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Dr. K Latha
Professor, Department of Obstetrics and Gynaecology, Rajah Muthiah Medical College and Hospital, Annamalainagar, Chidambaram, Tamil Nadu, India

Dr. Vanathi
Assisstant Professor, Department of Obstetrics and Gynaecology, Rajah Muthiah Medical College and Hospital, Annamalainagar, Chidambaram, Chidambaram, Tamil Nadu, India

Dr. Indhuja S
Final Year Post Graduate, Department of Obstetrics and Gynaecology, Rajah Muthiah Medical College and Hospital, Annamalainagar, Chidambaram, Chidambaram, Tamil Nadu, India

Corresponding Author:
Dr. K Latha
Professor, Department of Obstetrics and Gynaecology, Rajah Muthiah Medical College and Hospital, Annamalainagar, Chidambaram, Chidambaram, Tamil Nadu, India

Comparative study of Ulipristal and Ormeloxifene in treatment of uterine fibroids

Dr. K Latha, Dr. Vanathi and Dr. Indhuja S

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Abstract
Aim: This study was conducted among reproductive age women between 30-50 yrs diagnosed with uterine fibroids to compare the efficacy and safety of Ormeloxifene and Ulipristal in treatment of uterine fibroids.
Methodology: Prospective interventional study was conducted from May 2021 to September 2022 among 40 patients diagnosed with uterine fibroids who were randomly divided into two groups, 20 patients in each group, Group 1 were given Ormeloxifene and group 2 were given Ulipristal
Results: Mean fibroids size reduced in patients who took Ulipristal than in Ormeloxifene group which was statistically significant. Mean HB CONC increased in Ulipristal group than in Ormeloxifene group which was statistically insignificant.
Conclusion: Ulipristal is better as compared to ormeloxifene in reduction of fibroid size. Ulipristal also reduced menstrual blood loss and improved hemoglobin levels when compared to Ormeloxifene.

Keywords: Uterine fibroids, Ormeloxifene, Ulipristal, PBAC chart

Introduction
Uterine leiomyomas are the most common benign uterine tumours affecting around 20-25% women in the fertile age group. The pathogenesis of the tumour is still not well understood. Hence, medical management of this condition is still in its nascent stage.
It has now been postulated that a genetic mutation leading to an alteration of intra- tumorogenic estrogen metabolism might be responsible in the pathogenesis. There is an increased transcription and expression of Estrogen Receptors (ER) in the myoma as compared to normal myometrium [14]. Progesterone receptors have also been demonstrated in myomas. Thus both estrogen and progesterone play an important role in tumor growth and maintenance and it is intuitive to assume that therapeutic hormonal manipulation affecting estrogen and progesterone may be effective in medical management of fibroids.
The treatment should be individualized and based on the symptoms, size, and location of fibroids. The patients' age, preservation of fertility or the uterus, availability of therapy, and experience of the therapist should be taken into account while deciding the therapy. Symptomatic uterine fibroids may be treated medically, surgically, or with a combination of both [2].
Medical therapies act by controlling symptoms, reducing the fibroid volume, and reducing menstrual blood loss. Many drugs such as Oral Contraceptive Pills (OCPs), gestrinone, danazol, mifepristone, ulipristal and GnRH analogues have been tried in clinical trials. But, despite achieving a modest reduction of fibroid size and clinical improvements in menorrhagia and dysmenorrhoea, these have not become popular. This is due to different disadvantages of the agents used.
Selective Estrogen Receptor Modulator (SERM) antagonises the effect of estrogen on uterine & breast tissue and stimulates its effect on vagina, bone, cardiovascular and central nervous system. Ormeloxifene is a third generation SERM.
Selective Progesterone Receptor Modulator (SPRM) modulates P-receptor activity with proapoptotic /antiproliferative effects on fibroid cells, hence controls heavy menstrual bleeding and shrinks fibroids. Ulipristal is a SPRM.
The primary objective of the study is to compare the efficacy of drugs ormeloxifene and ulipristal in reducing the size of uterine fibroids. The secondary outcome is assessing the reduction in blood loss, improvement in hemoglobin & decrease in endometrial thickness [13].

Ormeloxifene

Selective Estrogen Receptor Modulators (SERMS) that selectively bind to estrogen receptors and act as estrogen agonists in some tissues and estrogen antagonists in others seem an attractive agent for medical management of fibroids. Preclinical studies have confirmed that SERMS (tamoxifen, raloxifene) reduce myoma size by 40-60% in rats. Clinical studies have also shown that raloxifene significantly reduces mean uterine and leiomyoma size. These initial success reports prompted the use of another SERM Ormeloxifene in uterine leiomyomas. This drug has already been approved for use as a contraceptive pill and in treatment of menorrhagia. Its role in uterine fibroids is yet to be explored. Ormeloxifene is a third generation SERM which antagonizes the effect of estrogen on uterine and breast tissue and stimulates its effect on vagina, bone, cardiovascular and central nervous system [13].

Thus, when used in perimenopausal women it does not cause uterine stimulation, prevents bone loss, does not increase the risk of breast cancer, lowers cholesterol level and maintains cognitive function of the brain. It has the additional advantage of reducing premenstrual symptoms, mastalgia and dysmenorrhea. It is cheap with a long half-life, allowing biweekly/weekly dosing. It has minimum side effects in the form of nausea, dyspepsia and rarely cystic ovaries. Ormeloxifene has an edge over raloxifene (the commonest SERM studied so far in fibroids) in having a longer half-life allowing a less frequent dosing schedule, having a better metabolic control. Thus, ormeloxifene is possibly useful in fibroids with good tolerability [5].

Toxicity

Toxicity information regarding ormeloxifene is not readily available. Patients experiencing an overdose are at an increased risk of severe cardiovascular adverse effects.

Ormeloxifene in standard biweekly dosage is effective in preventing further growth of uterine fibroids and reduces menstrual blood loss when prescribed for a short period of 6 months. Thus, it may be used as an interim treatment to delay operation especially in patients who need improvement in general condition.

Ulipristal

Ulipristal acetate is a progesterone receptor modulator that has previously been approved as a postcoital contraceptive. As progesterone promotes the growth of uterine fibroids, blocking its receptor may reduce their size. The dose used for this indication can inhibit ovulation and lead to amenorrhoea which will be of benefit to women who have heavy menstrual bleeding related to their fibroids. Treatment should begin in the first week of a menstrual period. The single daily dose is rapidly absorbed. There is extensive metabolism involving cytochrome P450 3A4. Ulipristal should therefore not be taken with inducers of this enzyme, such as carbamazepine, phenytoin and St John's wort, or with inhibitors such as erythromycin. The half-life of ulipristal is about 38 hours with most of the metabolites being excreted in the faeces. No studies have been done in women with impaired hepatic or renal function [2].

The approval of ulipristal for the treatment of fibroids appears to have been mainly based on four trials PEARL I and II were short term while PEARL III and IV studied repeated courses of treatment [8].

Ulipristal acetate (ELLA) was the first agent in the novel selective progesterone receptor modulator class to gain the FDA's approval for use as an oral Emergency Contraceptive tablet in the U.S.

Women with severe renal or hepatic impairment should not receive this drug because of the lack of data regarding safety and efficacy in these patient populations [11].

Usage

UPA has been recommended for the following indications:

- The preoperative treatment of women with fibroids of 3 cm or more in diameter
- Intermittent treatment in women who are not eligible for surgery, for example where the risks of surgery outweigh the benefits or where the woman declines surgical treatment.

Ulipristal acetate is generally well tolerated, and its adverse effects and risks are considered to be no more severe than those of levonorgestrel. In clinical trials, the most prevalent AEs included headache, nausea, fatigue, dizziness, abdominal pain, and dysmenorrhea; these adverse effects were considered to be mild to moderate in severity and spontaneously resolved.

The PEARL I study was a double-blind, randomized, placebo controlled, multicentre trial that showed significant reduction of fibroid volume compared to baseline after 13 weeks of 5-10 mg UPA ($p<0.001$). The Pearl II study showed that the use of 10 mg UPA for 12 weeks was comparable to the monthly use of 3.75 mg of leuprolide acetate for 3 months for the improvement of symptoms such as uterine bleeding and the reduction in fibroid size.[2] PEARL III study investigated the impact of a 10-day course of the progestin norethisterone acetate (NETA) on the timing and magnitude of menstruation during the UPA off-treatment period. Compared to the placebo, NETA was associated with the expedited return of menstrual bleeding and also a significant reduction in menstrual bleeding in the UPA off treatment period. Use of UPA 10 mg daily for up to 4 courses showed progressive reduction in the fibroid volume and the menstrual bleeding with increase in duration of therapy. Women receiving NETA experienced the return of menstrual periods after a median of 15 days following the end of the fourth UPA treatment course, in contrast to 30 days among women receiving the placebo ($p<0.001$) [1].

The VENUS I compared 5 and 10 mg UPA doses to placebo. Three months of UPA reduced the impact of fibroid related symptoms.

Materials and Methods Used

Type of study: Prospective interventional comparative study.

Time frame of study: October 2021 to September 2022.

Study population: Study will be conducted among women aged 20-50 yrs. diagnosed with uterine fibroid in the Gynaecology OPD of Rajah Muthiah Medical College & Hospital, Annamalai University after getting written informed consent.

Inclusion criteria

1. Women of age 21-50 yrs. diagnosed with single-multiple fibroids if they were symptomatic (menorrhagia, dysmenorrhoea, abdominal lump, dull aching lower abdominal pain dyspareunia).
2. Non pregnant women.
3. Both nullipara & multipara.

Exclusion criteria

1. Malignancies, hematological, renal & liver disease.
2. Current genital infection.
3. Women desiring pregnancy.
4. Hypersensitivity to the drug.

Materials and Methods used

Hemoglobin was measured by automated hematology analyser. Menstrual blood loss was assessed by PBAC (Pictorial Blood loss Assessment Chart) which is a semi quantitative assessment that takes into account the number of pads soaked, their degree of soakage, passage of clots and episodes of flooding. A score of 100 or more amounts to menorrhagia.

A complete general and gynaecological examination was done. Blood testing was done for haemoglobin, liver and kidney function tests.

USG was performed at the beginning of the study and after 6 months of treatment to ascertain uterine and leiomyoma size, number of tumors, endometrial thickness and also to exclude other pelvic pathologies. Uterine and fibroid volume was calculated by the ellipsoid method with the formula V=0.5233(D1xD2xD3) [25], where D1, D2 and D3 were the longitudinal, transverse and cross-sectional diameters respectively.

Statistical analysis was performed using the SPSS 9.0 package. Data were expressed as Mean ± SD. Paired t test was used to evaluate differences between leiomyoma sizes, endometrial thickness, PBAC scores and haemoglobin levels at entry and after six months of treatment. The difference between the two proportions of the nominal data was analyzed by Z-test. P Value < 0.05 was considered statistically significant.

Results

Table 1: Show Fibroid and Hemoglobin

			N	Mean	SD	T	P Value
Fibroid	Ulipristal	Pre treatment	20	33.8	38.4	6.9	< 0.001
		Post treatment	20	29.5	36		
	Ormeloxifene	Pre treatment	20	33.9	38.4	2.5	0.0241
		Post treatment	20	32.2	36.2		
Hemoglobin	Ulipristal	Pretreatment	20	6.94	1.25	9.2	0.001
		Post treatment	20	9.80	0.43		
	Ormeloxifene	Pre treatment	20	7.44	0.68	14.6	0.001
		Post treatment	20	8.48	0.61		

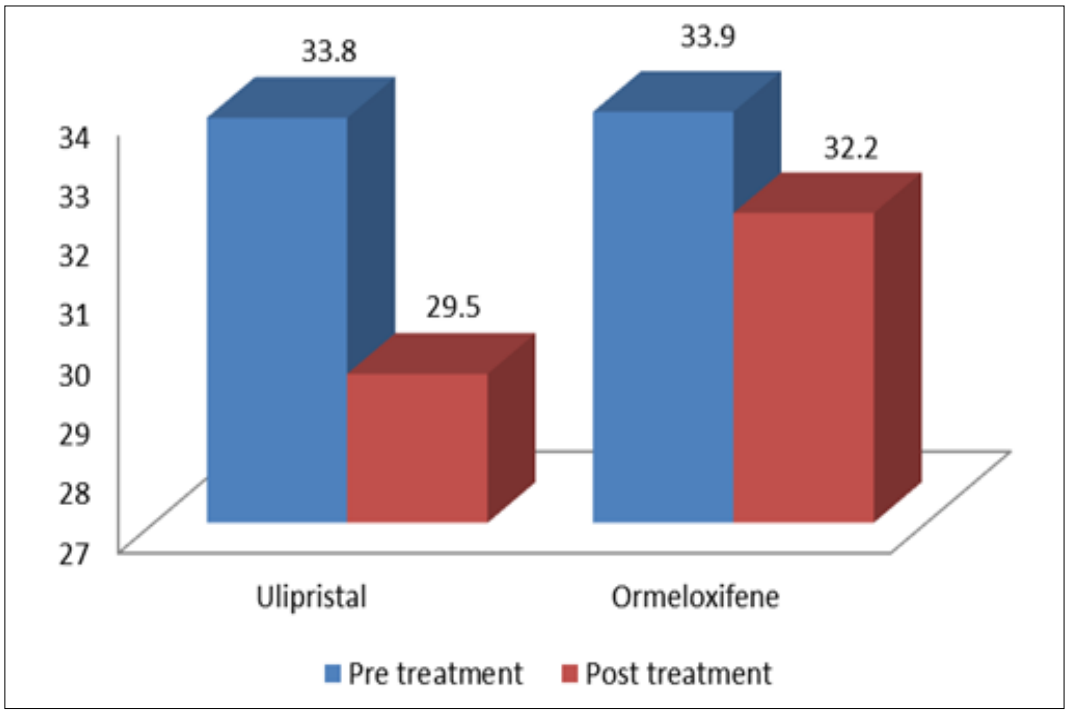

Fig 1: Show Fibroid describe Ulipristal and Ormeloxifene

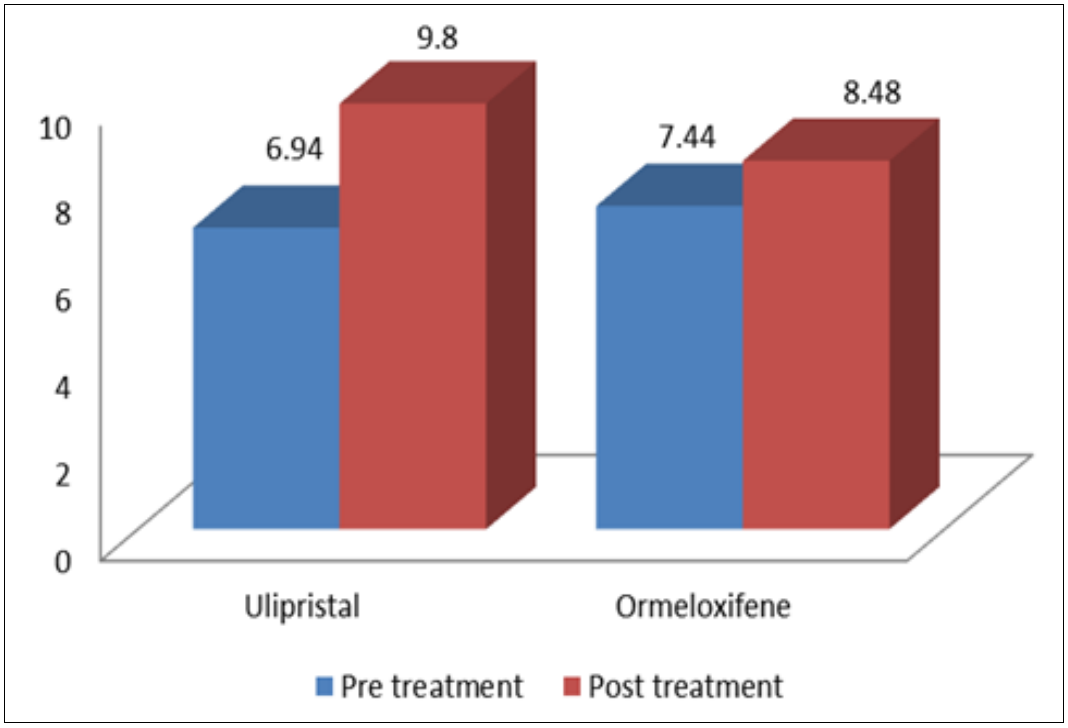

Fig 1: Show Fibroid describe Ulipristal and Ormeloxifene

Discussion and Summary

After approval from the institutional ethical committee, 40 female patients aged 30-50 yrs., diagnosed with uterine fibroids were included in the study. Patients were randomly divided into two groups. After getting written informed consent, to half of patients, Ormeloxifene 60 mg was given orally twice a week for 6 months; to the other half, Ulipristal 10 mg once daily was given for 3 months.

Follow up was done at monthly interval and at end of 6 months clinically and by ultrasound. LFT & RFT investigations were done.

In both groups, maximum patients were between 35-52 yrs (mean age = 44.6±4.27 in group 1 & 43.95 +_4.32in group 2). All patients had BMI between 25-42 (mean BMI = 31.95 ±3.36 in group 1 & 31.56±3.56 in group 2). Age of menarche for all patients ranged between 12 & 17 (mean age of menarche=13 for both groups. In both groups parity was between 1 & 4.

Distribution of pretreatment hemoglobin and endometrial thickness was statistically similar in two groups. All the patients had moderate to severe anemia.

There was significant reduction in PBAC Score from 1st month to 6th month in both the groups which signifies less menstrual blood loss on treatment with Ormeloxifene & Ulipristal.

Among the two groups, Hemoglobin concentration increased from mean HB of 6.94±1.25 to 9.80±0.43 in case of Ormeloxifene and from 7.44±0.68 to 8.48±0.61 in case of Ulipristal. Thus Ulipristal showed increase in hemoglobin which was statistically significant.

Among the two groups, the mean pretreatment fibroid volume in case of ormeloxifene was 33.8 which reduced to 29.5 post treatment. The mean pre treatment fibroid volume in case of Ulipristal was 33.9 which reduced to 32.2.

Liver functional tests and renal function tests were periodically done and followed in both the groups. No serious adverse effects were noted in both the groups.

Conclusion

Ulipristal was effective in reduction of fibroid size & improvement in hemoglobin concentration. UPA is the most effective pharmacological management of fibroids and in many cases it may be an alternative to surgical treatment. This study shows the possible place of UPA as a preoperative option or as a medical therapy alternative to surgery, the safety profile, and with improvement of symptoms, quality of life, and pain.

Ormeloxifene also showed improvement in hemoglobin concentration and reduction in endometrial thickness.

SERM such as ormeloxifene in standard biweekly dosage is effective in preventing further growth of uterine fibroids and reduces menstrual blood loss when prescribed for a short period of 6 months. The drug does not have significant side effects and is available at a low cost. However, it role as the sole medical method in fibroid management needs to be assessed by more robust studies in future.

Conflict of Interest

Not available

Financial Support

Not available

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