Selective progesterone receptor modulators for fertility preservation in women with symptomatic uterine fibroids†

Mohamed Ali1,2 and Ayman Al-Hendy1,∗

1Department of Obstetrics and Gynecology, Medical College of Georgia, Augusta University, Augusta, Georgia, USA and 2Clinical Pharmacy department, Faculty of pharmacy, Ain Shams University, Cairo, Egypt

∗Correspondence: Division of Translational Research, Department of Obstetrics and Gynecology, Medical College of Georgia (MCG), Augusta University CB-2208, 1120 15th St., Augusta, GA 30912, USA. Tel: +706-721-3833; Fax. 706-721-6211; E-mail: aalhendy@Augusta.edu

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Abstract

Uterine fibroids (UFs, AKA leiomyoma) are the most important benign neoplastic threat to women’s health, with costs up to hundreds of billions of health care dollars worldwide. Uterine fibroids caused morbidities exert a tremendous health toll, impacting the quality of life of women of all ethnicities, especially women of color. Clinical presentations include heavy vaginal bleeding, pelvic pain, bulk symptoms, subfertility, and obstetric complications. Current management strategies heavily lean toward surgical procedures; nonetheless, the choice of treatment is generally subject to patient’s age and her desire to preserve future fertility. Women with UF who desire to maintain future fertility potential face a dilemma because of the limited treatment choices that are currently available to help them achieve that goal. Recently, ulipristal acetate the first of the promising family of oral selective progesterone receptor modulators has been approved for UF treatment in Europe, Canada, and several other countries and is under review for possible approval in the USA. In this review article, we discuss recent advances in the management options against UF with a bend toward oral effective long-term treatment alternatives who are particularly suited for those seeking to preserve their future fertility potential. We also explore the transformative concept of primary and secondary UF prevention using these new anti-UF agents. We envision a remarkable shift in the management of UF in future years from surgical/invasive treatment to orally administrated options; clearly, this potential shift will require additional intense clinical research.

Summary Sentence

We focus on oral long term anti-UF treatment options which can benefit those seek to preserve future fertility. We explore the transformative concept of primary/secondary UF prevention using these agents. We envision a futuristic shift in the UF management from invasive treatment to oral one.

Key words: uterine fibroids, selective progesterone receptor modulators, ulipristal acetate, fertility preservation, treatment, prevention.

Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| ActRIIB | Activin receptor type |
| Alk4 | Activin receptor-like kinase 4 |
| ART | Assisted reproductive techniques |
| AUB | Abnormal uterine bleeding |
| BMD | Bone mineral density |

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COCs  Combined oral contraceptives
E2  Estrogen
EC  Emergency Contraceptive
ECM  Extracellular matrix
EMA  European Medicines Agency
ER  Estrogen receptor
GnRH  Gonadotropin releasing hormone
HIFU  High intensity focused ultrasound
HMB  Heavy menstrual bleeding
IGFRI  Insulin-like growth factor receptor-I
IR  Insulin receptor
IVF  In Vitro Fertilization
LA  Leuprolide acetate
P4  Progesterone
PAECs  Progesterone receptor modulators associated endometrial changes
PEARL  PGL4001 (UPA) efficacy assessment in reduction of symptoms due to uterine leiomyomata
PK  Pharmacokinetic
PR  Progesterone receptor
SPRMs  Selective progesterone receptor modulator
TGFβ  Transforming growth factor β
TNF-α  Tumor necrosis factor alpha
UF  Uterine fibroids
UPA  Ulipristal acetate
VEGF  Vascular endothelial growth factor

Introduction

Uterine fibroids (UFs) or leiomyoma are considered the most common benign solid monoclonal smooth muscle tumors in women of reproductive age with a prevalence rate of 70%–80% in women by 50 years of age, making it a substantial health care burden with significant quality-of-life impact [1]. Uterine fibroids originate from myometrium when a normal myometrial stem cell is sufficiently altered eventually leading to the emergence of a somatic mutation such as Med12 mutation, and converting that stem cell into a fibroid tumor initiating cell [2–4]. Each fibroid lesion is an independent mutagenic event as evidenced recently by the detection of an assortment of Med12 mutation in different UF lesion in the same uterus [5,6]. Patients with UF develop various symptoms over time such as bulk symptoms include pelvic pressure and pain, dysmenorrhea, dyspareunia, and constipation [7], but the most common UF-related symptoms is heavy menstrual bleeding (HMB), as 80% of women with UF experience menorrhagia and menometrorrhagia which often leads to iron deficiency anemia [7]. Additionally, various obstetrical complications such as miscarriage, premature labor, postpartum hemorrhage, and placental abruption can also be provoked by UF [8]. In the USA alone, UF’s have a total economic cost estimated to range between 6 and 34 billion dollars annually. This embraces direct costs of management such as surgery, hospital admissions, outpatient visits, and medications, in addition to the indirect costs attributed to loss of wages, disability, and other obstetric complications [9].

Uterine fibroids and fertility

Uterine fibroids have a negative impact on female infertility. Uterine fibroids are present in 5%–10% of women with infertility and remarkably are the only detectable cause of infertility in up to 2.5% of these cases [10]. Most of these cases (65%) are attributed to inadequate endometrial receptivity to embryo implantation secondary to deleterious effects of UF on endometrium [11]. Uterine fibroids may also affect both transport of sperms and uterine contractility, this was confirmed indirectly via promising fertility performance after removal of UF’s [12]. Many studies were conducted to address the possible effect of UF’s on the outcome of assisted reproductive techniques (ART), including in vitro fertilization and intracytoplasmic sperm injection, as compared to those without UF’s. These studies showed a reduced rate of implantation, pregnancy, and live birth with increase in miscarriage rate among women with UF’s, especially submucosal and intramural lesions [13,14]. Current literature call for removal of submucous (type 0) fibroid and possibly cavity distorting intramural fibroid (types 1–2) to optimize ART supported pregnancy outcomes. While removal of intramural fibroids (necrosis distorting, types 3–5) of any size and especially if less than 4 cm is still controversial [7,15–20].

Role of progesterone in pathogenesis of uterine fibroids

Female sex steroids, estrogen (E2) and progesterone (P4), play a major role in UF pathogenesis [21]. This has been proven epidemiologically, clinically, and at the molecular level [22–24]. Size of UF is increased at early stage of pregnancy along with the increase in circulating E2 and P4, while a paradoxical stabilization and eventual decrease in size are observed during late pregnancy and postpartum period, which is attributed to the increase in myometrial differentiation and extracellular matrix remodeling [25–27]. Interestingly, high parity was found to be protective against UF relative to nulliparous women [28] while early menarche increases the risk of UF development [29].

Classically, UF’s were thought to be mainly E2-dependent tumors, based on their chronological association with the reproductive age besides the overexpression of estrogen receptors (ERs) alpha as well as aromatase enzyme in UF’s relative to normal myometrium [30,31]. Furthermore, encouraging anti-fibroid findings using medications that decrease E2 production such as gonadotropin releasing hormone (GnRH) analogs [32], aromatase inhibitors [33], and selective ER modulators [34] supported that notion.

Recently, another important role for E2 has been identified, which is to support both progesterone receptors (PR A & B) induction and facilitating PR ligands action on target cells [35]. Uterine fibroid cells exhibit an increase in the expression of both PR isoforms in response to estradiol [36]. Interestingly, the overexpression of dominant-negative (nonfunctional) ER results in decrease in the PR expression in human UF cells [37]. It is therefore suggested that E2 primary role in UF pathogenesis is to maintain PR levels and it is indeed P4 that promotes UF growth and progression [38].

A growing number of clinical and experimental studies support the pivotal role of P4 in UF growth and development [39]. For example, the mitotic activity in UF’s is higher during the secretory phase of the menstrual cycle (when P4 is dominant) than during the proliferative phase (when E2 is dominant) [40], and also increased proliferation of UF cells in vitro when exposed to both E2 and P4 [41]. Finally, a UF xenograft animal model showed that P4 is imperative for proliferation of UF tumor cells and formation of UF lesions [38].

Progestrone actions on the female reproductive system are mainly mediated via PR which is synthesized from a single gene and expressed as two main protein isoforms (PR-A, PR-B) [42]. Both PR A/B are extensively expressed in UF’s as compared to normal myometrium from the same patient [43]. PR-B is the transcriptional activator of the progesterone-responsive genes, while PR- A is the...
Figure 1. Role of progesterone in uterine fibroids pathogenesis. Progesterone, in response to estrogen, affects different cellular functions such as proliferation, apoptosis, and extracellular matrix deposition, either directly on fibroid cell via progesterone receptors or indirectly via paracrine effect on fibroid stem cells which give rise to more fibroid cells. Abbreviations: PCNA, proliferating cell nuclear antigen; BCL2, B-cell lymphoma 2; ECM, extracellular matrix; EGF, epidermal growth factor; TGFβ, transforming growth factor β; PR, Progesterone receptor.

Treatment options for uterine fibroids

Many women, if given the option, would prefer medical treatment for their UF over a surgical solution to avoid the possible risks associated with surgery, and preserve their uterus for future fertility and also for psychological/feminine reasons [54,55]. Selecting a specific UF treatment primarily depends on patient’s age, her symptoms, her preferences, and most importantly her reproductive plans. Currently, there are limited number of treatment options available for UF patients who desire future fertility [56,57].

Detailed description of surgical and traditional non-surgical treatment options against UF is beyond the scope of this review article and has been addressed with excellent reports recently [48,58]. In this article, we will focus on UF treatment options with a bend toward their effect on preservation of fertility potential.

Surgical interventions

Hysterectomy

Uterine fibroids are the leading gynecological cause of hospital admission, as ~200 000 of the 600 000 hysterectomies performed each year in the USA are due to UF [59]. Hysterectomy completely removes the fibroids, however, deprives these women of being able to naturally conceive for the rest of their lives. In addition, minor and major surgical complications can occur [60,61]. Currently, due to various social and financial reasons, many women postpone their first pregnancy to the later part of their reproductive years, so the request for uterine preservation, to maintain fertility, is becoming an increasingly urgent need in the gynecologist’s daily practice in women with symptomatic UF [62].
Myomectomy

Another surgical option to manage women with symptomatic UF is myomectomy, with a rate of ~30,000 conducted annually in USA [9]. It aims to remove tumor only and retains the uterus. Yet, it is still considered a major surgical operation with potential morbidity and significant risks of UF recurrence [63]. Furthermore, there is a high risk of postoperative adhesion formation which makes the positive impact of myomectomy on UF-related infertility rather doubtful [64]. Laparoscopic or hysteroscopic radiofrequency myomectomy is a relatively recent modality with limited data on its impact on subsequent fertility [65]. Hysteroscopic myomectomy for intracavitary submucous (FIGO type 0–1) is one area where high-quality evidence strongly suggests positive impact on subsequent fertility [66].

Non-surgical interventions

Less invasive procedures such as uterine artery embolization uses embolus to block blood flow to the tumor, which consequently reduces fibroid size and its associated symptoms [67]. However, it has been connected to potential complications such as premature ovarian failure, chronic vaginal discharge, occasional pelvic sepsis, and may have limited efficacy when the fibroids are large [67]. Additionally, there is a debate regarding its effect on future fertility, with a general acceptance in the field that it should not be considered for those who plan future pregnancy [68].

Magnetic resonance-guided focused ultrasound also known as high intensity focused ultrasound (HIFU) uses focused ultrasound energy to thermally ablate UF tissue [69]. HIFU may be effective in select cases, but a recent randomized placebo-controlled study showed its limited durable effect and the high rate of additional subsequent fibroid related procedures [70]. Generally, nonhysterectomy procedures are typically associated with a high rate of symptoms recurrence from either regrowth of pre-existing fibroid or new UF tumor formation.

Pharmacological treatment

Therapeutic drugs may offer excellent alternative options for many UF patients, including those who desire more conservative management approach, women approaching menopause (perimenopause), and particularly for young UF patients who wants to preserve their future fertility. Drug-based approaches have been traditionally used as preoperative adjuvant to reduce fibroid volume and not for long-term courses. Current medical therapies either fail to fully resolve symptoms or are associated with unacceptable side effects that limit their long-term use [57]. Current investigations in the field foresee UF drug treatment options for a major role beyond short-term presurgical adjuvant therapy, but rather as a viable long-term treatment options with sustained effectiveness, safety, affordability, and most importantly fertility preservation capability. Herein, we will briefly describe these various hormonal treatment modalities with special emphasis on ulipristal acetate (UPA).

Combined oral contraceptives and levonorgestrel intrauterine system

Gynecologists generally considered the use of combined oral contraceptive pills (COCs) as their first choice to control UF-related abnormal uterine bleeding (AUB); this is based on their suppressive effect on endometrial proliferation besides being accessible with low cost and relatively good safety profile [71]. However, COCs have limited efficacy as well as lack of ability to reduce tumor size [71]. Following the same concept, FDA approved in 2009 the use of levonorgestrel intrauterine system to treat women with HMB. However, studies have shown conflicting results on its efficacy in controlling UF-related bleeding [72–75].

Gonadotropin releasing hormone agonists and antagonists

GnRH agonist was one of the first medical therapies to be used in UF treatment. In 1999, the FDA approved the short-term use of leuproide acetate (LA) as a preoperative hematologic improvement adjunct in women with symptomatic UF who are accompanied with anemia. Its action is based on induction of hypoestrogenic state as a result of pituitary GnRH receptor downregulation with subsequent decrease of gonadal steroids, thus putting patient in pseudomenopause state and reducing fibroid size and symptomatology [19,71,76]. However, it causes a wide range of side effects such as hot flushes, vaginal dryness, and mood swings to serious ones as bone demineralization and decreased bone mineral density (BMD), thus limiting LA use to a maximum of 3- to 6-month duration [77]. Being expensive besides the rapid recurrence of UF symptoms within 3 months of treatment cessation limits the use of this approach for long-term therapy [78].

GnRH antagonists as cetorelix and ganirelix have been used with advantage over the agonists of bypassing the initial flare effect due to receptor stimulation (up to 15 days), thus allowing them to show faster improvement of bleeding pattern [77,79]. Yet, several reasons prohibit widespread use of the antagonists generally in symptomatic treatment of UF such as high price, requirement of daily administration, and lack of clinical trial-based evidence of their superiority over the agonist [78,80].

Currently, several phase III randomized controlled clinical trials are being conducted to evaluate the utility of novel orally active GnRH antagonist such as elagolix, relugolix, and OBE2109 either with or without add-back therapy in women with symptomatic UF [81–83].

Selective estrogen receptor modulators

Although preclinical data appeared to be promising regarding the use of selective ER modulators such as tamoxifen or raloxifene in the treatment of UFs, clinical trial results were unsatisfactory [34].

Selective progesterone receptor modulators

Selective progesterone receptor modulators (SPRMs) are relatively new class of synthetic steroid ligands with a PR-target and tissue-selective effects of mixed agonist and antagonist activities [84]. They have several current indications including emergency contraception (EC), termination of pregnancy, premenstrual syndrome, and assisted reproduction [85]. Furthermore, as they may have direct effects on endometrial and fibroid cells, they are also investigated for therapeutic utility against UF, AUB, dysmenorrhea, endometriosis, and more recently breast cancer prevention [86]. Mifepristone was the first member of this class that has expanded to include asoprisnil, onapristone, UPAP, lonaprisan, vilaprisan, and telapristone (Figure 2). The agonistic/antagonistic nature of interaction between each ligand and PR, with subsequent effects on target genes, is based on cell type, molecular environment, and selective recruitment of co-activators or co-repressors. Furthermore, SPRMs have minimal effect on serum estrogen levels and so they are not expected to induce menopausal-like symptoms or subsequent bone loss [84,85,87,88]. Figure 2 highlights the SPRM family members, other than UPAP, and their current research direction.

Pending additional clinical trial evaluation, SPRMs are poised to provide additional options in the management choices against UF and may provide viable alternative to surgery for women seeking
fertility preservation (medical myomectomy). In the following sections, we will briefly describe the state of the art of the commonly studied SPRMs against UFs with emphasis on UPA as the forefront SPRM already approved for use against UF in Europe, Canada, and several other countries.

**Mifepristone.** Mifepristone was the first SPRM, with predominantly, almost pure, antagonistic effect, to be investigated in UF management [89]. A recent systematic review concludes its efficacy in reducing bleeding and improving quality of life albeit without significant reduction in UF volume. Unfortunately, safety concerns were raised due to its associated risk of endometrial hyperplasia and therefore it is no longer recommended for UF management and its current use is primarily for pregnancy termination [89,90].

**Asoprisnil.** Asoprisnil was developed for symptomatic treatment of endometriosis, UF, and dysfunctional uterine bleeding. It resulted in reduction in fibroid size and improvement in HMB. Unfortunately, it has not been taken further in clinical trials in recent years due to failing phase III clinical trial in 2008 which is attributed to unsafe changes in the endometrial lining of the uterus [91–93].

**Telapristone.** Also known as Proellex, telapristone has been evaluated for treatment of symptoms associated with endometriosis and UF. However, phase III studies were suspended because of significant increases in liver enzymes [94]. At present time, there is an ongoing phase II clinical trial started on 2014 that aims to evaluate both safety and efficacy of lower oral as well as vaginal doses of telapristone acetate [95].

**Vilaprisan.** A novel SPRM which recently passed a 12-week phase I clinical trial successfully, in which most of the women who took the medication at daily dose of 1–5 mg reported absence of menstrual bleeding. These results supported the initiation of advanced clinical trials to evaluate vilaprisan in women with symptomatic UFs [96].

**Ulipristal acetate.** It is our belief that the interest in this oral agent will soon increase in the USA as a novel and much-needed therapy for the medical management of UFs. UPA (Figure 3) is being evaluated not only as a presurgical adjuvant but also for long-term use with special utility in women with symptomatic UFs who are seeking fertility preservation. Hence, the present work aims at providing a comprehensive summary of its main features as clinical pharmacology, pharmacokinetic (PK) properties, and safety as well as its clinical utility in UF management.

**Pharmacology.** UPA is a synthetic steroid derived from 19-norprogesterone, and has tissue-specific mixed agonist/antagonist effects with noted preferential binding in the uterus, cervix, ovaries, and hypothalamus [97]. UPA is characterized by its superior selectivity for PRs, even higher than P4 itself, and it increases apoptosis and decreases proliferation via numerous mechanisms including increase in alkaline phosphatase activity, upregulation of cleaved caspase-3, and downregulation of both tumor necrosis factor alpha (TNF-α) and Bcl-2 expression [98]. UPA also induces apoptosis by activating the mitochondrial and TNF-related apoptosis-inducing ligand (TRAIL) pathways and eliciting endoplasmic reticulum stress [98]. It was also shown that UPA suppresses the expression of angiogenic factors such as vascular endothelial growth factor (VEGF) and adrenomedullin in cultured human fibroid cells [99]. Furthermore,
Figure 3. Chemical structures of ulipristal acetate and its metabolites.

Figure 4. Mechanism of action of ulipristal acetate (UPA). UPA binds to pituitary gland, endometrium, and uterine fibroids to elicit its actions via modulations of several markers that regulate different cell functions such as proliferation, apoptosis, extracellular matrix deposition, and angiogenesis. Abbreviations: PAEC, Progesterone Receptor Modulators associated Endometrial Changes; UPA, Ulipristal Acetate; TRAIL, TNF-related apoptosis-inducing ligand; BCL2, B-cell lymphoma 2; TNF, Tumor Necrosis Factor Alpha; VEGF, Vascular Endothelial Growth Factor; ADM, Adrenomedullin; MMPs, Matrix Metalloproteinases; EMMPRIN, Matrix Metalloproteinase Inducer; TIMP, Tissue Inhibitor of Metalloproteinases.

UPA reduces collagen deposition in the extracellular matrix (ECM), resulting in shrinkage of ECM volume [100]. UPA was also shown to inhibit the expression and functions of activin A in UF cells which was proven to increase ECM expression. It also decreases activin binding proteins, follistatin, activin receptor type (ActRIIB), and activin receptor-like kinase 4 (Alk4) mRNA expressions. In addition, it was able to block the activin A-induced increase in fibronectin or VEGF-A mRNA expression [101]. Moreover, ECM deposition in UF is also reduced by UPA due to increasing both matrix metalloproteinases (MMPs) and ECM metalloproteinase inducer (EMMPRIN) while reducing tissue inhibitor of metalloproteinases (TIMPs) [100,102]. Finally, UPA also increases the ratio of progesterone receptor isoforms (PR-A/PR-B) as it decreases PR-B receptor expression while increases PR-A so UPA inhibits progesterone-mediated effects on fibroid cells [98–101, 103–108]. Figure 4 summarizes UPA mechanisms of action presented in the literature so far.

A retrospective study of tissues collected from women treated preoperatively with UPA versus placebo-treated controls demonstrated that UPA supported low proliferation rate in UF cells, stimulated cell death, and intensely reduced ECM in UF lesions [102].

**Pharmacokinetics.** UPA has a good oral bioavailability, mainly excreted in feces, and less than 10% is excreted in the urine. It is extensively metabolized by the liver via CYP3A4-mediated N-demethylation giving rise to its main metabolites N-monodemethylated (PGL4002) and N-didemethylated UPA (PGL4004) (Figure 3). Therefore, concomitant use of potent
CYP3A4 inducers such as rifampicin, phenytoin, and phenobarbital or inhibitors such as ketoconazole and erythromycin is not recommended to avoid either treatment failure or toxicity, respectively [109,110].

By assessing the PK of a single oral dose of UPA (5 mg) in healthy female volunteers, UPA rapidly reached peak concentrations within 1 h after administration, with the apparent terminal half-life time \( (t_{1/2}) \) ranging from 35 to 43 h, thus allowing one oral administration per day dosage [111]. Multiple dosing of UPA exhibited a PK profile consistent with that of a once-daily regimen [111].

Rate of absorption of UPA is pH dependent so concomitant administration with drugs that increase gastric pH as proton pump inhibitors can slightly modify PK parameters [112]. No dramatic changes are observed when administered either with or without food [113]. Interestingly, trough UPA concentrations were generally comparable in healthy participants and UF patients [114,115].

As AUB is a frequent symptom of UF with concomitant iron deficiency anemia, iron salts are commonly prescribed in UF patients. These salts are traditionally known to inhibit the bioavailability of other concurrently taken drugs. However, PK studies concluded that its effect is minimal on UPA bioavailability and of no clinical significance. As UPA is mainly metabolized in liver, it is not recommended for patients with moderate-to-severe hepatic impairment unless closely monitored. However, it is safe, without dose modification, in mild cases [116].

Although conception is unlikely during UPA intake due to its ovulation suppression, it is still contraindicated in pregnancy as the safety data regarding its teratogenicity are unknown. So backup contraceptive favorably barrier methods such as condoms must be used. While COCs or progestin only pills are not recommended, they are used. While COCs or progestin only pills are not recommended, they might reduce UPA therapeutic effect [117].

Indications. In February 2012, European medicines agency (EMA) approved the use of 5 mg UPA tablets (Emsya) as a preoperative treatment for moderate-to-severe symptoms of UF in adult women of reproductive age, with a treatment duration limited to 3 months which extended to two courses of 3-month treatments in early 2014 [83]. In May 2015, UPA was approved for long-term intermittent treatment as follows, the first cycle starts with the first days of menstruation and then the subsequent course should begin with the next menstruation. In 2013, UPA received a Health Canada approval for the same indication of EMA under the name Fibristal [110,118].

In 2010, the FDA in the USA licensed the use of UPA at the dose of 30 mg (Ella) as an EC, due to its inhibition of ovulation and rapid effects on endometrium that may play a role in the prevention of implantation. Approval for UPA by FDA for the treatment of UF is pending and anticipated in near future, likely in 2018.

Advantages over gonadotropin releasing hormone analogs. UPA can aid the operative treatment of UFs by reducing fibroid volume especially in cases of large UF that exceed 6 cm in diameter, multiple fibroids, or fibroids of unfavorable localization such as cervical UF. After approximately 7 days of UPA administration, a significant reduction in bleeding occurs and amenorrhea ensues with subsequent increase in hemoglobin level, which decreases or eliminates the necessity of blood transfusions, “autotransfusion effect.” [119]

In women treated with UPA, circulating estradiol levels are maintained in the midfollicular range throughout the treatment duration, unlike GnRH agonists which decreased serum E2 to postmenopausal levels. Thus, UPA use avoids the annoying climacteric side effects, such as BMD loss and vasomotor symptoms, and in turn improves patient satisfaction and compliance [115]. After treatment discontinuation, the ongoing effects of fibroid volume reduction appear to be more prolonged with UPA than with GnRH agonists [120]. Moreover, UPA has not been linked to increased risk of thromboembolic events unlike other anti-UF hormonal therapeutics [114]. Finally, GnRH analogs are expensive and in most cases require additional hormonal add-back therapy, while UPA shows improved quality of life and cost-effectiveness (discussed later in Pharmacoeconomics section) [115].

Pivotal clinical trials of ulipristal acetate. Several clinical trials have evaluated the efficacy of UPA in treatment of UF in terms of ability to reduce menstrual blood loss and reaching amenorrhea. They also evaluated its ability to reduce uterus and fibroid size as well as its impact on quality of life [114,115,121–128].

The most widely cited studies investigating anti-UF use of UPA are the European phase III studies, PGL4001 (UPA) Efficacy Assessment in Reduction of Symptoms Due to Uterine Leiomyomata (PEARLs I/II/III/IV) [114,115,121,125,129]. In 2016, the same group of investigators published an extension study with longer duration [121]. Table 1 summarizes all five UPA anti-UF seminal trials.

Interestingly, PEARL studies demonstrated that efficacy of UPA treatment is still maintained even during the off-treatment periods, which allows intermittent long-term UF treatment with advantages of rapid bleeding control and progressive fibroid reduction [115,130].

The first US-based phase III clinical trial was completed to assess the efficacy and safety of UPA (5 and 10 mg) vs a placebo (VENUS 1 study). The end points were amenorrhea and activity score in premenopausal women. This study showed promising results in terms of rate of and time to amenorrhea without any reported adverse events that required drug discontinuation [131]. In the same study, efficacy of UPA for UF treatment was explored in different racial (black vs non-Black) and BMI (≥30 kg/m² vs <30 kg/m²) groups with results highlighting efficacy of UPA regardless of race and BMI.

Safety evaluation. In PEARL III trial, treatment emergent adverse events occurred in 120 women (57.4%), but only 8 women (3.8%) had severe adverse events, including headache (16.3%) that lead to treatment withdrawal in five cases and abdominal pain (5.3%) but its incidence did not increase over time. No safety concerns in relation to liver function, other laboratory safety tests, hormone levels, ovarian or breast imaging, and ECGs were reported [114,115,129,132].

Endometrial safety and progesterone receptor modulators associated endometrial changes. UPA was associated with an increase in endometrial overgrowth known as PR modulators associated endometrial changes (PAECs). These are benign histologic changes of endometrial glands that appear dilated or cystic; nevertheless, the cells lack mitotic activity and changes are reversible within few weeks to a maximum of 6 months post-therapy. Moreover, the absence of stromal breakdown and glandular crowding makes it distinctive from hyperplasia. The National institute of health sponsored a workshop to further discuss PAEC in women taking UPA and other SPRMs with the help of expert gynecologic pathologists. The workshop concluded that no specimen fits the criteria of atypical hyperplasia or endometrial carcinoma and presenting changes differ from classic unopposed E2
Table 1. Summary of PEARL I-IV pivotal trials (with extensions).

| POCTitle | PEARL I 2012 [114] | PEARL II 2012 [115] | PEARL III with extension 2014 [129] | PEARL IV 2015 [125] | PEARL IV “extension” 2016 [121] |
|----------|-------------------|---------------------|------------------------------------|---------------------|---------------------------------|
| Study objective | To study efficacy and safety of ulipristal acetate (UPA) versus placebo for symptomatic uterine fibroid (UF) treatment before surgery | To study efficacy and side-effect profile of UPA as compared with those of leuprolide acetate (LA) for the treatment of symptomatic uterine fibroids before surgery | To investigate the efficacy and safety of UPA for long-term treatment of symptomatic UF | To study the efficacy and safety of two 12-week courses of UPA for intermittent treatment of symptomatic UF | To study the efficacy and safety of four 12-week courses of UPA for intermittent treatment of symptomatic UF |
| Treatment, patient number, dosage regimen, and duration | UPA 5 mg/day (96 patients), UPA 10 mg/day (98 patients), placebo/day (48 patients) for 13 weeks then perform surgery | UPA 5 mg/day (95 patients), UPA 10 mg/day (100 patients); LA 3.75 mg/month (95 patients) for 3 months | Four 3-month courses of UPA 10 mg daily, immediately followed by 10-day double-blind treatment with norethisterone acetate (10 mg daily) or placebo (209 patients start first course and 107 patients complete the four course) | Two repeated 12-week treatment courses (separated by a drug-free interval of daily 5 or 10 mg of UPA (451 patients): 228 patients take 5 mg, 223 patients take 10 mg) | Four repeated 12-week treatment courses of daily 5 or 10 mg UPA (451 patients) |
| Primary outcome | Efficacy of UPA in term of control of uterine bleeding, reduction of fibroid volume | UPA is not inferior to LA in reducing the uterine bleeding in term of proportion of patients with controlled bleeding at end of study | Amenorrhea at the end of each UPA course | Amenorrhea at the end of both UPA courses | Endometrial safety in term of frequency of nonphysiological changes of biopsies and confirm efficacy of UPA |
| Secondary outcome | Bleeding pattern, amenorrhea, hemoglobin, hematocrit, and ferritin values, pain, quality of life | Bleeding pattern, amenorrhea, hemoglobin, hematocrit, and ferritin values, pain, quality of life | Reduction of the three largest fibroids | Reduction of the three largest fibroids | General safety, laboratory parameters, amenorrhea, controlled bleeding, fibroid volume, quality of life, and pain |
| Notes | All patients received 80 mg iron supplementation once daily during the active treatment | Iron supplementation was left to the discretion of the treating physician | Double-blinded and placebo-controlled study toward the administration of progestin after the end of each UPA treatment course | Double-blinded and placebo-controlled study toward the administration of progestin after the end of each UPA treatment course | Data focus on the new findings from treatment courses 3 and 4 as well as the four treatment courses combined |

---Fibroid-related menorrhagia was evaluated by the Pictorial Blood Assessment Chart (PBAC) score and was considered significant for inclusion when it was higher than 100 on days 1–8 of menstruation

---Fibroid-associated anemia was considered significant when the hemoglobin level was lower than 10.2 g/dl
| Outcome | PEARL I 2012 | PEARL II 2012 | PEARL III with extension 2014 | PEARL IV 2015 | PEARL IV extension 2016 |
|---------|--------------|--------------|-----------------------------|--------------|-------------------------|
| PBAC < 75 at 13 weeks | UPA 5 mg/day 91% (P < 0.001) | UPA 5 mg/day 90% (P < 0.001) | UPA 10 mg Course 1 Not reported | UPA 5 mg 2 course 81.1% | UPA 5 mg 4 courses 67.1% |
| Amenorrhea at end of treatment | UPA 10 mg 92% (P < 0.001) | UPA 10 mg 98% (P < 0.001) | UPA 10 mg Course 2 88.5% | UPA 10 mg Course 3 88.2% | UPA 10 mg 2 courses 86% |
| Reduction in UF volume at 13 weeks | LA 89% (P < 0.001) | LA 89% (P < 0.001) | UPA 10 mg Course 4 89.7% | UPA 10 mg 4 courses 73% | UPA 10 mg 4 courses 60.5% |
| Days to amenorrhea | 50% within 10 days | 70% within 10 days | 7 | 4 | 5 after both cycles |
| Notes | UPA treatment for 13 weeks effectively controlled excessive bleeding due to UF and reduced the size of the fibroids | Both daily 5-mg and 10-mg UPA were noninferior to once-monthly LA in controlling uterine bleeding and were significantly less likely to cause hot flashes | —Repeated 3-month UPA courses effectively control bleeding and shrink fibroids in patients with symptomatic UF | Repeated 12-week courses of daily oral UPA (5 and 10 mg) effectively control bleeding and pain, reduce fibroid volume, and restore QoL in patients with symptomatic fibroids | With the recently registered indication of intermittent treatment with UPA, the absence of endometrial and laboratory safety findings associated with long-term therapy is of special interest to clinicians |
effect in terms of absence of mitosis and its reversibility. Another study re-analyzed PEARL I and II endometrium tissues and recommended that pathologists must be aware of these PEAC changes to avoid initial misdiagnosis [1,114,115,121,125,129,133–136].

Interestingly, a recent case report was published regarding a prolonged exposure to UPA for 5 years in a woman with benign metastasizing UFs, endometrial biopsies were collected at established intervals for endometrial safety assessment, and the result indicated absence of any evidence of endometrial hyperplasia or neoplasia [137].

Studies on the rate of pregnancy after completing UPA therapy have been conducted. These studies demonstrated that the endometrium is of sufficient quality for blastocyst implantation [138]. Patients treated with UPA were able to conceive quickly and easily, pregnancy rate in one study was 71%, and all the babies were born healthy [138].

Teratogenicity. There is limited data available about UPA teratogenicity when used as ECs due to its high efficiency. Besides, if conceptions were to happen, most women choose to terminate it [139]. From the little data available when used as a treatment for UFs, none reported any teratogenic effect [140,141].

Pharmacoeconomics. Pharmacoeconomic and outcome research studies were, and still being, conducted to study the cost-effectiveness of UPA as either an add-on or alternative therapy option to surgery, with positive results showing a favorable cost-effectiveness ratio [142]. A Canadian economic study evaluated the cost utility of preoperative UPA administration relative to LA in women with moderate-to-severe symptoms of UFs. It showed an emphasizing domination of UPA strategy over LA, as it provided patients with more quality-adjusted life years (0.177 versus 0.165) at a lower cost ($1273 versus $1366) with fewer side effects and faster bleeding control [143]. A similar study was conducted in Mexico, concluding that UPA is a cost-effective alternative to surgery, as 21% of the patients treated with UPA avoided hysterectomy, which translates to $47,614,017 USD being saved for every 1000 patients [144].

Clinical applications and future directions. As UPA finds its way as a viable treatment option for women with symptomatic UF, it is clear that a new treatment paradigm is evolving. It is anticipated that UPA will not only be beneficial in the treatment of moderate to severe UF, but also it can be exploited to postpone/eliminate the need for surgery especially in women desiring fertility preservation.

Primary/secondary prevention of uterine fibroids with ulipristal acetate

Aiming for a comprehensive use of UPA, we thought about developing a UF-specific risk assessment triage algorithm (Figure 5), with possible subsequent use of UPA for UF primary prevention in women at highest risk for future UF development. To apply such
Table 2. Risk factors for uterine fibroid.

| Risk Factor                        | Reference  |
|------------------------------------|------------|
| Age                                | [145]      |
| Ethnicity (black vs. non-Black)    | [146–148]  |
| Obesity/overweight                 | [149–151]  |
| Vitamin D deficiency/insufficiency | [152]      |
| COMT polymorphism                  | [153]      |
| ER polymorphism                    | [154]      |
| Early menarche                     | [29]       |
| Parity                             | [28]       |
| Tobacco, caffeine, and alcohol     | [148]      |
| Family history of uterine fibroids | [155, 156] |
| Higher TGF-β3 serum concentrations | [156]      |

algorithm, asymptomatic reproductive age women can be screened for well-established UF risk factors (listed in Table 2). Women deemed to be at high UF risk, determined based on additional clinical research to determine the contribution of each risk factor individually as well as combination thereof, can then be further evaluated by appropriate examination and imaging modalities. Based on these tests, women can be triaged into one of three possible scenarios: (1) women with moderate-to-severe UF burden can then enter a treatment protocol and offer various UF-specific treatment options including oral treatment options; (2) women with mild/early-stage UF disease may benefit from a secondary prevention protocol to either halt fibroids progress or appearance of new ones. This same secondary prevention approach can also be applied for women with incidental finding of UF, patients after myomectomy to decrease the rate of recurrence, or young women with symptomatic UF but no immediate plans for pregnancy; (3) women at high risk for future UF development but currently with UF-free uteri (in imaging studies) may be activated in a primary prevention protocol to preclude or delay the development of UF. Figure 6 summarizes these case scenarios that may benefit from availability of UPA (and other oral-specific anti-UF therapies) in the future. To the extent of available data from clinical trials to date, these cases who desire fertility preservation can be safely treated with UPA, up to four cycles, 3 months each, followed by close monitoring and retreatment as needed (Figure 7). Clearly, these proposals will need to be carefully vetted in well-designed clinical trials and likely to evolve and undergo multiple tuning as collective experience with UPA and other novel anti-UF treatments accumulates. We envision a remarkable shift in the management of UF in future years from surgical/invasive treatment to orally administered options; clearly, this potential shift will require additional intense clinical research.

Conclusions

UPA will most likely usher the era of oral long-term treatment for women with symptomatic UFs and can be exploited for safe nonsurgical fertility preservation (medical myomectomy) as well. It may also support the transformational concept of UF primary and/or secondary prevention in presymptomatic/early symptomatic women, respectively. The field has advanced enough and is ripe to develop a robust UF risk assessment tool to identify women who are either racially, genetically, biochemically, or anthropometrically predisposed to future UF development. Further studies are urgently needed to delineate the appropriate place of UPA as well as other SPRMs in the anti-UF armament.

Conflict of interest: Ayman Al-Hendy is a consultant for Allergan plc, Bayer, Repros, and AbbVie.

![Figure 6](https://academic.oup.com/biolreprod/article-abstract/97/3/337/4096253/53123)

**Figure 6.** Clinical applications of ulipristal acetate in uterine fibroid (UF) treatment/prevention. List of case scenarios that may benefit from availability of ulipristal acetate in the three different protocols of treatment, primary, and secondary prevention.
Figure 7. Proposed treatment algorithm for ulipristal acetate use in uterine fibroid-related clinical profiles who desire fertility preservation. Different uterine fibroid-related clinical profiles who desire future fertility will administer ulipristal acetate or other oral agents for a 3-month cycle, up to four cycles, followed by close monitoring and retreatment as needed. ART, assisted reproductive techniques; SPRM, selective progesterone receptor modulator.

1. Women with symptomatic uterine fibroids (Treatment)
2. Women with unexplained infertility associated with uterine fibroids (Treatment)
3. Women with early/minimally symptomatic uterine fibroids (Secondary prevention)
4. Women post-myomectomy with residual uterine fibroid disease (Secondary prevention)
5. Women with incidental pre-symptomatic fibroids (Primary prevention)

Desire immediate pregnancy
- Start pursuing conception either naturally or ART as indicated.

Desire FERTILITY preservation

Desire FERTILITY preservation

Do not Desire immediate pregnancy
- Monitor
- Consider restart SPRM treatment if symptoms/fibroids growth return

SPRM up to 4 courses (3 months each)

Satisfactory response

Desire immediate pregnancy

Unsatisfactory response

Consider other treatment options

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