ORIGINAL RESEARCH PAPER

Volume-7 | Issue-5 | May-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

ROLE OF ORMELOXIFENE, ORAL PROGESTOGENS & LOW DOSE ORAL CONTRACEPTIVE PILLS IN ABNORMAL UTERINE BLEEDING - A COMPARATIVE STUDY

Gynaecology

Dr. Payal Jadaun Senior Resident, Department of Obstetrics & Gynecology, F.H. Medical College & Hospital, Tundla, Firozabad (U.P.), INDIA

Dr. Prerna Jain* Associate Professor, Department of Obstetrics & Gynecology, F.H. Medical College & Hospital, Tundla, Firozabad (U.P.), INDIA. *Corresponding Author

Dr. Ramona Perhar Assistant Professor, Department of Obstetrics & Gynecology, M.L.N. Medical College, Allahabad (U.P.), INDIA.

Dr. Meena Dayal Professor, Department of Obstetrics & Gynecology, M.L.N. Medical College, Allahabad (U.P.), INDIA.

ABSTRACT

OBJECTIVE:- To compare the efficacy of ormeloxifene ,norethisterone and low dose oral contraceptive pills in abnormal uterine bleeding.

METHODS :- 96 women with abnormal uterine bleeding were selected randomly and divided into 3 groups . Group 1 was given ormeloxifene 60 mg twice a week for 12 weeks followed by 60 mg once a week for next 12 weeks. Group 2 was given 5 mg norethisterone twice daily for 21 days. Group 3 was given low dose oral contraceptive pills containing 30 µg of ethinyl estradiol and 150 µg levonorgestrel from day 1 of the menstrual cycle to day 21 and for 6 consecutive cycle. Follow up was done at 3 and 6 months by analyzing PBAC score, hemoglobin and endometrial thickness.

RESULT:- The reduction in mean PBAC score with ormeloxifene (245.5 to 65.65) was significantly more than that seen with norethisterone (236.4 to 108.5) and low dose oral contraceptive pills (226.8 to 97.5) after 6 month of treatment (<0.0001).The increase in hemoglobin level and reduction in endometrial thickness were also found to be significantly more with ormeloxifene than norethisterone and low dose oral contraceptive pills. No major side effects were reported in any group.

CONCLUSION: Ormeloxifene is more effective and well tolerated with superior compliance than norethisterone and low dose oral contraceptive pills in medical treatment of abnormal uterine bleeding.

KEYWORDS

Ormeloxifene, Oral progestogens, Low dose oral contraceptive pills, Abnormal uterine bleeding

Introduction

Abnormal uterine bleeding is defined as "bleeding from the uterine corpus that is abnormal in volume, regularity and/or timing" Menorrhagia is socially embarrassing, physically incapacitating condition and has great financial drain. About 10-15 % of women experience episodes of abnormal uterine bleeding at sometime during the reproductive years of their life. It is common during extremes of reproductive life, following pregnancy and during lactation.

Abnormal uterine bleeding can occur at any time between menarche and menopause in ovulatory or anovulatory cycles. The later tends to be more common at puberty and after the age of 40, times at which irregular ovulation is often encountered.Altered hypothalamic – pituitary- ovarian function and /or local changes in prostaglandins production can give rise to abnormal uterine bleeding. It is typically characterized by heavy and prolonged flow with or without breakthrough bleeding1.

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 AUB. Because of the morbidity associated with the surgical procedures, the ACOG recommends beginning with medical management before resorting to surgical interventions2. Medical treatment of menorrhagia should aim to relieve symptoms, improve quality of life and avoid the risk of surgery.

Oral contraceptive pills are commonly used for this purpose but being a hormonal drug, it is contraindicated in certain conditions. Norethisterone is still the most frequently prescribed drug, serving 38% of the patient population, the reason being cost effectiveness and lesser side effects[3].

Ormiloxifene is one of the Selective Estrogens Receptor Modulators (SERM) which binds with high affinity to estrogen receptors and mimics the effect of estrogen in some tissues but act as estrogen antagonist in others4. It acts as estrogen antagonist in uterus (endometrium) which leads to endometrial atrophy hence decreases menstrual blood loss.

The present study was undertaken to evaluate and compare the effect of ormeloxifene as compared to norethisterone and low dose oral contraceptive pills in abnormal uterine bleeding.

Material and Methods

This prospective study was carried out on 108 women of age 20 to 40 years attending out patient department and indoor cases of Swaroop Rani Nehru Hospital and Kamala Nehru Memorial Hospital, Department of Obstetrics and Gynaecology, M.L.N Medical College Allahabad over a period of twelve months during the year 2015-2016.

Women between 20 and 40 years of age with complain of heavy and prolonged menstrual bleeding were recruited for the study.

The exclusion criteria were pelvic pathologies like uterine fibroids, suspected adenomyosis, malignancies of uterus/ cervix/ ovary/ vagina/ endometrial hyperplasia with atypia; medical diseases– liver dysfunction, heart disease, migraine, stroke, renal disease, hypo/hyperthyroidism, platelet disorders or coagulopathy, previous history of thrombosis, pregnancy, abortion, use of IUCDs or oral contraceptives, lactating women in first 6 months of post-natal period, hypersensitivity to the drug.

The cases were divided into three groups. The first group included those cases who received ormeloxifene 60 mg twice a week for 12 weeks followed by 60 mg once a week for next 12 weeks, second Group included cases who were given 5 mg norethisterone twice daily for 21 days for 6 consecutive cycle and third group included who received low dose oral contraceptive pills containing 30 µg of ethinyl

estradiol and 150 µg levonorgestrel from day 1 of the menstrual cycle to day 21 cyclically for 6 months Informed consent was taken.A thorough systemic, gynaecological examination and routine investigations including hemoglobin and endometrial thickness by USG were done at first visit. Follow up was done at 3 months and 6 months or earlier if needed. Menstrual blood loss was measured objectively by a pictorial blood loss assessment chart (PBAC) score as described by Higham et al5. The women were asked to maintain menstrual calendar and use certain sanitary products which have been shown to have similar absorbent capacities and record the number of sanitary products used each day and the degree of soiling of each pad used. Number and size of clots passed were also noted. Scores were assigned to different degree of soiling of sanitary products and number and size of clot`s passed [Table /Fig–1].

Table/Fig.-1 : PBAC scoring

Pads		
1point	For each lightly stained pad	
5points	For each moderately stained pad	
20points	For each completely saturated pad	
Clots/Flooding		
1point	For each small clot (Australian 5 cent coin)	
5points	For each large clot (Australian 50 cent coin)	
5points	For each episode of flooding	

A PABC score of greater than or equal to 100 indicates menstrual blood loss greater than or equal to 80 ml and is considered diagnostic for menorrhagia. The primary outcome measures were menstrual blood loss, hemoglobin concentration and endometrial thickness.

Observations and Results

Out of 108 patients enrolled, 96 completed the study and 12 lost the follow-up [Table -2].31 patients received Ormeloxifene (group 1), 33 patients were given Norethisteron (group 2) and 32 patients were prescribed oral contraceptive pills (group 3).

Table-2 : Distribution of Cases

	DRUG USED	NO. OF CASES	PERCENTAGE
1.	Ormeloxifene	31	32.29 %
2.	Norethisterone	33	34.37 %
3.	OCP	32	33.33 %
Total		96	100 %

Age of the treated patients ranged between 20 to 40 years and maximum number of patients were in the age group between 31 to 35 years[Table-3]. Parity of patients was comparable in all the three groups.Maximum number of cases were in ≥ three parity.

Table-3 : Age Group

AGE GROUP (years)	GROUP -1 (n=31)		GROUP -2 (n=33)		GROUP -3 (n=32)		TOTAL
	NO.	%	NO.	%	NO.	%	
20- 25	5	16.12%	6	18.18%	6	18.75%	17
26- 30	6	19.35%	8	24.24%	7	21.87%	21
31- 35	11	35.48%	10	30.30%	9	28.12%	30
36- 40	9	29.03%	9	27.27%	10	31.25%	28
TOTAL	31		33		32		96
MEAN	31.83±5.209		31.27±5.222		31.69±5.491		

Menstrual blood loss (assessed by PBAC score), hemoglobin level and endometrial thickness were observed before starting treatment and then after 3 and 6 months of treatment.

In group 1, mean PBAC score before treatment was 245.4, which was decreased significantly to 65.65 after 6 months of treatment with ormeloxifene. The mean pretreatment PBAC score in group 2 was 236.4 which reduced to 86.33 after 6 months of therapy with norethisteron. In Group 3 mean pretreatment PBAC score was 226.8 which reduced to 97.5[Table-4].

TABLE - 4 : PBAC Score pretreatment, at 3 months and at 6 months

Groups/ PBAC Score	Group-1 (n =31)	Group-2 (n =33)	Group-3 (n =32)	P value within different groups
Pretreatment PBAC score mean	245.5	236.4	226.8	0.0974
PBAC score mean at 3 months	132.8	144.4	157	0.0122
PBAC score mean at 6 months	65.65	86.33	97.5	<0.0001
P value within same group	<0.0001	<0.0001	<0.0001	

In group 1, mean hemoglobin level before treatment was 8.05 gm%, which was increased significantly to 10.11 gm% after 6 months of treatment. The mean pretreatment hemoglobin level in group 2 was 8.08 gm% which was increased to 9.56 gm% after 6 months of therapy. In Group 3 mean hemoglobin increased from 8.15 gm % to 9.39 gm % after 6 months[Table-5].

TABLE- 5 : Haemoglobin (gm/dl)

Groups/ Haemoglobin	Group-1 (n =31)	Group-2 (n =33)	Group-3 (n =32)	P value within different groups
Pretreatment Mean	8.055	8.082	8.153	0.3681
Mean at 3 months	8.832	8.597	8.813	<0.0001
Mean at 6 months	10.11	9.567	9.391	<0.0001
P value within same group	<0.0001	<0.0001	<0.0001	

Table -6 shows the comparison of reduction in mean endometrial thickness among all the three groups. In group 1, mean endometrial thickness before treatment was 8.97mm, which was reduced significantly to 6.05mm after 6 months of treatment. The mean pretreatment endometrial thickness in group 2 was 9.10 mm which was decreased to 7.17 mm after 6 months of therapy. In Group 3, mean endometrial thickness decreased from 9.07 mm to 7.93mm after 6 months.

TABLE -6 : Endometrial Thickness (mm)

Groups/ Endometrial Thickness	Group-1 (n =31)	Group-2 (n =33)	Group-3 (n =32)	P value within different group
Pretreatment Mean	8.971	9.109	9.075	0.2195
Mean at 3 months	7.013	8.091	8.231	<0.0001
Mean at 6 months	6.058	7.176	7.931	<0.0001
P value within same groups	<0.0001	<0.0001	<0.0001	

Serious side effects which warrant discontinuation of drug were not seen in any group.Amenorrhea was the most common symptom in Group 1, seen in 16 women. However some or other side-effects were seen in few patients as shown in Table-7.

TABLE - 7: Side Effect Profile of the Drug

Side Effects	Group-1	Group-2	Group-3
Nausea & Vomiting	0	2	4

Weight Gain	0	2	6
Headache	1	3	5
Spotting	0	4	0
Amenorrhea	16	0	0

DISCUSSION

Abnormal uterine bleeding accounts for most of the referrals to gynaecological OPD.There are varieties of treatment available for abnormal uterine bleeding, from medical therapy to minimally invasive surgery to conventional hysterectomy. However, medical treatment should be the preferred modality of treatment when possible. In this study maximum numbers of cases (83.33%) were of age group 31 to 35 years age. Maximum number of cases were in P3 and ≥P4.

In this study the Pictorial Blood loss Assessment Chart (PBAC) Scoring was done accordingly to assess menstrual blood loss.In Group-1 decrease in mean PBAC score was found to be extremely significant (P< 0.0001) which was reduced from 245.5 to 65.65 after 6 months.Mean PBAC score in Group-2 was reduced from 236.4 to 86.33 & reduced from 226.8 to 97.5 in Group-3 at six months which was also significant in both the groups (P< 0.0001).Shreya et al (2015) noted significant decrease in PBAC Score after treatment with ormeloxifene. A favorable decrease similar to our study was noted in mean PBAC score from 320 to 60 (p<0.001)6.Results of Chitrangada et al (2014) were in accordance with our data.In their study the reduction in mean PBAC score with ormeloxifene (196.46 to 79.57) was significantly more than seen with norethisterone(186.35 to 105.76)7.Our findings regarding decrease in mean PBAC score after treatment with ormeloxifene and oral contraceptive pills were almost similar with findings of Khare et al (2014)[8].

In this study the mean Hb in Group 1, Group 2 & Group 3 after six months of treatment was 10.11 gm% ,9.56 gm% and 9.39 gm% respectively. The increase in Hb in all the three groups was statistically significant (P<0.0001) ,with better improvement in Group 1 among all the three groups. Similar to our study Shazia et al (2014) noted significant increase in hemoglobin concentration from 8.1 to 9.4 gm/dl with a rise of 1.3 gm/dl (p<0.05) after treatment with ormeloxifene9.Our results were also comparable with the results of Jacob KJ et al (2015)10. The increase in hemoglobin levels were found to be more significant with ormeloxifene than norethisterone in their study (9.68 gm% to 11.07gm% vs. 10.17gm% to 10.58 gm% respectively, p value <0.05).

In our study the endometrial thickness before treatment in Group 1, Group 2 and Group 3 were 8.97 mm ,9.1 mm and 9.07 mm respectively which were comparable to each other. Significant reduction in endometrial thickness was noted in all the three groups. After six months, endometrial thickness in Group 1 ,Group 2 & Group 3 was reduced to 6.05 mm ,7.17 mm and 7.93 mm respectively which was statistically significant (p<0.001).

In the study done by Neha A et al (2013) mean pretreatment endometrial thickness was reduced from 11.35 mm to 9.4 mm after 3 months and to 8.13 mm after 6 months of therapy with ormeloxifene (p<0.0001)11. These results are similar to our study. Chitrangada et al(2014)7showed in their study that the initial average endometrial thickness was 5.49 in Ormeloxifene Group and 5.08 in Norethisterone group. The endometrial thickness changed to 4.49 in case of Ormeloxifene and 4.83 in case of Norethisterone, showing a significant decrease in the former compared to later and the inter group variation was significant. These findings are in accordance with the result of our study.

CONCLUSION

It was concluded from the present study that all the three drugs were effective in treating abnormal uterine bleeding. However Ormeloxifene was found to be superior to norethisterone in treating AUB and norethisterone was found to be superior to low dose oral contraceptive pills in the management of AUB. Based on the results ,ormeloxifene is well tolerated and without serious side effects, hence can be used as a safe alternative for other medical management of AUB. It has a convenient dose schedule of once or twice a week and is cost effective. It can be used in any age group and is oncologically protective to the breast and endometrium.

REFERENCE

1. Chen BH, Guidice LC. Dysfunctional uterine bleeding. West J med. 1998,Nov;169(5):280-84.
2. Masand D, Gupta S, Patel J. To observe effect of Ormeloxifene in medical management of dysfunctional uterine bleeding. Journal of Evolution of Medical and Dental Sciences. 2015;4:587-97.
3. Lethaby A, Irvine GA, Cameron IT. Cyclical progestogens for heavy menstrual bleeding [Online]. Available from: Cochrane Database of systematic reviews; 2008.
4. Bellad Girija C, Lakshmi K. S. "Ormeloxifene in the Management of Dub". Journal of Evidence based Medicine and Healthcare; Volume 2, Issue 38, September 21, 2015; Page: 6125-6131.
5. Higham JM, O'Brien PMS, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. Br J Obstet Gynaecol. 1990;97:734-9.
6. Thapa Shreya, Agrawal Rani Nisha, ChaubeyLavina. Efficacy of ormeloxifene in dysfunctional uterine bleeding: a boon too many. Shreya, et al. Int J Pharm 2015; 5(3): 936-942.
7. Chitrangada , Singh Kumar Satyajeet, Subrata Nag. A double blinded randomized controlled trial to compare Ormeloxifene and Norethisterone in the treatment of Dysfunctional Uterine BleedingIOSR Journal of Dental and Medical Sciences (IOSR-JDMS) Volume 13, Issue 1 Ver. VII. (Jan. 2014), pages- 52-55.
8. Veena Khare, Gopa Ghosh, Pooja Patil, Nidhi Nagar. "Ormeloxifen HCL vs. Combined Oral Contraceptive Pill in Treatment of DUB". Journal of Evolution of Medical and Dental Sciences 2014; Vol. 3, Issue 04, January 27; Page: 1026-1033.
9. Shazia et al. Efficacy and Safety of Ormeloxifene in the Management of Dysfunction
10. Uterine Bleeding, IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 13, Issue 6 Ver. V (Jun.2014), PP 39-42.
11. Jacob KJ, Mini, Deepak AV. A comparative study on the effectiveness of ormeloxifene versus norethisterone in the management of perimenopausal dysfunctional uterine .IAIM, 2015; 2(7): 87-92.
12. Agarwal N, S. Singh. The efficiency and safety of ormeloxifene in dysfunctional uterine bleeding. IOSR Journal of Pharmacy and Biological sciences 2013;5(5):18-21.