

RESEARCH ARTICLE

Effectiveness and safety of ormeloxifene and medroxyprogesterone acetate in dysfunctional uterine bleeding – A prospective interventional quasi-randomized interval clinical studyArathy R¹, Santosh Pillai², Sreedevi N S³, Rajeev Aravindakshan⁴, Rajmohan G⁵, Sujith J Chandy⁶

¹Department of Pharmacology, Sree Gokulam Medical College and Research Foundation, Venjaramoodu, Kerala, India, ²Department of Pharmacology, Pushpagiri Institute of Medical Sciences Research Centre, Tiruvalla, Kerala, India, ³Department of Obstetrics and Gynaecology, Pushpagiri Institute of Medical Sciences Research Centre, Tiruvalla, Kerala, ⁴Department of Community and Family Medicine, All India Institute of Medical Sciences, Mangalagiri, Andhra Pradesh, India, ⁵Scientist E3, HLL Lifecare Ltd., Trivandrum, Kerala, India, ⁶Department of Pharmacology and Clinical Pharmacology, Christian Medical College, Vellore, Tamil Nadu, India

Correspondence to: Santosh Pillai, E-mail: drsantosh74@gmail.com

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ABSTRACT


Background: Progestogens and selective estrogen receptor modulators are used in treating dysfunctional uterine bleeding (DUB). There is a lack of consensus regarding the best agent. **Aim and Objective:** To compare the effectiveness and safety of ormeloxifene and medroxyprogesterone acetate (MPA) in DUB. **Materials and Methods:** A comparative evaluation of gynecology outpatients with DUB at a tertiary care teaching hospital by a prospective interventional quasi-random design. Patients having DUB were allocated into two groups based on treatment with ormeloxifene ($n = 20$) and MPA ($n = 20$). Each patient was followed up for 3 months and evaluated for: (a) Menstrual blood loss assessed using pictorial blood loss assessment chart (PBAC) score and presence of clots, (b) endometrial thickness, (c) hemoglobin (Hb) level, (d) assessment of symptoms, and (e) adverse effects. Mann–Whitney U test and Chi-square test were used to compare both groups. **Results:** There was a significant reduction in PBAC score and passage of clots compared to baseline in both groups. An increase in Hb was statistically significant in MPA group. Decrease in PBAC score, increase in Hb, and decrease in endometrial thickness after treatment was not significant between groups. In ormeloxifene group, symptoms significantly improved after 1 month and 75% patients had amenorrhea. **Conclusion:** Ormeloxifene, with less frequent administration and higher tolerability, can be used as an effective alternative to MPA for controlling menstrual blood loss.

KEY WORDS: Menstrual Blood Loss; Progestogen; Selective Estrogen Receptor Modulators**INTRODUCTION**

Abnormal uterine bleeding interferes with woman's social, economical, personal, and emotional quality of life.

Dysfunctional uterine bleeding (DUB) is abnormal uterine bleeding in the absence of any systemic, organic, or iatrogenic cause.^[1] Medical therapy forms the primary treatment option in DUB. The different medical options available are nonsteroidal anti-inflammatory drugs, antifibrinolytics, progesterone, combined estrogen and progesterone, gonadotropin-releasing hormone agonists, danazol, and levonorgestrel-releasing intrauterine systems.

With anovulation, the resulting unopposed estrogen stimulation causes the proliferation of endometrium and erratic bleeding. Progestins halt endometrial growth

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and allow for an organized sloughing following their withdrawal.^[2] Thus, they are successful in anovulatory DUB. Progestins alone cannot be used in ovulatory DUB. Medroxyprogesterone acetate (MPA), a progestogen with weak androgenic and antiestrogenic property, is often used for DUB. Hormonal adverse effects may be a drawback. Ormeloxifene, a nonsteroidal selective estrogen receptor modulator (SERM), is increasingly being used for DUB. It being a nonhormonal drug with a longer half-life may ensure better compliance. Its anti-cancer activities in breast,^[3] head and neck, and chronic myeloid leukemia cells are also being studied. Ormeloxifene is an optimally designed SERM for the treatment of DUB because of the estrogen antagonistic action in the uterus and breast and mildly estrogenic action in vagina, bone mineral density, central nervous system, and serum lipids^[4-6] The objective of the study was, therefore, to compare the effectiveness and safety of ormeloxifene with MPA in patients with DUB in terms of: (a) Menstrual blood loss, (b) endometrial thickness in proliferative phase, (c) blood hemoglobin (Hb) level, (d) subjective assessment of symptoms, and (e) adverse effect profile.

MATERIALS AND METHODS

This was a prospective quasi-randomized comparative evaluation of outpatients with DUB at a tertiary care teaching hospital. Women attending the gynecology outpatient clinic of a tertiary care teaching hospital, with DUB in the age group 35–50 years, were prescribed either MPA or ormeloxifene on a consecutive basis over a period of 15 months. The patients excluded were those with severe anemia, intrauterine contraceptive device or oral contraceptive pill users, autoimmune disease, thyroid, liver or coagulation disorders, renal disease, stroke, migraine, previous history of thrombosis, lactating woman, and woman desirous of future pregnancy. The study design was a prospective interventional quasi-random study. The study got approval from the Institutional Review Board and Institutional Ethics Committee of the hospital.

A non-inferiority study typically shows that a new treatment is not worse than an existing treatment. The non-inferiority limit in this study was set at 15% points. If there were to be a true difference in favor of the experimental treatment of 20% (90% vs. 70%), then 32 patients were required to be 80% certain that the upper limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) would exclude a difference in favor of the standard group of more than 15%. Required sample in each group hence was at least 16 and we took a sample size of 20 in each group.

For each patient, an initial clinical examination which included per-speculum and per-vaginal examination was done. Blood Hb, platelet count, packed cell volume, pregnancy test (if a history of amenorrhea present), thyroid-stimulating hormone,

activated partial thromboplastin time, Papanicolaou smear, pelvic ultrasound, and endometrial sampling were done to exclude any other possible causes of abnormal uterine bleeding. The study commenced after getting written informed consent from all study participants.




Allocation of every patient into two groups was carried out by the treating gynecologist alternately among consecutive patients. Ormeloxifene group ($n = 20$) received ormeloxifene 60 mg twice weekly with an interval of 3 days for 3 successive cycles. MPA group ($n = 20$) received MPA 10 mg for a period of 21 days from day 2 of cycle for three consecutive cycles. Each patient was followed up on a monthly basis for 3 months. A comparative evaluation of two treatment groups was done based on the following variables: Menstrual blood loss, passage of clots, blood Hb level, endometrial thickness in proliferative phase (day 8–day 12 of cycle) by transvaginal ultrasound, subjective assessment of symptoms, and assessment of adverse effects of drugs. The patients were asked to keep up a menstrual diary noting the days of bleeding, range of sanitary napkins used, degree of staining of each napkin, range and size of clots passed, events of bleeding, presence of abdominal pain, and alternative symptoms if any. Menstrual flow loss was assessed using a pictorial blood loss assessment chart (PBAC) score.^[7] The scoring system used for scoring the chart was developed by Higham *et al.*^[7] 1990. The scoring is shown in Figure 1. PBAC score >100 ⁷ was considered as menorrhagia. The PBAC score could be a simple and precise tool for semi-objective measuring of menstrual blood loss.^[8] The chart comprises a series of diagrams signifying lightly stained, moderately stained, and heavily stained sanitary pad. The presence of clots based on size and the flooding was also counted. The patient was taught to fill the PBAC chart. The women were asked to fill the chart during the menstrual cycle and bring it during their next appointment in the hospital. Blood Hb level and endometrial thickness in the beginning before starting treatment was noted. During the first and subsequent 3 months, PBAC score was recorded. After 3 months, transvaginal ultrasound was repeated to assess endometrial thickness in the proliferative phase. Blood Hb was also repeated after 3 months. Patient's subjective assessment of improvement of symptoms was recorded monthly. This was recorded as mild improvement, marked improvement, no improvement, and worsening of symptoms.

PBAC scoring system is shown in Figure 1.

The adverse effects due to drugs, such as amenorrhea or hypomenorrhea, spotting, breakthrough bleeding, stress urinary incontinence, uterovaginal prolapse, and weight gain, were noted. Relief from dysmenorrhea was also followed up. A predesigned pro forma was used to collect the data.

Statistical Analysis

PBAC score, presence of clots, hemoglobin, and endometrial thickness of the two groups were presented as categorical/

For each lightly stained pad 		1 point
For each moderately stained pad 		5 points
For each completely saturated pad 		20 points
Clots	Small (smaller than a rupee coin)	1
	Large (larger than a rupee coin)	5
Flooding	For each episode of flooding	5

PBAC – Pictorial Blood-loss Assessment Chart

Figure 1: Pictorial blood assessment chart scoring system

grouped variables. Subjective assessment of improvement and decrease in dysmenorrhea were compared between the two groups. Within-group comparison of variables before and after treatment was also done. Mann–Whitney U test and Chi-square tests were applied to compare between two groups. $P < 0.05$ was considered as statistically significant.

RESULTS

The two groups were comparable as per the distributions of age groups (Chi-square = 1.448; $P = 0.694$) and parity (Chi-square = 7.00; $P = 0.221$). Mean age of patients in ormeloxifene group was 47 (31–50) years and in MPA group was 43.3 (30–50) years. About 90% of patients in both groups had proliferative endometrium. Nineteen patients in both groups (95%) had clots before starting treatment. About 65% of patients in ormeloxifene arm and 50% in MPA arm had dysmenorrhea. Mean PBAC score before starting treatment in ormeloxifene group was 307.3 (± 82.65) and in MPA group was 297.15 (± 87.96) ($P = 0.705$).

After 1 month

Mean PBAC score after one month in ormeloxifene group was 52.9 (± 110.29) and in MPA group was 98.2 (± 67.25) ($P = 0.003$). The percentage decrease in mean PBAC score compared to baseline in ormeloxifene arm was 82.79% and in MPA arm was 66%. About 95% of patients in ormeloxifene arm and 80% of patients in MPA arm did not have clots after 1st month of therapy. No significant difference was noted in the reduction of dysmenorrhea among ormeloxifene and MPA groups after 1 month.

After 2 months

Mean PBAC score after 2 months in ormeloxifene group was 38.55 (± 85.97) and in MPA group was 65.5 (± 50.56)

($P = 0.013$). The percentage decrease in mean PBAC score compared to baseline in ormeloxifene arm was 87.46% and in MPA arm was 77.92%. There was no difference between both groups in the reduction of clots, as 95% of patients in both groups did not have clots after 2 months. There was no significant difference between both drugs in reducing dysmenorrhea.

After 3 months

Mean PBAC score after 3 months in ormeloxifene group was 34.2 (± 82.21) and in MPA group was 77.7 (± 61.91) ($P = 0.002$). Percentage reduction in mean PBAC compared to baseline after 3rd month in ormeloxifene group was 88.87% and in MPA group was 73.85%. No statistically significant difference was observed among ormeloxifene group and MPA group in the reduction of clots. About 95% of patients in both groups did not have clots after 3rd month of therapy. Within-group analysis showed that both ormeloxifene and MPA affected a significant reduction in menstrual blood loss [Table 1]. No statistically significant difference in the reduction of dysmenorrhea was observed among ormeloxifene group and MPA group.

Figure 2 shows the Hb before and after treatment in both groups. Mean Hb (%) before treatment in ormeloxifene group was 11.27 (± 1.34) and in MPA group was 11.00 (± 0.99) ($P = 0.989$). Mean Hb after treatment in ormeloxifene group was 11.92 (± 0.916) and in MPA group was 11.85 (± 0.921) ($P = 0.947$). Increase in hemoglobin after treatment was statistically significant only in MPA group (Chi-square = 8.737; P value = 0.120 and Chi-square = 12.407; P value = 0.030 in ormeloxifene and MPA, respectively).

Mean endometrial thickness (mm) before treatment in ormeloxifene group was 11.43 (± 4.94) and in MPA group was 11.77 (± 4.75) ($P = 0.583$). Mean endometrial thickness after treatment in ormeloxifene group was 11.11 (± 6.15) and in MPA group was 8.46 (± 3.68) ($P = 0.091$). Reduction in endometrial thickness after treatment was not statistically significant in both the groups (Chi-square = 4.050; $P = 0.542$ and Chi-square = 6.630; $P = 0.085$ in ormeloxifene and MPA, respectively).

Figure 3 shows the endometrial thickness before and after treatment in both groups.

Table 2 shows the subjective assessment of symptoms after treatment in both the groups. Ormeloxifene had significantly greater acceptability compared to MPA after 1st month.

Assessment of the safety of drugs

The adverse effects noted in the two groups during the treatment are shown in Table 3.

Table 1: PBAC score in both groups

PBAC score	Ormeloxifene				MPA			
	Pre-treatment	After 1 month	After 2 months	After 3 months	Pre-treatment	After 1 month	After 2 months	After 3 months
≤100	0	16	16	17	0	12	16	14
101–200	3	2	3	2	3	7	4	5
201–300	6	0	0	0	6	1	0	1
301–400	8	2	1	1	9	0	0	0
401–500	3	0	0	0	2	0	0	0

Chi-square = 55.12; *P* < 0.0001, Significant Chi-Square = 60.604; *P* < 0.0001, Significant

PBAC score: Pictorial blood loss assessment chart score, MPA: Medroxyprogesterone acetate

Table 2: Subjective assessment after treatment

Subjective improvement	After 1 month*		After 2 month#		After 3 month ^s	
	Ormeloxifene <i>n</i> (%)	MPA <i>n</i> (%)	Ormeloxifene <i>n</i> (%)	MPA <i>n</i> (%)	Ormeloxifene <i>n</i> (%)	MPA <i>n</i> (%)
No improvement	1 (5)	0 (0)	1 (5)	0 (0)	1 (5)	1 (5)
Mild improvement	2 (10)	11 (55)	2 (10)	8 (40)	2 (10)	7 (35)
Marked improvement	17 (85)	9 (45)	17 (85)	12(60)	17 (85)	12 (60)
Worsening of symptoms	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

*Chi-square=9.69; *P* = 0.008, Significant #Chi-square = 5.46; *P* = 0.065; Not significant ^sChi Square = 3.64; *P* = 0.162; Not significant

MPA: Medroxyprogesterone acetate

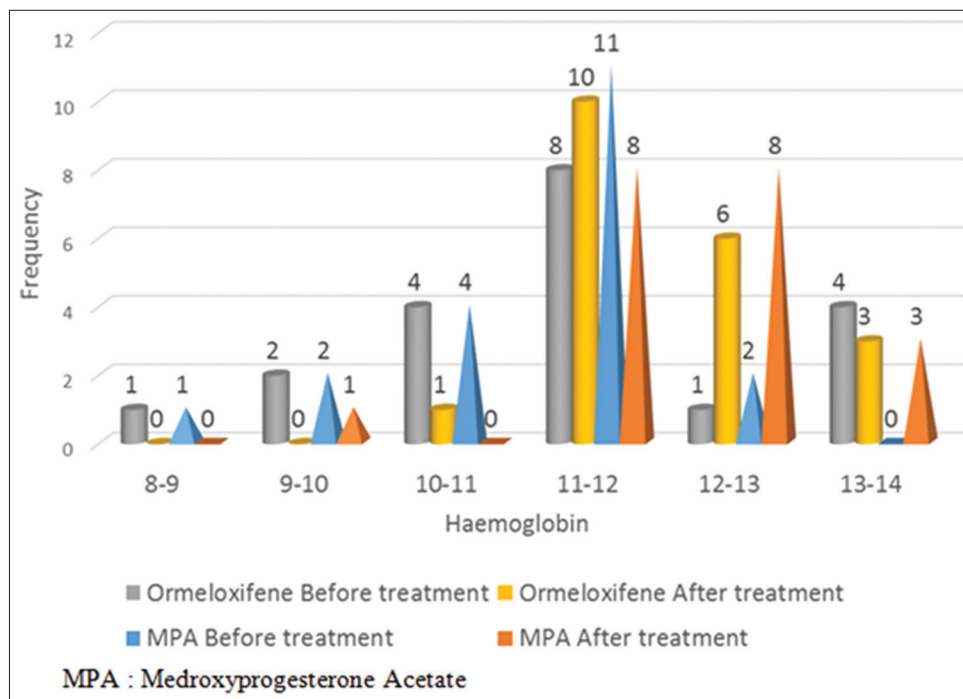


Figure 2: Hemoglobin before and after treatment in both groups

Amenorrhoea was the most common adverse effect reported. About 75% of patients in ormeloxifene group had amenorrhoea compared to only 25% in MPA group. This difference was significant (*P* = 0.004). Five patients (25%) in MPA group had weight gain.

DISCUSSION

Both ormeloxifene and MPA effectively controlled menorrhagia by 1st month, as shown in Table 1. After the 3rd month, however, more patients in the ormeloxifene group

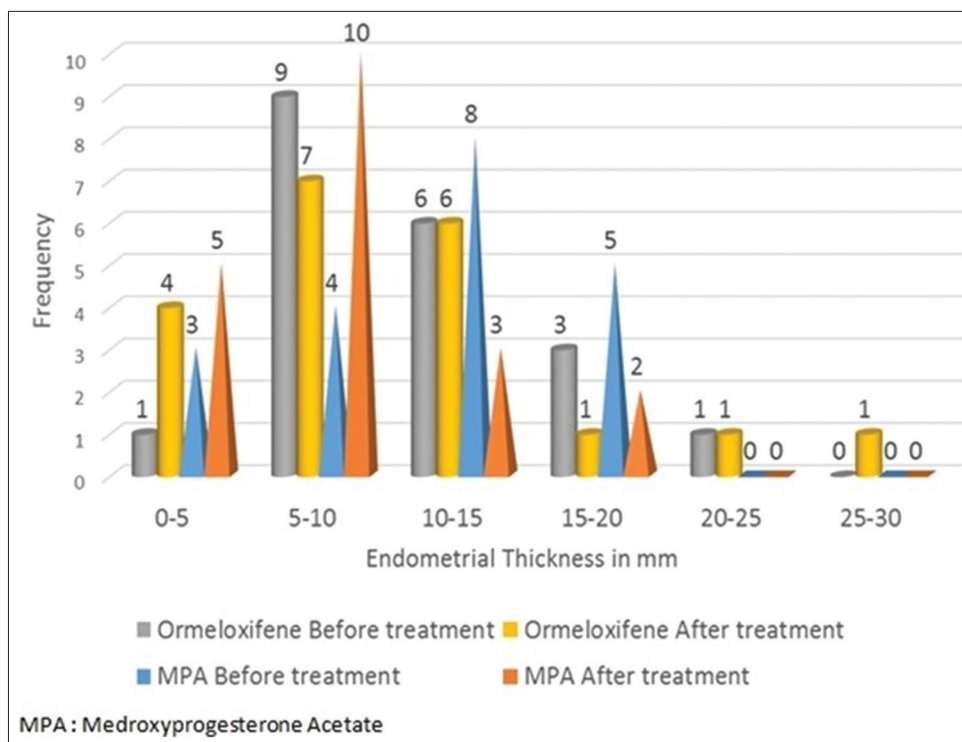


Figure 3: Endometrial thickness before and after treatment in both groups

Table 3: Adverse effects noted

Adverse effect	Ormeloxifene n (%)	MPA n (%)
Amenorrhoea	15 (75)	5 (25)
Hypomenorrhoea	2 (10)	2 (10)
Spotting	0	3 (15)
Stress urinary incontinence	1 (5)	1 (5)
Uterovaginal prolapse	1 (5)	1 (5)
Weight gain	1 (5)	5 (25)
Urinary frequency	1 (5)	1 (5)
Urinary retention	1 (5)	0
Aphthous ulcer	1 (5)	0
Gastritis	0	1 (5)
Drowsiness	0	1 (5)
Nipple discharge	1 (5)	0

MPA: Medroxyprogesterone acetate

had a PBAC score ≤ 100 as compared to those in the MPA group. Nineteen patients (95%) in both groups had clots before starting treatment. The percentage reduction in the number of patients with clots after treatment in both groups is 90%. There was an increase in Hb level in both groups due to the reduction in menstrual blood loss. It was not statistically significant in ormeloxifene group ($P = 0.120$) but was significant in MPA group ($P = 0.030$). The most common endometrial pattern in ormeloxifene and MPA group was proliferative endometrium, observed in 18 patients (90%). There was a decrease in endometrial thickness after treatment in both groups, but the reduction was not statistically significant between groups. The subjective

improvement in symptoms was more in ormeloxifene group compared to MPA group in a significant manner. ($P = 0.008$). Hence, the acceptability of ormeloxifene was better compared to MPA. After 3 months, 17 patients (85%) revealed a marked subjective improvement in ormeloxifene arm as compared to 12 patients (60%) in MPA arm. After 3 months of therapy, dysmenorrhoea was absent in five out of seven patients (71.43%) in ormeloxifene group and in six out of 10 patients (60%) in MPA group who initially had dysmenorrhoea. Amenorrhoea was the most common adverse effect in ormeloxifene group, which was significantly higher compared to MPA group ($P = 0.004$).

Shravage et al.^[9] found that 94.59% in ormeloxifene group and 45.71% in MPA group had PBAC score < 100 after 3rd month. Agarwal et al.^[10] observed that 80% women in ormeloxifene group and 30% women in norethisterone group had PBAC score < 100 after 3 months. Unlike other studies, there is a greater reduction in PBAC score in progesterone group in our study. This might be due to the perimenopausal nature of the population studied. In a study by Kaur et al.,^[11] the reduction in PBAC score was 41.4% in 3 months of treatment with ormeloxifene. The percentage reduction in the number of patients with clots after treatment is comparable to a study done by Agarwal et al.^[10] They observed improvement by the absence of clots in 56.52% of patients after 3 months and 80.43% after 6 months of treatment with Ormeloxifene. In a study by Ravibabu et al.,^[12] 59% had significant improvement from the passage of clots after 6 months of treatment with ormeloxifene. The most common endometrial pattern observed correlates with the study

done by Agarwal *et al.*^[10] Greater subjective improvement in symptoms in ormeloxifene group is also evident in the study done by Bhattacharyya and Banerji.^[13] In that study, marked subjective improvement was noted in 81.67% in ormeloxifene group and 35% in norethisterone group (12 days every cycle for six cycles) after 3 months. The greater subjective improvement in progesterone group in our study, unlike the other study, might be due to the greater reduction in PBAC score obtained in progesterone group in our study. Kumari and Prakash^[14] observed a marked improvement in symptoms in 57.14% of patients after 3 months of treatment with Ormeloxifene. Other studies also revealed a decrease in dysmenorrhea more in ormeloxifene group after therapy. Grover *et al.*^[15] found that dysmenorrhea either decreased or disappeared in 62.5% of patients in ormeloxifene group. Biswas *et al.*^[2] observed that dysmenorrhea was relieved in 78.26% in ormeloxifene group.

The higher incidence of amenorrhea in ormeloxifene group was supported by the results obtained in a study done by Bhattacharyya and Banerji.^[13] They observed amenorrhea in 63.63% of patients in ormeloxifene group. With proper counseling, amenorrhea was a desirable adverse effect for the majority of perimenopausal women.

The most appropriate medical option for the treatment of DUB is still debatable. Ormeloxifene is yet to gain popularity in the field of DUB. It is as effective as progestogens like MPA in decreasing menstrual flow loss in DUB. It has a long plasma half-life of 1 week, which permits twice-weekly administration. However, progestogens like MPA have to be taken twice a day for 21 days every menstrual cycle. The convenient dose schedule of ormeloxifene facilitates patient compliance. MPA causes weight gain, spotting, and breakthrough bleeding. Being a nonhormonal preparation, Ormeloxifene is free of these adverse effects. The common adverse effect of ormeloxifene was amenorrhea.

The strengths of this study were that it was investigator-driven and used a prospective design with a quasi-randomized design, thereby removing any allocation bias. The patients were objectively followed with all the investigations appropriate for the clinical condition. There were minimal drop-outs from the initially enrolled participants. The efficacy and safety endpoints were met in the majority of the subjects and have enabled the study results to be made standard of care in the institute. The limitation of this study was its relatively small sample size. This may limit generalizing the conclusion to the population. However, comparability between the two groups is evident through our study. It would be good to follow-up and confirm these initial findings with a larger and longer study, which will help to demonstrate the long-term effects of ormeloxifene on the menstrual cycle.

CONCLUSION

In patients with DUB, both ormeloxifene and MPA were effective in reducing menstrual blood loss. Subjective improvement in symptoms was higher in ormeloxifene arm compared to MPA arm in a significant manner after the initial month of treatment. With less frequent administration, better tolerability, and compliance, ormeloxifene was found to be a better alternative to MPA for controlling menstrual blood loss.

If effectiveness and safety are further confirmed by larger studies, ormeloxifene could be a first-line treatment option in DUB.

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