



## COMPARATIVE EVALUATION OF THE EFFECTIVENESS OF ORMELOXIFENE V/S NORETHISTERONE IN PERIMENOPAUSAL ABNORMAL UTERINE BLEEDING

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### ABSTRACT

**Background:** Menstrual disorders are the second most common gynecological conditions resulting in hospital referral's and OPD. The objective of this study was to compare the efficacy and safety of these two drugs ormeloxifene and norethisterone which is rapidly emerging as a safe and effective agent for AUB (abnormal uterine bleeding). **Methods:** 300 women presenting with AUB randomly allocated 2 equal groups, Group I, which received 60 mg Ormeloxifene twice a week for 12 weeks followed by once a week for next 12 weeks and Group II, which received 5 mg Norethisterone twice daily for 21 days for 6 cycles. The primary outcome were reduction in menstrual blood loss [measured by fall in PBAC (Pictorial Blood Loss Assessment Chart) score and subjective assessment] and rise in hemoglobin level. **Results:** The reduction in Mean PBAC score with ormeloxifene was significantly more than with norethisterone at 6 months. Rise in hemoglobin concentration was more with Ormeloxifene group. No major side effects were reported in any group. **Conclusion:** Both drugs are effective in treating peri-menopausal AUB, but ormeloxifene is superior to norethisterone in reducing menstrual blood loss, as well as improving peri-menopausal symptoms. Clinical significance: Better and effective medical management will reduce need for hysterectomies and its long term complications.

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### INTRODUCTION

Longevity of women is increasing beyond 80 years. It is time to shift our attention, so that at fifty we should be prepared for another 30 years to come. We have done and are doing a lot for 30s and 40s it is time to shift to the 50s and properly manage problems like Abnormal Uterine Bleeding(AUB). So that quality of life can be improved. As a women approaches menopause, the cycle length become more irregular because fewer cycle are ovulatory.(1)

Abnormal uterine bleeding (AUB)-menstrual bleeding both abnormal in time and abnormally heavy. Although the women of any age group can be affected with abnormal uterine bleeding (AUB), it is more commonly experienced by women of 35-45 years of age.

Structural cause of AUB include the PALM in PALM-COEIN (Polyps, Adenomyosis, Leiomyoma, Malignancy/Hyperplasia) (2)

Nonstructural cause of AUB include the COEIN in PALM – COEIN (Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic, NOS).

For all women, the evaluation of excessive and abnormal periods includes a thorough medical and gynecologic history, the exclusion of pregnancy, the consideration of possible malignancy, and a careful gynecologic examination.

Abnormal bleeding either intermenstrual or postcoital can be caused by cervical lesions. Bleeding can result from endocervical polyps and infectious cervical lesions, such as condylomata, herpes simplex virus ulcerations, chlamydial cervicitis or cervicitis caused by other organisms.

Additional laboratory or imaging studies may be indicated if the diagnosis is not apparent on the basis of examination and history.

In any patient of heavy menstrual bleeding, an objective measurement of hematologic status should be performed with a complete blood count to detect anemia or thrombocytopenia. A TSH level and chlamydia testing should be considered. Because of the possibility of a primary coagulation problem, screening coagulation studies should be ordered where appropriate.

The consensus report of an international expert panel recommends measurement of CBC, platelet count and function, PT, activated PTT, VWF and fibrinogen to be assessed in collaboration with a hematologist. (3)

A pelvic ultrasonographic examination is the best initial technique for evaluating the uterine contour endometrial thickness and ovarian structure (4) CT or MRI should be reserved for specific indication, such as exploring the possibility other intra-abdominal pathology or adenopathy.

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Endometrial sampling should be performed to evaluate abnormal bleeding in women who are at risk for endometrial pathology including polyps, hyperplasia, or carcinoma. Attention should be directed to establishing a cause of abnormal bleeding.

In most cases, medical therapy is effective in managing abnormal bleeding and should be attempted before surgical management.(1)

Antifibrinolytics, non-steroidal anti-inflammatory drugs (NSAIDs), progesterone, combined estrogen and progesterone, danazole, gonadotropin releasing hormone analogues and levonorgesterol-releasing intrauterine system have all been used with different results in the management of dysfunctional uterine bleeding. Noretisterone, a progesterone, is commonly used for this purpose but being a hormonal drug, it is associated with side effect such as stroke heart disease breast cancer dementia, fluid retention, breakthrough bleeding spotting etc.

Selective estrogen receptor modulator drugs (SERM) selectively bind with high affinity to estrogen receptors and mimic the effect of estrogen in the same tissue but act as estrogen antagonist in others.

Ormeloxifene is one of the 3rd generation selective estrogen receptor modulator (SERM). It is the best known as a non-steroidal oral contraceptive taken once a week. It is one of those few drugs which are pride our nation as it is developed by Central Drugs Research Institute(CDRI), Lucknow, India. It is contraindicated in polycystic ovarian disease, cervical growth recent history of jaundice. It is category C drug in pregnancy.(5)

Ormeloxifene not only preferred as an oral contraceptive but also useful for management of abnormal uterine bleeding and advanced breast cancer(6). In the pharmacological management of AUB the standard dosage is 60 mg orally twice weekly once a week for period of 12 weeks followed by weekly once in the next 12 weeks.

The safety profile of ormeloxifene is excellent with very few side effect like nausea, headache, weight gain delayed or prolonged menstrual period. Unlike progesterone, ormeloxifene does not produce spotting, breakthrough bleeding or menorrhagia.

#### **Aims and Objectives**

1. The aim of this study is to highlight the role of Ormeloxifene as a drug treatment modality in AUB and compare it with one of the most commonly used drug Norethisterone.
2. To evaluate the safety and efficacy of Ormeloxifene.
3. To evaluate the safety and efficacy of Norethisterone.

#### **MATERIAL AND METHODS**

This is a prospective comparative study conducted in Department of Obstetrics and Gynaecology department Government Medical College and Attached Hospital Kota Rajasthan (India) during the specified period from the January 2020 to December 2021 taken up for study.

In this prospective and comparative study of 300 perimenopausal women between age of 35-52 years presenting with abnormal uterine bleeding without any organic and

systemic cause enrolled. Ethical approval taken from institutional ethical committee.

The cases were advised to maintain a menstrual diary to record the total no of days of bleeding, no of sanitary pad used degree of soaking of each pad number and size of clots passed, and if dysmenorrhea experienced.

In this study objective assessment of menstrual blood loss done by following method advised by Higham *et al.*, Pictorial Blood Loss Assessment Chart(PBAC).

#### **PBAC SCORE**

##### **PADS SCORE**

Lightly soiled pad	1
Moderately soiled pad	5
Severely soiled pad	20

##### **CLOTS SCORE**

Small clots	1
Large clots	5
Flooding	5

A PBAC score  $\geq 100$  indicate a menstrual blood loss  $>80$ ml is considered diagnostic for menorrhagia.(6)

All patients instructed to use a sanitary napkins of the same brand which have been shown to have similar absorbent capacities and scored depending upon the level of soiling and passage of clots as follows. PBAC score of given cycle obtained by adding scores depending on number of pad used, level of soiling and number and size of clots passed.

After making the diagnosis of DUB from history clinical examination and investigations, patient randomly divided into two groups.

#### **Group 1**

Patient in this group treated with Ormeloxifene 60 mg orally twice per week for 3 cycle then once a week next 3 cycle.

#### **Group 2**

Patient in this group treated with Norethisterone 5 mg from day 1 of menstrual cycle to day 21 for 6 consecutive cycle. During the treatment period each patient followed-up monthly. Menstrual blood loss assessed during each period by PBAC.

#### **Inclusion criteria**

Allperi-menopausal women between 35-52 years presenting with abnormal uterine bleeding without any organic, systemic and iatrogenic causes included in this study.

#### **Exclusion criteria**

1. Patient who were pregnant, lactating with history of heart disease, hypertension, migraine, polycystic ovarian disease, Liver and Kidney impairment and thyroid dysfunction excluded.
2. Patient with fibroid uterus, adenomyosis, atypical endometrial hyperplasia, bleeding disorders.
3. Patient having organic, systemic and iatrogenic causes.

#### **RESULTS**

Women were divided into two groups with similarity related to duration of symptoms, parity, age and socioeconomic status. Women in both groups were compared with pre-treatment mean of hemoglobin level and PBAC score.

1. Pretreatment mean hemoglobin concentration in Group I was 9.99 gm% which was significantly increased to 11.75 gm% at 6 months with Ormeloxifene 'p'0.004. Pretreatment hemoglobin concentration in Group II was 9.89 gm% which was significantly increased to 11.00 gm% at 6 months with norethisterone (p<0.05)
2. The mean values of used pads in group I was 9.86/day before treatment then decrease after treatment upto 1.45/day.

The mean value of used pads in group in group II was 10.80/day before treatment then decreases after treatment upto 3.13/day.

3. The mean value of no. passage of clots group I was 2.62 before treatment then decreases upto 0.04 after treatment.

The mean value of no. of passage of clots in group II 2.47 before treatment then decreases upto 0.55 after treatment.

4. No any significant side effects reported in bot Groups of the patients.

Ormeloxifene was found to be more effective than Norethisterone, can be considered as the first line of treatment.

## DISCUSSION

Bleeding among reproductive aged women internationally is estimated to be between 3-30%, with higher incidence occurring around menarche and perimenopause. Many studies are limited to heavy menstrual bleeding (HMB) but when irregular and intermenstrual bleeding are considered, prevalence rises to 35% or greater.

Treatment goal for patients with AUB include regulation of menstrual cycle, minimization of blood loss and improvement in quality of life.

In 2011 FIGO changed the names to prevent confusion menorrhagia is now called HMB' Heavy Menstrual Bleeding. (7) Menometrorrhagia is now called abnormal uterine bleeding.

In the present study, the reduction in menstrual blood loss (as assessed by fall in PBAC score and patient's subjective assessment), rise in hemoglobin concentration, major side effects and efficacy of both drugs were assessed.

The cases in both groups matched well with regards to mean age, parity, socioeconomic status and duration of symptoms. The pretreatment mean PBAC score, mean hemoglobin level were also comparable in both the Groups. The most common presenting complaint was irregular BPV. Secretory endometrium and cystic glandular hyperplasia of endometrium were the most common endometrial pattern in both groups.

Pap smear and endometrial biopsy done to all patients. No any significant findings present in Pap smear but secretory phase and cystic glandular hyperplasia most common endometrial pattern in both Groups in our study which was compare to one study of DrPia Muriel Cardoso 2016 conducted in the Department of Obstetric and Gynecology, Goa Medical College, Bambolim, Goa, in which Proliferative and Glandular Hyperplasia endometrium were the most common endometrial pattern in both groups(8).

Pretreatment mean hemoglobin concentration in Group I was 9.99 gm% which was significantly increased to 11.75 gm% at 6 months with Ormeloxifene p value (0.004).Pretreatment hemoglobin concentration in Group II was 9.89 gm% which was significantly increased to 11.00 gm% at 6 months with Norethisterone (p<0.001)

On comparing the both groups, rise in hemoglobin level was more with Ormeloxifene and the difference was statistically significant (p 0.004)

The increase in hemoglobin concentration occurred maximally seen with Ormeloxifene also seen in previous studies.

In study of DrPia Muriel Cardoso there was rise in mean hemoglobin concentration from 8.52gm%-10.5gm% at 6 months treatment with Ormeloxifene. (p<0.05)(8)

And there was rise in hemoglobin concentration from 8.28gm%-8.7gm% at 6 months with norethisterone(p<0.01)

On comparing both groups, rise in hemoglobin level was more with Ormeloxifene and the difference was statistically significant (p<0.05) like our study.

The mean values of used pads in group I was 9.86/day before treatment then decrease after treatment up-to 1.45/day .The mean value of used pads in group in group II was 10.80/day before treatment then decreases after treatment up-to 3.13/day. The mean value of no passage of clots in group I was 2.62 before treatment then decreases up-to 0.04 after treatment. The mean value of no of passage of clots in group II 2.47 before treatment then decreases up-to 0.55 after treatment.

The reduction in mean PBAC score with Ormeloxifene was significantly more than Norethisterone at 6 months p value <0.001 which was similar to previous studies like by Dr.Devi LT and Drpoojaagrawal (9,10)

No any significant side effect reported in both groups of the patients in our study. Amenorrhoea/Hypomenorrhoea was a common symptoms seen with Ormeloxifene in different studies with wide range of 8% to 63%.(11)

At the end of the study both the groups showed the reduction in PBAC score, rise in hemoglobin level.

**Table no 1** Distribution of cases of according to Age Groups

Age Group (Years)	Group I		Group II		Total	
	No.	%	No.	%	No.	%
30-35	43	28.67	35	23.33	78	26.00
36-40	47	31.33	45	30.00	92	30.67
41-45	35	23.33	47	31.33	82	27.33
46-50	25	16.67	23	15.33	48	16.00
Total	150	100.00	150	100.00	300	100.00

Chi-square = 2.703 with 3 degrees of freedom; P = 0.598

Age

Group	N	Mean	SD	Median	Min.	Max.	'p' Value*
Group I	150	40.36	5.26	40	30	50	0.825
Group II	150	40.49	5.17	40	30	49	

**Table no 2** Comparision of Hb before and after treatment

Hb	Group	N	Mean	SD	Median	Min.	Max.	'p' Value*
Hb before treatment	Group I	150	9.99	1.28	10	7	13	0.508
	Group II	150	9.89	1.29	9.9	7	12.7	
Hb after treatment	Group I	150	11.75	7.32	11	8.2	100	0.211

Change in Hb	Group II	150	11.00	0.95	11	8.9	13	0.584
	Group I	150	1.16	0.93	1	0	4	
	Group II	150	1.10	0.86	1	-0.7	4	

\*Unpaired 't' test

Hb	Treatment	N	Mean	SD	Median	Min.	Max.	'p' Value*
Group I	Before	150	9.99	1.28	10	7	13	0.004
	After	150	11.75	7.32	11	8.2	100	
Group II	Before	150	9.89	1.29	9.9	7	12.7	<0.001
	After	150	11.00	0.95	11	8.9	13	

**Table no 3** Distribution of patients according to PBAC score

PADS	Group	N	Mean	SD	Median	Min.	Max.	'p' Value*
PADS before treatment	Group I	150	9.86	7.86	5	1	20	0.205
	Group II	150	10.80	7.83	5	1	20	
PADS after treatment	Group I	150	1.45	1.27	1	1	5	<0.001
	Group II	150	3.13	2.43	5	1	20	
Change in PADS	Group I	150	8.41	7.68	4	0	19	0.042
	Group II	150	7.67	8.06	4	-4	19	

\* Mann-Whitney test

PADS	PADS	N	Mean	SD	Median	Min.	Max.	'p' Value*
Group I	Before	150	9.86	7.86	5	1	20	<0.001
	After	150	1.45	1.27	1	1	5	
Group II	Before	150	10.80	7.83	5	1	20	<0.001
	After	150	3.13	2.43	5	1	20	

\* Wilcoxon Signed Rank Test

Clots	Group	N	Mean	SD	Median	Min.	Max.	'p' Value*
Clots before treatment	Group I	150	2.62	2.17	1	0	5	0.388
	Group II	150	2.47	2.22	1	0	5	
Clots after treatment	Group I	150	0.04	0.20	0	0	1	<0.001
	Group II	150	0.55	0.72	0	0	5	
Change in Clots	Group I	150	2.58	2.16	1	0	5	<0.001
	Group II	150	1.93	1.93	1	0	5	

\* Mann-Whitney test

Clots	Clots	N	Mean	SD	Median	Min.	Max.	'p' Value*
Group I	Before	150	2.62	2.17	1	0	5	<0.001
	After	150	0.04	0.20	0	0	1	
Group II	Before	150	2.47	2.22	1	0	5	<0.001
	After	150	0.55	0.72	0	0	5	

\* Wilcoxon Signed Rank Test

**Table no 4** Distribution of patients according to ADR (adverse drug reaction)

ADR	Total (N=300)		Group I (N=150)		Group II (N=150)		'p' Value*
	No.	%	No.	%	No.	%	
Abdominal Pain	3	1.00	0	0.00	3	2.00	0.246
Nausea	2	0.67	0	0.00	2	1.33	0.478
Vomiting	4	1.33	0	0.00	4	2.67	0.131
Dizziness	5	1.67	0	0.00	5	3.33	0.071
Breast Tenderness	3	1.00	0	0.00	3	2.00	0.478
Weight Gain	2	0.67	1	0.67	1	0.67	0.478
Delayed Period	1	0.33	1	0.67	0	0.00	1.000

## CONCLUSION

The ideal therapy to treat AUB should be a designer drug which can block the action of estrogen on the endometrium, but not its beneficial actions in the body.

Ormeloxifen (ORM) is found an effective non hormonal drug used for menorrhagea. The ease of administration of drug facilitate patients compliance and acceptability and marked relief of symptoms results in higher patients satisfaction therefore ormeloxifene should be the drug of choice in patients of AUB. Ormeloxifene was found to be superior to Norethisterone in management of AUB. No major side effects were seen with either of the drugs. Even though the treatment with Norethisterone had good results, our study concludes that Ormeloxifene as more effective drug for treatment of AUB. Patient compliance was good as the dose schedule for treatment was convenient and the drug was c well tolerated.

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## Clinical significance

Over 75,000 hysterectomies are carried out every year with 30% of them being done for menstrual disturbances, especially menorrhagia.

Though this surgical option is relatively safe, concern has been expressed about possible long term complications of hysterectomy like premature ovarian failure, cardiovascular disease, and urinary dysfunction and other physiological and psychological consequences Thus, it is better to go for effective medical therapy in preference to surgical treatment.

## References

1. Agrawal P, Shinde U *et al*, Efficacy of ormiloxifene vs norethister one in the management of perimenopausal DUB,VIMSHSJ;2019;6:30-3
2. ACOG Committee opinion no. 651: Menstruation in girls and adolescents: Using the menstrual cycle as a vital sign. *Obstet Gynecol* 2015; 126(6): e143-e146.
3. ChawlaSK, Bucha A *et al*, Use of centchroman (saheli) in conservative management of menorrhagia: Our experience. *Indian J obstetgynecol Res* 2017;4:220-4
4. Curtis KM, Jatlaoui TC, Tepper NK, *et al*. U.S. selected practice recommendations for contraceptive use, 2016. *MMWR Recomm Rep* 2016;65(4):1-66.
5. Devi LT *et al*, Ormiloxifene in the management of dysfunctional uterine bleeding. *Int J Reprod Contracept Obstet Gynecol* 2018;7:1886
6. DeepikaDhananjaya *et al*, Comparative study between ormiloxifene and norethisterone in the improvement of menstrual blood loss in AUB; *Int J Current Med Pharmaceut Res.*2016;2(10):758-61
7. DrPia Muriel Cardoso *et al*. a comparative study of the efficacy of ormiloxifene and norehisterone in perimenopausal dysfunctional uterine bleeding, 2016; *IOSR journal of dental and medical sciences.*15.57-62
8. DivyaVardaini *et al*, Comparision of efficacy and safety of ormiloxofene and cyclical progesterone in ovulatory Abnormal uterine bleeding; *Asian Journal of Pharmeceutical and clinical Research* Vol 13, (11) 2020;178-180
9. Karmakar S, Deshpande H *et al*, Ormiloxifene-A new treatment modality in Dysfunctional uterine bleeding, Efficacy and Safety. *Indian J Obbstet Gynecol Res* 2016;(3) 225-228
10. Munro MG *et al*, FIGO Menstrual disorder committee. The two FIGO systems for normal and abnormal uterine bleeding symptoms; *Int J GynecolObstet* 2018 ;143:393-408
11. Swati get, Shruti Singh *et al*, Comparision between ormiloxifene and norethisteron in reducing menorrhagia in DUB; *IJRCOG*:2018 Dec;7(12) 4966-4971