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Ulipristal Acetate (UPA): An Alternative Option to Surgery for Uterine Fibroids in Reproductive Age: A Review

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Abstract

Uterine fibroids are common in females of reproductive age and substantially affecting fertility and quality of life. Current management strategies mainly involve surgical interventions. For treatment, options available are surgical and non-surgical, but the mode of management leans on several factors, such as severity of symptoms, patient's age, myoma characteristics, desire to preserve uterus and fertility. Alternative approach to surgery for the treatment of symptomatic females with uterine myomas has been recognized. Ulipristal acetate (UPA) has been the first selective progesterone-receptor modulator (SPRM) approved for the pre-operative and long-term management of uterine fibroids. There are evidences promoting an important role for progesterone pathways in the pathophysiology of uterine fibroids which supports the use of ulipristal acetate. The availability of alternative choices to surgical intervention is very necessary especially for those willing to preserve uterus and fertility. One of the alternatives is with ulipristal acetate, which has been proven to treat fibroid symptoms effectively.

Keywords

Myoma, Females, Uterine Fibroids, Selective Progesterone Receptor Modulator (SPRM), Ulipristal Acetate (UPA)

1. Introduction

Uterine fibroids are common in females of reproductive age with the prevalence of occurrence up to 80% by age of 50 [1]. Grossly, fibroids are round, rubbery, tumors that when dissected exhibit in whorls. They possess a distinct autonomy from the neighboring myometrium because of a thin outer connective tissue

layer. They are monoclonal tumors of uterine smooth muscles thus, originating from the myometrium of the uterus [2]. Histologically, these tumors comprise smooth muscle and fibrous connective tissue, so named as uterine leiomyoma, myoma or fibromyoma. These tumors are composed of large amounts of an extracellular matrix (ECM) containing fibronectin, collagen, proteoglycans [2]. Although many fibroids are asymptomatic, in 20% - 50% of cases, they can cause abnormal uterine bleeding (AUB), fertility issues, anemia and bulk symptoms [3]. 30% of leiomyomas cases cause morbidity due to abnormal uterine bleeding (heavy menstrual bleeding causing anemia), and pelvic compressions (urinary symptoms, tenesmus and constipation) [4] [5]. Clinical presentation of uterine fibroids includes infertility, menorrhagia, pelvic pressure or abdominal pain, a decline in quality of life, and or obstetrical complications [6]. Uterine fibroids represent a high health burden currently and are highly prevalent. Almost 30% of females with fibroid seek treatment because of morbidities such as abdominal pain, menorrhagia, pressure symptoms and/or infertility [7]. Current treatment is chiefly surgical and is expensive too. The costs for treatment together for the health care system as well as patients with fibroid must be balanced against the cost of untreated diseased conditions, and costs of continuing or frequent investigations and treatment modalities [8]. Regardless of their size, asymptomatic leiomyomas usually can be observed and surveilled with an annual pelvic examination. Leiomyomas in general is slow-growing. In the past, most preferred surgical removal of a large, asymptomatic leiomyomatous uterus because of concerns regarding increased later operative morbidity and cancer risks. Various surgical procedures and different management methods are used in the treatment of uterine fibroids surgically, as myomectomy, minimal invasive surgery (MIS) such as (laparoscopic and hysteroscopic myomectomy), or hysterectomy if definitive treatment is required. The choice of appropriate treatment is decided on the basis of responsible factors, such as the fibroid location, patient's age and with the wish to preserve fertility, accompanying diseases and the patient's preferences. Hysterectomy remains the mainstay treatment option, because it is the only classic treatment that also excludes the possibility of recurrence [9] [10]. Non-surgical conservative interventions include the uterine artery embolization, radiofrequency myolysis, focused energy delivery system [11], and as well with the medical therapy. In others, medical therapy is used as a short-term preoperative adjunct. Also, because these tumors generally regress postmenopausally, some females elect medical treatment to alleviate symptoms in expectance of menopause. In some females with symptomatic leiomyomas, long-term medical therapies may be preferred. Medical therapy with progestin-releasing intrauterine devices (IUD), progestins, and gonadotrophin-releasing hormone agonists (GnRHa) are also approved for fibroid treatment. GnRH agonist was the first medical therapy used for the management of myomas. Leuprolide acetate was a GnRH agonist, as a pre-operative adjunct was approved by FDA in 1999, for short term use in females with symptomatic myomas [12].

2. GnRH Agonists

At the time of follicular phase when GnRH agonists are introduced, initial stimulation of follicle stimulating hormone (FSH) and luteinizing hormone (LH) release occurs, recognized as a blaze effect. With the continuous or as opposed to pulsatile GnRH agonists administration, the down-regulation of pituitary GnRH receptors occurs, that inhibits production of FSH and LH and subsequently of the gonadal steroids [13]. This results in ultimately a hypoestrogenic state, that contributes to the pharmacologic efficacy of the GnRH agonists [14], since myoma growth is stimulated by estrogen. Various studies have indicated that tumor size shrinkage may be directly proportional to the number of estrogen receptor (ER) positive cells [15] [16]. Commonly reported adverse effect of GnRH agonists are allied to hypoestrogenic state, with major limitation for long term use leading to vaginal dryness, hot flushes, and mood changes [13]. Hypoestrogenic state over the long term results in decreased bone mineral density (BMD) leading to bone demineralization [15] [17]. Other disbenefit to the management includes speedy regrowth of myomas after the termination of treatment and also includes the relatively high cost of the treatment [17] (**Figure 1**).

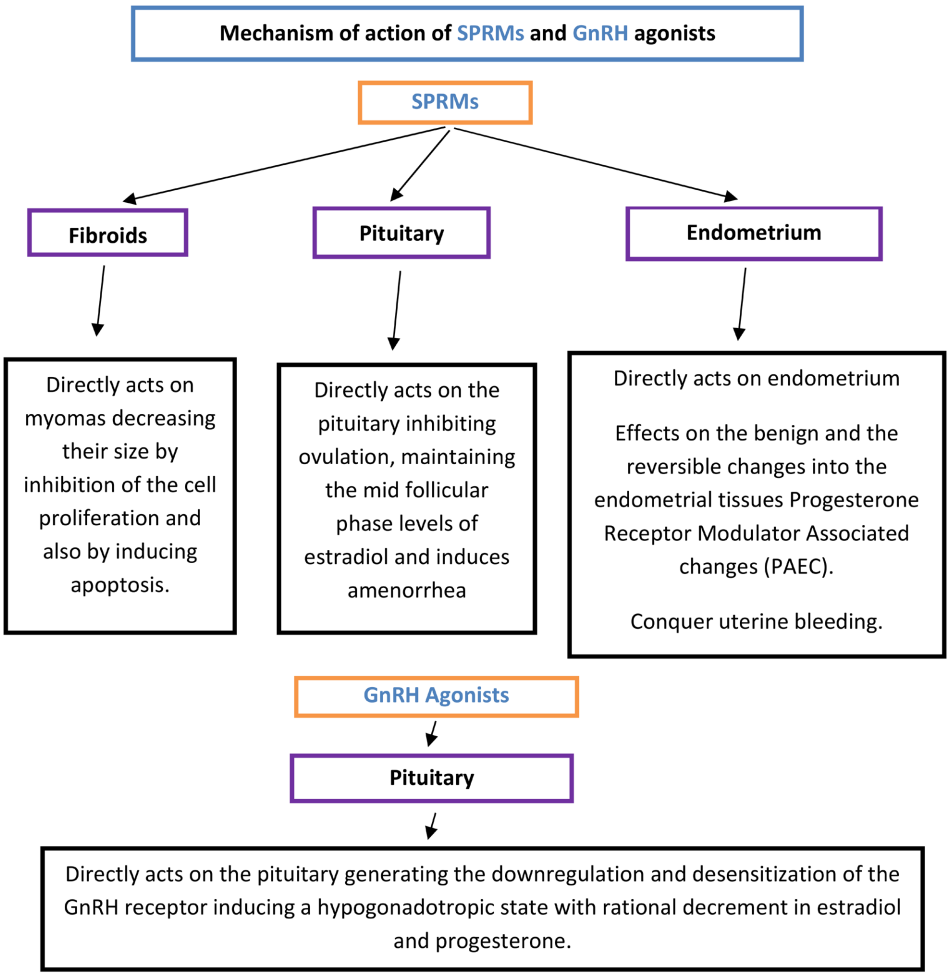

Figure 1. Mechanism of action of SPRMs and GnRH agonists.

3. Route of Progesterone in Pathophysiology of Uterine Myoma

Uterine myomas are estrogen and progesterone sensitive tumors. Also, estrogen and progesterone and their receptors have a consequential impact on myoma growth. Consequently, they develop during the reproductive years. After menopause, myomas generally shrink, and new tumor development is infrequent. Myomas themselves create a hyperestrogenic environment, which appears requisite for their growth and maintenance. Previously, estrogen was known to be the consequential growth factor in development of myoma. However, already a number of studies reported that elevated expression of both, the progesterone receptor A (PR-A) and progesterone receptor B (PR-B) in myoma tissue in the 1990s [18], compared with adjacent normal myometrium. More recently, it has been discovered that the progesterone and progesterone receptors (PRs) are required for cellular proliferation and myoma growth. The ratio of estrogen receptor to progesterone receptor (PR) is higher in myoma cells than in the normal myometrial cells [19]. The function of progesterone in promoting their growth has been increasingly accentuated during the last decade, and has stimulated interest in modulating progesterone pathways [2] [20] as reported in a recent review paper [7]. These sex steroid hormones likely mediate their effect by stimulating or inhibiting transcription or cellular growth-factor production. There is evidence from pharmacological and histological studies, that progesterone and its receptors play a cardinal role in uterine myoma growth [2] [21] [22]. Greater proliferative activity, illuminated by the proliferating cell nuclear antigen and mitotic index, was noticed in myomas during the secretory (luteal) phase [18]. Progesterone and the growth factor signaling route both are interconnected and govern numerous physiological processes such as apoptosis, proliferation, and differentiation. To date, epigenetic and genetic factors, cytokines, ECM components, chemokines, growth factors, and sex steroids have been associated as being involved in the pathogenesis of myomas [2] [9] [20]. Very recently, Tsigkou *et al.*, showed that PR-B mRNA and PR-A and PR-B proteins were more concentrated in leiomyomas then in matched myometrium [23].

4. Selective Progesterone Receptor Modulators (SPRMs) and Myoma

Progesterone plays a superior role in promoting the development of myomas. This fact directs the possibility of using selective progesterone receptor modulators (SPRMs), while the effect of progesterone on target tissues is modified by progesterone receptors. SPRMs are synthetic compounds that compete at progesterone receptor binding site, demonstrating either antagonistic activity or agonistic activity on progesterone receptor [10]. Having established the critical role of progesterone in the growth and development of myomas we can modulate the progesterone pathways using SPRMs. Inarguably, Ulipristal acetate (UPA) is an SPRM that acts on progesterone receptors (PRs) in endometrial and myometrial

tissues and inhibits ovulation, but maintains the normal levels estradiol and follicle-stimulating hormone (FSH), without causing any antiglucocorticoid activity [24]. Whether SPRMs acts predominantly as agonists or antagonists it depends on their structure and how it changes the progesterone receptor conformation, leading to the disclosure or inactivation of exacting binding domains, leading to interactions of corepressors and/or coactivators with the progesterone receptors. SPRMs are designed to compete at the progesterone receptor binding site in tissue-specific manner. Ulipristal acetate (UPA), telapristone acetate, asoprisnil, and mifepristone are four family members of the compound selective progesterone receptor modulator (SPRMs) have been explored in phase II clinical trials [2] [25]. Drug summary is explained below (**Table 1**) [26].

Ulipristal acetate has two potential applications; the preoperative management in patients requiring surgery, and the long-term management in patients those who refuse surgery or have contraindications for surgery. UPA differs from the other available hormonal medical therapies for the management of uterine myomas in terms of both route of administration and mechanism of action. The preoperative administration of UPA controlled bleeding in 90% of patients with uterine myomas, and more effective than placebo and not inferior to the intramuscular injection of leuprolide acetate. Additionally, UPA obtained the rapid control of bleeding and quickly improved hemoglobin and hematocrit levels of these females, in PEARL I-II trials [27] [28]. The need for choices to surgical intervention in the treatment of myomas is eminently real, particularly for females desiring to conserve their fertility [7]. New option now exists, with selective progesterone receptor modulators (SPRMs) proven to treat myoma symptoms effectively. Selective progesterone receptor modulators (SPRMs) have shown promising results with shrinkage of uterine leiomyomas and a prolonged clinical

Table 1. Drug summary.

Drug name (Generic)	Ulipristal Acetate
Pharmacologic class	SPRM (Selective Progesterone Receptor Modulator)
Chemical formula	$C_{30}H_{37}NO_4$
Indication	Ulipristal acetate (UPA) is indicated for both preoperative and intermittent treatment of moderate and even severe symptoms of the uterine myomas in an adult female of reproductive age.
Pharmacology	Ulipristal acetate (UPA) acts as a progesterone agonist or antagonist depending upon the target tissues, and presence or absence of progesterone. Its primary pharmacodynamic property is to block reversibly at the progesterone receptor at its target tissues (cervix hypothalamus, ovaries, uterus). Ulipristal acetate pertains to the family of drugs known as selective progesterone receptor modulators (SPRMs).
Dosage/Dosage form	5 mg OD/tablets
Route of administration	Oral

effect with treatment [10]. Additionally, Ulipristal acetate (UPA) leads to alter the expression of angiogenic factors, adrenomedullin and vascular growth factor, which tends to have higher expression in myomas than in the normal myometrium [29]. Ulipristal acetate is a selective progesterone receptor modulator, approved in 2012 by EMA [30], as pre-operative therapy and recently since (September 2016) it is used as an exclusive medical treatment in symptomatic females with uterine myomas [31]. Ulipristal acetate potentially modulates the progesterone-receptor activity and exerts pro-apoptotic anti-proliferative effects on myoma cells without suppressing estradiol to non-physiologic levels, inducing menorrhagia discontinuation and often myoma shrinking [24]. Since 2012, several substantial studies have illuminated that single and repeated three-month ulipristal acetate courses are able to effectively control bleeding and shrink myomas in patients with symptomatic indications [9]. Using ulipristal acetate pre-operatively facilitates surgery by reducing myoma mass and restores the higher hemoglobin level [32]. The PEARL III and IV trials [24] [33], proposed the safety of long-term intermittent and efficacy of UPA treatment that may allow a long-term therapy in premenopausal females with myoma in order to control their symptoms until the onset of spontaneous menopause, and it could be a valuable alternative for patients who are contraindicated for surgery and who wish avoiding surgery. After treatment discontinuation, menstruation usually returns within 4 - 5 weeks, but myoma and uterine mass reduction can be sustained for up to six months [24]. Thus, ulipristal acetate positively effects on symptoms and even quality of life still persists after cessation of treatment and pregnancies have been newly reported in previously infertile female [34] [35]. After ulipristal acetate treatment, pregnancies have been reported. Twenty-one females wanted to conceive, obtaining eighteen pregnancies, which resulted in twelve births of thirteen healthy babies and six early miscarriages [36]. Luycks *et al.* published a case report in 2016 about a woman whose fibroids had mostly disappeared after treatment with UPA and pregnancy [34].

5. Significance of Ulipristal Acetate over Mifepristone

Number of researchers individually considered about the effect of mifepristone and ulipristal acetate on uterine myomas and found both of the selective progesterone receptors modulators (SPRMs) are very effective for the treatment of uterine myoma [37]. Mifepristone is being used since 2002, whereas ulipristal acetate has recently been introduced for myomas [26]. Improvements in fibroid related symptoms (menstrual blood loss, pressure symptoms, pelvic pain) were diminished by use of mifepristone. Also on dose dependent form 2.5 - 50 mg/day for 3 - 6 months and high dose up to 50mg were found effective in improving the fibroid related symptoms with decrease in fibroid volume by 26% - 57% and also inducing amenorrhoea in 41% - 100% [38]. According to Ashish R. Kale *et al.*, in the management of myomas by mifepristone and ulipristal acetate was associated with shrinkage of myoma size, pain, as well as diminished blood

loss. Accordingly, it was found ulipristal was much more effective when introduced in patients with myoma size having 3 - 5 cm. Whereas myoma size of less than 3 cm mifepristone was found to be more effective. Hence, concluded from this research both of these medicines can be implemented for the management of symptomatic myomas. Thus, Ulipristal Acetate should be preferred over mifepristone if the size of myoma found more than 3 cm [39].

6. Significance of Ulipristal Acetate over Levonorgestrel as Emergency Contraception

Further study and research displayed that SPRMs actively persists in preventing ovulation up to 120 hrs even after the unprotected coitus, whereas, levonorgestrel only remains 50% active after 72 hrs [40]. UPA is as secure as levonorgestrel when used up to 72 hrs after intercourse [41] [42], and the risk of pregnancy was about half to the UPA users compared to levonorgestrel users when introduced within 120 hrs of intercourse. The prevalence of side effects after using 30 mg UPA or 1.5 mg levonorgestrel is correspondent [42]. No metabolic adverse effects have been illuminated with use of UPA [43].

7. Drug Interactions

More than 50% therapeutic agents are found that are metabolized by human-CYP3A4 [44]. Ulipristal acetate (UPA) is metabolized by CYP3A4 in vitro. UPA is likely to interact with substrates of CYP3A4, like rifampicin, rifabutin, phenytoin. The potent inducers of CYP3A4 are rifampicin, rifabutin, coadministration with these drugs, they can diminish a drug plasma concentration up to 20 - 40 fold, effecting negatively to the drug efficacy [45]. Hence, concomitant use with these agents is not recommended. Since Ulipristal acetate is acutely metabolized by the hepatic CYPs, CYP inhibitors or inducers can alter its metabolism [46]. It might also interact with the progestogens such as levonorgestrel and other substrates of progesterone receptor, hormonal contraceptives, as well as with glucocorticoids.

8. Contraindications

Ulipristal acetate should not be taken by those females who are with severe liver diseases because of its CYP-mediated metabolism. Before taking the drug, pregnancy must be excluded as UPA is contraindicated in pregnancy.

9. Conclusion

Although uterine myomas are commonly treated surgically, this review shows the possible place of UPA as a medical therapy alternative to surgical treatment, who are not the candidate for surgery or those who refuse surgery due any reason. UPA has been studied in large clinical trials. It was found that this drug maximizes its potential benefits particularly when fertility preservation is the goal, bleeding control, improvement of the symptoms, pain, and apart from

these benefits, improvement in quality of life and myoma volume reduction is possible even after cessation of therapy. In uterine fibroid management, there is a critical need for alternatives to surgical intervention, so the necessity for medical interventions will endure and it is likely that the current medical options will continue to evolve.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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