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# Uterine fibroid management: Today and tomorrow

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## Abstract

Current treatments for fibroids are mainly surgical and expensive, so alternatives need to be found. It is, therefore, vital to develop and evaluate alternatives to surgical procedures, especially when fertility preservation is the goal. Selective progesterone receptor modulators (SPRMs) are synthetic compounds that have either an agonistic or antagonistic impact on target tissues determined by their binding to progesterone receptors. Their mixed activity depends on recruitment of cofactors that regulate transcription along so-called genomic pathways, as well as nongenomic interactions with other signaling pathways. There is no doubt that surgery remains indicated in some instances, but we must now establish whether use of SPRMs (notably ulipristal acetate) allows less invasive surgery or even complete avoidance of surgery. Long-term intermittent administration of ulipristal acetate will undoubtedly change our approach to the management of uterine fibroids according to the International Federation of Gynecology and Obstetrics classification, which provides a comprehensive basis for different treatment options. When considering less invasive techniques (uterus-sparing options like myomectomy), the choice is guided by the size, number and location of fibroids, as well as the personal experience of the gynecologist and available equipment. There is now a growing body of evidence pointing to the crucial role of progesterone pathways in the pathophysiology of uterine fibroids. SPRMs should, therefore, be considered an alternative to surgical therapy, or at least an adjunct to surgery, as illustrated in the algorithms. 

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

## 1. Introduction

Uterine fibroids (also known as leiomyomas or myomas) are the most commonly encountered noncancerous tumors to develop in or around the uterus.[1–4] Their clinical presentation is diverse and may include pelvic masses, pelvic pain, infertility and obstetric complications.[1,5,6]

### 1.1. Risk factors

1. *Race* (Fig. 1)

African–American women are at greater risk of being affected by uterine fibroids, particularly at an earlier age.[8,9] A similar trend has been observed elsewhere, notably among women of African origin living in Europe.

2. *Age* (Fig. 1)

In previous studies, the average growth rate was found to be 9% over 6 months, but growth rates are known to differ between races and when age is taken into account (Fig. 1).

3. *Genetic factors*

Some specific genetic alterations are linked to fibroid growth.[10,11]

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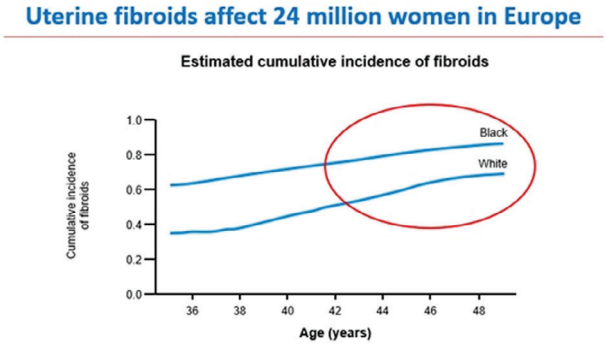


**Figure 1** Prevalence of uterine fibroids according to race and age. Adapted from Baird *et al.*[7]

4. *Early menarche and parity*

Menarche at an early age increases the risk of developing fibroids, while pregnancy has been found to have a protective effect. However, the mechanism involved has not been fully elucidated.

5. *Other factors*

An association has been reported between alcohol and caffeine intake and an elevated risk of developing uterine fibroids. A diet rich in red meat also appears to increase this risk, while smoking decreases it, but the reasons remain unknown.[2,12]

### 1.2. Classification

The International Federation of Gynecology and Obstetrics (FIGO) classification[13] describes eight types of fibroids, as well as a hybrid class (association of two myoma types) (Fig. 2). Because different types of fibroids are often present at the same time (depending on site), this classification offers a more representative 'map' of myoma distribution that can be used to establish new algorithms for their treatment.

### 1.3. Diagnosis

#### 1.3.1 *Pelvic examination and vaginal ultrasound*

Examination of the pelvis may reveal an enlarged uterus or mass, which can be confirmed by ultrasound, the gold standard evaluation tool for uterine fibroids. Its widespread availability allows easy and inexpensive confirmation in almost all instances. One of its advantages is the ability to reconstruct the coronal plane of the uterus by three-dimensional imaging technology.[14,15]

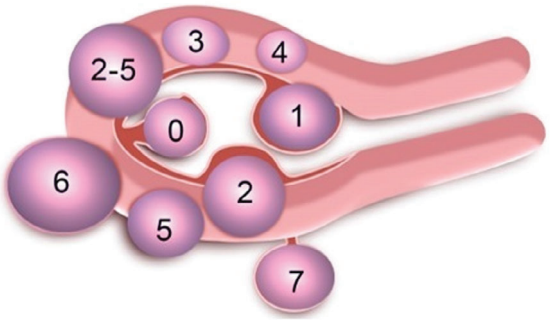


**Figure 2** International Federation of Gynecology and Obstetrics classification of uterine fibroids according to Munro *et al.*[13] Fibroid types range from 0 to 8. 0, pedunculated, intracavitary; 1, submucosal, <50% intramural; 2, submucosal, ≥50% intramural; 3, contact with endometrium, 100% intramural; 4, intramural; 5, subserosal, ≥50%, intramural; 6, subserosal, <50%, intramural; 7, subserosal, pedunculated; and 8, other (e.g., cervical, parasitic). Where two numbers are given (e.g., 2–5), the first number refers to the relationship with the endometrium, while the second number refers to the relationship with the serosa; for example, 2–5, submucosal and subserosal, each with less than half its diameter in the endometrial and peritoneal cavities respectively. Fibroid classification sketch republished with permission from Munro *et al.*,[13]

#### 1.3.2 *Hysteroscopy*

Diagnostic hysteroscopy may be performed in an outpatient setting, as it is straightforward and does not require any anesthesia.[16] Ultrasound with a saline infusion should be considered a complementary examination when hysteroscopic myomectomy is indicated. In case of irregular bleeding or combined risk factors like obesity or chronic anovulation, hysteroscopy may be combined with endometrial biopsy.

#### 1.3.3 *Magnetic resonance imaging*

Magnetic resonance imaging (MRI) provides information on the number of fibroids, their size and location, vascularization, relationship with the endometrial cavity and serosal surface and boundaries with normal myometrium (Fig. 3).

## 2. Why We Need New Options

Current treatments for fibroids are mainly surgical and expensive, so alternatives need to be found.

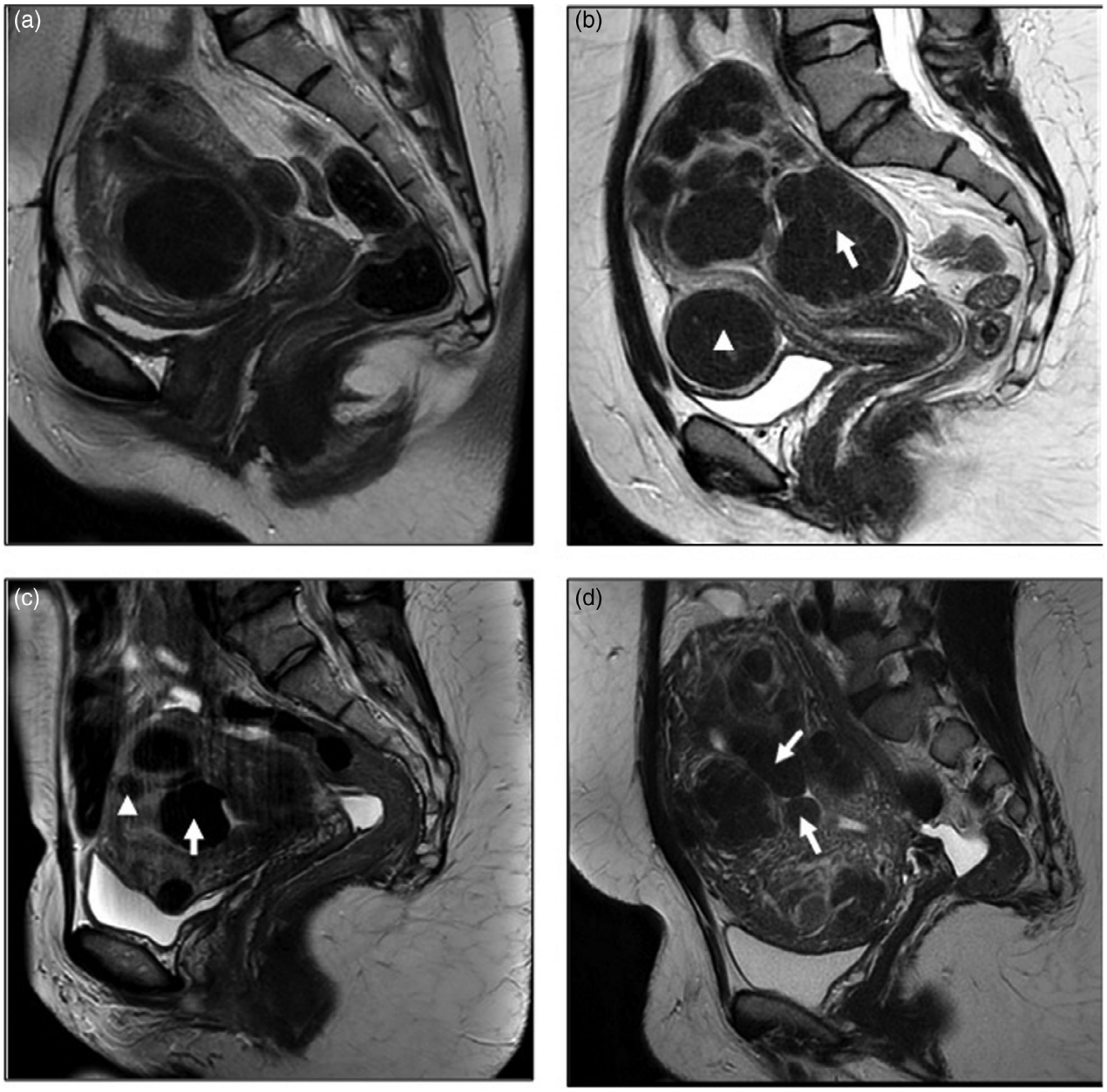


**Figure 3** Magnetic resonance imaging of fibroids. Midline sagittal T2-weighted images show different types of myomas according to the International Federation of Gynecology and Obstetrics classification.[13] Fibroids vary in size, number and site in the uterus. (a) Submucosal type 2 myoma. (b) Large type 2–5 myoma (white arrow), submucosal and subserosal, with less than half its diameter in the endometrial and peritoneal cavities respectively. Subserosal type 5 myoma (subserosal, ≥50% intramural) (arrowhead). (c) Submucosal type 2 myoma (≥50% intramural) (white arrow). Intramural type 4 myoma (arrowhead). Small type 5 myomas (black arrows). (d) Multiple myomas, two of which are type 0–1 (intracavitary) (white arrows).

Indeed, among 600 000 hysterectomies performed each year in the USA, around a third are for fibroids, with costs for their management estimated to be in excess of $2 billion a year.[17] It is, therefore, vital to develop and evaluate alternatives to surgical procedures, especially when fertility preservation is the goal.[6]

### 2.1. Molecular mechanism of action of selective progesterone receptor modulators

Selective progesterone receptor modulators (SPRMs) are synthetic compounds that have either an agonistic or antagonistic impact on target tissues determined by their binding to progesterone receptors,[12,18–20] with different effects according to tissue type.[21–23] Their mixed activity depends on recruitment of cofactors that regulate transcription along so-called genomic pathways, as well as nongenomic interactions with other signaling pathways (Fig. 4). Despite a number of recent hypotheses,[24] it is not known exactly how SPRMs alleviate menstrual bleeding.[25]

Ulipristal acetate (UPA) has been studied in four large randomized controlled trials (RCTs). These blinded phase III clinical studies PGL4001's (a code name for ulipristal acetate) efficacy assessment in reduction of symptoms due to uterine leiomyomata (PEARL) showed promising results in terms of both efficiency and safety.[26–30] Other SPRMs are still under development.

#### 2.1.1 *Short-term use before surgery*

UPA was initially approved for short-term use (3-month course) prior to surgery based on the first two blinded RCTs (PEARL I and II), where it was compared with either a placebo or gonadotropin-releasing hormone (GnRH) agonist.[26,27] These trials measured changes in blood loss, time needed to achieve control of bleeding, and fibroid volume reduction and regrowth at 3 months. UPA treatment looked promising[26,27] and yielded a number of positive findings: (i) a significant decrease in *menstrual bleeding*, calculated by the pictorial blood loss

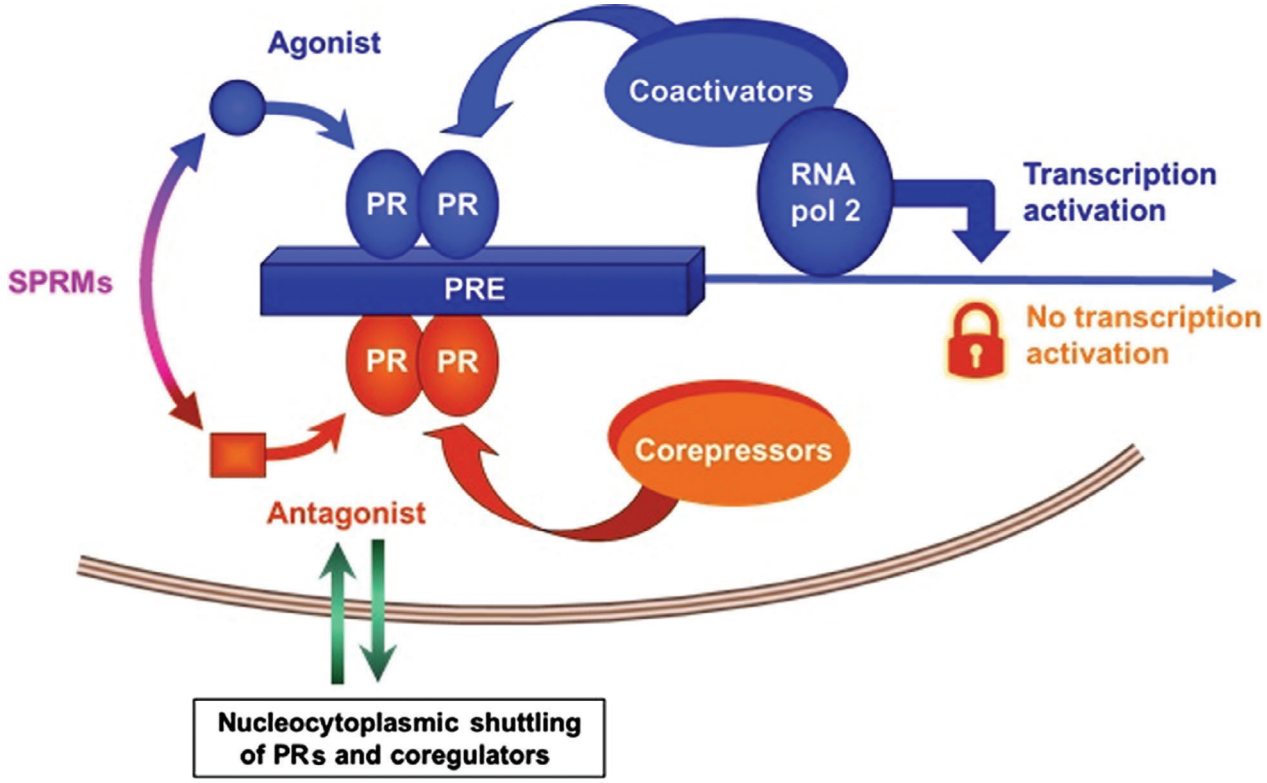


**Figure 4** Mechanism of action of selective progesterone receptor modulators (SPRMs). SPRMs have a direct impact on uterine fibroids, endometrium and the pituitary gland by a mechanism involving gene transcription regulation. SPRMs bind to progesterone receptors (PRs) with high selectivity and affinity. Once bound to SPRMs, PR dimers show agonist, antagonist or mixed activity. Agonist function is mediated by recruitment of coactivators in the promoting region of target genes, triggering transcription activation. Conversely, antagonist function of SPRMs is mediated by recruitment of corepressors that prevent transcription of target genes. Nucleocytoplasmic shuttling of PRs and coregulators regulates the availability of these partners to control gene expression, and leads to nongenomic signaling in the cytoplasm (adapted from Refs. 18,19).

assessment chart,[31] was observed at 10 days in more than 90% of women given a 3-month course of UPA, compared to 50% in the GnRH agonist group and 10% in the placebo group at the same time point; (ii) the *median time* needed to achieve control of bleeding was also shorter in the UPA group (5–7 days) than in the GnRH agonist group (30 days); and (iii) *fibroid volume* fell by around 35% after 3 months of UPA treatment, showing a sustained effect (up to 6 months) after treatment completion, while GnRH agonist-treated patients experienced a 23% rate of regrowth of their fibroids at 3 months and a return to screening levels by 6 months post-treatment.

### 2.1.2 *Longer-term use*

UPA may facilitate surgery by shrinking fibroids, or even help avoid the need for surgery altogether (Table 1). The sustained effect observed at 3 months in short-term RCTs (PEARL I and II) prompted further blinded RCTs (PEARL III and IV) investigating up to 4 intermittent 3-month courses of UPA, including off-treatment intervals (of approximately 2 months).[28,29,32] The prespecified primary outcome of PEARL IV, namely the basis for licensing its longer-term use, was the percentage of women achieving amenorrhea during the first two courses[29] and over all four courses combined.[32]

The benefits and adverse effects of longer-term UPA treatment for bleeding fibroids are presented in Table 1. The results show that UPA can be used to correct anemia, as demonstrated in PEARL I.[26]

As SPRMs induce endometrial changes, it is recommended that UPA be administered in an *intermittent* mode (3-month therapy course followed by an interval of around 8 weeks, allowing two menstrual bleeds) to reverse any such changes. UPA should be taken at the approved daily dose of 5 mg for 3 months.

## 3. Novel Algorithms, with a Special Emphasis on Infertility

There is no doubt that surgery remains indicated in some instances, but we must now establish whether use of SPRMs (notably UPA) allows less invasive surgery or even complete avoidance of surgery. Long-term intermittent administration of UPA will undoubtedly change our approach to the management of uterine fibroids according to the FIGO classification, which provides a comprehensive basis for different treatment options.[13]

### 3.1. Type 0 and type I myomas

If type 0 myomas are present, cutting the pedicle by hysteroscopy is indicated. For type 1 myomas less than 3 cm in size, hysteroscopic myomectomy is easily performed by experienced surgeons. If a fibroid is of type 1 but larger than 3 cm, or if the patient

**Table 1** Benefits and side effects of long-term treatment with 5 mg ulipristal acetate for large fibroids associated with heavy menstrual bleeding

| Population: A total of 228 premenopausal women aged 18–50 with moderate-to-severe symptoms of uterine fibroids (at least 1 fibroid >3 cm) treated with courses of ulipristal acetate (UPA) 5 mg/day (PEARL IV study), the only dose approved by the European Medicines Agency | | | |
|---|---|---|---|
| | UPA 5 mg | | |
| Benefits | | Side effects | |
| • Amenorrhea | | | |
| ≤1 day of spotting within 5 weeks | | • Hot flushes | |
| After 2 courses combined | 62% | After course 2 | 4% |
| After 4 courses combined | 49% | After course 4 | 3% |
| • Controlled bleeding | | • Breast pain/discomfort | |
| No heavy bleeding AND ≤8 days bleeding during the last 2 months of treatment | | After course 2 | 1% |
| After 2 courses combined | 81% | After course 4 | 1% |
| After 4 courses combined | 67% | | |
| • Change in 3 largest fibroids | | • Headache | |
| Median change in volume from baseline | | After course 2 | 6% |
| After course 2 | 54% smaller | After course 4 | 2% |
| After course 4 | 67% smaller | | |

Adapted from Donnez *et al.*[33] reproductive BioMedicine online 2018.

presents with anemia, medical therapy (SPRMs or GnRH agonist) is indicated to decrease myoma size and restore hemoglobin levels.[6]

### 3.2. Type 2 or type 2–5 myomas (single or multiple) distorting the uterine cavity (Donnez and Dolmans)

Treatment depends on a number of factors, as follows[6]:

*Young infertile women of reproductive age wishing to conceive*

If myomas are multiple (≥2) or of different types (type 2–5), as is commonly the case, medical therapy (SPRMs) can be given in two courses of 3 months, as established in clinical trials with UPA.[29,34] Thereafter, a reevaluation is made, with three possible outcomes:

1. The uterine cavity is no longer distorted, and the patient can attempt to conceive naturally or undergo assisted reproductive techniques, if indicated.
2. Myoma regression is significant (≥25%) but the uterine cavity remains distorted, or the myoma remains large due to its considerable volume at baseline, so surgery is indicated.
3. In approximately 20% of cases (poor responders), the response to medical therapy is inadequate, so surgery is the only option.

*Young women of reproductive age with symptomatic myomas wishing to preserve their fertility, but with no immediate desire to conceive*

Regression of myoma size (≥25% in 80% of patients) and control of bleeding (in >90% of patients) allow avoidance of surgery and restoration of hemoglobin levels.

There is no pressing need for surgery when there is no immediate wish to conceive, an especially crucial consideration for women of African descent. Indeed, African and African-American women stand a greater chance of developing symptomatic myomas at an earlier age than Caucasian women.[7] Recurrence rates after myomectomy can reach almost 50% after an interval of 4–5 years, and the risk of pelvic adhesions is obviously significantly increased after repeat myomectomy.[34,35]

*Premenopausal women presenting with symptomatic myomas with no desire to conceive, but wishing to preserve their uterus*

In the majority of cases, premenopausal patients with symptomatic myomas present with multiple myomas. They are often suitable candidates for medical therapy.

Indeed, subjects treated with 5 mg UPA for four courses of 3 months showed a clinically significant volume reduction[34] that increased from 62.3% after one course to 78.1% after four courses, suggesting added benefits with repeated courses.

In case of a good response, treatment can be stopped after two to four courses and the patient reassessed. Repeat therapy may be proposed if and when symptoms recur, as no endometrial hyperplasia was diagnosed in subjects given 5 mg UPA for eight courses of 3 months.[36]

## 4. Side Effects

UPA appears to have few serious side effects. Minor adverse events are detailed in Table 1, but these tend to decline with repeated courses.[30,36] Trials have monitored a number of conditions arising from side effects associated with UPA, and outcomes to date (at approximately 4 years) have not identified any particular safety concerns.[36]

### 4.1. Can it be harmful?

The safety profile of UPA during single[26,27] and multiple[6,29,30,36] treatment courses was well documented in the four clinical RCTs and no safety issues emerged from physical examination, vital signs or electrocardiograms. The most frequently encountered side effects were hot flushes, breast pain/discomfort and headaches. However, there was no increase in their incidence with repeated courses (Table 1), but actually a trend toward fewer adverse events.[32] All coagulation parameters were evaluated in detail in one of the longer-term studies (up to four courses) and found to be unchanged,[34] and no venous thromboembolism was reported in any of the four PEARL studies.[26,27,29,32,34] There were small but nonsignificant increases in mean cholesterol and triglyceride values, but the median ratio of total cholesterol/high-density lipoprotein cholesterol remained the same.[29,32] Mean levels of liver enzymes did not alter during long-term studies, and any sporadic surges were never associated with increases in bilirubin in the four PEARL trials.[26–29,32] Nevertheless, UPA is not recommended in patients with moderate or severe hepatic impairment.

### 4.2. Endometrial changes

SPRMs induce formation of large cystic glands in the endometrium and changes within the stromal compartment, including fibroblasts and the vasculature.[28,29,37]

In all conducted trials, these changes remained non-cancerous, but were present in almost 70% of patients during treatment.[6,25–27,29,32,34] Cystic and stromal changes appear to be reversible and benign, returning to screening levels (±10%) 2 months after completion of therapy in all the PEARL studies.[6,28,29,32] Moreover, in a very recent, extended PEARL III trial, neither atypical hyperplasia nor endometrial adenocarcinoma were reported in women undergoing eight courses of UPA treatment.[36]

### 4.3. Liver test: Enzymes and bilirubin

The European Medicines Agency announced temporary restrictive measures in February 2018, as five cases of drug-induced liver injury (DILI), four of which needed liver transplants, were potentially linked to UPA (Esmya) administration. The Pharmacovigilance Risk Assessment Committee (PRAC) subsequently made provisional recommendations advising physicians not to take on new patients or begin new treatment courses.

DILI can be *intrinsic* or *idiosyncratic*. The intrinsic form can affect all individuals to varying degrees and the reaction is generally stereotypic and dose-dependent (as with acetaminophen [paracetamol]). The idiosyncratic form affects only rare susceptible individuals and shows a less dose-dependent response and greater diversity in latency, presentation and course. UPA is not a member of any of the therapeutic classes of drugs associated with an elevated risk of DILI.

Detailed review of the latest phase III trials showed isolated transient increases in several liver function tests before, during and/or after treatment in a very small number of patients.[33,38] Indeed, some individuals exposed to a therapeutic dose of UPA may go on to develop idiosyncratic DILI, with potentially serious clinical consequences. Unfortunately, no biomarkers are currently available to identify susceptible patients prior to drug treatment.

Considering that only five acute liver failures occurred among 765 000 patients, and no signs of liver injury were reported in the clinical trials,[38] one could postulate that this is a very rare idiosyncratic event. Excluding patients with liver anomalies or disorders at screening and checking liver enzymes throughout treatment would minimize the risks further.

In May 2018, the status of UPA as a potential DILI-inducing agent was neither confirmed nor excluded, and the PRAC issued further recommendations designed to minimize the risks of liver injury, allowing patients to resume treatment.[33]

## 5. Conclusion

When considering less invasive techniques (uterus-sparing options like myomectomy), the choice is guided by the size, number and location of fibroids, as well as the personal experience of the gynecologist and available equipment. There is now a growing body of evidence pointing to the crucial role of progesterone pathways in the pathophysiology of uterine fibroids. Large clinical trials have been conducted to investigate long-term intermittent administration of SPRMs. Two or more 3-month courses of UPA have been shown to maximize its potential benefits in terms of bleeding control and fibroid volume reduction. SPRMs should, therefore, be considered an alternative to surgical therapy, or at least an adjunct to surgery, as illustrated in the algorithms.[6]

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## Disclosure

JD 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 upon PregLem's full acquisition by the Gedeon Richter Group. There was no relationship between the stock payment value and future commercial performance of the studied drug. MMD and LF have no conflict of interest to declare.

## References

1. Donnez J, Jadoul P. What are the implications of myomas on fertility? A need for a debate? *Hum Reprod* 2002; **17**: 1424–1430.
2. Islam S, Protic O, Giannubilo SR *et al.* Uterine leiomyoma: Available medical treatments and new possible therapeutic options. *J Clin Endocrinol Metab* 2013; **98**: 921–934.
3. BS. Uterine fibroids. *N Engl J Med* 2013; **369**: 14.
4. Drayer SM, Catherino WH. Prevalence, morbidity, and current medical management of uterine leiomyomas. *Int J Gynaecol Obstet* 2015; **131**: 117–122.

5. Stewart EA. Clinical practice. Uterine fibroids. *N Engl J Med* 2015; **372**: 1646–1655.
6. Donnez J, Dolmans MM. Uterine fibroid management : From the present to the future. *Hum Reprod Update* 2016; **22**: 665–686.
7. Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative invidence of uterine leiomyoma in black and white women: Ultrasound evidence. *Am J Obstet Gynecol* 2003; **188**: 100–107.
8. Wise LA, Palmer JR, Harlow BL *et al.* Risk of uterine leiomyomata in relation to tobacco, alcohol and caffeine consumption in the black Women's health study. *Hum Reprod* 2004; **19**: 1746–1754.
9. Wise LA, Laughlin-Tommaso SK. Epidemiology of uterine fibroids: From menarche to menopause. *Clin Obstet Gynecol* 2016; **59**: 2–24.
10. Mäkinen N, Mehine M, Tolvanen J *et al.* MED12, the mediator complex subunit 12 gene, is mutated at high frequency in uterine leiomyomas. *Science* 2011; **334**: 252–255.
11. Mehine M, Kaasinen E, Aaltonen LA. Chromothripsis in uterine leiomyomas. *N Engl J Med* 2013; **369**: 2160–2161.
12. Kim JJ, Sefton EC. The role of progesterone signaling in the pathogenesis of uterine leiomyoma. *Mol Cell Endocrinol* 2012; **358**: 223–231.
13. Munro MG, Critchley HO, Broder MS, Fraser IS. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. FIGO working group on menstrual disorders. *Int J Gynaecol Obstet* 2011; **113**: 1–2.
14. Andreotti RF, Fleischer AC. Practical applications of 3D sonography in gynecologic imaging. *Radiol Clin North Am* 2014; **52**: 1201–1213.
15. Wong L, White N, Ramkrishna J, Araujo Júnior E, Meagher S, Costa Fda S. Three-dimensional imaging of the uterus: The value of the coronal plane. *World J Radiol* 2015; **7**: 484–493.
16. Bettocchi S, Nappi L, Ceci O, Selvaggi L. What does 'diagnostic hysteroscopy' mean today? The role of the new techniques. *Curr Opin Obstet Gynecol* 2003; **15**: 303–308.
17. Flynn M, Jamison M, Datta S, Myers E. Health care resource use for uterine fibroid tumors in the United States. *Am J Obstet Gyncol* 2006; **195**: 955–964.
18. Chabbert-Buffet N, Meduri G, Bouchard P, Spitz IM. Selective progesterone receptor modulators and progesterone antagonists: Mechanisms of action and clinical applications. *Hum Reprod Update* 2005; **11**: 293–307.
19. Bestel E, Donnez J. The potential of selective progesterone receptor modulators for the treatment of uterine fibroids. *Expert Rev Endocrinol Metab* 2014; **9**: 79–92.
20. Chabbert-Buffet N, Esber N, Bouchard P. Fibroid growth and medical options for treatment. *Fertil Steril* 2014; **102**: 630–639.
21. Donnez J, Arriagada P, Donnez O, Dolmans MM. Current management of myomas: The place of medical therapy with the advent of selective progesterone receptor modulators. *Curr Opin Obstet Gynecol* 2015; **27**: 422–431.
22. Moravek MB, Yin P, Ono M *et al.* Ovarian steroids, stem cells and uterine leiomyoma: Therapeutic implications. *Hum Reprod Update* 2015; **21**: 1–12.
23. Bouchard P, Chabbert-Buffet N. The history and use of the progesterone receptor modulatorulipristal acetate for heavy menstrual bleeding with uterine fibroids. *Best Pract Res Clin Obstet Gynaecol* 2016; **40**: 105–110.
24. Whitaker LH, Murray AA, Matthews R *et al.* Selective progesterone receptor modulator (SPRM) ulipristal acetate (UPA) and its effects on the human endometrium. *Hum Reprod* 2017; **32**: 531–543.
25. Williams ARW, Bergeron C, Barlow DH, Ferenczy A. Endometrial morphology after treatment of uterine fibroids with the selective progesterone receptor modulator, ulipristal acetate. *Int J Gynecol Pathol* 2012; **31**: 556–569.
26. Donnez J, Tatarchuk TF, Bouchard P *et al.* Ulipristal acetate versus placebo for fibroid treatment before surgery. *N Engl J Med* 2012; **366**: 409–420.
27. Donnez J, Tomaszewski J, Vázquez F *et al.* Ulipristal acetate versus leuprolide acetate for uterine fibroids. *N Engl J Med* 2012; **366**: 421–432.
28. Donnez J, Vázquez F, Tomaszewski J *et al.* Long-term treatment of uterine fibroids with ulipristal acetate. *Fertil Steril* 2014; **101**: 1565–73 e1-18.
29. Donnez J, Hudecek R, Donnez O *et al.* Efficacy and safety of repeated use of ulipristal acetate in uterine fibroids. *Fertil Steril* 2015; **103**: 519–27.e3.
30. Donnez J, Donnez O, Matule D *et al.* Long-term medical management of uterine fibroids with ulipristal acetate. *Fertil Steril* 2016; **105**: 165–173.e4.
31. Higham JM, O'Brien PMS, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *Br J Obstet Gynaecol* 1990; **97**: 734–739.
32. Donnez J, Arriagada P, Marciniak M, Larrey D. Liver safety parameters of ulipristal acetate for the treatment of uterines fibroids: A comprehensive review of the clinical development program. *Expert Opin Drug Saf* 2018; **17**: 1225–1232.
33. Donnez J, Donnez O, Dolmans MM. Safety of treatment of uterine fibroids with the selective progesterone receptor modulator, ulipristal acetate. *Expert Opin Drug Saf* 2016; **15**: 1679–1686.
34. Donnez J, Donnez O, Dolmans MM. With the advent of selective progesterone receptor modulators, what is the place of myoma surgery in current practice? *Fertil Steril* 2014; **102**: 640–648.
35. Malone LJ. Myomectomy: Reccurence after removal of solitary and multiple myomas. *Obstet Gynecol* 1969; **34**: 200–209.
36. Fauser BCJM, Donnez J, Bouchard P *et al.* Safety after extended repeated use of ulipristal acetate for uterine fibroids. *PLoS One* 2017; **12**: e0173523.
37. Mutter GL, Bergeron C, Deligdisch L *et al.* The spectrum of endometrial pathology induced by progesterone receptor modulators. *Mod Pathol* 2008; **21**: 591–598.
38. Donnez J. Liver injury and ulipristal acetate: An overstated tragedy? *Fertil Steril* 2018; **110**: 593–595.


 