrees of soiling of sanitary napkins and number and size of clots passed. A PBAC score of greater than or equal to 100 was considered diagnostic of menorrhagia. The main outcome measures were MBL, passage of clots, blood haemoglobin (Hb) level and endometrial thickness (ET) in proliferative phase by TVS. Haemoglobin estimation and endometrial thickness was measured at start of therapy and after 6 months of treatment. Subjective improvement and any side effects experienced by patients were noted.

Results

Total numbers of enrolled patients were 342, group I (ormeloxifene) include 111 patients, group II (norethisterone) include 114 and group III (low dose oral contraceptives) includes 117 subjects.

Table- 1: Agewise Distribution Of Study Subjects

Age	Group I (n=111)	Group II (n= 114)	Group III (n= 117)
21-30	31(28%)	23(20%)	28(24%)
31-40	57(52%)	68(62%)	66(56%)
41-50	23(20%)	23(20%)	23(20%)

Total number of enrolled patients were 342, group I (ormeloxifene) include 111 patients, group II (norethisterone) and group III (conventional oral contraceptive, MALA-N) out of which 20 patients were lost in follow up due to various reasons and were not included in present study.

Table – 2: Patients Who Left Out The Study Group Due To Side Effects

Group I N= 111		Group II N= 114		Group III N= 117			
No. Of pt.	%	No. Of pt.	%	No. of Pt.	%	Total no. of patients	%
4	3.6	7	6.1	11	9.9	22	6.83

Above table shows that out of remaining 322 patients 22 patients (6.83 %) were such who left out treatment due to one or more side effects of the treatment modality. Out of these 3.6% were from group I, 6.1% from group II and 9.9% from third group.

Maximum numbers of patients were multipara in all three study groups about 61 % and 5.3% were nulliparous and mostly were of lower socio-economic status.

Table 3: Factors Affecting Complaiance with Medical Treatment

	GROUP I ORMELOXIFENE ((n= 100) %		Group II (Norethisterone) (n= 100) %		Group III (OCPs) (n= 100) %	
Affordability	60	60	20	20	100	100
Acceptability	90	90	24	24	45	45

Above table shows that affordability as well accessibility in group III was 100% in comparison to other two groups, because of freely available in hospital supply.

Ormeloxifene group have comparatively fair affordability as well as acceptability.

Table 4: Comparision of PBAC Score between Three Groups

PBAC	0 months		3 months			6 months		
GROUP	Mean	SD	Mean	SD	P value	Mean	SD	P value
ORMELOXIFENE (GROUP I)	127.54	9.87	81.41	13.34	<0.001	36.95	27.51	<0.001
NORETHISTERONE (GROUP II)	127.20	9.69	97.40	10.11	<0.001	77.46	10.16	<0.001
OCP (GROUP III)	128.06	9.40	107.76	10.32	<0.001	96.70	10.54	<0.001

This table shows that mean PBAC score before treatment was 127.54 with standard deviation ± 9.87 and at the end of 6 month mean is 36.95 and standard deviation ± 27. 51 which means, there is significant reduction in PBAC score in ormeloxifene group and reduction in norethisterone group was from 127.20 to 77 .46 and in OCP group there is reduction in mean PBAC scoring from 128.06 to 96.70. Using student paired t test it was found that there was significant difference within the groups as $p<0.001$. On comparing drug group I with drug group II value is highly

significant as p value <0.001 similarly when compared with drug group III result is highly significant, p<0.001.

On comparing drug group II with drug group III, the result is highly significant both in 3 and 6 months as p<0.001.

Table-5: Comparative Evaluation of Hemoglobin In All Three Group

HB	0 months		3 months			6 months		
GROUP	Mean	SD	Mean	SD		Mean	SD	P value
ORMELOXIFENE (GROUP I)	7.87	0.84	10.71	0.71		12.18	0.4	<0.001
NORETHISTERONE (GROUP II)	8.19	0.39	9.96	0.55		11.10	0.49	<0.001
OCP (GROUP III)	8.11	0.91	9.15	0.78		10.05	2.47	<0.05

Above table show significant improvement in haemoglobin from 7.87% to 12.18% Within 6 months in group I. Rise in haemoglobin in group I is highly significant and comparison to group II and group III as P<0.001. Similarly, haemoglobin level is increased more in group II in comparison to group III.

Table - 6: Comparative Evaluation In Endometrial Thickness Redection In All Three Group

ET	0 months		3 months			6 months		
GROUP	Mean	SD	Mean	SD	P value	Mean	SD	P value
ORMELOXIFENE (GROUP I)	9.82mm	1.97	7.67mm	1.33	<0.001	5.87	0.74	<0.001
NORETHISTERONE (GROUP II)	9.74mm	1.92	8.47mm	1.73	<0.001	6.45	1.28	<0.001
OCP (GROUP III)	9.70mm	1.86	8.91mm	1.73	<0.001	7.71	1.60	<0.001

There is also decrease in endometrial thickness from mean 9.74 mm to 6.4 mm in ormeloxifene group, from 9.74 mm to 6.45 mm in norethisterone group and 9.74mm to 7.71 mm in OCP group within 6 months treatment.

Table -7: Comparative Evaluation of Improvement In Endometrial Thickness Among All Three Study Groups

ET	3 month			6 month		
Group	T	P value	Inference	T	P value	Inference
I Vs II	3.66	<0.001	Sig	3.92	<0.001	Sig
I Vs III	5.68	<0.001	Sig	10.43	<0.001	Sig
II Vs III	1.79	>0.05	Non Sig	6.14	<0.001	Sig

About table shows that on comparing drug group I with drug group II value is highly significant as p value <0.001 similarly when compared with drug group III result is highly significant, p <0.001.

On comparing drug group II with drug group III result is non-significant in first three month as P>0.05 but by the end of six months, the value is significant at P<0.001

Table 8: Comparsion of Adverse Effects of All Three Groups

Side Effects	GROUP I	GROUP II	GROUP III
Amenrhhorea	15	0	0
Hypoamenorhhoea	73	0	0
Weight Gain	0	6	2
Gi Symptoms	0	20	17
Pain Abdomen	1	15	0
Breakthrough Bleeding	5	11	15
Ovarian Cyst	12	0	0

In group I, 73% patients developed hypo menorrhea and 15% patients developed amenorrhoea and 12% develop ovarian cyst .In norethisterone group, the major side effect was nausea/vomiting (20%) followed by breakthrough bleeding. In OCP group, Nausea/vomiting (17%) followed by breakthrough bleeding (11%) and weight gain occur in 2 % of OCP users.

Discussion

In our study, maximum number of patients(>50%) were from age group of 31-40 years and it was seen that most of the above patients were multiparous (36%-50%) and this was most probably because multiparity may lead to alteration in hypothalmopituitary ovarian axis. Our results were comparable to other studies that were conducted; one of the studies is done by Ravibabu, komaram et. al .Major bulk of the patients belonged to underprivileged group (>62%). Patients belonging to middle and upper socioeconomic class were 31.3% and 6.6% respectively. By this data it seems that abnormal uterine bleeding is more common in low socioeconomic group women. But this fallacy is because of > 90% of patients were from lower or middle socioeconomic group.

In our study >80% of patients were persistently complaint with the treatment in ormeloxifene group while at the other end compliance was very poor (<25%) with the treatment in MALA-N group While affordability and accessibility of OCP was 100% because it was being available free of cost in our government supply.

Those patients with anovulatory cycles may benefit from an exogenous control of the pattern of bleeding by the use of hormonal preparations. 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. A good medical treatment will reduce hysterectomies and associated morbidity and mortality.[11] When an effective contraception is also required the use of either OCP or levonorgestrel releasing intra uterine device are the suitable choices. When all three study groups were compared with each other using student paired t test it was found that ormeloxifene scored better in all three parameters i.e. PBAC, ET, and Hb and our results were comparable to the results of other studies.

In a similar study, Bhattacharyya et al studied 180 cases of DUB, who had completed child bearing and were above 35years, were randomly assigned to ormeloxifene, progesterone and iron groups. They used similar dose of ormeloxifene with shorter duration of norethisterone of 10 mg daily for 12 days (from 14th day) in each cycle as compared to 21 days in our study. Iron group was given as 60 mg of elemental iron daily. They also found ormeloxifene to be superior to norethisterone in reducing menstrual blood loss. The increase in haemoglobin concentration occurred maximally with ormeloxifene which were comparable to our study which marked improvement in haemoglobin concentration. [12]

In our study, we analysed the efficacy of Ormeloxifene in patients with AUB and our results suggested significant reduction in Mean PBAC score from 12.54 to 36.95 ($p<0.001$) which was comparable with the studies conducted by Kriplani et al and Dadich et al.[13]

Kripalani et al [14] studied the efficacy and the safety of ormeloxifene in the management of menorrhagia. It was a pilot study and it was found that Ormeloxifene was an effective and safe therapeutic option for the medical management of menorrhagia. Similar to the present study, Neha Agarwal et al [15] found that 22 patients out of 32 had amenorrhoea at end of 4 months of treatment and 90.09% had reduction of menstrual blood loss. Studies by Chitrangada et al, Uma gupta et aland Ravibabu et al, all have shown similar results indicating Ormeloxifene superior to Norethisterone in reducing menstrual bloodloss.[16,17] This study result was compared to study by Sweta et al. [18] where mean pre-treatment MBL was assessed by pictorial blood chart (PBAC score) and was reduced by 79.9% with treatment with ormeloxifene similarly to our study (p-value≤0.001). The rise in the mean haemoglobin level at the end of treatment was1.65g/dl (18.17%) (P-value≤ 0.001).

In our study major side effect in group I was hypo menorrhoea (73%) and amenorrhoea in 15% and ovarian cyst was seen in 12% of patients which was an ultrasound findings. Headache, giddiness and abdominal pain was seen in 2%, 3% and 1% of the patients respectively, comparable to other studies some patients also had stress urinary incontinence, genital prolapse . Norethisterone was not found to be gut friendly in our study as 20% patients developed nausea and vomiting and 15% of the patients complained of abdominal pain, break through bleeding was fairly common (16%). Small number of patients developed Spotting, weight gain8% and 6% respectively, 17% of the patients who were on MALA-N had nausea and vomiting, 11% patients had break through bleeding and in small number of patients weight gain was seen.

Conclusion

Ormeloxifene was found to be an excellent drug in controlling dysfunctional uterine bleeding without effecting normal endocrinal and physiological parameters. It is a non steroidal option for treating AUB – COEIN in patients needing simultaneous contraception or in whom steroids are contraindicated, Ormeloxifene has beneficial effects on bones which may be an added advantage in perimemopausal women. It is suitable for women with hypertension, diabetes and thrombo-embolic disease where steroidal agents are contraindicated. Basis for weekly dosing schedule of Ormeloxifene are the long elimination half -life and a long-lasting estrogen antagonist action .It leads to a significant reduction in menstrual blood loss and a significant decrease in endometrial thickness without any major side effect.

Though the results of the study are encouraging and Ormeloxifene is emerging as a good option

to the conventional treatment modalities available which are fraught with one or the other limiting factors, but it is not the answer to every case of AUB. Treatment needs to be individualized and patients should be offered and tried with treatment with other drugs interchanging before labelling it as failure to medical treatment and directly jumping over to more invasive procedures such as minor surgeries or hysterectomy.

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Etthical Approval: Study was approved by the institutional ethics committee.

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