Research Article

A Study of Ormeloxifene in Case of Dysfunctional Uterine Bleeding

Grover S[1], Chhabra A[2], Bindu S[3]

[1]**Dr. Suparna Grover**
Assistant Professor
Obs & Gynae
Punjab Institute of Medical Sciences
Jalandhar, Punjab, India

[2]**Dr. Ajay Chhabra**
Assistant Professor
Medicine
Punjab Institute of Medical Sciences
Jalandhar, Punjab, India

[3]**Dr Bindu Sainath**
Professor, Obs & Gynae
Shri MP Shah Medical College
Jamnagar, Gujrat, India

Received: 02-01-2013
Revised: 10-04-2013
Accepted: 20-04-2013

Correspondence to:
Dr. Suparana Grover
drajaychhabra@gmail.com

ABSTRACT

Background: *Menorrhagia accounts for 12% of all gynaecology consultations and is one of the most common causes of iron deficiency anaemia in females after nutritional anaemia.*

Objectives: *To evaluate the efficacy and side effects of ormeloxifene in cases of dysfunctional uterine bleeding.*

Material and Methods: *30 women aged 28-46 years who attended the outpatient gynaecology department in a tertiary care hospital with complaint of heavy menstrual flow were recruited for the study. Two pre-treatment baseline cycles were compared to the treatment cycles of ormeloxifene. The main outcomes measured were menstrual blood, blood haemoglobin levels and endometrial thickness in proliferative phase as studied by TVS. Data thus collected was compared and analysed statistically.*

Results: *Total number of bleeding days per year decreased by 76%. Total no. of pads soiled per cycle decreased by 76.3%. All the patients reported disappearance of clots, 66.66% within 1 month of the treatment only. Dysmenorrhoea was relieved in 62.5% patients. Mean increase in Hb was 0.42g%.*

Conclusion: *Ormeloxifene is very effective in improving all the parameters of blood loss in DUB including the no. of days of bleeding, no. of pads soiled and the passage of clots. Ormeloxifene has a good patient acceptability and compliance due to its minimal side effects, low cost and simple dosage schedule. In the peri-menopausal age group, drug is protective against breast malignancy and osteoporosis. Ormeloxifene has the potential to be an effective treatment for DUB and should always be considered amongst the treatment options.*

Key words: *Dysfunctional uterine bleeding, menorrhagia, ormeloxifene*

Introduction

Menorrhagia is defined as cyclical bleeding at normal intervals which is excessive in amount (total blood loss greater than 80 ml) or duration (lasting longer than 7 days). [1] It affects 10-33% of women at some stage of their lives. About 5% of women aged 30-49 years consult their general practitioner with this problem which also accounts for 12% of all gynaecology referrals. [2] This gynaecological problem is one of the most common causes of iron deficiency anaemia in females after nutritional anaemia. Dysfunctional uterine bleeding (DUB) is defined as any condition of abnormal uterine bleeding in the absence of pregnancy, neoplasm, infection or other intrauterine lesion.[3] Such bleeding is often the result of endocrinological dysfunction and is associated with absence of ovulation in 80-85% cases. [4] The cause of DUB is usually related to one of the three hormone imbalance conditions: oestrogen breakthrough bleeding, oestrogen withdrawal bleeding and progesterone breakthrough bleeding. [4] A wide range of treatment modalities are available which include medical therapy and surgical interventions.

Pharmacological management can be hormonal or non-hormonal. Hormonal agents include oestrogens, progesterones, combination of the two, androgens, danazol, GnRH agonists and the latest SERMS (Selective Oestrogen Receptor Modulators). Non-hormonal drugs like NSAIDs, ethamsylate and anti-fibrinolytics have also been found to be highly effective. Medical management has always been the first therapeutic option to be tried and if it fails to show results, one can resort to surgical interventions. Hysterectomy should be the last resort in the management of DUB. Because of the morbidity associated with the surgical procedures, the RCOG recommends beginning with medical management before resorting to surgical interventions. [2] The latest of the pharmacological agents that have become available for the treatment of DUB are selective oestrogen receptor modulators. These are designer drugs which have an affinity to the oestrogen receptor and act like oestrogens in some tissues and have anti-oestrogenic effects in others. [6] Ormeloxifene is one such SERM which has shown anti-oestrogenic effect in the uterus that forms the pharmacological basis of using it in DUB. The SERMs are unique compounds that have attracted great interest because of their potential for the prevention and treatment of bone loss and menorrhagia, although apparently being oestrogen antagonists in breast. The recent identification of 2 types of oestrogen receptor ERα and ERβ and our recently increasing awareness of the complexity of oestrogen receptor structure and function comes with the realization that this complexity is not an obstacle but a major therapeutic opportunity of finding a compound with a beneficial bone, cardiovascular and neurological profile without adverse effects on the reproductive tissues of breast and uterus. [7] The selective oestrogen receptor modulation is based upon the existence of 2 receptor isoforms of different ligand affinity coexisting in many *tissues,* the existence of at least 2 activating factors and the increasing number of coactivators and corepressors.

TYPES OF SERMs

I generation: Tripbenylethylene derivative- Tamoxifene, Droloxifene, Toremifene.

II generation: Benzothiophene derivative- Raloxifene

III generation: Ormeloxifene, Ospernifene, Arzoxipene, Lasoxifene

Chemistry of Ormeloxifene

The chemical name of ormeloxifene is Trans-7-methoxy-2, 2-dimethyl-3 -phenyl-4(4-(2-pyrrolidinoethoxy) phenyl(-chromanhydrochloride). Ormeloxifene is white to off white powder having m.p. of 163 0C to 166 0C and molecular weight of 493.5. The drug is very stable under normal conditions of storage. The presence of the specific bases such as pyrrolidine is optimal and imparts the highest degree of antagonistic character. The presence of the benzopyran group in ormelexifene defines its receptors binding ability and oestrogen agonistic activity.

Hence, this strategy has resulted in the development of a pharmacophore model that attributes the differences in effects on the uterus. Ormeloxifene competes with oestradiol for binding the cytosol receptors. It not only blocks the cytosol receptors but also causes their prolonged depletion and therefore its action lasts long after the drug has been

withdrawn unlike any other SERM used so far. [8]

Effects of Ormeloxifene

Ormeloxifene, like all other SERMs is oestrogen agonist in skeletal tissue. Animal studies have proven that it prevents bone loss. It can reverse, low or delay bone fractures just as OC pills, all the same without affecting the blood coagulability. [8] Ormeloxifene being an oestrogen antagonist can find usage in patients with advanced breast cancer. A better response to breast cancer in post and perimenopausal women in a dose of 60 mg thrice weekly for 4-6 weeks has been observed with figures comparable to tamoxifene., The responses were more marked for bone, pulmonary, soft tissue, skin and lymphnode metastasis than for liver metastasis. [8] Ormeloxifene has an antagonistic action in uterine endothelium that forms the basis of its use in the management of DUB. In a 12 month phase II trial, endometrial thickness was assessed by TVS and it increased by a mean of 5 mm in women who were treated with levormeloxifene in doses of 1.25 to 20 mg/day. However endometrial biopsy specimens revealed a normal, histologicaly quiescent profile for all dose groups with no evidence of oestrogen like stimulation. The urethra and trigone of the bladder are covered by nonkeratinising squamous epithelium of similar origin to the vagina. These tissues and fascial and muscular support elements have oestrogen receptors and respond to oestrogens. Thus all the SERMs, with their anti-oestrogenic action can cause genital prolapse in older patient and also urinary incontinence. [5] Ormeloxifene does not exhibit progestational, androgenic or antiandrogenic properties, likewise it does not affect the secretions of pituitary, thyroid or adrenal hormones in the usual therapeutic dosage.[10] Ormeloxifene/ centchroman is also marketed as oral contraceptive pill "*saheli*".

Materials and Methods

The study was conducted in the department of Obstetrics and Gynaecology at Shri MP Shah Medical College, Jamnagar during the period of July 2005 to February 2007.

SELECTION CRITERIA:

30 women aged 28-46 years who attended the outpatient gynaecology department with complaint of heavy menstrual flow were recruited for the study of which 22 came for regular follow up for 6 months of treatment and later also. All the women were multiparous having completed their families.

EXCLUSION CRITERIA:

(1) Postmenopausal bleeding
(2) Endometrial biopsy suggestive of atypical hyperplasia or malignancy
(3) Cervical dysplasia
(4) Fibroid uterus */* adenomyosis */* endometrial poly.
(5) Bleeding dyscrasia
(6) Clinical evidence of jaundice or hepatic dysfunction
(7) Hypersensitivity to the drug
(8) Uterine size >6 weeks gestational pregnant uterus.
(9) Women desirous of fertility.

Subjects were recruited at random from outpatient Department of Obstetric and Gynaecology after informed consent. Detailed history of menstrual problems was taken. General examination was done to assess the anaemia obesity and to rule out any signs and symptoms of bleeding disorders, hypothyroidism and jaundice.

Basal Metabolic Index (BMI) was calculated from patient's height and weight to study the relation of DUB with obesity.

A pelvic examination was done to rule out pregnancy, fibroid, adenomyosis or any other pathology. Baseline investigations were conducted for hemoglobin levels. TLC, DLC, bleeding time, clotting time platelet count, prothrombin time and peripheral smear for cell morphology were done to rule out bleeding dyscrasias. TSH levels were advised to rule out occult hypothyroidism. Pap smears were taken and endometrial biopsy was taken.[9] The drug was administered orally in the form of 60 mg tablet twice weekly (every Sunday and Thursday) for the first 12 weeks and then once a week (every Sunday) for another 12 week.

Patients were told to keep a record of their menstrual blood loss including the interval at which the menses were coming, number of days of bleeding, number of pads soiled and degree of soiling, history of passage of clots and dysmenorrhoea. Patients were asked to come for regular follow up every 30 days. On each follow up, they were asked about the blood loss and any other complaints. Hemoglobin estimation was done. A TVS was done for endometrial thickness and any other pathology. Two pre-treatment baseline cycles were compared to the treatment cycles of ormeloxifene. The main outcomes measured were menstrual blood, blood haemoglobin levels and endometrial thickness in proliferative phase as studied by TVS.

Results

The present study was conducted on 22 patients, 50 percent of patients were in the age group of 31-40 years and majority of them are illiterate and from low socio-economic group. Two-third patients were urban. No significant relation was found between DUB and parity of the patient, family history of abnormal uterine bleeding and history of tubal ligation. Obesity was present in 22.7% patients and 18.2% were overweight. A past history of PID was present in 22.7% patients that has been treated and cured before starting therapy. Fifty percent patients had taken some form of treatment in the past and were not relieved or temporarily relieved. Around 13 of patients had simple hyperplasia of endometrium and 2/3 had a normal histology report. There was only one case of complex typical hyperplasia.

Total of bleeding days per year decreased by 76% with the treatment. Maximum decrease was seen in patients with more pre-treatment bleeding days. Decrease in bleeding days varied from 44 to 149. (Table 1, 2) Total no. of pads soiled per cycle decreased by 76.3%. (Table 3) All the patients reported disappearance of clots, 66.66% within 1 month of the treatment only. Dysmenorrhoea was relieved in 62.5% patients who initially had this complaint. (Table 4)

Table: 1 Pre-treatment no. of bleeding days per year

No. of Bleeding days / year(Pre-treatment)	No. of Cases (n 22)	Percentage (%)
<100	10	45.4
101-150	4	18.2
151-200*	8	36.4

Table: 2 Post-treatment no. of bleeding days/year

No. of Bleeding days / year	No. of Cases	Percentage
0	2	9.5
1-20	1	4.8
21-40	15	71.4
41-60	3	14.3

*1 patient did not complete the treatment and underwent hysterectomy at 4 months of treatment cycle for heavy bleeding with increasing endometrial thickness.
*1 patient with heavy menses was 28 years old and had severe anaemia. 3 blood transfusions were given for correction of anaemia and stabilization of general condition before starting ormeloxifene therapy.

Table: 3 Total no. of pads soiled per cycle in all patients

	Pre-treatment	Post-treatment
Total No. of pads soiled per cycle for all patients	687	163
Mean no. of pads soiled per cycle	31.2	7.4

Table: 4 Dysmenorrhoea

Dysmenorrhoea	No. of Cases (n=8)	Percentage
Persisted	3	37.5
Decreased	2	25
Disappeared	3	37.5

An increase in endometrial thickness was seen in 3 patients (13.6%) 2 of these underwent hysterectomy. One was found to be having complex atypical hyperplasia and one had an endometrial polyp. The 3 patients were having regular normal menses. 50% showed a decrease in endometrial thickness by 1 to 2 mm. Average decrease was 2± 0.3mm. Mean increase in Hb was 0.42g%. Side effects were minimal and tolerable.

The incidence of functional ovarian cysts was 27%. One of these 6 patients had the cyst at the beginning of treatment that persisted at the end also. In the remaining *5* patients, cysts had developed during the course of treatment. The cysts had disappeared by the end of treatment in two patients and persisted in three patients. (Table 5) All these three patients eventually underwent hysterectomy and histopathological examination found all the cysts to be simple serous cysts.

Two patients (9%) had amenorrhoea at 4-6 months follow up after completion of treatment. Neither of these patients returned for follow up with complaint of return of menses till 1 year after completion of treatment. Four patients (18%) had temporary amenorrhoea followed by return of normal menstrual cycle.

At 3 months after finishing the treatment, *5* patients had undergone hysterectomy. Of the remaining 17 patients, 11.6% had amenorrhoea, 5.8% were having regular scanty menses and 82.3% had regular normal menses.

Hysterectomy was done in 23% patients. 1 patient not responding to 4 months of treatment was found to be having complex atypical hyperplasia. 1 patient had a fibroid polyp and 2 patients had endometrial polyps.

Table: 5 Ovarian Cyst

Ovarian Cyst	No. of Cases(n=22)	*%age*
Pre-treatment	1/22	4.5
During Treatment	6/22	27.3
Post-treatment	4/22	18.2

Table: 6 Follow up at 3 months after completing treatment

Menstrual Pattern	*No. of Cases (n=21*)*	*%age*
Regular menses	14	66.7
Amenorrhoea	2	9.5
Scanty menses	1	4.8
Hysterectomy	4	19

*1 patient did not complete the treatment and underwent hysterectomy at 4 months of treatment cycle for heavy bleeding with increasing endometrial thickness.

The Table 6 shows that 2/3 rd of patients had regular normal menses at 3 months follow up. *9.5%* had amenorrhoea and 4.76% were having regular scanty menses. 4 patients underwent hysterectomy.

Discussion

Decrease in no. of bleeding days was 76% in this study as compared to 67.9% in study of Laxmi [12] et al. All the patients in this study reported disappearance of clots in menstrual flow with the drug while the same was reported by 67.8% and 85.7% in Laxmi [12] et al and Biswas [13] et al study respectively. Improvement in dysmenorrhoea was observed in 62.5% patients in this study as against 81.8% and 78.3% in Laxmi [12] et al and Biswas [13] et al study respectively. Mean decrease in endometrial thickness was 2 mm in this study as against 3.6 mm in study by Biswas [13] et al. Mean increase in haemoglobin was 0.427g% in this study. Laxmi [12] et al and Biswas [13] et al found a mean increase in haemoglobin of 1.3 g/dL in their respective studies. The incidence of ovarian cyst with the use of ormeloxifene was 27.3% in this study as compared to 26.3% reported by Rajan [11] et al. Rajan, 1996 reported that none of the patients with cysts complained of pain in abdomen or pelvic tenderness and all the cysts regressed spontaneously. The study was done to evaluate the contraceptive and non-contraceptive benefits of ormeloxifene (ormeloxifene). In our study, cysts were all painless, they regressed spontaneously in 2 out of 5 patients and persisted in 3. All three were serous cysts as confirmed histopathologically after hysterectomy.

Ormeloxifene is very effective in improving all the parameters of blood loss

in DUB including the no. of days of bleeding, no. of pads soiled and the passage of clots. Along with being effective, the drug has a good patient acceptability and compliance due to its minimal side effects, low cost (compared to all alternative medical and surgical treatments) and simple dosage schedule.

In the peri-menopausal age group, the drug has an additional advantage of being potentially protective against breast malignancy and osteoporosis.

Considering the costs and complications of surgical treatments, medical therapy should always be tried first in cases of DUB. Ormeloxifene has the potential to be an effective treatment for DUB and should always be considered amongst the treatment options.

Failure to respond to ormeloxifene can be suggestive of some underlying organic pathology and patient needs to be re-evaluated for the same. Our study has found a significant incidence of ovarian cysts with the use of ormeloxifene. All the cysts were functional but further long term studies are needed to study the clinical significance of this side effect.

References

1. Bhatia N. Abnormal and Excessive Uterine Bleeding. In Neeraj Bhatia editor. Jeffcoate's Principles of Gynaecology. 5th Edition. London: Arnold Publishers; 2001.p.560.
2. Calvert K L. Review of Second Generation Endometrial Ablation Techniques. Obs and Gynaecol TODAY 2002;VII(2):371-76.
3. Davey DA. Dysfunctional Uterine Bleeding. In Whitfield CR editor. Dewhurst's Textbook of Obstetrics and Gynaecology for Post-graduates. 5th edition. London: Blackwell Scientific Publications; 1994.p.599.
4. Butler WJ. Normal and Abnormal Uterine Bleeding. In Rock AJ, Jones HW editors. Te Linde's Operative Gynaecology. 9th edition. Philadelphia: Lippincott Williams and Wilkins; 2003.p.461.
5. Speroff L, Glass RV, Kase NG. Clinical gynaecological endocrinology and infertility. 6th edition. Baltimore: Lippincott Williams and Wilkins; 1999.p.201-38.
6. Goldstein SR, and Nanavati N. Selective Oestrogen Receptor Modulator Levormeloxifene in the treatment of osteoporosis. American Journal of Obstetrics and Gynaecology 2002;187(3):521.
7. Beardsworth SA, Purdie DW and Kearney CE. Selective Oestrogen Receptor Modulator. In John Studd editor. Progress in Obstetrics and Gynaecology. 14th edition. London: Churchill Livingstone; 2000.p.386-99.
8. Panda SN. Ormeloxifene a new treatment modality in dysfunctional uterine bleeding. Guest Lecture in 45th All India Congress of Obstetrics and Gynaecology. 9th Jan. 2002.
9. Weeks AD, Duffy SRG. Abnormal uterine bleeding: Diagnosis and Management. In John Studd editor. Progress in Obstetrics and Gynaecology. 12th edition. London: Churchill Livingstone; 2006.p.309-23.
10. Sharma S, Kaur D, Mahajan A, Tandon V. Selective oestrogen receptor modulators. Asian Journal of Obstetrics and Gynaecology Practice. 2006;10(3):30-36.
11. Rajan R. Contraceptive and non contraceptive benefits of Ormeloxifene. Asian Journal of

Obstetrics and Gynaecology Practice 1996;1(1):65-71.
12. Laxmi M. Evaluation of efficacy of ormeloxifene in DUB and observation of its common adverse effects. [Thesis MD]. MGM Medical College, Indore University; 2003.
13. Biswas SC, Saha SK, Bag TS, Ghosh Ray SC. Ormeloxifene - A Selective Oestrogen Receptor Modulator for treatment of Dysfunctional Menorrhagia. Journal of Obstetric Gynaecology 2004;54(1):56-9.

Cite this article as: Grover S, Chhabra A, Bindu S. A Study of Ormeloxifene in Case of Dysfunctional Uterine Bleeding. Int J Med and Dent Sci 2013; 2(2): 162-169.
Source of Support: Nil
Conflict of Interest: No