Current management of myomas: the place of medical therapy with the advent of selective progesterone receptor modulators

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Purpose of review
To review the current management of myomas with the advent of selective progesterone receptor modulators.

Recent findings
Selective progesterone receptor modulators have proved effective and recent publications on the use of ulipristal acetate (UPA) have analyzed the performance of long-term intermittent utilization of 10 mg UPA given in repeated courses of 3 months. This long-term intermittent therapy maximizes the efficacy of UPA. Indeed, control of bleeding is achieved sooner after each course. With each subsequent course, a statistically greater number of patients show a fibroid volume reduction of more than 50%.

Summary
The choice of therapy is influenced by different factors, such as the severity of symptoms, tumor characteristics, age, and wish to preserve the uterus (and fertility). Use of UPA will undoubtedly modify the surgical approach.

Keywords
medical therapy, myomas, selective progesterone receptor modulators, ulipristal acetate

INTRODUCTION

Uterine fibroids (also known as myomas or leiomyomas) are the most common benign uterine tumors in women of reproductive age, occurring in 20–25% of women [1,2]. Depending on localization, the symptoms vary in frequency and severity, and include pelvic pain, pressure, dysmenorrhea, anemia caused by heavy bleeding, reduced quality of life, and infertility [3].

Current management strategies involve mainly surgical interventions, but the choice of treatment is guided by the patient's age and desire to preserve fertility and avoid 'radical' surgery such as hysterectomy [3,4]. In the early 1980s, hysterectomy was routinely proposed to women with submucous fibroids who did not wish to conceive. Since then, other surgical and nonsurgical approaches, including myomectomy by laparotomy or laparoscopy, uterine artery embolization, and other interventions performed under radiologic or ultrasound guidance [3–5], have been proposed.

Medical therapies with progestin, progestin-releasing intrauterine devices, and gonadotropin-releasing hormone agonist (GnRHa) are also available [6–8], but some small studies have reported that use of oral progestin may cause breakthrough bleeding and promote myoma growth [6]. GnRHa can be used as preoperative treatment [7,8], resulting in reversible reduction of myoma size and correction of anemia. However, because of safety concerns linked to artificially-induced menopause (loss of bone mineral density), such treatment is approved only for short-term therapy [7,8]. Progesterone plays an important role in promotion of myoma growth

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KEY POINTS

- UPA has proved to be the most effective medical treatment for fibroids.
- UPA can be used either as a preoperative adjunct to surgery or as medical therapy to avoid surgery.
- UPA treatment serves to control bleeding, thereby alleviating pain and anemia symptoms and consequently improving quality of life.
- Long-term intermittent treatment maximizes the efficacy of UPA.

[9,10]. Modulating the progesterone pathway represents one of the possibilities of medical therapy, opening the way to use of selective progesterone receptor modulators (SPRMs) [10]. In 2012, two prospective randomized studies concluded that treatment with ulipristal acetate (UPA) for 13 weeks effectively controlled excessive bleeding because of uterine fibroids and reduced their size [11,12]. The results of the first study on long-term intermittent (18 months) therapy with 10 mg UPA were published [13▪▪], demonstrating that this regimen (four courses of 3 months) maximizes the effect of UPA by inducing a very high rate of amenorrhea and reducing fibroid size. These findings were confirmed very recently and further showed that 5 mg UPA is as effective as 10 mg UPA for management of the symptoms of uterine fibroids [14▪▪].

Our review presents new algorithms of myoma management in 2015, taking into account recent developments in long-term intermittent therapy with SPRMs [13▪▪,14▪▪].

MODE OF ACTION

Selective progesterone receptor modulators and the progesterone receptor

The effects of progesterone on target tissues are mediated by the progesterone receptor, which belongs to the nuclear receptor family. Progesterone receptors are known to be upregulated in uterine fibroids compared with adjacent myometrium at the mRNA and protein levels [14▪▪]. Very recently, PR-B mRNA and PR-A and PR-B proteins were found to be more concentrated [15▪] and more abundant in fibroids than in adjacent myometrium.

SPRMs are synthetic compounds that compete at the progesterone receptor binding site, displaying either agonist or antagonist activity on progesterone receptors. When bound, this also results in dimerization and binding to the progesterone response element sequence, but induces an intermediate conformation, allowing the receptors to interact with coactivators and/or corepressors [16,17].

Whether a SPRM acts more as an antagonist or agonist depends on its structure and how it alters the progesterone receptor conformation, leading to exposure or inactivation of particular binding domains, which affect the association of corepressors and/or coactivators with the progesterone receptor [18]. This is impacted by the presence of coregulators in a particular cell type and by the ratio of coactivators and corepressors. The activity of an SPRM varies with tissue type and physiological context (e.g., pregnancy) and may be different from one cell type to another [18]. The mechanism of action of SPRMs on progesterone receptors is summarized in Fig. 1 [19].

Selective progesterone receptor modulators and their mechanism of action on uterine fibroids: uterine fibroid size reduction

In-vitro studies have demonstrated that progesterone stimulates fibroid cell proliferation, whereas SPRMs, such as asoprisnil, telapristone acetate, and UPA inhibit cell proliferation and induce apoptosis selectively in fibroid cells by downregulating antiapoptotic factors [16,17,20] and antifibrotic activity [21], and reducing or blocking growth factor expression [22,23].

Other mechanisms of action of SPRMs may contribute to their efficacy in decreasing the size of uterine fibroids and reducing associated heavy blood loss, such as a direct effect on uterine blood vessels, which has been evidenced *in vivo* with asoprisnil and mifepristone [24,25].

In a recent publication, Courtoy *et al.* [26] reported findings of cellular and tissue analysis of UPA-treated myomas and compared them with untreated myomas, evaluating proliferation, apoptosis, extracellular matrix (ECM) components, and matrix metalloproteinase-2 (MMP-2) expression. The authors demonstrated multifactorial and successive events involving maintenance of a low proliferation rate, transitory stimulation of cell death that is not caspase-3 dependent, and a dramatic reduction in the ECM, essentially after long-term treatment, which may be partially explained by increased MMP-2 expression. This suggests direct regulation of MMP-2 expression by UPA in myomas and it also identified MMP-2 as an important player in ECM resorption in myomas to reduce their volume.

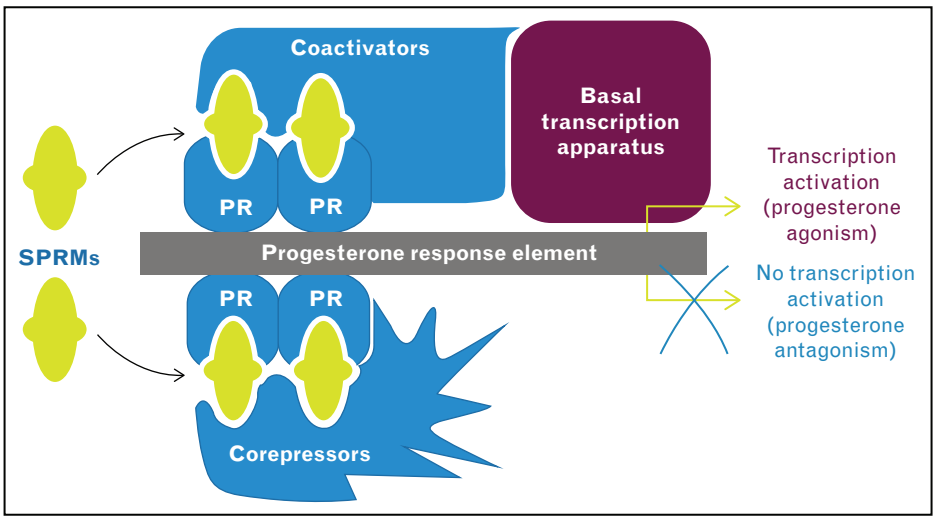


FIGURE 1. Activation of the progesterone receptor by progesterone and SPRMs. Binding of SPRM to progesterone receptor; SPRMs may act as agonists at the progesterone receptor, which will activate the transcription comparably to progesterone. In case of an antagonistic action, the SPRM competes with agonists for binding at the progesterone receptor and induces a conformational change, which allows a more potent recruitment of corepressors. The precise conformational change induced at the progesterone receptor, and consequently the balance of interaction with coactivators and corepressors depends upon the identity of the individual SPRM. In addition, the activity of each SPRM varies with tissue type and is influenced by the ratio of coactivators and corepressors in each cellular environment. SPRM, selective progesterone receptor modulator.

Selective progesterone receptor modulators and control of uterine bleeding and ovulation

It should be stressed that the interest of SPRM treatment for uterine fibroids is not only related to its ability to decrease fibroid size, but even more importantly to its impressive capacity to reduce uterine bleeding and control ovulation and the menstrual cycle. A high rate of bleeding control is reported with all SPRMs, with frequent occurrence of amenorrhea and this amenorrhea has been suggested to be because of a direct effect on the endometrium [27], and also partly related to anovulation [28].

However, the exact mechanism of action by which daily SPRM administration inhibits ovulation and leads to amenorrhea is not yet entirely clear [29]. Single-dose SPRM treatment in the follicular phase or around the luteinizing hormone peak can delay ovulation and follicular maturation, as demonstrated with UPA and mifepristone [30,31]. Chronic low-dose SPRM treatment (5 or 10 mg UPA) results in anovulation and amenorrhea in most women, without reducing endogenous estrogen secretion [11,12,13▪▪,14▪▪,28].

Selective progesterone receptor modulators and the endometrium

SPRMs have a very specific effect on the endometrium. Now described as PRM-associated endometrial changes (PAECs) [32,33], these changes were originally interpreted as simple endometrial hyperplasia, as the architecture of PAECs has similarities to simple endometrial hyperplasia and these new features could not be categorized in existing classification systems.

The appearance of cystically dilated glands was a frequent architectural finding after SPRM exposure. In its simplest form, scattered cysts were only moderately dilated, comparable to a disordered proliferative endometrium, as observed in case of unopposed estrogen in anovulation. Instead of a proliferative lining, which can be seen with hyperplasia, the glands were only weakly mitotic or sometimes secretory. Endometrial appearance appeared to differ according to agent, applied dose, and administration schedule. A panel of pathologists concluded that the endometrium could neither be classified as proliferative nor secretory, hence termed these findings PAECs [32]. Regarded as a benign condition, PAECs are characterized by an inactive and weakly proliferating epithelium, associated with asymmetry of stromal and epithelial growth resulting in prominent cystically dilated glands with mixed estrogen (mitotic) and progesterone (secretory) epithelial effects. Cystic dilatation of endometrial glands and an irregular architecture lined with inactive gland cells and a compact, non-decidualized stroma are now recognized as common PAEC features and do not occur in physiological states [17,33].

Therapeutic potential of selective progesterone receptor modulators

Because of their pharmacological properties, SPRMs have mainly been tested for indications associated with the role of progesterone, principally gynecological and oncological indications. Only a few SPRMs have been investigated [34–38] or are under development specifically for uterine fibroids.

UPA is the only molecule that has received marketing authorization for 3-month preoperative treatment of uterine fibroids. Three other SPRMs have also been tested for this indication: mifepristone [34–36], asoprisnil [37], and telapristone acetate [38]. All these SPRMs have consistently been shown to decrease fibroid and/or uterine volume and significantly reduce uterine bleeding and even induce amenorrhea.

USE OF ULIPRISTAL ACETATE FOR PREOPERATIVE MANAGEMENT OF UTERINE FIBROIDS: RESULTS FROM PEARL I AND PEARL II CLINICAL TRIALS

Treatment approaches to uterine fibroids have historically involved surgical removal of the fibroids or uterus. Less invasive endoscopic methods became the gold standard of myoma removal in the early 2000s, giving surgeons the choice of hysteroscopic or laparoscopic myomectomy (for review, see [39▪▪]).

However, there remained a need for alternatives to surgical intervention, particularly when fertility preservation was the goal, and for treatment that could produce significant and sustained efficacy, without effects of estrogen depletion, like hot flushes and bone loss, associated with GnRHa therapy.

Publication of the pivotal PEARL (PGL4001 Efficacy Assessment in Reduction of symptoms because of uterine Leiomyomata) I and PEARL II trials in 2012 [11,12] coincided with obtaining European approval for 5 mg UPA to be used for 3-month preoperative treatment of women with uterine fibroids.

PEARL I [11] was a randomized, double-blind, and placebo-controlled trial evaluating 3-month treatment with UPA tablets (5 or 10 mg daily) in women with symptomatic fibroids, excessive uterine bleeding and anemia. By 13 weeks, uterine bleeding was under control in 91% of women receiving 5 mg UPA, 92% of those receiving 10 mg UPA, but only 19% of those receiving a placebo. More patients achieved correction of anemia (hemoglobin >12 g/dl) by the end of the 3-month treatment period with UPA than with a placebo (85–89% vs. 77%, respectively). This effect is of high clinical relevance, given that it has been well documented that preoperative anemia, even to a mild degree, is associated with an increased risk of morbidity and mortality in patients undergoing surgery [40].

In a similar setting, PEARL II [12] compared 5 and 10 mg UPA tablets with the existing standard medical treatment with GnRHa (3.75 mg leuprolide acetate depot injection once monthly).

The key findings of this study demonstrated that uterine bleeding was controlled in 90% of patients receiving 5 mg UPA, 98% of those receiving 10 mg UPA, and 89% of those receiving leuprolide acetate. Median times to controlled bleeding were 5 to 7 days for patients receiving UPA (5 and 10 mg, respectively), and 21 days for those receiving leuprolide acetate. In both UPA groups, plasma estradiol levels were maintained in the mid-follicular range, whereas patients in the leuprolide group on average showed a significant reduction to postmenopausal levels.

Follow-up in a subgroup of women who did not undergo surgery after the 3-month study period showed that UPA had a sustained effect (up to 6 months) after the end of treatment. By contrast, GnRHa-treated women experienced rapid regrowth of fibroids, reaching almost pretherapy dimensions by 6 months posttreatment. Key efficacy results from the PEARL I and II trials are summarized in Fig. 2 [11,12].

LONG-TERM MEDICAL MANAGEMENT OF UTERINE FIBROIDS: RESULTS OF PEARL III AND PEARL IV CLINICAL TRIALS

Thanks to the sustained effect observed in PEARL I and II, additional intermittent courses of 12-week UPA treatment with off-treatment intervals are a potential option for the long-term medical management of fibroids.

The PEARL III study [13▪▪] was designed to evaluate the efficacy and safety of long-term intermittent open-label 3-month courses of 10 mg/day UPA for the treatment of symptomatic uterine myomas, each course followed by randomized, double-blind treatment with norethisterone acetate (NETA) or a placebo to explore any effect on the reversibility of PAECs or timing and magnitude of the next off-treatment menstruation.

After the first UPA course, amenorrhea occurred in 79% of women. Amenorrhea rates were respectively 89, 88, and 90% in women who received two, three, and four treatment courses. Median time to amenorrhea was 3.5 days from the start of treatment.

Median fibroid volume reduction from the baseline was 49.9, 63.2, 67.0, and 72.1% after one, two,

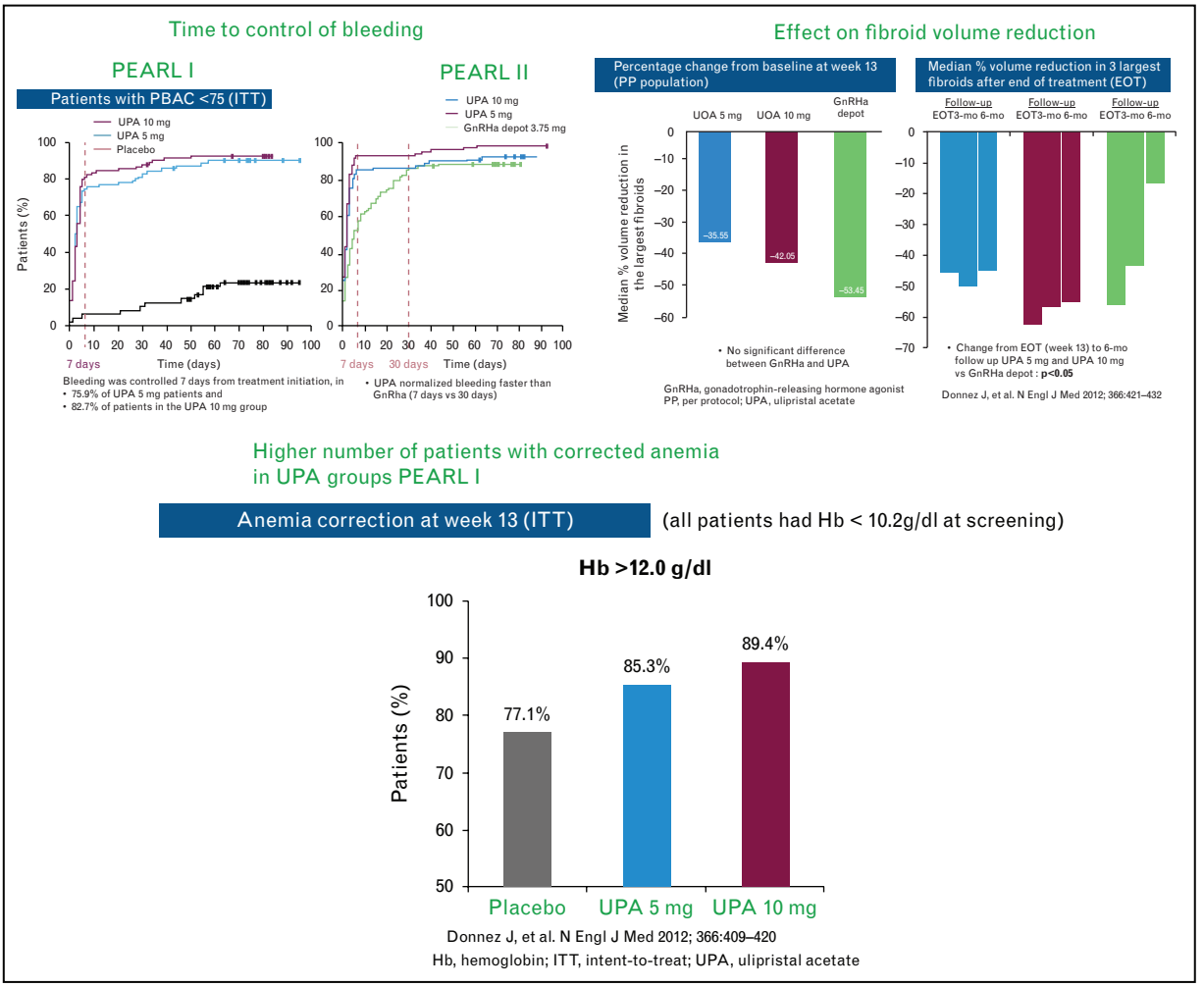


FIGURE 2. Effects of ulipristal acetate in bleeding control, fibroid volume reduction, and correction of anemia.

three, and four treatment courses, respectively (Fig. 3, [13▪▪]).

All endometrial biopsies showed benign histology without hyperplasia. NETA did not affect fibroid volume or endometrial histology, including PAECs. A 10-day course of progestin, administered immediately after each UPA treatment course, was associated with a significantly reduced and earlier occurrence of menstrual bleeding during off-treatment periods (Fig. 4, [13▪▪]). However, these findings are probably insufficient to suggest that progestins should be routinely used in conjunction with UPA treatment, unless there is a need to control the timing or amount of menstrual bleeding, for example, before a planned invasive procedure.

In conclusion, the results of PEARL III and its extension study indicate that administration of more than one course of UPA maximizes the potential benefits of treatment in terms of bleeding control and fibroid volume reduction, whereas the association of NETA is of limited clinical benefit.

The last clinical trial, PEARL IV [14▪▪], investigated the efficacy and safety of repeated 12-week courses of 5 or 10 mg UPA daily for intermittent treatment of symptomatic uterine fibroids. This double-blind, randomized study, including 451 patients with symptomatic uterine fibroids and heavy bleeding treated with repeated courses of 12 weeks each, showed that in the 5 and 10 mg treatment groups, respectively 62 and 73% of patients achieved amenorrhea with both treatment protocols. The proportion of patients achieving controlled bleeding was indeed >80% in both cases. After the second treatment course, the median reduction in fibroid volume from the baseline was 54 and 58% in patients receiving 5 and 10 mg UPA, respectively. Pain and quality of life improved in both groups.

With respect to primary end points, results with 10 mg UPA were consistent between the two studies, demonstrating amenorrhea rates ≥70%, comparable to those obtained with 5 mg [13▪▪,14▪▪].

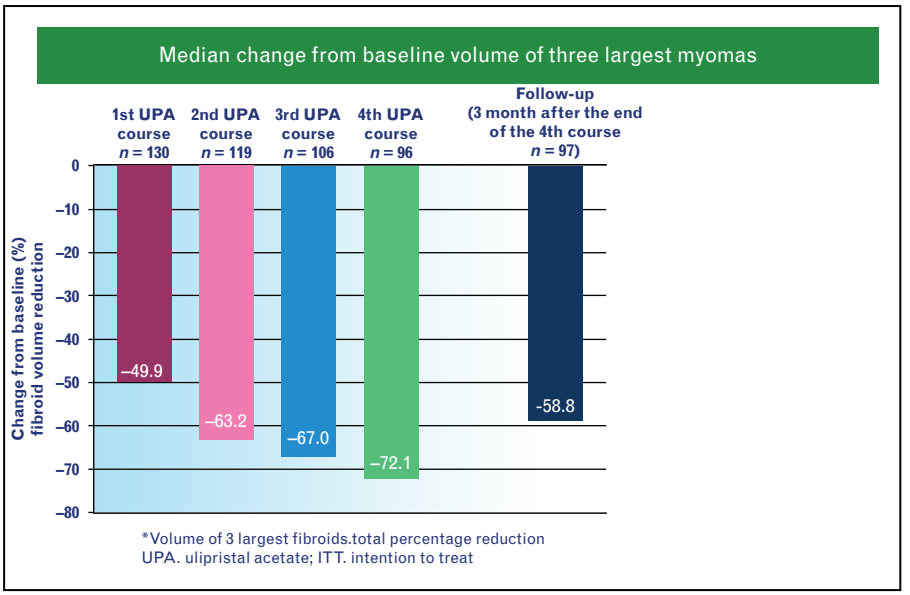


FIGURE 3. Fibroid volume reduction from PEARL III trial.

Resumption of menstruation after each course occurred after a similar interval in the two studies [13▪▪,14▪▪].

A first series of pregnancies after UPA treatment was recently reported. Twenty-one women wanted to conceive, and 15 patients (71%) succeeded, totaling 18 pregnancies, which resulted in 12 births of 13 healthy babies and six early miscarriages. Of these 15 patients, two had no surgery and conceived spontaneously [41▪▪].

CONCLUSION

Because SPRMs are now available and have proved effective, it is time to focus on a very important question: what is the remaining role of surgery with the advent of these drugs?

If surgery remains indicated, do these drugs enable less invasive surgery? Indeed, the real question is whether SPRMs (UPA) allow less invasive surgery or complete avoidance of surgery.

Two publications analyzed the efficacy of long-term intermittent use of 10 mg UPA given in repeated courses of 3 months, each course of treatment separated by two menstrual cycles (approximately 2 months) [13▪▪,14▪▪]. Such long-term intermittent therapy maximizes the efficacy of UPA. Indeed, control of bleeding is achieved sooner after each course, and the time to amenorrhea is shorter. With each subsequent course, a significantly greater number of patients showed a fibroid volume reduction of more than 50%. As a myoma is more or less a sphere (volume: $\frac{4}{3}\pi r^3$), a 30% reduction in diameter equates to an approximate 65% reduction in volume (Figs 2–4).

So the question remains open: will intermittent use of UPA change the approach to the management of uterine fibroids? To answer this question, it is important to consider the factors influencing the choice of therapy, such as the severity of symptoms (pain, bleeding), infertility related to myomas, tumor characteristics (volume, localization), age, wish to preserve the uterus, and wish to preserve fertility (Figs 5 and 6, [39▪▪]). Based on these factors, three new treatment algorithms can be proposed:

(1) Women <40 years of age presenting with symptomatic myomas distorting the uterine cavity and infertility (Fig. 5, [39▪▪]).

If type 0 myomas (International Federation of Gynecology and Obstetrics classification) are present, cutting the pedicle by hysteroscopy is indicated and no preoperative treatment is required [39▪▪]. For type 1 myomas (<3 cm), two options exist: either hysteroscopic myomectomy or UPA treatment in one or two courses of 3 months, followed by hysteroscopic myomectomy in case of inadequate response. In the majority of cases, hysteroscopic myomectomy for type 1 myomas is relatively easy to perform.

If (as is often the case) myomas are of type 1 but larger than 3 cm, or of type 2, UPA may be given in one or two courses of 3 months. Type 1 and 2 myomas often respond to this preoperative therapy and regress in size. Also, this reduction allows a hysteroscopic approach that can be planned after the first menstrual bleed induced by NETA (10 mg/10 days), administered immediately after UPA treatment [39▪▪]. It should be pointed out that in some cases (if myomas regress so much that they no longer distort the uterine cavity), surgery may not

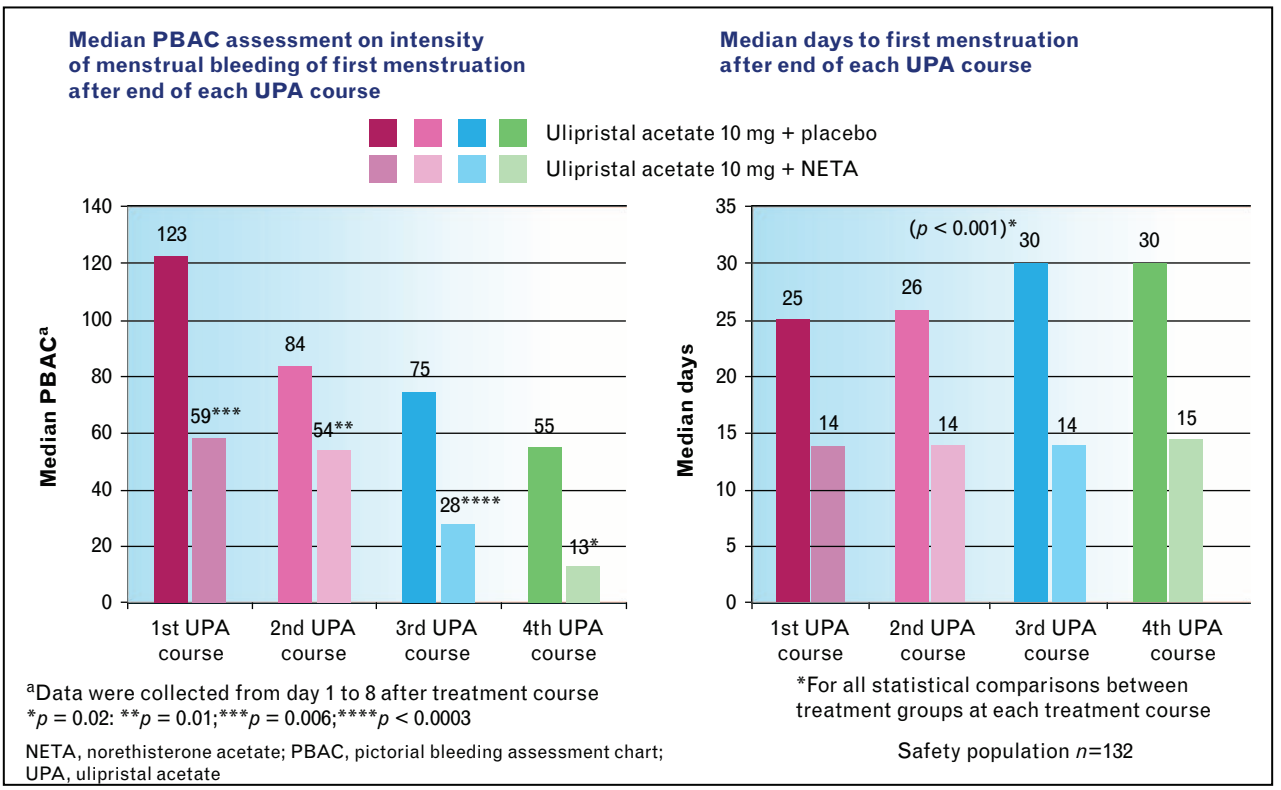
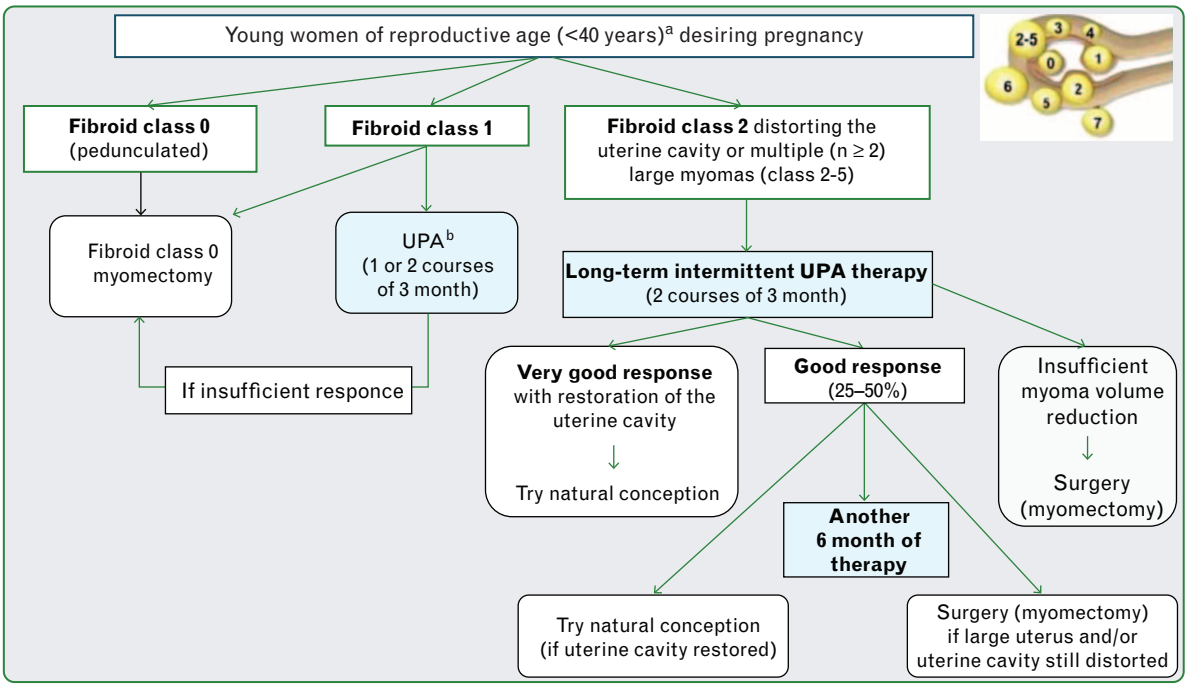


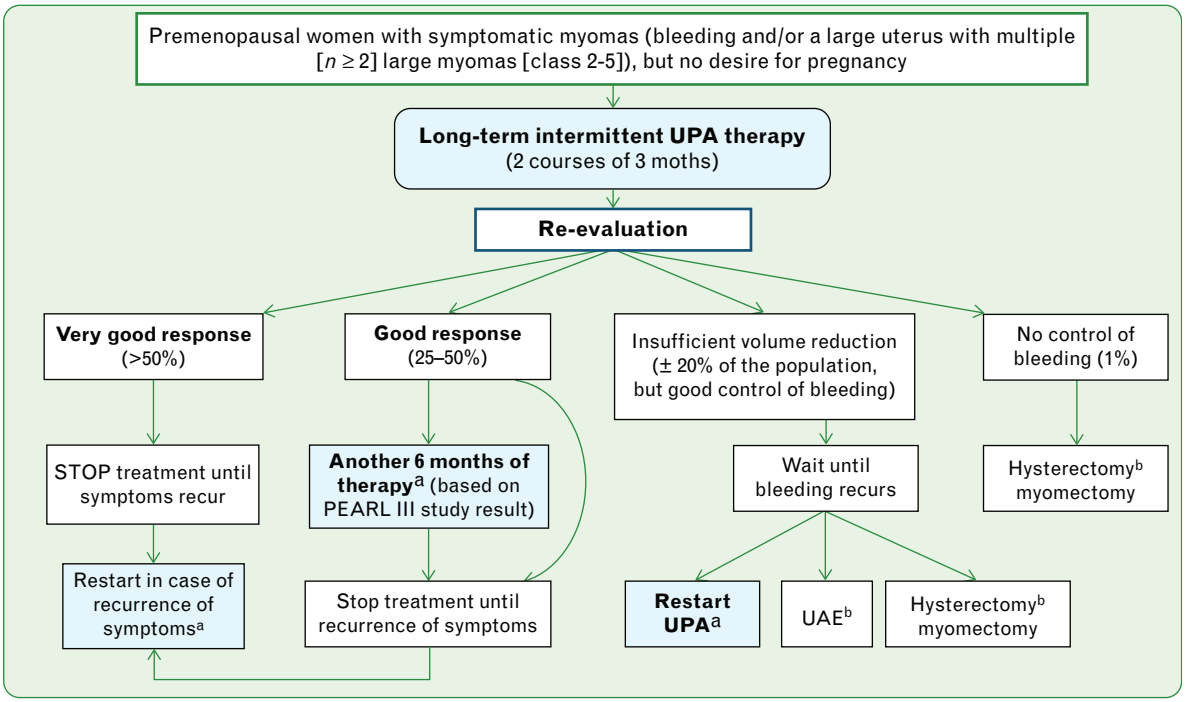
FIGURE 4. Effects of norethisterone acetate and placebo on intensity and time to menstruation after ulipristal acetate. PEARL III trial.



[a]After 40 years of age, any discussion about medical or surgical therapy should take into account the ovarian reserve and possible delay due to medical therapy

[b]Depending on the size

FIGURE 5. Women <40 years presenting with symptomatic myomas distorting the uterine cavity and infertility.



[a]Currently approved

[b]Depending on wish to preserve fertility

FIGURE 6. Premenopausal women presenting with symptomatic myomas but no desire for pregnancy who wish to keep their uterus.

be required. If the myomas are multiple (two to six) or of different classes (class 2–5), as is frequently observed, UPA can be given in two courses of 3 months.

After these two courses of 3 months, there are four possible outcomes:

(1) Myoma regression is very significant (>50% decrease in volume). The uterine cavity is no longer distorted, and the patient can try to conceive naturally or undergo assisted reproductive techniques, if indicated.
(2) Myoma regression is significant (>25% but <50%), but the baseline volume is so great that the indication for surgery remains. In this case, UPA may allow surgery to be performed by a laparoscopic approach once the hemoglobin level is normalized, avoiding laparotomy.
(3) Myoma regression is moderate (>25% but <50%), but the uterine cavity remains distorted. In this instance, two options should be discussed with the patient: either prolong medical therapy for another two courses of 3 months or proceed with surgery.
(4) Myoma regression is insufficient. Surgical indications should then be followed according to the size and site of myomas and treatment needs.

(a) Premenopausal women presenting with symptomatic myomas but no desire for pregnancy, who wish to keep their uterus (Fig. 6, [39▪▪])

If type 0 or type 1 myomas are present, the algorithm in Fig. 5 can be applied. In case of type 2 fibroids distorting the uterine cavity or multiple (R2) large myomas (class 2–5), long-term intermittent therapy may be proposed in the knowledge that the PEARL-III study clearly demonstrated that repeated courses of UPA maximize the effect. If after two courses of 3 months myoma regression (>50%) is such that the patient is free of symptoms, she can be observed until symptoms recur. Further courses of UPA may then be proposed. No data are so far available to determine the interval before recurrence, but a sustained effect was observed after treatment completion [12,13▪▪,14▪▪].

This proposed treatment could well prove beneficial in some instances. Indeed, if a young woman of 20 years were to present with multiple myomas and severe bleeding, she could undergo UPA treatment not only to restore hemoglobin levels, but also to avoid surgery. It is well known that myomas frequently recur after myomectomy (25% after 3 years), especially in young patients with a genetic predisposition, such as the African population. By treating these women medically, repeated

surgery responsible for pelvic adhesions and subsequent infertility, as well as the risk of uterine rupture during pregnancy, may be avoided.

We are not suggesting that UPA will eradicate all indications for myomectomy, but it does mean that surgery can be avoided in case of a very good response, or at least be postponed until the patient wishes to become pregnant (Fig. 6). In case of insufficient fibroid volume reduction or persistent bleeding, surgery (myomectomy) is indicated.

(3) Women >40 years presenting with symptomatic myomas (Fig. 6).

In premenopausal women with symptomatic myomas, long-term intermittent therapy may be proposed.

In case of a moderate response (>25 but <50% reduction), another two UPA courses can be given based on the results of the PEARL-III study [13▪▪], which showed that efficacy can be maximized this way. However, stopping UPA treatment until recurrence of symptoms may be considered another option.

In case of insufficient response in terms of fibroid reduction but good control of bleeding, it may be feasible to wait until bleeding recurs. In this instance, restarting UPA treatment or performing hysterectomy or uterine artery embolization may be three different options. In case of persistent heavy bleeding (1% of the intent-to-treat population), surgery is of course indicated [13▪▪].

In conclusion, among the latest possible therapeutic options [41▪▪], UPA has proved to be most effective for the medical management of fibroids [12,13▪▪,14▪▪,39▪▪] and will undoubtedly serve to modify the surgical approach. Also, this review evaluates the possible place of UPA as a preoperative adjunct to surgery, or as medical therapy to avoid surgery.

Further studies are now needed to confirm these new algorithms and assess the efficacy of UPA in terms of avoiding (or at least delaying) recurrence.

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None.

Conflicts of interest

J.D. has been a member of the Scientific Advisory Board (SAB) of PregLem S.A. since 2007. He held PregLem stocks related to SAB activities that he sold in October 2010 at PregLem's full acquisition by the Gedeon Richter Group. There is no relationship between stock payment value and future commercial performance of the study drug. The remaining authors have no conflict of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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