

The modern management of uterine fibroids-related abnormal uterine bleeding

Silvia Vannuccini, M.D., Ph.D.,^a Felice Petraglia, M.D.,^a Francisco Carmona, M.D., Ph.D.,^b Joaquim Calaf, Ph.D.,^c and Charles Chapron, M.D., Ph.D.^d

^a Division of Obstetrics and Gynecology, Department of Experimental, Clinical, and Biomedical Sciences, University of Florence, Careggi University Hospital, Florence, Italy; ^b Department of Obstetrics and Gynecology, Hospital Clínic of Barcelona, Barcelona, Spain; ^c Hospital Sant Pau, Autonomous University of Barcelona, Barcelona, Spain; ^d Département de Gynécologie, Obstétrique et Médecine de la Reproduction, Faculté de Santé, Faculté de Médecine Paris Centre, Centre Hospitalier Universitaire (CHU), Université Paris-Cité, Paris, France

Uterine fibroids (UFs) are the most common female benign pelvic tumors, affecting >60% of patients aged 30–44 years. Uterine fibroids are asymptomatic in a large percentage of cases and may be identified incidentally using a transvaginal ultrasound or a magnetic resonance imaging scan. However, in approximately 30% of cases, UFs affect the quality of life and women's health, with abnormal uterine bleeding and heavy menstrual bleeding being the most common complaints, along with iron deficiency (ID) and ID anemia. Medical treatments used for UFs-related abnormal uterine bleeding include symptomatic agents, such as nonsteroidal antiinflammatory drugs and tranexamic acid, and hormonal therapies, including combined oral contraceptives, gonadotropin-releasing hormone agonists or antagonists, levonorgestrel intrauterine systems, selective progesterone receptor modulators, and aromatase inhibitors. Nevertheless, few drugs are approved specifically for UF treatment, and most of them manage the symptoms. Surgical options include fertility-sparing treatments, such as myomectomy, or nonconservative options, such as hysterectomy, especially in perimenopausal women who are not responding to any treatment. Radiologic interventions are also available: uterine artery embolization, high-intensity focused ultrasound or magnetic resonance-guided focused ultrasound, and radiofrequency ablation. Furthermore, the management of ID and ID anemia, as a consequence of acute and chronic bleeding, should be taken into account with the use of iron replacement therapy both during medical treatment and before and after a surgical procedure. In the case of symptomatic UFs, the location, size, multiple UFs, or coexistent adenomyosis should guide the choice with a shared decision-making process, considering long- and short-term treatment goals expected by the patient, including pregnancy desire or wish to preserve the uterus independently of reproductive goals. (Fertil Steril® 2024;122:20–30. ©2024 by American Society for Reproductive Medicine.)

Key Words: Abnormal uterine bleeding, GnRH agonists, heavy menstrual bleeding, iron deficiency anemia, myomectomy, oral GnRH antagonists, uterine fibroids

Uterine fibroids (UFs) are the most common benign tumors in women all over the world, affecting up to 70% of women of reproductive age (1–3). Approximately 30% of UFs are incidentally diagnosed at the time of a routine pelvic examination or screening for another medical condition. Uterine fibroids are heterogeneous in size, number, location, and clinical presentation (4). The most common symptoms include abnormal uterine bleeding (AUB),

heavy menstrual bleeding (HMB), pelvic pain, bulky symptoms, and infertility, which affect patients' quality of life (QoL). Abnormal uterine bleeding that is caused by UFs is classified by the International Federation of Gynecology and Obstetrics (FIGO) as AUB leiomyoma (AUB-L) (5). Heavy menstrual bleeding is recognized as a subcategory of AUB that interferes with women's physical, social, emotional, or material QoL (6). Among symptoms caused by UFs,

AUB and HMB are the most impairing both from a woman's health and health care system perspectives (7–10). Symptomatic UFs with HMB as the main complaint were associated with significantly higher direct health care costs compared with UF or HMB alone (9). In fact, UFs remain the most common diagnosis among inpatient hospitalizations for gynecologic conditions in reproductive-age women, representing approximately 30% of hysterectomies (11, 12). Uterine fibroids are the cause of bleeding in almost half of women discharged from the hospital for acute episodes of bleeding and anemia in the context of AUB (13). Furthermore, AUB and HMB are relevant causes of iron deficiency (ID) and ID anemia (IDA), often overlooked conditions (14, 15), which in

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Correspondence: Silvia Vannuccini, M.D., Ph.D., Division of Obstetrics and Gynecology, Department of Experimental, Clinical, and Biomedical Sciences, University of Florence, Careggi University Hospital, Largo Brambilla, 50134, Florence, Italy (E-mail: silvia.vannuccini@unifi.it).

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turn determine a variety of nonspecific symptoms affecting both mental and physical health (16). Besides, on the background of UFs, HMB is the major determinant of perceived stress and menstrual distress, showing how the presence of this symptom has detrimental effects on QoL and a variety of domains in daily life (17, 18).

The magnitude of the effect caused by UFs-related AUB and HMB, both in terms of QoL impairment and health care costs for surgical intervention, explains the importance of adequate management of these symptoms (9). A balance of the different surgical, medical, or radiologic treatment options should be discussed with the patient, depending on the presentation of symptoms, their severity, UF number, size, and localization, and the clinical context, including the desire for pregnancy or to preserve the uterus independently of reproductive goals. Moreover, 79% of patients presenting with AUB or HMB prefer to avoid surgery, and 51% desire to preserve the uterus (19), facts that must be considered to decide the best-individualized treatment option. Over the past 2 decades, a shift toward more conservative interventions has been observed, thanks to newly available medical treatments that may help also before or after-surgical treatment (20, 21). Finally, a shared decision-making process should be used in treatment selection, considering expected long- and short-term treatment goals from the perspective of a patient-centered rather than fibroid-centered approach. Thus, the aim of the present review was to summarize the available evidence on medical, radiologic, and surgical options to treat UFs, focusing on their efficacy on AUB and HMB along with ID and IDA management.

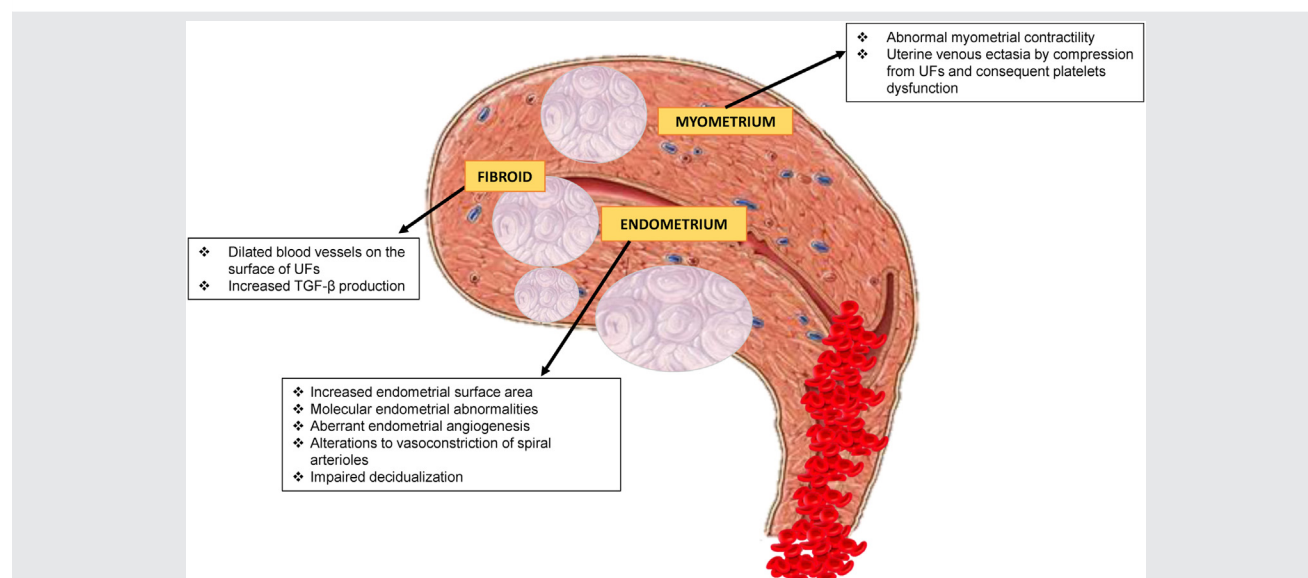
MECHANISMS OF AUB AND HMB IN UFS

Several theories have been proposed in the literature to establish a connection between UFs, AUB, and HMB. In fact, there is a lack of knowledge about the pathophysiology involved in AUB in the presence of structural conditions such as UFs or adenomyosis. It is debatable whether the excessive bleeding is a consequence of the presence of UFs or is caused by preexisting abnormalities in the endometrium, for instance, a “secondary endometrial disorder” (15, 22). The presence of UFs causes alterations in the endometrial vascular architecture and function, contributing to the production of angiogenic factors that support increased angiogenesis (23), such as vascular endothelial growth factor, platelet-derived growth factor, and endothelin-1. The increase in the surface area of the endometrium and the size of the uterine cavity, the presence of dilated blood vessels on the surface of UFs, the uterine venous ectasia caused by pressure from the fibroid, and the impaired myometrial contractility are additional factors to explain AUB and HMB when UFs are present (21). The aberrant angiogenesis, potentially involving disturbed vessel maturation, results in immature and fragile vessels (24). Furthermore, hemostasis appears to be disturbed because of platelet dysfunction compensated by increased vascular flow in engorged vessels, and an increase in the secretion of transforming growth factor β -3, all of which cause defective endometrial decidualization (25) (Fig. 1).

MEDICAL TREATMENT

Medical therapy is usually the first-line approach for UFs-related AUB and/or HMB (26). Medical options commonly

FIGURE 1



Mechanisms of AUB and HMB in uterine fibroids (UFs). AUB = abnormal uterine bleeding; HMB = heavy menstrual bleeding; TGF- β = Transforming Growth Factor-beta.

Vannuccini. Management of AUB in uterine fibroids. *Fertil Steril* 2024.

used to manage the bleeding are nonhormonal drugs (nonsteroidal antiinflammatory drugs [NSAIDs] and tranexamic acid), or hormonal drugs (combined oral contraceptives [COCs], levonorgestrel intrauterine systems, gonadotropin-releasing hormone [GnRH] agonists or oral antagonists, progesterone receptor [PR] modulators, or aromatase inhibitors [AI]) (27). No evidence of the superiority of one compound compared with another has been demonstrated, although some drugs entail more benefits and are more targeted for AUB and HMB management. Besides, most of the agents target the endometrium rather than directly the fibroid, resulting in a decrease in menstrual blood flow (Fig. 2).

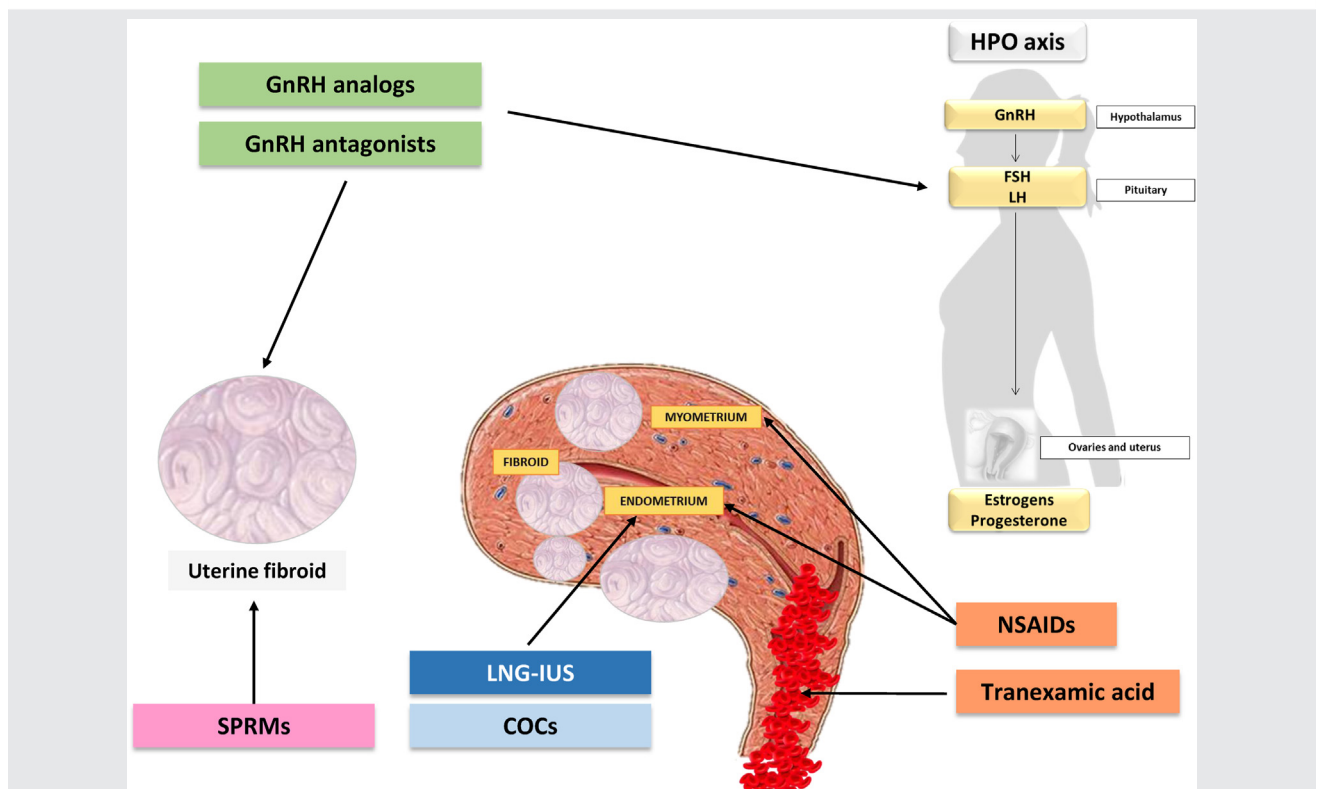
Over the last few years, some evidence has shown the potential role of vitamins and supplements, namely vitamin D and epigallocatechin gallate, in the treatment of UFs (28, 29). Animal studies, and more recently, human studies, showed that vitamin D administration may inhibit fibroid growth (30, 31). Regarding the management of HMB, green tea extract potentially decreases the menstrual flow (32, 33), although further studies are needed to make specific recommendations on that topic.

Nonhormonal treatments

Nonsteroidal antiinflammatory drugs. The NSAIDs act by inhibiting cyclooxygenase, thus reducing prostaglandin synthesis at the endometrial level, decreasing both menstrual bleeding and dysmenorrhea (26). Although NSAIDs are effective in reducing HMB compared with a placebo, they are less effective than tranexamic acid (34). Furthermore, limited data are available specifically on the efficacy of UFs-related HMB. However, NSAIDs are often used as a first option for patients who do not wish to undergo hormonal treatment.

Tranexamic acid. Tranexamic acid inhibits fibrinolysis by reversibly blocking plasminogen and is available in oral or intravenous formulations. It is effective in reducing menstrual blood loss by 26%–50%, surpassing the efficacy of NSAIDs alone (35). It can be used independently or in conjunction with an NSAID during days 1–5 of menstruation (36). Tranexamic acid is generally well tolerated, and there is no evidence suggesting an increased risk of thromboembolic events, even in patients at high risk (37). It represents an effective treatment for HMB (38, 39), both in acute and

FIGURE 2



Targets of medical treatment for uterine fibroids (UFs)-related heavy menstrual bleeding. Gonadotropin-releasing hormone (GnRH) agonists and antagonists act on GnRH pituitary receptors, reducing follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and consequently estrogens and progesterone, with a direct effect also on the UFs. Combined oral contraceptives (COCs) and levonorgestrel intrauterine system (LNG-IUS) act mainly on the endometrium. Selective progesterone receptor modulators (SPRMs) act on UFs, along with endometrium. Nonsteroidal antiinflammatory drugs (NSAIDs) act at the endometrial and myometrial levels, reducing bleeding by nonhormonal mechanisms. Tranexamic acid interferes with the coagulation cascade.

Vannuccini. Management of AUB in uterine fibroids. *Fertil Steril* 2024.

chronic settings, improving QoL. However, it acts on the bleeding symptom with no direct effect on UFs, not providing a long-term treatment option.

Hormonal treatments

Oral contraceptives and progestins. Combined oral contraceptives are commonly prescribed to address AUB and HMB, given their inhibiting effect on endometrial proliferation and consequent maintenance of a thin endometrium, which in turn reduces menstrual bleeding. However, the effectiveness of COCs in managing specifically UFs-related bleeding is limited. A randomized trial on a small group of patients with UFs-related HMB comparing combined hormonal vaginal rings vs. ultralow-dose COCs showed a reduction in menstrual blood loss of 72% and 62% at 6 months, respectively. However, HMB recurred after cessation of treatment, demonstrating only short-term efficacy, with one-third of patients not responding to the medication (40). Nevertheless, the use of COCs containing natural estrogens, such as estradiol valerate or 17- β -estradiol, combined with progestins, such as dienogest or norgestrel acetate, is more effective in reducing menstrual blood loss than other COCs in patients with HMB, albeit not in the case of UFs (41–44). Because the growth of UFs is influenced by both estrogens and progesterone levels (45–47), the use of COCs is not expected to significantly reduce fibroid volume or uterine size. Progestins, such as norethindrone acetate, may be used for HMB because of ovulatory cause, but the effects on UFs-related HMB are unclear and at most, only for the short term, given the related side effects (48).

Levonorgestrel intrauterine system. The 52-mg-levonorgestrel intrauterine system (LNG-IUS) is a T-shaped device that releases the drug locally. It represents an option for contraception and for the treatment of HMB overall (49). Because of its localized impact, LNG-IUS profoundly affects the endometrium, inducing atrophy and inactivity without suppressing ovulation (50). The 52-mg-levonorgestrel intrauterine system leads to a reduction in endometrial proliferation and an increase in apoptosis within the endometrial glands and stroma. The 52-mg-levonorgestrel intrauterine system significantly decreases the duration and amount of menstrual flow in women experiencing HMB and/or frequent irregular bleeding because of UFs (51), but no clinical reduction in fibroid size has been observed after the treatment (4). After 1 year of treatment, 40% of patients achieved amenorrhea, and 95% of those who were anemic at the time of insertion experienced resolution (52). The comparison with COC showed that LNG-IUS was more effective in reducing menstrual bleeding (53); moreover, as a long-term option, patients were more likely to persist in the use of this long-acting contraceptive method than other hormonal options (54). Side effects induced by the LNG-IUS, such as functional ovarian cysts, did not affect its acceptability (51). In some cases, LNG-IUS could serve as a straightforward and efficient substitute for surgical interventions aimed at treating AUB leiomyoma (55). However, it is more effective in alleviating the symptoms of AUB in cases of adenomyosis and endometrial hyperplasia, as well as in cases of AUB because of not other-

wise classified causes, than in cases of UFs (56). Despite its effectiveness, the increased risk of expulsion suggests that it may be a suitable option for carefully selected symptomatic women without uterine cavity distortion; the presence of submucosal fibroids in fact is a relative contraindication to the use of LNG-IUS. Unfortunately, women with UFs face an increased risk of device expulsion (12%–16% over up to 3 years) (4).

Selective progesterone receptor modulators. Selective PR modulators exert specific effects on PRs and can function as full PR agonists, and antagonists, or possess a mixed agonist and antagonist profile. Selective PR modulators impede the cellular proliferation of leiomyoma cells, promoting apoptosis, although sparing normal myometrial cells; besides, selective PR modulators induces the suppression of neovascularization in cultured leiomyoma cells (57).

Ulipristal acetate (UPA) has comparable effectiveness to GnRH analogs in diminishing uterine bleeding and can serve as adjunctive therapy to reduce fibroid size before myomectomy. Ulipristal acetate was shown to be very effective in fibroid volume reduction >50% after 6 months of treatment, with adequate control of uterine bleeding and restoration of hemoglobin levels (58–60). However, in May 2018, the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency determined that UPA might have played a role in the occurrence of certain instances of severe liver injury, leading to restrictions on its usage. Present knowledge suggests that UPA may contribute to idiosyncratic (rather than intrinsic) drug-induced liver injury (61). Currently, the European Medicines Agency indicates that 5-mg UPA can be used only for intermittent treatment of moderate-to-severe symptoms of UFs in adult women who have not reached menopause, when fibroid embolization and/or surgical treatment is not a suitable option, or have failed.

Mifepristone is the original PR modulator, widely known as RU-486 and primarily acknowledged as an antiprogesterone utilized for inducing abortion; it also has inhibitory effects on the growth of UFs by altering genes associated with cell proliferation and fibrosis (57). The off-label use of mifepristone significantly reduces UFs-related symptoms, whereas controversial results are available on fibroids and uterine volume (62, 63).

Selective estrogen receptor modulators. Selective estrogen receptor (ER) modulators are nonsteroidal ligands for ERs that exhibit specific actions on ER, acting either as agonists or antagonists and causing tissue-specific changes in gene expression. These drugs are commonly employed in the treatment of ER-positive breast cancer but have minimal benefits for treating symptomatic UFs, making them not recommended for this purpose (64).

Aromatase inhibitors. Aromatase inhibitors exert their action by blocking estrogen synthesis, primarily through the inhibition or inactivation of the microsomal cytochrome P450 enzyme aromatase. This enzyme is responsible for catalyzing the synthesis of estrogens from androgens via hydroxylation. Notably, aromatase messenger ribonucleic acid has been identified in 90% of UFs but is absent in normal myometrial

tissue. This observation suggests that AIs act to suppress the growth of fibroids by disrupting estrogen synthesis in these tumors (26). Aromatase inhibitors were thought to have fewer side effects and a quicker response compared with the GnRH agonist leuprolide acetate (65). However, a Cochrane review from 2013, centered on a single randomized controlled trial involving 70 patients treated with letrozole, concluded that there is inadequate evidence to endorse the use of AIs for the treatment of UFs (66).

GnRH agonists. Gonadotropin-releasing hormone agonists (leuprolide acetate, goserelin acetate, and triptorelin) are synthetic peptides structurally similar to endogenous GnRH but possess longer half-lives, greater receptor affinity, and increased potency (67). Continuous administration leads to down-regulation of pituitary GnRH receptors, reducing follicle-stimulating hormone and luteinizing hormone production, and subsequently gonadal steroid levels. This results in a hypoestrogenic state, crucial for the pharmacologic efficacy of GnRH agonists because UF growth is estrogen-stimulated. Several studies have shown that tumor shrinkage correlates with the number of ER-positive cells. Gonadotropin-releasing hormone agonists interfere with matrix metalloproteinase production and induce apoptosis, influencing tumor growth (68). In the first 3–6 months of treatment, most women experience a 30%–65% reduction in fibroid volume and symptom improvement, preserving the uterus (26, 69), although in 23% of cases a regrowth of UFs is observed at 3 months and returns to baseline by 6 months of cessation (70). Furthermore, GnRH agonists, either as 1- or 3-month depot formulations given as an intramuscular injection, cause significant hypoestrogenic side effects, which include vasomotor symptoms, vaginal dryness, sleep disturbances, myalgia, arthralgia, mood swings, and potential cognitive impairment. Prolonged use of GnRH agonists, exceeding 6 months, has been associated with approximately 6% bone loss (71). Long-term use may lead to bone demineralization and decreased bone mineral density (BMD), necessitating hormonal add-back therapy, which can include estrogens, progestins, or a combination of both. Therefore, the side effects imply short-term use, which may be helpful, conversely, when used as preoperative treatment. There is clear evidence that preoperative GnRH agonists reduce uterine and fibroid volume and increase preoperative hemoglobin levels (72). In cases of laparotomic or laparoscopic myomectomy, GnRH agonist before treatment reduces intraoperative blood loss and the need for blood transfusions (73). Ultimately, the most clinically relevant indication for preoperative GnRH agonist use is in the case of type 0–2 UFs, where a 3-month course with triptorelin and letrozole decreases the hysteroscopy time and the volume of fluid absorbed during hysteroscopic resection (74). Furthermore, GnRH agonists are a valuable option as a preoperative endometrial thinning agent before hysteroscopic destructive procedures for HMB, such as endometrial ablation (75). Apart from its use in the preoperative setting, given the risk of long-term hypoestrogenic adverse effects, treatment with GnRH agonists is limited to 6 months without add-back therapy and 12 months with add-back therapy. Thus, GnRH agonists are recommended

for the short-term treatment of UFs-related AUB and HMB and as a bridge to other treatment strategies, such as surgical management, menopause, or other medical therapies (76).

Oral GnRH antagonists. Oral GnRH antagonists competitively bind GnRH receptors, causing an immediate suppression of gonadotropin release. They rapidly induce a reversible menopausal state. They are available as oral formulations and do not induce an initial estradiol flare (77). Elagolix, relugolix, and linzagolix showed excellent control of UFs-related HMB, and, when combined with an add-back treatment, BMD is preserved, supporting these options for long-term management (78, 79).

Elagolix, in combination with estradiol and norethindrone, was approved in 2020 for the treatment of UFs-related HMB for up to 24 months of use. This preparation is available as 2 copackaged capsules: one contains elagolix 300 mg plus estradiol 1 mg plus norethindrone 0.5 mg to be taken in the morning, and the other contains elagolix 300 mg alone to be taken in the evening. Elagolix, in combination with add-back therapy, demonstrated a substantial reduction in menstrual blood loss from the baseline (>85% of participants), a higher percentage of women experiencing amenorrhea (>50% at 12 months), and an increase in hemoglobin level of >2 g/dL at 6 months than placebo (80). The benefit of add-back therapy is that it mitigates many of the hypoestrogenic side effects of elagolix (36), and the changes in BMD and lipid profiles may be reversible after discontinuation after up to 12 months of therapy (81). Moreover, concomitant adenomyosis does not appear to limit the effectiveness of fibroid-related HMB. (82). Because ovulation suppression with elagolix plus add-back is variable, it should not be considered a contraceptive agent (79).

Relugolix, in combination with the same tablet with add-back therapy, was approved in May 2021 for the treatment of UFs HMB for up to 24 months. Each tablet contains relugolix 40 mg plus estradiol 1 mg plus norethindrone acetate 0.5 mg in a single daily dose. Combination therapy may achieve a favorable benefit-risk profile, through the optimization of reproductive hormone level ranges, which control HMB, although maintaining healthy bone metabolism and preventing the appearance of vasomotor symptoms. Relugolix combination therapy demonstrated a swift and consistent reduction in menstrual blood loss (>70% of patients achieved the primary endpoint at 24 weeks), reduction of anemia, and an increased rate of amenorrhea, despite a small decrease in fibroid volume. By the first menstrual cycle after treatment, >50% blood loss reduction was observed, further decreased by 80% after 8-week treatment, remaining consistently reduced by 90% after 52 weeks of treatment, when >70% of patients were in amenorrhea. The treatment is generally well tolerated with few side effects, and particularly BMD was preserved through 2 years of treatment (83–85). Furthermore, a subanalysis showed that once daily relugolix combination therapy improved UFs-related HMB in most Black or African American women who participated in the study, supporting the efficacy and safety of this option to manage bleeding symptoms in the case of UFs (86).

Linzagolix is an oral GnRH antagonist available at a 100 mg or 200 mg dose once daily tablet and has been studied both with and without add-back therapy (1 mg estradiol and 0.5 mg norethisterone acetate). The lower dose (100 mg) causes a partial suppression of the hypothalamic-pituitary-ovarian axis, whereas the higher dose (200 mg) induces full suppression. Linzagolix, both at 100 or 200 mg, with or without add-back therapy, demonstrated a significant reduction in UFs-related HMB. Among patients undergoing 200 mg of linzagolix plus add-back therapy, the response rate was >75% at 24 weeks of treatment (87). Reductions in BMD were dose-dependent and improved with add-back therapy. The use of a once-per-day regimen of linzagolix 100 mg monotherapy, allowing a partial suppression, could potentially offer a distinct choice for the long-term management of symptomatic UFs in women who are unable to undergo concurrent hormonal add-back therapy (87). Otherwise, a high dosage with monotherapy could be an option when the main goal is bleeding cessation and the correction of anemia.

Surgical treatment

Surgical treatment remains the most widely used therapeutic option worldwide for UFs-related symptoms. Conservative and nonconservative approaches are available, depending on the number, the anatomic site, and the size of UFs, along with the patient's reproductive goals or preference, i.e., the wish to retain the uterus (88, 89). The minimally invasive route is recommended whenever feasible. However, when choosing a surgical approach, appropriate counseling on benefit-risk balance is needed, considering potential intraoperative surgical complications and the recurrence of UFs when a myomectomy is performed (90).

Myomectomy. Myomectomy is a conservative option for symptomatic UFs in patients who desire uterine preservation or wish to conceive in the future. Being a uterine-sparing treatment, the risk of recurrence should be discussed. The surgical approach may be hysteroscopic, laparoscopic, robotic, or abdominal. In the case of UFs-related AUB and HMB, submucosal fibroids, even at smaller sizes, are the main contributors to these symptoms, causing anemia in a relevant percentage of patients (91). In such cases of FIGO type 0, type 1, or type 2, the safety and efficacy of the hysteroscopic approach are undeniable (92, 93). Small UFs (<2 cm) are removed routinely in an outpatient setting, whereas bigger fibroids may entail a more complex procedure with a higher risk of intraoperative complications (perforation and/or damage to the surrounding myometrium and fluid intravasation), thus recommending an inpatient setting (20). Furthermore, in cases of big FIGO type 1 and 2 UFs, or whenever IDA coexists, pretreatment with either GnRH agonists or GnRH antagonists may facilitate surgery by reducing myoma size and improving hemoglobin levels before the procedure, along with preparing the uterine cavity and thinning the endometrium (21).

Conversely, establishing whether a patient is a potential candidate for laparoscopic rather than open abdominal myomectomy depends on the location, size, and number of UFs, but surgical expertise (e.g., laparoscopic suturing) is another

influential factor. Quality of life improvement has been demonstrated with all routes of myomectomy (94–96).

Hysterectomy. Uterine fibroids represent the primary benign indication for hysterectomy; however, this procedure should be recommended as a definitive surgical option among patients with symptomatic UFs who do not desire future childbearing or do not wish to retain their uterus, especially when medical treatment has failed (76). Hysterectomy improves QoL, even when compared with uterine-sparing options (97, 98). Minimally invasive approaches (laparoscopy or robotic-assisted laparoscopy) are preferred to laparotomy, because of decreased morbidity and mortality (99). A shared decision-making process with the patient is needed before choosing this nonconservative treatment. A discussion of all the available options and short- and long-term goals is advisable (100), considering the possible patient's preference to preserve the uterus.

Interventional radiologic procedures. Nowadays, for patients who do not desire definitive surgical treatment or do not respond to medical management, alternative uterine-sparing procedures are available. Interventional radiologic options include uterine artery embolization (UAE), high-intensity focused ultrasound, magnetic resonance high-intensity focused ultrasound, and radiofrequency ablation.

Randomized clinical trials support the efficacy of UAE as a minimally invasive option for the management of UFs-related AUB and HMB, especially for women who prefer to retain the uterus without reproductive wishes (101, 102). Uterine artery embolization, causing UFs devascularization and involution, is associated with a significant reduction in myoma and uterine volume and an improvement in bleeding scores (103, 104). When compared with hysterectomy or myomectomy, patients undergoing UAE have a decreased risk of transfusion and a shortened hospital stay, but they may also experience less favorable QoL (105, 106). A risk of reintervention should be also acknowledged (107, 108).

Among the conservative approaches, it is worth also mentioning the thermoablative techniques, namely the high-intensity focused ultrasound energy that induces coagulative necrosis in UFs. It can be realized under the guidance of ultrasound or a magnetic resonance imaging scan. An improvement in the QoL domain has been observed after treatment (109, 110), although a high rate of reintervention is reported (108, 111). However, the use of these techniques results mainly in UF volume reduction rather than AUB and HMB control.

Radiofrequency ablation is now emerging as a uterine-preserving and minimally invasive therapy for symptomatic UFs using elevated temperatures to produce tissue destruction, aiming mainly at volume reduction. It may be either laparoscopic or transcervical, with promising results because of improved QoL and symptom severity scores, although fertility results are still unclear and reintervention should be considered (112).

Management of IDA in UFs-related AUB and HMB

Iron deficiency and IDA are commonly encountered conditions among patients with UFs-related HMB because of either a chronic or acute episode of bleeding, although they are

frequently underdiagnosed and underestimated (15, 16). Given the impact of ID and IDA on physical and mental scores of QoL with chronic fatigue and impaired work productivity (113, 114), along with the effect of HMB itself, an adequate approach to UFs-related HMB should envisage the simultaneous management of IDA (115, 116). Besides, ID and IDA can have significant implications for patient outcomes in light of a surgical intervention. In fact, preoperative anemia is a known risk factor for increased morbidity (venous thromboembolism, surgical site infections, and hemorrhage) and mortality postsurgery when compared with nonanemic patients (117). Thus, the early identification and treatment of IDA are crucial, both preoperatively and during the medical management of UFs-related HMB. Besides, a preoperative hormonal treatment with either GnRH agonists or oral GnRH antagonists, inducing a reduction of bleeding up to amenorrhea, improves the outcome of the surgical treatment (72).

The optimal management of IDA involves iron supplementation, either orally or intravenously. A review of available clinical guidelines revealed that intravenous iron is recommended for severe anemia, in nonresponders to oral iron, or in cases where a rapid rise in hemoglobin level is required before surgery (118). Intravenous iron has been shown to lead to a greater increase in hemoglobin and ferritin levels compared with oral iron (119). Preventing and managing IDA requires a multifaceted approach, with early recognition, investigation of underlying causes, iron supplementation, and optimization of erythropoiesis.

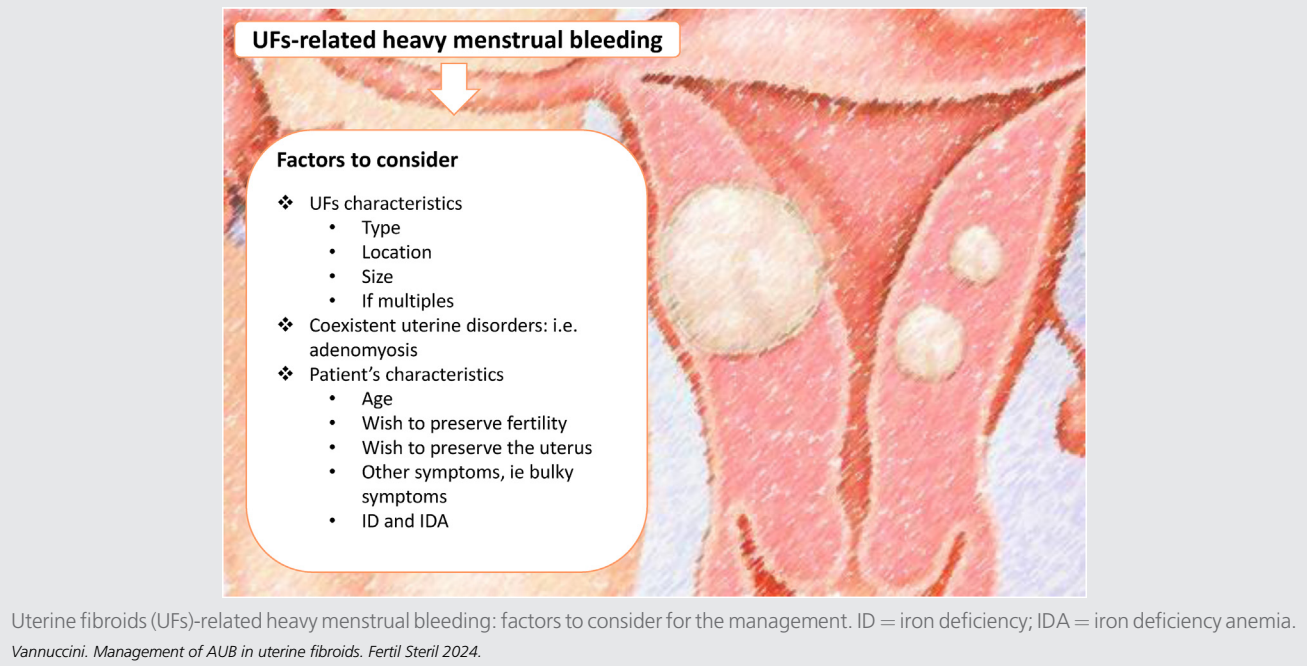
Management of UFs-related AUB in cases of coexistent adenomyosis

The cooccurrence of UFs and adenomyosis is common (120–122). Given the possibility of the coexistence of the 2 conditions, especially in the context of AUB and HMB, a management approach considering both uterine disorders is advisable. However, there are no currently approved pharmacologic options for adenomyosis, although LNG-IUS, GnRH agonists, and GnRH antagonists are used commonly to treat the bleeding symptoms of both conditions (82). Information about the presence of concomitant uterine disorders may be critical to individualizing therapeutic approaches.

Management of UFs-related AUB in perimenopause

The perimenopausal period is characterized by a higher incidence of both UFs and anovulatory cycles (123). The coincidence of these 2 conditions establishes a negative synergy that exacerbates the severity of fibroid-induced HMB. Treatment of UFs during perimenopause should carefully consider the balance between the advantages and risks of medical or surgical treatment and the likelihood of approaching menopause, thereby informing therapeutic counseling according to the patient’s preferences.

FIGURE 3



CONCLUSIONS

The modern management of AUB and HMB related to UFs requires an individualized approach on the basis of clinical profile, characteristics of UFs (location, size, multiple UFs, or coexistent adenomyosis), patients' preferences, and reproductive wishes (Fig. 3). Ideally, the ultimate goal of treatment should be to relieve UF symptoms while preserving the uterus. Medical treatment should be the first-line approach, considering also the introduction of new medical drugs labeled for UFs-related HMB, such as oral GnRHant. Besides, hormonal treatment may be helpful in the case of a surgical approach to enable concomitant management of ID and IDA and maximize patients' outcomes and QoL. A shared decision-making process should be the basis for treatment selection, considering the long- and short-term treatment goals expected by the patient.

CRediT Authorship Contribution Statement

Silvia Vannuccini: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Felice Petraglia:** Conceptualization, Writing – review & editing, Supervision. **Francisco Carmona:** Writing – review & editing, Supervision. **Joaquim Calaf:** Data curation, Writing – review & editing. **Charles Chapron:** Writing – review & editing, Supervision.

Declaration of Interests

S.V. reports honoraria for lectures from Gedeon Richter, unrelated to the present manuscript. F.P. has nothing to disclose. F.C. has nothing to disclose. J.C. has nothing to disclose. C.C. has nothing to disclose.

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