

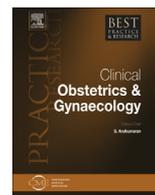


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The role of leiomyomas in the genesis of abnormal uterine bleeding (AUB)



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Abnormal uterine bleeding (AUB) is the major complaint in approximately one-third of gynecological visits in premenopausal women, and in >70% of appointments of perimenopausal and postmenopausal women. Uterine myoma is one of the main causes of AUB during menacme, especially when it is submucosal. The association of myoma and AUB may be related to several factors, from local alterations of angiogenic and vasoactive substances to changes in uterine contractility. The objective of this paper is to show the different associations of myoma and AUB.

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Abnormal uterine bleeding (AUB) is defined as bleeding from the uterine corpus, which is abnormal in duration, volume, and/or frequency, and mostly lasts for 6 months. Moreover, it is responsible for approximately one-third of the gynecological appointments in premenopausal women, and >70% of the visits of perimenopausal and postmenopausal women [1]. Menstrual disorders are common, with an annual prevalence of 53.0 per 1000 women in the United States of America [2].

The etiopathogenesis varies according to age groups and the origin of the condition may be in the lower genital tract, hypothalamus–hypophysis–ovary axis, and may be related to systemic and hormone alterations, such as coagulation and thyroid disorders. In order to manage this condition, it is crucial to identify or rule out the cause in order to provide adequate treatment. If all the causes are ruled out, the diagnosis of dysfunctional uterine bleeding is made.

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During menacme, structural uterine alterations, uterine polyps, and myomas are the main causes of AUB. In younger women, dysfunctional bleeding is more common. In 2011, based on an international consensus, the International Federation of Gynecology and Obstetrics (FIGO) established a system for the evaluation of AUB in patients during menacme and nonpregnancy, which was named PALM–COEIN (polyp, adenomyosis, leiomyoma, malignancy, and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified) [3]. It summarizes the most frequent causes of AUB.

During postmenopause, in the presence of hypoestrogenism, the most probable cause of AUB is endometrial atrophy, but some cases may be associated with polyps, myomas, or adenomyosis. In this age group, the presence of vaginal bleeding requires evaluation of the uterine cavity to rule out the presence of hyperplasia or neoplasia, because during this phase of life the most frequent complaint of patients with endometrial cancer is AUB, especially if associated with thickening of the endometrium [4].

Uterine fibroids are the most common tumors in women during childbearing age. They are benign nodules, of unicellular origin, and are asymptomatic in >50% of affected women. When symptomatic, they are associated with AUB, pelvic pain, infertility, and premature birth. AUB is the most frequent symptom of fibroids [5].

The bleeding caused by the uterine myoma occurs during the menstrual period, with heavier flow or prolonged period. Intermenstrual and postmenopausal bleeding are related to other types of uterine diseases, and adequate investigation should be made [5].

In 1956, Jacobson and Enzer described the correlation between the submucosal myoma and AUB, demonstrating that 57% of cases of AUB were found in submucosal myomas [6].

Even when the submucosal myoma is associated with AUB, its number and size, as well as its location, may interfere in symptoms. It is possible to associate the AUB of the uterine myoma with some factors:

- Increased endometrial surface.
- Increased uterine vascularization.
- Changes in uterine contractility pattern.
- Exposure and ulceration of the submucosal myoma surface.
- Degeneration of the myomatous nodule.
- Uterine venous ectasia by compression of the venous plexus by the nodules.

The presence of myomas inside the uterus would lead to increased endometrial surface, greater shedding area, and bleeding (Fig. 1).

The myoma is poorly irrigated, with peripheral vascularization, which could lead to bleeding by rupture of a surface vessel, in some cases (Fig. 2).

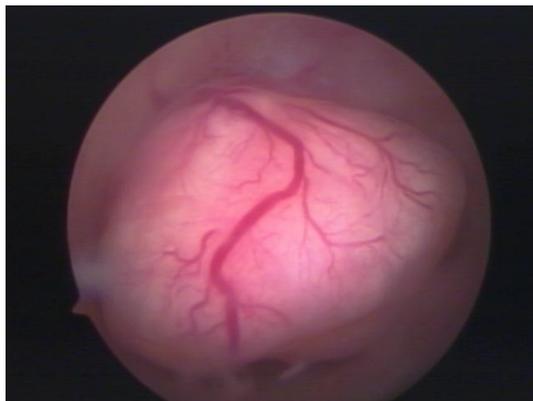


Fig. 1. Hysteroscopic view of submucous myoma.

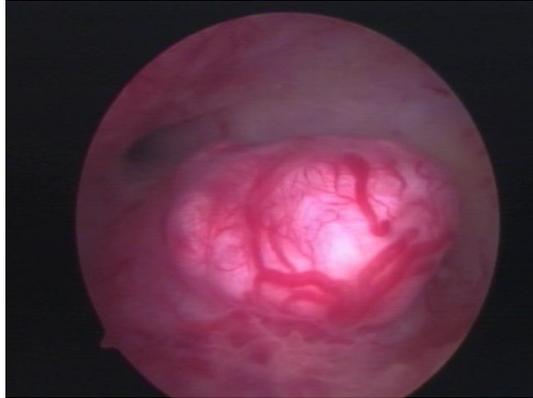


Fig. 2. Peripheral vascularization of submucous myoma.

There is a correlation between AUB and the degree of fibroid penetration in the uterine cavity. Submucous myomas (FIGO 0, 1, 2, and 3) are most frequently related to significant menorrhagia [7]. Some intramural fibroids can also be responsible for AUB. The mechanisms are unclear, but may include both microscopic and macroscopic abnormalities of the uterine vasculature, impaired endometrial hemostasis, or molecular deregulation of angiogenic factors, which are likely to be more frequent in myomas near the cavity [8].

Yang *et al.* [9] compared the hemoglobin levels of patients with single submucosal myomas, in the absence of other pathologies associated with menorrhagia, and concluded that the size of the myoma is the major factor associated with anemia. In addition, the degree of protrusion of the nodule into the uterine cavity also showed an association with hemoglobin levels. Patients with myomas measuring < 2 cm had similar hematimetric levels, regardless of the degree of protrusion of the myoma into the cavity. Myomas measuring 2–3.9 cm had an inverse association of the hemoglobin levels with the degree of protrusion. Myomas with <50% protrusion into the cavity had similar hemoglobin levels, regardless of the size of the nodule. In cases of myomas with a degree of protrusion of 50–79% and $\geq 80\%$, the hemoglobin levels were lower, as the nodule diameter increased.

The size of the myoma is related to AUB, provided it is in the uterine cavity or is distorting the cavity (FIGO 0, 1, 2, and 3). According to Wegienka *et al.*, nonsubmucosal leiomyomata were associated with essentially the same increase in heavy bleeding as submucosal leiomyomata of similar size [7] (Table 1).

The development of the leiomyomas seems to be related to the presence of angiogenic factors, matrix metalloproteinases (MMPs), and growth factors, such as the endothelial growth factor (EGF) and insulin-like growth factor-1 (IGF-1) [10–12]. The vascular endothelial growth factor (VEGF) seems to be associated with the growth of myomas. Its role is to induce angiogenesis, and it has already been described as being present at higher concentrations in deep endometriosis. Estrogen stimulates the production of VEGF by the endometrium, reinforcing the correlation between this factor and the development of myoma [13].

Korompelis *et al.* conducted a case–control study to compare the expression of MMP-2, MMP-9, their inhibiting factor TIMP-1, and VEGF, in patients with and without myomas. TIMP-1 is a tissue inhibitor of MMP-2 and MMP-9, and promotes inactivation of the metalloproteinases when connected. Metalloproteinases play a fundamental role in the process of remodeling the extracellular matrix, acting in its degradation. Moreover, Korompelis demonstrated higher serum levels of VEGF in patients with myoma as well as higher levels of VEGF in the myoma tissue as compared with normal myometrium. This difference in VEGF concentration in the tissues may confirm the importance of local angiogenesis as a growth and development factor of myomas. With regard to metalloproteinases, increased MMP-2 levels were identified in the myomatous tissue when compared with normal myometrium. MMP-2 acts by mediating the cleavage of type IV collagen, leading to instability of the

Table 1

Correlation between penetration of the myoma or distortion in the uterine cavity, size of the myoma, and intensity of the AUB.

Penetration/distortion	Degree of penetration (FIGO)	Size	Bleeding	Intensity
Yes	0, 1, 2, 3	< 2 cm	Yes	0 = 1 = 2 = 3
Yes	0, 1, 2, 3	2–3.9 cm	Yes	0 > 1 > 2 > 3
Yes	0, 1, 2, 3	≥ 4 cm	Yes	0 = 1 = 2 = 3
No	No	Any	No	No

extracellular matrix, and by cell–cell and cell–matrix interaction, thus interfering in cell proliferation and differentiation [14].

The presence of myoma, especially the submucosal type, leads to changes in uterine contractility, interrupting the normal peristaltic movement [15]. Uterine peristalsis is fundamental in the transport of the sperm for the fertilization process. This interference in uterine contractility may be associated with increased uterine bleeding, by impeding adequate hemostasis of the myometrial vessels.

In 2014, Kido *et al.* compared uterine peristalsis in patients with and without myomas, by using 3T magnetic resonance. The direction of the peristalsis was cervix – fundus in most patients, regardless of the presence of the nodule. Nevertheless, patients with myomatosis presented with a significant reduction of uterine peristalsis, corroborating the theory that the presence of the myoma would hinder the transmission of the contraction wave in normal myometrium [15,16]. In this study, the reduction of uterine peristalsis was not related to the size or location of the nodules, and the study only included patients with symptomatic myomas.

Vascularization of the myoma is generally peripheral, and when its growth is greater than its blood supply, there is degeneration and necrosis. This process is more frequent during the gestational period, when there may be accelerated growth of the myoma. In some cases, degeneration of the myoma can include nodule vascularization, leading to abundant transvaginal bleeding [17] (Fig. 3).

Clinical investigation of the uterine myoma in the diagnosis of AUB is initially conducted with ultrasonography, which identifies the presence of the myoma inside the uterus, the number of uterine myomata, besides ruling out endometrial diseases. Subsequently, hysteroscopy or hysterosonography may describe the level of penetration into the myometrium.

With hysteroscopy, it is possible to exclude other intrauterine causes of bleeding and conduct an anatomopathological study of the endometrium or of the identified lesions. Therefore, whenever possible, it should be indicated in the investigation of AUB. When assessing postmenopausal patients presenting uterine bleeding with or without myoma, it is mandatory to investigate the uterine cavity by hysteroscopy; if not possible, uterine curettage should be performed.

For cases with many large myomas, and concerns regarding degree of penetration or possible associated adenomyosis, magnetic resonance imaging (MRI) may be indicated. The best indication for

**Fig. 3.** Degenerated myoma with necrosis.

MRI is cases managed by conservative treatment and uterine volume $>375 \text{ cm}^3$. It is important to point out that in patients with AUB and ultrasonography showing uterine myoma, other causes of bleeding should be ruled out, because myoma may not be the cause, even when present, and most women with uterine myomas are asymptomatic (Fig. 4).

Myomas that cause AUB usually have surgical indication; to evaluate the difficulty or possibility of a hysteroscopic myomectomy, they should be classified. The European Society for Gynaecological Endoscopy (ESGE) classification describes the submucosal myoma in three levels: level 0 = completely inside the uterine cavity, level 1 = with its largest part inside the uterus, and level 2 = with its smallest portion in the uterine cavity [18]. Another classification, the STEPW (size, topography, extension, penetration, and wall), allows orientation before surgery, considering the complexity or the impossibility of a hysteroscopic myomectomy, based on five parameters: size, topography, extension of the base, penetration, and wall [19]. The hysteroscopic approach of myoma should be made by an experienced surgeon, because of the risk of uterine perforation and/or significant bleeding, besides a strict control of fluid balance. The classification of the myoma before surgery allows predicting difficulty of the procedure, the expected operative time, and risk of complications. The technique of direct mobilization of the myoma with Collins L-shaped electrodes may be a good alternative to the slicing technique in dealing with myomas with an extremely small myometrial mantle. In the direct mobilization technique, the nodule is safely and progressively migrated toward the uterine cavity, with the release of the myoma pseudocapsule from the myometrium [20,21] (Fig. 5).

Intramural or subserous myomas may have indication for surgery, when they are symptomatic. Pedunculated myomas may suffer torsion of their base, evolving with intense pain due to ischemia. The surgical approach to these myomas can be by laparoscopy or laparotomy, and either a myomectomy or hysterectomy may be performed depending on the patient's desire and number/size of the nodules. The use of power morcellators to reduce the volume of the nodules should be avoided because of the risk of morcellation of malignant lesions and disseminating the disease, except if this is performed inside a bag [22]. In the postmenopausal phase, the myoma tends to decrease in volume due to hypoestrogenism, and thus treatment of the nodule is not required. Rapid growth of the nodule during this period may indicate malignancy (leiomyosarcoma) and should be investigated. Patients submitted to elective surgery for myomatosis should have the hematimetric levels evaluated, and in the presence of anemia, this should be treated before the procedure. Selective progesterone receptor modulators and gonadotropin-releasing hormone analogs are effective in treating anemia and should be considered preoperatively in anemic patients [23].

Adenomyosis is another cause of AUB and its presence in the uterus with myoma is very frequent, which could lead to a difficulty in evaluating scientific articles when correlating the sites of the

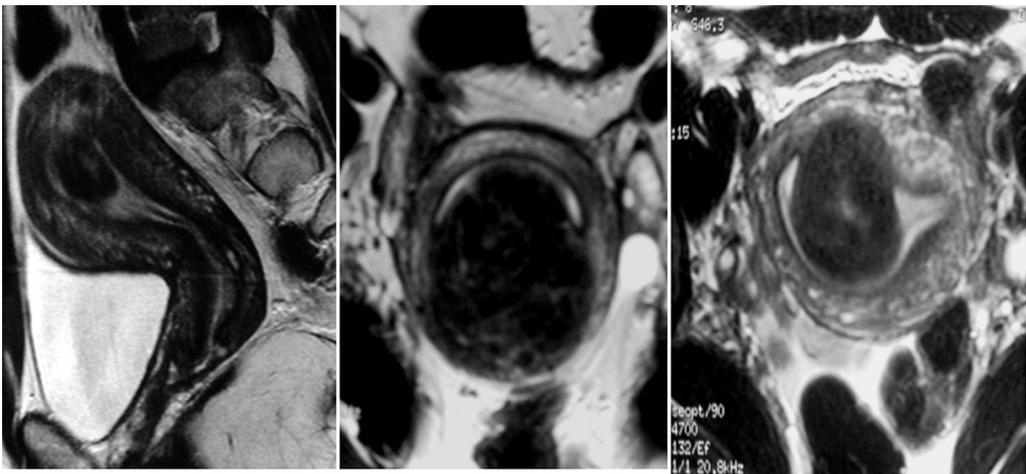


Fig. 4. MRI showing the degree of myoma penetration.

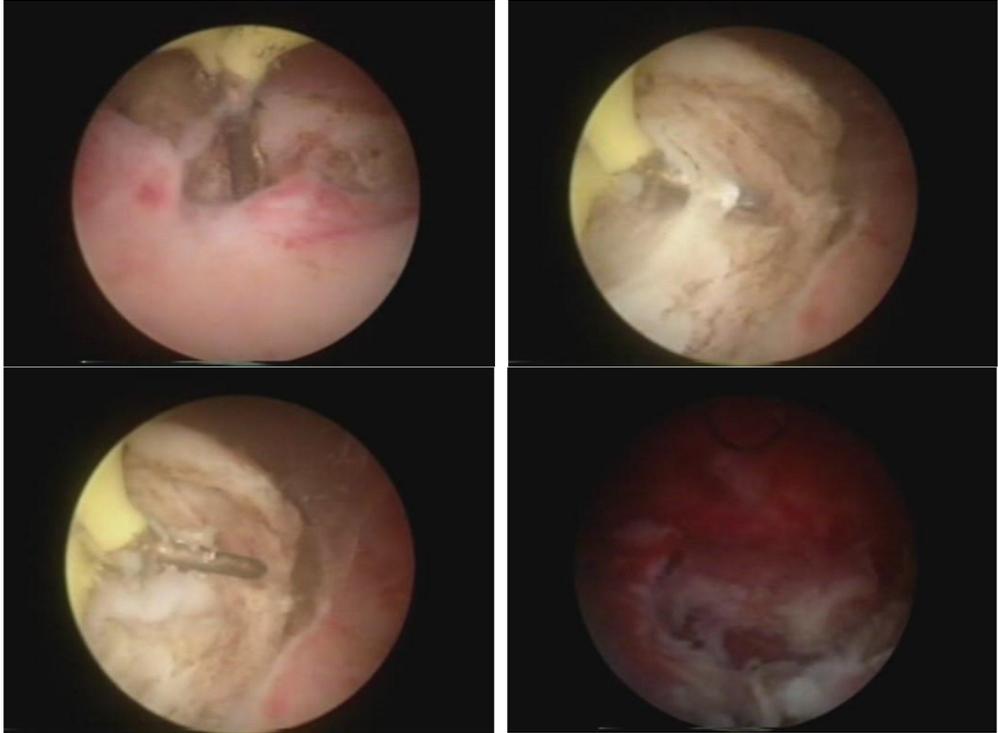


Fig. 5. Hysteroscopic myomectomy with direct mobilization technique.

myomas with AUB. This is because of the difficulty in diagnosing the image of adenomyosis, especially in the earlier studies.

The suggestion for investigation is to rule out uterine adenomyosis when assessing uterine myoma, both as a cause of bleeding and cause of infertility, so that a more precise correlation might be made of cause and effect.

Conflict of interest

There is no conflict of interest of the authors.

Practice points

Of the uterine myomas, the submucous type is more often related to AUB.

There is an evident correlation between the degree of penetration of the submucosal myoma in the uterine cavity and the intensity of the AUB.

The size of the submucosal myoma is a secondary parameter in correlating the degree of bleeding, and may have some correspondence in myomas measuring 2–3.9 cm, but depends primarily on the degree of penetration into the uterine cavity.

A submucosal myoma during postmenopause is rarely a cause of AUB in patients without hormone therapy; in some patients with hormone therapy, bleeding may occur.

The use of power morcellators should be avoided because of the risk of disseminating the malignant disease, unless this is performed inside a bag.

Anemia, when present, should be treated before the surgical approach of the myoma.

Research agenda

For future research, it is important to rule out adenomyosis in cases of patients with uterine myomas, because this disease is also associated with AUB, which causes lack of precision in study findings.

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