

Evaluation of the efficacy of Ormeloxifene in DUB Sanghmitra Kumari¹, Sushma Singh², Ishmat Khanam³, Prem Sagar Chaudhary⁴

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Abstract

Background: Dysfunctional uterine bleeding (DUB) is a common gynaecological disorder that usually ends up in hysterectomy and causes psychological and physiological stress. Medical management with hormones and NSAIDS has inherited side effects. Ormeloxifene, a selective estrogen receptor modulator, is emerging as a safe and effective agent for dysfunctional uterine bleeding. The objective of the study was to evaluate the role of ormeloxifene in medical management of dysfunctional uterine bleeding. **Methods:** 60 patients, on whom diagnosis of dysfunctional uterine bleeding was made, were included in the study. Patients were given ormeloxifene 60mg. The primary outcome measures were menstrual blood loss (assessed by pictorial blood assessment chart score), hemoglobin concentration and endometrial thickness. The secondary outcome measures were acceptability and side effects of ormeloxifene. **Results:** There was a significant reduction in mean PBAC after treatment. The mean hemoglobin concentration increased significantly. The mean pretreatment endometrial thickness decreased significantly after treatment with ormeloxifene ($p < 0.05$). 76.7% of the women showed marked subjective improvement in symptoms. The most common side effect reported was amenorrhea (13.3%). **Conclusion:** Ormeloxifene can be considered as an effective and safe therapeutic option for the medical management of dysfunctional uterine bleeding.

Keywords: DUB, Dysfunctional uterine bleeding, Ormeloxifene, SERM

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Introduction

Disorders of menstruation account for the most common reason for a gynaecological consultation among women of reproductive age group DUB is one such condition most commonly affecting women from extremes of reproductive age group[1]. Dysfunction uterine bleeding is abnormal uterine bleeding during menstrual cycle in the absence of organic pelvic pathology[2]. Blood loss more than 80 ml during the menstrual cycle affects upto 30% of reproductive aged women and accounts for 70% of all gynaecologic visits by perimenopausal women[4]. Dysfunction of HPO axis leads to anovulatory DUB in this age group with major implications on quality of life and health care costs[3]. Though hysterectomy is a suitable treatment modality, long term complication like premature ovarian insufficiency, urinary dysfunction has raised concerns[4]. Hence a majority of women are looking forward to an effective conservative medical therapy. Various pharmacological agents used in treatment of DUB are combined oral, progestogens, danazol, Gn RH agonists, PG synthetase inhibitors, anti-fibrinolytics and ethamsylate [5]. A reliable drug should meet requirements such as drug should be effective, easy to take, minimal cost and side effects

and have longest safety margin.[5]. Norethisterone is a progestogen widely used for treating DUB. Since it is a hormonal preparation, side effects such as stroke, heart disease, breast cancer, dementia, fluid retention, break through bleeding, spotting has been reported. As the name suggests SERM is a class of drug which has estrogenic action in some parts of the body and anti estrogenic in some parts.[6]. It has anti estrogenic effect on uterine and breast tissue and estrogenic effect on vagina, CVS and CNS. One of the drug that belongs to this group is Ormeloxifene. It is also popularly known as centchroman, which is a non-steroidal, non- hormonal oral contraceptive taken once in a week when used as contraceptive[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]. Since its usage from early 1990's in India, as a contraceptive medication, it has also been useful in treatment of DUB with a convenience in dosing pattern improving patient compliance.[9]. Nausea, headache, weight gain, delayed period are few adverse effect noted on taking the drug. Since it has less uterine side effects, prevents bone loss, no risk of breast cancer, has positive effect on lipids and CVS and maintains cognitive function of brain, it is the ideal drug to be used during perimenopausal age group[9]. 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.

Material and Methods

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This prospective, unicentric, study was conducted in the department of Obstetrics and Gynaecology, Vardhman Institute of Medical Sciences, Pawapuri, Nalanda, Bihar. The study was approved by the institutional research and ethical committee. This study was conducted over a period of 2 years from March 2019 to February 2020. An informed and written consent was obtained from all the participating subjects prior to the commencement of the study. The study sample consisted of 60 women attending our OPD 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

Peri-menopausal women
Diagnosed for DUB.

Exclusion criteria

Haemoglobin less than 9 g/dl,

Hypersensitivity

Use of IUCD

Any obvious pathology/ malignancies/ coagulopathies.

These peri-menopausal women with complaints of excessive bleeding during cycles, women with heavy menstrual bleeding were subjected to detailed history taking and physical examination, clinical examination includes per speculum, per vaginal examination to exclude organic pelvic pathology. Investigation like CBC, thyroid profile, coagulation profile, pap smear, pelvic USG for ET and to rule out pelvic pathology were done. After taking informed consent the subjects were treated with 60mg Ormeloxifene. Menstrual blood loss was measured by pictorial blood loss chart, endometrial thickness measured using ultrasound, hemoglobin measure by laboratory method. In order to standardize the PBAC, all subjects candidate for the study were instructed to use same brand of sanitary napkin. PBAC score was calculated by taking in to account number of pads used, number and size of clots passed, soakage of pads. Table-1

Table 1: PBAC score.

	Level of soiling	Score
Pads	Light	1
	Moderate	5
	Saturated	20
Clots	Size of a rupee coin or smaller	1
	Larger than a rupee coin	5

Statistical analysis

The data was tabulated in Microsoft Excel and was subjected to statistical analysis using SPSS Software Version 10.

Results

Table 2: Clinical profile of patients

Clinical profile of patients	Clinical parameter	Mean (range)
1	Age	34 years (21-50years)
2	Parity	3 (1-6)
3	Duration of symptoms in months	9.4 months(5-22)

Menstrual blood loss was assessed by PBAC and calculated at beginning, then at 3 months and at 6 months of treatment. The median pre-treatment PBAC score was 316 and reduced to 52 at six months (P<0.05). The mean hemoglobin of the patients at the start of treatment was 8.4g/dl. After six month, the mean HB was 9.8g/dl.

60 women with the diagnosis of DUB were included in the present study. The mean age of patients was 34 years with a range of 21-50 years. The mean parity was 3 and the mean duration of symptoms was 9.4 months (5-22 months range).

There was a significant increase in mean HB concentration with a rise of 1.4g/dl after 6 months of therapy with ormeloxifene (P<0.05). The pre and post treatment endometrial thickness was 10.8mm and 8.1 mm respectively with a significant decrease of 2.7mm (P<0.05).

Table 3: Out come of the study after 6 months.

Parameter	Pretreatment	Posttreatment	P value
Mean PBAC	316	52	<0.05
Mean HB (g/dl)	8.4	9.8	<0.05
Mean endometrial thickness (mm)	10.8	8.1	<0.05

Subjective improvement in the signs and symptoms of DUB was analyzed from patients. 23 patients (76.7%) had marked improvement in their symptoms, 4 (13.3%) patients had mild improvement in their

symptoms. 1 (3.3%) patient had aggravation of her symptoms for which her treatment was changed.

Table 4: Subjective assessment of symptoms

Subjective improvement	Number	Percentage
No improvement	2	6.7
Mild improvement	4	13.3
Marked improvement	23	76.7
Aggravation of symptoms	1	3.3
Total	30	100

Amenorrhea was observed in 4 (13.3%) patients and hypo menorrhea in 2 (6.66%) patients. Mild gastric upset, abdominal pain, nausea was observed in few patients and was not statistically significant.

Discussion

The traditional treatment for menorrhagia is Hysterectomy. While hysterectomy offers an effective cure, it is suitable only for those, who have no further wish to conceive. The procedure involves major surgery with significant postoperative morbidity. Endometrial ablation techniques offer an alternative surgical treatment option with significantly reduced postoperative morbidity. But again may be

unsuitable for women wishing to retain their menstrual and reproductive function, moreover this requires technical expertise, which is not routinely available. Ormeloxifene is a benzopyran SERM, which blocks the cytosol receptors by its competitive binding over estradiol. It has mild estrogenic activity on vagina, bone mineral density, CNS and lipids. The drug is primarily a potent estrogen antagonist but also has a weak agonist activity in selected tissues. The drug demonstrates a suppressive or a stimulatory effect on gonadotropin release. Such anti estrogens are expected to exert contraceptive effects. It normalizes the bleeding from uterine cavity

by regularizing the expression of estrogen receptors on endometrium and hence the drug was tried in patients with DUB. It is also a potent antiproliferative agent in Breast tissue. Additional benefit of this drug is that it decreases total cholesterol, LDL cholesterol by about 20 to 30%.

Conclusion

The ease of administration of the drug ormeloxifene facilitates patients compliance and acceptability and marked relief of symptoms results in higher patient satisfaction. Therefore, ormeloxifene should be the drug of choice in patients with DUB.

References

1. Bravender T, Emans SJ. Menstrual disorders. Dysfunctional uterine bleeding. *Pediatr Clin North Am.* 2015; 46(3):545-53.
2. Hoffman BL, Schorge JO, Schaffer JI, Halvorson M, Bradshaw KD, Gray F (Eds): Abnormal uterine Bleeding. In: Schorge JD editor. *Williams Gynaecology*, 2nd Ed. New York: McGraw-Hill, 2003, 219p.
3. Frick KD, Clark MA, Steinwachs DM. STOP-DUB Research Group. Financial and quality-of-life burden of dysfunctional uterine bleeding among women agreeing to obtain surgical treatment. *Women's Health Issues.* 2009; 19(1):70-8.
4. Calvert KL. Review of Second Generation Endometrial Ablation Techniques. *Obs and Gynaecol.* 2002; VII(2):371-6.
5. Tandon Annu M, Goel I. The effect of ormeloxifene, as elective estrogen receptor modulator, on the biomarkers of the endometrial receptivity and the pinopode development and its relationship with the fertility and the infertility in Indian subjects" *Fertility and Sterility.* 2009; 91(6):2298-307.
6. Singh MM. Centchroman, a selective estrogen receptor modulator, as a contraceptive and for the management of hormone-related clinical disorders. *Medicinal Research Reviews.* 2001;21(4):302-47.
7. Higham JM, O' Brein PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *Br J Obstet Gynaecol.* 1990; 97(8):734-9.
8. Dicker RC, Greenspan JR, Strauss LT. Complications of abdominal and vaginal hysterectomy among women of reproductive age in the United States. *American Journal of Obstetric and Gynecology.* 1982; 144:841-8.
9. Preston JT, Cameron IT, Adams EJ, Smith SK. Comparative study of tranexamic acid and norethisterone in the treatment of ovulatory menorrhagia. *British J Obstetrics Gynecology.* 1995; 102:401-86.
10. Kriplani A, Kulshrestha B, Agarwal N. Efficiency and safety of ormeloxifene in management of menorrhagia: a pilot study. *J Obstet Gynecol Res.* 2009; 35:746-52.
11. Dadich, S, Agarwal, M, Soni, R, Jain. Role of ormeloxifene in medical management of dysfunctional uterine bleeding. *Asian journal of Obs and Gynae Practice.* 2012; 6:28-31.
12. Dhananjay BS, Nanda SK. Role of sevista in management of uterine bleeding. *Journal of clinical diagnostic and Research.* 2013; 7(1):132-4.
13. Biswas SC, Saha SK. Ormeloxifene, A selective estrogen receptor modulator for treatment of dysfunctional menorrhagia. *Job stet Gynecol.* 2004; 54(1):56-9.
14. Anusyua B. Efficacy of a Selective Estrogen Receptor Modulator: 'Ormeloxifene' in Management of Dysfunctional Uterine Bleeding. *South Asian Federation of Obstetrics and Gynecology.* 2010; 2(3):207-11.

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