DOI: 10.7860/JCDR/2026/78490.23177

Original Article

Obstetrics and Gynaecology Section

Efficacy and Safety of Ormeloxifene in the Medical Management of Abnormal Uterine Bleeding: A Prospective Cohort Study

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ABSTRACT

Introduction: Abnormal Uterine Bleeding (AUB) is a frequent cause of morbidity in women, significantly impacting quality of life through heavy menstrual bleeding and anaemia. Ormeloxifene, a selective oestrogen receptor modulator, is increasingly adopted as a medical management option for AUB in India.

Aim: To evaluate the efficacy and safety of ormeloxifene in women with AUB attending a tertiary care hospital in North India.

Materials and Methods: This prospective cohort study was conducted in the Department of Obstetrics and Gynaecology at the Government Medical College and Hospital, Chandigarh, India, from September 2018 to September 2019. A total of 59 women meeting the inclusion criteria were enrolled in the study. All participants initiated ormeloxifene therapy. During the treatment and follow-up period, three women discontinued the study. Therefore, 56 women completed the full six-month course of therapy and were included in the final efficacy and safety analyses. Patients received ormeloxifene 60 mg biweekly for 12 weeks, followed by 30 mg biweekly for another 12 weeks. The primary outcome was reduction in menstrual blood loss, measured by the Pictorial Blood Loss Assessment Chart (PBAC). Secondary outcomes included change in haemoglobin and adverse effects. Data were analysed using Statistical Package for Social Sciences (SPSS) version 22.0, with significance set at $p<0.05$.

Results: The mean baseline PBAC score was 332.9 (range, 180-498), which decreased significantly after treatment ($p<0.001$). Mean haemoglobin increased from 9.44±1.6 g/dL to 12.22±1.3 g/dL ($p<0.001$). At six months post-treatment, 28.2% (13/47) of women, all perimenopausal, maintained amenorrhoea. The overall success rate at the end of therapy was 82.1%. Treatment failure occurred in 12.5% (7/56), primarily in those with anovulatory AUB, all of whom underwent hysterectomy. Adverse effects were mild and self-limited; no serious adverse events were reported.

Conclusion: Ormeloxifene is an effective and well-tolerated treatment for AUB, resulting in significant reductions in menstrual blood loss and improvements in haemoglobin levels, with minimal side-effects.

Keywords: Haemoglobin, Menstrual disorders, Non hormonal therapy, Patient outcomes

INTRODUCTION

The AUB is one of the most common gynaecological complaints affecting women in the reproductive and perimenopausal age groups. Epidemiological studies report that up to 30% of women worldwide experience AUB during their lifetime, with Indian data showing a prevalence of nearly 17% among women attending gynaecology clinics [1,2]. Heavy menstrual bleeding, a frequent manifestation of AUB, is a leading cause of iron deficiency anaemia, which further compounds patient morbidity and productivity loss [3].

Management of AUB remains challenging due to its heterogeneous aetiology, which may include hormonal imbalances, uterine structural abnormalities, or systemic conditions. Conventional pharmacologic options- such as non steroidal anti-inflammatory drugs, tranexamic acid, combined oral contraceptives and progestogens- provide inconsistent efficacy and are frequently limited by adverse effects, risk profiles, or patient co-morbidities [4]. Surgical interventions, while effective for refractory cases, are associated with operative risk and long-term consequences, making conservative management preferable, especially in perimenopausal women [5].

Ormeloxifene, a non steroidal selective oestrogen receptor modulator developed in India, has been widely used as a contraceptive and is increasingly adopted for medical management of AUB [6]. Its unique mechanism provides antiestrogenic effects on the endometrium, leading to reduced menstrual blood loss, while preserving beneficial estrogenic effects on bone and lipid metabolism [6]. Despite growing use, there is a relative paucity of prospective studies evaluating its effectiveness and safety profile in routine clinical practice. With this background, the present study was conducted to assess the efficacy and safety of ormeloxifene in women with AUB attending a tertiary care hospital in North India.

MATERIALS AND METHODS

The present prospective cohort study was conducted in the Department of Obstetrics and Gynaecology at the Government Medical College and Hospital, Chandigarh, India, from September 2018 to September 2019. The study was approved by the Institutional Research and Ethics Committee, GMCH, Chandigarh in a meeting held on 08.1202017 IEC Regd. No.ECR/658/Inst/PB/2014. All participants provided written informed consent in accordance with the Declaration of Helsinki.

Inclusion and Exclusion criteria: Women aged 18 to 52 years in the reproductive and perimenopausal age groups, presenting with chronic AUB were considered for inclusion. Women were excluded if they had acute AUB, endometrial hyperplasia or malignancy confirmed by endometrial biopsy, endometrial or submucosal fibroid polyps, renal, hepatic, or thyroid dysfunction, known coagulopathies, or pre-existing adnexal masses.

Study Procedure

All participants underwent a detailed clinical assessment, including medical, menstrual, obstetric and gynaecological history. Age, parity, duration and pattern of bleeding, severity of dysmenorrhoea and previous treatments were documented. General and pelvic examinations were performed. Laboratory investigations included complete blood counts, a coagulation profile and tests for liver, renal and thyroid function. Pelvic ultrasonography was performed to

evaluate uterine and adnexal pathology and to document baseline endometrial thickness (with a threshold of <12 mm considered normal in perimenopausal women). Endometrial aspiration biopsy was performed in all cases to exclude hyperplasia or malignancy.

Menstrual blood loss was objectively assessed using the PBAC; a score of ≥100 was considered indicative of heavy menstrual bleeding [7]. The severity of dysmenorrhoea was graded using the Visual Analogue Scale (VAS), which ranged from 0 (no pain) to 10 (the worst pain imaginable) [8].

Intervention: Ormeloxifene was administered orally at a dose of 60 mg twice weekly for the first 12 weeks, followed by 30 mg twice weekly for the subsequent 12 weeks. All participants received oral iron supplementation (60 mg elemental iron daily) throughout the 24-week treatment period with ormeloxifene, i.e., for a total of six months.

Follow-up and outcome assessment: Patients were evaluated at baseline, at 2- and 6-months during therapy and at three and six months after completion of treatment. The primary outcome was the change in menstrual blood loss as measured by PBAC score. Secondary outcomes included changes in haemoglobin concentration, severity of dysmenorrhoea (as measured by the VAS), changes in lipid profile and adverse events. Treatment failure was defined as persistent heavy menstrual bleeding, indicated by a PBAC score of ≥100 after three months of therapy.

STATISTICAL ANALYSIS

Data were analysed using SPSS version 22.0. Categorical variables were summarised as frequencies and percentages and continuous variables as mean±standard deviation. The Chi-square test was used for categorical data. Changes in quantitative parameters were assessed using paired t-tests. All statistical tests were two-sided, with significance set at p<0.05.

RESULTS

A total of 59 women meeting the inclusion criteria were enrolled in the study. All participants initiated ormeloxifene therapy. During the treatment and follow-up period, three women discontinued the study: two were lost to follow-up after completing the treatment phase and one withdrew consent during follow-up. Therefore, 56 women completed the full six-month course of therapy and were included in the final efficacy and safety analyses.

Baseline characteristics: The mean age of the participants was 42.1±5.7 years. The vast majority were multiparous 55 (93.2%), while 4 (6.8%) were primiparous. The mean baseline PBAC score was 332.9 (range: 180- 498) [Table/Fig-1].

All participants underwent pelvic ultrasonography and premenstrual endometrial aspiration biopsy before initiation of therapy. On ultrasonography, the most common abnormality detected was adenomyosis, present in 22 women (37.3%). Premenstrual endometrial aspiration biopsy revealed secretory endometrium in 50 women (84.7%) [Table/Fig-2].

Characteristics	Value
Total number of patients	59
Mean age (years)	42.1±5.7
Parity	Multiparous: 55 (93.2%) Primiparous: 4 (6.8%)
Duration of HMB (months)	18.5±8.5
Mean days of bleeding/cycle	15.2±5.4
Mean cycle length (days)	19.7±5.5
Baseline PBAC score	332.9 (range: 180–498) SD±88.3
Mean haemoglobin (g/dL)	9.44±1.6
Severity of dysmenorrhoea*	Severe: 44 (74.5%) Moderate: 3 (5.1%) Mild: 10 (16.9%) Absent: 2 (3.3%)

[Table/Fig-1]: Baseline demographic and clinical characteristics of the study population.
*Based on Visual Analogue Scale (VAS) at baseline

Variables	Number of patients (%)
Ultrasound	
Adenomyosis	22 (37.3%)
Type 2 fibroid (2.8-5.5 cm)	6 (10.2%)
Type 3 fibroid (1.5-4.5 cm)	3 (5.1%)
No obvious pathology	28 (47.4%)
Endometrial biopsy	
Secretory endometrium	50 (84.7%)
Disordered proliferative endometrium	6 (10.2%)
Proliferative phase endometrium	3 (5.1%)

[Table/Fig-2]: Baseline pathological findings on ultrasonography and endometrial biopsy (N=59).

Primary Outcome: Menstrual Blood Loss and Treatment Response

At baseline, 66.1% of women (n=39/59) were classified as having very heavy menstrual bleeding (PBAC >300), while the remaining 20/59 (33.9%) had heavy bleeding (PBAC 100–300.) At six months post-treatment, 11/47 (23.9%) experienced scanty bleeding and 13/47 (28.2%) continued to have amenorrhoea. These 13 women with persistent amenorrhoea at six months post-treatment were all in the perimenopausal age group [Table/Fig-3]. There was a statistically significant reduction in PBAC scores at each subsequent visit compared to baseline (p<0.001).

Treatment failure, defined as continued heavy menstrual bleeding despite therapy, occurred in 7/56 (12.5%) of women and these seven underwent hysterectomy at six months due to inadequate response. Two additional women were lost to follow-up after completing treatment, resulting in 47 women with post-treatment data available at both three and six months. As a result, [Table/Fig-3] presents PBAC scores only for women who completed the full course of therapy and remained in follow-up and excludes those who underwent hysterectomy due to treatment failure.

Regarding previous treatments, 42 women (71.2%) had received at least one prior pharmacologic therapy for AUB. Among them, 28 had used tranexamic acid, 12 had taken hormonal therapy (progestins or combined oral contraceptives) and seven had been treated with Non Steroidal Anti-inflammatory Drugs (NSAIDs). Despite these treatments, all participants continued to experience heavy menstrual bleeding, warranting inclusion in the current study.

Secondary outcomes: The mean pretreatment haemoglobin was 9.44±1.6 g/dL, which increased to 10.9 g/dL at the end of treatment and further to 12.22±1.3 g/dL at six months of ormeloxifene therapy (p<0.001).

Dysmenorrhoea

The VAS was used to evaluate the severity of dysmenorrhoea at baseline and after treatment. At the start of therapy, 44/59 (74.5%) of patients reported severe dysmenorrhoea, 10/59 (16.9%) mild, 3/59 (5.1%) moderate and 2/59 (3.3%) reported no dysmenorrhoea. "By the end of treatment, among the 50 women with available dysmenorrhoea scores, 17 (28.8%) reported no dysmenorrhoea, 23 (38.9%) mild, 8 (13.5%) moderate and 2 (3.3%) severe dysmenorrhoea. The reduction in severity of dysmenorrhoea was statistically significant (p<0.001)."

Hysterectomy and Poor Response

Poor response to treatment, defined as continuation of heavy menstrual bleeding despite therapy, was observed in 12.5% (n=7/56) of women. All seven women underwent hysterectomy at the end

PBAC score category	Before treatment (n=59)	2 months after treatment (n=59)	6 months after treatment (n=56)	3 months post-treatment (n=47)	6 months post-treatment (n=47)	p-value (vs. baseline)
Very heavy (>300)	39 (66.1%)	5 (8.4%)	1 (1.7%)	–	–	<0.001
Heavy (101-300)	20 (33.9%)	31 (52.5%)	9 (16.1%)	1 (2.1%)	–	<0.001
Moderate (11-100)	–	19 (32.2%)	19 (33.9%)	22 (46.8%)	23 (47.8%)	<0.001
Scanty (<10)	–	2 (3.3%)	7 (12.5%)	5 (10.6%)	11 (23.4%)	<0.001
Amenorrhoea	–	2 (3.3%)	20 (35.7%)	19 (40.4%)	13 (27.7%)	<0.001

[Table/Fig-3]: Changes in PBAC Score during treatment and post-treatment.
Chi-square test was used

of six months. Among these, four had adenomyosis on ultrasound and most were in the older age group (three each in the 40-45 years and 45-50 year groups, one in 50-55 years). Pretreatment histopathology in these women included secretory endometrium (n=2), proliferative endometrium (n=2) and disordered proliferative endometrium (n=3) [Table/Fig-4].

Characteristics	Subcategory	n
Age group (years)	40-45	3
	45-50	3
	50-55	1
Histopathology	Secretory endometrium	2
	Proliferative endometrium	2
	Disordered proliferative	3
Ultrasound finding	Adenomyosis	4
	Type 2 fibroid	1
	No obvious pathology	2

[Table/Fig-4]: Pretreatment disease characteristics in women who failed to respond to ormeloxifene (n=7).

Adverse Effects

"Most adverse effects were observed during the first three months of ormeloxifene therapy. Vague abdominal pain was reported by 13.5% (n=8), primarily within the first month. Dyspepsia and bloating (5.1%, n=3) also occurred early in treatment and were managed with proton pump inhibitors. Two women (4.3%, n=2/47) developed ovarian cysts, identified on routine ultrasound at 3 and 6 months; both were functional cysts that resolved spontaneously without intervention. Headache was reported in two women during the first two months and responded to NSAIDs. No serious adverse events were observed."

Lipid Profile

Lipid profile was assessed before and after six months of treatment. There was a statistically significant reduction in Low-Density Lipoprotein (LDL) and total cholesterol levels, while High-Density Lipoprotein (HDL) showed a non significant decrease [Table/Fig-5].

Lipid parameters	Pretreatment (mg/dL)	Post-treatment (mg/dL)	% Decrease	p-value paired t-test
HDL cholesterol	59.47	57.58	3.1%	0.08
LDL cholesterol	87.02	73.12	16.04%	<0.001
Total cholesterol	156.14	134.05	14.14%	<0.0001

[Table/Fig-5]: Change in lipid profile six months after treatment with ormeloxifene.

DISCUSSION

The AUB is a frequent and challenging gynaecological complaint, especially in the late reproductive and perimenopausal age groups. In the present prospective interventional study, ormeloxifene demonstrated significant efficacy and safety in reducing menstrual blood loss and improving haemoglobin levels in women with chronic AUB.

A significant and sustained improvement in haemoglobin was observed, with mean values rising from 9.44±1.6 g/dL at baseline to 12.22±1.3 g/dL at the end of therapy (p<0.001). The severity of dysmenorrhoea was also significantly reduced, with the proportion of women reporting severe pain decreasing from 74.5% at baseline to 3.3% at the end of treatment (p<0.001). These results are consistent with previous studies reporting significant reductions in menstrual blood loss and improvement in anaemia with ormeloxifene therapy [6,9-12].

Treatment failure was identified in 12.5% (n=7/56) of participants, all of whom subsequently underwent hysterectomy. Among these women, the majority had histological evidence of anovulatory endometrium, similar to report suggesting that non structural or anovulatory AUB may be less responsive to ormeloxifene [12]. However, Mir SA et al., also documented a significant therapeutic response to ormeloxifene in women with non structural AUB, reporting a reduction in mean bleeding duration from 16.88±6.46 to 7.76±1.55 days, an increase in haemoglobin from 8.56±0.77 to 10.1±0.87 g/dL and a decrease in PBAC score from 289.92±42.39 to 128.11±33.10 after three months of therapy. These findings support ormeloxifene's efficacy even in anovulatory or non structural cases and reinforce the need for further research to define predictors of non response [12].

Ormeloxifene was well-tolerated, with only mild adverse effects, including abdominal pain, dyspepsia and headache, all of which were managed conservatively. No serious adverse events were observed. A noteworthy secondary finding was the favourable effect on lipid profile, with significant reductions in LDL and total cholesterol at six months. This positive metabolic impact distinguishes ormeloxifene from other hormonal therapies, which may have adverse effects on lipid metabolism and cardiovascular risk profiles [13].

Compared to progestogens and combined oral contraceptives, ormeloxifene offers advantages in terms of reduced dosing frequency, greater patient compliance, lower risk of breast heaviness and mastalgia and potentially lower long-term risks [14].

The present study adds value to the existing literature by providing longer-term post-treatment follow-up and by highlighting the utility of ormeloxifene across both reproductive and perimenopausal women with chronic AUB. Persistent amenorrhoea in perimenopausal women and sustained haemoglobin improvements are clinically meaningful outcomes.

Limitation(s)

However, certain limitations must be acknowledged. The modest sample size and heterogeneity of the study population precluded randomisation and direct comparison with other agents. Some laboratory data were missing at follow-up and the lack of a placebo or active comparator arm limits broader generalisability.

CONCLUSION(S)

Ormeloxifene is a safe, effective and well-tolerated alternative for women with AUB, offering significant reduction in menstrual blood loss, improvement in anaemia and manageable side-effects. Its benefit is particularly notable in perimenopausal women and in those seeking non-surgical management. Further randomised controlled trials with larger, homogeneous populations are needed to define the optimal duration, dose and patient selection, especially for long-term use in younger women and those with anovulatory bleeding.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Feb 08, 2025
- Manual Googling: Nov 24, 2025
- iThenticate Software: Nov 28, 2025 (2%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Feb 05, 2025**
Date of Peer Review: **Apr 29, 2025**
Date of Acceptance: **Dec 03, 2025**
Date of Publishing: **May 01, 2026**