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A Comparative Study of the Efficacy of Ormeloxifene and Norethisterone in Perimenopausal Dysfunctional Uterine Bleeding and Perimenopausal Symptoms.

Dr Pia Muriel Cardoso

Abstract:
Background: *Dysfunctional Uterine Bleeding (DUB) is the most common cause of abnormal uterine bleeding, accounting for 20% of gynaecology office visits (1). Regarding the medical management of DUB, there is ambiguity in an evidence based approach, marked variation in current practice and continuing uncertainty regarding the most appropriate therapy. There are very few studies comparing the effect of ormeloxifene and progesterone in DUB.*
The objective of the study was to compare the efficacy and safety of these two drugs, Norethisterone and Ormeloxifene, a selective estrogen receptor modulator, which is rapidly emerging as a safe and effective agent for dysfunctional uterine bleeding.
Methods: *Sixty three women presenting with DUB were randomly allocated to 2 equal groups, Group-1, which received 60mg Ormeloxifene twice a week for 12 weeks followed by 60mg once a week for next 12 weeks and Group- 2, which received 5mg Norethisterone twice daily for 21 days for 6 cycles. The primary outcomes were reduction in menstrual blood loss [measured by fall in PBAC (Pictorial Blood loss Assessment Chart) score and subjective assessment], rise in hemoglobin level and decrease in endometrial thickness.*
Results: *The reduction in mean PBAC score with ormeloxifene (224 to 80) was significantly more than with norethisterone (253 to 165) at 6 months ($p<0.01$).*
The rise in hemoglobin concentration and fall in endometrial thickness were also significantly more with ormeloxifene than norethisterone (8.52g% to 10.5 g% vs. 8.28g% to 8.7g%, ($p<0.05$), and 12.09mm to 8.2mm vs. 12.07mm to 10.8mm, $p<0.05$, respectively). No major side effects were reported in any group.
Conclusions: *Both drugs are effective in treating perimenopausal DUB, but ormeloxifene is superior to norethisterone in reducing menstrual blood loss, as well as improving perimenopausal symptoms.*
Keywords: *Dysfunctional Uterine Bleeding (DUB), Norethisterone, Ormeloxifene, Selective Estrogen Receptor Modulator, Perimenopause.*

I. Introduction

Menorrhagia (menstrual blood loss >80 ml per cycle) affects 10-33% of women at some stage in their lives. (2) Over 75,000 hysterectomies are carried out every year with 30% of them being done for menstrual disturbances, especially menorrhagia. (3) Though this surgical option is relatively safe, concern has been expressed about possible long term complications of hysterectomy like premature ovarian failure, cardiovascular disease, and urinary dysfunction. Thus, more and more women are looking forward to an effective medical therapy in preference to surgical treatments.(4,5,6).

Dysfunctional Uterine Bleeding (DUB) is abnormal uterine bleeding in the absence of any systemic, organic or iatrogenic cause.(7) It is the most common cause of abnormal uterine bleeding which can affect any woman from menarche to menopause, occurring more commonly at the extremes of age. It has several adverse effects, including anemia, reduced quality of life and increased healthcare costs, being a major indication for referral to gynecological outpatient clinics (8).

Antifibrinolytics, non-steroidal anti-inflammatory drugs (NSAIDs), progesterones, combined estrogen and progesterones, danazol, gonadotrophin releasing hormone analogues and levonorgesterol-releasing intrauterine system have all been used with different results in the management of dysfunctional uterine bleeding. Even though a number of treatment modalities are available, a reliable drug for management of dysfunctional uterine bleeding should meet the requirements like drug should be effective, convenient to take, cost of the drug must be low, with minimal side effects and the drug should have longest safety margin. Norethisterone, a progestogen, is commonly used for this purpose but being a hormonal drug, it is associated with side effects such as stroke, heart disease, breast cancer, dementia, fluid retention, breakthrough bleeding, spotting etc. Selective estrogen receptor modulator drugs (SERM) selectively bind with high affinity to estrogen receptors and mimic the effect of estrogen in some tissues but act as estrogen antagonists in others.

Ormeloxifene (also known as centchroman) is one of the selective estrogen receptor modulators .It is a non-steroidal, non- hormonal oral contraceptive which is taken once in a week. In India, Ormeloxifene has been available as a birth control product since the early 1990s. It mediates its effects by high affinity interaction with estrogen receprots, antagonizing the effect of estrogen on uterine and breast tissue and stimulating effect on vagina, bone, cardiovascular system and central nervous system [9]. Ormeloxifene is not only preferred as an oral contraceptive, but also useful for management of dysfunctional uterine bleeding and advanced breast cancer [10]. In the pharmacological management of DUB the standard dosage is 60 mg orally twice weekly for a period of 12 weeks followed by weekly once in the next 12 weeks. The safety profile of Ormeloxifene is excellent with very few side effects like nausea, headache, weight gain, delayed or prolonged menstrual period. 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. SERMs in general and ormeloxifene in particular satisfy these requirements.[11,12] Unlike progesterone, ormeloxifene does not produce spotting, breakthrough bleeding or menorrhagia. Clinical studies have shown the effectiveness of ormeloxifene in DUB, but there are very few studies comparing the effect of ormeloxifene and progesterone in perimenopausal DUB.

The aim of this study was to assess the efficacy and safety of ormeloxifene in DUB and to compare it with norethisterone.

II. Methods

This is a prospective comparative study conducted in the Department of Obstetrics and Gynecology, Goa Medical College, Bambolim, Goa, in which 63 perimenopausal women presenting with abnormal uterine bleeding without any organic, systemic or iatrogenic cause were recruited. Ethical approval was taken from the institutional ethical committee. Informed consent was taken. The patients were asked to maintain a menstrual diary recording the days of bleeding, number of sanitary pads. The patient screening and recruitment was carried out at the outpatient clinics in Department of Obstetrics and Gynecology of Goa Medical College, which is a tertiary care teaching hospital. This was a prospective randomized study conducted between April 2012 and May 2015 with patients with subjective complaints of menorrhagia. The analysis was adhered to the declaration of Helsinki for Biomedical Research Involving Human subjects and study protocol was ethically permitted from Goa Medical College Ethical Committee. About 78 patients with subjective complaints of menorrhagia were enrolled for the study, and those with objectively demonstrable menorrhagia (63 patients), were included in statistical analysis. Inclusion criteria for subjects included; women in age group of 40-50 who attended outpatient department (OPD) with subjective symptoms of excessive MBL irrespective of bilateral tubal ligation. Exclusion criteria comprised of: Any organic pelvic pathology, acute heavy bleeding, hemodynamically unstable patients, postmenopausal bleeding, recent history or clinical evidence of jaundice, renal disease, polycystic ovary syndrome, chronic cervicitis or cervical hyperplasia, chronic illness, for example, tuberculosis, past history or family history of thromboembolic diseases, known or suspected cancer of breast or other estrogen-dependent cancers, hypersensitivity to drugs. Women in age group of 40-50 years who attended OPD with subjective symptoms of excessive MBL were at first subjected to the detail history taking and physical examination. History included her chief complaints, duration of her symptoms, history of present illness, obstetric history, menstrual history, H/O past illness, surgical history, family history, H/O medication including contraceptives, personal history, and any significant relevant history. Then a thorough clinical examination was performed which included; general survey, systemic and gynecological exam with special emphasis on pelvic exam along with per speculum, per vagina, and bimanual exam to exclude any organic pelvic pathology. All women underwent ultrasonography assessment of pelvic organs to exclude any previously missed uterine or adnexal pathology such as pregnancy complications and uterine fibroid adnexal mass.

Ultrasound also noted the endometrial thickness prior to the start of treatment, and again at 3 months and 6 months of treatment

In this study, objective assessment of MBL was done by following method as devised by Higham *et al*., pictorial blood loss assessment chart (PBAC).[13]

TABLE 1 .PBAC Score.

PADS	Lightly soiled	1
	Moderately soiled	5
	Saturated	20
CLOTS	Small(Smaller than rupee coin)	1
	Large (Larger than rupee coin)	5

All patients were instructed to use a sanitary napkin of the same brand which have been shown to have similar absorbent capacities and scored depending upon the level of soiling and passage of clots as follows. PBAC score of a given cycle was obtained by adding scores depending on numbers of pads used, level of soiling, and number and size of clots passed.

After making the diagnosis of DUB from history, clinical examination, and investigations, patients were randomly divided into two groups:

- Group 1: Patients in this group were treated with ORM 60 mg orally twice a week (wednesday and saturday) for total 12 weeks (n = 33)
- Group 2: Patients in this group were treated with norethisterone 5 mg from day 1 of the menstrual cycle to day 21 for 3 consecutive cycles (n = 30).

During the treatment period, each patient was followed-up monthly. Patient that did not follow strict follow-up protocol were excluded from the study. MBL was assessed during each period by PBAC. Various aspects of menstrual pattern and complaints associated DUB such as the amount of blood flow, duration, passage of clots, and dysmenorrhea were assessed during the follow-up period. Enquiry was made for any adverse effect of treatment during follow-up. Patient's improvement was assessed by performing blood Hb level before starting therapy, again at 3 months , and one more at 6 months of treatment. Patient's level of satisfaction was judged with personal feedback obtained from each patient, that is, general health, limitation of social activity sex life; effect on mood swings, effect on hot flushes ,wish to continue treatment with the same drug, to recommend this treatment modality to her relatives and friends with the same diagnosis. Data were compared using a *t*-test (paired and unpaired) and Mann-Whitney *U*-test for numerical variables and McNemar's Chi-square test for categorical variables. A $P < 0.05$ was considered significant. Friedman's ANOVA followed by Dunn's *posthoc* test was used for multiple comparisons in PBAC scores.

Among 104 DUB cases that attended hospital with the subjective complaint of excessive MBL, 26.92% (28 out of 102) revealed that menstrual blood loss is <80 ml/cycle (equivalent to PBAC score of <100) when assessed objectively.

Eight out of 76 (10.52%) patients did not complete the study as they were lost to follow-up. 4 patients of the progesterone group discontinued due to bloating and mastalgia, and 1 patient in the ormiloxifene group opted for hysterectomy.

Ultimately, 63 patients completed the study. 33 patients received treatment with ORM and 30 with norethisterone.

III. Results

The cases in both the groups matched well with regards to mean age, parity, socioeconomic status and duration of symptoms. The pretreatment mean PBAC score, mean hemoglobin level and mean endometrial thickness were also comparable in both the groups (Table 2). The most common presenting complaint was menorrhagia (60% in group A and 64% in group B). Proliferative and cstic glandular hyperplasia endometrium were the most common endometrial pattern in both groups. (Table 3).

Table 2: Clinical Parameters before the Start of Therapy

CLINICAL FEATURE	GROUP1	GROUP2	P VALUE
Mean Age	44.2	45.3	>0.05
Mean parity	4	4	>0.05
Socio economic status	III	III	>0.05
Mean Duration of symptoms (months)	8.4	7.6	>0.05
Mean PBAC Score	224	253	>0.05
Mean Hb gm%	8.52	8.28	>0.05
Mean Endometrial Thickness (mm)	12.09	12.07	>0.05

Table 3: Histopathology patterns of Endometrium.

ENDOMETRIUM	GROUP1 ORM n=33	Percentage (%)	Group 2 NOR n=30	
	No	Percentage	No	Percentage
Proliferative	13	39	10	33
Cystic glandular hyperplasia	12	36	11	36
Secretory	6	18	6	20
Irregular ripening	1	3	2	6
Irregular shedding	1	3	1	3
Total	33		30	

Table 4: Comparison of Ormeloxifene and Norethisterone.

Outcome	Pretreatment	After 3 months	After 6 months	P value
Mean PBAC score				
ORM	224	84	80	<0.01
NOR	253	174	165	
Mean Hb gm%				
ORM	8.52	9.2	10.5	<0.05
NOR	8.28	8.4	8.7	
Mean endometrial thickness (mm)				
ORM	12.09	9.2	8.2	
NOR	12.07	11.5	10.8	<0.05

Table 4 : Comparison of ormeloxifene and norethisterone with respect to outcome measures.

The mean pretreatment PBAC score with ormeloxifene was 224 which was significantly reduced to 84 after 3 months of therapy and to 80 after 6 months of therapy ($p<0.01$).

The mean pretreatment PBAC score with norethisterone was 253 which was significantly reduced to 174 after 3 months of therapy followed by a marginal decrease to 165 at 6 months ($p<0.01$).

On comparing both the groups, reduction in PBAC score was more with ormeloxifene and the difference was statistically significant ($p<0.01$).

The pretreatment mean hemoglobin concentration in group 1 was 8.52gm% which was significantly increased to 9.2gm% at 3 months and further increased to 10.5 gm% at 6 months with ormeloxifene ($p<0.01$).

The pretreatment mean hemoglobin concentration in group B was 8.28gm% which was significantly increased to 8.4gm% at 3 months with only a slight further increase to 8.7gm% at 6 months with norethisterone ($p<0.01$).

On comparing both the groups, rise in hemoglobin level was more with ormeloxifene and the difference was statistically significant ($p<0.05$).

The mean endometrial thickness (as measured in proliferative phase by trans-vaginal sonography) was significantly reduced from 12.09 mm to 9.2 mm after 3 months and further reduced to 8.2mm after 6 months of therapy with ormeloxifene ($p<0.01$).

With norethisterone, the mean endometrial thickness was significantly reduced from 12.07mm to 11.5mm after 3 months and to 10.8mm after 6 months of therapy ($p<0.01$). On comparing the two groups, reduction in endometrial thickness was more with ormeloxifene and the difference was statistically significant ($p<0.05$).

The fall in PBAC score was maximum in cases having cystic glandular hyperplasia in both the groups followed by proliferative and secretory pattern. The cases having irregular ripening and shedding did not respond well to either therapy.

Eighty-one percent of cases showed marked subjective improvement in menopausal symptoms like hot flushes and mood swings , as well as improvement in their sexual libido with ormeloxifene as compared to 66% with norethisterone. There was no improvement in 9% cases with ormeloxifene as compared to 10% with norethisterone. There was no worsening of symptoms in either group (Table 5).

Table 5 : Effect on Perimenopausal Symptoms

	Group 1 ORM		**Group 2 NOR**	
	No	%	No	%
No improvement	3	9	3	10
Mild improvement	3	9	7	23
Marked improvement	27	81	20	66
Worsening of symptoms	0	0	0	0
TOTAL	33	100	30	100

IV. Discussion:

In the present study, the reduction in menstrual blood loss (as assessed by fall in PBAC score and patient's subjective assessment), rise in hemoglobin concentration and decrease in endometrial thickness were significantly more with ormeloxifene than norethisterone after 6 months of therapy. The results were significant even after 3 months of therapy. There were no major side effects with either of the drugs.

In a similar study, Bhattacharjee et al[6] used similar dose of ormeloxifene with a shorter duration of norethisterone of 10 mg daily for 12 days (from 14th day) in each cycle as compared to 21 days in our study. They too found ormeloxifene to be superior to norethisterone in reducing menstrual blood loss. The reduction in mean PBAC score was significant in both groups but was more with ormeloxifene (108.7 to 62.48) than norethisterone (113.8 to 94.07). The increase in hemoglobin concentration occurred maximally with ormeloxifene. The reduction in endometrial thickness was significant but similar in both groups. There was marked improvement in 81.67% cases on ormeloxifene, which was comparable to our study, but in only 35% cases on norethisterone, which was much less than our study (66%). They found no improvement in 10% cases on ormeloxifene and 29% on norethisterone as compared to 9% and 10% in our study. Amenorrhea, hypomenorrhea, spotting, stress urinary incontinence and uterovaginal prolapse were observed with ormeloxifene and breakthrough bleeding and spotting were seen with norethisterone. A larger study to validate these deleterious side effects observed by ormeloxifene in their study is required. Shravage et al[14] compared ormeloxifene to another progesterone, medroxy progesterone acetate. They found an 85.7% reduction in menstrual blood loss with ormeloxifene as compared to 54.76% with medroxy progesterone acetate. The reduction in mean endometrial thickness was more with ormeloxifene, however this difference was not statistically significant, maybe because of shorter period of observation of 3 months. Kriplani et al[15] found a 99.7% reduction in median PBAC score in 4 months. Side effects like ovarian cyst, cervical erosion and discharge, gastric dyspepsia, vague abdominal pain and headache occurred in a few women.

Similar to the present study, Dhananjay et al[16] found a statistically significant increase in hemoglobin concentration (8.26 to 10.59g/dl; $p<0.001$) and a statistically significant decrease in the endometrial thickness (8.36 to 4.89mm; $p<0.001$) after 3 months of treatment with ormeloxifene. Dadhich et al[7]and Biswas et al[17] also found a significant reduction in median PBAC score and number of days of menstruation
and number of sanitary napkins used after 6 months of ormeloxifene therapy.

Amenorrhea / hypomenorrhea is a common symptom seen with ormeloxifene in different studies with a wide range of 8% to 63%.(14-17). It is more common in perimenopausal women. However, with proper counseling, the women find it a desirable symptom at this age.

In the present study, the most common endometrial pattern was proliferative as well as cystic glandular hyperplasia, followed by secretory endometrium. However, Kriplani et al[15] found secretory endometrium to be the most common pattern followed by proliferative and simple hyperplasia without atypia. The ultimate aim of pharmacological management of dysfunctional uterine bleeding is to restore the natural cycle of orderly endometrial growth and shedding. The choice of treatment must be opted in relation to several factors like presence of anovulatory or ovulatory cycles and the need for contraception. Patients preference, particularly the desire to avoid hormonal therapy also plays a major role

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