

**COMPARISON OF EFFICACY AND SAFETY OF ORMELOXIFENE AND CYCLICAL PROGESTERONE (NORETHISTERONE) IN OVULATORY ABNORMAL UTERINE BLEEDING**DIVYA VARDAINI<sup>1</sup>, RAKESH MISHRA<sup>2</sup>, RASHMI RANJAN<sup>3</sup>, SWAPNALI R BORADE<sup>4</sup>

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**ABSTRACT**

**Objective:** The objective of the study was to determine the efficacy and safety of ormeloxifene (ORM) versus norethisterone in controlling ovulatory abnormal uterine bleeding (AUB-O).

**Methods:** A prospective randomized comparative study of total 100 females of reproductive age in the age group 25–45 years with AUB-O. Patients were randomly divided in two groups of 50 each.

**Results:** ORM is more effective in reducing blood loss leading to improvement in mean hemoglobin and it also showed a higher ability to reduce endometrial thickness.

**Conclusion:** While both ORM and norethisterone are very effective drugs for AUB-O, ORM is safer, more cost-effective, non-steroidal, and non-hormonal drug with appropriate dosage and delivers better results for medical management of AUB-O. Therefore, ORM can be considered as the preferred drug in the management of AUB-O.

**Keywords:** Abnormal uterine bleeding, Ovulatory dysfunction, Endometrial hyperplasia, Ormeloxifene, Norethisterone, Selective estrogen receptor modulator, Hemoglobin, Heavy menstrual bleeding, Central nervous system.

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**INTRODUCTION**

Menstrual disorders are the second most common gynecological conditions in hospital referrals. Abnormal uterine bleeding (AUB) includes all patterns of uterine bleeding that does not follow the normal menstrual pattern. AUB is an abnormality in volume, regularity, and/or timing lasting for 6 months. According to the classification given by FIGO (International Federation of Gynecology and Obstetrics), AUB-O is categorized in FIGO- system 2 [1]. It includes conditions such as polyp, adenomyosis, leiomyoma, malignancy, hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and those not yet classified. AUB-O can affect women from adolescence to perimenopausal years.

More and more women are looking forward for better and more convenient medical treatment. Even though there are a number of treatments available, a reliable drug for the management of AUB should meet requirements such as effectiveness, convenience, cost-effectiveness with minimal side effects, and long safety margin.

Approaches to medical management have been hindered by highly variable and non-evidence-based prescribing habits and lack of understanding of mechanisms causing AUB-O. The ideal treatment for AUB should be a designer drug which can block the action of estrogen on the endometrium; it is beneficial actions on the other tissues. Selective estrogen receptor modulators (SERMs) are one such class of drugs which have both agonistic and antagonistic actions on estrogen receptors [2]. They have varied tissue response which behaves as an estrogen antagonist in uterus and breast, being mildly agonist action on vagina, bone mineral density, central nervous system, and serum lipids, making it the perfect SERM for AUB-O. The current study was undertaken to the hypothesis that ormeloxifene (ORM) is superior to cyclical progesterone therapy in the treatment of pre-menopausal AUB-O [3].

**MATERIALS****Place**

The study was carried at the Department of Obstetrics and Gynaecology of Mata Chanan Devi Hospital, Janakpuri, New Delhi.

**Study design**

A prospective randomized comparative study.

**Sample size**

A total of 100 female patients were enrolled in this study. It was calculated keeping in view at the most 5% risk, with a minimum 80% power and 5% significance level.

**Timeframe**

March 2019 to December 2019

**Inclusion criteria**

Females in the reproductive age group, 25–45 years with AUB-O, were in the study.

**Exclusion criteria**

Women with

- Uterine pathology, for example, uterine polyp, leiomyoma, adenomyosis, and iatrogenic endometrial disorder
- Pelvic pathology and malignancies
- Systemic disorders
- Any history of thrombosis, bleeding disorder
- Severe anemia (<7 g)
- Pregnancy, abortion, ectopic, increased bleeding due to IUCDS
- Consistent use of oral contraceptive
- Hypersensitivity to the drug
- History of breast malignancy

- Suspected adenomyosis
- Current genital infection.

### Methodology

The study was conducted after due approval of the Ethical Committee, Mata Chanan Devi Hospital, New Delhi. Patients were randomly divided in two groups of 50 each after taking informed consent from each patient who met the inclusion criteria. A thorough general and systemic examination was conducted before the study.

Patients enrolled in Group A received Tab ORM 60 mg twice a week, with a minimum gap of 3 days for 3 months. Likewise, patients enrolled in Group B received progesterone in the form of tablet 5 mg norethisterone twice a day for 21 days for 3 months starting from day 5 of the menstrual cycle. Hemoglobin (Hb) g% was evaluated and TVS was repeated for endometrial thickness (ET) in the proliferative phase (day 8–day 12 of the cycle) for each patient.

### Statistical analysis

Quantitative variables are expressed in terms of mean + SD and compared between groups using unpaired t-test and within groups across follow-ups using paired t-test. Qualitative variables are expressed in terms of frequencies/percentage and compared using Fisher's exact test. The data were tabulated in MS Excel and analysis was performed using Statistical Package for the Social Science (SPSS) version 16.0 software.

Improvement in Hb and reduction in ET were compared in the pre-treatment period in both the study groups. The p value was considered statistically significant if  $<0.05$ .

## RESULTS

### Demographic characteristics

All subjects were of Indian origin from New Delhi, India. The mean ages were 40.56 and 39.76 for ORM and norethisterone study groups, respectively.

### Mean Hb

The Hb levels were measured in both the study groups at regular intervals of time during the 3-months.

### ET

The ET of the two study groups was measured at regular intervals.

### Treatment outcomes

Ormeloxifene is more superior and effective than norethisterone and can be considered as the first line of treatment.

### Effectiveness

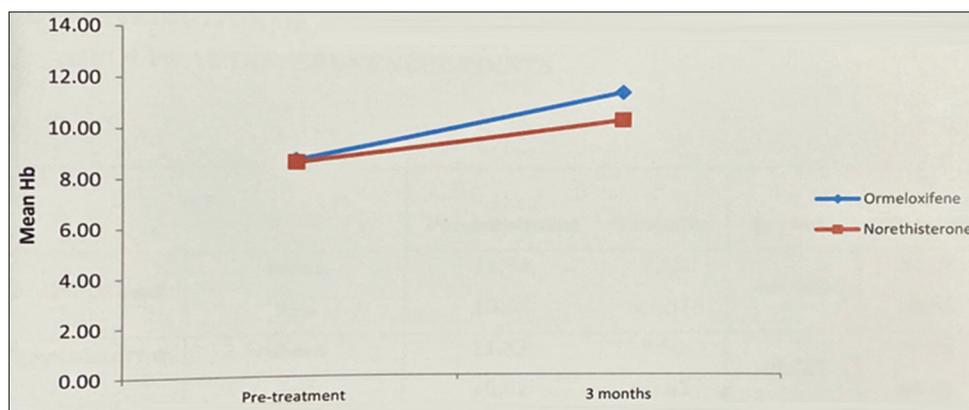
Ormeloxifene was found to be more effective than norethisterone.

### Safety

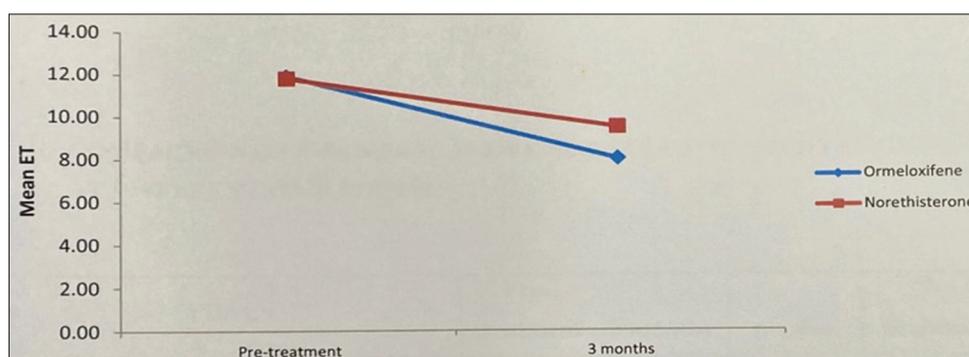
Ormeloxifene is safer than norethisterone.

## DISCUSSION

This study was conducted in Mata Chanan Devi Hospital, New Delhi, India. One hundred patients were enrolled in this study. The patients were divided into two groups – 50 patients were enrolled in Group A who accepted ORM treatment and the rest 50 patients were enrolled in Group B who accepted norethisterone treatment. The mean age of the population was 40.56 years in ORM and 39.76 years in norethisterone group. The majority of women were multiparous. Socioeconomic status was found to be relatively higher in ORM group, but the difference was not statistically significant ( $p=0.055$ ). Hence, both the groups were matched in age, parity, and socioeconomic status. Mean duration of symptoms was similar in both groups, that is, 25.32 months and 27.24 months in ORM and norethisterone groups, respectively. It was higher in norethisterone group, but the difference was not statistically significant ( $p=0.306$ ). Mean Hb at the time of presentation was 8.85 g% and 8.75 g% in ORM and norethisterone groups, respectively. Mean presenting Hb levels were comparable in both groups. Mean ET at the time of presentation was similar in both groups, that is, 11.94 mm and 11.83 mm in ORM and



Graph 1: Comparison of mean hemoglobin (g%) between study groups over 3 months



Graph 2: Comparison of endometrial thickness between the two study groups over 3 months

**Table 1: Mean age, parity, and duration of symptoms**

	ORM	Norethisterone	p-value
	Mean±SD	Mean±SD	
Age (years)	40.56±3.83	39.76±3.65	0.144
Parity	2.46±0.81	2.30±0.54	0.125
Duration of symptoms (months)	25.32±18.75	27.24±19.02	0.306

ORM: Ormeloxifene

**Table 2: Comparison of mean Hb (g%) between study groups**

Hb	Pre-treatment	3 months	p-value	% Increase
ORM				
Mean±SD	8.85±0.8	11.68±0.83	<0.001	32.40±6.28
Norethisterone				
Mean±SD	8.75±0.69	10.54±0.74	<0.001	20.80±7.1
p-value (O versus N)	0.257	<0.001	<0.001	<0.001

Hb: Hemoglobin, ORM: Ormeloxifene

**Table 3: Distribution of ET between the two study groups over 3 months**

ET	Pre-treatment	3 months	p-value	% Decrease
ORM				
Mean±SD	11.94±0.94	8.08±1.31	<0.001	32.36±9.92
Norethisterone				
Mean±SD	11.83±0.81	9.56±0.65	<0.001	19.09±4.41
p-value (O versus N)	0.261	<0.001	<0.001	<0.001

ET: Endometrial thickness, ORM: Ormeloxifene

norethisterone groups, respectively. ORM has been shown to be an effective and safe therapeutic option for the medical management of AUB. Chawla *et al.* [2], in their 2017 study, showed that use of centchroman (ORM) in conservative management of menorrhagia in premenopausal age group resulted in an increase of Hb level at the end of the study. Karmakar and Deshpande [3], in 2016, had done a study of efficacy and safety of ORM in a new treatment for DUB and the result was similar to our study. Jacob and Mini, [4] in their study in 2015, did a comparative study of both the drugs. Their result concluded that ORM is more effective than norethisterone in the reduction of ET and rise in Hb. This, too, is similar to our study.

Bhattacharyya and Anusuya [5], in their 2010 study, evaluated the efficacy of SERM, that is, ORM in the management of AUB. The results of the study showed that there was a marked relief of symptoms with a significant reduction of blood clots and rise in Hb. Hence, the study concluded that ORM is superior to norethisterone and may be prescribed as a first-line treatment in the woman who has completed childbearing. This was similar to the conclusion of our study. Agarwal *et al.* [6], in 2019, had done a similar study on the efficacy of ORM and norethisterone in the management of perimenopausal DUB. The result showed that ORM is more effective than norethisterone in reducing blood loss, improving Hb, and reducing ET in DUB. The results of this study are consistent with the results of our study.

Furthermore, a 2018 study by Devi and Nimonkar [7] showed that there was a statistically significant increase in Hb and statistically significant decrease in ET with ORM. They, therefore, concluded that ORM is safe, cost-effective, non-steroidal, and non-hormonal drug with convenient doses and better compliance, which is similar to our study. It was found to be an excellent drug in controlling the system of AUB without affecting the normal endocrinal and physiological parameters as a result that was similar to our study. Ravibabu *et al.* [8], in their 2013 study, showed that ORM was effective in reducing menstrual blood loss

in patients in the treatment of AUB in all age groups with effective therapeutic efficacy and least side effects. They also concluded that the compliance of patients is good because of the convenient dosage schedule and no need of taking the drug every day.

## CONCLUSION

AUB is the diagnosis in the majority of cases of HMB and accounts for a significant proportion of referrals to gynecologists. Both ORM and norethisterone can be good alternatives to the medical and surgical treatment of HMB with good efficacy.

There was an improvement in mean Hb in both the groups in this study, ORM being more effective as compared to norethisterone. Mean Hb at baseline and 3<sup>rd</sup> month of treatment was found to be 8.85% and 11.68 g%, respectively, with ORM and 8.75% and 10.54%, respectively, with norethisterone. Improvement in Hb was statistically significant in both groups (p<0.001).

In addition, ORM is superior to norethisterone in its ability to reduce ET. There was a statistically significant reduction in mean ET with ORM (from 11.94 mm down to 8.08 mm) (p<0.001) and norethisterone (from 11.83 mm down to 9.56 mm).

For a treatment course of 3 months, ORM was found to be more cost-effective.

As both ORM and norethisterone are very effective in reducing blood loss, they can be considered as first-line drugs in the management of AUB-O. Both are conservative modes of treatment and help to reduce the rate of hysterectomy and morbidity and associated mortality.

## AUTHORS' CONTRIBUTIONS

Dr. Jasleen Kaur, Consultant, Department of Obstetrics and Gynecology, MCDH, New Delhi, provided guidance in the preparation of the manuscript and reviewed it.

## AUTHORS' FUNDING

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## CONFLICTS OF INTEREST

The author declares no conflicts of interest.

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