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Original Research Article

A prospective observational study on efficacy of ulipristal acetate in treatment of uterine fibroids

Eshna Singh*, Vandana Khanijo, Jyothi Unni

Department of Obstetrics and Gynaecology, Jehangir Hospital, Pune, Maharashtra, India

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***Correspondence:**
Dr. Eshna Singh,
E-mail: eshnasingh@gmail.com

ABSTRACT

Background: Uterine fibroids are common benign tumors where management has traditionally been surgical. Ulipristal acetate (UPA) is a new, effective, and well-tolerated option for the preoperative treatment of moderate and severe symptoms of uterine fibroids. Objectives were to study the utility of UPA in treatment of uterine fibroids.
Methods: A prospective observational study was conducted in women aged 18-50 years presenting with menstrual abnormalities with fibroids to Jehangir Hospital, from 01 December 2017 to 30 September 2019. The 50 premenopausal women with at least one fibroid ≥3 cm in diameter and <8 cm, with heavy menstrual bleeding (HMB) or pain were included. 5 mg of UPA was given once daily for a period 3 months. Primary outcome was to determine symptomatic relief.
Results: Uterine bleeding was controlled in 96% patients whereas 100% had pain relief. Reduction of fibroid volume and size was noted in 60% patients. Favourable outcomes were seen in more cases of intramural fibroids as compared to sub-serosal and submucosal fibroids.
Conclusions: UPA proved to be an effective drug for symptomatic relief in patients with uterine fibroids. Although 60% patients showed reduction in fibroid size, the amount of reduction was not very significant in most of the patients.

Keywords: Fibroids, UPA, PBAC, HMB

INTRODUCTION

Uterine fibroids are the most common benign tumors of the female genital tract. They are clinically apparent in up to 25% of women.[1]

Estrogen production, especially continuous estrogen secretion is thought to be the most important risk factor for the growth of a myomatous fibroid.[2]

Non modifiable risk factors such as age and race are significant in the development of fibroids. A 2-3-fold incidence of fibroids has been found in black women, while the incidence of fibroids among Hispanic, Asian, and White women is similar. Modifiable risk factors such as physical activity, stress, diet, smoking, alcohol, and caffeine consumption modulate signalling pathways and molecular mechanisms involved in fibroid development and growth.[3]

Many fibroids remain asymptomatic. While in some women it can cause heavy or prolonged menstrual bleeding which may lead to anemia in women of reproductive age. Large fibroids and an enlarged uterus can also result in bowel and bladder dysfunction and abdominal lump. Other symptoms include painful menses, noncyclic pelvic pain, infertility, and recurrent miscarriage.[4]

Treatment options for symptomatic uterine fibroids include medical, surgical, and radiologically guided interventions. In recent times gonadotrophin-releasing hormone (GnRH) agonists and selective progesterone receptor modulators (SPRMs) are emerging as the most

effective medical therapy resulting in reduction of fibroid volume and symptomatic improvement in menstrual bleeding. The choice of treatment depends on the patient's personal treatment goals, as well as efficacy and need for repeated interventions.[5]

UPA is a new, effective, and well-tolerated option for the preoperative treatment of moderate to severe symptoms of uterine fibroids in women of reproductive age by displaying a better tolerability profile. It also keeps estradiol levels at mid follicular phase range, thereby reducing the incidence of hot flushes and has no impact on bone turnover.[1] UPA suppresses neo-vascularization, cell proliferation, and survival in leiomyoma cells by downregulating the expression of angiogenic growth factors, such as vascular endothelial growth factor (VEGF) and induces apoptosis.[6] In this study we evaluated use of UPA, an oral selective progesterone modulator (SPRM) for the pharmacological management of uterine fibroids.

Objectives

Objectives of the study were to determine symptomatic relief in women having fibroids after treatment with UPA, to study the possible adverse effects with the usage of UPA in patients with fibroids and to study the efficacy in reduction of fibroid size and volume pre and post-treatment.

METHODS

Study site

Study conducted at Jehangir hospital, Pune, Maharashtra, India.

Study population

All women aged 18-50 years presenting with menstrual abnormalities with fibroids to the gynaecology OPD were selected.

Study design

It was a prospective observational study.

Study duration

Study conducted from 01 December 2017 to 30 September 2019.

Sampling technique

It was a purposive sampling method.

Sample size estimation

Sample size was determined by using the effect sizes from the previously published study.[7]

$n=Z^2pq^2/(me)$

p=0.623 (62.3%) (Approximate estimate of the incidence of reduction in fibroid volume by 25%), q=0.377 (37.7%) (Complement of 'p': Approximate estimate of the incidence of non-reduction in fibroid volume by 25%),), Z=1.96 (score at 95% confidence interval), me=0.135 (margin of error), $n=1.96^2\times0.623\times0.377/(0.135^2)=49.51$.

Thus, the minimum sample size required according to this formula is 49.51 or 50.

Sample size was 50

The study was commenced after approval of ethics committee of the institution. This prospective observational study was conducted on eligible women aged 18-50 years. All women attending gynaecology OPD at Jehangir hospital from 1st December 2017 to 30th September 2019 and fulfilling the inclusion criteria were enrolled in the study. A written informed consent was obtained. All patients who were offered UPA were explained about the dosage, duration of treatment and related side effects.

Inclusion criteria

This included premenopausal women with at least one fibroid ≥3 cm in diameter and <8 cm, as assessed by ultrasonography, HMB with pictorial blood-loss assessment chart (PBAC) score >100 and uterine size <16 weeks of gestation were included.

Exclusion criteria

Previous uterine surgery including endometrial ablation or uterine artery embolization, history of previous or current uterine, cervical, ovarian, or breast cancer, significant finding on Papanicolaou test (PAP) smear within the past 12 months, endometrial hyperplasia with or without atypia within the past 6 months (In case of biopsies older than 6 months, these have to be repeated) ,large uterine polyp (>2 cm),calcified fibroids and/or a calcified uterus, severe coagulation disorder, one or more ovarian cysts ≥ 4 cm diagnosed by ultrasound, history of treatment for fibroid with an SPRM (Selective progesterone receptor modulator) including UPA, treatments with progestins (systemic or progestin-releasing intrauterine system), oral contraceptive pills and refusal to consent were excluded.

A detailed history including age, parity, relevant past medical and surgical history was taken. If pain was a symptom, timing and nature of pain in lower abdomen with respect to the menstrual cycle was noted. Calculation of pain score was done by visual analogue scale (VAS) ranging from 0-10 with higher scores indicating more severe pain. Menstrual bleeding was assessed with the use of the PBAC, a validated method used to objectively estimate blood loss. Monthly scores range from 0 (amenorrhea) to more than 300, with higher numbers

indicating more bleeding. Patients recorded the numbers of pads they used and the extent of soiling with blood. At screening, patients were taught to use the PBAC and were asked to complete it daily throughout the treatment period up to week 13.

General examination was performed. Pallor, if present was noted. An abdominal examination was done to look for any palpable mass in the cervix, uterus or adnexa. The size of any palpable mass was estimated in terms of uterine size in weeks. A speculum + vaginal examination was performed and findings noted.

Haemogram was done. If anemia was detected, patient was given additional oral iron tablets to improve the haemoglobin.

Assessment of fibroid size and endometrial thickness measurements were carried out by transabdominal (TAS)/ transvaginal (TVS) ultrasound at screening and end of treatment (week 13). At both visits (pre-treatment and after 3 months) size, volume and type (submucosal, intramural, sub-serosal) were noted.

For treatment of all eligible patients a dose of 5mg UPA was given once daily for a period 3 months. Women were advised that tablets could be taken with or without food. The first treatment course was started during the first week of menstruation. Patients were informed that treatment with UPA usually leads to a significant reduction in menstrual blood loss or amenorrhea within the first 10 days of treatment. Should the excessive bleeding persist, patients were asked to report to the OPD.

Although Ulipristal at the recommended dose would suppress ovulation in most women, others would still be at risk of pregnancy, hence a non-hormonal contraceptive was prescribed to all patients.

After European Union- wide review of UPA associated risk of liver injury, new guidelines were released by the medicine and healthcare products regulatory agency (MHRA) in August 2018. Thereafter liver function tests (LFTs) were performed before initiation, monthly during the course and after 2-4 weeks of completion of the course. Any adverse effects to UPA like headache, nausea, abdominal pain, hypersensitivity reaction, signs of liver injury such as jaundice were noted.

Assessment of pain score and other fibroid symptoms such as menorrhagia, dysmenorrhea was repeated at the end of the treatment course.

The change in symptoms as well as fibroid size and volume at the end of 3 months of treatment were noted.

Ethics approval

Approved by ethics committee, Jehangir hospital, Pune.

Statistical methods

The data on categorical variables is shown as n (% of cases) and the data on continuous variables is presented as mean and standard deviation (SD). Intragroup statistical comparison of means of continuous variables is done using paired t test. The underlying normality assumption was tested before subjecting the study variables to t test. All results are shown in tabular as well as graphical format to visualize statistically significant difference more clearly.

In the entire study, the p values less than 0.05 are considered to be statistically significant. All the hypotheses were formulated using two tailed alternatives against each null hypothesis (hypothesis of no difference). The entire data is statistically analyzed using statistical package for social sciences (SPSS ver 22.0, IBM corporation, USA) for MS Windows.

RESULTS

A total of 52 women with symptomatic fibroids presenting to the gynaecology OPD, who fulfilled the inclusion and exclusion criteria in the study period were enrolled. The primary outcome was symptomatic relief. The secondary outcomes were fibroid volume reduction, correction of anemia and evaluation of the adverse effects of the drug.

Out of the study population of 52 women, 1 was withdrawn from the study after 1 month due to deranged LFTs and the other one was lost to follow up.

Majority of women studied were in 40-49-year age group (Table 1).

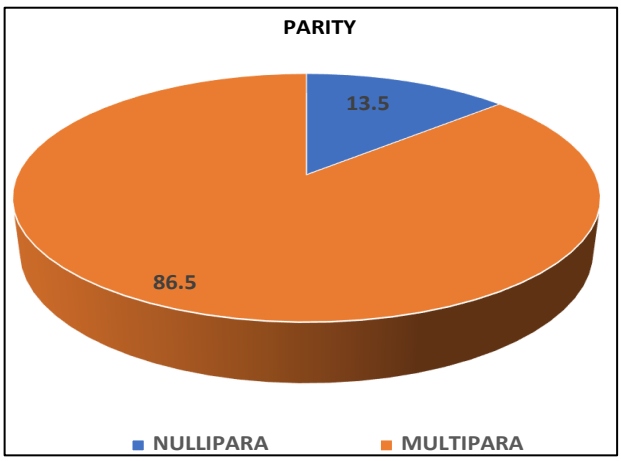

Figure 1: Parity.

A greater number of multiparous women presented with fibroids.

42.3% patients presented with HMB with pain and HMB each, 9.6% women reported only pain, whereas others had pressure symptoms and complained of lump in abdomen.

Most women had PBAC score of 100-199 (Figure 2) and complained of moderate intensity pain (VAS score-4-7) (Figure 3).

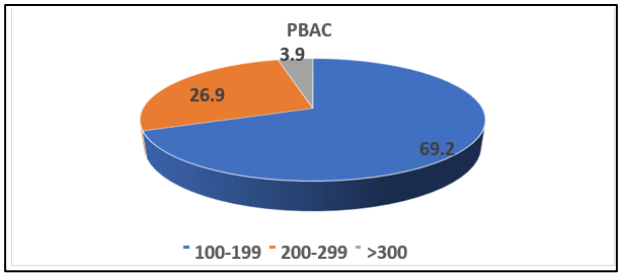

Figure 2: PBAC score.

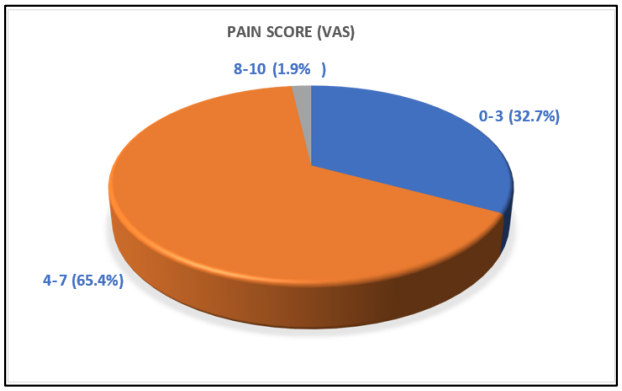

Figure 3: VAS pain score.

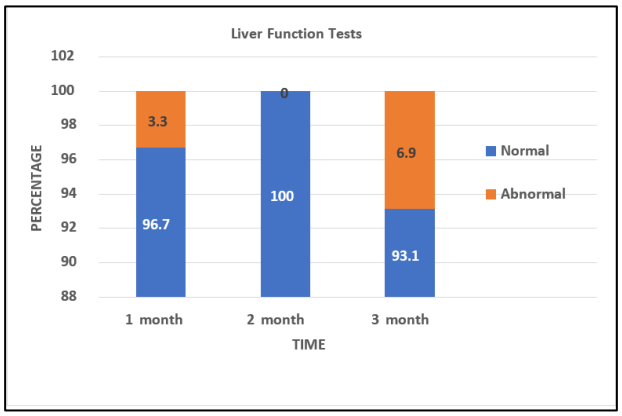

Figure 4: Liver function tests.

All fibroids were classified according to location based on the sonography report, intramural (82.7%) being the commonest of the three types.

After the EMA recommendations in June 2018, liver function tests were done prior to commencing treatment and monthly thereafter. A total of 30 patients got LFTs done. One patient had increased bilirubin and liver enzymes at the end of 1st month, hence was withdrawn from the study. Two patients had deranged liver enzymes after completion of three months treatment.

96% of patients attained amenorrhea by the end of treatment. Most patients (64%) achieved amenorrhea by the end of the first month. 100% patients were pain free during and after the course of treatment (Figure 5).

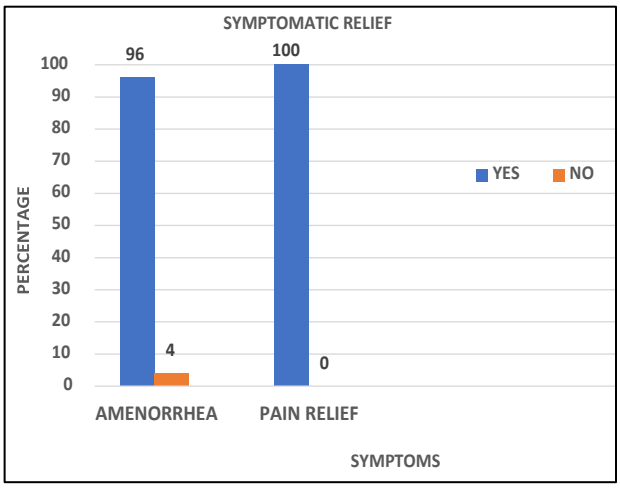

Figure 5: Symptomatic relief.

50% of women had haemoglobin in the range of 10-11.9 gm/dl after treatment, 96% showed an improvement in their haemoglobin levels. Post-treatment haemoglobin levels had significantly increased compared to the pre-treatment haemoglobin levels ($p<0.05$) (Table 3).

For intramural fibroids, mean post-treatment fibroid volume had significantly reduced compared to mean pre-treatment fibroid volume ($p<0.029$) whereas it did not in case of submucosal and subserosal fibroids ($p>0.739$ and >0.535 respectively).

Most patients did not have side effects whereas a few had hot flushes, nausea, pain in abdomen, 10% of patients had deranged liver function test with no serious liver injury.

Table 1: Age distribution.

Age group (in years)	N	Percentage (%)
20-29	3	5.8
30-39	19	36.5
40-49	30	57.7

Table 2: Symptomatic distribution.

Symptoms	N	Percentage (%)
HMB	22	42.3
PAIN	5	9.6
HMB + pain	22	42.3
Pressure symptoms	1	2
Lump in the abdomen	2	3.8
Total	52	100

Table 3: Type of fibroid.

Type of fibroid	N	Percentage (%)
Intramural	43	82.7
Subserosal	7	13.5
Submucosal	2	3.8
Total	52	100

Table 4: Comparison between pre and post treatment haemoglobin.

Haemoglobin (gm/dl)	Pre-treatment		Post-treatment	
	N	%	N	%
<8	2	3.8	0	0.0
8-9.9	9	17.3	2	4.0
10-11.9	19	36.5	25	50.0
≥12	22	42.3	23	46.0
Total	52	100.0	50	100.0
P value	<0.050			

Table 5: Comparison between pre and post treatment fibroid volume.

Volume (cm^3)	Intra-mural, (n=43)		Sub mucous, (n=2)		Sub serosal, (n=7)	
	Mean	SD	Mean	SD	Mean	SD
Pre-treatment	93.34	5.94	64.12	4.98	152.60	9.87
Post-treatment	82.95	6.07	53.95	5.42	166.40	8.55
% Change in volume	12.39	--	17.27	--	9.44	--
P value	0.029		0.739		0.535	

Table 6: Side effects.

Side effects	N	Percentage (%)
Pain in abdomen	1	2
Nausea	1	2
Hot flushes	1	2
Nil	47	94
Total	50	100

DISCUSSION

Many studies have been conducted to study the efficacy of UPA on treatment of fibroids. Since the PEARL studies, it gained popularity as a new effective drug for the management of leiomyomas.[7-10]

Our study was performed to study the efficacy of UPA in the management of fibroids in terms of symptomatic relief, reduction in fibroid size and volume on USG and also the adverse effects of the drug.

Fifty-two women aged between the 18-50 years presenting with symptomatic fibroids to Jehangir hospital gynaecology out patent department between December 2017 to September 2019, after application of inclusion and exclusion criteria were included in the study. Out of these women, one was lost to follow up, one had to discontinue treatment due to derangement of liver enzymes and fifty completed the course. Thus, the outcome was studied in fifty women.

Age

In our study we observed that majority of women (57.7%) were between 40- and 49-year age. The incidence was 5.8% and 36.5% in the 20-29 year and 30–39-year age group. However, the general incidence of fibroids is about 30-40% in women over the age of 40.[11]

Yu et al conducted a US-based population study on the incidence and prevalence of uterine fibroids. Incidence rates for fibroid were highest for the age group 45-49 years.[12]

Parity

Epidemiologic data suggest that pregnancy is protective against fibroids, and the protective effect is likely to be linked to events that occur late in pregnancy, at delivery or during the postpartum process. The incidence of fibroids in our study group was 86.5% in multiparous and 13.5% in primiparous women.

Terry et al conducted a prospective cohort study (nurses' health study II) including 116,609 female registered nurses aged 25-42. It was observed that a lower incidence of fibroids was seen with later age at menarche, longer menstrual cycles, parity, later age at first and last birth, shorter time since last birth, and breastfeeding.[13]

Symptoms

In our analysis 44.1% patients presented with HMB with pain and 42.3% patients had only HMB whereas 9.6% had pain alone. The 2% of patients complained of pressure symptoms and only 2% presented with lump in abdomen.

An epidemiological study was conducted on 2296 women (30-90 years; mean 49.3 years) in seven gynaecological outpatient departments in Germany during a time period of 16 months until March 2013. Similar to our study 45.1% of all myoma patients had problems with abnormal uterine bleeding (HMB or intermenstrual bleeding) and 28.2% suffered from pain (dysmenorrhoea or lower abdominal pain). Dyspareunia, urinary, and intestinal dysfunction were reported in less than 5% of cases.[14]

Menstrual disturbances

In our study 42.3% women presented with HMB, these women had frequent cycles and 42.3% with HMB and pain wherein the cycle length was prolonged. Bleeding was assessed by the pictorial blood loss assessment chart (PBAC).

In our study we took the cut off for HMB as PBAC score-100. The patients were categorized into three categories of PBAC score 100-199, 200-299 and >300. There were 69.2%, 26.9% and 3.9% women in these groups respectively.

In 2009 the uterine bleeding and pain women's research study (UBP-WRS) was conducted. Women with uterine fibroids reported significantly more often with bleeding symptoms than women without this diagnosis: heavy bleedings (59.8% vs. 37.4%), prolonged bleedings (37.3% vs. 15.6%), bleeding between periods (33.3% vs. 13.5%), frequent periods (28.4% vs. 15.2%), irregular and unpredictable periods (36.3% vs. 23.9%).[15]

Pain

The overall incidence of pain in patients with fibroids was 53.7% in our study. The nature of pain was spasmodic and occurred only during menstruation.

Pain was assessed by the VAS in our study. A score was assigned to every subject recruited ranging from 0-10. Mild pain ranged from 0 to 3, this was reported in 32.6%. Moderate pain (VAS score of 4-7) was reported in 65.3% of patients. VAS score of 8-10 indicates severe pain. This was reported in 1.9% of patients.

As seen in our study the prevalence of dysmenorrhea was more common in an international internet-based survey too where women with diagnosed uterine fibroids reported significantly more often with the following pain symptoms: pressure on the bladder (32.6% vs. 15.0%), chronic pelvic pain (14.5% vs. 2.9%), painful sexual intercourse (23.5% vs. 9.1%) and pain occurring mid-cycle, after and during menstrual bleeding (31.3%, 16.7%, 59.7%, vs. 17.1%, 6.4%, 52.0%).[15]

Pressure symptoms

2% patients had pressure symptoms i.e. urinary frequency.

Bochenska et al conducted a cross-sectional study on 195 premenopausal women seeking treatment for uterine fibroids. Women most commonly reported pressure in the abdomen (71%), heaviness or dullness in the pelvis (60%), frequent urination (56%), pelvic pain or discomfort (48%), sensation of incomplete bladder emptying (43%), and incomplete emptying at the end of a bowel movement (42%). Fewer women reported bother stress urinary incontinence (36%), urgency urinary incontinence (35%), and difficulty with bladder emptying (21%).[16]

Lump in abdomen

A total of 3.8% patients presented with a complaint of a lump in abdomen. On examination uterus was 16 weeks in size in both the cases.

Khyade et al conducted a prospective study including 50 cases in which 2 patients presented with lump in abdomen (4%). However maximum number of cases were with uterine size less than 12 weeks that is 36 (72%), with 12-24 weeks uterine size were 13 (26%).[17]

Liver function tests

After the European medicine agency (EMA) recommended several measures to minimise the risk of rare but serious liver injury with UPA, liver function tests were performed pre-treatment, monthly during the course of 3 months treatment and post treatment.[18]

A total of thirty patients underwent liver function tests from June 2018 out of which one patient was withdrawn from the study due to increase in bilirubin and liver enzymes after assessment one month after commencement. Two patients had deranged liver enzymes after completion of three months. However, the liver enzymes returned to normal after 3 months.

Symptomatic relief

In our study symptomatic relief was taken as the primary endpoint. Amenorrhea and pain relief was achieved in 96% and 100% of the patients respectively. 64% of patients attained amenorrhea within one month of

treatment with UPA. Two major studies namely PEARL and PREMYA have shown similar relief patterns.

PEARL I was a double-blind, placebo-controlled study, in which women with symptomatic fibroids who were planning to undergo surgery were randomised in a ratio of 2:2:1 to 5 mg/day or 10 mg/day UPA or placebo for 12-13 weeks. At baseline, PBAC scores ranged from 102 to 1645. After 13 weeks, PBAC score <75 was achieved in 19%, 91%, and 92% of women receiving placebo and 5 and 10 mg ulipristal, respectively. Reductions in pain from baseline assessed by a visual analogue scale on the short-form McGill pain questionnaire were similar for 5 and 10 mg Ulipristal. Amenorrhoea was achieved within 10 days of taking 5 mg Ulipristal in 73% of patients.[10]

PREMYA study was a multi-centre prospective, non-interventional study of patients, diagnosed with moderate to severe symptoms of uterine fibroids and undergoing a pre-operative treatment with UPA. Overall symptomatic change, as measured on the clinical global impression-improvement (CGI-I) scale, indicated that from the start of treatment, 60.1% of patients were 'much improved' or 'very much improved' at 3 months. This improvement rate reached to 47.9%, 48.5%, 48.4% and 51.2% of patients at months 6, 9, 12 and 15 respectively.[19]

Comparison between pre and post treatment haemoglobin levels.

Out of the 50 patients who completed the 3 months course of UPA, the percentage of women in the Hb-10-11.9 gm% group increased from 36.5% to 50% whereas the women in the ≥12 gm% group increased from 42.6 to 46%. The post-treatment haemoglobin level was significantly increased compared to pre-treatment haemoglobin value ($p<0.05$).

A similar trend was seen in a multicentric Italian study. Haemoglobin levels improved during treatment in 72 of 142 women. About 50% had a median haemoglobin level less than 9 gm/dL at baseline; after UPA treatment only 25% of women had haemoglobin level less than 12 gm/dl.[20]

A list of 134 patients treated with UPA from January 2013 to August 2015 was obtained from electronic pharmacy records at the heart of England foundation trust (HEFT). It showed an improvement in the haemoglobin levels, pre-treatment 33.6% of women had a haemoglobin level less than 11 gm/dL before treatment compared to 8.2% after.[21]

Fibroid volume reduction

Pre-treatment and post-treatment mean±SD of fibroid volume in intra-mural type of fibroid group was 93.34±5.94 cm^3 and 82.95±6.07 cm^3 respectively. The mean post-treatment fibroid volume was significantly reduced compared to mean pretreatment fibroid volume ($p=0.029$).

The pre-treatment and post-treatment mean±SD of fibroid volume in sub-mucous type of fibroid group was 64.12±4.98 cm^3 and 53.95±5.42 cm^3 respectively. The mean post-treatment fibroid volume did not differ significantly compared to mean pre-treatment fibroid volume ($p=0.0739$).

The pre-treatment and post-treatment mean±SD of fibroid volume in sub serosal type of fibroid group was 152.60±9.87 cm^3 and 166.40±8.55 cm^3 respectively. The mean post-treatment fibroid volume did not differ significantly compared to mean pre-treatment fibroid volume ($p=0.535$).

In the PEARL II study reductions in fibroid volume were 36%, 42%, and 53% in the women taking 5 and 10 mg ulipristal and leuprorelin respectively. Clinically significant reductions in volume ≥25% were seen in 5mg and 10mg groups after each treatment. The percentage of patients who achieved this reduction increased between the first and fourth treatments for 5 mg and 10 mg ulipristal.[8]

Adverse effects

The incidence of various adverse effects was evaluated in our study. 88.2% of patients reported no adverse effects whereas 1.9% patients complained of hot flushes post treatment.

Unlike our study a Korean study reported a varied range of side effects seen among 100 premenopausal women who received UPA for 4-12 weeks during 2016 to 2017. The most frequent adverse symptom among women with symptomatic relief from HMB was weight gain (27%) and fatigue (27%), followed by abdominal discomfort (21%), dry eye (18%), facial flushing (17%), dizziness (17%), headache (17%) and increased vaginal discharge (15%).[22]

In PEARL II hot flushes of any severity occurred in 26% (5 mg), 24% (10 mg), and 65% (leuprorelin). The authors concluded that ulipristal has superior tolerability, with a lower incidence of adverse side effects such as hot flushes and low levels of oestradiol in comparison to leuprorelin.[8]

As seen in our study UPA is an effective drug in the management of symptomatic fibroids.

Limitations of this study were the high cost of drug and after the EMA recommended several measures to minimise the risk of rare but serious liver injury with UPA**,** it was difficult to convince patients to take opt for this medical management of symptomatic fibroids. Hence, we had a limited sample size to conduct the study.

CONCLUSION

UPA proved to be an effective drug for symptomatic relief in patients with uterine fibroids. Most patients attained amenorrhea within 1 month of commencing treatment and

all patients were pain free during the 3 months period. It helped in building up the haemoglobin level in most women with symptomatic fibroids. The reduction in fibroid volume was statistically significant in case of intramural fibroids, however it was not significant in case submucous and subserosal fibroids. Thus, we conclude that UPA is an effective drug for pre-operative treatment of symptomatic fibroids.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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