# Efficacy of Ormeloxifene vs Norethisterone in the Management of Perimenopausal DUB

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**Abstract :**

**Background:** Disorders of menstruation are the most common reason for a gynaecological consultation among women of reproductive age group. Dysfunctional Uterine Bleeding is defined as abnormal uterine bleeding in the absence of organic, systemic or iatrogenic causes. It can be managed both medically and surgically. In medical management, several drugs have been used. However there is lack of studies suggesting the most appropriate drug. The objective of our study is to compare the treatment efficacy of Norethisterone acetate (a progesterone derivative) versus Ormeloxifene (selective estrogen receptor modulator) in the treatment of DUB. **Methodology:** Total of 100 perimenopausal women with DUB were enrolled in our prospective study. They were randomly assigned into group A and group B. Group A was treated with 60mg Ormeloxifene two times a week for 3 months followed by once a week for another 3months. Group B was treated with Norethisterone 5 mg two times a day from Day5 to Day26 for 6 months. Primary outcome parameters noted were reduction in menstrual blood loss that was measured by fall in Pictorial Blood Loss Assessment Chart (PBAC) score, increase in haemoglobin, and decrease in endometrial thickness at the end of study. **Results:** In our study, the reduction in mean PBAC score with Ormeloxifene was significantly more than that seen with norethisterone after 6 months of therapy. There was a significant increase in hemoglobin level and reduction in endometrial thickness with Ormeloxifene compared to norethisterone. Patients were more compliant to Ormeloxifene because of better tolerance and convenient dosage schedule. **Conclusion:** In our study Ormeloxifene was found to be more effective than Norethisterone in reducing blood loss, improving haemoglobin level and reducing endometrial thickness in DUB patients.

**Keywords:** Endometrial thickness, Haemoglobin, Norethisterone, Ormeloxifene, PBAC.

**Introduction:**

Disorders of menstruation are the most common reason for a gynaecological consultation among women of reproductive age group. DUB is one such condition most commonly affecting women at extremes of reproductive age group.[1] Dysfunctional Uterine Bleeding is defined as abnormal uterine bleeding in the absence of an organic disease[2] Menorrhagia (menstrual blood loss >80 ml per cycle) affects 10-33% of women at some stage in their lives. Dysfunction of HPO axis leads to anovulatory DUB in these age groups with major implications on quality of life and health care costs.[3] It can be managed both medically and surgically. Over 75,000 hysterectomies are carried out every year with 30% of them being done for menstrual disturbances, especially menorrhagia. Though hysterectomy is a suitable treatment modality, long term complications like premature ovarian failure, cardiovascular disease, urinary dysfunction, etc has raised concerns. Hence a majority of women are looking forward to an effective conservative medical therapy in preference to surgical treatment.[4] Pharmacological agents include combined oral contraceptive pills, progestogens, danazol, gonadotrophin releasing hormone (GnRH) agonists, prostaglandin synthetase inhibitor, anti-fibrinolytics, Ethamsylate and levonorgestrel-releasing intrauterine system. Norethisterone, a progestogen, is commonly used for this purpose but being a hormonal drug, it is associated with side effects such as breast cancer, dementia, fluid retention, breakthrough bleeding, spotting etc.[5] Ormeloxifene, a third generation Selective Estrogen Receptor Modulator (SERM) selectively acts on oestrogen receptors as agonist and antagonist in different reproductive tissues. It has anti-estrogenic action on endometrium and breast and estrogenic action on bones, vagina, liver, cardiovascular and central nervous system.[6] The ideal therapy in perimenopausal women is one that has no uterine stimulation, prevents bone loss, has no risk of breast cancer, has a positive effect on lipids and cardiovascular system and maintains cognitive function of brain. Ormeloxifene, satisfies all these requirements.[7] In the treatment of DUB, the standard dose is 60 mg orally two times a week for a period of 3 months followed by once a week in next 3 months.[8] Our study was conducted to compare the efficacy of Ormeloxifene with

Norethisterone in the treatment of perimenopausal DUB.

**Methodology:** This was a comparative study conducted in our Department of Obstetrics and Gynaecology, in which 100 perimenopausal women presenting with abnormal uterine bleeding were enrolled, divided in 2 equal groups (A&B). Ethical approval was obtained from the Institutional Ethical Committee. Informed consent was taken from all the patients willing to participate. A detailed history and clinical examination was done. Essential investigations were done to rule out any possible cause for abnormal uterine bleeding. These were complete blood cell count including haemoglobin level, pregnancy test, thyroid stimulating hormone, coagulation profile, pap smear, pelvic ultrasound (to measure endometrial thickness and rule out any pelvic pathology). 100 patients were divided in 2 groups by random allocation.

**Group A:** Received 60mg Ormeloxifene two times a week for 3 months followed by once a week for another 3months.

**Group B:** Received Norethisterone 5 mg two times a day from Day 5 to Day 26 for 6 month.

The cases were asked to maintain a menstrual diary with recording the days of bleeding, number of sanitary pads used, degree of soaking of each pad, number and size of clots passed, and dysmenorrhoea if experienced. The Pictorial Blood-Loss Assessment Chart (PBAC) Scoring was then done accordingly to assess menstrual blood loss, endometrial thickness measured using ultrasound and haemoglobin using laboratory method. At each visit a menstrual history was taken, and PBAC score was calculated. Haemoglobin concentration and endometrial thickness were measured after 3 months and 6 months of the treatment. Patients were asked for side effects.

All outcome measuring parameters were presented as Mean ± Standard Deviation and were analyzed using the student t test. Statistical significance was taken as $p \leq 0.05$.

**PBAC:**[9]

| PADS | Scores |
|---|---|
| Lightly soiled pads | 1 |
| Moderately soiled pads | 5 |
| Severely soiled pads | 20 |
| **CLOTS** | **Scores** |
| Small clots(less than one rupee coin) | 1 |
| Large clots(more than one rupee coin) | 5 |
| Flooding | 5 |

**Inclusion Criteria:**

- Perimenopausal women between 40 to 55yrs of age presenting with menorrhagia.

**Exclusion Criteria:**

- Bleeding disorders
- Medical disorders like thyroid dysfunction, renal disease, cardiovascular disease, liver dysfunction, stroke,etc
- Organic pelvic pathology

**Results:** Women were divided into two groups with similarity related to duration of symptoms, parity, age and socioeconomic status. Women in both groups were compared with pre-treatment mean of haemoglobin level, endometrial thickness and PBAC scores.

**Table 1:** Parameters before the Start of Therapy

| Groups | PBAC score | Hb (gm%) | Endometrial thickness (mm) |
|---|---|---|---|
| **Group A** | 285.34 | 9.1 | 7.4 |
| **Group B** | 234.56 | 9.2 | 6.9 |

**Group A:** Reported with pre-treatment mean Hb of 9.1 gm% with 7.8 mm of mean endometrial thickness and mean PBAC of 285.34 score. Group B: Reported with mean Hb 9.2 gm% with 6.8 mm of mean endometrial thickness and mean PBAC of 234.56 score.

**Table 2:** Reduction in PBAC score

| Groups | Pre-treatment PBAC | Post-treatment PBAC | Mean difference | P value |
|---|---|---|---|---|
| **Group A (Ormeloxifene) (n=50)** | 285.34 | 74.11 | 211.23 | <0.001 |
| **Group B (Norethisterone) (n=50)** | 234.56 | 108.21 | 126.35 | <0.001 |

After treatment group A showed reduction in PBAC score from 285.34 to 74.11 (p value <0.001). Group B showed reduction in PBAC score from 234.56 to 108.21(p value <0.001). Both the groups showed marked reduction in PBAC scores post treatment, although reduction was more in group A patients treated with Ormeloxifene.

**Table 3:** Rise in Haemoglobin level

| Groups | Pre-tretment Hb | Post-treatment Hb | Mean difference | P Value |
|---|---|---|---|---|
| Group A (ormeloxifene) | 9.1 | 11.4 | 2.3 | <0.001 |
| Group B (Norethisterone) | 9.2 | 10.5 | 1.3 | <0.002 |

The haemoglobin reported in group A at the end of treatment was 11.4 gm% as compared with group B women who reported 10.5 gm%. So, a mean increase of 2.3 gm% was reported in group A and 1.3 gm% in group B. Thus, though haemoglobin levels increased in both the groups, but rise was higher in Group A when compared with group B.

**Table 4:** Reduction in Endometrial Thickness (ET-mm)

| Groups | Pre-treatment ET | Post-treatment ET | Mean difference | P value |
|---|---|---|---|---|
| **Group A** | 7.8 | 5.4 | 2.4 | <0.001 |
| **Group B** | 6..8 | 5.7 | 1.1 | <0.001 |

Mean reduction of 2.4 mm of endometrial thickness was documented in group A women when compared with group B women who documented with mean reduction of 1.1 mm of endometrial thickness. The reduction of endometrial thickness with p value less than 0.001 was statistically significant in both the groups but mean decrease was more with group A compared to group B.

**Discussion:**

Dysfunctional uterine bleeding (DUB) is a common condition affecting quality of life of many women. Both medical and surgical treatment options are available. Our study compares the efficacy of Ormeloxifene and Norethisterone in perimenpopausal women. A total of 100 patients were enrolled in the study, divided equally in each group. Group A was given Ormeloxifene 60 mg twice a week for 3 months followed by once a week for 3 months while group B was given Norethisterone tablet 5 mg twice a day for 21 days followed by 7 days withdrawal for 6 months. Patients were followed up. Blood loss, haemoglobin concentration and endometrial thickness were measured at the end of treatment. All patients were in the age group of 40-55 years. Blood loss during menstrual cycles was assessed by means of pictorial blood assessment chart (PBAC). In this study, mean PBAC scores before treatment were 285.34 in group A and 234.56 in group B. It had reduced by 56.8% and 40.1% in groups A and B respectively. The efficacy of treatment was comparable in the two groups.

There was a significant reduction in group A compared to group B. A similar study conducted on 42 women with menorrhagia administering ormeloxifene 60mg twice weekly for 3 months and then once a week for 1 month showed reduction in menorrhagia by at 4 months.[10]

Ormeloxifene competes with estradiol for binding with cytosol receptors. It not only blocks but also causes their prolonged depletion and has long lasting post withdrawal effect. Ormeloxifene was thus, found to be more effective in reducing menstrual blood loss and controlling DUB compared to cyclical progesterone. Shravage et al compared ormeloxifene to another progesterone, medroxyprogesterone acetate. They found an 85.7% reduction in menstrual blood loss with ormeloxifene as compared to 54.76% with medroxyprogesterone acetate.[11]

In this study the mean Hb in group A after treatment was 11.4 gm% and that in group B was 10.5 gm% that is more in group A that was statistically significant. A similar study by Agarwal et al using ormeloxifene reported a statistically significant rise in Hb by 1.8%.[12]

In our study the endometrial thickness before treatment in group A and group B were 7.8 and 6.8 which were comparable. However, at the end of the treatment Ormeloxifene was found to cause significant reduction in endometrial thickness by 2.4 mm in group A compared to 1.1 mm in group B. Reduction in endometrial thickness is a definitive objective evidence showing reduction in menstrual blood loss. While both Ormeloxifene and Norethisterone exhibit antiestrogenic activity in the endometrium preventing endometrial proliferation, Ormeloxifene is more efficacious as it directly blocks the oestrogen receptors and thereby prevents mitogenic activity exhibited by oestrogen. A study conducted by Jacob et al using similar drugs showed reduction in endometrial thickness by both the drugs although the reduction was greater with Ormeloxifene compared to Norethisterone.[13]

In our study 20% cases in group A failed to respond to medical treatment with Ormeloxifene and ended in hysterectomy, 42% cases treated with Norethisterone needed surgical management. Failure rate was higher with Norethisterone compared to Ormeloxifene.

One of the major side effects with Ormeloxifene was amenorrhoea. This is due to hypoestrogenic effects causing delay in ovulation thereby lengthening the follicular phase. In majority of the subjects menstrual cyclicity returned to normal after 3-6 months. However, in our study patients were in the perimenopausal age group and amenorrhoea was acceptable.

Ormeloxifene has been associated with a number of advantages. It can be started at any time during the cycle unlike the progesterones. It is an effective endometrial haemostat controlling bleeding within 48 hours. It is economical compared to any drug. While preventing DUB it also offers perimenopausal bone and cardiovascular protection which is not seen with other drugs.

**Conclusion:**

Dysfunctional uterine bleeding is a common problem that is encountered in the gynaecology outpatient department. The main mode of management is pharmacological therapy. At the end of the study both the groups showed reduction in PBAC score, rise in haemoglobin level and reduction in endometrial thickness. Ormeloxifene was found to be superior to Norethisterone in the management of DUB. No major side effects were seen with either of the drugs. However this study was conducted over a small scale. Hence, to establish the definitive efficacy of the drug randomized controlled trials with larger subjects over a longer period of time comparing the drug with other medical agents are needed.

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