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 Médicine 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

Received April 29, 2024; revised and accepted April 29, 2024; published online May 8, 2024.
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).

Fertil Steril® Vol. 122, No. 1, July 2024 0015-0282

https://doi.org/10.1016/j.fertnstert.2024.04.041

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.

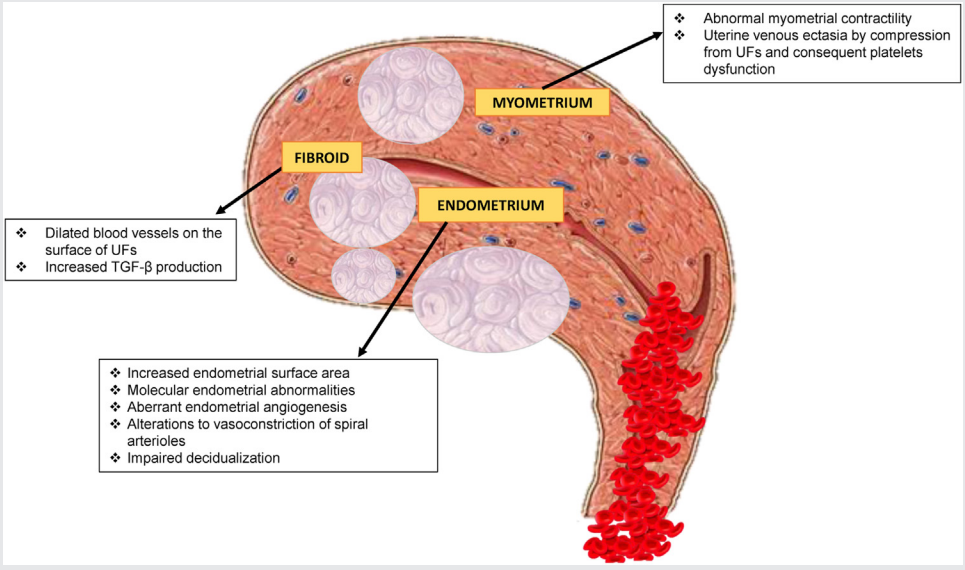
MECHANISMS OF AUB AND HMB IN UFS

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).

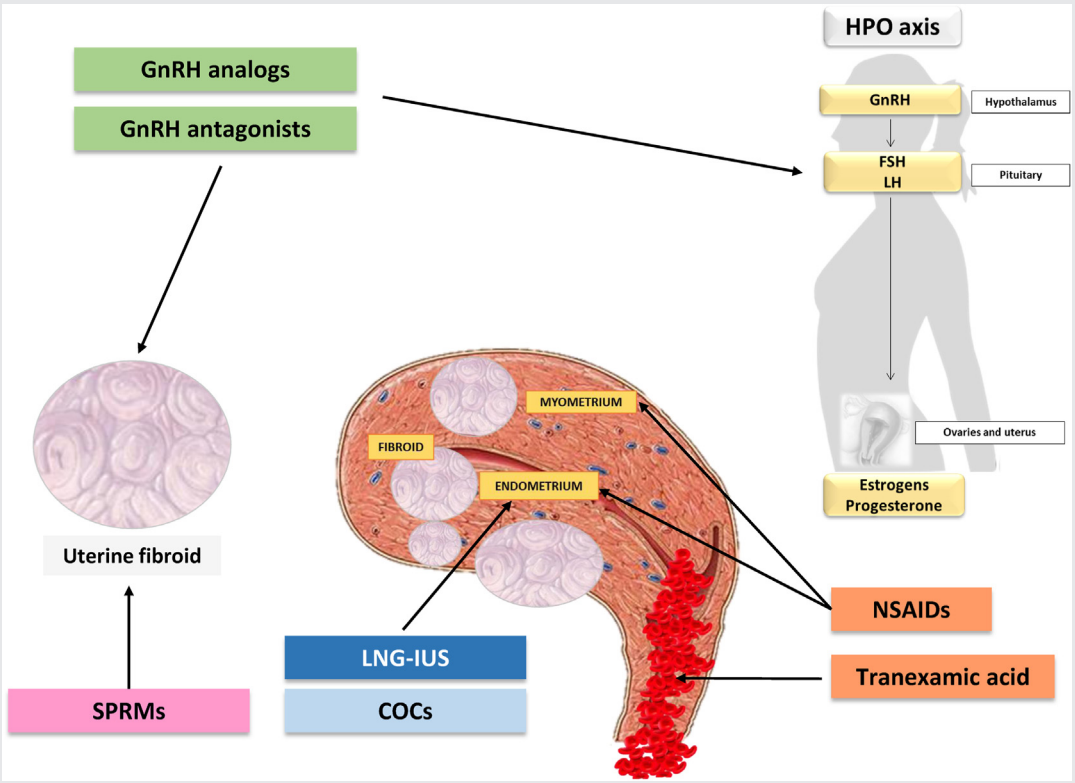
Over the last few years, some evidence has shown the potential role of vitamins and supplements, namely vitamin D and epigallocatechin gallate, in the treatment of UFs (28, 29). Animal studies, and more recently, human studies, showed that vitamin D administration may inhibit fibroid growth (30, 31). 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 nomegestrol 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 otherwise 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.

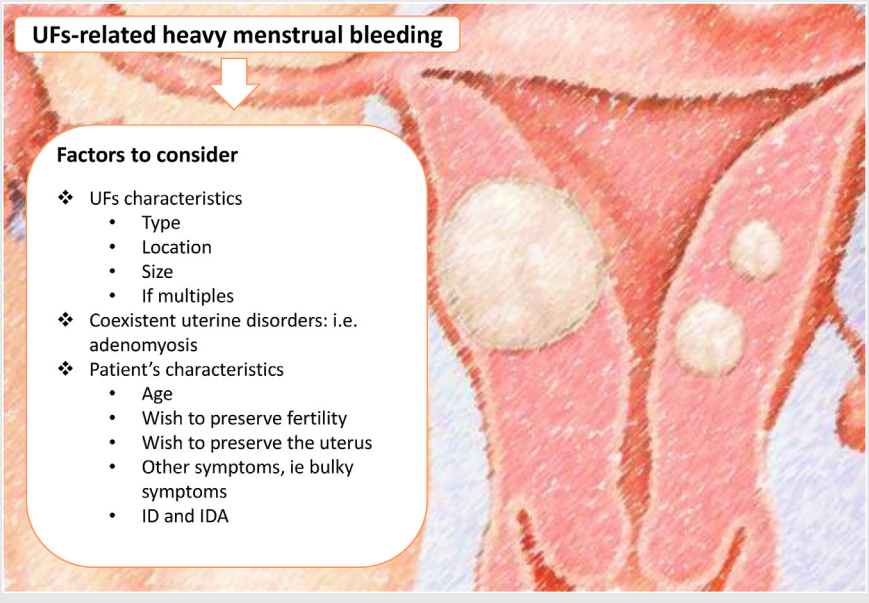
Management of UFs-related AUB in cases of coexistent adenomyosis

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



Uterine fibroids (UFs)-related heavy menstrual bleeding: factors to consider for the management. ID = iron deficiency; IDA = iron deficiency anemia.

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

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.

REFERENCES

1. Zimmermann A, Bernuit D, Gerlinger C, Schaefers M, Geppert K. Prevalence, symptoms and management of uterine fibroids: an international internet-based survey of 21,746 women, 12. BMC Women's Health; 2012:6.
2. Stewart E, Cookson C, Gandolfo R, Schulze-Rath R. Epidemiology of uterine fibroids: a systematic review. BJOG 2017;124:1501–12.
3. Giuliani E, As-Sanie S, Marsh EE. Epidemiology and management of uterine fibroids. Int J Gynaecol Obstet 2020;149:3–9.
4. Stewart EA, Laughlin-Tommaso SK, Catherino WH, Lalitkumar S, Gupta D, Vollenhoven B. Uterine fibroids. Nat Rev Dis Primers 2016;2:16043.
5. Munro MG, Critchley HOD, Fraser IS, the FIGO Menstrual Disorders Committee. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. Intl J Gynecol Obstet 2018;143:393–408.
6. 2021 Exceptional surveillance of heavy menstrual bleeding: assessment and management (NICE guideline NG88). London: National Institute for Health and Care Excellence (NICE); 2021. Available at: http://www.ncbi.nlm.nih.gov/books/NBK571008/. Accessed April 9, 2023.
7. Soliman AM, Yang H, Du EX, Kelkar SS, Winkel C. The direct and indirect costs of uterine fibroid tumors: a systematic review of the literature between 2000 and 2013. Am J Obstet Gynecol 2015;213:141–60.
8. Hasselrot K, Lindeberg M, Konings P, Kopp Kallner H. Investigating the loss of work productivity due to symptomatic leiomyoma. PLoS One 2018;13:e0197958.
9. Wang A, Wang S, Owens CD, Vora JB, Diamond MP. Health care costs and treatment patterns associated with uterine fibroids and heavy menstrual bleeding: a claims analysis. J Womens Health (Larchmt) 2022;31:856–63.
10. Al-Hendy A, Myers E, Stewart E. Uterine fibroids: burden and unmet medical need. Semin Reprod Med 2017;35:473–80.
11. Whiteman MK, Kuklina E, Jamieson DJ, Hillis SD, Marchbanks PA. Inpatient hospitalization for gynecologic disorders in the United States. Am J Obstet Gynecol 2010;202:541.e1–6.
12. Yu O, Scholes D, Schulze-Rath R, Grafton J, Hansen K, Reed SD. A US population-based study of uterine fibroid diagnosis incidence, trends, and prevalence: 2005 through 2014. Am J Obstet Gynecol 2018;219:591.e1–8.
13. Nelson AL, Ritchie JJ. Severe anemia from heavy menstrual bleeding requires heightened attention. Am J Obstet Gynecol 2015;213:97.e1–6.
14. Donnez J, Carmona F, Maitrot-Mantelet L, Dolmans M-M, Chapron C. Uterine disorders and iron deficiency anemia. Fertil Steril 2022;118:615–24.
15. 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;118:625–36.
16. Munro MG, Mast AE, Powers JM, Kouides PA, O'Brien SH, Richards T, et al. The relationship between heavy menstrual bleeding, iron deficiency, and iron deficiency anemia. Am J Obstet Gynecol 2023;229:1–9.
17. 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;30:1608–15.
18. Marsh EE, Al-Hendy A, Kappus D, Galitsky A, Stewart EA, Kerolous M. Burden, prevalence, and treatment of uterine fibroids: a survey of U.S. women. J Womens Health (Larchmt) 2018;27:1359–67.
19. Borah BJ, Nicholson WK, Bradley L, Stewart EA. The impact of uterine leiomyomas: a national survey of affected women. Am J Obstet Gynecol 2013;209:319.e1–20.
20. Donnez J, Dolmans MM. Uterine fibroid management: from the present to the future. Hum Reprod Update 2016;22:665–86.
21. Dolmans MM, Cacciottola L, Donnez J. Conservative management of uterine fibroid-related heavy menstrual bleeding and infertility: time for a deeper mechanistic understanding and an individualized approach. J Clin Med 2021;10:4389.
22. Jain V, Chodankar RR, Maybin JA, Critchley HOD. Uterine bleeding: how understanding endometrial physiology underpins menstrual health. Nat Rev Endocrinol 2022;18:290–308.
23. Navarro A, Bariani MV, Yang Q, Al-Hendy A. Understanding the impact of uterine fibroids on human endometrium function. Front Cell Dev Biol 2021;9:633180.
24. 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;24:7011.
25. Critchley HOD, Maybin JA, Armstrong GM, Williams ARW. Physiology of the endometrium and regulation of menstruation. Physiol Rev 2020;100:1149–79.
26. Kashani BN, Centini G, Morelli SS, Weiss G, Petraglia F. Role of medical management for uterine leiomyomas. Best Pract Res Clin Obstet Gynaecol 2016;34:85–103.
27. Barseghyan M, Chae-Kim J, Catherino WH. The efficacy of medical management of leiomyoma-associated heavy menstrual bleeding: a mini review. F S Rep 2024;5:4–8.
28. Ciebiera M, Ali M, Prince L, Jackson-Bey T, Atabiekov I, Zgliczyński S, et al. The evolving role of natural compounds in the medical treatment of uterine fibroids. J Clin Med 2020;9:1479.
29. 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;43:678–719.
30. Sharan C, Halder SK, Thota C, Jaleel T, Nair S, Al-Hendy A. Vitamin D inhibits proliferation of human uterine leiomyoma cells via catechol-O-methyltransferase. Fertil Steril 2011;95:247–53.

31. Arjeh S, Darsareh F, Asl ZA, Azizi Kutenaei M. Effect of oral consumption of vitamin D on uterine fibroids: A randomized clinical trial. Complement Ther Clin Pract 2020;39:101159.
32. Roshdy E, Rajaratnam V, Maitra S, Sabry M, Allah AS, Al-Hendy A. Treatment of symptomatic uterine fibroids with green tea extract: a pilot randomized controlled clinical study. Int J Womens Health 2013;5:477–86.
33. Grandi G, Del Savio MC, Melotti C, Feliciello L, Facchinetti F. Vitamin D and green tea extracts for the treatment of uterine fibroids in late reproductive life: a pilot, prospective, daily-diary based study. Gynecol Endocrinol 2022;38:63–7.
34. Lethaby A, Duckitt K, Farquhar C. Non-steroidal anti-inflammatory drugs for heavy menstrual bleeding. Cochrane Database Syst Rev 2013;(1):CD000400.
35. Leminen H, Hurskainen R. Tranexamic acid for the treatment of heavy menstrual bleeding: efficacy and safety. Int J Womens Health 2012;4:413–21.
36. MacGregor B, Munro MG, Lumsden MA. Therapeutic options for the management of abnormal uterine bleeding. Int J Gynaecol Obstet 2023;162(Suppl 2):43–57.
37. Shalaby MA, Maged AM, Al-Asmar A, El Mahy M, Al-Mohamady M, Rund NMA. Safety and efficacy of preoperative tranexamic acid in reducing intraoperative and postoperative blood loss in high-risk women undergoing cesarean delivery: a randomized controlled trial. BMC Pregnancy Childbirth 2022;22:201.
38. Lukes AS, Moore KA, Muse KN, Gersten JK, Hecht BR, Edlund M, et al. Tranexamic acid treatment for heavy menstrual bleeding: a randomized controlled trial. Obstet Gynecol 2010;116:865–75.
39. Bryant-Smith AC, Lethaby A, Farquhar C, Hickey M. Antifibrinolytics for heavy menstrual bleeding. Cochrane Database Syst Rev 2018;4:CD000249.
40. Agarwal N, Gupta M, Kriplani A, Bhatla N, Singh N. Comparison of combined hormonal vaginal ring with ultralow-dose combined oral contraceptive pills in the management of heavy menstrual bleeding: A pilot study. J Obstet Gynaecol 2016;36:71–5.
41. 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;117:777–87.
42. Fraser IS, Romer 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. Human Reprod 2011;26:2698–708.
43. Fraser IS, Jensen J, Schaefers M, Mellinger U, Parke S, Serrani M. Normalization of blood loss in women with heavy menstrual bleeding treated with an oral contraceptive containing estradiol valerate/dienogest. Contraception 2012;86:96–101.
44. Mansour D, Westhoff C, Kher U, Korver T. Pooled analysis of two randomized, open-label studies comparing the effects of nomegestrol acetate/17β-estradiol and drospirenone/ethinyl estradiol on bleeding patterns in healthy women. Contraception 2017;95:390–7.
45. Kim JJ, Kurita T, Bulun SE. Progesterone action in endometrial cancer, endometriosis, uterine fibroids, and breast cancer. Endocr Rev 2013;34:130–62.
46. Ishikawa H, Ishi K, Serna VA, Kakazu R, Bulun SE, Kurita T. Progesterone is essential for maintenance and growth of uterine leiomyoma. Endocrinology 2010;151:2433–42.
47. Donnez J. Uterine fibroids and progestogen treatment: lack of evidence of its efficacy: a review. J Clin Med 2020;9:3948.
48. Lethaby A, Irvine G, Cameron I. Cyclical progestogens for heavy menstrual bleeding. Cochrane Database Syst Rev 2008;(1):CD001016.
49. Bofill Rodriguez M, Dias S, Jordan V, Lethaby A, Lensen SF, Wise MR, et al. Interventions for heavy menstrual bleeding; overview of Cochrane reviews and network meta-analysis. Cochrane Database Syst Rev 2022;5:CD013180.
50. Sabbioni L, Petraglia F, Luisi S. Non-contraceptive benefits of intrauterine levonorgestrel administration: why not? Gynecol Endocrinol 2017;33:822–9.
51. Socolov D, Blidaru I, Tamba B, Miron N, Boiculese L, Socolov R. Levonorgestrel releasing-intrauterine system for the treatment of menorrhagia and/or frequent irregular uterine bleeding associated with uterine leiomyoma. Eur J Contracept Reprod Health Care 2011;16:480–7.
52. 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.
53. Sayed GH, Zakherah MS, El-Nashar SA, Shaaban MM. A randomized clinical trial of a levonorgestrel-releasing intrauterine system and a low-dose combined oral contraceptive for fibroid-related menorrhagia. Int J Gynaecol Obstet 2011;112:126–30.
54. Yao X, Stewart EA, Laughlin-Tommaso SK, Heien HC, Borah BJ. Medical therapies for heavy menstrual bleeding in women with uterine fibroids: a retrospective analysis of a large commercially insured population in the USA. BJOG 2017;124:322–30.
55. Senol T, Kahramanoglu I, Dogan Y, Baktiroglu M, Karateke A, Suer N. Levonorgestrel-releasing intrauterine device use as an alternative to surgical therapy for uterine leiomyoma. Clin Exp Obstet Gynecol 2015;42:224–7.
56. Atak Z, Rahımlı Ocakoğlu S, Ocakoğlu G. Levonorgestrel-releasing intrauterine device to treat abnormal uterine bleeding; not one treatment option fits all. J Turk Ger Gynecol Assoc 2023;24:246–51.
57. Islam MS, Afrin S, Jones SI, Segars J. Selective progesterone receptor modulators-mechanisms and therapeutic utility. Endocr Rev 2020;41:bnaa012.
58. Donnez J, Tomaszewski J, Vázquez F, Bouchard P, Lemieszczuk B, Baró F, et al. Ulipristal acetate versus leuprolide acetate for uterine fibroids. N Engl J Med 2012;366:421–32.
59. Donnez J, Tatarchuk TF, Bouchard P, Puscasiu L, Zakharenko NF, Ivanova T, et al. Ulipristal acetate versus placebo for fibroid treatment before surgery. N Engl J Med 2012;366:409–20.
60. Donnez J, Vázquez F, Tomaszewski J, Nouri K, Bouchard P, Fauser BC, et al. Long-term treatment of uterine fibroids with ulipristal acetate ★. Fertil Steril 2014;101:1565–73.e1–18.
61. Donnez J. Liver injury and ulipristal acetate: an overstated tragedy? Fertil Steril 2018;110:593–5.
62. Shen Q, Hua Y, Jiang W, Zhang W, Chen M, Zhu X. Effects of mifepristone on uterine leiomyoma in premenopausal women: a meta-analysis. Fertil Steril 2013;100:1722–6.e10.
63. Tristan M, Orozco LJ, Steed A, Ramírez-Morera A, Stone P. Mifepristone for uterine fibroids. Cochrane Database Syst Rev 2012;2012(8):CD007687.
64. Deng L, Wu T, Chen XY, Xie L, Yang J. Selective estrogen receptor modulators (SERMs) for uterine leiomyomas. Cochrane Database Syst Rev 2012;10:CD005287.
65. Shozu M, Murakami K, Segawa T, Kasai T, Inoue M. Successful treatment of a symptomatic uterine leiomyoma in a perimenopausal woman with a nonsteroidal aromatase inhibitor. Fertil Steril 2003;79:628–31.
66. Song H, Lu D, Navaratnam K, Shi G. Aromatase inhibitors for uterine fibroids. Cochrane Database Syst Rev 2013;(10):CD009505.
67. De Leo V, Morgante G, La Marca A, Musacchio MC, Sorace M, Cavicchioli C, et al. A benefit-risk assessment of medical treatment for uterine leiomyomas. Drug Saf 2002;25:759–79.
68. Khan KN, Kitajima M, Hiraki K, Fujishita A, Nakashima M, Ishimaru T, et al. Cell proliferation effect of GnRH agonist on pathological lesions of women with endometriosis, adenomyosis and uterine myoma. Hum Reprod 2010;25:2878–90.
69. Ciebiera M, Madueke-Laveaux OS, Feduniw S, Ulin M, Spaczyński R, Zgliczyńska M, et al. GnRH agonists and antagonists in therapy of symptomatic uterine fibroids – current roles and future perspectives. Expert Opin Pharmacother 2023;24:1799–809.
70. Madueke-Laveaux OS, Ciebiera M, Al-Hendy A. GnRH analogs for the treatment of heavy menstrual bleeding associated with uterine fibroids. F S Rep 2023;4(2 Suppl):46–50.
71. Lewis TD, Malik M, Britten J, San Pablo AM, Catherino WH. A Comprehensive Review of the Pharmacologic Management of Uterine Leiomyoma. Biomed Res Int 2018;2018:2414609.
72. Lethaby A, Puscasiu L, Vollenhoven B. Preoperative medical therapy before surgery for uterine fibroids. Cochrane Database Syst Rev 2017;11:CD000547.
73. de Milliano I, Twisk M, Ket JC, Huirne JA, Hehenkamp WJ. Pre-treatment with GnRHa or ulipristal acetate prior to laparoscopic and laparotomic myomectomy: a systematic review and meta-analysis. PLoS One 2017;12:e0186158.

74. Bizzarri N, Ghirardi V, Remorgida V, Venturini PL, Ferrero S. Three-month treatment with triptorelin, letrozole and ulipristal acetate before hysteroscopic resection of uterine myomas: prospective comparative pilot study. Eur J Obstet Gynecol Reprod Biol 2015;192:22–6.
75. Tan YH, Lethaby A. Pre-operative endometrial thinning agents before endometrial destruction for heavy menstrual bleeding. Cochrane Database Syst Rev 2013;(11)CD010241.
76. Management of Symptomatic Uterine Leiomyomas: ACOG Practice Bulletin. Number 228. Obstet Gynecol 2021;137:e100–15.
77. Ali M, A R S, Al Hendy A. Elagolix in the treatment of heavy menstrual bleeding associated with uterine fibroids in premenopausal women. Expert Rev Clin Pharmacol 2021;14:427–37.
78. Donnez J, Dolmans M-M. Fibroids and medical therapy: bridging the gap from selective progesterone receptor modulators to gonadotropin-releasing hormone antagonist. Fertil Steril 2020;114:739–41.
79. Archer DF, Ng J, Chwalisz K, Chiu YL, Feinberg EC, Miller CE, et al. Elagolix suppresses ovulation in a dose-dependent manner: results from a 3-month, randomized study in ovulatory women. J Clin Endocrinol Metab 2020;105:dgz086.
80. 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;382:328–40.
81. 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.
82. Muneyyirci-Delale O, Archer DF, Owens CD, Barnhart KT, Bradley LD, Feinberg E, et al. Efficacy and safety of elagolix with add-back therapy in women with uterine fibroids and coexisting adenomyosis. F S Rep 2021;2:338–46.
83. Al-Hendy A, Lukes AS, Poindexter AN 3rd, Venturella R, Villarroel C, Critchley HOD, et al. Treatment of uterine fibroid symptoms with Relugolix Combination Therapy. N Engl J Med 2021;384:630–42.
84. Al-Hendy A, Lukes AS, Poindexter AN, Venturella R, Villarroel C, McKain L, et al. Long-term relugolix combination therapy for symptomatic uterine leiomyomas. Obstet Gynecol 2022;140:920–30.
85. Al-Hendy A, Venturella R, Arjona Ferreira JC, Li Y, Soulban G, Wagman RB, et al. LIBERTY randomized withdrawal study: relugolix combination therapy for heavy menstrual bleeding associated with uterine fibroids. Am J Obstet Gynecol 2023;229:662.e1–25.
86. Stewart EA, Al-Hendy A, Lukes AS, Madueke-Laveaux OS, Zhu E, Proehl S, et al. Relugolix combination therapy in Black/African American women with symptomatic uterine fibroids: LIBERTY long-term extension study. Am J Obstet Gynecol 2024;230:237.e1–11.
87. 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;400:896–907.
88. Saridogan E. Surgical treatment of fibroids in heavy menstrual bleeding. Womens Health (Lond Engl) 2016;12:53–62.
89. Lazaridis A, Hirsch M, Pistofidis G, Odejinmi F. Surgical management of uterine fibroids. Curr Opin Obstet Gynecol 2023;35:440–5.
90. 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. In press.
91. Puri K, Famuyide AO, Erwin PJ, Stewart EA, Laughlin-Tommaso SK. Submucosal fibroids and the relation to heavy menstrual bleeding and anemia. Am J Obstet Gynecol 2014;210:38.e1–7.
92. Emanuel MH. Hysteroscopy and the treatment of uterine fibroids. Best Pract Res Clin Obstet Gynaecol 2015;29:920–9.
93. Valentine LN, Bradley LD. Hysteroscopy for abnormal uterine bleeding and fibroids. Clin Obstet Gynecol 2017;60:231–44.
94. Nicholson WK, Wegienka G, Zhang S, Wallace K, Stewart E, Laughlin-Tommaso S, et al. Short-term health-related quality of life after hysterectomy compared with myomectomy for symptomatic leiomyomas. Obstet Gynecol 2019;134:261–9.
95. 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.
96. Rodriguez-Triana VM, Kwan L, Kelly M, Olson TH, Parker WH. Quality of life after laparoscopic and open abdominal myomectomy. J Minim Invasive Gynecol 2021;28:817–23.
97. Kuppermann M, Learman LA, Schembri M, Gregorich SE, Jackson RA, Jacoby A, et al. Contributions of hysterectomy and uterus-preserving surgery to health-related quality of life. Obstet Gynecol 2013;122:15–25.
98. 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;229:275.e1–17.
99. Committee opinion no 701. choosing the route of hysterectomy for benign disease. Obstet Gynecol 2017;129:e155–9.
100. Donnez J, Arriagada P, Donnez O, Dolmans MM. Emerging treatment options for uterine fibroids. Expert Opin Emerg Drugs 2018;23:17–23.
101. Moss J, Christie A. Uterine artery embolization for heavy menstrual bleeding. Womens Health (Lond) 2016;12:71–7.
102. Yoon JK, Han K, Kim M-D, Kim GM, Kwon JH, Won JY, et al. Five-year clinical outcomes of uterine artery embolization for symptomatic leiomyomas: An analysis of risk factors for reintervention. Eur J Radiol 2018;109:83–7.
103. Ananthakrishnan G, Murray L, Ritchie M, Murray G, Bryden F, Lassman S, et al. Randomized comparison of uterine artery embolization (UAE) with surgical treatment in patients with symptomatic uterine fibroids (REST trial): subanalysis of 5-year MRI findings. Cardiovasc Intervent Radiol 2013;36:676–81.
104. Hartmann KE, Fonnesbeck C, Surawicz T, Krishnaswami S, Andrews JC, Wilson JE, et al. Management of uterine fibroids. Rockville (MD). Agency for Healthcare Research and Quality (US) 2017, Report No.: 17(18)-EHC028-EF.
105. Manyonda I, Belli A-M, Lumsden M-A, Moss J, McKinnon W, Middleton LJ, et al. Uterine-Artery Embolization or Myomectomy for Uterine Fibroids. N Engl J Med 2020;383:440–51.
106. Sirkeci F, Moss J, Belli AM, McPherson K, Daniels J, Manyonda I, et al. Effects on heavy menstrual bleeding and pregnancy of uterine artery embolization (UAE) or myomectomy for women with uterine fibroids wishing to avoid hysterectomy: The FEMME randomized controlled trial. Int J Gynaecol Obstet 2023;160:492–501.
107. Gupta JK, Sinha A, Lumsden MA, Hickey M. Uterine artery embolization for symptomatic uterine fibroids. Cochrane Database Syst Rev 2014;(12):CD005073.
108. Sandberg EM, Tummers FHMP, Cohen SL, van den Haak L, Dekkers OM, Jansen FW. Reintervention risk and quality of life outcomes after uterine-sparing interventions for fibroids: a systematic review and meta-analysis. Fertil Steril 2018;109:698–707.e1.
109. Tonguc T, Recker F, Ganslmeier J, Strunk HM, Pieper CC, Ramig O, et al. Improvement of fibroid-associated symptoms and quality of life after US-guided high-intensity focused ultrasound (HIFU) of uterine fibroids. Sci Rep 2022;12:21155.
110. Bitton RR, Fast A, Vu K-N, Lum DA, Chen B, Hesley GK, et al. What predicts durable symptom relief of uterine fibroids treated with MRI-guided focused ultrasound? A multicenter trial in 8 academic centers. Eur Radiol 2023;33:7360–70.
111. Laughlin-Tommaso S, Barnard EP, AbdElmagied AM, Vaughan LE, Weaver AL, Hesley GK, et al. FIRSTT study: randomized controlled trial of uterine artery embolization vs focused ultrasound surgery. Am J Obstet Gynecol 2019;220:174.e1–13.
112. Kwon CS, Abu-Alnadi ND. Updates on the surgical approach to fibroids: the importance of radiofrequency ablation. Semin Intervent Radiol 2023;40:335–41.

113. Friedman AJ, Chen Z, Ford P, Johnson CA, Lopez AM, Shander A, et al. Iron deficiency anemia in women across the life span. J Womens Health (Larchmt) 2012;21:1282–9.
114. Percy L, Mansour D, Fraser I. Iron deficiency and iron deficiency anaemia in women. Best Pract Res Clin Obstet Gynaecol 2017;40:55–67.
115. Critchley HOD, Babayev E, Bulun SE, Clark S, Garcia-Grau I, Gregersen PK, et al. Menstruation: science and society. Am J Obstet Gynecol 2020;223:624–64.
116. Critchley HOD, Munro MG, Shakur-Still H, Roberts I. Menstruation should not be overlooked in control of anaemia. Lancet 2021;397:26.
117. Murji A, Lam M, Allen B, Richard L, Shariff SZ, Austin PC, et al. Risks of preoperative anemia in women undergoing elective hysterectomy and myomectomy. Am J Obstet Gynecol 2019;221:629.e1–18.
118. Mansour D, Hofmann A, Gemzell-Danielsson K. A review of clinical guidelines on the management of iron deficiency and iron-deficiency anemia in women with heavy menstrual bleeding. Adv Ther 2021;38:201–25.
119. Ng O, Keeler BD, Mishra A, Simpson JA, Neal K, Al-Hassi HO, et al. Iron therapy for preoperative anaemia. Cochrane Database Syst Rev 2019;12:CD011588.
120. Taran FA, Weaver AL, Coddington CC, Stewart EA. Characteristics indicating adenomyosis coexisting with leiomyomas: a case-control study. Hum Reprod 2010;25:1177–82.
121. Brucker SY, Huebner M, Wallwiener M, Stewart EA, Ebersoll S, Schoenfisch B, et al. Clinical characteristics indicating adenomyosis coexisting with leiomyomas: a retrospective, questionnaire-based study. Fertil Steril 2014;101:237–41.e1.
122. Ates S, Ozcan P, Aydin S, Karaca N. Differences in clinical characteristics for the determination of adenomyosis coexisting with leiomyomas. J Obstet Gynaecol Res 2016;42:307–12.
123. Ulin M, Ali M, Chaudhry ZT, Al-Hendy A, Yang Q. Uterine fibroids in menopause and perimenopause. Menopause 2020;27:238–42.