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Abnormal uterine bleeding: The well-known and the hidden face

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Abstract

Abnormal uterine bleeding (AUB) is a bleeding from the uterine corpus that is abnormal in regularity, volume, frequency or duration. It encompasses heavy menstrual bleeding, irregular menstrual bleeding and intermenstrual bleeding, which are common symptoms among women of reproductive age, impacting their overall well-being. Menstruation involves interactions between endometrial epithelial and stromal cells, immune cell influx, and changes in endometrial vasculature. These events resemble an inflammatory response with increased vessel permeability, tissue breakdown, and the arrival of innate immune cells. However, the mechanisms of menstrual cessation are poorly understood. AUB can be related to structural causes (polyp, adenomyosis, leiomyoma, malignancy/hyperplasia) and nonstructural conditions (coagulopathy, ovulatory dysfunction, endometrial, iatrogenic). While transvaginal ultrasound is the primary method for the screening of intracavitary lesions, saline infusion sonohysterography is more accurate to detect endometrial polyps and submucous leiomyomas, while hysteroscopy with biopsy remains the reference method for a definitive diagnosis. The main goals in managing AUB are addressing and correcting the underlying primary cause, if possible, and establishing a

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Caio R.V. Leal: Methodology, Writing – original draft. **Silvia Vannuccini:** Methodology, Supervision, Validation, Writing – review & editing. **Varsha Jain:** Methodology, Supervision, Validation, Writing – review & editing. **Marie-Madeleine Dolmans:** Methodology, Supervision, Validation, Writing – review & editing. **Attilio Di Spiezio Sardo:** Methodology, Supervision, Validation, Writing – review & editing. **Ayman Al-Hendy:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Fernando M. Reis:** Conceptualization, Methodology, Supervision, Writing – review & editing.

regular bleeding pattern or amenorrhea, which can be done with antifibrinolytic agents, progestins, gonadotropin-releasing hormone agonists and antagonists, or surgical interventions, each one with specific indications and limitations. Further research is necessary to assess the effectiveness and the long-term effects of various medical and surgical treatments. Meanwhile, the availability of diagnostic methods such as transvaginal ultrasound and hysteroscopy and the universal distribution of medical treatments for AUB should be prioritized by policymakers to minimize the diagnostic and treatment delay and thus reduce the risk of AUB-related anemia and the need of hysterectomy.

Keywords

Abnormal uterine bleeding; Heavy menstrual bleeding; Leiomyoma; Adenomyosis; Menstruation

1. Introduction

Menstrual well-being is a fundamental aspect of one's overall health, as most women will experience menstruation from puberty to menopause. However, for tens of millions of women worldwide, menstruation consistently and severely impacts their physical, mental, and social health [1]. In the Netherlands, a cross-sectional survey among women aged 15–45 years found that 43.7% of the respondents had ever consulted their general practitioner regarding any menstruation-related symptoms and the two main menstruation-related symptoms were abdominal pain during period and heavy menstrual bleeding (HMB) [2]. Another survey found a prevalence of 27% of HMB and 63% of iron deficiency among responders from five European countries [3].

The International Federation of Gynecology and Obstetrics (FIGO) systems for nomenclature of symptoms of normal and abnormal uterine bleeding (AUB) in the reproductive years (FIGO AUB System 1) and for classification of causes of AUB (FIGO AUB System 2; PALM-COEIN) were first published together in 2011 and revised in 2018. The PALM-COEIN classification outlines both the structural (polyp, adenomyosis, leiomyoma, malignancy/hyperplasia) and nonstructural (coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, not otherwise classified) factors leading to AUB during the reproductive years [4,5].

FIGO defines AUB as a bleeding from the uterine corpus that is abnormal in regularity, volume, frequency or duration and occurs in the absence of pregnancy; the main symptoms placed under the umbrella term "AUB" are HMB, irregular menstrual bleeding and intermenstrual bleeding [4]. HMB is a common concern among women of reproductive age, impacting their overall well-being, and is estimated to affect around 20–50% of women at some point in their reproductive life [6,7]. In the 2018 FIGO revision, HMB was formally included as a symptom (not a diagnosis), defined as "excessive menstrual blood loss, which interferes with a woman's physical, social, emotional and/or material quality of life" [4]. Menstrual bleeding leads to unfavorable perceptions and restricted engagement in social and work-related activities, however, the impact is notably greater in women with HMB compared to those with normal menstrual flow, as shown by a community-based cross-sectional descriptive survey with 1547 Swedish women, aged 40–45 years. In this survey,

women with HMB exhibited significantly lower Health-Related Quality of Life across all domains when compared to women with normal menstrual bleeding [8]. In fact, the degree of HMB-related anemia correlates directly with a worse quality of life in this population [9].

Unfortunately, a considerable proportion of women experiencing AUB and, especially, HMB, do not seek medical care and, when they do, their physician usually does not prescribe any medication for iron deficiency [3]. A systematic literature review showed that three key themes emerged to characterize the obstacles faced by women when seeking care for AUB: issues related to health literacy, societal taboos, and concerns related to healthcare providers [10]. Therefore, those conditions are still under-diagnosed and poorly treated worldwide.

The aim of this review is to discuss the pathophysiology, diagnosis as well as medical and surgical treatments of AUB, emphasizing what is known and what is still unknown in the field.

2. Pathophysiology

2.1. What is known

Menstruation involves poorly understood interactions between the endocrine and immune systems. These interactions, influenced by the menstrual cycle phase, entail epithelial and stromal cells, immune cell influx, and changes in endometrial vasculature. These events resemble an inflammatory response with increased vessel permeability, tissue breakdown, and the arrival of innate immune cells, including neutrophils and macrophages [1].

In normal menstruating women, due to the decline in progesterone levels marking the conclusion of the menstrual cycle, the upper functional layer of the endometrium undergoes a synchronized spatial and temporal reaction, resulting in menstruation. This process involves local cellular and molecular changes such as endometrial apoptosis, the influx of inflammatory mediators, and the activation of matrix metalloproteinases. The peri-menstrual phase encompasses the shift of the endometrium from the secretory phase, through menstrual shedding and recovery, to the regenerative phase [1,11]. To stop menstrual bleeding and repair the endometrium, three interconnected processes are necessary: the narrowing of specialized spiral arterioles, maintaining hemostasis in the endometrial area, and the restoration of the damaged endometrial mucosa.

In women experiencing AUB due to alterations in the ovarian production of steroids (AUB-O) or related to medication (AUB-I), the decline in progesterone levels occurs unpredictably [1]. AUB-O can be subdivided into four categories, according to the presumed primary source, which can be abbreviated as “HyPO-P”: Hypothalamic, Pituitary, Ovarian, or polycystic ovary syndrome (PCOS) [4]. In AUB-O patients, irregular and heavy bleeding occurs due to the absence of cyclic sex steroid production. Anovulatory cases lead to continuous endometrial growth driven by estrogen, causing eventual necrosis and partial shedding as the thickened lining outgrows its blood supply. Oligoovulation can result in episodes of partial shedding and normal menses.

The main factor behind AUB-E is disruptions in the molecular and cellular processes that control the amount of blood shed during menstruation. Vasoconstriction may induce temporary tissue oxygen deficiency and trigger the stabilization of hypoxia-inducible factor 1, which orchestrates endometrial repair. There is evidence to suggest that this repair process is less robust in individuals with AUB-E [1,11]. In patients with AUB-E, the localized inflammatory reaction within the endometrium made after the drop in progesterone at the end of the menstrual cycle is heightened, leading to a counteraction in the increase of vasoactive substances that generates strong constriction of spiral arterioles that would restrict blood loss [1].

During menstruation, damage to blood vessels following endometrial injury leads to platelets binding to collagen within a damaged basement membrane, which triggers a cascade of events related to blood clot formation. Effective hemostasis is crucial in limiting menstrual blood loss during menstruation, and this mechanism is compromised in women with AUB linked to the clotting processes (AUB-C) [1,11].

2.2. What is not known

Despite the great advances in understanding the physiology of menstrual bleeding, many questions remain unanswered [12]. Above all, the mechanisms of menstrual cessation are poorly understood, and their complete decipherment is critical to solve unexplained cases of HMB. We still ignore the relative importance of hemostatic factors, vasoconstriction, luminal epithelium regrowth and cell migration to stop menstrual bleeding. Also, the role of endometrial decidualization in the subsequent self-limitation of menstrual bleeding remains elusive [12].

There is a true lack of knowledge about the pathophysiology involved in AUB in the presence of structural conditions (such as polyps, uterine fibroids or adenomyosis). Is excessive bleeding a consequence of a “secondary endometrial disorder” in those situations?

Several theories have been proposed in the literature to establish a connection between uterine fibroids and AUB. These include an augmentation 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 uterine fibroids, uterine venous ectasia caused by pressure from the fibroid, platelet dysfunction compensated by increased vascular flow in engorged vessels, irregular uterine contractility and peristalsis, elevated levels of matrix metalloproteinases in fibroids, alterations in the expression of potential angiogenic factors, and an increase in the secretion of Transforming Growth Factor β−3, all associated with reduced levels of Plasminogen Activator Inhibitor-1 and Antithrombin III [13]. In summary, it seems that fibroids cause AUB by interfering with myometrial contractility, paracrine signaling (growth factors, prostaglandins, endothelin, angiogenic factors) and hemostatic regulation (alteration in the expression of clotting factors and impairing in platelet action) in the endometrium, but all these pathways and interactions are complex and still poorly understood [1].

As of now, the underlying cause of AUB related to adenomyosis has not been definitively determined [14]. Adenomyosis entails the infiltration of the basal endometrial tissue into the myometrium, potentially due to disruptions in junctional zones, but other hypotheses

are made, including the “Tissue Injury and Repair” (TIAR) concept, where endometrial injuries during menstruation might lead to the misplacement of cells within the myometrium and a third theory suggests the involvement of endometrial stem cells. Adenomyosis might involve recurring tissue injuries, changes in cell types, and the transformation of smooth muscle within the myometrium, causing it to become progressively more fibrous [11]. Apparently, increasing lesional fibrosis would propagate to neighboring endometrial–myometrial interface and then to the eutopic endometrium, attenuating the hypoxia signaling. This, in conjunction with diminished supply of energy and macromolecules and attenuated inflammation in the endometrium, may result in impaired endometrial repair and, as a consequence, AUB in patients with adenomyosis [15].

Similar to fibroids and adenomyosis, there is a gap in scientific knowledge about AUB caused by endometrial polyps. Polyps are commonly found in women experiencing AUB, with varying prevalence depending on menopausal status. They are associated with stromal congestion leading to reduced blood flow, which could explain the subsequent uterine bleeding. Interestingly, there is no clear correlation between the size, number, or location of polyps and the occurrence of bleeding symptoms [13].

3. Diagnosis

3.1. What is known

AUB can be diagnosed through a detailed clinical examination (Fig. 1), since its definition is purely clinical: “bleeding from uterine corpus that is abnormal (…)” [16]. First, it is crucial to assess the medical/reproductive history and to perform a careful pelvic examination focused on ruling out other sites of bleeding and assessing current uterine bleeding, adnexal masses and the size of the uterus. In the context of AUB in patients of reproductive age, it is mandatory to exclude current pregnancy with a pregnancy test, even in patients who report no sexual activity or who are using contraceptives. The overall impact of HMB on daily life can be measured retrospectively with instruments like the Menstrual Distress Questionnaire (MEDI-Q) [17]. In patients with uterine fibroids, the menstrual distress is significantly associated to the presence of HMB and MEDI-Q increases as the amount of bleeding increases [18].

Transvaginal ultrasonography is the primary and most reliable method for the diagnosis and assessment of structural causes, such as uterine fibroids, endometrial polyps, and adenomyosis [19]. A hysteroscopy may be necessary to distinguish between intracavitary myomas and large endometrial polyps. Hysteroscopy can also serve the dual purpose of providing a histological diagnosis and delivering effective treatment in such cases. In specific situations, magnetic resonance imaging (MRI) may be performed to provide a more comprehensive evaluation of the patient, particularly in instances involving multiple myomas, preoperative planning or when other imaging techniques yield inconclusive results [20].

In regard to laboratory tests, a complete blood count is routinely conducted to identify anemia in all patients who complain about HMB. If there is a strong suspicion of a coagulation cascade disorder, additional tests such as prothrombin time (PT), activated

partial thromboplastin time (aPTT), platelet count, and international normalized ratio (INR) may be recommended [21]. If the clinical history suggests an ovulatory dysfunction, laboratory tests may include serum androgens, thyroid-stimulating hormone and prolactin, depending on the bleeding pattern and associated symptoms [19,21,22].

In select cases, endometrial tissue sampling is performed for patients with AUB based on the bleeding pattern and on their risk factors for endometrial malignancy. For women aged 45 and above, especially with intermenstrual bleeding, or in the postmenopausal period experiencing AUB, the initial diagnostic test of choice is hysteroscopy with an endometrial biopsy [19,23]. Additionally, women under the age of 45 with unregulated exposure to estrogen, including those with obesity and/or PCOS, as well as those who have not responded to treatment or are still experiencing persistent bleeding, should also undergo endometrial evaluation [19,23].

3.2. What is not known

While transvaginal ultrasound is the most available method for the screening of intracavitary lesions, evidence suggests that saline infusion sonohysterography (SIS) achieves better sensitivity and specificity to detect endometrial polyps and submucous leiomyomas. Nevertheless, hysteroscopy with biopsy remains the reference method for a definitive diagnosis of intrauterine conditions associated with AUB, with the advantage of allowing diagnosis and treatment at the same time, for instance the detection and removal of a polyp [24,25]. What is still unknown is whether three-dimensional SIS has advantages over two-dimensional SIS [25], and whether the menstrual cycle phase affects the accuracy of SIS [26].

The diagnosis of adenomyosis is continuously improving with standardization of ultrasound and MRI protocols and criteria [27–29]. Nevertheless, the relative importance of each ultrasound feature to rule in the hypothesis of adenomyosis is still uncertain [29], while the association of ultrasound findings with the severity of adenomyosis symptoms remains controversial [28]. Other zones of uncertainty in the diagnostic workup of AUB include the clinical applicability of pictorial methods to measure HMB [30,31], the diagnostic cut-off values of endometrial Doppler indexes to detect endometrial carcinoma [32], and the cost-effectiveness of performing endometrial sampling in the primary care setting during the initial evaluation of women with AUB [33].

4. Medical treatment

4.1. What is known

The primary objectives in managing AUB include addressing and correcting the underlying primary cause, if possible, and establishing a regular bleeding pattern or achieving amenorrhea (Fig. 1). Some endocrinopathies, such as hypothyroidism and hyperprolactinemia, can cause AUB-O and their proper treatments tend to restore regular ovulatory cycles, resolving AUB. Anovulatory cycles, as seen in PCOS patients or in adolescents, can cause AUB-O that respond well to gonadal steroid therapy (combined estrogen and progestin formulations, progestin-only pills or levonorgestrel intrauterine

device) [34]. Since iatrogenic-related AUB is generally caused by the use of medications, use of intrauterine devices (especially copper intrauterine device) or use of contraceptives or steroid hormones, changing or discontinuing these medications/devices tends to resolve the bleeding.

In patients with idiopathic AUB, nonsteroidal anti-inflammatory drugs (NSAIDs) and tranexamic acid can be used [35]. NSAIDs act by inhibiting cyclooxygenase, reducing prostaglandin production, and altering the balance between substances that affect blood flow and platelet aggregation, ultimately reducing AUB by up to 40% [36]. Tranexamic acid, available in oral and intravenous forms, is FDA-approved for AUB and is the first-line treatment for AUB without established cause. Its mechanism of action is competitively blocking plasminogen binding sites, preventing clot breakdown. In the context of AUB, women with elevated endometrial plasminogen activators and increased local fibrinolytic activity benefit from tranexamic acid, which has proven more effective than placebo, mefenamic acid, and luteal-phase progestins [36].

Several medical treatments have been proposed for the management of AUB related to fibroids. Antifibrinolytics and progestins, especially the levonorgestrel-releasing intrauterine system, can treat fibroid-related bleeding and may successfully reduce the symptoms, prevent anemia, improve quality of life and spare surgery, although they do not treat the underlying cause itself [35]. So far, the only medications consistently related to significant reduction in both bleeding and fibroid volume are Gonadotropin-Releasing Hormone (GnRH) agonists (leuprolide, goserelin, triptorelin), GnRH antagonists (elagolix, relugolix, linzagolix) and selective progesterone receptor modulators [37]. GnRH agonists can be used to boost hemoglobin level and facilitate the surgical technique by reducing the size of the fibroid. They can also be used in patients in the menopausal transition, in an attempt to avoid surgery, however causing hypoestrogenic side effects like bone loss and hot flushes [38].

Oral, nonpeptide GnRH antagonists have been approved for the treatment of HMB associated with uterine fibroids [39–44]. The oral route may be more comfortable, but it requires daily administration, while depot GnRH agonists can be administered at 90-day intervals. The most appealing advantages of oral GnRH antagonists for HMB treatment are the rapid onset of action, easy reversibility, and the possibility to titrate a dosage that only partly blocks the pituitary-ovary axis and reaches optimal serum estradiol levels, low enough to relief symptoms but not too low as to cause hypoestrogenic side effects. In the industry-sponsored clinical trials required before commercial approval, elagolix [39,43], relugolix [40,42] and linzagolix [41,44] were superior to placebo and reduced substantially the blood loss volume during treatment. However, the need of add-back therapy to adjust estradiol levels, a burden that limits the use of GnRH agonists, was not overcome by the new generation drugs. Elagolix was finally recommended to treat HMB in the regimen of 300 mg 2 times per day with add-back therapy of estradiol 1 mg and norethisterone acetate 0.5 mg once daily [39]. Relugolix is easier to use, requiring just one daily administration, but the formulation approved to treat HMB contains 40 mg of relugolix associated with 1 mg of estradiol and 0.5 mg norethindrone acetate (relugolix-CT) [40,45]. Linzagolix was approved in the European Union in June 2022 for the treatment of moderate to severe uterine fibroid symptoms, including the possibility of choosing a low dose (100 mg once daily)

without add-back therapy, or a higher dose (200 mg) associated with estradiol 1 mg and norethisterone acetate 0.5 mg [41,44].

4.2. What is not known

The main open questions about oral GnRH antagonists concern their cost-effectiveness, long term safety, and residual effects after prolonged treatment. Despite differences in their half-life and metabolism, the three available drugs (elagolix, relugolix and lesagolix) have the same pharmacodynamics which is based upon lowering serum estradiol and progesterone levels, and their primary goal in the treatment of HMB is to inhibit endometrial growth, thereby reducing menstrual bleeding. Considering that these are new, thus costly medication, it is reasonable to start treating HMB with oral contraceptives, tranexamic acid, or levonorgestrel-releasing intrauterine system as first line options and, in case of failure, to move towards GnRH antagonists [35,46]. Anyway, economic studies are missing to support future guidelines in the cost-effectiveness analysis of GnRH antagonists for the treatment of HMB and different reimbursements according to each country makes generalization difficult.

As for long term safety of GnRH antagonists, the studies published so far are restricted to 2 years follow-up, a limited time for a treatment that is intended to control symptoms since their worsening until menopause, which can take up to 15–20 years. The question of residual effect after treatment withdrawal has been partly answered by the recent LIBERTY randomized withdrawal study, showing that at least for relugolix-CT the HMB associated with uterine fibroids resumes soon after treatment discontinuation [45]. Whether the same phenomenon happens after interrupting treatment with other regimens and same class drugs is not stated, but highly probable.

5. Surgical treatment

5.1. What is known

Surgical therapy can be a viable choice for certain AUB patients. This includes those who either prefer not to pursue medical treatments or have experienced unsatisfactory side effects or ineffectiveness with such therapies. It is also a consideration for individuals with some structural causes of AUB that are unresponsive to medical treatment or those who desire a definitive solution, like a hysterectomy. Moreover, in today’s context, with more women opting for delayed pregnancies, it is increasingly common to encounter individuals dealing with AUB while also wanting to retain their uterus for future conception. Therefore, surgical interventions should be customized to the patient’s specific needs and as minimally invasive as possible [47].

Hysteroscopic techniques are the preferred method for diagnosing and treating polyps. They allow direct visualization and immediate removal of polyps and can often be performed on an outpatient basis, reducing costs and recovery time. Nowadays, technical and technological innovation with miniaturized instrumentation allows most of the procedures to be carried out in the outpatient surgery [48,49]. For larger polyps, cervical dilation may

be necessary, requiring hysteroscopic resection with general or local anesthesia and larger instruments [47,50].

The surgical management of adenomyosis can be through hysterectomy, when fertility preservation is not an issue, or conservative interventions that preserve the uterus. Various surgical techniques are available, but their effectiveness varies [47]. In cases of localized adenomyosis, surgical removal may be attempted with an approach similar to myomectomy. However, it can be challenging to fully extract focal adenomyosis due to difficulties in exposing the lesion and defining clear margins. The efficacy of this surgery varies, but recent studies suggest moderate symptom relief and a low recurrence rate, with a potential for improved fertility after surgery [51]. Endometrial ablation and resection aim to preserve the uterus while treating adenomyosis, however, they carry a high risk of failure, potential repeat surgery, and limited success rates [52,53].

In fibroid-related uterine bleeding, traditional management has relied on surgery, such as hysterectomy and myomectomy. Over the past two decades, a shift towards more conservative interventions has been observed [37]. In summary, the choice of treatment for symptomatic uterine fibroids in patients desiring pregnancy depends on the type, size, and location of the fibroids, as well as the patient's individual characteristics and fertility goals. Minimally invasive techniques like hysteroscopic and laparoscopic myomectomy are often recommended for preserving fertility, while open abdominal myomectomy is suitable for cases with numerous or large fibroids [54]. Timing treatment close to active pursuit of pregnancy is essential to minimize the risk of fibroid recurrence. Patient-specific considerations and surgeon expertise play a crucial role in selecting the most appropriate strategy.

Hysteroscopic myomectomy is a less invasive treatment for submucosal myomas, providing symptom relief, though more than one intervention may be needed according to the size [55]. Different surgical methods, such as laparoscopic or abdominal myomectomy, are available for intramural and subserosal myomas. The choice between these techniques depends on the patient's individual case, but laparoscopic myomectomy has advantages such as lower blood loss, reduced pain, and faster recovery [56]. The preoperative administration of GnRHa can reduce intraoperative bleeding and surgical risks. Robotic-assisted laparoscopic myomectomy offers advantages over conventional laparoscopic and open procedures, including intraoperative bleeding, postoperative complications, the need of blood transfusions and the duration of hospital stay following the surgery. However, those outcomes come with longer operation times and considerable higher costs [57].

Alternative approaches for fibroid management include uterine artery embolization (UAE). Patient satisfaction and quicker recovery are noted advantages of UAE, but it should not be proposed in patients desiring future pregnancies [20,58]. Despite uncertainty regarding their impact on fertility [59], myomectomy appears more beneficial than UAE [60].

5.2. What is not known

Further research is necessary to assess the effectiveness and long-term effects of various surgical treatments. One question that still needs investigation is how to avoid

iatrogenic intrauterine adhesions while treating polyps or leiomyomas with hysteroscopic surgery [59]. The role of preoperative medical treatments such as GnRH agonists or selective progesterone receptor modulators to reduce leiomyoma size, operative time and perioperative bleeding seems advantageous but requires further validation [47,59].

6. Conclusions

AUB is a symptom with many causes and therefore a single management strategy is unlikely to meet all patients' needs. The introduction of PALM-COEIN classification was a great step towards uniform diagnostic criteria and reliable etiological definition, with quality improvements in both research and clinical practice. Nevertheless, except for endometrial polyps and certain fibroids that can be removed efficiently by minimally invasive surgery, our therapeutic repertoire remains limited to invasive and sometimes sterilizing surgical interventions or to drugs that focus on hemostasis or ovarian steroid modulation (Fig. 2). The discovery of molecular mechanisms behind the physiological control of menstruation, along with the pathological mechanisms driven by uterine fibroids or adenomyosis should push innovation in the pharmacological approach of AUB, with new drugs designed to control fibrosis, inflammation, vasoconstriction and cell proliferation beyond sex steroids. Meanwhile, the availability of diagnostic methods such as transvaginal ultrasound and hysteroscopy and the universal distribution of medical treatments for AUB should be prioritized by policymakers to minimize the diagnostic and treatment delay and thus reduce the risk of AUB-related anemia and the need of hysterectomy.

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Biography

Fernando M. Reis is professor of Gynecology and Reproductive Medicine at Universidade Federal de Minas Gerais, Belo Horizonte, Brazil, and has been visiting professor at the universities of Siena and Paris. His current research interests include reproductive physiology, uterine fibroids and endometriosis.

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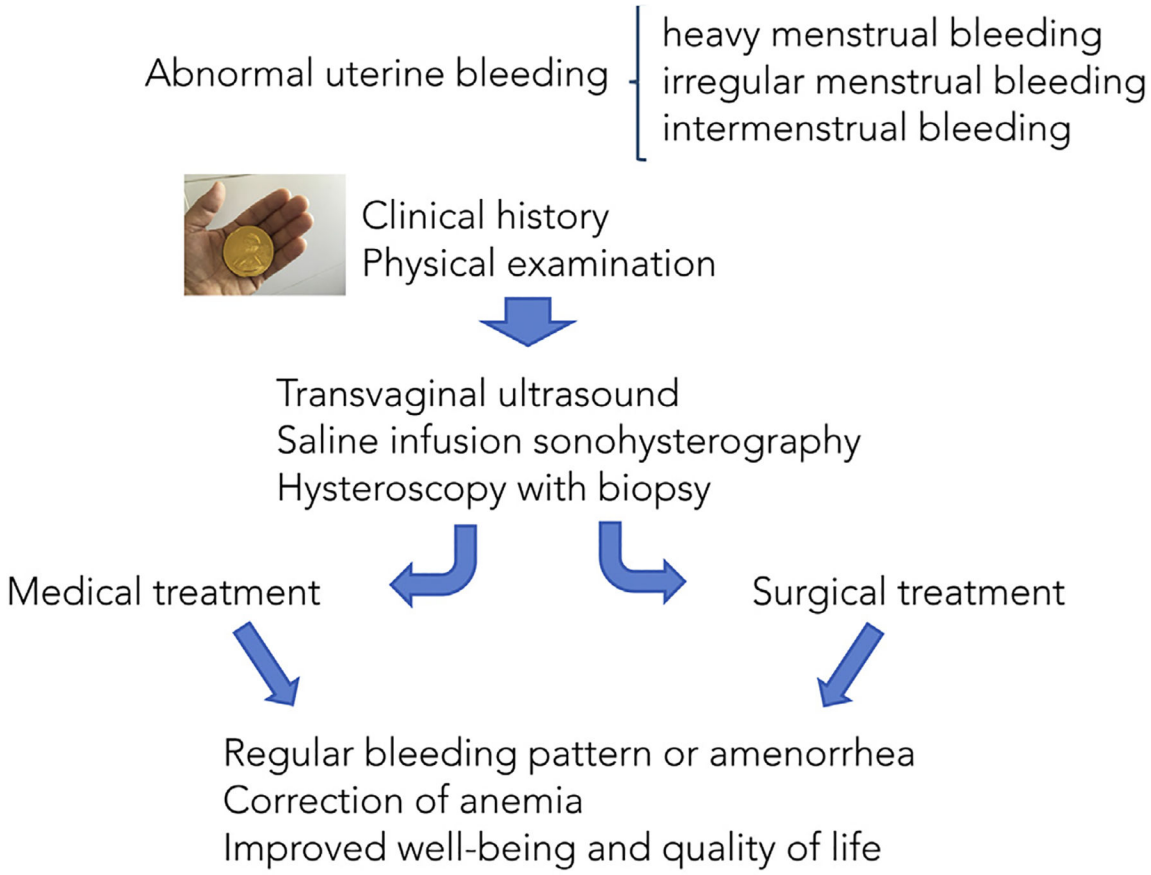

Fig. 1.

Management of abnormal uterine bleeding, from etiological investigation (PALM-COEIN) to therapeutic options and desired outcomes. Whenever possible the underlying causes should be treated, along with symptom control and correction of anemia.

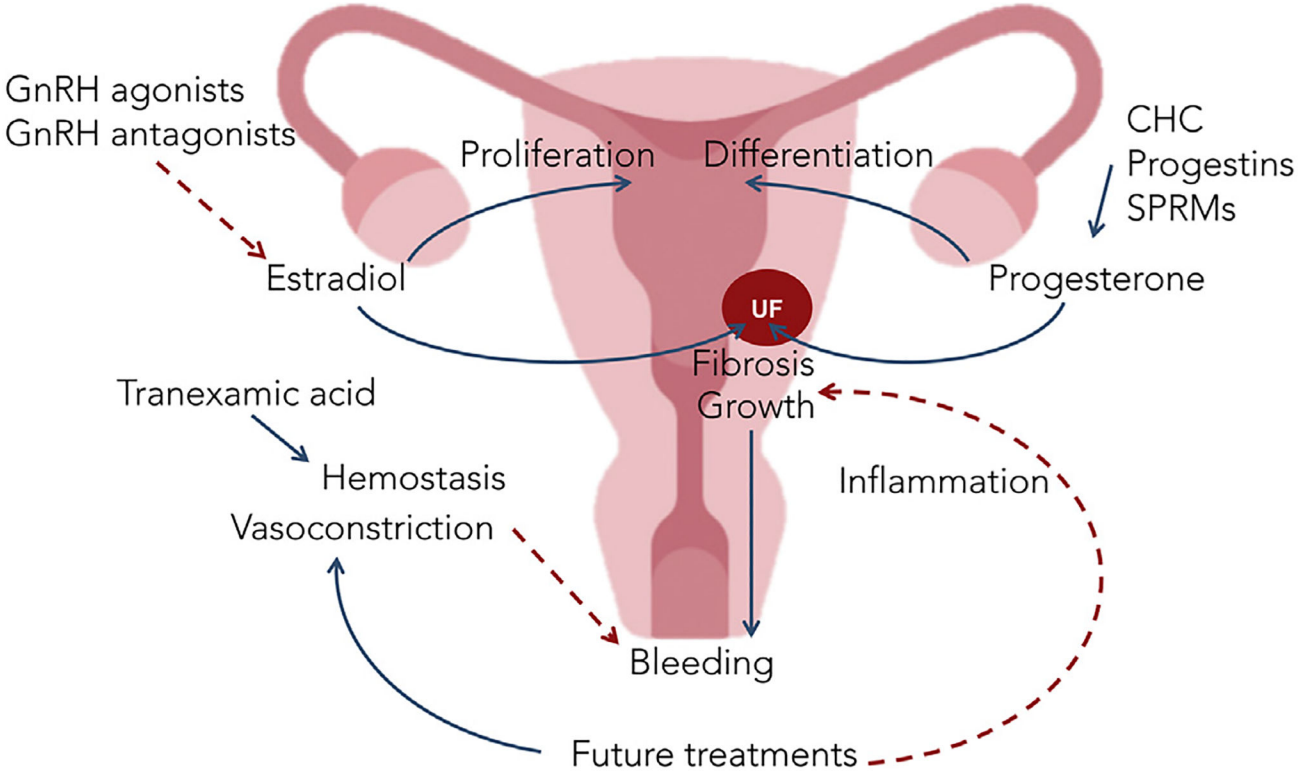

Fig. 2.
Mechanisms associated with uterine bleeding and the main targets of medical treatments.