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INFLUENCE OF ULIPRISTAL ACETATE THERAPY ON UTERINE FIBROID-RELATED SYMPTOMS AND ON UTERINE AND FIBROID VOLUME AND VASCULARITY INDICES ASSESSED BY ULTRASOUND

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ABSTRACT:

AIM: To investigate the modification on quality of life and on uterine and fibroids volume and vascularization after 3 months treatment with Ulipristal acetate (UPA).

METHODS: 42 premenopausal women were evaluated clinically for the symptoms complained and underwent ultrasound examination before and after 3 months therapy with UPA.

Uterine volume and uterine arteries pulsatility index (PI) and resistance index (RI) were assessed for each patient. Considering that some patients had more than one fibroid, vascularization (supplying vessel PI and RI), localization and size of a total of 73 fibroids were also recorded.

RESULTS: After 3 months of UPA patients had a significant improvement of symptoms ($p<0,05$). There was a statistically significant reduction in both uterine ($p=0,03$) and fibroid ($p= 0,01$) volume with a decrease of all fibroids vascular indices ($p<0,05$).

CONCLUSION: UPA therapy results to be effective in improving fibroid-related symptoms and in reducing fibroid volume and vascularization.

Introduction

Fibroids occur in 20-40% of women of reproductive age, being the most common female benign tumours1.The majority of fibroids is asymptomatic and requires no treatment.

However, the presence of uterine fibroids may lead to significant clinical symptoms such as heavy menstrual bleeding, painful menstruation, pelvic pain, pelvic pressure, urinary frequency or urgency and constipation2. The mainstay of treatment of symptomatic uterine fibroids is myomectomy or hysterectomy3, but minimally-invasive alternative treatments are also used in clinical practice like uterine artery embolization4. Medical therapies with progestin, progestin-releasing intrauterine devices, and gonadotropin-releasing hormone (GnRH) are also available, but several studies have reported important side-effects like breakthrough bleeding and increased myoma growth for oral progestin5 and artificially induced menopause for GnRH, which use is in fact approved only for short-term presurgical therapy6-[7].

Since progesterone plays a fundamental role in stimulation of myoma growth8, modulating its pathway with selective progesterone receptor modulators (SPRMs), such as Ulipristal acetate (UPA), represents one new possibility of medical therapy. UPA, thanks to its selective antiproliferative and proapoptotic action9, has in fact resulted effective in reducing bleeding and fibroid size[10].

It has also a direct effect on the endometrium and on the pituitary gland inducing amenorrhea without a negative influence on estradiol levels or an antiglucocorticoid ativity[11-12].

Ultrasound evaluation of uterine fibroids after UPA confirms a reduction in fibroid volume10, but the impact of the therapy on uterine and fibroid vascularization has not yet been well investigated. On the other hand, we know that Asoprisnil, another SPRM, has been shown to reduce uterine artery blood flow, which in fact contributes to its clinical effect[13].

The aims of this study were to investigate if, after 3-month therapy with UPA, patients noticed a significant symptomatic relief regarding all the symptoms complained earlier and if there were important changes in uterine and fibroids volumes and in their vascularization before and after treatment. Finally, we wanted to assess if the different classes of fibroid, according to FIGO classification, had different response to UPA.

Methods

The study was designed as a longitudinal prospective study and was conducted from November 2014 (since the approval of UPA in our country) through January 2016 in a single centre, at the Department of Obstetrics and Gynecology of the University Hospital of Verona, Italy.

The study involved premenopausal women with levels of follicle stimulating hormone (FSH) <20 IU/L and estradiol (E2) >20 pg/mL on days 2–4 of the menstrual cycle.

Women were eligible for the study if they had at least one symptomatic uterine fibroid type 2,3, 4, 5 or 6 according to FIGO classification, with the main diameter between 4 and 10 cm assessed by ultrasound. Moreover, they must not have any previous uterine surgery nor suspicious items of adenomyosis or any gynaecological malignancy. Women were selected after confirmation of no ongoing pharmacologic treatment and exclusion of current pregnancy. We did not consider for the study fibroid types 0, 1 and 7 because in these cases the recommended approach in our clinic is surgery if they are symptomatic. Any medical therapy is indicated before the intervention unless presence of severe anemia or other specific features.

All patients included in the study received 5 mg of Ulipristal Acetate (Esmya©, Gedeon Richter, Budapest, Hungary) per day for 3 months consecutively. Treatment was initiated during the first day of menstruation. Patients were informed that UPA decreases the volume of uterine myomas and improves heavy menstrual bleeding14,15 but no data is available about its action on the other symptoms complained by women with uterine fibroids; they were also informed about the possible adverse effects of UPA. Informed consent was obtained from all individual participants included in the study and they were requested to report the adverse effects arising during the use of the drug.

Patients included in the study were scanned with a transvaginal ultrasound check and evaluated clinically for the symptoms complained at least one month before starting the treatment (baseline) and one month after finishing the 3-month therapy with Ulipristal Acetate.

Fibroid-related menorrhagia was evaluated by the Pictorial Blood Assessment Chart (PBAC) score. This instrument is a self-administered pictorial chart that takes account of the number of sanitary pads and tampons used, presence of blood clots and episodes of bleeding. The one-month PBAC score was calculated from the addition of daily PBAC scores for 28 days. A PBAC score >100 during the first eight days of menstruation was defined menorrhagia16. Subjective feeling of pelvic pressure, urinary urgency and constipation were recorded using a simplified questionnaire containing two categories defined as “absent" or “present”. The visual analogue scale (VAS) pain score was used to determine presence/absence of pelvic pain (intermestrual pain and/or dysmenorrhea). The cut-off considered affirmative was of 5/10 or more.

All ultrasound examinations were performed using a Voluson E8 (General Electric Medical Systems, Milwaukee, USA) ultrasound system, equipped with a transvaginal transducer (frequency 6.5 MHz; field of view, 150 ; number of elements, 192) and were performed using the same power Doppler settings: pulse repetition frequency, 1.0 kHz; gain, 50%; wall filter, 1; frame average, 10; Doppler frequency, Gen.; line density, middle; balance, [11].

The following sonographic parameters were evaluated both before and after therapy: uterine volume and vascularization; fibroid localization, volume, maximum diameter and vascularization. Uterine volume (expressed in cm3) was calculated by measuring the maximum length and the anteroposterior and transverse diameters of the uterine corpus, using the ultrasound device software formula for the calculation of the uterine volume. Myoma volumes were measured by using the existing 2D ultrasound methods that make up part of the software system of the ultrasound device. FIGO subclassification system was used for defining myoma localization[17].

Uterine and fibroid vascularization were analyzed studying Doppler wave forms of the right and left uterine arteries and and of the myoma supplying vessel, respectively. They were expressed in terms of pulsatility index (PI) and resistance index (RI).

To reduce inter-observer variability associated to power Doppler, measurements were taken always by the same sonographer with 20 years of experience in obstetrics and gynaecology power Doppler evaluation. To reduce the intra-observer evaluation, we used standard rules for uterine and fibroid vessels sampling: uterine Doppler signal was obtained from the usual site of visualization of each uterine artery, near its origin from the iliac artery; while the fibroid signal was obtained from the core artery of the fibroid. The Doppler range gate was applied across each vessel and the blood flow velocity waveforms were recorded for three cardiac cycles; each measurement was repeated 3 times and the average was calculated and consider as final result (Figure 1).

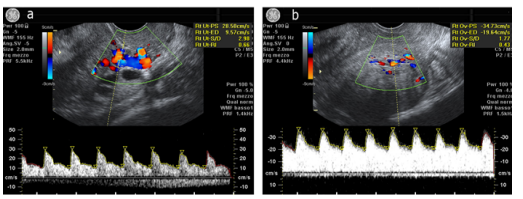

Figure 1 Examples of uterine artery (a) and fibroid supplying vessel (b) sampling for calculation of Doppler vascular indices.

Statistical Analysis

Data regarding symptoms are presented as frequencies and percentages while sonographic data are expressed as median ± S.D because of a non-normal distribution.

Statistical analyses were carried out with the SPSS 21.0 software.

Wilcoxon rank test and Student's t test were used for comparisons between clinical and sonographic features before and after treatment. Correlations were sought with Spearman's correlation coefficient.

The Kruskal-Wallis test was used to detect differences in fibroid response to treatment, in terms of volume and vascularization, among the different classes of fibroids.
P-values < 0,05 were considered statistically significant.

Results

In the period considered, 93 patients with symptomatic fibroids were selected for UPA therapy. 91 patients completed the treatment, while 2 interrupted before the end because of the side-effects: one had an urticarial reaction and one complained arthritic symptoms; all had immediate improvement after the suspension.

53 patients had the criteria to be included in the study but only 42 underwent the two clinical examinations and were therefore considered in this paper. Among these patients UPA treatment was in general well tolerated, only some mild adverse effects were recorded: headache (n = 11; 26.2%), hot flashes (n = 2; 4.7%), and nausea (n = 3; 7.1%).

The median age was 41 years (IQR, 30-53 years) and the median BMI 24,5 kg/cm^2 (19-33 kg/cm^2). 25 patients (59.5%) were of Caucasian racial origin, while 11 (26.3%) African, 2 (4.7%) Asians and 4 patients (9.5%) were South Americans.

More than half of patients were nulliparous (25 of 42, 59.5%) and 19 (45.2%) desired fertility. Considering previous surgery, 10 patients (23.8%) had already had myomectomy for symptomatic fibroids.

All patients followed correctly the instruction regarding the daily assumption of the therapy.

There were no adverse reactions to treatment in the group of patients selected for the study.

Patients' symptoms before and after treatment are shown in Table 1. After 3 months with UPA women had a significant improvement of all the symptoms complained before the treatment.

Table 1: Symptoms complained by the study population before starting the treatment and 3 months after Ulipristal Acetate (UPA) therapy.

Symptoms	N° pre treatment (%)	N° post treatment (%)	p
menorrhagia	24 (57.1%)	6 (14.3%)	0.001
Pelvic pressure	24 (57.1%)	1 (2.4%)	0.001
Pelvic pain	21 (50%)	1 (2.4%)	0.014
Urinary urgency/constipation	6 (14.3%)	0 (0%)	0.001

The percentages are calculated considering the total number of patients (n=42).

The median uterine volume before treatment was 269 (245.8-352.5) while after treatment was 211 (190-268) cm^3. This is a volume difference of 42 (19.7-90) cm^3 with a percentage of volume reduction of 14% from the baseline measurements ($p<0.05$).

The Spearman correlation test between the initial uterine volume and the percentage volume reduction after therapy showed a statistically significant positive correlation ($p<0.05$, $r=0.75$)

Regarding uterine power Doppler vascular indices, after 3 months of treatment right uterine artery PI increased from 1.70±0.58 to 1,86±0.49 (p=0.22) and left uterine artery PI from 1.90±0.64 to 0.83±0.12 (p=0.32). Considering uterine arteries RI, it increased from 0.78±0.14 to 0.81±0.13 (p=0.13) in the right artery and from 0.81±0.12 to 0.83±0.12 (p=0.30) in the left artery.

Fibroid main diameters, fibroid volumes and fibroid vascular indices, assessed before and after 3 months with UPA treatment are shown in Table 2. Considering that some patients had more than one fibroid, 73 fibroids was the total number of fibroids analyzed.

Table 2 Fibroid main diameters, fibroid volumes and fibroid vascular indices assessed before and 3 months after Ulipristal Acetate (UPA) therapy and the difference between the two values.

	Before treatment	After treatment	Δ (after-before)	p
Diameter(mm)	46.2±18.6	37.4±14.9	-8.8±9.6	0.01
Volume (cm^3)	60±58.5	40.3 ±40.2	-19.7±28.8	0.01
PI core artery	1.31±0.63	1.41±0.68	0.10±0.54	0.009
RI core artery	0.72±0.25	0.95±0.28	0.23±0.18	0.048

Data are given as mean± SD. PI, pulsatility index; RI, resistance index; Δ, difference.

The reduction of fibroid dimensions and volumes after 3 months of UPA therapy resulted statistically significant independently of their size, type or location (Figure 2).

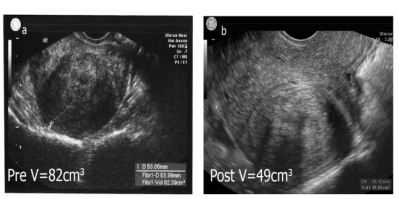

Figure 2 Volume assessment of type 6 fibroid before (a) and after (b) 3 months of Ulipristal acetate (UPA) treatment.

(a) Total fibroid volume= 82 cm2
(b) Total fibroid volume= 49 cm2

Moreover, in comparison with baseline indices obtained prior to treatment, fibroid supplying vessel PI and RI augmented significantly after the treatment, indicating a reduction of fibroid vascularisation after UPA (Figure 3).

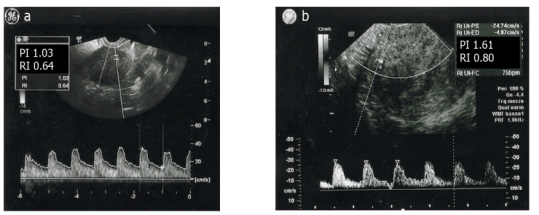

Figure 3 Doppler measurement of fibroid supplying vessel pulsatility index (PI) and resistence index (RI) before (a) and after (b) 3 months of Ulipristal acetate (UPA) treatment. After treatment (b) all vascular indices are decreased.

Dividing the 73 fibroids depending on their type, according to FIGO classification, we obtained 4 different groups because there were not type 3 fibroids in the study population. The different response to treatment among the groups, regarding modification of main diameter, volume and vascularization after and before treatment are reported in Table 3.

Table 3. Modification of main diameter, volume and vascularization in each class of fibroid considering the difference between values assessed after and before Ulipristal acetate (UPA) therapy

FIGO classification	number	Δdiameter (cm^3)(post-pre)	volume (cm^3) (post-pre)	Δ core artery PI (post-pre)	Δ core artery RI (post-pre)
2	4	-10,5±5,7	-31,8±26,6	0,28±0,79	0,09±0,21
4	19	-6,8±5,2	-10,7±20,4	0,21±0,73	0,09±0,15
5	22	-12,9±11,7	-33,1±37,41	0,16±0,33	0,03±0,23
6	28	-6,5±9,8	-13,7±22,6	0,15±0,50	0,016±0,32
p	0,086	0,033	0,412	0,393	

Data are given as mean± SD. PI, pulsatility index; RI, resistance index; Δ, difference.

The mean volume reduction was significantly higher in FIGO type 2 and 5 myomas in comparison with FIGO type 4 and type 6 myomas (p=0,033) and in particular type 5 fibroids resulted to have the highest response to treatment with a volume decrease rate of 42% after UPA.

However, there was not significant difference in diameter decrease or in vascularization reduction, considering fibroid supplying vessel flow parameters, among the different groups.

Discussion

The effects of Ulipristal acetate in controlling excessive bleeding due to uterine fibroids inducing amenorrhea and its action in reducing fibroid size were previously investigated by 2 large studies14,15 and recently confirmed by another one analysing the same outcomes on long-term intermittent therapy[18].

To the best of our knowledge, this study is the first to evaluate also the other invalidating symptoms involving women with uterine fibroids such as pelvic pain, feeling of pelvic pressure, urinary urgency and constipation. Our results show a significant improvement of all these symptoms after only 3 months of treatment, confirming one of the most important outcome of UPA: the improvement of health-related quality of life.

The mechanism of action of Ulipristal acetate is well known for what

that concerns its selective antiproliferative and pro-apoptotic activity and its effect on the pituitary gland and on the endometrium19-20. However, only one study has analysed the impact of the treatment on vascularization of uterine myomas calculating the three dimensional (3D) power Doppler vascular indices before and after 3-month therapy with UPA21. However, some authors consider 3D power Doppler vascular indices to have some limits in gynecology, artefacts are in fact rather common in case of tissue inhomogeneity and patient or probe movements because of the high sensitivity of the amplitude-based colour Doppler22-24. Considering and high tissue inhomogeneity in the fibroid documented after UPA we decided in our work to study standard Doppler waves with focus on PI and RI of uterine arteries and fibroid supplying vessels to evaluate uterine and fibroid vascularity. In fact, the use of power Doppler has some advantages in the study of uterine and myoma arteries, since it is sensitive to slow flow and small vessels and does not depend on the angle of insonation[25].

In our study statistically significant increase in PI and RI of fibroid supplying vessels were observed after 3 months of UPA, demonstrating a reduction of fibroid vascularization, that we suppose have a role in the shrinkage of leiomyomas. Our results show, in fact, that a 3-month treatment results in an overall 33% reduction of fibroid volume. This is consistent with the findings in literature reporting fibroid volume reduction between 21.2% and 36%14,15. Regarding uterine volume, after therapy it had a 14% reduction from its initial dimension with a mean volume variation of 42 cm3 which resulted significant; moreover, larger uteri resulted to have a higher decrease rate than smaller ones.

As to the aspect of vascularity, even if we found that UPA treatment resulted in an augmentation in all measured uterine power Doppler indices, this increase did not reach statistical significance suggesting that, even if UPA causes a reduction in uterine vascularization, there might be additional factors influencing regulation of the blood flow in the organ. Probably, the significant increased impedance to blood flow after treatment in leiomyoma supplying vessels, not found in uterine arteries, is a further proof that UPA has more determining effect on fibroid vascularization rather than on the entire uterine blood flow, but other studies are needed to confirm this statement.

Once analyzed fibroid volume and vascularization variations after therapy altogether, we tried to evaluate the same parameters in the different classes of fibroid, according to FIGO classification, and by comparing the results, to see if they had similar response to treatment. Our results show that the decrease in myoma volume was higher when they were intramural or with a predominant intramural component and in particular type 5 fibroids had the highest volume reduction (42%) after UPA.

A different response to treatment depending on the location of fibroids was observed also after uterine artery embolization (UAE)26 and the reason could be was the different vascularization. However, in our work there was not significant difference in diameter decrease or in vascularization reduction among the different groups, suggesting that unpaired vascularization can not be the only explanation. Probably there are additional factors, that may vary in the different classes, which contribute to these several responses to treatment. For this reason, in the future it might be interesting to evaluate, for example, if there is a different distribution of progesterone receptors in each fibroid type that can explain why the intramural ones have higher response to UPA.

This study has some limitations. First of all, the study group was relatively small and the patients were not blinded to the 3-month therapy with UPA and this may have influenced the improvement of the symptomatology (placebo effect). We are aware that the findings of this research should be interpreted as preliminary and other well-designed trials are recommended; in particular future randomized trials with adequate sample size should compare the 3-month UPA treatment with two repeated 3-month courses of treatment or even more courses, since UPA was shown to be well tolerated both in the current study and in previous investigations[14,15,18].

Another limitation of our study regards vascularization assessment: we only calculated standard power Doppler indices without evaluating 3D power Doppler indices too. It could be interesting in the future to compare the results obtained with the 2 techniques. The same concern is about volume detection too, even if the standard technique and the 3D volumetry have already shown to have similar accuracy in presence of regular fibroids[27].

In conclusion, our study confirms that UPA is becoming an alternative to hysterectomy as a treatment of fibroids. Fibroid vascularization decrease after UPA therapy is not only an interesting scientific observation but also provides a theoretical rationale for future studies that could investigate the possible relationship between initial fibroid vascularization and outcome of UPA treatment and in particular if a significant correlation exists between the initial Doppler indices and the shrinkage in leiomyoma size. This results can be useful in particular when myomectomy is indicated, to evaluate if a pre-surgical therapy with UPA is recommended or not. If the aim is just improving symptoms, UPA seems to be a good alternative to standard medical therapy because of its proved effectiveness and safety[10,28].

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