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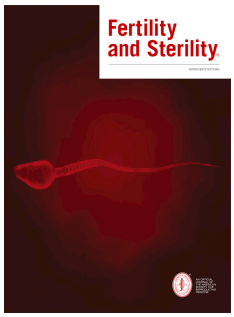

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The modern management of uterine fibroids-related abnormal uterine bleeding

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Abstract

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

Keywords: abnormal uterine bleeding, GnRH agonists, heavy menstrual bleeding, iron deficiency anemia, myomectomy, oral GnRH antagonists, uterine fibroids.

Introduction

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). Around 30% of UFs are incidentally diagnosed at the time of a routine pelvic exam or screening for another medical condition. UFs 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, affecting patients' quality of life (QoL). AUB that is caused by UFs is classified by the International Federation of Gynecology and Obstetrics (FIGO) as AUB-L (AUB-Leiomyoma) (5). Heavy menstrual bleeding (HMB) is recognized as 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 women's health and health care systems 'perspectives (7–10). Symptomatic UFs with HMB as the main complain 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 the cause of around 30% of hysterectomies (11,12). UFs is the cause of bleeding in almost half of women discharged from the hospital for acute episode of bleeding and anemia, in the context of AUB (13). Furthermore, AUB and HMB are a relevant cause of iron deficiency (ID) and ID anemia (IDA), often overlooked conditions (14,15), which in turns determine a variety of non-specific 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 on 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 explain the importance of an adequate management of these symptoms (9). A balance of the different surgical, medical or radiological treatment options should be discussed with the patient, depending on the presentation of symptoms, their severity, UFs number, size and localization, and the clinical context, including desire of pregnancy or to preserve the uterus independently of reproductive goals. Moreover, 79% of patients presenting 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 two decades, a shift towards more conservative interventions has been observed, thanks

to new available medical treatments which may help also before or after surgical treatment (20,21). Finally, a shared decision-making should be used in treatment selection, considering expected long- and short-term treatment goals, in the view of a patient-center rather than fibroid-center approach. Thus, the aim of the present review is to summarize the available evidence on medical, radiological and surgical options to treat UFs, focusing on the efficacy on AUB/HMB, along with ID and IDA management.

Mechanisms of AUB and HMB in uterine fibroids

Several theories have been proposed in the literature to establish a connection between UFs and AUB and HMB. In fact, there is a poor knowledge about the pathophysiology involved in AUB in the presence of structural conditions, such as UFs or adenomyosis. It is debatable if the excessive bleeding is a consequence of the presence of UFs or it is caused by pre-existing abnormalities in the endometrium (AUB-E), 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 which support increased angiogenesis (23), such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), endothelin-1. The increase extension in the surface area of the endometrium and in 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 due to platelet dysfunction compensated by increased vascular flow in engorged vessels, an increase in the secretion of Transforming Growth Factor β-3, all that causing defective endometrial decidualization (25) (Figure 1).

Medical treatment

Medical therapy is usually the first-line approach for UFs-related AUB and/or HMB (26). Medical options commonly used to manage the bleeding are non-hormonal drugs (non-steroidal anti-inflammatory drugs (NSAIDs) and tranexamic acid), or hormonal drugs (combined oral contraceptives, levonorgestrel intrauterine systems, gonadotropin-releasing hormone (GnRH) agonists or oral antagonists, progesterone receptors modulators or aromatase inhibitors) (27). No evidence of superiority of one compound compared to another has been demonstrated, even though some drugs entail more benefit and are more targeted for

AUB/HMB management. Besides, most of the agents target the endometrium, rather than directly the fibroid, resulting in a decrease of menstrual blood flow (Figure 2).

Over the last few years, some evidence showed 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, the green tea extract potentially decreases the menstrual flow (32,33), even though further studies are needed to make specific recommendations on that topic.

Non-hormonal treatments

Non-steroidal anti-inflammatory drugs

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

Tranexamic acid

Tranexamic acid inhibits fibrinolysis by reversibly blocking plasminogen and is available as 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 a 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 chronic setting, 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 (COCs) are commonly prescribed to address AUB and HMB, given their inhibiting effect on endometrial proliferation, with consequent maintenance of a thin endometrium, which in turns 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 versus ultra-low-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 a 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-beta-estradiol, combined with progestins, such as dienogest or nomegestrol acetate, is more effective to reduce menstrual blood loss than other COCs in patients with HMB, albeit not in case of UFs (41–44). Since the growth of UFs is influenced by both estrogens and progesterone (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 due to ovulatory cause, but the effects on UFs-related HMB is unclear and at most, only for short term, given the related side effects (48).

Levonorgestrel intrauterine system

The 52mg-levonorgestrel Intrauterine System (LNG-IUS) is a T-shaped device that releases the drug locally. It represents an option for contraception and for treatment of HMB overall (49). Due to its localized impact, LNG-IUS profoundly affects the endometrium, inducing atrophy and inactivity without suppressing ovulation (50). LNG-IUS leads to a reduction in endometrial proliferation and an increase in apoptosis within endometrial glands and stroma. LNG-IUS significantly decreases the duration and amount of menstrual flow in women experiencing HMB and/or frequent irregular bleeding due to UFs (51), but no clinical reduction in fibroid size has been observed following the treatment (4). After 1 year 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-L (55). However, it results more effective in alleviating symptoms of AUB in case of adenomyosis and endometrial hyperplasia, as well as in AUB due to not otherwise classified causes, than in case 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 use 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 Progesterone Receptor Modulators (SPRMs) exert specific effects on progesterone receptors (PRs) and can function as full PR agonists, antagonists, or possess a mixed agonist/antagonist profile. SPRMs impede the cellular proliferation of leiomyoma cells, promoting apoptosis while sparing normal myometrial cells; besides SPRM induce 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 prior to myomectomy. UPA showed to be very effective in fibroid volume reduction over 50% after 6 months treatment, with adequate control of uterine bleeding and restoration of hemoglobin levels (58–60). However, in May 2018, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agencies (EMA) 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 (DILI) (61). Currently, EMA 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, if fibroid embolization and/or surgical treatment are not suitable options or have failed.

Mifepristone is the original progesterone receptor modulator and it is widely known as RU-486 and primarily acknowledged as an antiprogesterone utilized for inducing abortion; it has also 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 modulators (SERMs) are non-steroidal ligands for estrogen receptors (ER) 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 (AIs) 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 mRNA has been identified in 90% of UFs but is absent in normal myometrial tissue. This observation suggests that aromatase inhibitors act to suppress the growth of fibroids by disrupting estrogen synthesis in these tumors. (26) AIs were thought to have fewer side effects and a quicker response compared to 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 (GnRHa)

GnRHa (leuprolide, goserelin, 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 FSH and LH production and subsequently gonadal steroid levels. This results in a hypoestrogenic state, crucial for the pharmacologic efficacy of GnRH agonists as UFs growth is estrogen-stimulated. Several studies have shown that tumor shrinkage correlates with the number of estrogen receptor (ER) positive cells. GnRHa interfere with matrix metalloproteinase (MMP) 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, while preserving fertility (26,69), even though in 23% of cases a regrowth of UFs is observed at 3 months and return to baseline by 6 months of cessation (70). Furthermore, GnRHa, either as one- or three-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, necessitating hormonal add-back therapy, which can include estrogens, progestins, or a combination of both. Therefore, the side effects imply a short-term use, which may be helpful, conversely, if used as preoperative treatment. There is clear evidence that preoperative GnRHa reduces uterine and fibroid volume and increases preoperative haemoglobin levels (72). In case of laparotomic or laparoscopic myomectomy, GnRHa pretreatment reduces intraoperative blood loss and the need for blood transfusions (73). Ultimately, the most clinically relevant indication for preoperative GnRHa use is in case of type 0-2 UFs, where a 3-months course with triptorelin and letrozole decreases the hysteroscopy time and the volume of fluid absorbed during hysteroscopic resection (74). Furthermore, GnRHa are a valuable option as a preoperative endometrial thinning agent before hysteroscopic destructive procedure for HMB, such as endometrial ablation (75). Apart from the use in the preoperative setting, given the risk of long-term hypoestrogenic adverse effects, treatment with GnRHa is limited to 6 months without add-back therapy and 12 months with add-back therapy. Thus, GnRH are recommended for the short-term treatment of UFs-related AUB/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 (GnRHant) 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 initial estradiol flare (77). Elagolix, relugolix and linzagolix showed an excellent control of UFs-related HMB, and, when combined with an addback treatment, bone mineral density is preserved, supporting these options also for long term management (81).

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 two co-packaged 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 (over 85% of participants), a higher percentage of women experiencing amenorrhea (more than 50% at 12 months) and an increase in hemoglobin level of more than 2 g per deciliter at 6 months than placebo (78). The benefit of add-back therapy is that it mitigates many of the hypoestrogenic side effects of elagolix (36), and the changes in bone mineral density and lipid profiles may be reversible following discontinuation after up to 12 months of therapy (79). Moreover, concomitant adenomyosis does not appear to limit the effectiveness for fibroid-related HMB. (80). As ovulation suppression with elagolix plus add-back is variable, it should not be considered a contraceptive agent (81).

Relugolix, in combination in 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 favorable benefit-risk profile, through the optimization of reproductive hormone ranges, which control HMB while maintaining healthy bone metabolism and preventing appearance of vasomotor symptoms. Relugolix combination therapy demonstrated a swift and consistent reduction in menstrual blood loss (over 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, over 50% blood loss reduction was observed, further decrease by 80% after 8-week treatment, remaining consistently reduced by 90% after 52 weeks treatment, when over 70% of patients were in amenorrhea. The treatment is generally well tolerated with few side effects, and particularly bone mineral density (BMD) was preserved through 2 years of treatment (82–84). Furthermore, a sub-analysis showed that once-daily relugolix combination therapy improved UFs-related HMB in most Black or African American women who participated in study, supporting the efficacy and safety of this option to manage bleeding symptoms in case of UFs (85).

Linzagolix is an oral GnRHant 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 the full suppression. Linzagolix, both at 100 mg or 200 mg, with or without add-back therapy, demonstrated a significant reduction in UFs-related HMB. Among patients undergoing a 200mg linzagolix

plus add back therapy, the response rate was over 75% at 24 weeks treatment (86). Reductions in bone mineral density 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 (86). Otherwise, high dosage with monotherapy could be an option, when the main goal is bleeding cessation and correction of anemia.

Surgical treatment

Surgical treatment remains the most widely used therapeutic option worldwide for UFs-related symptoms. Conservative and non-conservative approaches are available, depending on the number, the anatomic site and the size of UFs, along with patient's reproductive goals or preference, i.e. the wish to retain the uterus (87,88). The most minimally invasive route is recommended, whenever feasible. However, when choosing a surgical approach, an appropriate counselling on benefit-risk balance, considering also potential intraoperative surgical complications and recurrence of UFs, if a myomectomy is performed (89).

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 case of UFs-related AUB/HMB, submucosal fibroids, even at smaller sizes, are the main contributor to these symptoms, causing anemia in a relevant percentage of patients (90). In such cases of FIGO type 0, type 1, or type 2 the safety and efficacy of the hysteroscopic approach is undeniable (91,92). Small UFs (<2 cm) are routinely removed in an outpatient setting, whereas bigger fibroids may entail a more complex procedure, with higher risk of intraoperative complications (perforation and/or damage to surrounding myometrium and fluid intravasation), thus recommending an inpatient setting (20). Furthermore, in case of big FIGO type 1 and 2 UFs, or whenever IDA coexists, a pretreatment with either GnRHa or GnRHant may facilitate surgery by reducing myoma size and improving hemoglobin levels before the procedure, along with preparing the uterine cavity, 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 (eg, laparoscopic suturing) is another influent factor. QoL improvement has been demonstrated with all routes of myomectomy (93–95).

Hysterectomy

UFs 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 (96,97). Minimally invasive approaches (laparoscopy or robotic-assisted laparoscopy) are preferred to laparotomy, because of decreased morbidity and mortality (98). A shared decision-making with the patient is needed before choosing this non-conservative treatment. A discussion on all the available options and short and long-term goals is advisable (99), considering the possible patient's preference to preserve the uterus.

Interventional radiological 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 radiological options include uterine artery embolization (UAE), high intensity focused ultrasound (HIFU), magnetic resonance high-intensity focused ultrasound (MR-HIFU), radiofrequency ablation (RFA).

Randomized clinical trials support the efficacy of UAE as a minimally invasive option for management of UFs-related AUB/HMB, especially for women who prefer to retain the uterus, without reproductive wishes (100,101). UAE, causing UFs devascularization and involution, is associated with a significant reduction in myoma and uterine volume and an improvement in bleeding scores (102,103). 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 favourable QoL (104,105). A risk of reintervention should also be acknowledged (106,107).

Among the conservative approach, it is worth also mentioning the thermoablative techniques, namely the high intensity focused ultrasound energy, inducing coagulative necrosis of UFs. It can be realized under the guide of ultrasound or by MRI. An improvement in QoL domain has been observed following treatment (108,109), even though a high rate of reintervention is reported (107,110). However, the use of these techniques results mainly in UFs volume reduction, rather than AUB/HMB control.

Radiofrequency ablation (RFA) is now emerging as a uterine preserving and minimally invasive therapy for symptomatic UFs, by using elevated temperature to produce tissue destruction, aiming mainly to volume reduction. It may be either laparoscopic or transcervical, with promising results due to improved QoL and symptom severity scores, even though fertility results are still unclear and reintervention should be considered (111).

Management of iron deficiency anemia in uterine fibroids-related AUB/HMB

ID and IDA are commonly encountered conditions among patients with UFs-related HMB, due to either chronic or acute episode of bleeding, even though 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 (112,113), along with the effect of HMB itself, an adequate approach to UFs-related HMB should envisage the simultaneous management of IDA (114,115). Besides, ID and IDA can have significant implications for patient outcomes in view of a surgical intervention. In fact, preoperative anemia is a known risk factor for increased morbidity (venous thrombo-embolism, surgical site infections and hemorrhage) and mortality post-surgery when compared to nonanemic patients (116). Thus, the early identification and treatment of IDA is crucial, both preoperatively or during a medical management of UFs-related HMB. Besides, a preoperative hormonal treatment, with either GnRHa or oral GnRHant, inducing reduction of bleeding up to amenorrhea, improves the outcome of following surgical treatment (72).

An 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 non-responders to oral iron, or in case rapid rise of hemoglobin level is required before surgery (117). Intravenous iron has been shown to lead to a greater increase in hemoglobin and ferritin levels compared to

oral iron (118). Preventing and managing IDA requires a multi-faceted approach, with early recognition, investigation of underlying causes, iron supplementation, and optimization of erythropoiesis.

Management of uterine fibroids-related AUB in case of coexistent adenomyosis

The co-occurrence of UFs and adenomyosis is common (119–121). Given the possibility of co-existence of the two conditions, especially in the context of AUB/HMB, a management considering globally the uterine disorders is advisable. However, there are no currently approved pharmacologic options for adenomyosis, even though LNG-IUS, GnRHa and GnRHant are commonly used to treat the bleeding symptom of both conditions (80). The information of the presence of concomitant uterine disorders may be critical to individualize therapeutic approaches.

Management of uterine fibroids-related AUB in perimenopause

The perimenopausal period is characterized by a higher incidence of both UFs and anovulatory cycles (122). The coincidence of these two conditions establishes a negative synergy that exacerbates the severity of fibroid-induced HMB. UFs treatment 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.

Conclusions

The modern management of AUB/HMB related to UFs requires an individualized approach based on clinical profile, characteristics of UFs (location, size, multiple UFs or coexistent adenomyosis), patient’s preference and reproductive wishes (Figure 3). Ideally, the ultimate goal of treatment should be to relieve UFs symptoms while preserving the uterus. Medical treatment should be the first line approach, considering also the introduction of new medical drugs labelled for UFs-related HMB, such as oral GnRHant. Besides, hormonal treatment may be helpful also in case of a surgical approach to enable concomitant management of ID and IDA and maximize patient’s outcomes and QoL.

A shared decision-making should be the basis for treatment selection, considering long- and short-term treatment goals expected by the patient.

Figure legends

Figure 1. Mechanisms of AUB and HMB in uterine fibroids (UFs). *TGF-β, Transforming Growth Factor-beta.*

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 FSH and 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 endometrium. Selective progesterone receptors modulators (SPRMs) act on UFs, along with endometrium. Non steroidal anti-inflammatory drugs (NSAIDs) act at endometrial and myometrial level reducing bleeding, by non-hormonal mechanism. Tranexamic acid interferes with the coagulation cascade.*

Figure 3. UFs-related heavy menstrual bleeding: factors to consider for the management. *ID, iron deficiency; IDA, iron deficiency anemia.*

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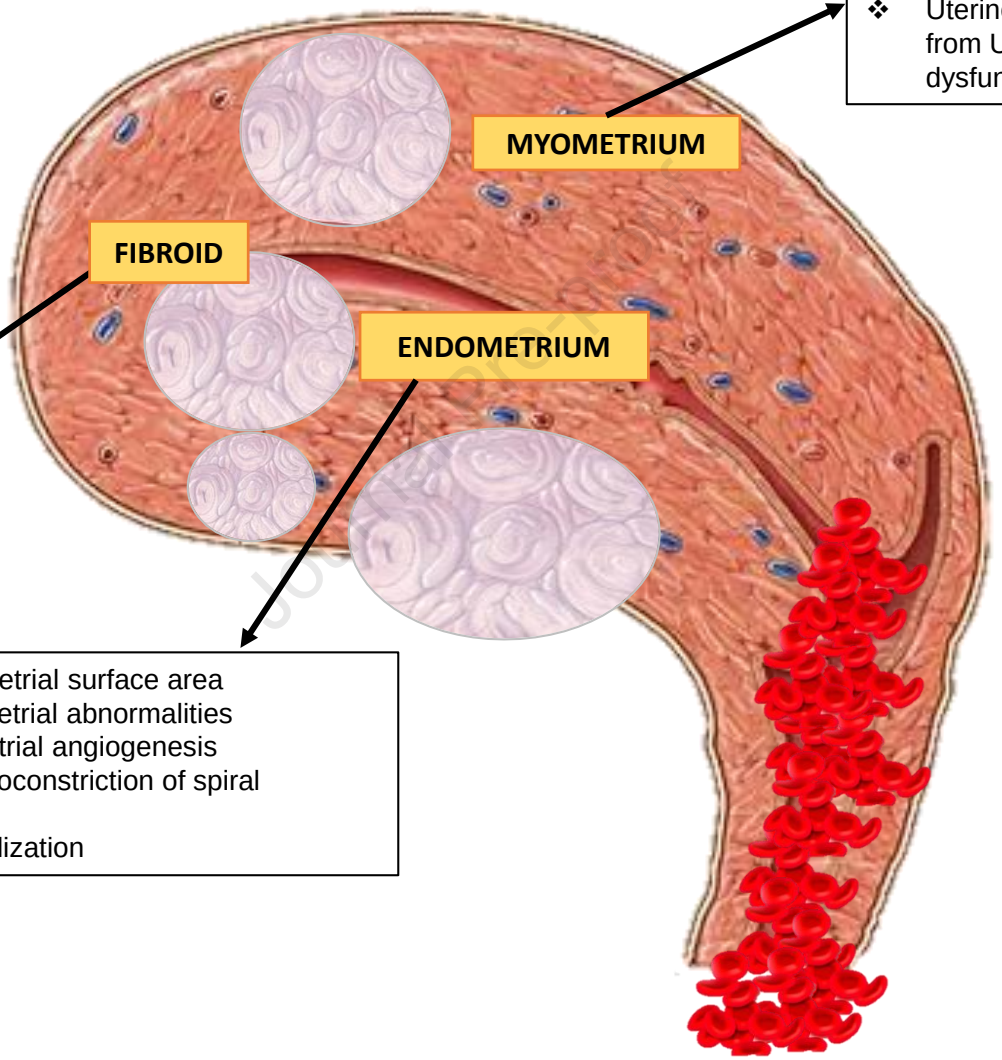

- Abnormal myometrial contractility
- Uterine venous ectasia by compression from UFs and consequent platelets dysfunction

- Dilated blood vessels on the surface of UFs
- Increased TGF-β production

- Increased endometrial surface area
- Molecular endometrial abnormalities
- Aberrant endometrial angiogenesis
- Alterations to vasoconstriction of spiral arterioles
- Impaired decidualization