Application of ulipristal acetate in female patients with uterine fibroids

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Abstract

OBJECTIVES: Uterine fibroids are the most common benign tumors in women of reproductive age. Evidence suggest that ovarian steroid hormones, in particular, progesterone play a major role in promoting leiomyoma development and growth. For the last years there was an extensive research on selective progesterone receptor modulators and their use in therapy. Ulipristal acetate (UPA) is one of these modulators. The aim of this paper is to evaluate efficacy and safety of oral ulipristal acetate for the treatment in women with symptomatic uterine fibroids.
METHODS: The study group comprised five patients with uterine fibroids. All patients received 5 mg of ulipristal acetate per day for three months.
RESULTS: The total volume of fibroids decreased by 33–68%. In all patients during the administration of UPA significant reduction of menstrual bleeding was observed. Increase of endometrial thickness without clinical significance was observed in two patients. No significant side-effects were observed during the treatment period.
CONCLUSIONS: 1) The volume of fibroids decreased from 33 to 68%. 2) The UPA administration effectively controlled excessive bleeding. 3) Treatment with UPA may modify the scope of the surgery. 4) UPA is a well-tolerated drug.

CASE REPORT

INTRODUCTION

Uterine fibroids are the most common benign tumors of the reproductive system. Their prevalence in women at childbearing age is estimated at a range of 20–40% (Baird *et al.* 2003). Not only steroid hormones, such as estrogens and progesterone, play an important role in etiology of fibroids, but also other local growth and genetic factors (Wolańska *et al.* 2008). Symptomatic fibroids, which cause heavy menstrual bleeding, pain and discomfort in the abdomen lead to a significant reduction in the life quality (Stewart *et al.* 2001). They may also be a cause of reproductive disorders (Wiswanathan *et al.* 2007). Uterine fibroids are treated with invasive procedures, such as enucleation of the fibroids and resection of the uterus, uterine vessels embolization, laser thermotherapy, myolysis or kriomyolysis (Stewart *et al.* 2003; Lefebvre *et al.* 2004; Kaminski *et al.* 2008; Marret *et al.* 2012). The options of fertility preserving surgeries are of a paramount meaning for women at childbearing age (Islam *et al.* 2013).

The important role of estrogen in the development of uterine fibroids has been known for quite a long time, however just in recent years,

greater attention has been focused on the importance of progesterone effect in the etiology of fibroids. It was described that progesterone stimulates proliferation and reduces apoptosis of fibroid cells. Progesterone effect is conducted through the interactions with progesterone receptor. The progesterone receptor belongs to the nuclear steroid receptor family. There are two isoforms of progesterone receptor PR-A and PR-B, encoded by a single gene located on the long arm of chromosome 11 (11q23). Progestogens may induce different responses dependent on the production and activity of the two forms of the receptor in the form of AA and BB homodimers or AB heterodimers in the target tissue. Transcriptional activity of A and B receptors depends on the differences between the target cells. In most cells, PR-B is a positive regulator of progesterone-responsive genes and PR-A inhibits the activity of PR-B (Speroff *et al.* 2007). Research indicates that the number and synthesis of progesterone receptors, both A and B isoforms, increase within the fibroid cells (Ishikawa *et al.* 2010). The inhibition of receptor activity can reduce cell proliferation in uterine fibroid (Chwalisz *et al.* 2005; Horak *et al.* 2012).

For years, studies on selective progesterone receptor modulators and their use in therapy have been conducted (Ohara *et al.* 2008). Ulipristal acetate (UPA) is considered as one of these modulators (Croxtall *et al.* 2012). UPA exerts tissue-specific and partial antagonist activity against progesterone. It modualtes progesterone receptors in fibroid cells, endometrium and pituitary gland. It reversibly blocks progesterone receptors in target tissues and modulates the transcription in a tissue-specific manner (Melis *et al.* 2012). Within fibroids, it exerts direct anti-proliferative, pro-apoptotic, and anti-fibroblast effect (Horak *et al.* 2012). UPA leads to the change in the proportion of A and B progesterone receptor isoforms, increases fibroid cell apoptosis by inducing mitochondrial TNF, reduces cell survival, and changes the composition of extracellular matrix by activating metalloproteinases (Yoshida *et al.* 2010).

UPA, at a dose of 5 mg, was approved by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) for the preoperative treatment in women during childbearing years with symptomatic uterine fibroids.

UPA was recently introduced on the market so the sharing of clinical experience with its use seems to be very necessary and interesting.

CASE

In this paper we present observations of five patients with uterine fibroids, who received 5 mg per day of UPA for three months. The therapy was introduced during the first days of the menstrual cycle. Heavy and painful menstrual periods were the indications for administration of UPA. Hysteroscopy and histopathological analysis of the tissue resected during surgery excluded other causes of bleeding, except for the submucosal fibroids. Data on the treated patients is shown in Table 1.

R.S. a female patient aged 44, that underwent three years ago an enucleation of subserosal uterine fibroid and endometrial cysts of the left ovary. Uterine fibroids was diagnosed in 2007. Currently, the patient suffers from very heavy, painful menstrual periods. In the ultrasound scan, before treatment with UPA, the largest volumes of fibroids were reported as: 12.8, 9.7, 9.7 cm^3, and after treatment, 14.8, 3.1, 9.2 cm^3 respectively. The total volume of fibroids before treatment was 32.2 cm^3, after the treatment 27.1 cm^3, thus the volume decreased by 15.83%. During a few months of follow-up after discontinuation of the UPA, a decrease in severity and

Tab. 1. The patients treated with the UPA in Department of Obstertics and Gynecology, Warsaw Medical University.

Initials	Age	BMI [kg/m²]	Labour	Missc.	Period length	Bleeding duration	Bleeding patterns	Diagnosis of leiomyoma	Volume of leiomyoma before treatment [cm³]	Volume of leiomyoma after treatment [cm3]	Change of leiomyoma volume [%]	EM thickness before treatmnet [mm]	EM thickness after treatmnet [mm]	Length of treatment ulipristal acete [months]
RS	44	28.6	0	0	28-30	7	excessive, painful	2007 (6 years)	12.8 9.7 9.7	14.8 3.1 9.2	15.62 68 5.2	3.0	12.0	3
EP	54	29.3	1	0	28	7	excessive	2010 (3 years)	55.3	54.2	2	9.0	6.0	3
MR	40	33.5	0	0	30-35	10	excessive	2006 (7 years)	22.4 22.4 22.4 22.4	7.7 33.1 17.96	65.6 47.76 46 19.8	7.4	13	3
IW	58	23.9	0	0	28	5-7	excessive	2000 (13 years)	57.8	37.3	35.47	6.0	6.5	3
IJ	39	20.8	0	0	28	5-7	excessive	2007 (6 years)	33.5	22.4	33.13	16.0	6.0	3

UPA - ulipristal acete, BMI - Body Mass Index, Missc - Misscariage, EM - Endometrium.

length of menstrual bleeding was observed. The patient did not decide on surgical treatment.

E.P. a female patient aged 54 with uterine fibroids diagnosed 3 years ago, abundant, irregular menstrual bleeding. The patient delivered once by a cesarean section. Currently she suffers from hypertension and kidney stones. In the ultrasound scan, a uterine fibroid of 55.3 cm^3 volume was described. After 3 months with the UPA treatment, the fibroid reduced by 2%. One month after discontinuation of the treatment, heavy bleeding re-initiated. Decision on surgical treatment was undertaken. The patient was qualified for hysterectomy.

M.R. a female patient aged 40 with infertility, uterine fibroids diagnosed 7 years ago, suffers from heavy bleeding and long menstrual periods. In an interview, submucosal fibroid resection surgery was performed twice and surgery of an ovarian cyst enucleation was performed. In the ultrasound scan, before the beginning of treatment, four fibroids of 22.4 cm^3 volume each, were reported, with a total volume of 89.6 cm^3. After the end of the treatment, three of them reduced their volume to 7.7 cm^3, 12.1 cm^3 and 17.96 cm^3 respectively, one increased its volume to 33.1 cm^3. The total fibroid volume decreased to 70.86 cm^3, i.e. about 43.8%. After a three-month treatment with UPA, hysteroscopy and enucleation of two submucosal fibroids were conducted. Currently, a laparoscopy and enucleation of subserosal fibroids is planned, as well as resection of a hydrocele on the fallopian tube. The patient wants to get pregnant.

I.W. a female patient aged 58 with uterine fibroids diagnosed 13 years ago, with irregular, heavy menstrual bleeding. During three-months treatment with UPA, the volume of fibroid decreased significantly (by 35.47%) from 57.8 cm^3 to 37.3 cm^3. Currently, the follow-up of the patient is 6 months. At that time, no menstrual bleeding was reported.

I.J. a female patient aged 39 with uterine fibroid diagnosed 6 years earlier, with regular cycles and abundant menstrual bleeding. In 2009, the patient underwent enucleation surgery for fibroids. One year after the surgery, the presence of new fibroids was reported. After three months with UPA treatment, fibroid decreased by 33.13% , from 33.5 cm^3 to 22.4 cm^3. After discontinuation of UPA, menstrual bleeding became moderate and regular. Before UPA administration, the surgery was not possible due to technical reasons. After the end of treatment, due to the reduction of fibroid volume, enucleation surgery became technically possible. In this patient, postoperative course was complicated by deep vein thrombosis .

All patients during the three-months treatment with UPA were found to tolerate the drug well. They did not report any adverse effects. None of the patient reported vaginal bleeding during the treatment.

Based on volume measurements, the majority of uterine fibroids observed in the ultrasound scan decreased. The total volume of fibroids decreased by 33–68%. Two fibroids only slightly reduced their volume by 2% and 5.2%. In all patients during the administration of UPA, inhibition of menstrual bleeding was reported.

DISCUSSION

According to our observation, after three-months treatment, the volume of most fibroids decreased from 33 to 68%. The administration of UPA may be beneficial in reduction of heavy, long menstrual bleeding, which may be important in making the decision on treatment. The observed results of the study group are consistent with the observations reported by other authors. In February 2012 in the New England Journal of Medicine, PEARL I and PEARL II studies evaluating the efficacy of the UPA administration were published (Donnez *et al.* 2012). In the PEARL I study, 242 patients with uterine fibroids (the size corresponds to <16th week of pregnant women uterus), heavy bleeding and anemia (average hemoglobin concentration was 10.2 g/dl) were evaluated. After 13 weeks of treatment, the volume of the fibroids decreased by 21% on average. In more than 90% of patients, the reduction of menstrual bleeding was reported. In PEARL II study, one evaluated 307 patients with excessive bleeding from the uterus and uterine fibroids, with size corresponding to a pregnant uterus <16th weeks of gestation were evaluated of pregnant women uterus. In this study UPA and gonadoliberin agonist (GnRH) were compared. The inhibition of bleeding from the uterus was achieved in 90% of patients receiving 5 mg of UPA, in 98% receiving 10 mg of UPA and in 89% receving GnRH agonist. Fibroids volume was reduced by 36% on average in the group receiving 5 mg of UPA, 42% in the group receiving 10 mg of UPA and 53% in case of GnRH administration. Other authors, after the end of treatment with UPA at a dose of 5 mg, observed inhibition of bleeding from the uterus in 90% of patients and fibroid volume reduction from 25% to 36% (Talaulikar *et al.* 2012).

There are reports on increased risk of endometrial thickness related to the administration of UPA. Endometrial progesterone receptors block may lead to endometrial thickening and modifications (Spitz *et al.* 2009). Previous studies have shown that the observed alterations are reversible and do not have the characteristics of a proliferative process (Mutter *et al.* 2008). In our group of patients, in case of two patients, we observed the increase in the endometrial thickness – with no clinical significance. After discontinuation of UPA, bleeding was not increased.

Ulipristal acetate is a well-tolerated drug. During its administration, the patients did not report any adverse effects. In the absence of the above-mentioned symptoms, and due to the decline of heavy menstrual bleeding, the medication was very-well evaluated by the female patients. Moreover, patients would like to receive therapy longer than three months. Safety and

efficacy of the extended therapy were discussed in PEARL III study. Initial results of PEARL III study were presented at Barcelona, Spain 2013 (A stand alone scientific symposium Ulipristal acetate as a treatment for uterine fibroids: clinical data and experience).

The main advantages resulting from the administration of UPA were associated with the ability to defer and reduce the scope of the surgery. Reduction of fibroids volume can significantly improve the conditions of surgery. It can also, as in the case of perimenopausal women, change completely the qualification for the surgery.

The UPA administration may allow to avoid surgical treatment of the uterine fibroids in some cases and may also contribute to the improvement of general health (Reron *et al.* 2004).

The clinical effects and good tolerance of UPA are encouraging for future treatment.

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