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Review Article

Medical treatment for heavy menstrual bleeding

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ABSTRACT

Heavy menstrual bleeding, or menorrhagia, is subjectively defined as a "complaint of a large amount of bleeding during menstrual cycles that occurs over several consecutive cycles" and is objectively defined as menstrual blood loss of more than 80 mL per cycle that is associated with an anemia status (defined as a hemoglobin level of <10 g/dL). During their reproductive age, more than 30% of women will complain of or experience a heavy amount of bleeding, which leads to a debilitating health outcome, including significantly reduced health-related quality of life, and a considerable economic burden on the health care system. Although surgical treatment might be the most important definite treatment, especially hysterectomy for those women who have finished bearing children, the uterus is still regarded as the regulator and controller of important physiological functions, a sexual organ, a source of energy and vitality, and a maintainer of youth and attractiveness. This has resulted in a modern trend in which women may reconsider the possibility of organ preservation. For women who wish to retain the uterus, medical treatment may be one of the best alternatives. In this review, recent trends in the management of women with heavy menstrual bleeding are discussed.

Introduction

Heavy menstrual bleeding (HMB), defined as a blood loss of more than 80 mL per cycle and often accompanied with anemia, is a major reason for gynecologic consultations around the world. Women with HMB experience a diminished quality of life and a loss of work productivity, and face high expenses for medical services [1]. Various terms have been used to describe HMB, including menometrorrhagia, metrorrhagia, menorrhagia, and polymenorrhea. The confusing and inconsistently applied nomenclature and the lack of standardized methods for investigation and categorization of the various potential etiologies make it difficult to compare studies performed by different investigators or research groups. Therefore, a universally accepted system of nomenclature and classification seems to be a necessary step in the evolution of collaborative research and evidence-based application of results to clinical practice [1]. In addition, an accurate diagnosis based on a universally accepted system of nomenclature and classification might offer a better understanding of the pathophysiology of HMB, which would help physicians make better decisions regarding the management of women with this condition. After an effective treatment, good control of the patient's symptoms and signs will improve her quality of life [2–4].

To clearly demonstrate HMB, the Menstrual Disorders Working Group of the International Federation of Gynecology and Obstetrics (FIGO) has proposed abandoning the use of one common term, "dysfunctional uterine bleeding" [5]. There are nine main categories, arranged according to the acronym PALM–COEIN (polyp, adenomyosis, leiomyomas, malignancy, hyperplasia–coagulopathy,

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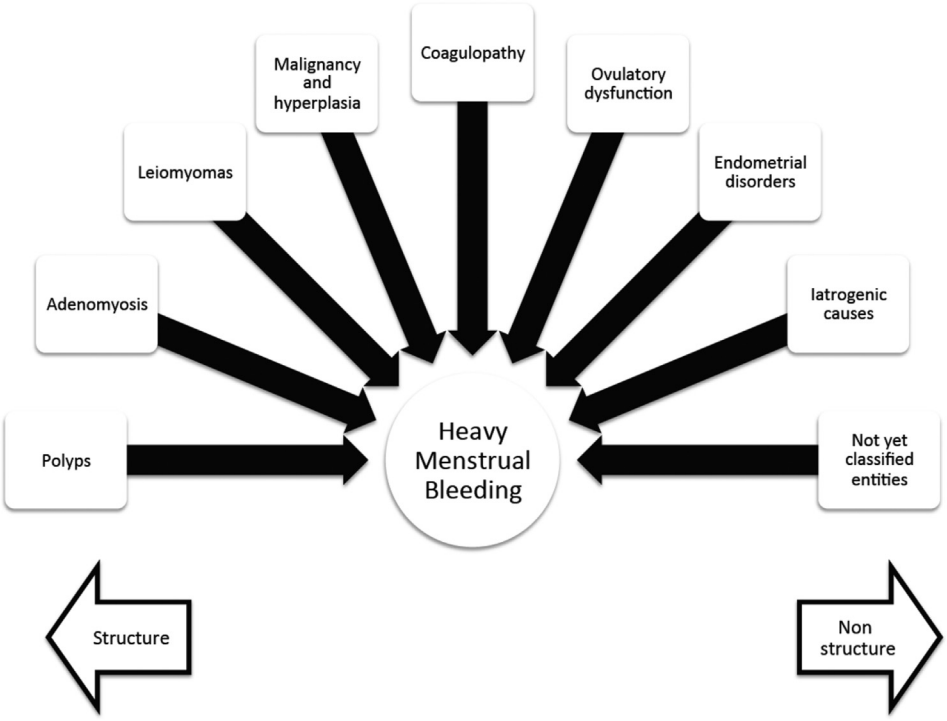

Figure 1. PALM–COEIN (polyp, adenomyosis, leiomyomas, malignancy, hyperplasia- coagulopathy, ovulatory dysfunction, endometrial disorders, iatrogenic causes and not-yet-classified entities) system for heavy menstrual bleeding.

ovulatory dysfunction, endometrial disorders, iatrogenic causes and not-yet-classified entities) (Figure 1). The PALM categories include polyp, adenomyosis, leiomyomas, and malignancy and hyperplasia [5]. In general, the components of PALM are structural etiologies, which can be measured visually because they can be evaluated by clinical examination, imaging techniques, or histopathology [6]. It is difficult to define a COEIN status by imaging or histopathology, since COEIN is related to nonstructural entities [6], including coagulopathy, ovulatory dysfunction [7], endometrial disorders by exclusion of other identifiable abnormalities in women of reproductive age; , iatrogenic causes, such as insertion of an intrauterine system [8] or medicine directly impacting the endometrium [9], interfering with blood coagulation mechanisms (warfarin, heparin, and low-molecular-weight heparin) [10], and influencing the systemic control of ovulation, and not-yet-classified entities, including chronic endometritis [11], arteriovenous malformation [12], myometrial hypertrophy, and possible future entities.

The primary classification system reflects only the presence (1) or absence (0) [5,6], and cannot totally show the severity of diseases. Therefore, a secondary classification system may be needed in some subgroups. For example, leiomyomas involving the endometrial cavity [submucosal (SM)] need to be distinguished from others (O) because SM lesions are most likely to contribute to the genesis of HMB [5]. Tertiary subclassification of leiomyoma types requires the clinicians to determine the relationship between the leiomyomas and the endometrium, myometrium, and serosa [13]. SM types are 0 (pedunculated intracavitary), 1 (<50% intramural), and 2 (≥50% intramural), and the others are 3 (contracts endometrium, 100% intramural), 4 (intramural), 5 (subserosal ≥50% intramural), 6 (subserosal <50% intramural), 7 (subserosal pedunculated), and 8 (includes cervical or parasitic and other lesions not related to the myometrium) [14].

The PALM–COEIN system not only allows clinicians and researchers to identify and classify women with HMB in a systematic manner, but also provides reliable information for research purposes and for epidemiological and prevalence studies in different settings [15]. This classification is useful for patient-tailored therapy, especially for differential stages of women's reproductive years and for different patterns of HMB [15]. It is important to keep in mind that many of these causes of HMB can be asymptomatic, and that HMB itself might be the first symptom or the only symptom presented by patients [16,17].

Strategy to evaluate women with HMB

Measuring menstrual blood loss accurately is impractical because of the complexity of the techniques [15]. Therefore, HMB could be defined as “excess menstrual blood loss interfering with women's physical, emotional, social and material quality of life.” HMB can occur alone or in combination with other symptoms. Normal limits of menstruation in women include: (1) a menstrual period frequency ranging from 24 days to 38 days; (2) duration of blood flow ranging from 4 days to 8 days; and (3) the volume of monthly blood flow ranging from 5 mL to 80 mL [6]. The cause of HMB can be clearly separated from structural and nonstructural problems. Therefore, all women with HMB should be treated in as diligent and comprehensive a fashion as is practicable, given the clinical situation and the available resources [5]. That is to say, we need to establish necessary parameters to achieve an accurate diagnosis and treatment for women with HMB (Figure 2).

Clinicians should perform a careful evaluation of a woman of reproductive age with HMB, to ensure that the bleeding is not related to an undiagnosed pregnancy and is emanating from the cervical os, rather than from another location [5]. The bleeding should be confirmed, in the absence of any other identifiable source [18]. In addition, a structured history, including the age of the woman, regularity of menstrual cycles and accompanying menstruation problems (for example, dysmenorrhea), beginning and frequency of HMB, symptoms or signs of a tendency to bleed, bruises, epistaxis, and a family history, should be taken and

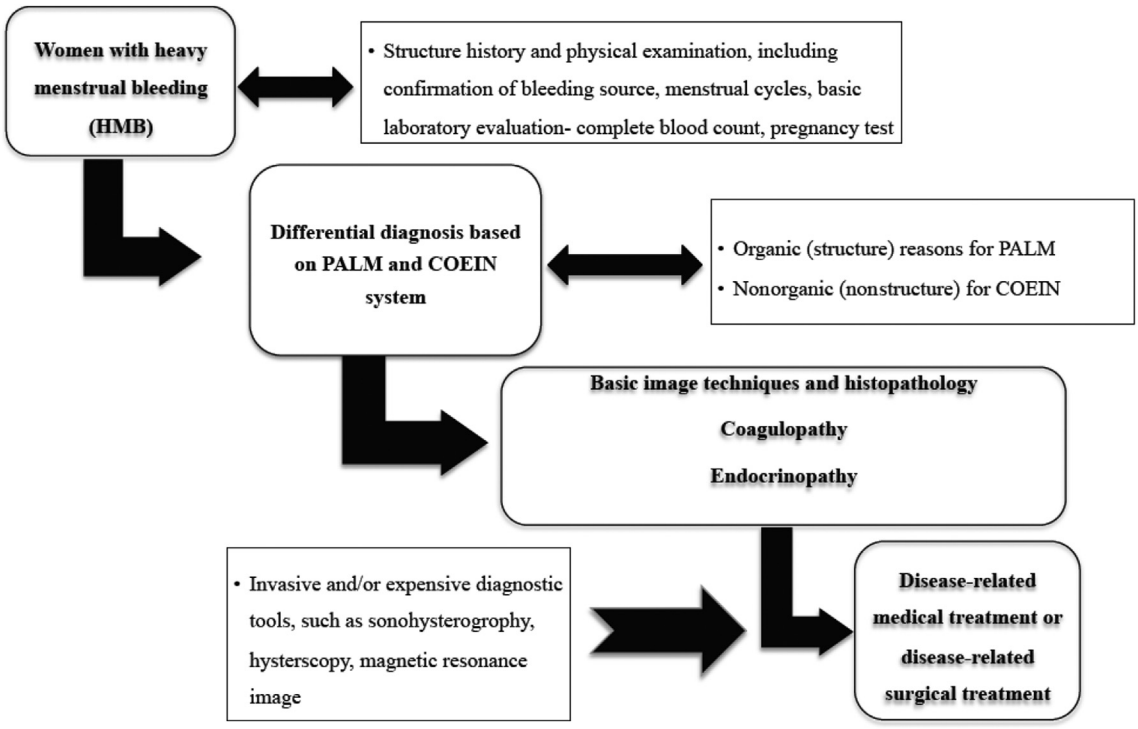

Figure 2. Algorithm for evaluation of women with heavy menstrual bleeding. HMB = heavy menstrual bleeding.

evaluated. Specialists, such as hematologists, should be consulted, if coagulopathy problems, which occur in approximately 13% of women with HMB, cannot be totally excluded [14].

Basic technologies for investigation of different causes include transvaginal ultrasound (and/or transabdominal ultrasound), tissue biopsy, histology, and diagnostic hysteroscopy. Transvaginal ultrasound might be one of the most convenient, economical, and useful image modalities to evaluate women with HMB. Adequate quality to display myometrial and endometrial features clearly is important for ideal imaging by transvaginal ultrasound. Endometrial sampling should be considered in women over a certain age, usually 45 years, and with a family history of genetic disorders, such as hereditary nonpolyposis colorectal cancer syndrome [19], since the possibility of endometrial cancer should be excluded [20], even though ovulation disorders are also frequently noted in women during the menopausal transition. To detect adenomyosis, its variance (adenomyoma), or submucosal myoma more accurately, magnetic resonance imaging may be needed, although it is not practical at the present time [21–23].

Medical treatment

In women with definite causes of HMB, therapeutic choices should be based on the PALM–COEIN system. For polyps, surgical removal is highly recommended, especially the use of minimally invasive procedures, such as hysteroscopy [24,25]. For certain types of leiomyomas, for example, SM leiomyomas, surgical removal is frequently required, although medical treatment can work in some cases. Hysteroscopic resection, by either a one- or two-step procedure, or after preoperative hormonal therapy, including gonadotropin-releasing hormone agonist (GnRH agonist) and/or ulipristal acetate (one of the selective progesterone receptor modulators—SPRMs) [26–28], has been well accepted as the treatment of choice [29,30]. Endometrial lesions should be managed based on the pathological findings. Precancer lesions, including endometrial hyperplasia with and/or without atypia, or some early-stage and well-differentiated (Grade 1) endometrioid-type endometrial cancers, could be managed conservatively. These conservative treatments include high-dose progestin and/or other hormonal therapies [20,31]. However, conservative medical treatment for women with endometrial precancer or endometrioid cancer is not totally free of risk. The following criteria or considerations should be carefully evaluated: (1) the potential oncologic risk should be assessed, since the persistent, progressive rate of cancer is 15–25%; (2) a good candidate for conservative treatment should be younger than 40 years, should have a need to give birth, and have an ability to give birth; (3) the disease should be limited to 2009 FIGO IA and this diagnosis should be confirmed by gynecologic–pathologic experts; (4) the treated women should have good compliance and not have any contraindication to high-dose progestins; (5) the women should be informed that the initial response rate of the drugs ranges from 50% to 70%; (6) these conservative treatments often include hormones, such as medroxyprogesterone, megestrol, and levonorgestrel-releasing intrauterine system (LNG-IUS) ± GnRH agonist; (7) the hormone dosage should be administered adequately, and the frequently used medication includes 200–800 mg medroxyprogesterone and 80–320 mg megestrol; (8) the women should have excellent compliance and adequate surveillance, which should occur every 2–6 months; (9) after conservative medical treatment, these women have only a 30–40% chance of a successful reproductive outcome; and (10) these patients need counseling by well-trained team workers [31,32].

Coagulation problems and endocrinopathy could be managed based on their definite causes. Iatrogenic causes could be managed by removal of the iatrogenic factors and modification of dosage use. Other important causes of HMB include not-yet-classified entities, such as chronic endometritis, especially chlamydial infection [33], arteriovenous malformation, myometrial hypertrophy, and possible future entities. Some of these not-yet-classified entities could be managed by antibiotics and embolization [34].

Women with uterine leiomyoma and/or adenomyosis can be managed with medical treatment. Our previous studies reviewed

this extensively [35–38]. Some medications, including SPRMs, gestrinone, danazol, progestins, oral pills, LNG-IUS, and GnRH agonist are discussed.

Among these medications, SPRMs, including ulipristal acetate, mifepristone, asoprisnil, lonaprisan, telapristone acetate, PRA-910, ZK 136799, and onapristone, inhibit endometrial proliferation or suppress leiomyoma and/or adenomyotic lesions, resulting in inhibition of prostaglandin production and shrinkage of leiomyoma and/or adenomyotic lesions, and endometrial atrophy, suggesting that these beneficial effects of SPRMs treatment may reflect changes in the endometrial morphology and/or the absence of bleeding [39]. A recent head-to-head comparison study showed that ulipristal acetate (one of the SPRMs) was superior to placebo and not inferior to leuprolide acetate (one of the GnRH agonists) for the control of HMB. More than 90% of women treated with ulipristal acetate had a clinically significant decrease in bleeding, and approximately three-fourths became amenorrheic [39]. The SPRMs might be promising agents in the management of uterine fibroid-related HMB; however, a potential safety issue for the endometrium is still concerned [40].

Evidence regarding the use of oral pills as treatment for women with symptomatic fibroids is very scarce and of low quality; therefore, a recent systematic review questioned the real efficacy of oral pills in women with symptomatic uterine fibroids [41].

LNG-IUS has been found to be more effective than oral medication as a treatment for HMB [42,43]. In addition, LNG-IUS is associated with a greater reduction in HMB and improved quality of life, and appears to be more acceptable in long-term treatment, but is associated with more minor adverse effects compared to oral therapy [41]. Therefore, some physicians have recommended that LNG-IUS should be used as a first-line medical therapy for HMB in women not seeking pregnancy [42].

The 2011 report of the Agency for Healthcare Research and Quality on comparative management of uterine fibroids showed that, despite the prevalence and possible complications of uterine fibroids, few published studies examining the effectiveness of treatment strategies exist [44]. Few therapies are approved by the Food and Drug Administration for fibroids; leuprolide acetate, a GnRH agonist approved in 1995 for preoperative treatment of fibroids, is a gold-standard drug in the management of women with uterine fibroid- and/or adenomyosis-related symptoms or signs. However, leuprolide acetate, with much more profound suppression of estradiol levels, significantly more hot flashes, and more substantial effects on markers of bone turnover, had a relatively poor side-effect profile in women during their reproductive age. Therefore, the add-back therapy of GnRH administration is often suggested.

In women without definite organic lesions, such as those related to endometrial, uterine, or endocrine and hematologically abnormal causes, HMB remains poorly understood and poses a major challenge to developing novel, efficient therapies for HMB [15]. The ultimate goal of any form of treatment is to reduce the amount of menstrual blood. Medical treatment has always been considered the first-line treatment for women with HMB, as a means of achieving the goal of uterine preservation [45,46]. Conservative uterine-sparing surgery or hysterectomy tends to follow failed or ineffective medical treatment.

Matteson et al [1] conducted a systematic review that included 26 published articles, and found that a significant reduction of blood loss in women with HMB presumed secondary to endometrial dysfunction was achieved with a 71–95% reduction in the use of LNG-IUS, a 35–70% reduction in the use of combined oral pills, an 87% reduction in the use of an extended cycle of oral progestins (>21 days), a 26–54% reduction in the use of antifibrinolytics (tranexamic acid), and a 10–52% reduction in the use of nonsteroidal anti-inflammatory drugs (NSAIDs) [1]. However, luteal-phase progestins should be used only in special cases, since nearly all the abovementioned therapeutic strategies, including LNG-IUS (a reduction of 71% compared with 22%, $p < 0.001$), NSAIDs (a reduction of 67% compared with 52%, in a small sample-size comparison, $n = 32$), and antifibrinolytics (a reduction of 45% compared with 20%, $p < 0.001$), were all superior to luteal-phase progestin treatment, with a reduction of 20–67% [1]. In addition, antifibrinolytics were superior to NSAIDs (a reduction of 54% compared with 10%, $p < 0.001$) for reduction of HMB. LNG-IUS was superior to combined oral pills (a reduction of 83% compared with 68%, $p = 0.002$) and NSAIDs (a reduction of 95% compared with 23%, $p < 0.001$) [1].

The cost of medications can be referenced from Table 1. Antifibrinolytics, such as 250-mg tranexamic acid, cost US$0.1/tab, are prescribed as two tabs three times per day and are often used to cover the whole menstrual period. NSAIDs, such as 200 mg mefenamic acid or naproxen, are US$0.1–1/tab, often prescribed as one tab twice or three times per day, and often used during attacks of HMB. Medroxyprogesterone (5 mg) is US$0.1/tab; however, it often requires 20–40 mg/day. In addition, extended use is preferred; suggesting that use for more than 14 days or continuous use without more than 7 missed days might have a good therapeutic effect. The monthly expense of oral pills is US$10–30. LNG-IUS costs US$100–200 per set; however, the effectiveness is

Table 1
Summary of the useful medications for women with heavy menstrual bleeding.

Drugs	Cost [a]	Opinion and effects compared with placebo
Antifibrinolytics (tranexamix acid)	2.5	Well tolerated, fewer side effects, a definite therapeutic value (26–54% reduction)
NSAIDs	1–2	GI and renal effects, allergy, a definite therapeutic value (10–52% reduction)
Progestins	10–15	Irregular bleeding, nausea/vomiting, mood swings, hot flush, increased body weight, a definite therapeutic value in extended use (87% reduction)
Gestrinone	80	Seborrhea, hypertrichosis, increased body weight, the risk of metabolic syndrome such as unfavorable effects on serum cholesterol lipoprotein distribution, a definite therapeutic value (50–70% reduction)
Danazol	40–100	Seborrhea, hypertrichosis, increased body weight, and the risk of metabolic syndrome such as unfavorable effects on serum cholesterol lipoprotein distribution (50–70% reduction)
OC	10–20	Irregular bleeding, hypercoagulation status, nausea/vomiting, headache, a definite therapeutic value (35–70% reduction)
LNG-IUS	3–4	Irregular bleeding, abdominal pain, a definite therapeutic value (71–95% reduction)
GnRH-a	120–200	Frequent and intolerable hypoestrogenic side effects, including vasomotor syndrome, genital atrophy, mood instability, a negative impact on bone health, and also a possible bad influence on cardiovascular health; a definite therapeutic value (reduction of >95%)

GI = gastrointestinal; GnRH-a = gonadotropin-releasing hormone agonist; LNG-IUS = levonorgestrel-releasing intrauterine system; NSAIDs = nonsteroidal anti-inflammatory drugs; OC = oral contraceptives or oral pills.
[a] Cost: US dollars per cycle.

maintained for 5 years. The final medication is GnRH agonist, which is the most expensive (US$150/month), and many women with HMB taking GnRH agonist might be compromised by severe menopause-related problems, as shown above. Therefore, GnRH agonist is seldom considered as the first-line treatment in the management of women with HMB; it is often used for special indications, such as long-term suppression of *in vitro* fertilization and embryo transfer, and pre- and postoperative adjuvant therapy.

Comments

Based on the above evidence, the Taiwan Society of Gynecology Systematic Review Group has developed clinical practice suggestions for medical treatment of HMB, which include the following: (1) clinicians should use the FIGO PALM–COEIN system to perform a structured history review and physical examination to detect organic and/or nonorganic lesions that can be reversed by definite treatment; (2) no definite cause-related HMB can be managed using a step-by-step strategy, based on cost effectiveness and patients' preference (low cost, more convenience, few adverse events, and high compliance); (3) in the situation of B status, two agents could be used as a choice, including that LNG-IUS is preferred for women with HMB needing contraception; the use of two tabs of tranexamic acid three times per day is often preferred to cover the whole menstrual period for any woman without an organic-related HMB; and (4) patient-tailored therapy should always be considered.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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End note

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