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The current place of medical therapy in uterine fibroid management

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A B S T R A C T

Uterine fibroids (also known as leiomyomas or myomas) are the most common form of benign uterine tumors. Current management strategies mainly involve surgical interventions, but the choice of treatment is guided by patient's age and desire to preserve fertility or avoid “radical” surgery. Surgical and non-surgical approaches include hysterectomy myomectomy by hysteroscopy, myomectomy by laparotomy or laparoscopy, uterine artery embolization, and magnetic resonance-guided focused ultrasound surgery.

The need for alternatives to surgical intervention is very real, especially for women seeking to preserve their fertility.

There is growing evidence of the crucial role of progesterone pathways in the pathophysiology of uterine fibroids, and the efficacy of long-term intermittent use of selective progesterone receptor modulators such as ulipristal acetate was recently demonstrated by randomized controlled studies.

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Introduction

Uterine fibroids (also known as leiomyomas or myomas) are the most common form of benign uterine tumors [1–5]. They are monoclonal tumors of uterine smooth muscle, thus originating from the myometrium [6,7]. They are composed of large amounts of extracellular matrix (ECM) containing collagen, fibronectin, and proteoglycans [6]. Leiomyomas occur in 50%–60% of women, increasing to 70% by the age of 50 [7]. In 30% of cases, leiomyomas cause morbidity because of abnormal uterine bleeding (heavy menstrual bleeding inducing anemia) and pelvic pressure (urinary symptoms, constipation, and tenesmus) [1,8].

Why we need new options [5,8]?

Fibroids are highly prevalent and represent a high health burden. Indeed, about 30% of women with leiomyomas requests treatment because of morbidities such as heavy menstrual bleeding, abdominal pain, pressure symptoms, and/or infertility [5]. Current treatments are mainly surgical and expensive. Among 600,000 hysterectomies performed each year in the USA, 200,000 are for fibroids, and health care costs for the management of leiomyomas were estimated to be over $2 billion per year [9]. The cost of therapy both to the health care system and women with fibroids must be balanced against the cost of untreated disease conditions, and the cost of ongoing or repeated investigations and treatment modalities [10].

The future of medical therapy

Evidence of the crucial role of progesterone pathways in the pathophysiology of uterine fibroids

To date, genetic and epigenetic factors, sex steroids, growth factors, cytokines, chemokines, and ECM components have been identified as being implicated in the pathogenesis of leiomyomas [2,3,11–14]. Of course, estrogen and progesterone and their respective receptors also have a very significant impact on leiomyoma growth [6].

The initial event that triggers the first stages of tumorigenesis nevertheless involves somatic mutations [6].

In the past, estrogen was considered to be the major growth factor in myoma development. However, already in the 1990s, a number of studies reported increased expression of both progesterone receptor A (PR-A) and progesterone receptor B (PR-B) in leiomyoma tissue [15,16] compared with adjacent normal myometrium. Higher proliferative activity, demonstrated by proliferating cell nuclear antigen and the mitotic index, was observed in leiomyomas during the luteal (secretory) phase [16]. Very recently, Tsigkou et al. showed that PR-B mRNA and PR-A and PR-B proteins were more concentrated in leiomyomas than in matched myometrium [17]. There is evidence from histological and pharmacological studies, that progesterone and its receptors play a key role in uterine fibroid growth [6,18–24]. Progesterone can cause rapid, membrane-initiated effects, independent of gene transcription, that alter the production of second messengers involved in cell signaling transduction pathways. Progesterone and growth factor signaling pathways are interconnected and govern numerous physiologic processes such as proliferation, apoptosis, and differentiation [6].

SPRMs and fibroids (Fig. 1)

Four members of the family of compound selective progesterone receptor modulators (SPRMs) have been investigated in phase II clinical trials: mifepristone, asoprisnil, ulipristal acetate (UPA), and telapristone acetate [1–20,25–28]. All were shown to decrease leiomyoma size and reduce uterine bleeding in a dose-dependent manner [5].

Having established the crucial role of progesterone in the growth and development of myomas, we can modulate the progesterone pathway by using SPRMs. SPRMs are synthetic compounds that exert either an agonistic or antagonistic effect on PRs. Their binding allows these receptors to interact with coactivators and/or corepressors, and this is further effected by the presence of coregulators in a

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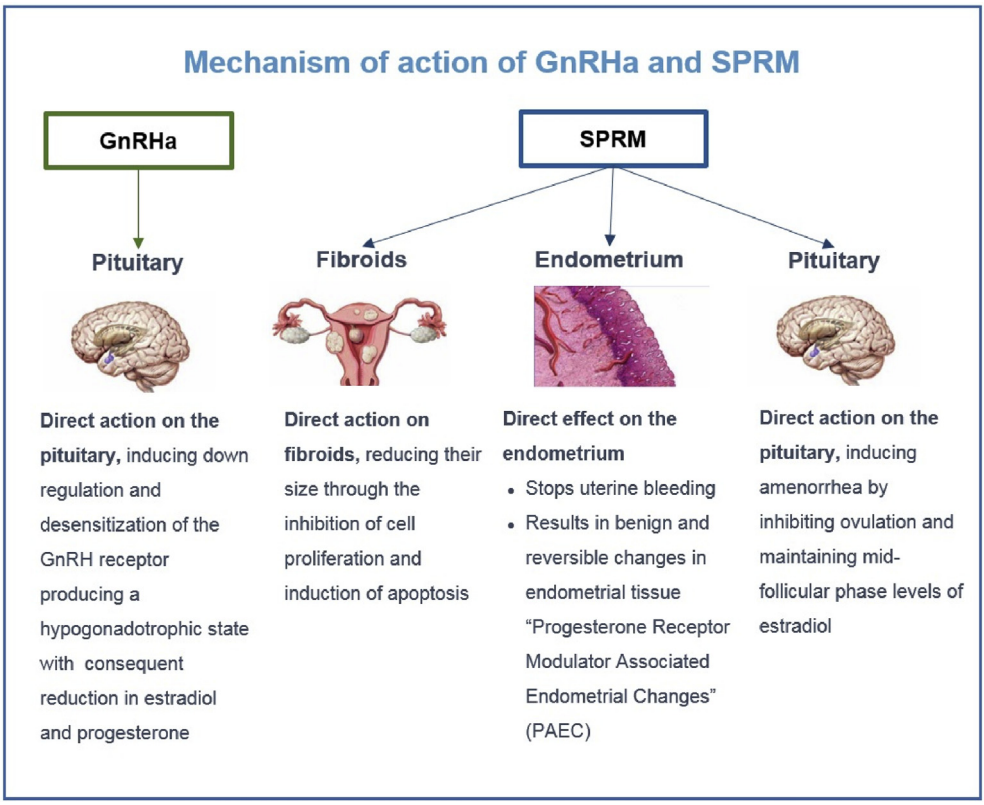

Fig. 1. Mode of action of GnRH agonists and SPRMs (Selective Progesterone Receptor Modulators). GnRH agonists have a direct impact on the pituitary. SPRMs have a direct impact on fibroids, endometrium, and the pituitary (with permission of Hum. Reprod. update).

particular cell type, which dictates whether an SPRM acts more as an agonist or antagonist [20]. Their activity is also mitigated by tissue types and physiological contexts [5,6,22,24].

In two randomized trials [29,30], UPA was compared to a placebo and to leuprolide acetate (a GnRH agonist). Uterine bleeding was controlled in more than 90% of patients receiving a 3-month course of UPA, and the median times to control bleeding were shorter in the UPA group (5–7 days) than in the GnRH agonist group (21 days). The subsequent correction of anemia was clinically relevant [29–31], as it has been well documented that preoperative anemia, even to a mild degree, is associated with an increased risk of morbidity and mortality in patients undergoing surgery [32,33]. UPA was also found to have a sustained effect (up to 6 months) in women who did not undergo surgery after the 3 month study period, while those treated with GnRH agonist experienced rapid regrowth of their fibroids, by 6 months post-treatment [29,30].

Importantly, the induced effects on the endometrium, now described as progesterone receptor modulator (PRM)-associated endometrial changes (PAECs) [34], present in almost 70% of patients at the end of treatment, have proved to be benign and reversible, as they disappear 2 months after the end of therapy [29,30,34,35]. Safety has also been well documented in pharmacokinetic studies following multiple doses [36].

Long-term intermittent administration of SPRMs, opening up new treatment perspectives

Because of the sustained effect observed in the first two trials [29,30], additional intermittent (12-week) courses of SPRMs with off-treatment intervals may be an alternative for long-term medical

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management of fibroids. The results of the first long-term intermittent administration study suggested that more than one course of SPRMs can maximize its potential benefits in terms of bleeding control and fibroid volume reduction [37] (Fig. 2).

The latest clinical trial was initiated to investigate the efficacy and safety of four repeated 12-week courses of either 5 or 10 mg UPA daily for intermittent treatment of symptomatic uterine fibroids [38–40]. This study demonstrated a similar degree of response in both treatment groups. We therefore decided to propose the dose of 5 mg UPA daily for the long-term management [38,40]. The percentages of subjects identified as being in amenorrhea after individual treatment courses (1, 2, 3, and 4 in the study) were 75.8%, 84.1%, 86.4%, and 87.5% in the 5 mg group [38,40]. The pictorial blood assessment chart (PBAC) [42] score was measured levels at screening were 224.0, dropping significantly with each subsequent course, and finally reaching 77.5 after course 4 [38,40]. The percentage of subjects with a clinically significant volume reduction of $\geq$25% increased from course 1 to course 4 (from 62.3% to 78.1%). This was also proved by the volume reduction of the three largest fibroids which was increased from course 1 to course 4. The findings of this study therefore demonstrate that repeated courses considerably maximize the impact of treatment.

The safety profile of UPA during multiple treatment courses was well documented in different study [38–42]. Safety assessments, including vital signs, physical examinations and laboratory analyses, and reported adverse events (AEs) both on and off treatment, showed repeated intermittent administration of UPA to be well tolerated. The vast majority of AEs (97.6%) were of mild or moderate severity. Headaches and hot flushes were the most frequently reported AEs (11% of subjects in any treatment course), but the frequency of these events decreased with each additional treatment course. Breast pain or discomfort was observed in 3% of subjects. In this series of 451 women [38–40] serious AEs related to medication included five cases of menorrhagia; one bipolar disorder, one spontaneous myoma expulsion, one abdominal pain, and one back pain. No safety concerns were identified from physical examination, vital signs, ovarian ultrasound, or ECG.

On the basis of available data related to endometrial safety after up to 4 treatment courses, no increased occurrence of more serious conditions of the endometrium, such as hyperplasia with atypia or endometrial carcinoma, was noted. The frequency of SPRM-associated non-physiological endometrial changes (PAEC) is not increased with repeated treatment courses, reaching 13.3% after a fourth treatment course, and returning to pretreatment levels within 3 months of completion of treatment. A recent study confirmed the endometrial safety after up 8 treatment courses [41]. These data further confirm the rapid reversibility of PAEC following completion of treatment and subsequent menstruation.

A recent study by Courtoy et al. suggested an important role of UPA in collagen degradation induced by matrix metalloproteinase 2 (MMP-2), offering an explanation for the sustained beneficial effect. Indeed, this study strongly points to multifactorial mechanisms of action involve: 1) increased apoptotic index rate and 2) ECM remodeling concomitant with stimulation of MMP-2 expression [14].

Novel approaches and algorithms, with a special emphasis on infertility

To address the question of which therapy to adopt, it is crucial to consider key factors determining the management of uterine fibroids: patient age, severity of symptoms (pain, bleeding, and infertility), wish to preserve the uterus and/or fertility, localization of fibroids according to FIGO classification, and myoma volume. The approaches described below are according to the FIGO classification [42].

Type 0 myomas

If type 0 myomas are present, cutting the pedicle by hysteroscopy is indicated.

Type 1 myomas

In the majority of cases, hysteroscopic myomectomy for type 1 myomas is relatively straight forward for experienced surgeons, especially in case of type 1 myomas less than 3 cm in size. In case of

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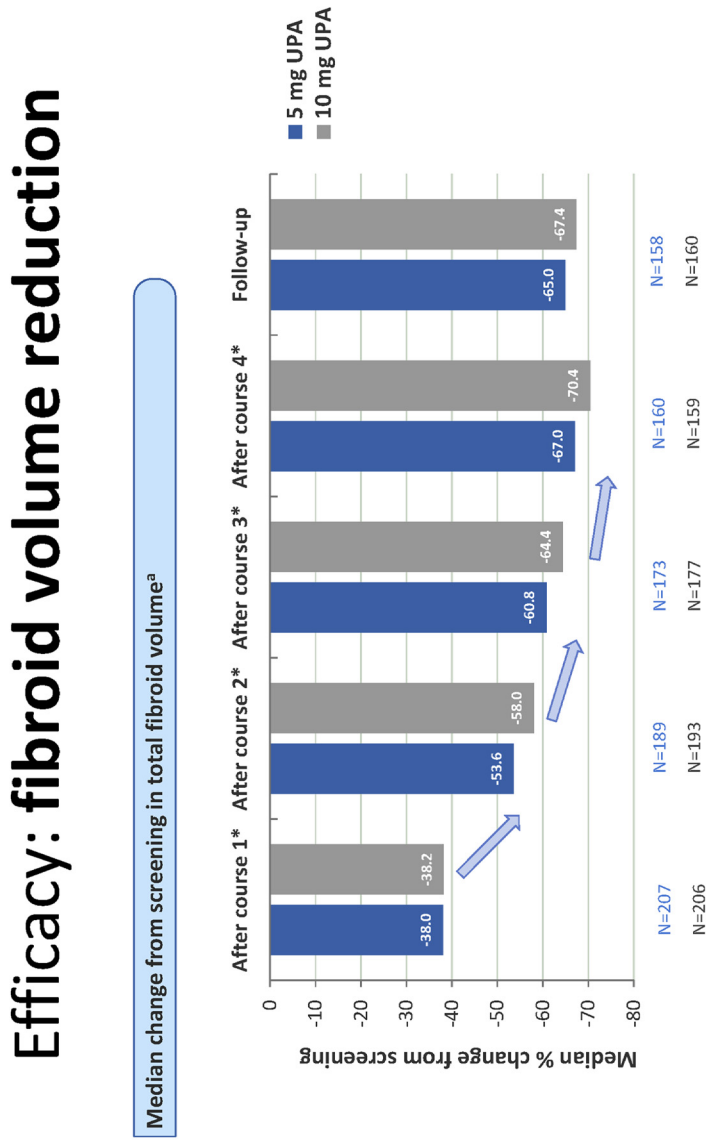

Fig. 2. Uterine fibroid reduction from screening to course 4 and follow-up. No difference was observed in terms of efficacy (fibroid volume reduction) between the dose of 5 mg and 10 mg. The daily dose of 5 mg was therefore chosen. Moreover, it should be noted that the second course maximizes the effect of the first one.

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type 1 myomas more than 4 cm in size, it may be appropriate to reduce the myoma size preoperatively by giving on or two courses of UPA.

Type 2 or type 2–5 myomas (single or multiple) distorting the uterine cavity

Premenopausal women presenting with symptomatic myomas and with no desire for pregnancy, but a wish to keep their uterus (Fig. 3). Isolated type 2 fibroids are relatively rare in premenopausal women. In the majority of cases, patients with symptomatic myomas have an enlarged uterus with multiple myomas or large myomas of type 2–5.

Our latest results [38–40] led us to slightly modify previously published algorithms [5] for this group of women. Indeed, in subjects treated with 5 mg UPA for four courses of 3 months, the percentage of patients with a clinically significant volume reduction increased from 62.3% after 1 course to 78.1% after 4 courses, suggesting increased benefits with repeated courses. The percentage of women showing a clinically significant reduction of >50% also increased from course 1 (37.2%) to course 4 (63.8%). Moreover, the median PBAC score during the off-treatment period decreased with each subsequent course.

In case of a good response (characterized by a clinically significant volume reduction and/or control of bleeding), treatment can be stopped after four courses and the patient is re-evaluated. Repeated therapy may be proposed when the symptoms recur, as no endometrial hyperplasia was diagnosed in subjects who took 5 mg UPA for eight courses of 3 months. In this context, the goal is to reach

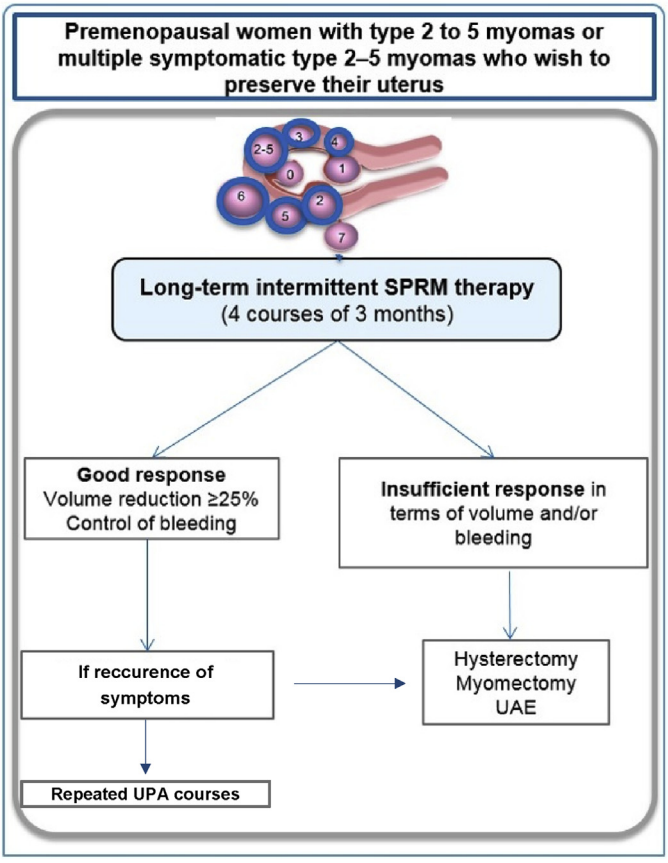

Fig. 3. Management of type 2 to 5 myomas or multiple myomas (type 2–5) in premenopausal women wishing to preserve their uterus. In this case, long-term (four courses of 3 months) intermittent therapy with SPRMs is proposed. Fibroid classification cartoon republished with permission from Munro et al., 2011.

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menopause without the need for surgery. Data indicating that SPRMs exert an anti-proliferative effect in breast tissue are also reassuring [43]. Some studies reported antiproliferative effects on the endometrium after SPRM courses of up to 6 months [44].

Research agenda

SPRMs have opened up new avenues to explore in fibroid medical therapy, to both treat symptoms and postpone or eliminate the need for surgery. Future clinical trials should focus on prevention strategies, such as preventing occurrence in women genetically predisposed to this condition, and avoiding recurrence after surgery in women at high risk (i.e., those of a young age or with a family history).

Conclusion

Symptomatic uterine fibroids require surgical and/or medical therapy according to the severity of symptoms, age, infertility, wish to preserve the uterus, and FIGO classification. Current strategies involve mainly surgical intervention, such as hysterectomy, myomectomy by hysteroscopy, and myomectomy by laparoscopy or laparotomy. Hysterectomy provides the most effective treatment for fibroids but is not appropriate in many cases. The choice between less invasive techniques (uterine-sparing options such as myomectomy) is guided by the size, number, and location of fibroids, and the personal experience of the gynecologist and available equipment.

The need for medical therapy remains a reality, as it is essential that new treatments be developed to be able to offer as there is a pressing need for alternatives to surgical intervention, particularly when fertility preservation is the goal.

There is growing evidence of the crucial role of progesterone in pathways in the pathophysiology of uterine fibroids by using SPRMs. UPA (one member of the SPRM compound family) has been studied in large clinical trials, and it was found that more than one 3-month course of UPA maximizes its potential benefits in terms of bleeding control and fibroid volume reduction.

In conclusion, asymptomatic fibroids do not require treatment once the diagnosis is confirmed by ultrasonography or MRI. Women should be made aware of all available treatment options (medical, radiological, and surgical), and why they may or may not be appropriate. Gynecologists now have new tools in their armamentarium, thus opening up novel strategies for the management of uterine fibroids.

Authors' roles

JD, OD, and MMD contributed equally to the research and interpretation of data discussed in the manuscript and approved the final version. OD receives and fees for lectures and coverage of travel expenses to investigator meetings of PEARL studies from the Gedeon Richter Group.

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Conflicts of interest

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 has no conflict of interest to declare.

OD has no conflict of interest to declare.

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