Journal of Endometriosis and Uterine Disorders 7 (2024) 100080

Contents lists available at ScienceDirect

Journal of Endometriosis and Uterine Disorders

journal homepage: www.elsevier.com/locate/jeud

Review

An update on the management of uterine fibroids: personalized medicine or guidelines?

Eduard Mension [a], Joaquim Calaf [b], Charles Chapron [c], Marie Madeleine Dolmans [d], Jacques Donnez [e], Louis Marcellin [c], Felice Petraglia [f], Silvia Vannuccini [f], Francisco Carmona [a,*]

[a] Department of Obstetrics and Gynecology, Hospital Clínic of Barcelona, Spain
[b] Hospital Sant Pau, Autonomous University of Barcelona, Barcelona, Spain
[c] Département de Gynécologie, Obstétrique et Médecine de la Reproduction, AP-HP, Centre Hospitalier Universitaire (CHU) Cochin, F-75014, Paris, France
[d] Gyne Unit, Society for Research into Infertility (SRI), Université Catholique de Louvain, Brussels, Belgium
[e] Pôle de Recherche en Gynécologie, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain (UCL), Gynecology Department, Cliniques Universitaires Saint-Luc, Brussels, Belgium
[f] Obstetrics and Gynecology, Department Experimental, Clinical and Biomedical Sciences, University of Florence, Careggi University Hospital, Florence, Italy

ARTICLE INFO

ABSTRACT

During the last decades relevant advances have been made in understanding the pathophysiology of uterine fibroids (UFs) and their formation from smooth muscle cells by the stimulation of hormonal and genetic pathways. Although 50–75% of UFs are considered to be non-clinically relevant when non-asymptomatic, the main clinical symptoms and signs of UFs are abnormal uterine bleeding (AUB), pelvic pain and/or bulk symptoms and reproductive failure. The first diagnostic tool recommended is transvaginal ultrasound (TVUS), usually providing a clear and straightforward diagnosis. In order to standardize the description of TVUS findings and to facilitate guidelines to provide clearer and targeted recommendations, different UF reporting systems are being used, such as the Morphological Uterus Sonographic Assessment criteria, the FIGO Classification and the STEPW/Lasmar Classification. In specific cases other complementary imaging techniques may be required.

Depending on the presentation of symptoms, their severity, and the clinical context of each patient, different options may be proposed and individualized. Since many UFs are asymptomatic, in these cases no medical or surgical intervention would be necessary. In symptomatic UFs physicians should individualize the treatment considering other factors beyond the UF type or morphology. Tranexamic acid, levonorgestrel intrauterine devices, selective progesterone receptor modulators, oral contraceptives, GnRH antagonist +/− addback therapy and surgical procedures, are among the different therapeutic options that clinicians should discuss with the patient. Nevertheless, the heterogeneity of UFs intrinsic stem cells may directly affect the response to targeted treatments, making a variable response to treatments plausible for each UF.

1. Introduction

Uterine fibroids (UFs) are the most common tumor-driven disorder in women's, impairing the daily quality of life of millions of women worldwide, since up to 70–80% of the female world population present a UF during their 50 s [1]. Moreover, this phenomenon not only causes discomfort but produces a huge economic burden in terms of medical and surgical treatments, as well as indirect costs due to reduced work productivity [2].

During the last decades relevant advances in the knowledge of the pathophysiology of UFs have been made, revealing new potential diagnostic and therapeutic approaches that may provide a paradigmatical change to the management of this disease.

The aim of the present review is to highlight the basic and clinical research advancements in the diagnosis and treatment of UFs.

2. Methods

A PubMed and Google Scholar search for peer-reviewed original and review articles related to the management of UFs published in English until October 2023 was performed. The main basic and clinical updates were evaluated, including the review of guidance documents, most recent

* Corresponding author.
E-mail address: fcarmona@clinic.cat (F. Carmona).

http://doi.org/10.1016/j.jeud.2024.100080
Received 24 February 2024; Received in revised form 25 April 2024; Accepted 25 April 2024
Available online 26 April 2024

scientific evidence and other documents discussing and making recommendations to harmonize differences.

3. Results and discussion

3.1. Pathophysiology

The molecular mechanism that produces the transformation of regular myometrial smooth muscle cells (SMCs) into a UF is a complex multifactorial process involving many stakeholders.

The formation of a UF starts with the stem cell precursors of the SMCs, that receive several "hits" driven by classical risks factors: age, ethnicity, and obesity [3,4], and also by hormonal and genetic pathways. Stem cells altered by these factors are eventually transformed into fibroid SMCs, and promote the creation of abnormal extracellular matrix (ECM) around these cells, leading to the creation of a UF.

3.1.1. Genetic and epigenetic features

Despite the belief that UFs are chromosomically "stable", somatic mutations are thought to be present in up to 70–80% of UFs [5]. Some germline mutations have been associated with an increased risk of presenting UFs, the most important being the mutation of the fumarate hydratase gene (a tumor suppression gene in chromosome 1q42.3-q43), also associated with cutaneous leiomyosis and renal cell carcinoma [6].

The most important advances in our knowledge of UFs have been made in the description of somatic cytogenetic and epigenetic abnormalities. Most cytogenetic abnormalities lead to the impairment of growth cytokines, such as high-mobility group AT-hook, G protein-coupled receptor 10, cut-like homeobox 1 and the mediator complex subunit 12 (*MED12*), with *MED12* mutations being reported in up to 70–80% of UFs analyzed [7].

According to recent findings, *MED12* has demonstrated to be a key factor for the growth of SMCs and their peritumoral environment, increasing the number of tumor-associated fibroblasts (TAFs), producers of ECM [8]. Notwithstanding, the mutation of *MED12* has been found to be present in SMCs but not in TAFs conforming UFs, and *MED12* mutations appear to be inversely related to the size of the UFs, despite the inactivation of *MED12* resulting in the upregulation of transforming growth factor beta (TGF-β), an ECM-promoting factor.

Moreover, epigenetic mechanisms, such as DNA methylation, histone modification and changes in miRNA may have as much influence as cytogenetic abnormalities in the development of UFs. Hypermethylation of genes, such as transcription factor Krüppel-like factor 11), a tumour suppression gene, has been observed in fibroid cells, as well as in the methylation of specific DNA methyltransferases (DNMTs), that may alter signaling pathways, such as the PI3K-AKT-MTOR [9]. Furthermore, increased methylation of DNMTs has been observed in UFs as compared with normal myometrial tissue [10].

3.1.2. Hormonal dependence

UF cells are known to respond to estrogens and progesterone stimulus during the reproductive age of women, and thus, when menopause occurs, UFs tend to shrink due to the decline of these hormonal stimuli [11]. In the past the main cause of the development of UFs was attributed to estrogens and their ability to stimulate ECM formation through cytokine pathways. However, nowadays the focus has shifted to progesterone-related pathways, due to evidence showing that one of the main roles of estrogen may be the induction of progesterone receptors (PRs) in UFs [12]. Additionally, animal experiments confirmed that stimulation of PRs is sufficient to promote the growth of UFs [11]. Observational studies in patients with UFs showed increased growth in response to progestins, whereas others reported a reduction in tumor size when using antiprogestins [13]. Since then, studies have largely focused on progesterone. High PR levels have been associated with decreased intermenstrual bleeding and dysmenorrhea, while, on the other hand, a high density of PRs may stimulate leiomyoma growth, despite attenuating the clinical symptoms related to endometrial shedding [4].

Molecular studies have shown heterogeneity when assessing the proportion of SMCs in UFs, even in different UFs from the same patient. Furthermore, laboratory testing revealed the tendency of SMCs to present more PRs than TAFs, which tend to express more estrogen receptors. This heterogeneity in the proportion of SMCs and mutations may directly affect the response to targeted treatments, making variable response to treatments plausible in patients presenting several UFs [14].

3.2. Diagnosis of uterine fibroids

The first line technique for the diagnosis of UFs is transvaginal ultrasound (TVUS) since the 2011 International Federation of Gynecology and Obstetrics (FIGO) consensus stated that TVUS can map the location of UFs in the uterus evaluated [15]. However, following the implementation of TVUS, difficulties have been described in standardizing the reporting of TVUS findings, especially when assessing large volume fibroids, which account for up to 36% of classification discrepancies [16].

The Morphological Uterus Sonographic Assessment (MUSA) criteria describe the ultrasonographic features of the myometrium and myometrial lesions [17]. These criteria provide a detailed description of the characteristics of UFs including number, size, localization, echogenicity, acoustic shadow, vascularization, fibroid type (according to the FIGO classification), and minimal distance to serosa and to the mucosa. One of the main difficulties for clinicians when performing UF mapping is to evaluate the involvement of the endometrial junctional zone (JZ) [16]. When the JZ is affected by a UF, the clinical presentation and the response to treatments may be completely different. Submucosal UFs are classified using the STEPW/Lasmar Classification which attempts to provide diagnostic information for difficult and complex hysteroscopic UF resection [18].

Another major issue is when UFs with the same FIGO classification present different symptoms, depending on the involvement of the outer or inner myometrium. This key point is missed when using only the FIGO system, whereas the classification of these UFs would be more precise if MUSA criteria, which assess the minimal distance to serosa and mucosa, were used [17]. UFs affecting the JZ appear to present fewer cytogenetic abnormalities, and increased expression of oxytocin receptors, presenting a different pattern of vascularization. They are also more responsive to gonadotropin-releasing hormone (GnRH) analogs with fewer recurrences after surgery. Furthermore, the MUSA criteria provide information of UF vascularization using power Doppler. Different patterns and scores of vascularization have been linked to the possibility of fibroid growth, showing that the greater the vascularization, the greater the growth [19]. Thus, depending on myometrium involvement and vascularization, clinicians can provide better targeted treatments to patients.

Nevertheless, magnetic resonance imaging (MRI) appears to be superior when assessing more than four fibroids or a uterus larger than 375 cm^3 or equivalent to a uterus in gestational weeks 14–15, and may be helpful in cases of coexisting endometriosis [20] or in differentiating UFs from uterine sarcomas, supporting the superiority of MRI especially in these cases [21].

During the last decade, other complementary techniques have been introduced and provide precise uterine mapping of UFs in specific cases:

1 Hysteroscopy and sonohysterography may help to evaluate submucosal UFs before surgery, having a high level of accuracy and facilitating sample obtention when needed [22];
2 Elastography may have a role in the differential diagnosis of the presence of UFs with adenomyosis, along with the follow-up of non-invasive treatments, since fibroid stiffness is different from normal myometrium. Furthermore, some studies have also assessed the role of elastography in determining the prognosis of UFs and as a tool to select future treatments [23].

3 Contrast-enhanced ultrasound has been described as a future tool for UF mapping using endovenous microbubbles to enhance the microvasculature of the myometrium. Although this method is still under investigation, the visualization of micro-vessels in the myometrium may help to differentiate fibroids from malignant uterine tumors [24].

3.3. Clinical management of uterine fibroids: medical treatment or surgery?

Before the recommendation of a specific UF treatment, it is mandatory to consider and weigh the different surgical and medical treatment options available. The main symptoms of UFs are heavy menstrual bleeding (HMB) or abnormal uterine bleeding (AUB), pelvic pain and/or bulk symptoms and reproductive failure and, thus, depending on the clinical presentation, symptom severity, and the comorbidities of each patient, different options may be proposed and individualized. Current guidelines do not offer clear algorithms relying on robust clinical evidence of outcomes [25]. It is important to highlight that 50–75% of UFs are considered to be non-clinically relevant, and therefore, no medical or surgical intervention is needed [26]. For this reason, in order to avoid overtreatment, we strongly advocate expectant management in cases which are asymptomatic or with mild symptoms, after a shared decision-making approach with the patient.

Nonetheless, when UFs are surgically removed, some authors suggest that secondary prevention of UF relapse should be considered. The Evidence-Based Approach for Secondary Prevention (ESCAPE) of UF management suggests different approaches, such as setting a screening and supplementation of vitamin D, as secondary future preventive options [27,28].

3.3.1. Treatment of abnormal uterine bleeding

The most common symptom presented in patients with UFs is AUB. This is possibly due to the increased extension of the endometrial layer and to microscopic myometrial venous dilatations [29] caused by aberrant production of vascular endothelial growth factor, vascular endothelial growth factor A, endothelin-1, epidermal growth factor, and platelet-derived growth factor, which support increased angiogenesis [30], and are also identified by doppler 3D-TVUS [31]. Furthermore, hemostasis appears to be altered by a TGF-induced cascade of cytokines, causing defective endometrial decidualization, reduced hemostasis and abnormal myometrial contractions [32].

Several medical treatments are available for UF-related AUB. Considering that guidelines do not provide strong evidence comparing treatment options, physicians should individualize the treatment considering other factors beyond the UF type or appearance in imaging studies. The MEnstrual DIstress questionnaire (MEDI-Q), for instance, quantifies menstruation-related distress, and may help to identify and adequately follow the impact of UFs on well-being, [33,34].

Moreover, 79% of patients presenting AUB prefer to avoid surgery, and 51% prefer to preserve the uterus, and these preferences must be taken into account when deciding the best individualized treatment option [35]. Despite the need for tailored treatments, some recommendations and evidence regarding different treatments may guide clinicians in deciding the best option in each case [36]:

Tranexamic acid

Tranexamic acid is an antifibrinolytic treatment that has demonstrated to be effective to treat HMB in the general population. Many guidelines propose this drug as a first line non-hormonal treatment for AUB caused by UFs, despite the limited evidence on the use of tranexamic acid in the specific management of UFs [37]. Moreover, it has a favorable safety profile and is well tolerated [38].

Levonorgestrel loaded– intrauterine device

When used as an intrauterine device (IUD), progestins, such as levonorgestrel (LNG), have demonstrated to reduce HMB in patients with or without UFs by inducing endometrial decidualization and atrophy within a period of 3 months [39]. LNG is believed to inhibit the proliferation of UF cells and induce their apoptosis. However, no clinical reduction of UF growth has been demonstrated after the use of a LNG-IUD, and therefore LNG-IUD should not be recommended to treat UF symptoms other than AUB [40]. Moreover, in patients presenting UFs which distort the uterine cavity, the risk of IUD expulsion is increased and should be considered when recommending this treatment approach [41].

Selective progesterone receptor modulators

Selective progesterone receptor modulators (SPRMs) induce collagen degradation through matrix metalloproteinase 2 and an increase of the apoptotic index rate of UF cells. Accordingly, ulipristal acetate (UPA) produces a rapid and effective onset of action reducing both fibroid and uterine volume, together with a reduction of HMB, anemia and pain [42,43]. These benefits were demonstrated in two randomized clinical trials which confirmed the efficacy of UPA therapy continuously for 3 months compared with placebo or GnRH agonists [43,44]. UPA showed a decrease in UF size and total uterine bleeding in a dose-dependent manner in an up to 2-year follow-up. Uterine bleeding was controlled in more than 90% of patients receiving a 3-month course of UPA, and subsequently, relevant control in anemia was reported. Moreover, secondary effects derived from induced menopause were avoided with the use of UPA compared to a GnRH agonist [45].

Nevertheless, in the last years some reports of rare, albeit serious, liver injury have been made, and the European Medicines Agency (EMA) and other regulatory agencies have recommended to significantly limit the use of daily UPA for UF treatment [46].

Other SPRMs, such as vilaprisan, are currently under study, and the recent randomized controlled ASTEROID 3 trial showed promising results in efficacy and safety to control HMB caused by UFs [47].

Oral contraceptives

Combined oral contraceptives (COCs) are a widely accepted form of birth control, and some studies have also evaluated non-contraceptive therapeutic benefits associated with their use. The combination of estradiol valerate (E2V)/dienogest (DNG) has been accepted by the Food and Drug Administration and EMA for the treatment of HMB. This recommendation was based on double-blind, placebo-controlled randomized controlled trials showing the reduction of total bleeding by its antiproliferative effects on the endometrium. However, regarding the specific use of COCs to treat UFs, evidence is very scarce and of low quality. According to a systematic review, the real efficacy of this option remains controversial, despite some trials showing that COCs were more effective than placebo in reducing tumor size and controlling AUB [48–51].

GnRH-antagonist +/− addback

A new generation of medical treatments for UFs recently appeared in the market. Oral GnRH antagonists, such as as elagolix, relugolix and linzagolix, seem to be effective in treating AUB/HMB associated with UFs. These new drugs may be combined with an addback therapy of 1 mg estradiol and 0.5 mg norethindrone acetate once daily. When combined for addback, this combination apparently mitigates the hypoestrogenism-related side effects (such as hot flushes, increased mean serum lipid levels, and loss of bone mineral density) of the GnRH antagonists, without decreasing the benefits in efficacy. Despite having a short follow-up, results of oral GnRH antagonists treatment showed significant improvements in menstrual blood loss, with 87.9% of study participants achieving a menstrual blood loss volume of less than 80 mL per month at 12 months [52–55].

Surgery

Hysterectomy or myomectomy can be proposed among the different approaches for UF surgery. Hysterectomy is the complete excision of the uterus, an approach with clear superiority in controlling bleeding and pain compared to myomectomy (presenting increased hemoglobin levels and pain control in 70–90% of patients at 2 years of follow-up). It is recommended as a definitive treatment for HMB in patients who do not wish future childbearing and understand the risks associated with major surgery and possible future complications [56].

Myomectomy involves the resection of UFs while preserving the uterine anatomy. It may be performed by hysteroscopy or abdominally by different approaches. Hysteroscopic myomectomy is recommended as a first line treatment in FIGO 0–1 UFs and higher FIGO types in selected cases, presenting symptomatic improvement at 6–12 weeks of the procedure and very low reintervention rates at 5 years of follow-up [57]. Abdominal myomectomy improves quality of life measures in short-term and long-term follow-up. However, there is no evidence that myomectomy improves HMB after surgery [37], and symptom improvement appears to decline over time compared to hysterectomy [58,59]. Moreover, the recurrence rate of UFs excised by abdominal myomectomy approaches was 25% at 3 years of follow-up [25–60].

Alternative treatments

Nonetheless, alternatives treatments to medical or surgical options may be suitable for specific patients. Uterine artery embolization (UEA) is an effective treatment for AUB according to randomized trials showing a decrease of HMB [61,62]. UEA, as well as abdominal myomectomy, tend to present symptom recurrence, but a decreased risk of blood transfusion and shorter hospitalization is reported compared to surgery [59]. Some studies have assessed obstetric results after UEA vs. myomectomy, presenting some controversies related to an increased risk of miscarriage and preterm birth with UEA [61]. Thus, UEA may be an option for patients not suitable for surgery or with completed childbearing desire.

3.3.2. Pelvic pain and bulk symptoms

Patients presenting bulk symptoms due to UFs may often present other associated symptoms, although in these cases clinician should seek a strategy to either decrease the size or surgically remove the UFs, apart from treating the additional symptoms.

Some medical options may be useful to reduce UF size; SPRMs, such as UPA, demonstrated a reduction in UF volume, despite the EMA currently advising against this approach [45,46]. GnRH agonists have been suggested as pre-surgical treatment, due to their ability to reduce UF volume. Nevertheless, a high incidence of adverse effects related to hypoestrogenism and frequent regrowth to pretreatment levels, following 3–9 months after cessation of treatment, explain why this treatment is primarily used as a bridge therapy to surgery [37,63].

The role of the new oral GnRH antagonists is still not well defined in this field, but they may represent a future option to consider since the administration of GnRH antagonists without addback therapy seems to reduce bulk symptoms. Finally, despite UEA having demonstrated their effectivity in reducing HMB related to UFs, they do not seem to significantly improve bulk-related symptoms [61,62].

3.3.3. Reproductive failure

When evaluating treatment options for reproductive failure in UFs, the individualized impact of each UF in the uterus should be evaluated.

According to some trials, serosal UF without impact on the uterine cavity do not seem to affect *in-vitro* fertilization (IVF), however UFs affecting the JZ may impair reproductive outcomes [64,65]. Hysteroscopic excision of FIGO 0–2 UFs seems to improve pregnancy rates after IVF [66]; in fact, most guidelines recommend this practice. However, according to two Cochrane revisions, there are no strong data supporting these recommendations. Therefore, neither hysteroscopic removal of submucosal UFs nor abdominal myomectomy of any FIGO UF subtype seem to significantly improve pregnancy rates or decrease miscarriage rates [67,68]. Thus, an individualized approach is needed.

Notwithstanding, some authors have suggested that some UFs-related mechanisms may have detrimental effects on pregnancy, irrespective of whether the UF affects the uterine cavity or not [67]. These detrimental effects may be due to the production of cytokines and inflammatory mediators by UFs, altering the endometrium and myometrium through oxidative stress, impaired endometrial and myometrial blood supply, defective endometrial receptivity and gene expression. Besides, transforming growth factor beta-3 (TGF-β3) and HOXA-10 have shown to be independently related to negative obstetrical outcomes apart from the UF compression itself [69]. Hence, according to these non-bulk-related mechanisms, the option of intramural UFs also being detrimental to pregnancy outcomes has been suggested. Thus, a controversial debate to recommend to surgically remove or not intramural UF affecting the JZ (or FIGO 3) up to 3−4 cm is still ongoing [69,70]. Due to this argument, alternative approaches to intramural UFs distorting the uterine cavity or larger than 3 cm have being considered, such as the use of GnRH agonists or antagonists, as well as reducing volume therapy with the aim of shrinking intramural UFs and normalizing the JZ. If restoration of the uterine cavity is achieved, an immediate IVF is recommended; on the other hand, if uterine cavity distortion persists, surgery might be proposed [71,72].

Given these circumstances, the benefits and risks of myomectomy should be individualized when treating women for reproductive failure and should consider the individual surgical risks, and the further increased risk of cesarian section adherences and other potential risks after uterine surgical interventions.

3.4. Management of special situations

Apart from managing the most common symptoms of UF, we should be aware of special clinical situations that may complicate patient management.

3.4.1. Coexistence of endometriosis and adenomyosis with fibroids

Endometriosis and adenomyosis are two entities that share common symptoms with UFs, such as dysmenorrhea and pain, and may hinder their diagnosis and management. Moreover, endometriosis and adenomyosis have also been linked to decreased pregnancy rates, and thus, coexistence with UFs may represent a therapeutic challenge [73].

Notwithstanding, despite endometriosis and UF both being estrogen-dependent diseases, they present a completely different response to progesterone: endometriosis is characterized by progesterone resistance, whereas UFs grow under the influence of progesterone [74,75].

According to some studies, endometriosis and adenomyosis are often associated, and in spite of being two differentiated entities, they may share common pathophysiologic origins and symptoms. On the other hand, the molecular pathways of UFs seem to be completely different, and thus, the therapeutic approach should point to different targets [76]. Regardless of these different molecular pathways, some authors have found an association between the presence of endometriosis and adenomyosis and UFs. Lin et al. showed that patients presenting UFs have a 6-fold higher risk of presenting endometriosis compared to controls [77]. Conversely, having endometriosis doubles the risk of having UFs [78]. According to genetic metanalysis data, these associations may be due to a possible common genetic origin, relating genetic alterations of UFs to endometriosis, despite presenting different molecular pathways [79].

Surprisingly, in some studies assessing the comorbidities of endometriosis patients undergoing IVF, TVUS findings showed a prevalence of only 3% of UFs in these patients, and these were mostly intramural and subserous [80].

There are still limited data on the association between UFs and endometriosis-adenomyosis, but some links appear to be present and thus, clinicians must be aware of possible relationships in order to assess and discard the presence of concomitant endometriosis and adenomyosis when UFs are diagnosed [81]. Information regarding the presence of concomitant lesions may be critical to individualize therapeutic approaches since they may increase the risk of adverse obstetric outcomes and hinder surgical interventions of UFs.

3.4.2. Management of perimenopausal women

The incidence of UFs is higher in the last decade of reproductive life (40–50 years). Along the same time period, the decrease in oocyte quality

impairs the quality of ovarian cycles with shorter luteal phases or anovulation. These dysovulations are an independent cause of AUB and establish a negative synergy to increase the severity of UF-induced AUB [32]. Since menopause leads to the resolution of both UF growth and menstrual bleeding [82,83], treatment of UFs in perimenopause should individually consider the balance between the advantages and risks of medical treatment and the probability of oncoming menopause in order to carry out therapeutic counseling according to guideline recommendations and patient wishes [84].

At the present time, medical treatment of UFs is warranted in women approaching menopause. It is reasonable to consider a sequential strategy with a short-lasting first step aimed at reducing tumor size and hematological recovery with GnRH analogs alone, followed by more extended treatment with any of the other medical alternatives (GnRH antagonists + addback, LNG-IUD, oral contraceptives) until menopause.

3.5. Future prespectives

New medical options are transforming the therapeutic approach to UFs. Thanks to better knowledge of the pathogenesis underlying the formation and growth of UFs, targeted drugs are already available to treat this condition. However, there are future pathogenetic research prospects studying other potential therapeutic endpoints, such as epigenome and epitranscriptomics, and the impact of miRNA present in exosomes excreted from UFs that appears to be increased in cases of AUB [35,85].

On the other hand, not only molecular targets are being assessed, but artificial intelligence is being evaluated for use as a complementary diagnostic tool, presenting an average accuracy of 90% and possibly being a helpful instrument in the near future for not only the diagnosis of UFs but also the prediction of response to treatments [86,87].

5. Conclusions

Emerging treatment alternatives are becoming available for managing the primary symptoms of uterine fibroids, offering physicians a plethora of tools to enhance both the quality of life and fertility prospects of patients. While international and national guidelines provide valuable frameworks for decision-making, the diverse nature of UFs means that robust data supporting these guidelines are lacking. Consequently, a tailored approach must weigh medical and surgical interventions, prioritizing personalized treatment with in-depth consideration of innovative long-term medical alternatives, potentially comparable to surgery in mitigating UF-related symptoms.

Author contributions

E. Mension: Investigation, Methodology, Writing – original draft, Writing – review & editing.

J. Calaf: Conceptualization, Resources, Visualization, Validation, Writing – review & editing.

C. Chapron: Conceptualization, Resources, Visualization, Validation, Writing – review & editing.

M.M. Dolmans: Conceptualization, Project administration, Resources, Visualization, Validation, Writing – review & editing.

J. Donnez: Conceptualization, Project administration, Resources, Visualization, Validation, Writing – review & editing.

L. Marcellin: Conceptualization, Resources, Visualization, Validation, Writing – review & editing.

F. Petraglia: Resources, Visualization, Validation, Writing – review & editing.

S. Vannuccini: Conceptualization, Resources, Visualization, Validation, Writing – review & editing.

F. Carmona: Conceptualization, Resources, Supervision, Visualization, Validation, Writing – review & editing.

Funding

The authors declared that no grants were involved in supporting this work.

Authors' roles

All authors contributed in the bibliographic search, data analysis, data interpretation and study writing.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgments

The present manuscript reports the discussion made at the Society of Endometriosis and Uterine Disorders (SEUD) Forum held in October 2023 (Sevilla, Spain). We would like to express our gratitude to the SEUD team participating in this review.

References

[1] Catherino WH, Parrott E, Segars J. Proceedings from the national institute of child health and human development conference on the uterine fibroid research update workshop. Fertil Steril 2011;95(1):9–12.
[2] Cardozo ER, Clark AD, Banks NK, Henne MB, Stegmann BJ, Segars JH. The estimated annual cost of uterine leiomyomata in the United States. Am J Obstet Gynecol. 2012;206(3):211.e1-9.
[3] Yang Q, Ciebiera M, Bariani MV, Ali M, Elkafas H, Boyer TG, et al. Comprehensive review of uterine fibroids: developmental origin, pathogenesis, and treatment. Endocr Rev. 2022;43(4):678–719.
[4] Pavone D, Clemenza S, Sorbi F, Fambrini M, Petraglia F. Epidemiology and risk factors of uterine fibroids. Best Pract Res Clin Obstet Gynaecol. 2018;46:3–11.
[5] Styer AK, Rueda BR. The epidemiology and genetics of uterine leiomyoma. Best Pract Res Clin Obstet Gynaecol. 2016;34:3–12.
[6] Tomlinson IP, Alam NA, Rowan AJ, et al. Multiple Leiomyoma Consortium. Germline mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer. Nat Genet. 2002;30(4):406–10.
[7] Tomlinson IP, Alam NA, Rowan AJ, Barclay E, Jaeger EE, Kelsell D, et al. MED12, the mediator complex subunit 12 gene, is mutated at high frequency in uterine leiomyomas. Science. 2011;334(6053):252–5.
[8] Heinonen HR, Sarvilinna NS, Sjöberg J, Kämpjärvi K, Pitkänen E, Vahteristo P, et al. MED12 mutation frequency in unselected sporadic uterine leiomyomas. Fertil Steril. 2014;102(4):1137–42.
[9] Navarro A, Yin P, Monsivais D, et al. Genome-wide DNA methylation indicates silencing of tumor suppressor genes in uterine leiomyoma. PLoS One. 2012;7(3): e33284.
[10] Navarro A, Yin P, Monsivais D, Lin SM, Du P, Wei JJ, et al. DNA hypomethylation and imbalanced expression of DNA methyltransferases (DNMT1, 3A, and 3B) in human uterine leiomyoma. Gynecol Oncol. 2003;90(1):123–30.
[11] Ishikawa H, Ishi K, Serna VA, Kakazu R, Bulun SE, Kurita T. Progesterone is essential for maintenance and growth of uterine leiomyoma. Endocrinology. 2010;151 (6):2433–42.
[12] Bulun SE, Moravek MB, Yin P, Ono M, Coon 5th JS, Dyson MT, et al. Uterine leiomyoma stem cells: linking progesterone to growth. Semin Reprod Med. 2015;33 (5):357–65.
[13] Bulun SE. Uterine fibroids. N Engl J Med. 2013;369(14):1344–55.
[14] Yang Q, Ciebiera M, Bariani MV, Ali M, Elkafas H, Boyer TG, et al. Comprehensive review of uterine fibroids: developmental origin, pathogenesis, and treatment. Endocr Rev. 2022;43(4):678–719.
[15] Munro MG, Critchley HO, Broder MS, Fraser IS. FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet. 2011;113 (1):3–13.
[16] Laughlin-Tommaso SK, Hesley GK, Hopkins MR, Brandt KR, Zhu Y, Stewart EA. Clinical limitations of the International Federation of Gynecology and Obstetrics (FIGO) classification of uterine fibroids. Int J Gynaecol Obstet. 2017;139(2):143–8.
[17] Van den Bosch T, Dueholm M, Leone FP, Valentin L, Rasmussen CK, Votino A, et al. Terms, definitions and measurements to describe Sonographic features of myometrium and uterine masses: a consensus opinion from the Morphological Uterus Sonographic Assessment (MUSA) group. Ultrasound Obstet Gynecol. 2015;46(3):284–98.
[18] Lasmar RB, Xinmei Z, Indman PD, Celeste RK, Di Spiezio Sardo A. Feasibility of a new system of classification of submucous myomas: a multicenter study. Fertil Steril. 2011;95(6):2073–7.
[19] Nieuwenhuis LL, Keizer AL, Stoelinga B, Twisk J, Hehenkamp W, Brölmann H, et al. Fibroid vascularisation assessed with three-dimensional power Doppler ultrasound is

a predictor for uterine fibroid growth: a prospective cohort study. BJOG. 2018;125 (5):577–84.
[20] Dueholm M, Lundorf E, Hansen ES, Ledertoug S, Olesen F. Accuracy of magnetic resonance imaging and transvaginal ultrasonography in the diagnosis, mapping, and measurement of uterine myomas. Am J Obstet Gynecol. 2002;186(3):409–15.
[21] Raffone A, Raimondo D, Neola D, Travaglino A, Giorgi M, Lazzeri L, et al. Diagnostic accuracy of MRI in the differential diagnosis between uterine leiomyomas and sarcomas: a systematic review and meta-analysis. Int J Gynaecol Obstet. 2023.
[22] Bittencourt CA, Dos Santos Simões R, Bernardo WM, Fuchs LFP, Soares Júnior JM, Pastore AR, et al. Accuracy of saline contrast sonohysterography in detection of endometrial polyps and submucosal leiomyomas in women of reproductive age with abnormal uterine bleeding: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2017;50(1):32–9.
[23] Stoelinga B, Hehenkamp WJ, Brölmann HA, Huirne JA. Real-time elastography for assessment of uterine disorders. Ultrasound Obstet Gynecol. 2014;43(2):218–26.
[24] Stoelinga B, Juffermans L, Dooper A, de Lange M, Hehenkamp W, Van den Bosch T, et al. Contrast-enhanced ultrasound imaging of uterine disorders: a systematic review. Ultrason Imaging. 2021;43(5):239–52.
[25] Management of Symptomatic Uterine Leiomyomas: ACOG Practice Bulletin, Number 228. Obstet Gynecol. 2021;137(6):e100–15.
[26] Stewart EA, Cookson CL, Gandolfo RA, Schulze-Rath R. Epidemiology of uterine fibroids: a systematic review. BJOG 2017;124:1501–12.
[27] Ali M, Bariani MV, Vafaei S, Omran MM, Yang Q, Madueke-Laveaux OS, et al. Prevention of Uterine Fibroids: molecular mechanisms and potential clinical application. J Endometr Uterine Disord. 2023;1:100018.
[28] Vafaei S, Ciebiera M, Omran MM, Ghasroldasht MM, Yang Q, Leake T, et al. Evidence-based approach for secondary prevention of uterine fibroids (The ESCAPE Approach). Int J Mol Sci. 2023;24(21):15972.
[29] Bereza T, Lis G, Mitus J, Sporek M, Chmielewski P, Kolber W, et al. Blood vessels of the intratumoral septa in uterine leiomyomata. Folia Med Cracov. 2013;53(2):99–106.
[30] Don EE, Middelkoop MA, Hehenkamp WJK, Mijatovic V, Griffioen AW, Huirne JAF. Endometrial angiogenesis of abnormal uterine bleeding and infertility in patients with uterine fibroids-A systematic review. Int J Mol Sci. 2023;24(8):7011.
[31] Keizer AL, Niewenhuis LL, Hehenkamp WJK, Twisk JWR, Brölmann HAM, Huirne JAF. Fibroid vascularisation assessed with 3D Power Doppler as predictor for fibroid related symptoms and quality of life; a pilot study. Facts Views Vis Obgyn. 2021;13(4):387–94.
[32] Vannuccini S, Jain V, Critchley H, Petraglia F. From menarche to menopause, heavy menstrual bleeding is the underrated compass in reproductive health. Fertil Steril. 2022;118(4):625–36.
[33] Vannuccini S, Rossi E, Cassioli E, Cirone D, Castellini G, Ricca V, et al. Menstrual Distress Questionnaire (MEDI-Q): a new tool to assess menstruation-related distress. Reprod Biomed Online. 2021;43(6):1107–16.
[34] Vannuccini S, Clemenza S, Cassioli E, Rossi E, Castellini G, Ricca V, et al. Uterine fibroids, perceived stress, and menstrual distress: a key role of heavy menstrual bleeding. Reprod Sci. 2023;30(5):1608–15.
[35] Stewart EA, Laughlin-Tommaso SK, Catherino WH, Lalitkumar S, Gupta D, Vollenhoven B. Uterine fibroids. Nat Rev Dis Primers. 2016;2:16043.
[36] Bofill Rodriguez M, Dias S, Jordan V, Lethaby A, Lensen SF, Wise MR. Interventions for heavy menstrual bleeding; overview of Cochrane reviews and network meta-analysis. Cochrane Database Syst Rev. 2022;5(5):CD013180.
[37] Hartmann KE, Fonnesbeck C, Surawicz T, Krishnaswami S, Andrews JC, Wilson JE, et al. Management of uterine fibroids. Comparative Effectiveness Review No. 195. Rockville, MD: Agency for Healthcare Research and Quality; 2017.
[38] Eder S, Baker J, Gersten J, Mabey RG, Adomako TL. Efficacy and safety of oral tranexamic acid in women with heavy menstrual bleeding and fibroids. Womens Health (Lond). 2013;9(4):397–403.
[39] Grigorieva V, Chen-Mok M, Tarasova M, Mikhailov A. Use of a levonorgestrel-releasing intrauterine system to treat bleeding related to uterine leiomyomas. Fertil Steril 2003;79:1194–8.
[40] Sangkomkamhang US, Lumbiganon P, Pattanittum P. Progestogens or progestogen-releasing intrauterine systems for uterine fibroids (other than preoperative medical therapy). Cochrane Database Syst Rev. 2020;11(11):CD008994.
[41] Zapata LB, Whiteman MK, Tepper NK, Jamieson DJ, Marchbanks PA, Curtis KM. Intrauterine device use among women with uterine fibroids: a systematic review. Contraception 2010;82:41–55.
[42] Courtoy GE, Donnez J, Marbaix E, Dolmans MM. In vivo mechanisms of uterine myoma volume reduction with ulipristal acetate treatment. Fertil Steril 2015;104:426e34.
[43] Donnez J, Vázquez F, Tomaszewski J, Nouri K, Bouchard P, Fauser B.C., et al. PEARL III and PEARL III Extension Study Group. Long-term treatment of uterine fibroids with ulipristal acetate. Fertil Steril. 2014101(6) 1565-73.e1-18.
[44] Donnez J, Tomaszewski J, Vázquez F, Bouchard P, Lemieszczuk B, Baró F, et al. PEARL II Study Group. Ulipristal acetate versus leuprolide acetate for uterine fibroids. N Engl J Med. 2012;366(5):421–32.
[45] Barlow DH, Lumsden MA, Fauser BC, Terrill P, Bestel E. Individualized vaginal bleeding experience of women with uterine fibroids in the PEARL I randomized controlled trial comparing the effects of ulipristal acetate or placebo. Hum Reprod. 2014;29:480–9.
[46] Murji A, Whitaker L, Chow TL, Sobel ML. Selective progesterone receptor modulators (SPRMs) for uterine fibroids. Cochrane Database Syst Rev 2017 Issue 4. Art. No.: CD010770.
[47] Al-Hendy A, Zhou YF, Faustmann T, Groettrup-Wolfers E, Laapas K, Parke S, et al. Efficacy and safety of vilaprisan in women with uterine fibroids: data from the ASTEROID 3 randomized controlled trial. F S Sci. 2023;4(4):317–26.
[48] Nappi RE, Serrani M, Jensen JT. Noncontraceptive benefits of the estradiol valerate/dienogest combined oral contraceptive: a review of the literature. Int J Womens Health. 2014;6:711–8.
[49] Fraser IS, Römer T, Parke S, Zeun S, Mellinger U, Machlitt A, et al. Effective treatment of heavy and/or prolonged menstrual bleeding with an oral contraceptive containing estradiol valerate and dienogest: a randomized, double-blind Phase III trial. Hum Reprod. 2011;26(10):2698–708.
[50] Jensen JT, Parke S, Mellinger U, Machlitt A, Fraser IS. Effective treatment of heavy menstrual bleeding with estradiol valerate and dienogest: a randomized controlled trial. Obstet Gynecol. 2011;117(4):777–87.
[51] Moroni RM, Martins WP, Dias SV, Vieira CS, Ferriani RA, Nastri CO, et al. Combined oral contraceptive for treatment of women with uterine fibroids and abnormal uterine bleeding: a systematic review. Gynecol Obstet Invest. 2015;79(3):145–52.
[52] Donnez J, Taylor HS, Stewart EA, Bradley L, Marsh E, Archer D, et al. Linzagolix with and without hormonal add-back therapy for the treatment of symptomatic uterine fibroids: two randomised, placebo-controlled, phase 3 trials. Lancet. 2022;400 (10356):896–907.
[53] Al-Hendy A, Lukes AS, Poindexter 3rd AN, Venturella R, Villarroel C, Critchley HOD, et al. Treatment of uterine fibroid symptoms with relugolix combination therapy. N Engl J Med. 2021;384(7):630–42.
[54] Schlaff WD, Ackerman RT, Al-Hendy A, Archer DF, Barnhart KT, Bradley LD, et al. Elagolix for heavy menstrual bleeding in women with uterine fibroids. N Engl J Med. 2020;382(4):328–40.
[55] Simon JA, Al-Hendy A, Archer DF, Barnhart KT, Bradley LD, Carr BR, et al. Elagolix treatment for up to 12 months in women with heavy menstrual bleeding and uterine leiomyomas. Obstet Gynecol 2020;135:1313–26 Med 2020;382:328–340.
[56] Madueke-Laveaux OS, Elsharoud A, Al-Hendy A. What we know about the long-term risks of hysterectomy for Benign Indication-A Systematic Review. J Clin Med. 2021;10 (22):5335.
[57] Laughlin-Tommaso SK, Lu D, Thomas L, Diamond MP, Wallace K, Wegienka G, et al. Short-term quality of life after myomectomy for uterine Fibroids from the COMPARE-UF Fibroid Registry. Am J Obstet Gynecol 2020;222:345 e1–22.
[58] Wallace K, Zhang S, Thomas L, Stewart EA, Nicholson WK, Wegienka GR, et al. Comparative effectiveness of hysterectomy versus myomectomy on one year health-related quality of life in women with uterine fibroids. Fertil Steril 2020;113:618–26.
[59] Anchan RM, Spies JB, Zhang S, Wojdyla D, Bortoletto P, Terry K, et al. Long-term health-related quality of life and symptom severity following hysterectomy, myomectomy, or uterine artery embolization for the treatment of symptomatic uterine fibroids. Am J Obstet Gynecol 2023;229(3):275.e1–275.e17.
[60] Capezzuoli T, Aslan B, Vannuccini S, Orlandi G, La Torre F, Sorbi F, et al. Recurrence of uterine fibroids after conservative surgery or radiological procedures: a narrative review. Reprod Sci. 2023.
[61] Moss JG, Cooper KG, Khaund A, Murray LS, Murray GD, Wu O, et al. Randomised comparison of uterine artery embolisation (UAE) with surgical treatment in patients with symptomatic uterine fibroids (REST trial): 5-year results. BJOG 2011;118:936–44.
[62] de Bruijn AM, Ankum WM, Reekers JA, Birnie E, van der Kooij SM, Volkers NA, et al. Uterine artery embolization vs hysterectomy in the treatment of symptomatic uterine fibroids: 10-year outcomes from the randomized EMMY trial. Am J Obstet Gynecol 2016;215:745.e1–745.e12.
[63] Kamath MS, Kalampokas EE, Kalampokas TE. Use of GnRH analogues pre-operatively for hysteroscopic resection of submucous fibroids: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2014;177:11–8.
[64] Somigliana E, Reschini M, Bonanni V, Busnelli A, Li Piani L, Vercellini P. Fibroids and natural fertility: a systematic review and meta-analysis. Reprod Biomed Online. 2021;43(1):100–10.
[65] Bai X, Lin Y, Chen Y, Ma C. The impact of FIGO type 3 fibroids on in-vitro fertilization outcomes: a nested retrospective case-control study. Eur J Obstet Gynecol Reprod Biol. 2020;247:176–80.
[66] Pritts EA, Parker WH, Olive DL. Fibroids and infertility: an updated systematic review of the evidence. Fertil Steril 2009;91(4):1215–23.
[67] Bosteels J, van Wessel S, Weyers S, Broekmans FJ, D'Hooghe TM, Bongers MY, et al. Hysteroscopy for treating subfertility associated with suspected major uterine cavity abnormalities. Cochrane Database Syst Rev. 2018;12(12):CD009461.
[68] Metwally M, Raybould G, Cheong YC, Horne AW. Surgical treatment of fibroids for subfertility. Cochrane Database Syst Rev. 2020;1(1):CD003857.
[69] Dolmans MM, Isaacson K, Zhang W, Gordts S, Munro MG, Stewart EA, et al. Intramural myomas more than 3-4 centimeters should be surgically removed before in vitro fertilization. Fertil Steril. 2021;116(4):945–58.
[70] Sunkara SK, Khairy M, El-Toukhy T, Khalaf Y, Coomarasamy A. The effect of intramural fibroids without uterine cavity involvement on the outcome of IVF treatment: a systematic review and meta-analysis. Hum Reprod. 2010;25(2):418–29.
[71] Donnez J. Intramural myomas-related infertility: should the myomas be removed? Not easy to reach a consensus. Fertil Steril. 2021;116(4):943–4.
[72] Luyckx M, Squifflet JL, Jadoul P, Votino R, Dolmans MM, Donnez J. First series of 18 pregnancies after ulipristal acetate treatment for uterine fibroids. Fertil Steril. 2014;102(5):1404–9.
[73] Horton J, Sterrenburg M, Lane S, Maheshwari A, Li TC, Cheong Y. Reproductive, obstetric, and perinatal outcomes of women with adenomyosis and endometriosis: a systematic review and meta-analysis. Hum Reprod Update. 2019;25(5):592–632.
[74] Donnez J, Dolmans MM. Uterine fibroid management: from the present to the future. Hum Reprod Update 2016;22(6):665–86.
[75] Bourdon M, Santulli P, Bordonne C, et al. Presence of adenomyosis at MRI reduces live birth rates in ART cycles for endometriosis. Hum Reprod. 2022;37(7):1470–9.

[76] Bourdon M, Santulli P, Bordonne C, Millisher AE, Maitrot-Mantelet L, Maignien C, et al. Focal adenomyosis of the outer myometrium and deep infiltrating endometriosis severity. Fertil Steril. 2020;114(4):818–27.
[77] Lin KY, Yang CY, Lam A, Chang CY, Lin WC. Uterine leiomyoma is associated with the risk of developing endometriosis: a nationwide cohort study involving 156,195 women. PLoS One. 2021;16(8):e0256772.
[78] McGrath IM, Montgomery GW, Mortlock S. Insights from Mendelian randomization and genetic correlation analyses into the relationship between endometriosis and its comorbidities. Hum Reprod Update. 2023;29(5):655–74.
[79] Gallagher CS, Mäkinen N, Harris HR, Rahmioglu N, Uimari O, Cook JP, et al. Genome-wide association and epidemiological analyses reveal common genetic origins between uterine leiomyomata and endometriosis. Nat Commun. 2019;10(1):4857.
[80] Capezzuoli T, Vannuccini S, Fantappiè G, Orlandi G, Rizzello F, Coccia ME, et al. Ultrasound findings in infertile women with endometriosis: evidence of concomitant uterine disorders. Gynecol Endocrinol. 2020;36(9):808–12.
[81] Chapron C, Vannuccini S, Santulli P, Abrão MS, Carmona F, Fraser IS, et al. Diagnosing adenomyosis: an integrated clinical and imaging approach. Hum Reprod Update. 2020;26(3):392–411.
[82] Hale GE, Manconi F, Luscombe G, Fraser IS. Quantitative measurements of menstrual blood loss in ovulatory and anovulatory cycles in middle- and late-reproductive age and the menopausal transition. Obstet Gynecol. 2010;115(2 Pt 1):249–56.
[83] Fuldeore MJ, Soliman AM. Patient-reported prevalence and symptomatic burden of uterine fibroids among women in the United States: findings from a cross-sectional survey analysis. Int J Womens Health. 2017;9:403–11.
[84] Treloar AE, Boynton RE, Behn BG, Brown BW. Variation of the human menstrual cycle through reproductive life. Int J Fertil. 1967;12(1 Pt 2):77–126.
[85] Ali M, Bariani MV, Vafaei S, Omran MM, Yang Q, Madueke-Laveaux OS, et al. Prevention of Uterine Fibroids: molecular mechanisms and potential clinical application. J Endometr Uterine Disord. 2023;1:100018.
[86] Shahzad A, Mushtaq A, Sabeeh AQ, Ghadi YY, Mushtaq Z, Arif S, et al. Automated uterine fibroids detection in ultrasound images using deep convolutional neural networks. Healthcare (Basel). 2023;11(10):1493.
[87] Chen M, Kong W, Li B, Tian Z, Yin C, Zhang M, et al. Revolutionizing hysteroscopy outcomes: AI-powered uterine myoma diagnosis algorithm shortens operation time and reduces blood loss. Front Oncol. 2023;13:1325179.

Francisco Carmona is the Chief of Gynecology at Hospital Clínic in Barcelona and Director of its Endometriosis Unit. Full Professor at the University of Barcelona; he has published over 170 peer-reviewed articles; his total IF is above 800 with an h index of 36. He's author of more than 65 book chapters and 8 complete books; reviewer for nearly 30 scientific journals; serves as Editor in Chief of Clínica e Investigación en Ginecología y Obstetricia. He has been involved in 279 courses or congresses, delivering more than 300 lectures. He's a Founding Member and current President of the Society for Endometriosis and Uterine Disorders and the Spanish Society for the Study of Myomas and Endometriosis.