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REVIEW

Insights on Medical Therapy for Uterine Fibroids: A Review

Giovanni Pecorella · Andrea Morciano · Radmila Sparic · Safak Hatirnaz · Mykhailo Medvediev · Antonio Malvasi · Gianluca Raffaello Damiani · Andrea Tinelli

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ABSTRACT

Uterine fibroids constitute the most prevalent benign neoplasms within the female reproductive system, impacting a substantial proportion of women by the age of 50 years. While a significant number of these tumors remain asymptomatic, they have the potential to induce abnormal uterine bleeding (AUB), pelvic discomfort, pain, anemia, and infertility, thereby considerably diminishing the quality of life. Pharmacological intervention occupies a pivotal position in the management of fibroids, particularly for individuals who desire to preserve uterine function, postpone surgical intervention, or opt for noninvasive alternatives. Over the preceding two decades, the landscape of medical treatment has undergone significant expansion. Conventional therapeutic options, such as GnRH agonists and hormonal contraceptives, continue to be beneficial in specific contexts; however, their limitations regarding tolerability, skeletal safety, and sustained efficacy are widely acknowledged. Oral GnRH antagonists, which include elagolix, relugolix, and

G. Pecorella · A. Tinelli (✉)
Department of Obstetrics and Gynecology, and CERICSAL (CEntro Di RIcerca Clinico SALentino), Veris Delli Ponti Hospital, Scorrano, Lecce, Italy
e-mail: andreatinelli@gmail.com

G. Pecorella
e-mail: giovannipecorella2690@gmail.com

A. Morciano
Department of Obstetrics and Gynecology, Cardinal Panico Hospital, Tricase, Lecce, Italy
e-mail: drmorciano@gmail.com

R. Sparic
Clinic for Gynecology and Obstetrics, University Clinical Centre of Serbia, 11000 Belgrade, Serbia
e-mail: radmila@rcub.bg.ac.rs

R. Sparic
Faculty of Medicine, University of Belgrade, 11000 Belgrade, Serbia

S. Hatirnaz
Department of Obstetrics and Gynecology, Mediliv Medical Center, Samsun, Turkey
e-mail: safakhatirnaz@gmail.com

S. Hatirnaz
School of Health Sciences, Kent University, Istanbul, Turkey

M. Medvediev
Department of Obstetrics and Gynecology, Dnipro State Medical University, Dnipro 49044, Ukraine
e-mail: medvedev.mv@gmail.com

A. Malvasi · G. R. Damiani
Department of Biomedical and Human Oncological Science (DIMO), University of Bari, Policlinico of Bari, Bari, Italy
e-mail: antoniomalvasi@gmail.com

G. R. Damiani
e-mail: damiani14@alice.it

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linzagolix, signify a substantial progression, providing rapid and reversible suppression of ovarian hormone synthesis with dose-dependent effects and enhanced convenience. Clinical investigations demonstrated substantial reductions in excessive menstrual bleeding, enhancements in anemia, and improvements in quality of life associated with these pharmacological agents, particularly when administered in conjunction with hormonal add-back therapy. Alternative interventions, including selective progesterone receptor modulators (SPRMs), progestins, aromatase inhibitors, and antifibrinolytics, exhibit variable effectiveness and are optimally utilized within defined clinical frameworks. Concerns regarding safety, especially in relation to hepatic toxicity associated with SPRMs, have prompted regulatory limitations and underscore the necessity for ongoing pharmacovigilance. Tailored therapeutic approaches that consider reproductive objectives, symptomatology, comorbid conditions, and patient preferences are of paramount importance. Innovative treatment modalities that target nonhormonal mechanisms, such as extracellular matrix remodeling, angiogenesis, and gene modulation, provide promising prospects for future uterus-sparing interventions. This narrative review evaluates the current and advancing landscape of medical therapies for uterine fibroids, presenting evidence-based perspectives to inform clinical decision-making within an increasingly personalized therapeutic context.

Keywords: Uterine fibroids; Leiomyoma; Medical therapy; GnRH antagonists; SPRMs; Nonsurgical treatment

Key Summary Points

Uterine fibroids are the most common benign tumors in women of reproductive age, and medical therapy plays a pivotal role in symptom control, fertility preservation, and surgical delay or avoidance.
GnRH antagonists represent the most effective current medical option, with rapid onset of action, predictable efficacy, and better tolerability compared to GnRH agonists, especially when combined with add-back therapy.
Selective progesterone receptor modulators (SPRMs), though promising, face regulatory limitations due to concerns about hepatic safety, underscoring the need for better tolerated alternatives or refinements in their use.
Non-hormonal and natural treatments, such as EGCG, offer a uterus-sparing and low-risk approach for selected patients, particularly those who prefer or require non-hormonal strategies.
Future therapeutic directions include targeted molecular agents and AI-assisted personalization of medical treatment, aiming to improve efficacy, safety, and alignment with individual patient profiles.

INTRODUCTION

Uterine fibroids (UFs), or leiomyomas (Fig. 1), are the most prevalent benign tumors of the female genital tract, affecting approximately 30–50% of women during their reproductive years [1]. Although myomectomy and hysterectomy have long been common surgical alternatives, they are risky and may impair fertility. About 25–30% of individuals have substantial clinical signs, such as irregular uterine bleeding, pelvic pressure, infertility, or anemia, even though many remain asymptomatic (Fig. 2). These symptoms frequently affect quality of life and necessitate medical or surgical intervention [2]. As a result, uterine fibroids constitute

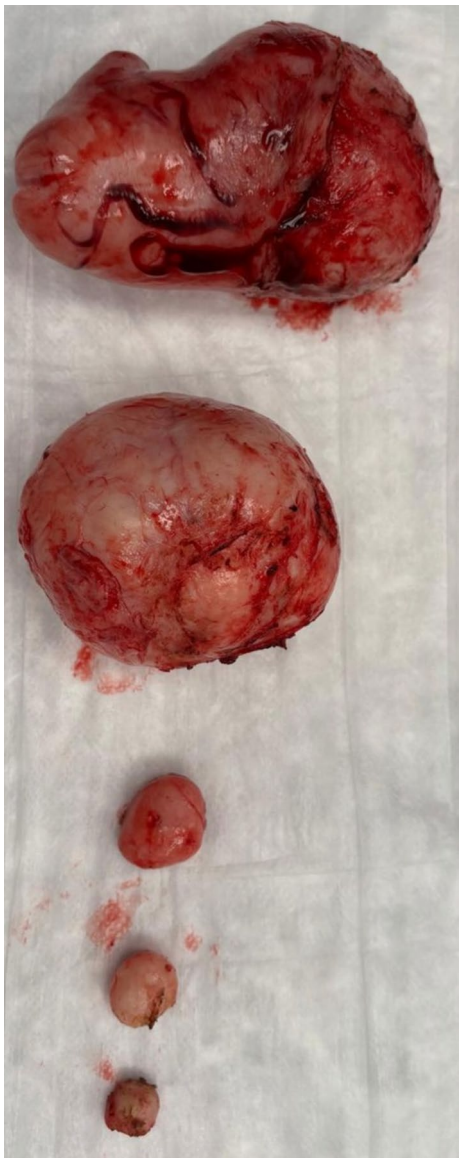

Fig. 1 Image of uterine fibroids (UFs), or leiomyomas, removed during a multiple myomectomy

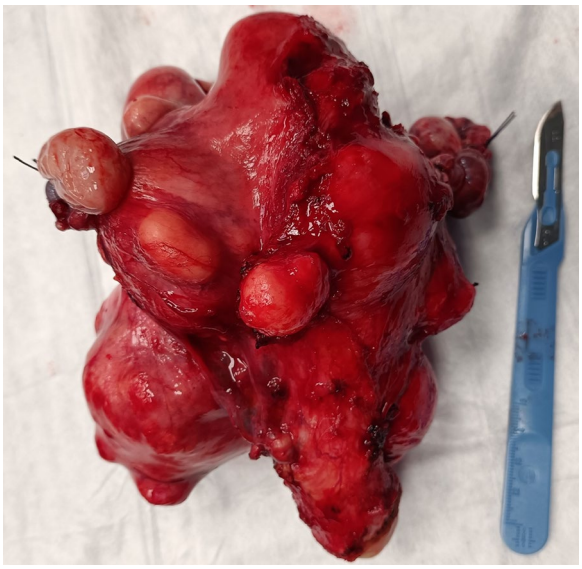

Fig. 2 Image of a large uterus deformed by numerous uterine fibroids, of various sizes, which was removed because of uterine bleeding, pelvic pressure, and anemia

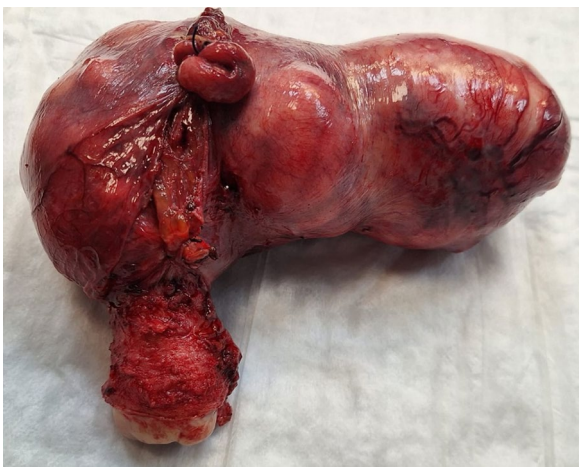

Fig. 3 Uterus removed by hysterectomy, deformed by a large left lateral fibroma, with symptoms resistant to drug therapy

one of the leading indications for gynecological consultations and surgical interventions worldwide, particularly hysterectomy (Fig. 3) [3]. Fibroid genesis and pathophysiology are intricate and multifaceted. From a biological standpoint, uterine fibroids are now widely recognized as monoclonal tumors arising from a single genetically altered myometrial smooth muscle cell. Somatic mutations—most commonly involving the *MED12* gene, but also *HMGA2*, *FH*, and *COL4A5–COL4A6* rearrangements—represent early driver events in fibroid development. These genetic alterations interact with a hormonally responsive uterine environment, in which estrogen and

progesterone act as key promoters of tumor growth, extracellular matrix accumulation, and vascularization [4, 5]. A major factor is hormonal modulation, with progesterone and estrogen both acting as important stimulants of fibroid growth. The receptors for these hormones are overexpressed in fibroid tissues as opposed to the nearby myometrium. Fibroid formation is influenced by a number of routes besides steroid hormones, including as growth factors (like TGFβ and IGF), cytokines, extracellular matrix remodeling, somatic mutations (like *MED12*, *HMGA2*), and epigenetic changes [4, 6–8]. Racial disparities are also evident, with Black women experiencing a higher incidence, earlier onset, larger and more symptomatic fibroids [9, 10]. Traditionally, surgery has been the main treatment method for fibroids. While myomectomy maintains the uterus and is still the preferred surgical procedure for women seeking conception, hysterectomy offers a conclusive treatment [11]. However, the growing demand for uterine-sparing and fertility-preserving treatments, together with the advent of minimally invasive techniques and novel pharmacologic agents, has significantly shifted the therapeutic paradigm toward individualized, conservative, and less invasive strategies [12, 13]. Consequently, the optimal treatment plan for uterine fibroids should be individualized and based on a comprehensive evaluation of symptom severity, fibroid characteristics (number, size, and location), patient age, reproductive goals, comorbidities, and personal preferences. Medical therapy may represent a first-line option for symptom control, a bridge to surgery or assisted reproduction, or a long-term uterus-sparing strategy in selected patients. Rather than competing with surgical approaches, pharmacologic treatments are increasingly integrated into a stepwise, patient-centered management algorithm aimed at balancing efficacy, safety, and quality of life [13–15]. Particularly for women looking for short-term discomfort relief, preoperative optimization, or surgical alternatives, medical therapy has grown in importance as part of fibroid management [13, 14]. Although surgery remains the only definitive treatment for uterine fibroids, medical therapies play an increasingly important role in fertility preservation, short-term symptom control, and as uterus-sparing alternatives or bridges to surgical intervention [14, 15]. The potential of a number of medication classes to control fibroid growth or alleviate related symptoms has been studied throughout the last 20 years. These include oral contraceptives, progestins, aromatase inhibitors, selective progesterone receptor modulators (SPRMs), gonadotropin-releasing hormone (GnRH) agonists and antagonists, and antifibrinolytic drugs, all of which have demonstrated differing levels of effectiveness and tolerance [16, 17]. More recently, the development of oral GnRH antagonists such as elagolix, relugolix, and linzagolix with or without hormonal add-back therapy has opened new avenues for long-term medical management, combining efficacy with improved convenience and safety profiles [18, 19]. These agents represent the most recent advancement in medical therapy, enabling sustained and reversible symptom control without surgery. In parallel, emerging mechanism-based approaches targeting extracellular matrix remodeling and angiogenesis are being explored as future uterus-sparing options [13, 20, 21]. In parallel, safety concerns regarding SPRMs (particularly ulipristal acetate) have prompted a reassessment of their role in fibroid therapy. The integration of these agents into clinical practice demands a nuanced understanding of their mechanisms of action, indications, limitations, and impact on patient-centered outcomes [22]. The clinical use of medical therapies for uterine fibroids is also influenced by their adverse effect profiles. Hypoestrogenic symptoms and bone mineral density (BMD) loss may occur with GnRH analogues, hepatic toxicity has limited the use of SPRMs, and other hormonal or nonhormonal treatments are associated with variable tolerability, underscoring the need for careful patient selection and monitoring [14, 23]. The goal of this narrative review is to present a thorough and current summary of uterine fibroids medical treatments. We will evaluate the current pharmacologic choices critically, talk about their mechanisms and clinical data, and investigate how they fit into the larger treatment protocol.

Future directions in fibroid pharmacotherapy, long-term treatment plans, fertility issues, and new agents will all receive particular focus.

Ethical Approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. Consent for the processing of data and material related to patient hospitalization, including video of the procedure or diagnostic tests, was obtained. This confirmed the anonymous use of patient data, diagnostic tests, and procedures for publication purposes.

Pathophysiology and Rationale for Medical Therapy

Uterine fibroids, or leiomyomas, are benign monoclonal tumors originating from the smooth muscle cells of the myometrium [24]. Despite the fact that their exact etiology is still unknown, mounting data points to a complex pathophysiology that includes environmental, genetic, hormonal, and epigenetic variables. Since both estrogen and progesterone encourage proliferation, extracellular matrix deposition, and apoptosis suppression, they are known to be key regulators of fibroid growth. The hormone reliance of fibroid tissues is highlighted by the constant overexpression of progesterone receptors (PR-A and PR-B) and estrogen receptors (ER-α) in comparison to the surrounding normal myometrium [5, 25]. Several growth factors, including transforming growth factor beta (TGFβ), insulin-like growth factor (IGF), platelet-derived growth factor (PDGF), and epidermal growth factor (EGF), influence the development and progression of fibroid disease in addition to steroid hormones. These factors all contribute to angiogenesis, fibrosis, and cell proliferation [26]. The accumulation of extracellular matrix components—collagen, fibronectin, and proteoglycans—not only alters the mechanical properties of fibroids but also contributes to their symptomatic profile, including increased uterine size and abnormal bleeding [27, 28]. Recurrent somatic mutations, particularly in the mediator complex subunit 12 (*MED12*), which is present in up to 70% of fibroids, as well as abnormalities in *HMGA2*, *FH*, and *COL4A5-COL4A6* have been discovered by recent genomic investigations. Different molecular subtypes of fibroids, each with specific development characteristics and therapy responsiveness, may be defined by these genetic changes [4, 7]. Medical therapy has become a logical and focused strategy to inhibit fibroid growth, reduce symptoms, and possibly postpone or eliminate the need for surgical intervention because of the pivotal roles that steroid hormones and growth factor signaling play in the pathophysiology of fibroids [21]. By targeting key mechanisms of fibroid proliferation and vascularization, pharmacologic agents offer an individualized, uterus-sparing approach that aligns with patient-centered goals, especially in women seeking fertility preservation or minimally invasive treatment options [14, 29].

CURRENT MEDICAL TREATMENTS

Gonadotropin-Releasing Hormone (GnRH) Agonists

GnRH agonists were among the first pharmacologic agents developed specifically for the medical management of uterine fibroids [30]. When taken continuously, these synthetic analogues downregulate pituitary GnRH receptors, resulting in a hypogonadotropic hypogonadal state. Initially, they stimulate the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [31]. Most women experience fibroid shrinking and amenorrhea as a result of the drop in circulating estrogen levels to postmenopausal ranges. GnRH agonists, including leuprolide acetate, goserelin, and triptorelin, have been shown in clinical trials to lower uterine volume by as much as 40–60% in 3–6 months of treatment. For individuals having a myomectomy or hysterectomy, they are very useful in reducing abnormal uterine bleeding (AUB), treating anemia, and enhancing preoperative conditions. Additionally, by decreasing fibroid size, short-term use may enable less invasive surgical techniques [32]. However, the

Table 1 Comparison of GnRH analogue therapy with and without add-back treatment in women with symptomatic uterine fibroids

Class	Examples	Mechanism	Effect on bleeding	Effect on fibroid size	Main side effects	Fertility impact
GnRH agonists	Leuprolide, triptorelin	Downregulates GnRH receptors → ↓E2/P4	Strong (up to 90%)	High (40–60%)	Hot flashes, bone loss, flare effect	Temporary suppression
GnRH antagonists	Elagolix, relugolix, linzagolix	Competitive GnRH receptor blockade	Strong (70–80%)	Moderate (25–50%)	Mild vasomotor, BMD loss (add-back mitigates)	Reversible suppression
SPRMs (withdrawn/suspended)	Ulipristal acetate	PR modulation → antiproliferative	Strong (up to 90%)	Moderate (20–35%)	Liver toxicity, endometrial changes	Unknown
CHCs	EE/levonorgestrel, EE/norethindrone	Inhibits ovulation, stabilizes endometrium	Mild–moderate (30–50%)	Minimal	Nausea, VTE risk in high-risk patients	Fertility resumes after stop
Progestins (oral or LNG-IUS)	NETA, MPA, LNG-IUS	Endometrial atrophy	Moderate (up to 80%)	Variable	Irregular bleeding, weight gain	Preserved
Aromatase inhibitors	Letrozole, anastrozole	↓ Peripheral estrogen synthesis	Moderate (30–50%)	Moderate (30–50%)	Arthralgia, bone loss	Reversible
Antifibrinolytics	Tranexamic acid	Inhibits fibrinolysis	Moderate (30–50%)	None	Nausea, risk of thrombosis	Neutral

Add-back therapy with low-dose estrogen and progestin is used to alleviate hypoestrogenic side effects such as vasomotor symptoms and bone loss while maintaining the clinical benefits of fibroid volume reduction and menstrual suppression

BMD bone mineral density, *CHCs* combined hormonal contraceptives, *E2* estradiol, *EE* ethinylestradiol, *GnRH* gonadotropin-releasing hormone, *LNG-IUS* levonorgestrel-releasing intrauterine system, *MPA* medroxyprogesterone acetate, *NETA* norethisterone acetate, *P4* progesterone, *PR* progesterone receptor, *SPRMs* selective progesterone receptor modulators, *VTE* venous thromboembolism

adverse impact profile of GnRH agonists limits their clinical relevance. Hot flashes, dry vagina, mood swings, and loss of BMD are all examples of hypoestrogenic symptoms that may arise, particularly with extended use. As a result, in order to minimize adverse effects and maintain bone health, treatment is usually limited to 6 months unless it is coupled with add-back medication, usually low-dose estrogen and progestin [23]. Despite these limitations, GnRH agonists remain an important option in selected clinical scenarios, such as rapid symptom control, preoperative optimization, or when surgery must be postponed. Their role, however, has declined with the advent of newer agents, particularly oral GnRH antagonists, which offer similar efficacy with improved tolerability and easier administration [23, 33]. See Table 1.

Gonadotropin-Releasing Hormone (GnRH) Antagonists

One significant development in the medical treatment of uterine fibroids is the use of oral GnRH antagonists. Antagonists bind competitively to pituitary GnRH receptors and immediately decrease the release of FSH and LH, in contrast to agonists, which first generate a brief hormonal flare [34].

This results in a rapid reduction of circulating estradiol to low physiological or near-menopausal levels (typically 20–50 pg/mL), which in turn leads to a significant improvement in fibroid-related symptoms, particularly AUB [35]. Three oral GnRH antagonists have reached clinical use or late-phase development: elagolix, relugolix, and linzagolix [36]. The main benefits of oral administration, dose flexibility, and quick reversibility are shared by all of these agents, despite differences in half-life, peak suppression levels, and necessary add-back procedures. In clinical trials, 76–84% of women experienced a ≥ 50% reduction in menstrual blood loss (MBL) during a 6-month period when using elagolix 300 mg twice daily with add-back therapy [37]. Relugolix combination therapy (40 mg relugolix + 1 mg estradiol + 0.5 mg norethindrone acetate once daily) demonstrated ≥ 50% MBL reduction in 73% of patients in LIBERTY 1 and 71% in LIBERTY 2, versus 19% and 15% in the placebo arms, respectively [38]. Moreover, a mean hemoglobin increase of 2.5 g/dL was observed at week 24 in patients with anemia treated with relugolix combination therapy, accompanied by uterine volume reductions of 25–30% [19]. At 24 weeks, the lumbar spine's BMD decrease was less than 1%, and with continued treatment, it stabilized. Similarly, a 200-mg dosage of linzagolix with add-back decreased MBL by ≥ 50% in 75–78% of women, with a mean fibroid volume reduction of up to 45%, according to the PRIMROSE 1 and 2 studies; 56–60% of women responded well to the 100-mg dose without add-back, enabling customized estrogen exposure depending on personal tolerance and contraindications [39]. Elagolix, while primarily approved for endometriosis-associated pain, showed efficacy in reducing AUB in 72–80% of women in the Elaris UF-1 and UF-2 trials. However, discontinuation rates due to hypoestrogenic symptoms were higher than with relugolix or linzagolix, and liver enzyme elevations were reported in 3–4% of cases, prompting regulatory caution [40, 41]. Oral antagonists avoid the flare phenomena, improve symptom management more quickly (usually within 2–4 weeks), and do not require injections like GnRH agonists do. Better adherence and long-lasting clinical effect are supported by their consistent estradiol suppression and easy administration. However, accessibility, insurance coverage, and costs—which in some areas are frequently more than US $500 per month—may prevent widespread adoption. Furthermore, long-term data on the best length of therapy, the impact on future fertility, and recurrence rates following withdrawal are currently being gathered [42]. In routine clinical practice, GnRH antagonists are particularly valuable in women seeking nonsurgical solutions, those with anemia requiring stabilization before surgery, or those desiring a temporary but effective symptom control strategy. Their role in bridging therapy, fertility planning, and personalized care algorithms continues to expand as real-world data accumulate [43]. See Table 2.

Table 2 Summary of pivotal randomized controlled trials evaluating oral GnRH antagonists in women with uterine fibroids and heavy menstrual bleeding [19, 38–41]

Trial	Agent	Design/population	Primary endpoint	Key results	Duration
LIBERTY 1	Relugolix combo	RCT, $n = 388$ women with HMB due to fibroids	% with MBL reduction ≥ 50%	73% achieved ≥ 50% MBL reduction vs 19% placebo ($p < 0.001$)	24 weeks
LIBERTY 2	Relugolix combo	RCT, $n = 382$	Same as LIBERTY 1	71% response vs 15% placebo ($p < 0.001$); Mean Hb ↑ 2.5 g/dL in anemic patients	24 weeks
PRIMROSE 1	Linzagolix	RCT, $n = 526$	% with MBL reduction ≥ 50%	75% (200 mg + add-back); 56% (100 mg without add-back)	24 weeks
PRIMROSE 2	Linzagolix	RCT, $n = 535$	Same as PRIMROSE 1	78% (200 mg); 60% (100 mg)	24 weeks
ELARIS UF-1	Elagolix + ABT	RCT, $n = 412$ women with fibroids and HMB	% with MBL reduction ≥ 50%	84.1% response vs 8.7% placebo ($p < 0.001$); significant QoL improvement	6 months
ELARIS UF-2	Elagolix + ABT	RCT, $n = 378$	Same as UF-1	77% response vs 10% placebo; lower volume reduction than with GnRH agonists	6 months

All agents demonstrated significant reductions in menstrual blood loss compared to placebo, with variable efficacy based on dose and use of add-back therapy. Improvements in hemoglobin levels and quality of life were also observed across studies

ABT add-back therapy, *GnRH* gonadotropin-releasing hormone, *Hb* hemoglobin, *HMB* heavy menstrual bleeding, *MBL* menstrual blood loss, *RCT* randomized controlled trial, *QoL* quality of life

Selective Progesterone Receptor Modulators (SPRMs)

A unique class of pharmaceutical products known as SPRMs was created specifically to treat uterine fibroids. SPRMs modulate gene expression in a way that inhibits fibroid cell proliferation, induces apoptosis, and reduces extracellular matrix deposition—all crucial processes in fibroid growth and maintenance—by binding to progesterone receptors (PR-A and PR-B). Because SPRMs do not result in a hypoestrogenic condition like GnRH analogues do, they have a better tolerability profile with regard to vasomotor symptoms and bone loss [22, 44]. Upristal acetate (UPA), the most researched SPRM, was first authorized in Europe for the intermittent treatment of moderate-to-severe fibroid symptoms. UPA 5 mg daily produced amenorrhea in 73–89% of patients within 10 days in the PEARL I and II trials, and following a 3-month therapy, mean fibroid volume reductions were 21–35% [45, 46]. These results were comparable to those of leuprolide, but with significantly fewer hot flushes and less impact on BMD. Moreover, UPA demonstrated sustained efficacy with repeated courses, and improvements in hemoglobin levels and quality of life were well documented [47]. However, the clinical use of UPA was profoundly impacted by reports of drug-induced liver injury (DILI), including rare but serious cases of acute hepatic failure requiring transplantation [48]. As of 2020, the European Medicines Agency (EMA) suspended UPA

for fibroid treatment following an extensive pharmacovigilance review [49]. The choice was influenced by the lack of a trustworthy predictive biomarker, even though the absolute risk of serious hepatic impairment was extremely low. Liver enzyme increases were observed in about 1.5% of treated women. In most countries, UPA is no longer indicated for the treatment of uterine fibroids and its use has been formally restricted to emergency contraception only, following regulatory decisions by the EMA (EMEA/H/C/001027) [50]. Other SPRMs, including telapristone acetate and vilaprisan, showed initial promise in preclinical and phase 2 trials but encountered development setbacks due to concerns over endometrial safety and potential hepatotoxicity [22]. As of now, no SPRM is approved for the treatment of uterine fibroids in the USA, and the clinical role of SPRMs remains uncertain pending the development of safer, tissue-selective compounds with improved hepatic safety profiles [20]. In addition, the high cost of SPRMs has represented a further barrier to their widespread adoption in routine clinical practice, particularly when long-term or repeated treatment courses are required [22]. SPRMs are a prime example of the difficulties in converting targeted endocrine medicines into long-term treatment plans, despite their pharmacological appeal and early clinical success. Reintroducing SPRMs into clinical practice in the future will probably necessitate strict liver monitoring guidelines, solid long-term safety evidence, and perhaps the use of pharmacogenetic markers to choose patients.

Hormonal and Nonhormonal Pharmacologic Therapies

Beyond GnRH analogues and SPRMs, several other pharmacologic agents are used in the symptomatic management of uterine fibroids, particularly in women who are not surgical candidates or who prefer noninvasive approaches [51]. These include combined hormonal contraceptives (CHCs) [52], progestins [53], aromatase inhibitors (AIs) [54], and antifibrinolytic agents [55]. While most of these treatments are not approved specifically for fibroids, they are frequently employed in clinical practice for control of AUB and related symptoms [56]. Women with tiny fibroids are frequently prescribed CHCs, which contain both progestin and estrogen, to control their periods and lessen menstrual bleeding. CHCs can reduce menstrual blood loss by 30% to 50%, according to several observational studies and randomized trials, but they do not appreciably reduce the amount of fibroid tissue [14, 57, 58]. Women who are hemodynamically stable and do not exhibit bulk symptoms or considerable uterine enlargement are best suited for their use. Continuous regimens or extended-cycle formulations may help decrease bleeding, particularly in younger individuals who are not immediately pursuing pregnancy [59, 60]. Progestins, such as medroxyprogesterone acetate and norethindrone acetate, have also been empirically used to reduce bleeding. However, the effectiveness of progestins varies, and in certain situations, local progesterone receptor activation may encourage the formation of fibroid tissue [61]. The levonorgestrel-releasing intrauterine system (LNG-IUS), while not formally indicated for fibroids, can significantly reduce menstrual blood loss in women with small-to-moderate submucosal fibroids or in those with concomitant adenomyosis [62]. In observational studies, bleeding reduction rates up to 80% have been reported, with improved hemoglobin levels and patient satisfaction. Expulsion rates, however, are higher in cases of significant uterine cavity distortion [63, 64]. By preventing peripheral aromatization, AIs such as letrozole and anastrozole lower the synthesis of estrogen. After 3–6 months of AI medication, small trials have demonstrated uterine volume reductions of 30–50% in addition to symptom relief [65]. Nonetheless, concerns about bone loss, hot flashes, and lipid metabolism limit their use to select populations, such as perimenopausal women or those with contraindications to estrogen-containing therapies [66]. Tranexamic acid is the main antifibrinolytic drug that works well for both acute and intermittent AUB management. They stabilize clot formation by

preventing plasminogen activation. Tranexamic acid is especially helpful for women who would rather not take hormonal therapies or who are waiting for a final therapy because it can lower menstrual blood loss by up to 40%. It must be taken periodically during menstruation, though, and it has no effect on the size or growth of fibroid tissue [57, 67]. All things considered, these treatments are often less successful than targeted medications at lowering the burden of fibroid disease, even if they can provide significant advantages in certain situations, particularly for short-term symptom relief or as a supplement to other treatments. However, they are useful parts of the therapeutic arsenal owing to their accessibility, familiarity, and good safety profiles, especially when tailored to the demands and comorbidities of the patient [68].

Personalized Treatment Strategies

The one-size-fits-all approach to treating uterine fibroids has given way to a customized, patient-centered strategy. A variety of clinical factors must be taken into account while customizing treatment, such as the intensity of the symptoms, age, reproductive objectives, fibroid features (number, size, and location), comorbidities, and patient preferences for medicinal as opposed to surgical treatments [15]. Reproductive planning is an important consideration when choosing a treatment. Age-related uterine changes may significantly influence fibroid behavior, symptom severity, and response to medical therapies [69]. On the other hand uterine-preserving methods are given priority when women are looking to become pregnant in the future. By reducing fibroid volume, correcting anemia, and managing bleeding prior to assisted reproductive methods or surgical myomectomy, medical therapy may act as a bridge to conception [70]. Among medical options, GnRH antagonists with or without add-back therapy can be used for temporary symptom control in the pre-conception period. However, their suppressive effects on ovulation and the endometrium necessitate drug discontinuation before attempting pregnancy [71]. On the other hand, women who have finished having children or who are nearing menopause might benefit from longer-term medical care to prevent or postpone surgery. Controlling symptoms with CHCs, LNG-IUS, or antifibrinolytics may be adequate for perimenopausal women, particularly if fibroid growth is slowing [72]. For those with significant bulk symptoms or anemia, oral GnRH antagonists particularly linzagolix 100 mg without add-back may provide effective symptom relief without exposing the patient to estrogen or progestins, a relevant consideration in women with hormone-sensitive conditions [73]. The suitability of different treatments is largely determined by the comorbidities of the patient. For instance, unless used in conjunction with add-back therapy, GnRH agonists and antagonists are typically contraindicated in women with severe osteoporosis or cardiovascular risk factors [74]. Estrogen-containing contraceptives are avoided in women at risk of thromboembolic disease, favoring progestin-only or nonhormonal options [75]. In cases of severe liver disease, SPRMs are contraindicated because of concerns about hepatotoxicity, while tranexamic acid should be used with caution in patients with thrombotic predisposition [22, 76]. Decision-making is also influenced by patient preferences for the treatment's length, cost, anticipated adverse effects, and mode of administration. While some women may be willing to endure temporary hormonal side effects in exchange for symptom relief, others may place a higher priority on avoiding injections or surgery. To match treatment objectives with expectations, lessen decisional conflict, and enhance long-term adherence, shared decision-making and open counseling are crucial [77]. Finally, access to medicines, especially expensive ones such as oral GnRH antagonists, is influenced by socioeconomic and cultural variables. Regional differences in insurance coverage and governmental clearances impact how applicable clinical trial results are in the real world. As a result, while upholding the values of evidence-based, customized care, physicians must modify their therapeutic approach within the framework of regional healthcare systems or basing on fertility desire (Fig. 4) [78].

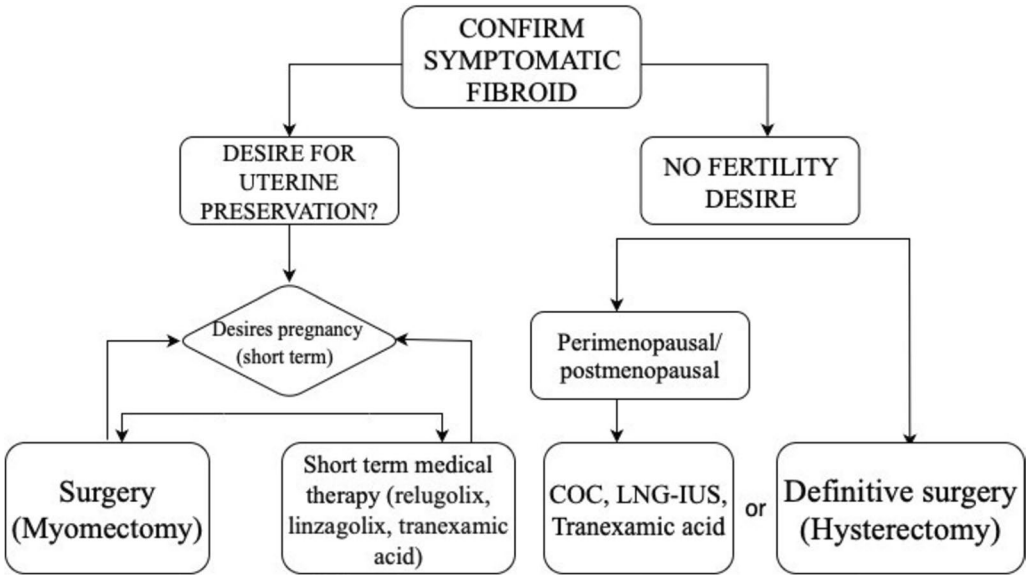

Fig. 4 Proposed algorithm for the medical management of uterine fibroids based on fertility desire. This decision-making framework delineates a sequential methodology to assist healthcare practitioners in the selection of medical interventions for symptomatic uterine fibroids, categorized by the patient's fertility objectives. Therapeutic options encompass oral GnRH antagonists, with or without adjunctive therapy, as well as hormonal and non-hormonal alternatives, and, when clinically indicated, a referral for surgical intervention. Medical therapy may be contemplated even in scenarios lacking fertility aspirations, provided that surgical options are either contraindicated or voluntarily declined

Emerging and Investigational Therapies: What's Really New in the Pharmacological Treatment of Uterine Fibroids

Significant unmet requirements remain in the treatment of uterine fibroids despite advancements in pharmacologic treatments, especially with regard to long-term safety, fertility preservation, and avoiding intrusive procedures. Targeted, tissue-specific, and molecularly guided therapies are replacing generic hormonal suppression in recent research efforts [79, 80]. Recent evidence suggests that artificial intelligence-driven models may further optimize diagnostic accuracy and personalized treatment selection in uterine fibroid management [81].

Hormonal Innovations with Improved Safety Profiles

Next-generation SPRMs are under development with the goal of maintaining the antifibrotic and antiproliferative benefits of agents such as ulipristal acetate, while minimizing hepatic toxicity and endometrial risks [44]. These include SPRMs with selective receptor isoform modulation and altered metabolism (e.g., nonhepatic clearance pathways). Routes of administration such as vaginal rings and transdermal patches are also being explored to reduce systemic exposure. However, the long-term safety and regulatory acceptance of these novel agents remain under evaluation [82, 83].

Nonhormonal and ECM-Targeted Therapies

The extracellular matrix (ECM) plays a central role in fibroid pathophysiology, contributing to tissue stiffness, abnormal signaling, and volume expansion [84]. Therapies targeting ECM remodeling such as matrix metalloproteinase (MMP) inhibitors, TGF-\u03b2 pathway blockers, and lysyl oxidase-like (LOXL) inhibitors are gaining interest for their potential to reduce fibroid size without suppressing the hypothalamic-pituitary–gonadal axis. Although most data remain preclinical, these compounds may offer safer long-term options for women unable or unwilling to use hormonal agents [85, 86].

Antiangiogenic and Vascular Modulation Strategies

Fibroids are highly vascularized tumors, and disruption of their blood supply presents an attractive therapeutic angle [87]. Agents targeting vascular endothelial growth factor (VEGF), angiopoietins, or tyrosine kinase pathways are under study to suppress fibroid perfusion and growth [87]. While none have reached regulatory approval for fibroid-specific use, early-phase trials and combination strategies (e.g., with GnRH antagonists) are ongoing [88].

Epigenetic and Genomic Modulators

Fibroid subtypes exhibit distinct genomic alterations, particularly in *MED12*, *HMGA2*, and *FH* genes [89]. While application of gene-editing technologies such as CRISPR-Cas9 in this area remains theoretical at this stage, pharmacologic targeting of associated downstream pathways (e.g., Wnt/β-catenin signaling, histone deacetylases, and DNA methyltransferases) is in progress. These approaches aim to offer subtype-specific treatment, potentially revolutionizing fibroid care through personalized molecular medicine [8, 90].

Immune and Microbiome-Based Therapies

Emerging evidence implicates local immune dysregulation and microbiota alterations in fibroid pathogenesis and treatment resistance. Preclinical studies suggest that anti-inflammatory agents or microbiome-targeted interventions (e.g., antibiotics, probiotics, or even fecal transplantation) could modulate fibroid behavior or improve response to therapy. While still speculative, these concepts are part of a growing effort to integrate reproductive immunology into fibroid management [91, 92].

Innovative Drug Delivery Systems

A key limitation of current therapies lies in systemic side effects. Novel delivery systems including nanoparticle-based uterine artery targeting, intrauterine depot systems, and fibroid-specific injectable formulations are being engineered to enhance local drug concentrations and reduce off-target effects. These platforms may optimize the efficacy-safety balance for both hormonal and nonhormonal agents [93, 94]. Future prospective studies are also needed to evaluate the potential role of these agents in the secondary prevention of fibroid recurrence after myomectomy.

A practical algorithm summarizing the key decision points for medical therapy selection is presented in Fig. 1.

Natural Compounds in Fibroid Management: Focus on Epigallocatechin Gallate (EGCG)

EGCG, the most abundant catechin in green tea (*Camellia sinensis*), has gained increasing attention as a nonhormonal, nonpharmacologic compound with potential therapeutic applications in uterine fibroids. Beyond EGCG, other natural compounds—including vitamin D and D-*chiro*-inositol (DCI)—have been explored as potential nonpharmacological options for uterine fibroids, and available clinical evidence increasingly suggests that beneficial effects may derive from combined or complementary actions rather than isolated supplementation. Vitamin D deficiency has been consistently associated with uterine leiomyomatosis, while DCI has been reported to exert antiestrogenic effects through downregulation of aromatase expression/activity

[95–98]. As a polyphenolic flavonoid, EGCG exerts pleiotropic biological effects including antiproliferative, antifibrotic, antioxidant, and antiangiogenic activities, making it an attractive candidate for conservative, uterus-sparing treatment strategies in fibroid disease [99]. Preclinical studies have demonstrated that EGCG significantly inhibits fibroid cell proliferation by modulating multiple signaling pathways. In vitro experiments using human leiomyoma cell lines have shown that EGCG induces G1 cell cycle arrest and apoptosis via downregulation of cyclin D1 and Bcl-2 and upregulation of Bax and p21 expression [100]. Furthermore, EGCG suppresses ECM accumulation through inhibition of collagen type I and fibronectin expression, while attenuating the TGFβ signaling pathway, a central driver of fibrosis in fibroid pathogenesis [100, 101]. Animal models provide further support for EGCG's therapeutic role. In a study by Zhang et al., oral administration of EGCG (1.25 mg/kg/day) in an Eker rat model resulted in a 35% reduction in fibroid volume after 8 weeks, associated with decreased expression of proliferating cell nuclear antigen (PCNA) and vascular endothelial growth factor (VEGF), confirming both antiproliferative and antiangiogenic effects [102]. The most compelling clinical evidence to date comes from a randomized, double-blind, placebo-controlled pilot trial conducted by Roshdy et al., which evaluated EGCG 800 mg/day for 4 months in women with symptomatic uterine fibroids. The treatment group experienced a mean fibroid volume reduction of 32.6% versus a 24.3% increase in the placebo group. Significant improvements in symptom severity scores (SSS) and quality of life (UFS-QOL) were also observed, without notable adverse effects [103]. In addition to its direct antifibroid activity, EGCG has systemic antioxidant and anti-inflammatory properties that may modulate hormonal sensitivity and chronic inflammation, both of which are implicated in fibroid pathophysiology. EGCG inhibits nuclear factor-kappa B (NF-κB) and reduces reactive oxygen species (ROS), thereby potentially limiting the pro-inflammatory microenvironment that favors fibroid progression [104]. Despite its promising profile, EGCG has limitations that warrant caution. Its oral bioavailability is relatively low, and optimal dosing regimens for sustained therapeutic effects remain to be defined. Interindividual variability in absorption and metabolism, as well as the lack of large-scale randomized controlled trials, limits the generalizability of existing data. Moreover, while green tea extracts are generally well tolerated, rare cases of hepatotoxicity have been reported, particularly with high doses or concentrated formulations, suggesting a need for liver function monitoring in prolonged use [105]. Nevertheless, EGCG constitutes a novel, nonpharmacological adjunct or alternative in the management of uterine fibroids, particularly for women who are either averse to or incapable of undergoing hormonal or surgical interventions. Its significance may be particularly pronounced in the context of early-stage disease, during expectant management, or in conjunction with conventional therapies to augment efficacy and mitigate adverse effects. Future research should endeavor to elucidate optimal dosing regimens, treatment duration, and long-term safety profiles, as well as to investigate synergistic combinations with hormonal or targeted therapeutic agents. The integration of EGCG into evidence-based clinical algorithms may facilitate the development of more individualized, low-risk therapeutic approaches in the management of fibroids.

Clinical Perspectives

Over the past 20 years, the medical treatment of uterine fibroids has changed dramatically, progressing from a few hormonal suppression techniques to a wide range of increasingly effective treatments. With their rapid onset of action, superior tolerability over conventional medications, and extremely successful control of AUB, oral GnRH antagonists have completely changed the nonsurgical therapy landscape. However, the removal of SPRMs from standard clinical use emphasizes how crucial post-marketing surveillance and strict long-term safety monitoring are to gynecologic pharmacotherapy.

Choosing a treatment nowadays necessitates a customized strategy that incorporates patient-specific elements such as age, comorbidities, reproductive objectives, symptom burden, and

hormonal sensitivity. In this regard, oral GnRH antagonists provide flexible, reversible, and patient-friendly alternatives appropriate for both short- and intermediate-term use, especially when combined with add-back therapy. Even though they are less effective at reducing volume, hormonal and nonhormonal medications can still be useful for controlling symptoms in patients who are carefully chosen, particularly in situations with limited resources or when systemic therapy is contraindicated. In the future, new treatments that focus on nonhormonal processes including gene regulation, angiogenesis, and extracellular matrix remodeling may even replace existing treatments.

These strategies, while still in the early stages of development, have the potential to provide uterus-preserving, highly focused treatments with less systemic side effects. This is especially crucial for women who want to get pregnant or who are ineligible for hormonal manipulation. A patient-centered, multidisciplinary framework that incorporates shared decision-making, transparent risk and benefit communication, and an awareness of the patient's values and preferences must continue to guide clinical decision-making. Clinicians will need to keep up with the changing body of data as additional treatment options become accessible, making sure that the therapy approach fits with both patient objectives and scientific advancements.

CONCLUSIONS

More accuracy, adaptability, and customization are hallmarks of the current era of medical therapy for uterine fibroids. Ensuring that all women with fibroids may take advantage of the entire range of contemporary therapeutic options will require sustained innovation, excellent clinical research, and fair access.

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Declarations

Conflict of Interest. All authors, Giovanni Pecorella, Andrea Morciano, Radmila Sparic, Safak Hatirnaz, Mykhailo Medvediev, Antonio Malvasi, Gianluca Raffaello Damiani, Andrea Tinelli, declare that they have no conflicts of interest.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. Consent for the processing of data and material related to patient hospitalization, including video of the procedure or diagnostic tests, was obtained. This confirmed the anonymous use of patient data, diagnostic tests, and procedures for publication purposes.

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