Original Research Article

# Comparative study of Ormeloxifene and Medoxyprogesterone acetate in abnormal uterine bleeding

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## Abstract

**Background:** Abnormal Uterine Bleeding (AUB) is a significant debilitating clinical condition and affects 14-25% of women of reproductive age and up to 50% of peri-menopausal women. Present study was aimed to find out the effectiveness of ormeloxifene against medroxyprogesterone acetate (MPA) for non-structural causes of AUB and also for adenomyosis (structural cause). **Material and Methods:** Present study was single-center, randomized control study, conducted in patients with age between 20 to 55 years, diagnosed as non-Structural causes of AUB, Adenomyosis. Total 100 subjects were randomly divided into one of the following two groups (50 each) using computer generated random numbers, into Group O – Ormeloxifene 60 mg twice a week for 3 months followed by 60 mg once a week for 1 month and Group M - Medroxyprogesterone acetate (MDPA) 10 mg twice a day from day 5 to day 25 of the menstrual cycle. **Results:** General characteristics such as age, BMI, medical co-morbidities were comparable in both groups and difference was not significant statistically. Most of the study cases in present study were multi-para (85%) with no difference between study groups. A total of 47% females had DUB for less than 6 months while in 13% and 40% cases symptoms were from 6-12 months and over 12 months respectively. Major presenting complaints were menorrhagia (77%), meterorrhagia (26%) and continuous bleeding (14%). Both the groups were comparable with respect to presenting complaints. Fall in number of bleeding days, Mean Pictorial blood loss assessment chart (PBAC) score, increase in haemoglobin levels and decrease in endometrial thickness was significantly more in Ormeloxifene group as compared to Medoxyprogesterone acetate ($p<0.05$). **Conclusion:** Ormeloxifene should be preferred in the management of abnormal uterine bleeding as it has the better efficacy in terms of reducing the blood loss reduce and can help to improve anemia.

**Keywords:** Ormeloxifene, Medoxyprogesterone acetate, abnormal uterine bleeding, endometrial thickness.

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## INTRODUCTION

Abnormal Uterine Bleeding (AUB) is a significant debilitating clinical condition and affects 14-25% of women of reproductive age and up to 50% of peri-menopausal women.[1-3] It may have a significant impact on women's personal, social, physical and quality of life with significant financial burden to the country's economy.[4] Among the medical treatment of AUB, there are various options as combined oral contraceptives, progestins (oral or intramuscular), levonorgestrel intrauterine device, antifibrinolytics such as tranexamic acid and danazol, gonadotropins releasing hormone, etc., but every treatment option has its own benefits and risks, and in some cases cost is also an issue.[5] Ormeloxifene/centchroman, a nonsteroidal, selective estrogen receptor modulator (SERM), with potent estrogen antagonistic action on uterus as well as breast tissue and mild agonistic action on bone mineral density. It is very effective, reducing up to 70 % blood loss with minimal side effects, has an easy dosing schedule, and cost efficient.[5,6,7] Medroxyprogesterone acetate (MPA) is a progestin, a synthetic variant of the human hormone progesterone, inhibits secretion of pituitary gonadotropins, thereby preventing follicular maturation and ovulation (contraceptive effect); inhibits

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spontaneous uterine contraction; transforms proliferative endometrium into secretory endometrium; produces antineoplastic effect in advanced endometrial or renal carcinoma.[8,9,10] Present study was thus an attempt to find out the effectiveness of ormeloxifene against medroxyprogesterone acetate (MPA) for non-structural causes of AUB and also for adenomyosis (structural cause).

## MATERIAL AND METHODS

Present study was single-center, randomized control study, conducted in department of obstetrics and gynaecology, at Department of Obstetrics and Gynaecology, BJ Medical College, Pune, India. Study duration was of 2 years (Dec 2018 - Nov 2020). Study was approved by institutional ethical committee.

**Inclusion criteria-** Patients with age between 20 to 55 years, diagnosed as non-Structural causes of AUB, Adenomyosis.

**Exclusion criteria–** patients with leiomyoma, Polyps, Adnexal masses, Breast Malignancy, Endometrial hyperplasia with atypia. Carcinoma cervix, Ovarian carcinoma were excluded.

Study was explained to patients and written informed consent was taken, After detailed history and clinical examination, every patient was subjected to the introduction to assessment of Pictorial blood loss assessment chart (PBAC) scoring, and evaluated for hemoglobin level, endometrial thickness on ultrasonography, and endometrial biopsy and Pap smear.

Pictorial blood loss assessment chart (PBAC) was used to measure the amount of menstrual blood loss. Scores of 1, 5, 20 are given to slightly soiled, moderately soiled, and saturated pad, respectively. Score 1 is given to the small clot and 5 to the large clot. PBAC score up to 10 is considered as scanty flow, 10–100 as moderate flow, 100–300 as heavy flow, and more than 300 as very heavy flow. PBAC score more than 100 is considered as blood loss more than 80 ml diagnostic of menorrhagia.[11]

Total 100 subjects were randomly divided into one of the following two groups (50 each) using computer generated random numbers: Group O- Ormeloxifene 60 mg twice a week for 3 months followed by 60 mg once a week for 1 month. Group M- Medroxyprogesterone acetate (MDPA) 10 mg twice a day from day 5 to day 25 of the menstrual cycle

Follow-up was done at 2nd and 4th month, and again at each follow-up the clinical characteristics of bleeding, PBAC score, hemoglobin level, and endometrial thickness were assessed and the side effects of therapy, if any, were also noted.

The quantitative data was represented as their mean ± SD. Categorical and nominal data was expressed in percentage. The t-test was used for analyzing quantitative data, or else non parametric data was analyzed by Mann Whitney test and categorical data was analyzed by using chi-square test. The significance threshold of p-value was set at <0.05. All analysis was carried out by using SPSS software version 21.

## RESULTS

Present study included a total of 100 cases of DUB, who were randomly divided into one of the following two groups (50 each) using computer generated random numbers in Group O (Ormeloxifene) and Group M (Medroxyprogesterone acetate - MPA) General characteristics such as age, BMI, medical co-morbidities were comparable in both groups and difference was not significant statistically.

**Table 1:** General characteristics

| Characteristics | Group O (Mean ± SD) | Group M (Mean ± SD) | p- value |
|---|---|---|---|
| Age (yrs) | 42.84 ± 4.95 | 41.92 ± 4.69 | 0.34 |
| BMI (Kg/m2) | 24.85 ± 3.68 | 24.14 ± 4.07 | 0.36 |
| Medical co-morbidities present | 19 (38%) | 19 (38%) | 1.0 |

Most of the study cases in present study were multi-para (85%) with no difference between study groups. A total of 47% females had DUB for less than 6 months while in 13% and 40% cases symptoms were from 6-12 months and over 12 months respectively.

**Table 2:** Comparison of study groups as per obstetric history, duration of symptoms

| Characteristics | Group O (%) | Group M (%) | Total |
|---|---|---|---|
| Parity | | | |
| Nulli-para | 4 (8 %) | 4 (8 %) | 8 (8 %) |
| Primi | 4 (8 %) | 3 (6 %) | 7 (7 %) |
| Multi | 42 (84 %) | 43 (86 %) | 85 (85 %) |
| Duration of Symptoms | | | |
| < 6 months | 25 (50 %) | 22 (44 %) | 47 (47 %) |
| 6-12 months | 7 (14 %) | 6 (12 %) | 13 (13 %) |
| > 12 months | 18 (36 %) | 22 (44 %) | 40 (40 %) |

Major presenting complaints were menorrhagia (77%), meterorrhagia (26%) and continuous bleeding (14%). Both the groups were comparable with respect to presenting complaints.

**Table 3:** Comparison of study groups as per presenting complaints

| Presenting Complaints | Group O (%) | Group M (%) | Total (%) | p- value |
|---|---|---|---|---|
| Menorrhagia | 39 (78 %) | 38 (76 %) | 77 (77 %) | 1 |
| Metrorrhagia | 14 (28 %) | 12 (24 %) | 26 (52 %) | 0.82 |
| Polymenorrhoea | 3 (14 %) | 1 (2 %) | 4 (4 %) | 0.12 |
| Polymenorrhagia | 3 (6 %) | 4 (8 %) | 7 (7 %) | 1 |
| Continuous Bleeding | 7 (14 %) | 7 (14 %) | 14 (14 %) | 1 |

Mean bleeding days in Ormeloxifene (O) and Medoxyprogesterone acetate (M) group cases was 7.84 and 7.96 days (p-0.58). At the 2nd month follow up, the bleeding days reduced to 3.91 and 4.86 days and by 4th month, reduced to 2.12 and 3.19 days respectively. The fall in number of bleeding days was significantly more in Ormeloxifene group as compared to Medoxyprogesterone acetate ($p<0.05$).

**Table 4:** Mean comparison of days of bleeding at baseline and during follow up

| days of bleeding | Group O (Mean ± SD) | Group M (Mean ± SD) | p- value |
|---|---|---|---|
| Baseline | 7.84 ± 1.06 | 7.96 ± 1.11 | 0.34 |
| 2 month | 3.91 ± 1.36 | 4.86 ± 1.31 | 1.0 |
| 4 month | 2.12 ± 1.90 | 3.19 ± 1.91 | <0.05 |

Mean Pictorial blood loss assessment chart (PBAC) score in Ormeloxifene (O) and Medoxyprogesterone acetate (M) group cases was 237.6 and 241.12 (p-0.71). At the 2nd month follow up, the PBAC score reduced to 48.58 and 72.04 and by 4th month, reduced to 18.68 and 32.76 respectively. The fall in PBAC score was significantly more in Ormeloxifene group as compared to Medoxyprogesterone acetate ($p<0.05$).

**Table 5:** Comparison of Pictorial blood loss assessment chart (PBAC) score

| PBAC | Group O (Mean ± SD) | Group M (Mean ± SD) | p- value |
|---|---|---|---|
| Baseline | 237.60 ± 46.38 | 241.12 ± 48.14 | 0.71 |
| 2 month | 48.58 ± 47.86 | 72.04 ± 47.32 | <0.05 |
| 4 month | 18.68 ± 30.26 | 32.76 ± 33.53 | <0.05 |

Mean haemoglobin levels in Ormeloxifene (O) and Medoxyprogesterone acetate (M) group cases was 9.51 and 9.66 gm% (p-0.66). At the 2nd month follow up, the haemoglobin levels improved to 11.07 and 10.13 gm% and by 4th month, increased to 12.12 and 11.11 gm% respectively. The increase in haemoglobin levels by the end of 4th month was significantly more in Ormeloxifene group as compared to Medoxyprogesterone acetate ($p<0.05$).

**Table 6:** Mean comparison of haemoglobin levels at baseline and during follow up

| Hemoglobin (gm%) | Group O (Mean ± SD) | Group M (Mean ± SD) | p- value |
|---|---|---|---|
| Baseline | 9.51 ± 1.61 | 9.66 ± 1.78 | 0.66 |
| 2 month | 11.07 ± 1.67 | 10.13 ± 1.70 | 0.09 |
| 4 month | 12.12 ± 1.68 | 11.11 ± 1.84 | <0.05 |

Mean endometrial thickness in Ormeloxifene (O) and Medoxyprogesterone acetate (M) group cases was 9.75 and 9.53 mm (p-0.76). At the 2nd month follow up, the thickness reduced to 8.01 and 8.61 mm and by 4th month, reduced to 6.72 and 8.20 mm respectively. By the end of 4th month, the decrease in endometrial thickness was significantly more in Ormeloxifene group as compared to Medoxyprogesterone acetate ($p<0.05$).

**Table 7:** Mean comparison of endometrial thickness at baseline and during follow up

| Endometrial Thickness | Group O (Mean ± SD) | Group M (Mean ± SD) | p- value |
|---|---|---|---|
| Baseline | 9.75 ± 3.45 | 9.53 ± 3.44 | 0.76 |
| 2 month | 8.01 ± 3.10 | 8.61 ± 3.23 | 0.41 |
| 4 month | 6.72 ± 2.91 | 8.20 ± 3.02 | <0.05 |

## DISCUSSION

The FIGO categorized AUB based on structured medical history, laboratory tests, Ultrasound and or hysteroscopy based techniques.[5] The classification is based on the acronym "PALM- COEIN", which stands for Polyp, Adenomyosis, Leiomyoma, Malignancy (and Hyperplasia) and comprises structural pathologies assessed visually.[5] The COEIN group stands for coagulopathy, ovulatory disorders, endometrial, iatrogenic, not otherwise classified and relates to non-structural etiologies that cannot be assessed by imaging or histopathology. Treatment of menorrhagia includes various medical and surgical management. Surgical treatment is often needed for all structural causes, while for the non- structural causes,

medical treatment should be the first choice. The choice of treatment depends on the cause, age, severity of bleeding, fertility status, need for contraception, and the treatment available at the center. Mean age of the cases with abnormal uterine bleeding was 42.38 years, difference was not significant between the study groups. Similar findings were observed in other studies. Dhamangaonkar PC *et al.*[12] observed the average age of the cases was 43.39 years (34-53 years). Gupta R *et al.* [13] in their study observed mean age as 43 years. In present study, Nullipara, primi-para and multi-para cases were 8%, 7% and 85% respectively. No difference was observed between the study groups with respect to obstetric history. Dhamangaonkar PC *et al.*[12] in their study observed 15.7% were primipara, 81.4% were multipara, while 2.9% patients were unmarried. Gupta R *et al.*[13] observed 3.3% as primi-para while 96.7% as multi-para. Major presenting complaints were menorrhagia (77%), meterorrhagia (26%) and continuous bleeding (14%). A total of 47% females had DUB for less than 6 months while in 13% and 40% cases symptoms were from 6-12 months and over 12 months respectively. Panda *et al.*[14] series had 60% cases of menorrhagia followed by Polymenorrhagia and Metrorrhagia. Goyal *et al.*[15] in their study also observed menorrhagia as the commonest presenting symptom in the study population (58%) followed by metrorrhagia, menometrorrhagia and continuous bleeding >21 days. In a study, Chhikara A *et al.*[16] observed the most common symptoms as menorrhagia (40%) followed by metrorrhagia 38%, polymenorrhagia (12%) and postmenopausal bleeding (10%). In a similar type of study, Jyotsna Sharvage *et al.*[6] noted mean pre-treatment PBAC scores in group A and group B were 262.26 and 238.71 ml respectively. The mean PBAC scores at the end of the study period were 73 and 108 in group A and B respectively, reporting an overall reduction in mean blood loss by 85.7 and 54.76% ($p = 0.0205$) in group A and B respectively. Thus, there was a significant reduction in blood loss in the group receiving ormeloxifene. In a similar study by Zeepee Godha *et al.*,[17] there were 240 patients in group A and 200 in group B. Reduction in median PBAC score was 79.4 % in group A and 75 % in group B after 4 months of treatment. The mean duration of bleeding reduced to 4.8 from 9 in group A and 5 from 8.7 in group B. Mean hemoglobin was increased from 8.6 to 9.8 g % in group A and from 8.7 to 9.9 g % in group B. Moulan AKS *et al.*,[18] in their study observed mean PBAC score in group A and B as 243.3 each which reduced to 103 in group A as compared to 171.3 in group B. Similarly median hemoglobin levels increased to 11gm% from 9 gm% in group A as compared to 10gm% from 9 gm% in group B. The difference was statistically significant. Zeepee Godha *et al.*,[17] studied cases of DUB, who were randomized into two groups: group A - ormeloxifene and group B - medroxyprogesterone acetate. Mean endometrial thickness reduced from 7.7 mm to 6.8 mm in group A and from 7.4 mm to 6.9 mm in group B. Similarly, Moulan AKS *et al.*,[18] in their study observed that median endometrial thickness reduced to 7 mm from 9 mm in group A as compared to 8 mm from 9 mm in group B. The difference was statistically significant ($p<0.05$). Jyotsna Sharvage *et al.*,[8] also observed in their study that reduction in the mean endometrial thickness was more in ormeloxifene group. However, this was not statistically significant ($p = 0.0942$). Similar findings were noted in present study. Thus to summarize, our study showed that efficacy for non-structural causes of AUB and also for adenomyosis (structural cause) was more with ormeloxifene, as assessed by reduction in days of blood loss, PBAC score, rise in hemoglobin level and reduction in endometrial thickness. Also no major side effects were seen with ormeloxifene. A convenient dose schedule and cost effectiveness of ormeloxifene further increases its compliance. Present study thus recommends use of ormeloxifene as a first choice intervention for non-structural etiologies of abnormal uterine bleeding.

## CONCLUSION

Ormeloxifene should be preferred in the management of abnormal uterine bleeding as it has the better efficacy in terms of reducing the blood loss reduce and can help to improve anemia. The reduction in the mean endometrial thickness was also more in with ormeloxifene. Present study thus recommend use of ormeloxifene as a first choice intervention for cases of non-structural etiologies of abnormal uterine bleeding.

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