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**Original Research Article**

# Comparative evaluation of the efficacy and safety of ormeloxifene and norethisterone in abnormal uterine bleeding

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## ABSTRACT

**Background:** Abnormal uterine bleeding is a typical condition for women of reproductive age. It can be painful and uncomfortable, create social disgrace, and have a considerable impact on health-related quality of life. Several studies have shown that ormeloxifene and norethisterone are useful in the treatment of abnormal uterine bleeding, however there is a scarcity of data comparing the efficacy and safety of these medicines.
**Methods:** A prospective comparative study was conducted over 100 women, age group of 30-50 years, attending the gynecology outpatient department with subjective complaints of heavy menstrual bleeding at a tertiary care hospital, in Hyderabad. Group A (n=50) received 60 mg of ormeloxifene and Group B (n=50) received 5mg of norethisterone, respectively. Ethical approval was taken from the institutional ethical committee.
**Results:** 38% aged 41-45, 86% had irregular cycles, 76% reported subjective improvement in group A, and 38% in group B. Group A showed a mean difference of 80.22 in decreasing PBAC score, 0.70 in hemoglobin rise, and 3.5 in decreasing ET, while group B showed 53.70 in PBAC decrease, 0.28 in hemoglobin rise, and 1.76 in endometrial thickness reduction. Both groups have no notable side effects and no significant p value.
**Conclusions:** Reducing PBAC score, subjective improvement, hemoglobin, and endometrial thickness with ormeloxifene and norethisterone works. Ormeloxifene has a far greater effect than norethisterone and has fewer adverse effects.

**Keywords:** Abnormal uterine bleeding, Norethisterone, Ormeloxifene

## INTRODUCTION

Abnormal uterine bleeding (AUB) is a prevalent issue that affects women of reproductive age. It can cause pain and suffering, leading to significant social shame and having a substantial impact on health-related quality of life.[1] AUB can lead to decreased productivity and may necessitate surgical procedures such as a hysterectomy.[2] The prevalence exhibits variation across different countries. The reported prevalence of AUB in India is approximately 17.9%.[3]

Abnormal uterine bleeding is characterized as any bleeding that deviates from the expected frequency and volume of a typical menstrual cycle.[4] Uterine abnormalities Endocrinologic dysfunction frequently leads to abnormal ovulation, which commonly causes bleeding. The main cause of this condition, accounting for 80-90% of cases, is a disruption in the hypothalamus-pituitary axis. This leads to anovulatory cycles, with chronic anovulation being the most common cause.[5] Chronic anovulation results in unopposed estrogen stimulation of the endometrium, leading to irregular

breakdown and shedding. The condition is caused by several endocrine factors, including thyroid problems, hyperprolactinemia, hormone-producing ovarian tumors, Cushing's disease, and most notably Stein-Levinthal syndrome.

Dysfunctional uterine bleeding refers to abnormal bleeding from the uterus that does not have any identifiable biological, systemic, or iatrogenic etiology.[6] Approximately 15-20% of cases of abnormal uterine bleeding are associated with ovulation.[7] These cases typically involve the presence of secretory endometrium and are more likely to be caused by an underlying organic pathology. A dysfunctional corpus luteum after ovulation can lead to abnormal uterine bleeding with ovulatory dysfunction (AUB-O). This leads to insufficient stabilization of the endometrium, causing irregular shedding. Irregular shedding happens when there is a protracted corpus luteum, meaning that the progestogenic support is not stopped after the usual 14 days, but instead persists for longer. This is a case of ovulatory dysfunctional uterine bleeding (AUB-O).[8]

Current treatments are either hormonal (progestogens, combined estrogen and progestogens, danazol, gonadotropin-releasing hormone analogs, and levonorgestrel-releasing intrauterine device) or non-hormonal (antifibrinolytics, non-steroidal anti-inflammatory medicines). The latest medications include selective estrogen receptor modulator, which binds to estrogen receptors with high affinity and acts as agonists in some tissues and antagonists in others depending on mRNA transcription configuration.[9]

Norethisterone, a progestogen, is frequently employed to treat abnormal uterine bleeding,[10-12] whether it is connected with ovulation or not. However, due to its hormonal nature, it carries the risk of adverse effects including stroke, heart disease, breast cancer, dementia, fluid retention, breakthrough bleeding, and spotting.

Ormeloxifene is a third-generation compound that functions as a selective estrogen receptor modulator, specifically targeting estrogen receptors.[13] It exerts an antiestrogenic impact on the endometrium and breast while having an estrogenic effect on bone, vagina, cardiovascular system, and central nervous system.[14] Ormeloxifene is the favored choice not just for oral contraception but also for treating dysfunctional uterine hemorrhage and advanced breast cancer. During the initial twelve weeks of usage, consuming the Ormeloxifene pill is recommended twice weekly. From the thirteenth week onwards, it should be taken once per week.[15]

The objective of this study was to assess and contrast the effectiveness and safety of ormeloxifene and norethisterone in the treatment of Abnormal Uterine Bleeding (AUB-O).

## METHODS

A prospective comparative study was conducted over 100 women (April 2016 to March 2017), age group of 30-50 years attending the gynecology outpatient department with subjective complaints of heavy menstrual bleeding in Muslim Maternity and children's hospital, in Hyderabad. Ethical approval was taken from the institutional ethical committee. Randomly selected gynecology outpatients aged 30-50 with subjective complaints of excessive menstrual bleeding without organic or iatrogenic causes were recruited. The patients gave informed consent. Patients kept menstrual diaries to document bleeding days and pad usage.

### *Group allocation*

Group A (Ormeloxifene 60 mg): 50 patients in this group are treated with ormeloxifene 60 mg orally twice a week (wednesday and saturday) for a total of 12 weeks followed by 60mg once a week for the next 12 weeks.

Group B (Norethisterone 5mg): 50 patients in this group are treated with 5mg of norethisterone twice daily for 21 days for 6 cycles.

### *Inclusion criteria*

100 patients of reproductive age group 30-50 years with complaints of heavy menstrual bleeding are selected for the study.

### *Exclusion criteria*

Patients with known organic pelvic pathologies, acute heavy bleeding, hemodynamically unstable patients with postmenopausal bleeding, malignancies of the genital tract, bleeding disorders, liver diseases, history of thromboembolic disorders, and lactating women were excluded.

### *Study procedure*

Women who fulfilled the above criteria were counseled and given details of the study. A predesigned clinical data sheet organizes all case clinical data. All women have a thorough history and physical. Her chief complaints, duration of symptoms, history of present illness, obstetric history, and menstrual history included age of menarche, number of days of bleeding, number of pads used per day, associated clots and size, whether cycles were regular or irregular, duration of bleeding (normal or prolonged, consistent or variable), onset of abnormal menses (premenarcheal, sudden, gradual), and temporal association.

Then a thorough clinical examination was performed which included a general examination to assess nutritional status, and pallor, and rule out any signs of bleeding disorders, hypothyroidism, hyperthyroidism,

and jaundice. Systemic and gynecological examination with special emphasis on pelvic exam along with per speculum, per vagina bimanual exam to exclude any organic pelvic pathology. All women underwent ultrasonography assessment of pelvic organs to exclude any previously missed uterine or adnexal pathology such as pregnancy complications and uterine fibroid adnexal mass. Ultrasound also noted the endometrial thickness before the start of treatment and again at one month, three months, and six months of treatment.

Each patient was monitored weekly during treatment. Blood flow, length, clot passage, and dysmenorrhea were examined. Adverse effects during treatment were investigated. Treatment was assessed by hemoglobin rise, endometrial thickness decrease, symptom alleviation, and quality of life improvement.

***Statistical analysis***

Data was analyzed using SPSS software. Data were expressed as Mean±SD and p value <0.05* was considered statistically significant.

## RESULTS

Figure 1 shows the number of patients according to their different age categories. Out of the total 100 patients, 17% patients were in the age group 30-35 years, 25% were in the age group 36-40, 38% were in the age group 41-45, and 20% were in the age group 46-50 years, respectively.

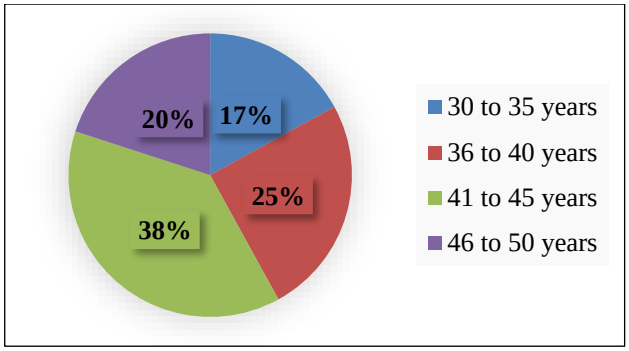


**Figure 1: Age-wise distribution.**

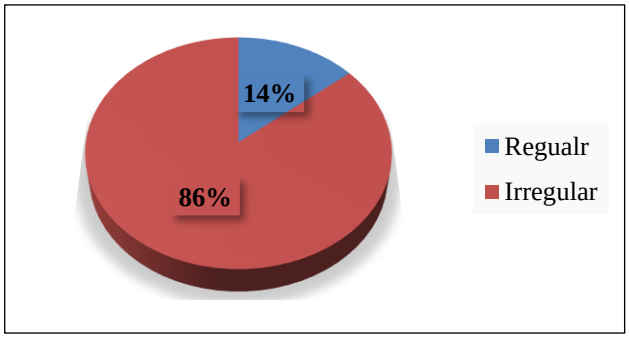


**Figure 2: Menstrual bleeding pattern.**

Figure 2 shows among 100 patients 14% had regular cycles whereas 86% had irregular cycles.

**Table 1: Effects of study drugs on subjective improvement.**

| Drugs used | | Subjective improvement | | | Total |
|---|---|---|---|---|---|
| | | No | Mild | Marked | |
| **Ormeloxifene** | Frequency | 5 | 7 | 38 | 50 |
| | % | 10.0 | 14.0 | 76.0 | 100.0 |
| **Norethisterone** | Frequency | 8 | 23 | 19 | 50 |
| | % | 16.0 | 46.0 | 38.0 | 100.0 |
| **Total** | Frequency | 13 | 30 | 57 | 100 |
| | % | 13.0 | 30.0 | 57.0 | 100.0 |
| **Chi-square value** | df | p value | | | |
| 15.559 | 2 | <0.001* | | | |

The significance is indicated as *

**Table 2: Comparison of effects of study drugs.**

| Variables | Drugs used | Mean ± (SD) | | Mean difference | Paired t test | p value |
|---|---|---|---|---|---|---|
| | | Before treatment | After treatment | | | |
| **PBAC score** | Ormeloxifene | 202.44 (48.16) | 122.22 (45.6) | 80.22 | t= 11.8 | <0.001* |
| | Norethisterone | 215.86 (51.4) | 162.16 (46.0) | 53.70 | t= 10.7 | <0.001* |
| **Haemoglobin (mg/dl)** | Ormeloxifene | 8.50 (0.7) | 9.2 (0.7) | 0.70 | t= -7.8 | <0.001* |
| | Norethisterone | 8.35 (0.6) | 8.63 (0.53) | 0.28 | t= -6.0 | <0.001* |
| **Endometrial thickness (mm)** | Ormeloxifene | 11.08 (2.46) | 7.60 (2.30) | 3.5 | t= 9.7 | <0.001* |
| | Norethisterone | 10.81 (2.53 | 9.05 (1.83) | 1.76 | t= 6.8 | <0.001* |

The significance is indicated as *

**Table 3: Comparison of side effects of study drugs.**

| Drugs used | | Side effects | | | | | Total |
|---|---|---|---|---|---|---|---|
| | | No side effect | Nausea | Weight gain | Headache | Oligomenorrhea | |
| **Ormeloxifene** | Frequency | 43 | 1 | 1 | 1 | 4 | 50 |
| | % | 86.0 | 2.0 | 2.0 | 2.0 | 8.0 | 100 |
| **Norethisterone** | Frequency | 33 | 9 | 5 | 2 | 1 | 50 |
| | % | 66.0 | 18.0 | 10.0 | 4.0 | 2.0 | 100 |
| **Total** | Frequency | 76 | 10 | 6 | 3 | 5 | 100 |
| | % | 76.0 | 10.0 | 6.0 | 3.0 | 5.0 | 100 |
| **Chi-square value** | df | p value | | | | | |
| 12.516 | 4 | 0.014* | | | | | |

The significance is indicated as *

Table 1 compares the subjective improvement in patients of group A and group B, here 10% of patients had no relief,14% had mild relief and 76% had marked relief in group A whereas 16% had no relief 46% had mild relief and 38% had marked relief in group B. both groups had significant p value but a greater number of patients were satisfied in group A compared to group B.

Table 2 shows the comparison of both drugs on PBAC, Hb, and ET in both groups, patients in group A showed a mean difference of 80.22 in decreasing PBAC score, a mean difference of 0.70 in the rise of hemoglobin, a mean difference of 3.5 in decreasing ET whereas patients under group B showed mean difference of 53.70 in decrease of PBAC, mean difference of 0.28 in rise of hemoglobin and mean difference of 1.76 in reducing endometrial thickness.

Table 3 shows the side effects of the drugs in both group A and group B. there are no major side effects in the groups and the p value is not significant in either group.

## DISCUSSION

The present study was conducted over 100 patients with complaints of heavy menstrual bleeding, the age group included in this study is from 30-50 years, 17% of patients were in the age group 30-35, 25% were in the age group 36-40,38 % 41-45, 20% in age group in 46 -50 years.

Biswas et al in the year 2004, carried out a study on ormeloxifene a selective estrogen receptor modulator for treating dysfunctional menorrhagia, where the age group 30-51 years was predominant, and the mean age was 39.2.[16]

Ganotra et al conducted a study that showed a mean duration of heavy menstrual bleeding as 9.4 months, in comparison to the present study showed a mean duration of bleeding of 6.17 which was less compared to the previously mentioned study.[17]

The present study shows that 76% of patients treated with ormeloxifene in group A had marked improvement similar to studies done by Kumar et al and Muriel et al.[18,19] Whereas 74% of patients had marked relief with norethisterone, compared to the present study, only 38% had marked relief with norethisterone. In the present study, 46% of patients also had mild improvement of symptoms with norethisterone which is more compared to other studies, very few people did not have any improvement with either drug.

In the present study patients treated with ormeloxifene showed a reduction in PBAC score with a mean difference of 80.22, ($p<0.001$*) compared to norethisterone with a mean difference of 53.70 ($p<0.001$*). Patients treated with ormeloxifene showed an increase in hemoglobin with a mean difference of 0.70 and the norethisterone group had an improvement in hemoglobin with a mean difference of 0.28. Patients treated with ormeloxifene had a decrease in endometrial thickness with a mean difference of 3.5 and patients treated with norethisterone had a decrease in endometrial thickness with a mean difference of 1.76.

Another study done by Agarwal et al, showed that patients under group A had a decrease in PBAC from 216 to 84 and group B had a decrease from 232 to 170, rise in Hb in group A was 7.52 to 10.4 and group B was 7.48 to 8.6, decrease in ET was from12.12 to 8.4 in group A and in group B 12.05 to 9.8.[20]

A similar study conducted by Jacob et al, showed a reduction in PBAC from 277.36 to 70.11 in group A compared to group B with a reduction of PBAC score from 246 to 108.5, increase in Hb from 9.6 to 11.07 in group A and 10.17 to 10.58 in group B.[21] The reduction in ET was 7.8 to 5.3 in group A and 6.7 to 5.9 in group B.

A study conducted by Sanchita et al, showed similar results with a significant decrease in PBAC score with both the drugs, an increase in hemoglobin, and a reduction in ET but when both groups were compared patients on the drug ormeloxifene had better results as compared to another group of patients on norethisterone.[22]

In the present study most common side effect experienced was oligomenorrhoea in 8% of patients and common side effects noticed by patients were nausea in 18% and very few experienced weight gain, headache, oligomenorrhoea.

36.4% of patients experienced amenorrhoea with ormeloxifene and 12.5% experienced breakthrough bleeding with norethisterone. Komaram et al, in their study showed that 10% had amenorrhoea, 4% experienced giddiness, 4% had abdominal pain and 2% had headaches, respectively.[23]

The present research study included a number of limitations, the most significant of which were its limited study time and its very small sample size.

## CONCLUSION

The ultimate aim of pharmacological management is to restore the natural cycle of orderly endometrial growth and shedding. The choice of treatment must be opted about several factors like the presence of ovulatory or anovulatory cycles and the need for contraception.

The majority of patients responded well to the medical therapy. Both ormeloxifene and norethisterone are effective in treating these cases by a reduction in PBAC score, subjective improvement, rise in hemoglobin, and reduction in endometrial thickness. However, the effect is significantly more with ormeloxifene, thus ormeloxifene was found to be superior to norethisterone, and there are no major side effects with either of the drugs.

This study was conducted over a short duration; hence to establish the definitive efficacy of the drug randomized controlled trials with larger subjects over a longer period comparing the drug with other medical agents is needed.

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