

Ormeloxifene: The Perfect Alternative for the First-line Management of Abnormal Uterine Bleeding

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ABSTRACT

Aim: The aim of this work was to study the role of Ormeloxifene in the management of abnormal uterine bleeding (AUB).

Methods: Fifty-one patients with heavy menstrual bleeding with ages between 18 and 50 years were included in the study. The women with post-menopausal bleeding, fibroids, uterus size of more than 8 weeks, polycystic ovarian syndrome (PCOS), and ovarian cysts were excluded. Ormeloxifene (60 mg) twice a week for 12 weeks and then once a week for the next 12 weeks was given to every patient in the study group. The outcome was assessed by the pictorial blood assessment chart (PBAC) score, hemoglobin (HB) level, and endometrial thickness.

Results: About 88.24% of patients responded well to treatment as depicted by a significant reduction in the PBAC score to a level <100. The mean PBAC score decreased linearly from 354 to 40 at the end of 24 weeks of treatment. Mean endometrial thickness reduced from 8.25 to 6.01. The mean level of hemoglobin level increased from 11.41 to 11.86. *P*-value of all the parameters were <0.05 and hence statistically significant.

Conclusion: Ormeloxifene can be used as a first-line drug for the management of AUB.

Keywords: Abnormal uterine bleeding, Centchroman contraception, Ormeloxifene pictorial blood assessment chart Score

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INTRODUCTION

Abnormal uterine bleeding is defined as the variation in regularity, frequency, duration, and amount of blood loss from the normal menstrual cycle.¹ It is one of the most frequent reasons to visit a gynecologist.² The prevalence of AUB is around 15% in the general population and it increases with age, being as high as 70% in perimenopausal females.³ It affects nearly 33% of women at least once during their lifetime.⁴ Untreated long anovulatory cycle may result in hyperplasia and endometrial cancer.⁵ Thus, it clearly reflects a negative impact on physical, financial, mental, and social aspects of life.⁴ The treatment is decided on the basis of presentation and severity of bleeding, age of the person, etiology, requirement for contraception, and the availability of treatment modality at the hospital.⁴ The available medical treatment options are oral or intramuscular progesterone, levonorgestrel intrauterine system (LNG-IUS), anti-fibrinolytic agents like tranexamic acid and ethamsylate, gonadotropins releasing hormone, and combined oral contraceptives pills. Each treatment choice has its own advantages and indications to use but may be associated with disadvantages like high cost and serious side effects.^{6,7} Prolonged use of daily oral contraceptives has problems like poor compliance and the risk of side effects like the life-threatening thromboembolism.^{1,4} The role of LNG-IUS in AUB is now well-established and is considered to be the foremost option in medical management, but its high cost limits its ubiquitous use.⁸ Surgical treatment often resorted in case of failure of medical management. More than 50% of hysterectomies done in our country are because of AUB and among these half have no structural abnormality in the post-surgical specimen.³

Ormeloxifene or Centchroman is a selective estrogen receptor modulator, which is developed in CDRI Lucknow as a contraceptive by the name of Saheli.⁹ It is a non-hormonal, non-steroidal, once-a-week oral pill, which makes it more compliant, with estrogenic

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effects on bones, vagina, and blood and anti-estrogenic effects on the uterus and breast.^{9,10} It inhibits the proliferation of endometrial lining and decreases endometrial thickness hence leading to decreased blood loss and ultimately an increase in Hb level.⁹ The best therapy, especially in perimenopausal women, is one that does not stimulate the uterine endometrium, has no effect on bone mineral density, has no derangement of lipid profile or detrimental effect on the cardiovascular system, and has no risk of breast cancer. Ormeloxifene fulfills all these requirements.¹⁰ Hence, this study was carried out to study the utility and safety profile of Ormeloxifene as a first-line treatment option in the management of AUB.

METHODS

This prospective study was carried out in the Department of Obstetrics and Gynaecology, Kasturba Hospital, New Delhi, India on 51 women with AUB after clearance from the institutional ethics committee. The women with post-menopausal bleeding, puberty menorrhagia, bleeding associated with systemic illness, infertility, uterus size of more than 8 weeks, PCOD or ovarian cyst, and structural cause of AUB as fibroid >3 cm, and uterine polyp

Table 1: Different parameters among the study cohort before and after treatment

Parameters	Pretreatment	After 3 months	After 6 months	p-value
Days of flow	7.725	4	1.8	<0.001
Cycle length	30	31	46	<0.001
Amenorrhoea	0%	8%	49%	<0.001
Dysmenorrhoea (present)	43%	5.8%	2%	<0.001
Passage of clots (present)	68%	3.9%	1.9%	<0.001
Pbac score	354	112	40	<0.001
Hemoglobin level	11.41	11.55	11.86	<0.01
Endometrial thickness	8.25		6.01	<0.001

or any suspicion for carcinoma uterus or endometrial atypia were excluded from the study.

Detailed history and examination were performed including cycle length, duration of bleeding, after informed consent, and the PBAC score was calculated for each woman. All relevant investigations were performed including ultrasonography and histopathology of the endometrium by endometrial aspiration in the pre-menstrual phase. Ormeloxifene (60 mg) twice a week for 12 weeks followed by once a week for the next 12 weeks was given to them. Patients were asked to keep records of their menstrual cycles, number of days of bleeding, and amount of mean blood loss. Follow-ups were made at 1, 3, and 6 months of therapy to assess the improvement of symptoms. At each visit number of bleeding days, cycle length, the PBAC score, the passage of clots, flooding, dysmenorrhoea, and any side effects were noted in detail. Hemoglobin and ultrasonography were repeated after 6 months of treatment.

RESULTS

The success rate with therapy was 88% and the only side effect seen in the present study was nausea seen in 12% of patients during the course of treatment. There was a significant improvement in all the parameters like the PBAC score, cycle length, duration of bleeding per cycle, and passage of clots (Table 1). The improvement of dysmenorrhoea seen in 43 to 2% was an added benefit in these women. This was also corroborated by objective improvement in hemoglobin levels and endometrial thickness on ultrasonography, at the end of treatment.

DISCUSSION

Medical therapy for heavy menstrual bleeding should aim to relieve symptoms, improve quality of life, and avert surgical management. Ormeloxifene had beneficial effects on bleeding parameters when it was used as a contraceptive. This led to trials of its use in AUB and now it has been approved by the Indian Drug Regulatory Authorities for this indication.² Ormeloxifene has the benefit of an easy dosage of once a week, very few side effects, and being non-steroidal in nature.

Ormeloxifene resulted in improvement of all parameters of blood loss in AUB including number of days of bleeding, number of

pads soaked per day and the passage of clots, and the PBAC score. The mean PBAC score reduced from 354 at the time of enrollment to 112 at the end of third month and 40 at the end of sixth month. The similar was reported by Kanchan and Prajwala¹¹ in a study on the effect of Ormeloxifene in AUB, where pre- and post-treatment PBAC scores at 3 and 6 months follow-up were 280, 65, and 32, respectively.

The mean duration of bleeding was 7.725 days at enrollment, which was reduced linearly to 4.0 on the third month and further reduced to 1.8 after the sixth month of treatment. At the time of enrollment, 35 (69%) patients out of 51 gave history of passage of clots which improved in most of the women except 2%. Only one patient gave history of the passage of clots after 6 months of treatment.

Godha et al.¹² conducted a comparative study between Ormeloxifene and medroxyprogesterone acetate (MPA). All parameters were better controlled with Ormeloxifene as compared to MPA. The median PBAC score was reduced in 79.4% by Ormeloxifene as compared to 75% by MPA. The mean duration of bleeding was reduced to 4.8 days from 9 with Ormeloxifene as compared to MPA where it was 5 days from 8.7. The mean hemoglobin increased from 8.6 to 9.8 gm% with Ormeloxifene vs 8.7–9.9 gm% with MPA; the reduction in endometrial thickness was observed from 7.7 to 6.8 mm with Ormeloxifene and from 7.4 to 6.9 mm with MPA.

In a double-blind study by Shrivage et al.,¹³ Ormeloxifene was found to be significantly more effective in reducing menorrhagia (87.71% of women) as compared to MPA (where it was effective in 54.76%) in the treatment of dysfunctional uterine bleeding (DUB) (p-value: 0.0205).

Amenorrhoea is frequently observed with Ormeloxifene and is the desired outcome especially in perimenopausal women. Amenorrhoea was seen in four patients (8%) after treatment for 3 months and in 25 patients (49%) after 6 months of treatment. In the study of Shrivage et al.,¹³ amenorrhoea developed in 56% of patients at the end of 6 months, which is comparable to our study.

Improvement in dysmenorrhoea is also an added benefit with Ormeloxifene therapy as seen in the study where out of 22 only 1 patient reported dysmenorrhoea after treatment. In the study by Kriplani et al.,¹⁴ improvements in dysmenorrhoea with a reduction in the visual analog scale (VAS) score from 6.3 to 1.5 was observed on treatment with Ormeloxifene.

The mean hemoglobin also improved in the present study from 11.41 to 11.55 after taking treatment for 3 months and further increased to 11.86 after 6 months of treatment. A comparative study of Ormeloxifene and norethisterone was conducted by Shahab et al.¹⁵ in 300 patients of DUB. The PBAC score improvement was seen in 87.5% along with an increment of hemoglobin by 1%.

The mean endometrial thickness was 8.25 mm at the beginning of the study, and it was 6.01 after 6 months of treatment. There is statistically significant reduction in endometrial thickness.

In a study conducted by Devi et al.,¹⁶ the mean endometrial thickness reduced from 11 to 8.21 mm after treatment of DUB by Ormeloxifene.

In a study by Bhattacharyya and Banerji,¹⁷ Ormeloxifene was compared with norethisterone in women with DUB, and it was found superior in terms of marked improvement in symptoms (81.67% vs 35%), increase in hemoglobin, reduction in the PBAC

score, and passage of clots. They recommended it as the medicine of choice, especially in women who have completed their family.

CONCLUSION AND CLINICAL SIGNIFICANCE

Ormeloxifene is an extremely safe and effective drug for the medical management of AUB with an excellent safety profile. Also, it is cost-effective with once a week dose schedule of the drug, which results in good compliance. Thus, the oral Centchroman may be used as a first-line of medical management of AUB especially for patients who wish to preserve fertility and in whom hormonal treatment is not recommended and/or contraindicated. It is especially a more suitable choice in perimenopausal women to tide over that period and in whom amenorrhoea is welcomed, in patients who are at high risk of surgery, and also in young women who desire contraception.

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