ABSTRACT: OBJECTIVE: To study the effect of ormeloxifene in dysfunctional uterine bleeding in premenopausal age group by measuring menstrual blood loss by PBAC score, effect on blood hemoglobin levels and effect on endometrial thickness. METHODS: 35 cases of DUB of age 40 years and above coming to Gynecological OPD were recruited for study after applying exclusion criteria. 60 mg of Ormeloxifene was given twice a week for 3 months and then once a week for 1 month. Patients were followed-up at 1, 3 and 4 months of therapy and then at 3 months after treatment stopped. Menstrual blood loss was measured objectively by pictorial blood loss assessment chart (PBAC) score. RESULTS: The pretreatment median PBAC score was 587 with a range of 186-893. After 4 months of treatment, mean PBAC scores reduced to 76.94±77.73 with a mean change of 490.05±155.4. Which is statistically highly significant (P0.001). 26 (81.25%) patients were cured of menorrhagia at the end of 4 months of treatment. 2 patients had no response and underwent hysterectomy. Amenorrhoea occurred in 22 patients at the end of 4 months of therapy and persisted in 18 patients at 3 months of follow-up after therapy while 1 patient had PBAC scores in the heavy range but much less than her pretreatment levels. Adverse effects included vaginal discharge (15.62%), vague abdominal pain (12.5%), gastric upset (6.25%), headache (6.25%) and ovarian cyst (3.12%). CONCLUSION: Ormeloxifene is an effective and safe therapeutic option for the medical management of perimenopausal DUB.

KEYWORDS: Centchroman, Menorrhagia, DUB, Ormeloxifene, Pictorial blood loss assessment chart

INTRODUCTION: DUB is defined as a state of abnormal uterine bleeding without any clinically detectable organic, systemic and iatrogenic cause. It is the most common menstrual disorder that can affect any women from menarche to menopause.¹

A large proportion of these cases will subsequently undergo a hysterectomy, which is the definitive cure for menorrhagia, but hospitalization and anesthesia are required with its associated risk of morbidity and mortality and the procedure is not suitable for women who wish to preserve their fertility or for women nearing menopause.

A good medical treatment will reduce hysterectomies and associated morbidity and mortality. Levonorgestrol intrauterine system (LNG IUS) in menorrhagia is now considered to be the reference treatment in medical management, but its cost limits its widespread use. Ormeloxifene is a non-steroidal, non-hormonal, pharmacologically inert, selective estrogen receptor modulator (SERM) and has been in use as a weekly oral contraceptive for approximately last 20 years, particularly in India, where it was originally developed. It has anti-estrogenic and hence anti-proliferative effect on endometrium, hence used as a quick and effective endometrial hemostat for dysfunctional uterine bleeding, irrespective of the type of DUB.² It acts as estrogen antagonist in the uterus and breast.
It has mild estrogenic action on vagina, bone mineral density, CNS and serum lipids besides it is oncologically protective (Protects against breast and endometrial carcinoma).

**METHODS:** This Hospital based interventional Study was conducted in Department of Obstetrics and Gynecology, Pannadhay Hospital, R.N.T. Medical College, Udaipur. A total of 35 patients of DUB were recruited for study.

All patients were clinically evaluated and menstrual blood loss assessed with PBAC scores. Scores more than 100 was defined as menorrhagia. Hemograms were performed. USG was done to rule out any pelvic pathology and to measure ET. Endometrial aspiration was performed in all cases. Ormeloxifene in a dose of 60 mg twice a week for 3 months and then once a week for next 1 month was given starting from the 1<sup>st</sup> day of menstrual period. Follow-ups were made at 1, 3 and 4 months of therapy and after 3 months of completion of treatment to assess improvement of symptoms. At each visit, days of bleeding, cycle length, PBAC score and any side effects were recorded in detail. Each patient’s subjective amount of bleeding was assessed by PBAC score. An arbitrary PBAC score of 10 or less was defined as scanty flow, between 10 and 100 was defined as moderate flow, >100 was defined as heavy bleeding and more than 300 was defined as very heavy bleeding. Hemoglobin and ultrasonography was repeated after 4 months of treatment. Repeat endometrial aspiration was performed in patients whose endometrial thickness was found to be >8mm.

**RESULTS:** Patient Profile: 35 cases of DUB were recruited. There were 3 drop-outs, so results of 32 patients was analyzed. The mean age in our study was 41.73±5.03 years. All of them being of perimenopausal age group. Most patients were multiparous. At the time of recruitment majority (87.5% i.e. 28/32) of patients had PBAC scores in the very heavy range (>300), most of patients (53.06%) had regular flow with duration ≥8 days.

Before starting treatment, mean ET was 7.41±2.30, endometrial aspiration revealed proliferative endometrium in 63.26%, secretory endometrium was in 26.53%, simple hyperplasia without atypia was seen in 6.12% and menstrual phase in 4.08%. After 4 months of treatment, repeat endometrial aspiration was taken in 4 patients who had ET >8 mm in USG. Proliferative endometrium was seen in 2 patients, secretory in 1 patient simple hyperplasia without atypia in one, and none revealed atypia.

**Response on Menstrual Blood Loss:** At the end of first month of treatment, only 28.12% (i.e. 9 out of 32) of patients had PBAC scores in the very heavy range, 4 patients had a PBAC score of less than 100, indicating that Ormeloxifene is effective from the first cycle itself.

At the end of 4 months of treatment, majority of patients had a PBAC score of less than 100 (93.75%) including patients with amenorrhoea. Only 2(6.25%) patients had PBAC scores in the very heavy range which is statistically significant. Thus, 93.75% patients were relieved of menorrhagia at the end of treatment which is highly significant (Efficacy of 93.75%).

Mean PBAC score before treatment was 543.92 ± 167.09 [Mean±SD] with a range of 186-893. At 4<sup>th</sup> month of treatment - Mean PBAC score was reduced to 76.94±77.73 with a mean change of 490.05±185.94 (90.09%). 22 patients out of 32 had amenorrhoea at end of 4 months of treatment and percentage reduction of the end of 4 months of treatment was 90.09%. Majority of patient’s i.e.18 (56.25%) had duration of bleeding ≥8 days before treatment. At completion of 4 months of treatment only 2 patients had duration of flow ≥8 days.
Amenorrhea occurred in most of the patients. At the end of 4 months of treatment 68.75% (22 patients out of 32) had amenorrhea. At the end of 3 months of follow-up amenorrhea persisted in 18 patients i.e. 56.25%. In our study amenorrhea occurred in majority of patients and persisted in them as they probably passed into menopause.

Mean ET before treatment was 7.41±2.30 and after treatment after 4 months decreased to 6.82±2.26 and thus mean change was 0.59±2.05 (P-value being less than 0.05). This change being statistically significant.

Mean Hb levels before treatment was 9.32±0.40gm/dl which after 4 months of treatment increased to 10.00±0.81gm/dl with a mean change of 0.60±0.50. This change being statistically highly significant (P-value <0.001).

Presence of Clots: 43.75% patients reported absence of blood clots at first follow-up after 1 month of treatment and 90.62% after 4 months of treatment which is highly significant.

Improvement in Dysmenorrhoea was noted in 15.62% of patients. No patient complained of dysmenorrhoea after 4 months of treatment as compared to 5 patients before treatment.

Majority of patients (57.15%) had no adverse effects with Ormeloxifene with 4 months of treatment. The adverse effects which were observed were mild and included white discharge per vaginum (15.62%), vague abdominal pain (12.5%), gastric upset (6.25%) headache (6.25%) and simple ovarian cyst (3.12%).

DISCUSSION: The present study was designed to assess the effectiveness of Ormeloxifene in management of dysfunctional uterine bleeding in premenopausal age group as drug therapy to avoid large number of operative procedures. Medical treatment of menorrhagia should aim to relieve symptoms, improve quality of life and avoid the risk of surgery. Many women remain menorrhagia despite decrease in menstrual blood loss by 50% with treatment with tranexamic acid, mfenemic acid, norethisterone or ethamsylate\(^3\)\(^4\) and non-compliant due to daily dosing or their side-effects. Basis for weekly dosing schedule of Ormeloxifene are the long elimination half-life and a long lasting estrogen antagonist action.\(^5\)

Ormeloxifene is effective in treatment of menorrhagia. There was significant improvement on various aspects of menstrual patterns and complaints associated with menorrhagia.

We noticed a significant reduction in menstrual blood loss from the very first cycle itself. Mean blood loss reduced to 252.23 from a pretreatment level of 543.92. (P-value <0.001). Kriplani et al (2007),\(^1\) also observed significant reduction at the first follow-up at 2 months of treatment. The effect did not plateau and a further significant reduction was noticed in subsequent cycles. Reduction in menstrual blood loss at 4 months was markedly greater than that achieved with other oral drugs used to treat menorrhagia.\(^6\) Similar results were observed by Biswas Subhash Chandra et al (2002),\(^7\) and Kriplani et al (2007).\(^1\)

Amenorrhoea was noted in 22 patients (i.e. 68.75%) at the end of 4 months of treatment, as all of them being perimenopausal, so it was welcome change for them. Similarly, Kriplani et al (2007),\(^1\) observed amenorrhea in 42.9%.

In our study amenorrhea occurred in majority of patients all of them being of age group 40 years and above and persisted in them as they probably passed into menopause. This finding is similar to study done by Biswas Subhash Chandra et al (2002),\(^7\) in which amenorrhea was mostly noted in older (>41 years) age group rather than in younger age group. Thus, the age of the patient significantly affects the occurrence of amenorrhea with the therapy.
91.67% of patients reported absence of clots after 4 months of treatment. These findings are similar to earlier studies done by Prasad S (2000),8 Biswas Subhash Chandra et al (2002),7 and Kriplani et al (2007).1

In our study there was statistically significant decline in mean endometrial thickness after treatment and evaluation of endometrium in whom endometrium thickness was more than 8 mm revealed no atypia, which corroborates well with previous studies.1,7

Ormeloxifene possesses an excellent therapeutic safety index, safe for chronic administration as has been documented in Phase III trials and has been used as a oral contraceptive since then. Centchroman is non-steroidal, has none of the side-effects commonly associated with oral contraceptives9 no effect on hypothalamo-pituitary axis, protective for breast and endometrial cancer. Hence, also highly suited for long-term therapy in elderly high risk subjects. In addition, in present study few mild side-effects were noticed, none of which were severe enough to warrant intervention. Although there is concern of cystic enlargement of ovaries, in our study only one patient developed simple ovarian cyst (Size3x3cm), Kriplani et al (2007),1 observed ovarian cyst in only 7.1% cases. Prasad S (2000)8 observed functional cysts (2.5±7.1cm diameter) in 22.8% of patients, which regressed spontaneously.

CONCLUSION: Ormeloxifene is a safe and effective drug for the medical management of dysfunctional uterine bleeding. It significantly reduces menstrual blood flow starting from the first month itself and effect lasts even after 3 months of follow-up. The other benefits are, that it is non-steroidal, pharmacologically and metabolically safe and oncologically protective. It causes no major or persistent side-effects and is well tolerated. Also, it is cost-effective and dose schedule of the drug results in good compliance.

Thus, oral Centchroman may be used as a first-line medical management of DUB especially for perimenopausal women to tide over that period and in whom amenorrhea is welcome, and also these women often have other co-morbid conditions that make them unfit or high risk for surgery. It can also be used for those who wish to preserve fertility and in whom steroidal treatment is not recommended and or contraindicated. Findings of present study need to be confirmed by more double-blind placebo-controlled randomized trials with larger number of subjects with longer follow-up and comparative studies.

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| PBAC Score | Before Treatment | After 1 Month | After 4 Months | After 3 Months Follow Up |
|------------|-----------------|--------------|---------------|-------------------------|
| Very Heavy (>300) | 28(87.5%) | 10(31.25%) | 1(3.12%) | 0(0.00%) |
| Heavy(>100-<300) | 4(12.50%) | 17(53.12%) | 1(3.12%) | 1(3.33%) |
| Moderate(11-100) | 0(0.00%) | 4(12.50%) | 4(12.50%) | 6(20.00%) |
| Scanty(<10) | 0(0.00%) | 0(0.00%) | 4(12.50%) | 5(16.67%) |
| Amenorrhoea | 0(0.00%) | 1(3.12%) | 22(68.75%) | 18(60.00%) |
| Total | 32(100.00%) | 32(100.00%) | 32(100.00%) | 30(100.00%) |

Table 1: Distribution According to PBAC Scores of the Subjects at Various Intervals

| | Before Treatment | After 1 Month | After 3 Months | After 4 Months | After 3 Months Follow Up |
|----------|-----------------|--------------|---------------|---------------|-------------------------|
| Mean± SD | 543.92± 167.09 | 252.23± 122.89 | 127.54± 73.41 | 76.94± 77.73 | 40.21± 35.33 |
| Mean Change± SD | 291.69± 136.98 | 417.54± 147.95 | 490.05± 185.94 | 497.58± 163.29 |
| P-value | <.001 | <.001 | <.001 | <.001 |
| Significance | HS | HS | HS | HS |
| Maximum | 893 | 586 | 371 | 395 | 136 |
| Minimum | 186 | 0 | 0 | 0 | 0 |
| Range | 186 - 893 | 0 - 586 | 0 - 371 | 0 - 395 | 0 - 136 |
| Median Baseline PBAC Score | 587 | 217 | 106 | 0 | 0 |

Table 2: Mean±SD of Volume (PBAC Score) at Various Intervals

| | Before Treatment | After 4 Month | Mean Change±SD | P-value | Significance |
|----------|-----------------|--------------|---------------|---------|--------------|
| ET | 7.41±2.30 | 6.82±2.26 | 0.59±2.05 | <.05 | Sig |

Table 3: Comparison of Mean±SD of Endometrial Thickness before and After 4 Months of Treatment
Mean±SD | Mean Change±SD | P-value | Significance
--- | --- | --- | ---
| Before Treatment | After 4 Month | | |
Hb | 9.32±0.70 | 10.00±0.81 | 0.68±0.50 | <.001 | HS

Table 4: Comparison of Mean±SD of Hb of Subjects Before and After 4 Months of Treatment

| Side Effects | No. | % |
| --- | --- | --- |
| White Discharge Per Vaginum | 5 | 15.62 |
| Vague Abdominal Pain | 4 | 12.50 |
| Gastric Dyspepsia | 2 | 6.25 |
| Headache | 2 | 6.25 |
| Ovarian Cyst | 1 | 3.12 |
| None | 18 | 56.25 |
| **Total** | **49** | **100.00** |

Table 5: Distribution According to Side Effects of Ormeloxifene After 4 Months of Treatment

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