Preoperative treatment of uterine leiomyomas with ulipristal acetate

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Abstract

Background: Uterine leiomyomas are the most common benign uterine tumours in women. They are symptomatic in 20 to 50 % of cases. Symptoms associated with leiomyomas include heavy, prolonged menstrual bleeding leading to anaemia, dysmenorrhoea, pelvic pressure and pain, impaired function of adjacent organs, such as bladder and bowel, and reproduction dysfunction. Options for medical therapy are currently limited to preoperative reduction of symptoms related to uterine bleeding and fibroid size. Recently, selective progesterone receptor modulators (SPRM) have been introduced and approved in preoperative treatment of leiomyomas. The aim of our study was to assess the efficacy of preoperative treatment with SPRM ulipristal acetate (UPA) on leiomyoma shrinkage and haemoglobin (Hb) concentration improvement.

Methods: Fifty patients with symptomatic leiomyomas were assigned for preoperative treatment with 5 mg of UPA daily for 12 weeks. Before and a week after the UPA treatment was completed, leiomyoma volume was measured, and Hb concentrations and the amount of uterine bleeding were assessed. The outcomes were changes from baseline in leiomyoma volume and the proportion of patients with controlled bleeding after the treatment.

Results: After the completion of UPA treatment there was a mean volume reduction of the largest myoma by 33.3 %, whereas the mean volume reduction of up to 3 largest myomas was 32.3 %. Volume reduction was in both cases statistically significant. During the treatment course 41 (82.0 %) women were amenorrhoeic and the other 9 (18.0 %) had a significant reduction in uterine bleeding. The reduction in bleeding was accompanied by improvement in Hb levels in all patients.

Conclusion: Preoperative treatment with UPA for 12 weeks effectively reduces leiomyoma volume and facilitates or even makes laparoscopic surgery feasible. It is also beneficial for correcting anaemia, which is of outmost importance for postoperative recovery.

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1 Introduction

Leiomyomas are the most common benign uterine tumours, being encountered in 30–70 % of women in fertile period (1). Fibroids are monoclonal tumours of the smooth muscle of the endometrium; they contain large quan-

tities of collagen-, fibronectin- and proteoglycan-containing extracellular matrix (2). Approximately a fifth to a half of women with leiomyomas present with symptoms that adversely affect their health or quality of life. Most frequently the complaints include prolonged and/or excessive menstrual bleedings that cause anaemia, dysmenorrhoea, pains due to pressure exerted on adjacent organs, and less frequently infertility and bladder and bowel dysfunction. The very origin of leiomyomas has not yet been fully explained, but it is well known that these tumours are hormone-dependent. Fibroid growth is mainly influenced by ovarian steroid hormones estrogens and progesterone as well as by local growth factors (3,4).

Treatment is required in patients with symptoms and in cases of rapidly growing myomas. In pregnancy-planning women with asymptomatic myomas, these must be removed only if they cause deformities of the uterine cavity. Unfortunately, there has been no medicine yet that could completely remove myomas, and neither is it expected to be available in the near future (5,6). Therefore, despite certain non-surgical options for myoma treatment, such as embolisation of the uterine artery and MRI-guided focused sonography, hysterectomy or myomectomy still remain the most common treatment modalities. Most patients can be operated laparoscopically or hysteroscopically, however, such a treatment approach has limitations in terms of the number and size of myomas or the uterus itself (7). Medication treatment is generally limited to the alleviation of symptoms prior to surgery, in particular of heavy bleedings and anaemia, as well as to the reduction of myoma size (8). Presently, the only substances registered for medical treatment of leiomyomas are gonadoliberin agonists (GnRHa) and ulipristal acetate (UPA), a selective progesterone receptor modulator, which has been registered in Europe since 2012. GnRHa induce a transient menopause. Due to a decrease in oestrogen and progesterone levels, the uterus and myomas are temporarily reduced and (menstrual) bleedings discontinued, which can be beneficial before the planned surgical intervention. GnRHa have several adverse effects due to the induced hypo-oestrogen state, including the loss of bone density, which renders them unsuitable for prolonged use. They are also less suitable for myoma reduction prior to myomectomy, as the cleavage plane between the normal myometrium and myoma is obscured (9,10,11).

Presently, SMPR seem to be the most promising medications for preoperative treatment of leiomyomas. The latest SMPR studies also indicate the safety of ulipristal acetate (UPA) for long-term use. Such long-term treatment could help to avoid the need of surgery particularly in premenopausal women (12,13,14). UPA triggers the apoptosis of myoma cells, thus reducing myoma volume by up to 46 %, and by inhibiting ovulation induces amenorrhoea in up to 90 % of patients (12,15). UPA does not affect the baseline values of gonadotropic hormones and therefore does not cause hypo-estrogenism (16). SMPR treatment may cause a benign, nonphysiological, non-proliferative histological change of the endometrium, the so-called progesterone receptor modulator associated endometrial changes (PAEC) (17,18). This change vanishes spontaneously within a few weeks to months after discontinuation of UPA treatment (12,15,19).

The aim of our study was to obtain further knowledge on the use of new medication for preoperative treatment of myomas, since so far such studies have been rather scarce and performed most-

ly in patients with heavy myoma-related bleedings but not also in those with other symptoms. We were particularly interested in the effect of UPA on the reduction of myoma and the improvement of blood counts, as the research so far was focused primarily on reducing bleeding and improving the quality of life.

2 Subjects and methods

2.1 Subjects and measurements

Our prospective non-randomised study was carried out at the Department of Human Reproduction, Division of Gynaecology of the University Medical Centre Ljubljana in the period between October 2013 and December 2016. The study group consisted of 50 patients with myomas and symptoms who required surgical treatment. Additional criteria for inclusion were as follows: the largest myoma diameter more than 3 cm and functional ovaries. Postmenopausal patients, patients with unexplained uterine bleedings and those who had been receiving hormone replacement therapy in the last six months were not included in the study. The study group subjects were aged 26–57 years (mean 43.4 years, SD 7.33).

Prior to the planned surgical intervention, all patients were prescribed UPA at a dosage of 5 mg/day through 12 weeks, which was to be taken in the first 4 days of their menstrual cycle in accordance with the prescribing instructions.

All of them had haemoglobin concentration determined before the beginning of therapy. Anaemic patients were additionally prescribed an iron supplement in form of tablets (100 mg of ferric oxide per day), if it had not been already prescribed by their selected physician. Prior to the beginning of UPA treatment, all patients included in the study underwent ultrasonography (US) to have the diameters of up to 3 largest myomas measured in 2 planes. The mean diameter served as the basis for calculating the volume of up to 3 largest myomas using the formula for the volume of a sphere ($V = 4/3\pi r^3$). One to two weeks after completed UPA treatment, the same US measurements of up to 3 largest myomas were repeated and Hb concentration re-determined.

In all subjects we monitored the parameters that were relevant for assessing the effectiveness of preoperative UPA treatment: change in the volume of all measured myomas and the largest myoma, change in uterine bleeding during therapy, change in Hb concentration, and any side effects were recorded. At the end of the treatment, the endometrial thickness was evaluated by ultrasonography, and in patients who underwent hysterectomy, the tissue was histologically examined.

Taking into account possible measurement errors, UPA treatment was considered successful in those patients in whom the total myoma volume was reduced by at least 10 %. In Week 13 to 16 from the beginning of UPA treatment all patients underwent laparoscopic surgery. The type of surgical intervention was determined with respect to the number of myomas, possible former surgeries for myoma, patient's age, desire for conception and preservation of the uterus. Four patients (8.0 %) had total laparoscopic hysterectomy (TLH), 25 (50.0 %) supracervical laparoscopic hysterectomy (SLH) and 21 (40.0 %) had laparoscopic myomectomy. As many as 14 (28.0 %) patients wished to get pregnant after completed therapy while 7 (14.0 %) only wished to have their uterus preserved. In patients with only myoma removal, we subjectively assessed the

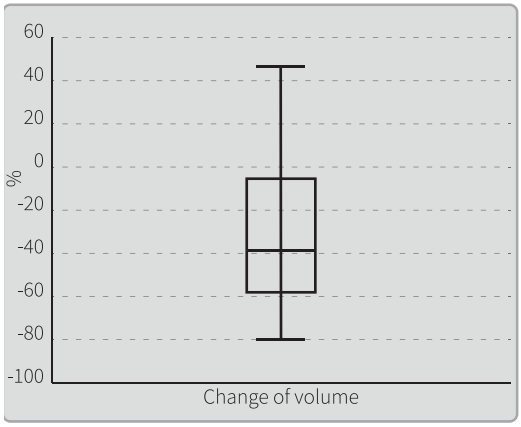

Figure 1: Median (1st and 3rd quartile, min./max.) change in the sum of volumes of up to 3 largest myomas.

cleavage plane between myoma and the myometrium, or the difficulty of myoma enucleation and its consistency.

All the US measurements and surgeries were performed by the first author of this article.

As our study covered only preoperative treatment with a drug that has already been registered for this type of therapy while all other procedures were compliant with the routine used in other patients scheduled for myoma surgery, an ethical assessment of the research was not required.

Table 1: Indications for surgery

Indications	No. of patients	%
Hypermenorrhoea	17	34.0
Hypermenorrhoea and dysmenorrhoea	14	28.0
Dysmenorrhoea	5	10,0
Hypermenorrhoea, dysmenorrhoea, pain	4	8.0
Hypermenorrhoea, dysmenorrhoea, growing myomas	4	8.0
growing myomas, dysmenorrhoea	2	4.0
Growing myomas, pain	4	8.0
Total	**50**	**100.0**

2.2 Statistical methods

The normal distribution of the observed variables was verified by Shapiro-Wilk's test. Since the variables were distributed normally, the results were shown as averages with a standard deviation (SD). The difference in myoma volume before and after UPA treatment, and the difference in Hb concentration before and after treatment were tested with dependent t-test for paired samples. Confidence intervals were calculated. Statistical analyses were performed using Statistica 8.0 software (StatSoft Inc.). Statistical significance cut-off value was set to $p < 0.05$.

3 Results

Table 1 presents indications for surgery in study patients. Fourteen patients (28.0 %) had 1 myoma, 9 (18 %) had 2 and 27 patients (54.0 %) had 3 or more myomas. Out of 50 patients, 41 (82.0 %) were anaemic with Hb concentration lower than 120 g/L.

During UPA treatment, 41 (82.5 %) patients were amenorrhoeic while the remaining 9 (18.0 %) had only light cyclical bleedings.

After completed UPA treatment, the mean volume of the largest myoma decreased by 33.3 % (95 % CI [-41.8; -24.9]) and the total mean volume of 3 largest myomas by 32.3 % (95 % CI [-41,3; -23,3]). In both cases, the volume decrease was statistically significant (Table 2).

In 37 (74.0 %) patients the mean myoma volume decreased by more than 10 %. In these patients after completed UPA treatment, the mean volume of the

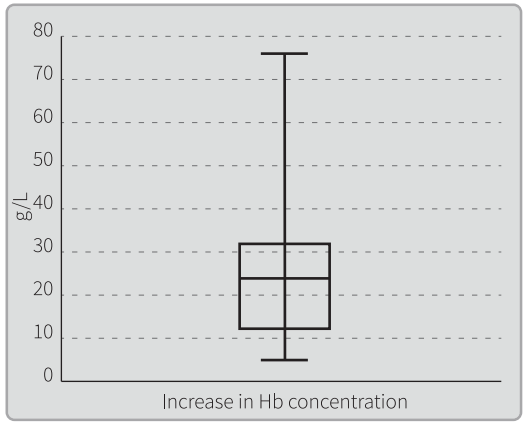

Figure 2: Median (1st and 3rd quartile, min/max.) increase in Hb concentration after completed UPA treatment.

largest myoma decreased by 47.6 % (95 % CI [-53.3; -41.9]) and the total mean volume of 3 largest myomas by 48.5 % (95 % CI [-54.0; -43.0]).

Figure 1 shows the median change in the sum of volumes, the first and third quartiles, and the lowest and highest values in percentages of up to 3 largest myomas.

In all subjects we noted an increase in the concentration of Hb by 24.3 g/l on average (from 5 to 76 g/l, SD 16.32 g/l, 95 % CI [19.8; 28.8]), the difference being statistically significant ($p < 0.001$). Figure 2 shows an increase in the concentration of Hb after completed UPA treatment.

Adverse side effects were noted in 11 (22.0 %) patients (Table 3). None of the patients with side effects sought medical help or discontinued their UPA treatment. Four (8.0 %) of the patients experienced mild hot flashes, 7 (14.0 %) mild to moderate occasional headache, 3 (6.0 %) experienced breast swelling, and 1 (2.0 %) patient reported loss of appetite and mild hair loss. Multiple side effects were reported by 4 (8.0 %) patients. After completed UPA treatment, ultrasonography revealed endometrial thickening (> 16 mm) in 7 (14.0 %) patients. In four of them who underwent hysterectomy PAEC was histologically confirmed while the remaining 3 only had myomas removed and therefore histological examination of the endometrium was not performed.

In patients with myomectomy the cleavage plane between fibroids and the myometrium was well preserved. We have also noted that in UPA treated patients myomas are slightly softer than in those who do not receive preoperative UPA treatment.

4 Discussion

Presently, medical treatment of myomas most frequently precedes the planned surgery in order to reduce myoma volume and improve the patient's

Table 2: Volume change of the largest myoma and total myoma volume change in ml and percentages before the beginning and after competed UPA treatment. Data are expressed as mean volume (standard deviation) and 95 % confidence interval (CI) for volume change in ml and the percentage change in %.

Myoma volume	Before UPA (ml)	After UPA (ml)	Dvol. (ml)	95 % CI (Dvol. in ml)	p (Dvol. in ml)	Dvol. (%)	95 % CI (Dvol. in %)
The largest	153.6 (178.0)	97.7 (132.6)	-56.0 (133.3)	[-93.0; -19.1]	0.004	-33.3 (30.5)	[-41.8; -24.9]
Min/Max	11.0/927.1	6.0/833.9	278.5/-767.3			50.1/-82.7	
Total 3 largest	191.7 (197.4)	123.5 (144.5)	-68.0 (145,5)	[-108.3; -27.7]	0.002	-32.3 (32.6)	[-41.3–23.3]
Min/Max	14.7/1074.6	10.3/518.4	282.2/-822.3			47.2/-79.2	

blood count, as well as for research purposes (20,21). Our study has shown that a preoperative UPA treatment efficiently reduces myoma volume in the majority of patients, thus facilitating or even enabling the endoscopic surgery. Not only the duration of surgery is shorter in smaller myomas but the myoma size may also influence the loss of blood during the procedure (22,23). Despite the fact that ours was not a randomised controlled study, which is undoubtedly a drawback, the results are nevertheless similar to those obtained in groups of study subjects receiving the same dose of UPA in the few randomised controlled studies that have been performed to date by a single research group.

An advantage of our study is that – for the difference from PEARL studies which included only patients with hypermenorrhoea and myomas smaller than 100 mm – our study also included patients with myomas exceeding 100 mm in diameter and with other myoma-related symptoms. The authors of studies PERL II and IV have found that preoperative UPA treatment effectively decreases myoma volume. The total volume of the three largest myomas decreased by 36 % and 38 % (median) in 97 and 228 subjects respectively, receiving UPA at a dose of 5 mg. In 50 subjects in our study, the total volume of the largest myomas was found to have decreased by 32.3 % on average (95 % CI [-41.3; -23.3]) (15,24).

No difficulties were encountered in patients with myomectomy as the cleavage plane between myomas and the myometrium was well preserved. We have noted, however, that in UPA treated patients myomas were slightly softer than in those who did not receive preoperative UPA treatment. These subjective findings were also confirmed by other investigators participating in the studies where patients received preoperative UPA treatment (25). According to our treatment success criteria requiring at least a 10 % myoma volume reduction, the treatment was unsuccessful in 26.0 % of the patients. A recent research has

Table 3: Adverse side effects in individual patients.

Patient	Hot flashes	Headache	Breast swelling	Loss of appetite	Mild hair loss
1		+			
2	+	+			
3			+		
4				+	+
5	+	+	+		
6		+			
7		+			
8		+	+		
9	+				
10	+				
11		+			

shown that UPA treatment in younger patients and/or those with large myomas could be unsuccessful (8).

After UPA treatment, all our study patients presented with a statistically significant increase in Hb concentration. During treatment, most of them (82.0 %) were amenorrhoeic, while the others presented with significantly decreased bleeding and as a result of that an improved or normalised blood count, which was consisted with the findings of Donnez et al. (15,19). A recent study has shown that outcomes of non-cardiac surgical procedures are worse in anaemic patients. Namely, even a low-grade anaemia (haematocrit in females < 36 %) significantly affects 30-day postoperative morbidity and mortality in patients who underwent a major non-cardiac surgery (26).

UPA medication is available in the form of 5 mg tablets. The medicine is taken once a day for 12 weeks and the application starts in the first week of menstrual bleeding. This three-month treatment cycle can be repeated several times. Re-treatment starts during the second menstrual period after the completed previous treatment cycle. Menstruations are generally restored within 4 weeks from the completed treatment (27). The most frequent side effect of UPA treatment is amenorrhoea, which however is desirable. Other frequent adverse effects include headache, fatigue, nausea, abdominal pain, dizziness, acnae, muscular and skeletal pains, hot flushes, ovarian cysts and breast tenderness. UPA is not recommended in patients with severe renal impairment, with moderate or severe hepatic insufficiency, and in patients under 18 years of age. The use is further contraindicated in the case of hypersensitivity to the active substance or to any of the excipients, in women who are pregnant or breastfeeding, who bleed from the genitals for unknown reason or cause unrelated to uterine myoma, and in patients with cervical, ovarian or breast cancer (28).

In its document EMA/355940/2018, Pharmacovigilance Risk Assessment Committee (PRAC) at the European Agency for Medicines published recommendations on measures to reduce the risk of complications arising from possible hepatotoxicity of UPA, which were adopted by the Committee for Medicinal Products for Human Use (CHMP) on 1 June 2018.

Before starting UPA treatment, all patients must undergo liver function tests. If the value of liver enzymes is twofold the upper normal value, this medicine must not be prescribed. Functional liver tests should be repeated every month in the course of therapy, and then 2–4 weeks after completed treatment. If the values of liver enzymes are three times above the upper normal value, the treatment should be discontinued and the patient carefully monitored. Multiple UPA cycles should only be prescribed to patients who are not eligible for surgery. Prior to the planned surgery, only one cycle of UPA should be prescribed (29).

In our study, in most patients, amenorrhea or a significant reduction in uterine bleeding was achieved within a short time, which was the desired effect. Approximately a fifth of the patients reported mild adverse side effects, most often a headache, which is comparable to other studies (12,15,19,24).

The use of UPA has been studied in PEARL I, PEARL II, PEARL III, PEARL III extension, and PEARL IV clinical trials. In PEARL I, researchers compared the use of UPA and placebo in patients with symptoms, who were planned to undergo surgery. All of them were receiving iron and UPA at a dosage of 5 mg/day (96 subjects) or 10 mg/day (98

subjects) or placebo (48 subjects) for 12 weeks. The amount of uterine bleeding, the blood count before and after treatment and the size of myomas were monitored. It was found that both dosage regimens of UPA treatment effectively controlled uterine bleeding (most patients were amenorrhoeic after 10 days of UPA use), improved blood count and reduced the median myoma volume by 21 % (19).

In PEARL II trial, the effectiveness of UPA 5 mg (97 subjects) or 10 mg (103 subjects) was compared to GnRHa leuprolide acetate (101 subjects) for preoperative treatment of symptomatic myomas. It was found that the difference between two groups of subjects who received 5 mg or10 mg of UPA per day was not statistically significant compared to monthly injections of leuprolide acetate to reduce uterine haemorrhage due to myoma. Bleeding was found to have decreased in 90.0 % of patients receiving 5 mg UPA, in 98.0 % of patients receiving 10 mg UPA, and in 89 % of patients receiving leuprolide acetate. Furthermore, the patients receiving UPA had significantly fewer hot flashes (10.0 % and 11.0 % respectively in UPA groups vs. 40.0 % in leuprolide acetate group). The preliminary results also showed a prolonged effect of myoma volume reduction in non-operated-on patients. In the leuprolide acetate group, myomas started to regrow already a month after the last dose, while in the UPA groups, most patients showed no evidence of myomas regrowth after 6 months (15).

PEARL III (209 subjects) and PEARL III extension (132 subjects) trials were carried out to establish the efficacy and safety of long-term use of UPA for the treatment of patients with symptomatic myomas. In most patients, 4 cycles of UPA taken with intermittent pauses resulted in amenorrhoea and a further decrease in myoma size. These data indicate that UPA may trigger apoptosis and reduce myoma cell proliferation, which could result in regression of the disease (12,14,19).

In PEARL IV too, likewise in former two trials, the authors tested the efficacy and safety of long-term UPA use in patients with symptomatic myomas. The study subjects received 5 mg (228 subjects) or 10 mg (223 subjects) of UPA for 12 weeks with intermittent pauses so that they started taking UPA again during the second menstruation following a completed previous cycle. During UPA use, the majority of patients in both groups were amenorrhoeic (69.6 % and 74.5 % respectively). The difference between the groups with 5 mg and 10 mg UPA was not statistically significant. In both groups, the myoma volume was reduced by 25 % or more in 78.0 % and 80.1 % of patients respectively, the difference also not being statistically significant. This study further confirmed the efficacy and safety of long-term treatment with UPA (13,24).

The first few successful pregnancies were reported in a follow-up study of the patients who participated in PEARL II and PEARL III clinical trials, and who later on wanted to become pregnant. Following preoperative UPA treatment, as many as 21 patients wanted to become pregnant, and 15 (71.0 %) of them succeeded. Thirteen healthy children were born (12 deliveries), while 6 women had spontaneous abortion in the early pregnancy. In two pregnant patients, myomas disappeared almost completely, so that surgery was deemed unnecessary. The researchers also did not notice any regrowth of myomas in pregnancy, which indicates a prolonged effect of myoma size reduction (30). A few cases of successful pregnancies after UPA treatment of symptomatic myomas without the

need for subsequent surgery have been described (31,32).

5 Conclusions

Our research has shown that preoperative UPA treatment efficiently reduces the size of myomas and improves blood count, which facilitates or enables the use of the most advanced methods of endoscopic surgery and reduces the risk of postoperative complications. Despite the shortcomings of this study, which was not a randomised controlled one, the results are in line with those obtained by the few randomised controlled trials that have been carried out so far. In our, as well as in other studies, UPA was tolerated well by the patients, and had relatively few side effects. Nevertheless, a lot of further research on the efficacy and, above all, of the safety of UPA will have to be carried out, as in the recent months there has been a suspicion of possible hepatotoxicity of this medicinal product.

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