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Original Research Article

Ormeloxifene can be used as first line drug in abnormal uterine bleeding: a cross sectional prospective interventional study

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ABSTRACT

Background: Abnormal uterine bleeding (AUB), affecting up to 30% of women globally, disrupts quality of life due to heavy or irregular menstrual bleeding without a clear underlying cause, untreated anovulatory cycle leads to hyperplasia and endometrial cancer. DUB can occur from menarche to menopause. Ormeloxifene, a selective estrogen receptor modulator (SERM), offers potential advantages for DUB treatment. Its tissue-specific effects provide both estrogenic and anti-estrogenic properties, potentially regulating AUB. This study aimed to evaluate its efficacy in managing various types of AUB (excluding pregnancy, incomplete abortion and malignancy conditions) due to its tissue-specific effects, which provide both estrogenic and anti-estrogenic properties.
Methods: This cross-sectional prospective, single-center study enrolled 112 patients (menarche to perimenopause) experiencing abnormal vaginal bleeding. attending gynae OPD at Sparsh hospital (January 2023-Mar 2024). Patients with suspected malignancies, pregnancy and incomplete abortions were excluded.
Results: Ormeloxifene treatment significantly improved hemoglobin levels (mean increase: 1.92 g/dl, $p<0.001$) and reduced endometrial thickness (mean reduction: 2.37 mm, $p<0.001$) across all patient. Additionally, bleeding scores (PBAC score) decreased significantly (mean reduction: 245.1, $p<0.001$), indicating effective control of abnormal bleeding. Notably, 4 out of 66 patients with dysfunctional uterine bleeding (DUB) did not respond to treatment.
Conclusions: Our findings suggest ormeloxifene as a potential first-line therapy for various forms of DUB, particularly for women at reproductive extremes who may tolerate delayed or infrequent periods. This could be especially beneficial considering the potential side effects associated with other treatment options.

Keywords: DUB, Puberty menorrhagia, Ormeloxifene

INTRODUCTION

Abnormal uterine bleeding (AUB), has a varied prevalence pattern across different countries like United States, United Kingdom and African countries.[1] AUB has up to 30% more incidence when approaching menarche and perimenopause stage. As per the national health portal (NPH), there is a 17.9% prevalence of AUB in India.[2]

Ormeloxifene, a third generation estrogen receptor (ER) modulator, has the basic pharmacological role of acting like estrogens in some tissues of the vagina, cardiovascular, bone, CNS along with having antiestrogenic properties in the uterus and breast.[3] Widely marketed since 1990s as Centchroman, it was initially used extensively as a non-hormonal oral contraceptive.[4] While it being used as a contraceptive, it was observed to also help in menorrhagia and endometriosis as well, which led to further investigations in the form of extensive clinical trials for approval. Ormeloxifene was found to normalize uterine bleeding in the cavity, by regularizing premenstrual symptoms.[2]

Ormeloxifene is a safe first line treatment for AUB as it has no negative effects on the cardiovascular health of the patient as well as no detrimental effects on the lipid profile

and bone mineral density as well. There is also no evidence of the risk of breast cancer with its prolonged usage.[5,6] The basic mechanism of action of this drug substance is that it enables the inhibition of endometrial lining proliferation, which decreases the thickness of the endometrium. As the thickness reduces, less blood is lost which in turn helps in increasing the haemoglobin levels in the body.[4,5]

Untreated anovulatory cycle may lead to hyperplasia and endometrial cancer.[7] Wide range of surgical and medical modalities are available. Medical treatment options include oral or intramuscular progesterone, levonorgestrel intrauterine system (LNG-IUS), anti-fibrinolytic agents like tranexamic acid oral contraceptive pills and gonadotropin releasing hormones. each medication has its own disadvantages.[8] Prolonged use of oral contraceptive pill has life threatening thromboembolism.[6,8]

Ormeloxifene does not cause spotting or menorrhagia.[9-11] The effect of this SERM on the vascular endothelium leads to decrease in blood loss thereby amelioration of symptoms of dysfunctional uterine bleeding. Dose is 60 mg twice weekly for 3 months followed by weekly for the next 3 months. Drug is metabolised in the liver and its half-life is 170 hours. Highest concentration is found in the liver followed by uterus.

This study was planned to find out use efficacy of ormeloxifene in any type of uterine bleeding excluding bleeding due to pregnancy and incomplete abortion.

METHODS

This was a hospital based, cross-sectional prospective interventional study. In this study, the patients from menarche to perimenopausal age group were included, who came to gynae OPD for treatment of abnormal bleeding PV. This was a single centre study done in Sparsh hospital from January 2023 to March 2024. All eligible candidates included in the study after explaining them regarding study and written consent was taken.

Inclusion criteria

Puberty menorrhagia patients and all women having AUB after excluding pregnancy, incomplete abortion and malignancy were included in study.

Exclusion criteria

Patients with pelvic inflammatory disease, endometrial hyperplasia with atypia, liver disease, hypo and hyper thyroid, heart disease, renal disease, platelet disorder or any coagulopathy, incomplete abortion, hypersensitivity to ormeloxifene were excluded.

Data collection

A total of 112 patients attending Sparsh Hospital gynae OPD for AUB PV due to any gynaecological cause except malignancy, pregnancy and bleeding due to incomplete abortions were included in this study.

Detailed obstetric and menstrual history were documented. General examination, per abdominal and bimanual examination done. Blood loss was assessed by a pictorial blood assessment chart (PBAC). PBAC is the simple and less time-consuming procedure for objectively assessing blood loss. PBAC score more than 100 indicates blood loss more than 80 ml and is considered diagnostic of menorrhagia routine blood examination done. Transvaginal or trans abdominal USG is done.

USG was done to measure endometrial thickness and for other pelvic pathology.

After this all patients were treated with 60 mg of ormeloxiphene twice a week for 12 weeks followed by, weekly dose for next 12 weeks. Patients of puberty menorrhagia treated with 30 mg biweekly for 12 weeks followed by weekly for 3 months. Dose was reduced due to their less age.

Patients were called monthly. At each visit, a detailed history was taken. USG was done after 6 months and Hb and endometrial thickness was repeated. Pretreatment and post treatment values were compared.

Statistical analysis

Jamovi software was used for statistics work.

RESULTS

Our study investigated the effectiveness of ormeloxifene in managing various types of AUB, excluding malignancy, pregnancy and incomplete abortion. A total of 112 patients (age range: 12-48 years, mean: 32.5 years) were recruited and categorized based on their underlying pathology. Out of all patients, 5 patients of fibroid, 9 of poly cystic morphology of ovary, 6 of adenomyosis, 5 of ovarian cyst, 8 patients of post medical abortion of irregular bleeding, 9 patients of puberty menorrhagia, 4 patients of post DMPA irregular bleeding and 66 patients of DUB without any structural cause. Age distribution is presented in Table 1.

Table 1: Age distribution of patients.

Parameters	Age (in years)
N	112
Missing	0
Mean	32.5
Median	34.5
Standard deviation	9.51
Minimum	12
Maximum	48

Treatment with ormeloxifene significantly improved hemoglobin levels, indicating reduced blood loss (Table

2). The average haemoglobin level increased by 1.92 g/dl (from a mean of 7.33 g/dl to 9.25 g/dl) after six months of treatment. This improvement was statistically significant (paired-samples t test, p<0.001).

Table 2: Descriptive Hb assessment of participants after 6 months of treatment.

Parameters	Hb before treatment	Hb after treatment
N	112	112
Missing	0	0
Mean	7.33	9.25
Median	7	9
Standard deviation	0.665	0.729
Minimum	6	7
Maximum	8	11

Ormeloxifene treatment also effectively reduced endometrial thickness across all patient groups (Table 4). The mean endometrial thickness decreased by 2.37 mm (from a mean of 6.28 mm to 3.91 mm) after six months. This reduction was statistically significant (paired-samples t-test, p<0.001), suggesting a potential mechanism for controlling abnormal bleeding.

The PBAC scoring system was employed to assess menstrual bleeding severity. Ormeloxifene treatment led to a significant decrease in PBAC scores (mean reduction: 245.1 points, from a mean of 329 to 83.9) (Table 6). This statistically significant improvement (paired-samples t test, p<0.001) indicates effective control of abnormal bleeding patterns.

It is important to note that four out of 66 patients with DUB did not experience a significant response to ormeloxifene treatment. Further research is needed to explore potential reasons for treatment resistance in this subgroup.

Overall, the findings of this study suggest that ormeloxifene may be a promising first-line therapy for managing various types of AUB, with significant improvements observed in hemoglobin levels, endometrial thickness, and bleeding control.

Table 3: Paired sample t test.

Parameters		Statistic		Df	P value
Hb before treatment	Hb after treatment	Student's t	-31.5	111	<0.001

This result shows that Hb of participants are significantly raised after treatment due to remarkably decreased bleeding per vaginally.

Table 4: Descriptive analysis of effect of treatment on endometrial thickness.

Parameters	Endometrial thickness before treatment	Endometrial thickness after treatment
N	112	112
Missing	0	0
Mean	6.28	3.91
Median	6	3.2
Standard deviation	2.58	1.54
Minimum	3	2
Maximum	16	11

Table 5: Paired sample t-test.

Parameters		Statistic		Df	P value
Endometrial thickness before treatment	Endometrial thickness after treatment	Student's t	15	111	<0.001

Endometrial thickness is decreased significantly after treatment in all age group and different disease patients. P<0.001, which is significant.

Table 6: PBAC scoring before and after treatment.

Parameters	PBAC score before treatment	PBAC score after treatment
N	112	112
Missing	0	0
Mean	329	83.9
Median	320	70
Standard deviation	70.7	65.7
Minimum	130	35
Maximum	480	430

Table 7: Paired sample t test of PBAC scoring.

Parameters		Statistic		Df	P value
PBAC scoring before treatment	PBAC scoring after treatment	Students t	32.3	111	<0.001

DISCUSSION

Most of the patients attending gynae OPD are due to complaints of menorrhagia and other types of menstrual complaints. Dysfunctional uterine bleeding is a diagnosis of exclusion. It occurs mostly in extremes of ages. Disturbances in the menstrual cycle occur most commonly during menarche and perimenopausal age group. But it can occur at any age. Women in the reproductive age group who wish to retain fertility, pharmacological approaches are only available options. Some drugs are effective against anovulatory causes others against ovulatory causes.

SERMs are drugs that act in specific ways at each of the ER sites in different tissues.[12] Ormeloxifene is an optimally designed SERM with varied tissue response. It is effective in treatment of DUB at any age. It is effective in treatment of premenstrual syndrome in peri menopausal women. Medication is cost effective and compliance is good due to convenient dosing schedule.

SERM is a class of drug which has estrogenic effects in some parts of the body and antiestrogenic effects in other parts of the body.[13] It has anti estrogenic effect on uterine and breast tissue and estrogenic effect on vagina, CVS and CNS. One of the drugs of this group is ormeloxifene. It is a non-hormonal nonsteroidal drug taken once in a week when taken as contraceptive.[14]

In DUB standard dose is 60 mg biweekly for 3 months followed by once weekly for 3 months .it has also been useful in treatment of DUB with a convenient dosing pattern, improving patient compliance.[15]

Nausea, headache, weight gain and delayed period are few side effects.

Results of our study showed remarkable improvement in patients' condition, 96.5% patients showed improvement of symptoms, which is comparable to the study by Bhattacharya et al, Dadhich et al and Agrwal et al which showed mark improvement in 81.6%, 92%, and 88.335 of patients respectively.[15-17] 4 patients were not relieved by this treatment. All 4 patients were from the perimenopausal age group. They had a hysterectomy.

Drug was well tolerated and there were no significant side effects. Amenorrhea was the most common side effect seen in 15 (13.39%) patients. Out of this 3 were from the puberty menorrhagia group and 12 from the perimenopausal age group. Delayed menses was a common complaint.

All patients with puberty menorrhagia responded very well. Compliance with drugs is very good in these patients. These age group patients had delayed cycle, which is also a normal pattern of menstrual cycle in this age group after menarche for 2 years. The effect of this drug is excellent without affecting normal endocrine and physiological parameters in these young girls.[18]

Irregular bleeding following DMPA injection was very well managed by this drug regime.

Irregular bleeding following medical termination of pregnancy also responded to this treatment.

Nine patients in the perimenopausal group were previously taking norethisterone, but not responding on that treatment then switched over to ormeloxifene treatment and responded to this drug.

No. of patients of puberty menorrhagia, DMPA injection and medical termination of pregnancy, were less in this study. To validate the effect of this drug on abnormal vaginal bleeding due to these causes require a large sample size study.

Limitations

Our study included 112 women. Sample size was small, especially of puberty menorrhagia, medical termination of pregnancy and irregular bleeding after DMPA injection. This study was done at a single hospital only. We only followed up with the women for six months. A larger study with long follow up is needed to see if ormeloxifene is safe and effective over a longer time.

CONCLUSION

According to the result of this study, this conclusion could be drawn that ormeloxifene could be the drug of choice in patients with abnormal bleeding, especially in DUB of extreme ages. Patients of this group are not much bothered by delayed menses and oligomenorrhoea caused by ormeloxifene. This drug could be used for irregular bleeding following DMPA injection and medical termination of pregnancy.

Recommendations

This study suggests ormeloxifene could be a first-line treatment for many women with abnormal vaginal bleeding, especially in DUB of extreme ages. Women in this age group are not much bothered by delayed periods of oligomenorrhea caused by ormeloxifene. More research

is needed to confirm these findings, but ormeloxifene shows efficacy as a new treatment option for various types of AUBs.

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