

# NEW OPTION IN PHARMACOLOGICAL TREATMENT OF UTERINE FIBROIDS: SELECTIVE PROGESTERONE RECEPTOR MODULATORS

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**Abstract:** *The most frequently identified benign tumor in women is represented by the uterine fibroids with various symptoms: metrorrhagia, dysmenorrhea, anemia, pelvic pain. Nowadays because none of the approved medical treatments has proven able to completely eliminate uterine fibroids, surgery represents the main treatment strategy. Due to its contribution in the growth of leiomyomas, progesterone plays an important role. The purpose of this study is to review the data available regarding the safety and effectiveness of the selective progesterone receptor modulators (SPRM) used in uterine fibroids treatment. A review of the literature was performed between September 2015- January 2016 aiming to identify the studies mentioning the use and effectiveness of SPRM in uterine fibroids treatment. A total of 37 studies were identified, 9 matching inclusion criteria. All studies included in our research gave information regarding drug safety, potential benefits, metrorrhagia control and mass reduction of the fibroid. The results were that the pain and life quality showed marked improvement even after therapy interruption. Among all SPRM available (UPA- ulipristal acetate, asoprinisil, telapristone acetate and GnRh agonists), the treatment with UPA revealed a fast metrorrhagia control and a reduction in the mass dimension, both effects persist even after cessation of medication.*

**Key words:** *selective progesterone receptor modulators, metrorrhagia, uterine fibroids, ulipristal acetate.*

## 1. Introduction

The most frequent benign tumors identified in women of reproductive age are uterine fibroids. Incidence of this pathology is up to 25%, appearing in about 35% of women in menopause [43]. Hormonal role is recognized favoring

tumor development, but leiomyoma etiology is not fully understood [37].

Main symptoms are dysmenorrhea, abnormal uterine bleeding, dyspareunia and cyclic or non-cyclic pelvic pain. Uterine fibroids represent the most frequent reason for hysterectomy worldwide [53]. Fibroids can also impair fertility causing pregnancy loss or

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complicating pregnancies (premature onset of labor, severe hemorrhage post-partum) [10].

### **1.1. Current treatment option for uterine fibroids**

Hysterectomy represents the cure of uterine fibroids as symptoms disappear postoperatively without any chance of recurrence. Characteristic for the contemporary lifestyle is the pregnancy postponing to 30-40 years old, age specific for a peak in uterine fibroids development and symptomatology [56]. Taking this into account, the radical surgical treatment is out of question, determining a raise of demands of treatments that preserves the fertility.

Abdominal myomectomy stays the main pillar despite being a major surgical intervention with a high morbidity, capable of compromising fertility through adhesion formation and also the risk of uterine pathology recurrence. In the last years, various therapeutic choices were used, including laparoscopy, vaginal myomectomy and embolization of the uterine arteries [9], [46], [48]. These therapies do not only present with a wide range of effectiveness, but also with high prices. The ideal alternative would be a cheap treatment administered orally, once or twice a week, having minimal secondary effects inducing fast fibroid regression and diminishing associate symptoms, showing a higher or similar efficacy to surgical and radiological treatments but not interfering with fertility. Medical treatment can be used to control associated symptoms also allowing to schedule the surgery in better terms (a better hemoglobin value or a mass

reduction of the leiomyoma). Frequently, in order to control the bleeding, a product called Danazol is used. Despite its frequent use, no randomized controlled clinical study showed benefits in their use in the treatment of uterine fibroids. Moreover, a panel of secondary effects were described among which we mention: acne, hirsutism, weight gain, irritability, muscle pain and hot flashes [29]. Combine contraceptive pills are often used in young women in order to control menorrhagia and dysmenorrhea. Unfortunately, such therapy was poorly investigated in patients with symptomatic uterine fibroids. An intrauterine device with levonorgestrel can determine a reduction of menorrhagia, its effect of mass reduction still representing a subject of debate [23], [39].

Before the introduction of selective progesterone receptors modulators (SPRM) in the pharmaceutical field, the most effective medical treatment both for conservative and preoperative purposes were the GnRh agonists. The treatment reduces significantly the symptomatology (bleeding, anemia and pain) and is capable to reduce the fibroids mass [31]. Effects are temporary, uterine fibroids reaching the initial sizes few months after therapy cessation [42]. Besides, the chemical castration induced by GnRh agonists leads to menopause symptoms thus restricting their use on a long-term.

Recently there is scientific proof that SPRMs are effective for both symptom relieve and fibroid size reduction [11, 12]. The benefits of these drugs will probably lower the role of surgery in the uterine fibroids management. UPA can allow a less invasive surgical intervention and in some cases, can totally replace it.

*Therapeutically methods used in uterine fibroid treatment*

Table 1

Therapy	Study group	Benefits	Drawbacks	Fertility preservation
GnRh agonists [4]	Preoperative therapy for young or preclimacteric women	Non-invasive	-temporary treatment allowing uterine fibroid recurrence -secondary effects	Fertility preservation
GnRh antagonists[31]	Preoperative therapy for young or preclimacteric women	Non-invasive	-temporary treatment allowing uterine fibroid recurrence -secondary effects	Fertility preservation
Oral contraceptive [35]	Patients with small fibroids and menstrual disorders	Non-invasive	Metrorrhagia, no impact on fibroid size	Fertility preservation
Progestative treatment [25]	Women diagnosed with uterine fibroid	Non-invasive	Diminished secondary effects	Non-significant data
Myomectomy [13], [38]	Women with visible nodules	Invasive Fertility preservation	Fibroid recurrence, surgical morbidity	Uterine rupture risk in a future pregnancy
UAE (embolization of uterine artery) [3]	Women diagnosed with symptomatic uterine fibroid, no matter the size and number	Hole uterus is treated, no blood loss or surgery needed	Increased costs, post-intervention pain, radiation exposure similar to 2-3 CT, need of trained staff	Decrease in the ovarian reserve, placental pathology and post-partum bleeding
Hysterectomy [28], [44]	Pre-climacteric women	Radical therapy	Fertility loss, high mortality and morbidity, increase costs	Total loss of fertility
Myolysis / cryomyolysis [28], [44]	Women presenting small nodules	Outpatient clinic suitable procedure	Adhesion formation risk, less suitable for large fibroids or future pregnancy	Fertility impairment due to adhesions, uterine rupture risk in a future pregnancy, pathological placental formation risk

## 2. Objective of the study

The goal of this study is to revise the available data concerning safety and efficacy of SPRMs in the treatment of uterine fibroids.

## 3. Material and Methods

**Inclusion criteria:** The studies included in this review show both clinical and ultrasound diagnostic aspects of the patients, with the associated symptomatology of uterine fibroids: metrorrhagia, pelvic pain and anemia.

**Searching strategy:** Systematic literature research was performed between

September 2015- January 2016 aiming to identify studies matching the inclusion criteria mentioned above. Various basadates were searched (PubMed, Medscape), using the MeSH terms: selective progesterone receptor modulators, metrorrhagia, uterine fibroids, ulipristal acetate. The research was limited to the studies published between January 2007-december 2015, without language restriction. After applying the exclusions criteria, a number of 37 studies were identified. The titles and abstracts of the papers were evaluated by 2 independent reviewers in order to determine the eligibility for the present study.

**Exclusion criteria:** Studies were excluded when matching one of these criteria: unfit study population (study performed on another disease, not uterine fibroids), publication not reporting results of the original studies, editorials, clinical recommendations. Based on these criteria, 22 studies were excluded from our research. Full texts of the 15 remaining studies were assessed to check if they match the inclusion criteria. After applying the inclusion criteria, 9 studies were identified and analyzed, being added in this systematic review. Our research was performed on retrospective, prospective or clinical trials. None of the studies analyzed were excluded due to language or study group size.

**Data extraction:** Data extraction was performed and checked by each author in order to control data accuracy. Descriptive data included: study group size, used therapy and dosage, results of each study.

#### 4. Results

As shown in table 2, the only therapeutic option showing remarkable results regarding uterine fibroid size reduction is UPA. Considering either *Grzechicinska et al* in 2014 (reduction with 54% in dimension) or *Donnez et al* 2012 (reduction with 42% in dimension), the results show the same: a 5-mg dose applied in both situation exhibit superior effects to a bigger dose (determining poorer results) [11, 12], [24].

According to study results, 3 months of treatment determines reduction of tumor

size from 33 to 68%. UPA administration can be useful in blood loss decrease, important effect when deciding the treatment. Results obtained in this research match comments reported by other authors. In 2012 New England Journal of Medicine published the results of PEARL I and II trials regarding efficacy of UPA usage. PEARL I evaluated 242 patients with uterine fibroids (uterine size corresponding to a 16-week pregnancy), massive hemorrhage and secondary anemia (average hemoglobin level: 10.2 g/ dL) [11].

After 13 weeks of treatment, the fibroid size decreased on average by 21%. On more than 90% of patients a decrease in the menstrual blood flow was noticed. PEARL II assessed 307 patients showing excessive bleeding [12]. Fibroid size was decreased in the study group receiving 5 mg UPA by 36% and in those receiving 10 mg UPA by 42%. Other studies concluded an obvious bleeding inhibition in 90% of patients receiving UPA in 5 mg doses, size reduction of the fibroid varying from 25% to 36% [52].

*Filicori et al.* were the first to show that GnRh agonists decrease the size of the leiomyoma in rats [18]. The first clinical study performed by *Maheux et al.* [34] demonstrated the tumor decrease using this therapy in 3 patients. A drop in the size of the fibroids was noticed in patients undergoing GnRH treatment for at least 3 months [19], [45]. All this data suggests that growth of fibroids is estrogen dependent.

Summary of studies included in the review

Table 2

Authors	Year	Study type	Treatment period	Drug	Patient number	Results	
						Fibroid size reduction	Amenorrhea
Chwalisz et al [7]	2007	R, DB, PC	3 months	Asoprisnil	<b>129 patients</b> -Placebo (31) -Asoprisnil 5 mg (33) -Asoprisnil 10 mg (29) -Asoprisnil 25 mg (36)	+1 % -14 % -9 % -17 %	0 % 16 % 36 % 70 %
Levens et al [32]	2008	R, DB, PC	3 months	Ulipristal acetat	<b>22 patients</b> -Placebo (8) -UPA 10 mg (8) -UPA 20 mg (6)	+6 % -36 % -21 %	0 % -87,5 % -100 %
Wilkens et al [55]	2008	R, PC	3 months	Asoprisnil	<b>31 patients</b> -Placebo (10) Asoprisnil 10 mg (12) Asoprisnil 25 mg (11)	+4,9 % -0,4 % -25,8 %	7,3 % 1,2 % 0,2 %
Engman et al [16]	2009	R, PC	3 months	Mifepristone 50 mg /zi	<b>30 patients</b> -Placebo (16) -Mifepristone (14)	+6 % -28 %	-12 % -24 %
Feng et al [17]	2010	R, PC	3 months	Mifepristone 2, 5/5mg /zi	<b>62 patients</b> -Placebo (19) -Mifepristone (43)	+17,7 % -17,6 %	NR
Nieman et al [41]	2011	R, DB, PC	3 months	Ulipristal acetat	<b>38 patients</b> -Placebo (12) -UPA 10 mg (13) -UPA 20 mg (13)	+7 % -17 % -24 %	0 61,5 % 92 %
Donnez et al [11]	2012	R, DB, PC	3 months	Ulipristal acetat	<b>237 patients</b> -Placebo (48) -UPA 5 mg (95) -UPA 10 mg (94)	+3 % -21 % -12 %	6 % 73 % 82 %
Donnez et al [12]	2012	R, DB	3 months	Ulipristal acetat Leupraprelin acetat (3, 75 mg / month)	<b>281 patients</b> -UPA 5 mg (95) -UPA 10 mg (93) -Leupraprelin acetat 3, 75 mg (93)	-42% -53% -36%	89 % 80 % 75 %

Authors	Year	Study type	Treatment period	Drug	Patient number	Results	
						Fibroid size reduction	Amenorrhea
Grzechicinska et al [24]	2014	R, PC	3 months	Ulipristal acetat	<b>5 patients</b> -UPA 5 mg (5)	<b>-54%</b>	<b>NR</b>
Wiehle et al [54]	2008	R, DB, PC	3 months	Telapriston acetat	<b>NR</b> <b>-Placebo</b> - Telapriston acetat (12, 5 mg /day) Telapriston acetat (25 mg / day) Telapriston acetat (50 mg / day) Leuprorelin acetat (3, 75 mg / month)	<b>-10, 6%</b> <b>-17, 9 %</b> <b>-40, 3%</b> <b>-40, 3%</b> <b>-32, 6%</b>	

In a study on a placebo versus a control group, the GnRh agonist named leuprorelin (3, 75 mg) led to a bleeding suppress by 85% in patients with preoperatively anemia. The therapy using leuprorelin caused hot flushes in 67% of the patients [51]. When disrupting the GnRh agonist treatment, the uterine Vol./uterine fibroid ratio starts to raise again in the upcoming 3 to 12 months [20]. GnRh agonists were approved only for short term treatment due to obvious bone mineral density loss registered.

Preoperative use of GnRh agonists determined a switch of the surgical technique, the vaginal approach being favored to the abdominal one, decreasing thus the intraoperative blood loss. Secondary effects of GnRh agonists such as hot flushes and vaginal atrophy have negative impact on the results [20, 51]. Cessation of both therapies led to a return to the initial size of the fibroid [47]. Progesterone impact on fibroid growth determined an increased consideration towards modulating the progesterone pathway. Pilot study results and results of studies using asoprisnil, mifepristone

telapristone or UPA suggested these substances as ideal candidates in the fibroid therapy [14], [32].

Moreover, SPRMs show a specific effect on the endometrium determining antiproliferative effects, leading to a fibroid mass reduction or even to amenorrhea [27]. In both vivo and vitro, UPA represents a powerful selective modulator of the progesterone receptors with effects on the myometrium receptors [1, 2], [21]. UPA possess antiproliferative, antifibrotic and proapoptotic effects. These effects target only the fibroid cell and not the healthy myometrium.

Two small, second phase studies (study groups of 18, respectively 38 patients) reveal a drop in the uterine and fibroid size in those women treated with UPA [32, 41]. A 3 months' treatment with 10/20 mg of UPA/day resulted in few excessive bleeding cases and to a significant Vol. reduction, the 20-mg dosage being superior in effects to the 10-mg treatment. Fast bleeding control, better preoperative preparation by higher levels of hemoglobin and reduction in size of the fibroids are the main benefits of the treatment with UPA (5

mg per os, 1 tablet/ day for a maximum of 3 months).

Another advantage of patients opting for medical treatment is the sustained effects, fibroids doesn't show a growth after cessation of the treatment. In a series of clinical studies, UPA was shown to reduce both menstrual blood loss and fibroid size, thus improving life quality. Unlike GnRh, UPA shows no estrogen specific effect such as decreased bone mineral density.

Safety and efficacy of short term and symptomatic treatment of uterine fibroids with UPA was proved in Europe [11, 12]. 13 weeks of oral treatment with UPA, 5 mg/day (96 women) or 10 mg/day (98 women) was compared to placebo in women showing fibroids, menorrhagia and anemia [11]. All patients received iron supplements. The objectives of this study were bleeding control and fibroid mass reduction by week 13 following the schedule of the surgery. In the 13<sup>th</sup> week of treatment, uterine bleeding was controlled in 91% of women receiving 5 mg UPA, in 92% of women receiving 10 mg of UPA and in 19% of the placebo group. The 13 weeks' treatment with UPA decreased effectively the bleeding and the size of uterine fibroids.

#### 4. Discussions

Literature data shows that progesterone and progesterone receptors play a key role in the development of the uterine fibroids [15]. *Kovaks and colleagues* proved in several clinical trials a higher concentration of both isoforms of progesterone receptors (PR-A and PR-B) in the fibroid tissue compared to normal myometrium [30]. Progesterone favors fibroid growth due to the 2 pathophysiological pathways: upregulation of the epidermal growth factor, Bcl-2 protein expression and downregulation of tumor necrosis factor [36].

SPRMs are a new PR ligand class presenting specific selective tissue effects on targeted cells. UPA is a synthetic SPRM, active orally, characterized by an antagonist effect on progesterone specific tissue, reducing fibroid cell proliferation and inducing apoptosis through a raise in the expression of cleaved caspase-3 and a reduction in Bcl-2 expression. On the other hand, it downregulates the expression of angiogenic growth factors and receptors. UPA inhibits neovascularization, cell proliferation and survival in the fibroid cell, but not in the normal myometrium [5], [8].

It also possesses central action on the hypothalamic-pituitary-ovarian axis and inhibits or delays the ovulation. Despite all this, UPA does not interfere with the basal level of luteinizing and follicle-stimulating hormone, estradiol level remaining within normal limits (60-150 pg/mL). As a result, UPA's final result is not an estrogen deficit, the patients do not present symptoms associated to estrogen deficit. UPA induces amenorrhea in most women due to its interaction to progesterone receptors. It is important to notice that UPA must not be used as a contraceptive because it can decrease the fertility spontaneously during treatment.

On a long-term, clinical studies express concern regarding SPRMs effects on endometrium, finding suitable the study of endometrial tissue specimens in women receiving SPRMs treatment, mifepristone, asoprisnil and UPA [26], [40], [49], [50]. Histological studies concluded the lack of evidence, supporting mitosis consistent to the antiproliferative effect of SPRMs. No biopsy revealed atypical hyperplasia.

Concerning the endometrium modification, during the UPA treatment of 3 months in women without endometrium thickening it was noticed a tendency of endometrium decrease compared to placebo [6], [49].

There were no adenocarcinomas or premalignant lesions diagnosed. Pathological alterations were noticed in 58% of patients receiving 5 mg UPA, in 59% of those receiving 10 mg UPA and 12% of those receiving leuprolid acetate [26]. Thus, it is suggested that the thickening of the endometrium in women showing low mobility correlates to cystic glandular expansion and not to endometrium hyperplasia. Latest results of clinical studies show safety of UPA usage. Unlike other SPRMs, UPA doesn't produce hepatic toxicity.

Reports on UPA effects on prolactin serum level are different, some suggesting that ovarian cyst are more common in treated women with abnormal ovulation, are small in size, asymptomatic and resolve spontaneously [6]. Evidence available until present advocates for a reduction in the size of the fibroid, a decrease of the menstrual blood flow and for amenorrhea treatment, resolving anemia too. Thereby, its effect is to facilitate the surgical intervention.

#### **UPA and pregnancy**

Recently, *Luyckx and colleagues* reported the first series of pregnancies obtained after UPA treatment for uterine fibroids. 21 of the 52 patients included in the study opted to conceive after treatment [33]. Among these, 19 were subjected to myomectomy after UPA and 2 did not undergo surgery at all. Two of them obtained pregnancy with no surgical intervention as uterine fibroids regressed significantly.

Grossly, 15 patients conceived (71%) a total of 18 pregnancies. Among these 18 pregnancies, 12 led to birth of 13 healthy babies and 6 finished though an abortion (33%). Of those 5 miscarriages, 3 of the pregnancies resulted after FIV. The average time length for obtaining a pregnancy after treatment cessation was 10 months [22].

This study showed no maternal complication related to uterine fibroids during pregnancy or postpartum. There was no significant growth of fibroid during pregnancy, probably due to apoptosis induced by UPA. This shows that endometrium alteration is reversible and endometrium is still capable of implantation after treatment.

#### **5. Conclusions**

The need of a simple, prompt and safe treatment capable of solving uterine fibroid symptoms not interfering with fertility represents a current issue with a particular significance. The effectiveness in reducing menstrual blood flow along with other benefits highlights the potential superiority of UPA treatment compared to GnRH analogs. Nowadays UPA is authorized for preoperative treatment of uterine fibroids in a 3 months' cycle which can be repeated once. This treatment is not meant to bypass a surgical intervention but when fibroid symptoms disappear, the problem of delaying or canceling the surgery is frequent. Studies show efficacy and safety when long-term, intermittent UPA treatment is performed for symptom control.

Still no validated medical treatment is capable of removing fibroids, making surgery the best treatment for symptomatic uterine fibroids. Hysterectomy is in many cases the choice treatment despite the fact that it causes infertility in women of reproductive age. UPA can represent a good alternative for women desiring a pregnancy, for those wishing to avoid a surgery or before a surgical intervention as it reduces surgical invasiveness. The heterogeneity characterizing these therapeutic alternatives requires more clinical studies in order to identify the optimum UPA indications in patients with symptomatic uterine fibroids.

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