

The Role of Ormeloxifene in the Management of Dysfunctional Uterine Bleeding: A Prospective Clinical Study

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ABSTRACT

Introduction: The term dysfunctional uterine bleeding (DUB) is used for abnormal uterine bleeding occurring in the absence of identifiable pathology. A number of drugs are available for management of DUB – nonsteroidal anti-inflammatory drugs (NSAIDs), tranexamic acid, ethamsylate, hormones like OCP, progestins etc. The present study was done to determine the efficacy and safety of Ormeloxifene in the management of DUB.

Material and Methods: This prospective clinical study involved 75 patients with DUB who were treated with Ormeloxifene 60 mg tablet twice a week for first 12 weeks and then once a week for next 12 weeks. They were followed up at 4th, 8th, 12th and 24th week of treatment. The outcome was studied by assessment of menstrual blood loss by PBAC score, Hb level in g/dl, endometrial thickness in mm, relief of dysmenorrhoea and any side effects of drugs. Paired T Test and Wilcoxon signed rank test was used to see the effect of drug.

Results: The median PBAC score was significantly reduced from 265 to 27 after 6 months (P<0.001). The mean hemoglobin concentration was significantly increased from 9.15 g/dl to 10.36 g/dl at 6 months (P<0.001). The mean endometrial thickness was reduced from 11.81 mm to 7.63mm after 6 months (P<0.001). 84% women showed marked subjective improvement in symptoms. There were no major side effects of the drug.

Conclusion: Ormeloxifene, with its convenient dose schedule, is an effective and safe alternative in the management of dysfunctional uterine bleeding.

Keywords: Dysfunctional Uterine Bleeding, Menorrhagia, Ormeloxifene, Treatment

INTRODUCTION

Abnormal uterine bleeding (AUB) is a symptom and not a disease. AUB is an overarching term used to describe any departure from normal menstrual cycle pattern. The key characteristics are regularity, frequency, heaviness and duration of flow but each of these may exhibit considerable variability¹. When causes are demonstrable they are grouped as organic, but when causes are not obvious they are labelled as dysfunctional uterine bleeding (DUB). AUB includes both organic causes and DUB. The term dysfunctional uterine bleeding is used for abnormal uterine bleeding without any structural, organic or iatrogenic cause. It is essentially a diagnosis of exclusion².

DUB is often classified into ovulatory and anovulatory. Ovulatory DUB can present either as polymenorrhea and polymenorrhagia or simply heavy or prolonged menses

at normal intervals. Regular heavy or prolonged menses in ovulatory DUB is due to corpus luteum defects either irregular ripening, or irregular shedding of the endometrium³, or due to abnormal stimulation from the hypothalamic-pituitary axis which occurs in conditions like post pregnancy where pituitary function is disturbed, or day to day stress elevating factors. Anovulatory bleeding results from estrogen withdrawal, reflecting the transient fall in estrogen level accompanying regression of a follicular cohort, or from estrogen breakthrough due to focal breakdown of an overgrown and structurally fragile endometrium under continuous estrogen stimulation⁴.

The key to successful clinical management of DUB is to recognize the responsible mechanism whether ovulatory or anovulatory. The medical options for initial management of DUB include antifibrinolytics, nonsteroidal anti-inflammatory drugs (NSAIDs), combined estrogen and progesterones or progesterones alone, high dose estrogens, gonadotropin-releasing hormone analogues, anti-gonadotropins such as danazol and levonorgestrel releasing intrauterine systems. A reliable drug for management of dysfunctional uterine bleeding should meet the requirements like the drug should be effective, convenient to take, cost should be low, have minimal side effects and should have long safety margin. Ormeloxifene (also known as Centchroman) is one of the selective estrogen receptor modulators⁵ (SERM) a class of medications which acts on the estrogen receptor (ER). It is a non-steroidal, non-hormonal oral contraceptive developed by Central Drug Research Institute, Lucknow⁶.

It mediates its effects by high affinity interaction with estrogen receptor, antagonizing the effect of estrogen on uterine and breast tissue and stimulating effect on vagina, bone, cardiovascular system and central nervous system³. Very few studies are available on ormeloxifene for the treatment of dysfunctional uterine bleeding. In this era of organ conservation ormeloxifene can serve as a good alternative to hysterectomy. With this background, the present study was done to evaluate the efficacy and safety of ormeloxifene in the management of DUB.

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MATERIAL AND METHODS

The study was conducted in the department of Obstetrics and Gynaecology, Rajendra Institute of Medical Sciences, Ranchi from 1st April, 2015 to 30th September, 2016 after taking approval from the ethical committee. It was a prospective clinical study of 24 weeks duration on 75 women with dysfunctional uterine bleeding.

A thorough evaluation was done which included a detailed history, physical examination general and systemic, lab investigations, ultrasound (both trans-abdominal and trans-vaginal), and endometrial aspiration biopsy to confirm the inclusion and exclusion criteria.

Inclusion criteria consisted of women aged between 25 to 49 years, with the diagnosis of DUB with cycle length of 21 to 35 days and who agreed to comply with study requirements like keeping of monthly log of vaginal bleeding, reporting of side effects of ormeloxifene, having ultrasound examinations and endometrial biopsy during the study period and follow up visits.

Exclusion criteria included any obvious pelvic pathology, malignancies, coagulopathies, haemoglobin less than 9 g/dl, any hypersensitivity to the drug, use of IUCD and COC. Then a written informed consent was taken after explaining the procedure, advantages and its consequences in their own language.

75 Patients meeting the inclusion criteria were treated with Ormeloxifene 60 mg tablet twice a week for first 12 weeks and then once a week for next 12 weeks. Treatment schedule was continued irrespective of menstrual periods. The patients were advised to come for follow up at 4th, 8th, 12th and 24th weeks of treatment initiation or earlier if required for aggravation of symptoms or any other adverse effects. Pictorial blood loss assessment chart (PBAC)⁷ was used to measure the menstrual blood loss. PBAC score of greater

than or equal to 100 which indicated a menstrual blood loss greater than or equal to 80 ml was considered diagnostic of menorrhagia. Haemoglobin level in g/dl, endometrial thickness in mm by trans-vaginal sonography, scoring of dysmenorrhea by Visual Analog Scale (VAS) was done at the beginning of the treatment, and then at 12th and 24th weeks of the study. Subjective assessment of symptoms and side-effects was done by interviewing the patient at each follow-up at the end of 4th, 8th, 12th, and 24th weeks of treatment.

Statistical methodology

Predesigned case record forms were used for collecting the data obtained from pre-treatment baseline cycle and post treatment cycle with ormeloxifene at 24th week which served the purpose of source data verification document. The data was compiled and subjected to statistical analysis using statistical package for social sciences (SPSS Inc, Version 20.0). Paired T Test and a Wilcoxon Signed Rank Test were used to see the effect of drug. 5% level of significance was considered for these tests. Data pertaining to the degrees of dysmenorrhea and subjective assessment of symptoms were first converted on Likert Scale and then analyzed by paired T test.

RESULTS

Figure 1 show details of patients recruited in study and loss during follow up. Nine patients were lost to follow-up during the entire course of treatment. Three patients opted for hysterectomy. During the final analysis of the data at the end of 24 weeks, these 12 cases were excluded from the study.

Patient profile

The mean age of patients was found to be 39.87 years (Graph 1). The mean parity was 3.07. Maximum patients (49.33%) presented with menorrhagia (Graph 2) with a mean duration of 8.6 months. Among the 75 patients included in the study 86.7% had a normal size uterus. The mean endometrial

| Sl. No | PBAC score | Menstrual blood flow | Pre-treatment | | 12 weeks | | 24 weeks | |
|--------|------------|----------------------|---------------|-------|-----------|-------|-----------|-------|
| | | | No (n=63) | % | No (n=63) | % | No (n=63) | % |
| 1. | 0 | Nil | 0 | 0 | 10 | 15.87 | 17 | 26.98 |
| 2. | 0-10 | Scanty | 0 | 0 | 0 | 0 | 2 | 3.17 |
| 3. | 10-100 | Moderate | 0 | 0 | 26 | 41.27 | 31 | 49.21 |
| 4. | 100-300 | Heavy | 32 | 50.79 | 21 | 33.33 | 7 | 11.11 |
| 5. | >300 | Very heavy | 31 | 49.21 | 6 | 9.52 | 6 | 9.52 |
| | | Total | 63 | | 63 | | 63 | |

Table-1: Assessment of blood loss by PBAC Score

| Sl. No | Duration | Median (n=63) | Range | P value |
|--------|---------------|---------------|---------|------------------------|
| 1. | Pre-treatment | 265 | 121-723 | <0.001 (z = -6.901) |
| 2. | 12 weeks | 83 | 0-602 | |
| 3. | 24 weeks | 27 | 0-559 | |

Table-2: Comparison of median PBAC score between pre-treatment level and post treatment level at 24 weeks

| Sl. No | Duration | Mean (n=63) | SD | 95% CI | P value |
|--------|---------------|-------------|------|-------------|---------------------|
| 1. | Pre-treatment | 11.81 | 0.62 | 3.668-4.681 | <0.001 (t=16.47) |
| 2. | 24 weeks | 7.63 | 2.20 | | |

Table-3: Comparison of mean endometrial thickness (mm) between the pre-treatment level and post treatment level at 24 weeks.

| S. No | Duration | Mean (n=63) | SD | 95% CI | P value |
|-------|---------------|-------------|------|----------------|-----------------------|
| 1. | Pre-treatment | 9.15 | 0.13 | -1.395- -1.017 | <0.001 (t= -12.74) |
| 2. | 24 weeks | 10.36 | 0.77 | | |

Table-4: Mean haemoglobin level (g/dl) before treatment and after treatment at 24 weeks.

| S. No | Subjective assessment of symptoms | 4 weeks (n=63) | | 8 weeks (n=63) | | 12 weeks (n=63) | | 24 weeks (n=63) | |
|-------|-----------------------------------|----------------|-------|----------------|-------|-----------------|-------|-----------------|-------|
| | | No | % | No | % | No | % | No | % |
| 1. | No Improvement | 17 | 26.98 | 15 | 23.81 | 13 | 20.63 | 12 | 19.05 |
| 2. | Mild Improvement | 40 | 63.49 | 23 | 36.51 | 14 | 22.22 | 3 | 4.76 |
| 3. | Marked Improvement | 6 | 9.52 | 25 | 39.68 | 36 | 57.14 | 48 | 76.19 |
| 4. | Aggravation of Symptoms | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Total | 63 | | 63 | | 63 | | 63 | |

Table-5: Subjective assessment of symptoms

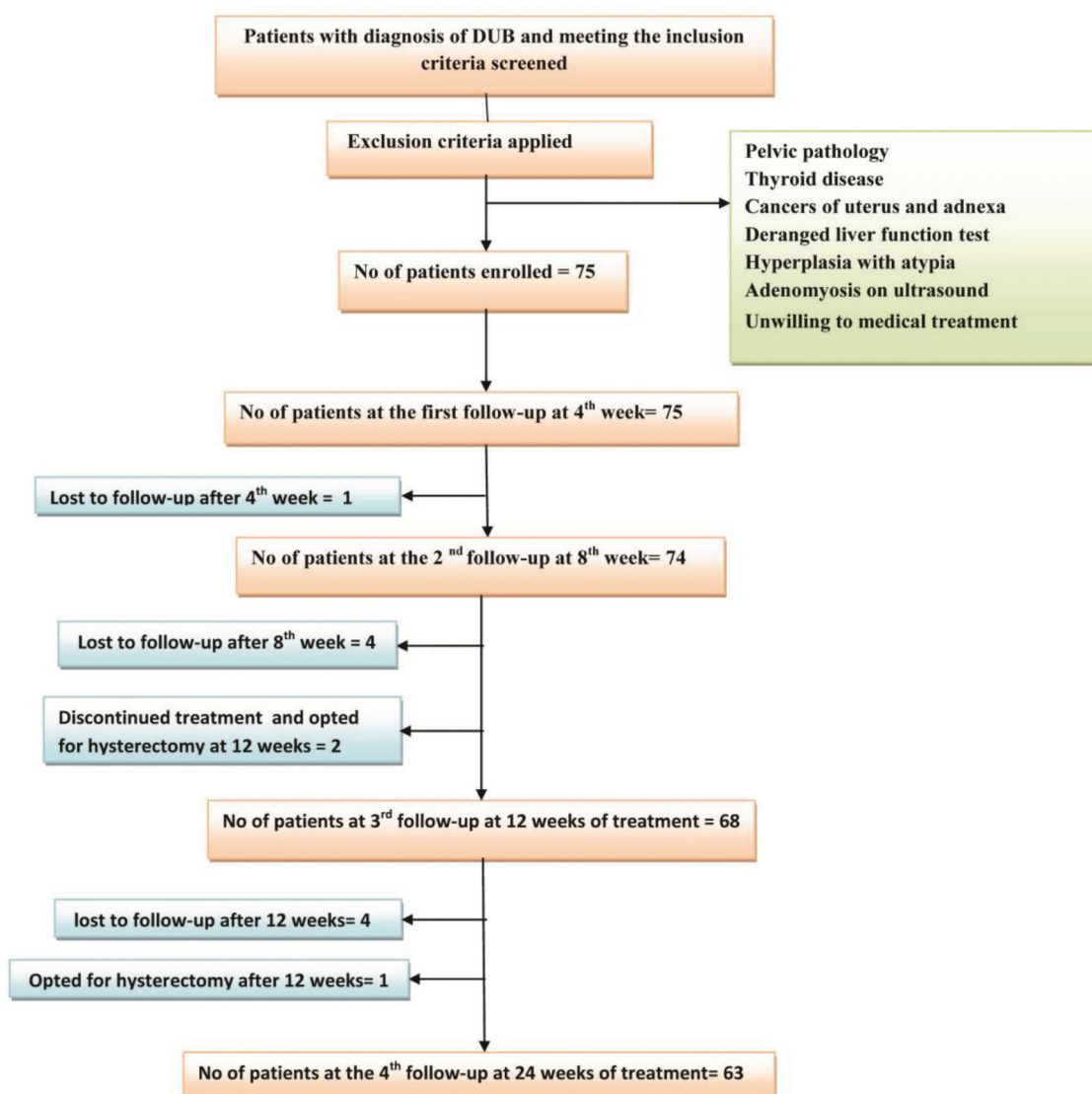


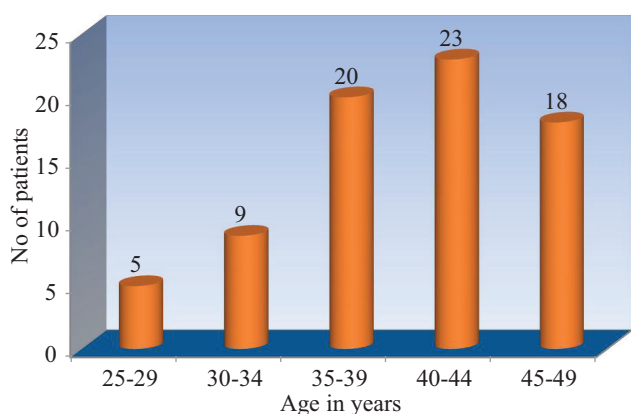
Figure-1: Disposition tree showing details of the patients recruited in the study and loss in follow up

thickness at the beginning of treatment was 11.81 mm.

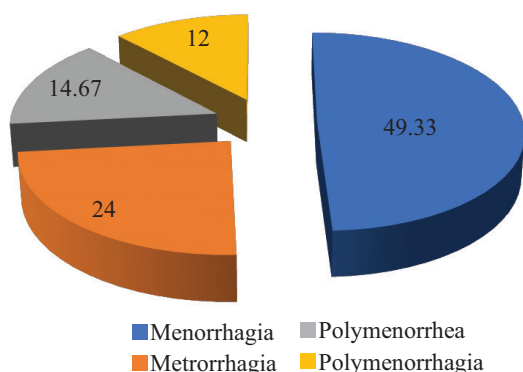
Reduction of menorrhagia by PBAC (Pictorial Blood Assessment Chart) score:

Before starting the treatment of DUB with ormeloxifene, 50.79% patients in the study group had a PBAC score more than 100 indicating heavy menstrual blood flow, and rest 49.21% patients had PBAC score more than 300 indicating

very heavy blood flow (Table 1). There was marked reduction in the median PBAC score from its pre-treatment level of 265 (range 121-723) to 83 at the end of 12 weeks and further to 27 (range 0-559) at the end of 24 weeks, ($P < 0.001$) (Table 2). Thus there was 89.81% reduction in the menstrual blood loss after 6 months of therapy. Ormeloxifene significantly reduced menstrual blood loss in 79.36% patients. 26.98%



Graph-1: Age



Graph-2: Presenting complaint

had amenorrhea, and 52.38% patients had regular, scant to moderate blood loss with treatment and 20.63% patients were still in the menorrhagic range.

Endometrial thickness

Table 3 shows that the mean endometrial thickness at the beginning of treatment was 11.81 mm, which was reduced to 7.63mm at 24 weeks showing a marked reduction of 4.18 mm (35.39%) from its pre-treatment level. Amongst the 63 patients who completed the treatment with ormeloxifene for 24 weeks, one patient showed no decrease in endometrial thickness, 5 patients showed mild decrease and 57 patients showed marked decrease in endometrial thickness. Increase in endometrial thickness was seen in 1 patient at the end of 12 weeks but the patient was later on lost to follow-up.

Haemoglobin level

Table 4 shows that mean haemoglobin level before starting the treatment was 9.15 g/dl which reached 10.36 g/dl ($P < 0.001$) by the end of 24 weeks showing an increase of 1.21 g/dl (13.22%). The increase in haemoglobin level was probably due to control of heavy menstrual bleeding.

Relief of dysmenorrhea:

Table 5 shows subjective assessment of symptoms. Ormeloxifene relieved dysmenorrhea. 76.19% patients showed marked improvement, and 4.76% showed mild improvement in symptoms, but 19.05% were not satisfied as determined by the subjective assessment of symptoms.

Side-effects

Table 6 shows adverse effects of ormeloxifene which included gastric upset and vague abdominal pain in 4.76%

patients and headache in 3.17% patients. Amenorrhea in 26.98% patients though discussed with side effects actually served as a beneficial effect.

DISCUSSION

Dysfunctional uterine bleeding occurs more commonly in the first five years after menarche and during premenopausal period, but it can occur during reproductive period. For women with DUB who wish to retain fertility, pharmacological approaches are the only currently available options. Pharmacological agents such as NSAIDs, oral contraceptive pills, progesterones, danazol, GnRH agonists and anti-fibrinolytic drugs - all reduce menstrual blood loss, however the assets are limited to the duration of treatment. In our study we have analyzed the efficacy of ormeloxifene in patients with dysfunctional uterine bleeding and our results suggested that there was a significant reduction of menstrual blood loss.

The median PBAC score⁷ was reduced from 265 to 27 ($P < 0.001$), showing a reduction of 89.81% after 24 weeks in the present study. Biswas S. C et al (2004)⁸ found that the median PBAC score was reduced from 272 to 107.8 at the end of 24 weeks of treatment, showing a reduction of only 60.37% in the menstrual blood flow. Kriplani A et al (2009)⁹ conducted a pilot study in which the median PBAC score was significantly reduced from 388 to 5 at 4 months with 98.7% reduction ($P < 0.001$). Bhattacharyya T.K et al (2010)¹⁰ in his study, where 180 DUB cases in three groups were administered ormeloxifene, norethisterone and iron, concluded a marked reduction in mean PBAC score from 108.70 to 62.48 in the ormeloxifene group, but in norethisterone group it was reduced only to 94.07 from 113.87. Shrivage J et al (2011)¹¹ found an 85.7% reduction in menstrual blood loss (mean PBAC score from 262 to 73) after 3 months of therapy as compared to 54.67% with medroxy-progesterone. In another comparative study by Agarwal N et al (2013)¹³, there was 61.1% reduction in menstrual blood loss (mean PBAC score from 216 to 84) in ormeloxifene group compared to 26.7% with norethisterone (mean PBAC score from 232 to 170). In the study by Komaram R et al (2013)¹⁴ the median PBAC score was reduced only to 104.5 from its pre-treatment level of 253. Thus, from all these studies it was observed that ormeloxifene significantly reduces menstrual blood loss in DUB.

The mean endometrial thickness at the beginning of treatment in our study was 11.81 mm, which was reduced to 7.63 mm at the end of 24 weeks and the net reduction was 4.18 mm (35.39%) ($P < 0.001$). Similar results are reported in other studies. Biswas S.C et al (2004)⁸ found reduction of endometrial thickness from 11.4 mm pre-treatment to 7.8mm at the end of 24 weeks of therapy ($P < 0.001$). Kriplani A et al (2009)⁹ documented in their study a marked reduction in endometrial thickness after 4 months of therapy. In the study by Bhattacharyya T.K et al (2010)¹⁰, the pre and post treatment values differed significantly in all the three groups treated with ormeloxifene, norethisterone and iron respectively. In the study by Shrivage J et al (2011)¹¹ the

reduction in mean endometrial thickness was more with ormeloxifene as compared to medroxy-progesterone. In study by Agarwal N et al (2013)¹², the mean pre-treatment endometrial thickness was 11.35 mm which was reduced to 9.4 mm after 3 months of therapy and to 8.13 mm after 6 months. This was statistically not significant.

In our study the mean haemoglobin level at the end of 24 weeks after treatment with ormeloxifene was 10.36 g/dl compared to the pre-treatment level of 9.15 g/dl. The increase in haemoglobin was 1.21 g/dl (13.22%) at the end of 24 weeks ($P < 0.001$). Similar increase in Hb level was found in other studies^{8, 9}. Bhattacharyya T.K et al (2010)¹⁰ concluded increased Hb level in all three groups but maximum in patients who were given ormeloxifene followed by norethisterone and then iron. In study by Agarwal N et al (2013)¹³, the increase in mean haemoglobin concentration was more in ormeloxifene group than norethisterone group. 64% patients were relieved of dysmenorrhea at the end of 24 weeks in the present study ($P < 0.001$) which is almost similar to 66.7% in study by Kriplani A et al (2009)⁹. In the present study, marked improvement in symptoms was seen in 76.19% of patients. This is again similar to 78% improvement in menorrhagia reported by Kriplani A et al (2009)⁹ and 85.7% reported by Biswas S. C et al (2004)⁸.

Side effects, abdominal pain (4.76%) and headache (3.17%) were not severe enough to interfere with the compliance. Slightly more side effects were demonstrated in study by Kriplani A et al (2009)⁹ gastric upset (7.1%), vague abdominal pain and headache (4.8% cases). Amenorrhea occurred in 42.9% patients at the end of the treatment period of 4 months. No case of ovarian enlargement was found in our study as compared to the study by Kriplani A et al (2009)⁹ where 7.1% patients reported with ovarian enlargement after treatment with ormeloxifene. Biswas S.C et al (2004)⁸ concluded that ormeloxifene has very few side effects, limited to mild gastrointestinal symptoms (2.1%), weight gain (1.16%) and giddiness (1.17%). Thus there seems to be enough evidence to consider ormeloxifene as an ideal drug for the pharmacological management of dysfunctional uterine bleeding.

Lack of response and loss to follow up

In the present study, 19.05% patients had no improvement in symptoms after treatment for 24 weeks. Also 20.63% patients reported with a PBAC score more than 100 even after treatment. This lack of response could be attributed to some pathology which could not be ruled at the time of enrolment of patients with DUB in the study, or non-compliance with the drug dosing schedule, some metabolic disorders in the patients which could interfere with the metabolism and bioavailability of the drug, or simply a genetic refractoriness to the drug.

Out of the 9 patients lost to follow-up, 1 had no reduction in the PBAC Score, 4 had non-significant reduction in menstrual bleeding. Three patients opted for hysterectomy even before completing the entire treatment, 2 at the end of 12 weeks, and 1 later on. As RIMS is a tertiary health centre, a few cases

lost to follow-up could be attributed to the outstation patients coming from remote areas to seek treatment. Moreover some women who had completed their family, especially in the premenopausal and perimenopausal age group were not really convinced with medical treatment of heavy menstrual blood flow and readily opted for hysterectomy leading to their drop out from the study.

CONCLUSION

With its excellent safety profile, easy dosage schedule and proved efficiency in the treatment of dysfunctional uterine bleeding, ormeloxifene definitely gets an upper hand as compared to other treatment options like progesterones, combined oral contraceptive pills etc. in the pharmacological management of dysfunctional uterine bleeding. Ormeloxifene has a significant effect in reducing the endometrial thickness, decreasing the amount of menstrual blood loss, reducing dysmenorrhea and thereby improving the general condition of the patient as evident by the significant increase in mean haemoglobin level in the present study. Ormeloxifene is definitely a better alternative to hysterectomy in women who wish to avoid surgeries and maintain their reproductive functions. Considering its effectiveness, good patient acceptability, compliance, low cost and minimal side effects, ormeloxifene has a very good prospect in the management of dysfunctional uterine bleeding.

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