

Recent advances in managing and understanding menstrual disorders

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Abstract

Menstrual disorders are a major reason for gynaecological consultations worldwide and, unfortunately there are many different definitions and classifications of this condition. Clear definitions and terminology are necessary for scientific literature, particularly for clinicians, and for clinical trials comparing two treatments. The International Federation of Gynaecology and Obstetrics (FIGO) Menstrual Disorders Working Group has proposed abandoning the use of one common term, dysfunctional uterine bleeding (DUB), while continuing to use the terms abnormal uterine bleeding (AUB) and heavy menstrual bleeding (HMB). Furthermore, the group issued the PALM-COEIN classification system for menstrual disorders, which has quickly been adopted around the world. The PALM-COEIN system allows clinicians and researchers to identify and classify women with both AUB and HMB in a systematic manner, provides reliable information for research purposes and for epidemiological and prevalence studies in different settings, and supports accurate diagnoses and treatment. Additionally, this classification system is useful for selecting treatments appropriate for different stages of women's reproductive years and for different patterns of menstrual bleeding. Among the proposed treatments are the use of combined oral contraceptives, the levonorgestrel-releasing intrauterine system, tranexamic acid, mefenamic acid, and other nonsteroidal anti-inflammatory drugs (NSAIDs).

Introduction

Menstrual disorders are a major reason for gynaecological consultations around the world and, unfortunately, many different definitions and classifications are used for this condition. Among the most commonly used terms, DUB is defined in the UK as the regular, cyclic, predictable onset of uterine bleeding after the exclusion of other pathologies, but in the US as irregular uterine bleeding associated with ovulatory disorders [1]. Clear definitions and terminology are important for scientific literature, particularly for clinical practice, and for clinical trials that compare two treatments and whose inclusion criteria is a main menstrual disorder [2]. In addition, various terms used to describe HMB include menometrorrhagia, metrorrhagia and polymenorrhoea. In many cases, such differing terms make it extremely

difficult to interpret the patient's pathology or bleeding condition. As at intake a healthcare professional records the patient's history and typically recorded volume (heavy, normal or light), regularity (irregular, regular or absent), frequency (frequent, normal or infrequent), and duration (prolonged, normal or shortened) of menstrual episodes, each term could be interpreted differently across the globe.

HMB is a principal menstrual disorder, which has a negative impact on women's quality of life, causes the loss of working days, and incurs direct, considerable costs on healthcare systems worldwide [3]. HMB is defined as a blood loss of >80 ml per cycle (Table 1) [4]. However, only research centres can accurately measure menstrual blood loss due to the complexity of the techniques [5].

Table 1. Normal limits for menstrual patterns in women in the mid-reproductive years

Variables	Descriptive terms	Normal limits (5th–95th percentiles)
Frequency of menses (days)	Frequent	<24
	Normal	24–38
	Infrequent	>38
Regularity of menses (cycle to cycle variation over 12 months in days)	Absent	—
	Regular	Variation \pm 2 to 20
Duration of flow (days)	Irregular	Variation greater than 20
	Prolonged	>8.0
	Normal	4.5–8.0
	Shortened	<4.5
Volume of monthly blood loss (ml)	Heavy	>80
	Normal	5–80
	Light	<5

Adapted with permission from [8].

Therefore, for clinical purposes, HMB is defined as “excessive menstrual blood loss which interferes with the woman’s physical, emotional, social and material quality of life, and which can occur alone, or in combination with other symptoms” [6].

Causes of menstrual disorders

We need to establish the necessary parameters to achieve an accurate diagnosis and treatment for women with AUB. This is especially important with women who present with HMB, which can be defined differently in developed countries with access to the latest technologies, compared with low-resource settings characterised by economic and technological constraints [7]. It is important to note that an accurate diagnosis improves treatment, the goal of which is to improve the patient’s symptoms and quality of life.

Classification of menstrual disorders

In 2005, the FIGO Menstrual Disorders Working Group proposed abandoning some terms for menstrual disturbances, which are controversial, confusing and poorly defined, although they remain common in many scientific publications [8]. Many of these terms which are no longer recommended include English terms with Latin and Greek roots, and agreement was reached to abandon their usage. These terms include: menorrhagia, metrorrhagia, essential menorrhagia, idiopathic menorrhagia, primary menorrhagia, functional menorrhagia, ovulatory or anovulatory menorrhagia, hypermenorrhoea, hypomenorrhoea, menometrorrhagia, polymenorrhoea, polymenorrhagia, epimenorrhoea, epimenorrhagia, metropathica hemorrhagica, uterine hemorrhage and dysfunctional and functional uterine bleeding. It was recommended that the old term “dysfunctional uterine bleeding” be divided into three classifications: (1) disorders of endometrial origin (disturbances of the molecular mechanisms responsible for regulation of the volume of blood lost at menstruation); (2) disorders of the hypothalamic–pituitary–ovarian

axis; and (3) disorders of haemostasis, or nonstructural causes of AUB [9–11].

The most recent version of the International Statistical Classification of Diseases and Health Related Problems (ICD), the ICD-10 (2010) [12], still uses such terms as metrorrhagia, menometrorrhagia and polymenorrhoea (N91, N92, N93) for HMB symptoms not related to a pathological process. The ICD-10 does not state if these terms refer to a pathology, symptom or diagnosis made by a healthcare professional. The most important problem created by this ambiguity is the lack of reliable information about prevalence for health authorities and policy makers. From a research perspective, as the definition for menstrual irregularity varies in different settings as stated above, it becomes difficult to make comparisons among clinical studies.

Furthermore, the FIGO Menstrual Disorders Working Group introduced a new classification called the PALM-COEIN system of AUB [9]. The consensus established that AUB is an appropriate term because it includes several clinical symptoms (although the use of the word “menstrual” is not correct), but at the same time implies that it should exclude bleeding coming from the cervix or the lower genital tract. It is also proposed that acute AUB could be classified as “an episode of bleeding in a woman of reproductive age, who is not pregnant, that is of sufficient quantity to require immediate intervention to prevent further blood loss”. Additionally, chronic AUB is “bleeding from the uterine corpus that is abnormal in duration, volume, and/or frequency and has been present for the majority of the last 6 months” [13]. Table 1 shows a classification of normal and abnormal bleeding patterns.

As suggested by the acronym, the PALM-COEIN classification system includes nine categories: polyp, adenomyosis,

leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory disorders, endometrium, iatrogenic and not yet classified [13]. The categories indicated by the PALM acronym can be measured visually because they present structural abnormalities evaluated with clinical examination, imaging techniques or histopathology. Conditions classified in the COEIN group cannot be defined by imaging or histopathology. This classification system has the additional advantage of being usable at the primary care as well as specialist level. It is important to keep in mind that many of these causes of AUB can be asymptomatic, and that AUB itself might be the first symptom.

Polyyps

Polyyps are categorized as either absent or present and are diagnosed by ultrasound, hysteroscopy or both, preferably in combination with histopathology. Sub-classification might be developed based on the dimensions, location, number, morphology and histology of the polyyps.

Adenomyosis

Although the relationship between adenomyosis and AUB is unclear, some reports link adenomyosis to AUB [14]. Diagnosis is made by ultrasound, magnetic resonance imaging or histopathology, typically after hysterectomy.

Leiomyomas

Leiomyomas are classified by size, location (submucosal, intramural, subserosal or combination) and the number of lesions. In many cases, they are asymptomatic; however, in other cases, the first symptom is AUB.

Malignancy and premalignant conditions

Atypical hyperplasia and cancer are major causes of AUB and, importantly, can occur not only in the post-menopausal period but also during a woman's reproductive years. When a woman with AUB is diagnosed with a premalignant or malignant process, she should be classified according to the appropriate World Health Organisation or FIGO system.

Coagulopathy (systemic disorders of haemostasis)

This category includes the systemic disorders of haemostasis that are linked to AUB. Although a common cause in this category can be von Willebrand disease, other coagulopathies can also contribute to AUB. It is important to take these conditions into account because, generally, gynaecologists are not familiar with haemostasis diseases. It is also important to consider whether women are medicated with anticoagulants.

Ovulatory disorders

Women with ovulatory disorders typically present with AUB, which includes both unpredictable bleeding and

abnormal flow. However, some women can present with amenorrhoea, light and infrequent bleeding, and HMB (sometimes unpredictable), which needs medical intervention and, in some cases, emergency treatment. The aetiology could be polycystic ovarian syndrome, hypothyroidism, hyperprolactinemia, mental stress, obesity, post-bariatric surgery, post-solid organ transplantation, anorexia or extreme exercise.

Endometrial causes

If a woman presenting with AUB has cyclical ovulatory cycles and no other obvious cause for the bleeding disturbance, one should consider that the cause might be the endometrium. Most causes are associated with a deficiency in the local production of vasoconstrictors, including endothelin-1 and prostaglandin F_{2a}, or the excessive production of plasminogen activator [15,16]. However, clinicians do not have access to many diagnostic tests for these conditions.

Iatrogenic

For this classification, it is necessary to take into account the use of intrauterine contraceptives (copper- or levonorgestrel-releasing); gonadal steroids, such as hormonal contraceptive agents; anticonvulsants and antibiotics (rifampicin, griseofulvin); tricyclic antidepressants (amitriptyline, nortriptyline) and phenothiazines; and anticoagulant drugs, such as warfarin, heparin and low-molecular-weight heparin.

Not classified

Other important causes of AUB are included in this group, such as chronic endometritis, arteriovenous malformations and myometrial hypertrophy.

Treatments

HMB is a common problem that has significant effects on women's lives and can burden both patients and healthcare systems [17]. HMB accounts for 18.5% of gynaecologist office visits in the US and 20% in the UK [18]. More than 5% of UK women aged 30–49 consult family physicians about this problem each year [18]. In most cases, no pathology is found in women who present with HMB. In women with no endometrial, uterine or endocrine abnormal cause, HMB remains poorly understood, posing a major challenge to developing novel, efficient nonsurgical therapies for HMB.

As stated before, AUB describes a range of menstrual bleeding symptoms, of which the most common and important is HMB. The estimated worldwide prevalence of subjective, self-defined AUB varies greatly, from 4 to 52% [19]. Women with abnormal bleeding have a lower quality of life than the general female population. There

are considerable discrepancies between objective measures and women's perceptions of menstrual blood loss [20]. It is agreed that a normal bleeding episode results in menstrual blood loss of 30–40 ml [21], with an upper limit of 80 ml [6]. However, blood loss reported by women presenting is often less than 80 ml [22], indicating that patient distress is an important consideration.

The ultimate goal of any form of treatment is to reduce menstrual flow in order to improve quality of life. Pharmaceutical therapies have always been considered the first-line treatment for women complaining of excessive menstrual loss. Conservative and uterine-preserving treatment options are clearly preferred. Surgical treatment tends to follow failed or ineffective medical treatment [23].

Combined oral contraceptive with E₂ valerate and dienogest

To improve the unacceptable cycle control observed in clinical studies of ethinyl-estradiol (EE₂)-containing combined oral contraceptives (COCs), a new COC was developed, which combines estradiol valerate (E₂V) with the progestin dienogest (DNG), using a dynamic dosing regimen with an oestrogen step-down and a progestin step-up. A double-blind, placebo-controlled study showed that, in comparison to a placebo, oral E₂V/DNG is a highly effective, well-tolerated treatment for women with HMB, prolonged menstrual bleeding or heavy and prolonged menstrual bleeding without organic pathology. In the trial, E₂V/DNG recipients showed a rapid, large, sustained decrease in menstrual blood loss volume [24]. A multicentre, double-blind, randomized study found that a COC with E₂V/DNG was associated with an acceptable bleeding profile, comparable to that of an EE₂-containing COC [25].

E₂V/DNG COC provides an important treatment option which is reversible and also provides contraception for these women [26]. Women with HMB treated with this COC can expect a significant reduction in bleeding. The women who received E₂V/DNG pills reported significantly fewer bleeding/spotting days when compared to those who received EE/LNG [17.3 ± 10.4 vs. 21.5 ± 8.6, respectively, $P < 0.0001$, reference period 1 (days 1–90) and 13.4 ± 9 vs. 15.9 ± 7.1, respectively, $P < 0.0001$, reference period 2 (days 91–180)]. This pattern was also observed through cycles 1–7, the occurrence of scheduled withdrawal bleeding per cycle was 77.7–83.2% with E₂V/DNG and 89.5–93.8% with EE/LNG pills ($P < 0.0001$ per cycle). This therapy also showed few adverse events [27]. Thus, the use of a dynamic dosing regimen, which incorporates different (stepped-down) doses of E₂V administered alone or in combination with different (stepped-up) doses of DNG, has resulted in an E₂-containing

COC a bleeding profile superior to that of other EE₂-containing COCs.

Levonorgestrel-releasing intrauterine system

The levonorgestrel-releasing intrauterine system (LNG-IUS, Mirena®) was developed as a contraceptive device and initially licensed for contraceptive use in the UK in 1995 for three years, extended to five years in 1998 [28]. It became available in the US in 2009. The device contains 20 µg of LNG and the steroid is released in a controlled dose over 24 hours for up to 5 years. The effects of the LNG-IUS are mostly local and prevent endometrial proliferation, and some women also have suppression of ovulation. Although developed as a contraceptive, LNG-IUS also reduces menstrual blood loss [29].

The LNG-IUS cannot be used by women with abnormal uterine cavities because the risk of expulsion is unacceptably high [30]. Two recent reviews showed a 71 to 96% reduction in menstrual blood flow and 20 to 30% amenorrhoea during the LNG-IUS use [31,32]. In a review, it was shown that the menstrual blood loss reductions reported in the randomized clinical trials were between 71 and 96% [32,33].

In a recently published, multicentre, randomized trial [34] comparing LNG-IUS with common medical treatments for women with menorrhagia, LNG-IUS and the common medical treatments reduced HMB's adverse effects. The study allocated at random 571 women with menorrhagia to treatment with the LNG-IUS or medical treatment (tranexamic acid, mefenamic acid, combined estrogen-progestogen, or progesterone alone). The Menorrhagia Multi-Attribute Scale (MMAS) was the patient-reported score outcome (ranging from 0 to 100), assessed over a 2-year period. MMAS scores improved from baseline to 6 months in both the LNG-IUS group and the medical treatment group (mean increase, 32.7 and 21.4 points, respectively; $P < 0.001$ for both comparisons). The improvement was significantly greater in the LNG-IUS group than in the medical treatment group (mean between-group difference, 13.4 points; 95% confidence interval [CI], 9.9 to 16.9; $P < 0.001$). Additionally, LNG-IUS was more effective at reducing the negative effects on quality of life, including work, social and family life and psychological and physical well-being, although no significant between-group difference was observed regarding the domain of mental health.

Tranexamic acid

Tranexamic acid is a plasminogen activator inhibitor that is able to control HMB by inhibiting the dissolution of thrombosis. Oral tranexamic acid has been associated with reduced menstrual blood loss volume. However, it is

not a contraceptive, cannot regulate the menstrual cycle, and could be used in women with uterine fibroids [35,36].

A recent study with a new oral formulation of tranexamic acid in women with cyclic HMB showed that during treatment tranexamic acid was well tolerated with a good safety profile and may be used as a therapy for HMB [37]. Furthermore, it was reported [38] that a reduction in HMB was observed during therapy with tranexamic acid when compared with placebo. In two trials, tranexamic acid produced a significant reduction in mean blood loss (-94.0 , 95% CI, -151.4 to -36.5 ; $P:0.001$) and a significant change in mean reduction of blood loss (-110.2 , 95% CI, -146.5 to -73.8) compared with placebo. However, this improvement was not accompanied by a perceived improvement in monthly menstrual blood loss by the women [35,38].

Other researchers assessed the use of tranexamic acid on HMB. They observed a reduction in menstrual blood loss of 46.7% (95% CI, 47.9–51.6%) with tranexamic acid [39] and others showed that oral tranexamic acid, 2.0 to 4.5 g daily, for 4 to 7 days per cycle reduced blood loss by 34–59% [6]. However, comparing the LNG-IUS to tranexamic acid and other conventional medical therapies, a significantly large decrease in the number of bleeding days (mean, 4.0) in the LNG-IUS group compared with other therapies (mean, 2.8 days) was observed. Furthermore, the mean reduction in the number of spotting days was 0.3 days and 1.4 days, respectively [40].

Nonsteroidal anti-inflammatory drugs (such as mefenamic acid)

NSAIDs are a proposed therapy in ovulatory HMB [41,42] because their use reduces menstrual loss. NSAIDs (e.g. mefenamic acid) approved for the treatment of HMB might also alleviate dysmenorrhoea, but they have a limited effect on the reduction of HMB [42]. When comparing LNG-IUS and mefenamic acid, after six cycles the median menstrual blood loss was 5 ml in the LNG-IUS group and 100 ml in the mefenamic acid group ($P<0.001$). The median pictorial blood loss assessment chart (PBAC) score was 159 in the mefenamic acid group and 25 in the LNG-IUS group [41]. Furthermore, the use of mefenamic acid in women with AUB induced by etonorgestrel-releasing implant showed that four weeks after initial treatment, a bleeding free-interval of >20 days was found in 56.5% and 21.7% of the women treated with mefenamic acid or placebo, respectively [42]. The UK National Institute for Health and Clinical Excellence presented information about the use of NSAIDs in the management of HMB and stated that it was associated with a 20–40% reduction in blood loss. Although the use of mefenamic acid showed a reduction in menstrual flow of 29%, naproxen and

ibuprofen also showed a reduction of blood loss of 26% and 16%, respectively [42].

Conclusions

Discarding many terms related to menstrual disturbances, including dysfunctional uterine bleeding, would greatly benefit clinicians and researchers. As shown by this review, women with AUB can have one or multiple potential causes of abnormal bleeding, and the accuracy of their diagnosis might depend on the degree of sophistication of the facility at which they seek consultation. The PALM-COEIN system allows clinicians and researchers to identify and classify women with abnormal bleeding and provides reliable information on classification and for comparisons in research settings. The PALM-COEIN classification system is practical and offers the healthcare professional accurate diagnoses and adequate treatment according to the aetiology. For this reason we strongly recommend adoption of this classification for AUB and HMB. Furthermore, possible medical treatments include the use of the LNG-IUS, the use of a novel COC with E₂V and DNG, NSAIDs and tranexamic acid.

Abbreviations

AUB, abnormal uterine bleeding; COC, combined oral contraceptive; DNG, dienogest; DUB, dysfunctional uterine bleeding; E₂V, estradiol valerate; EE₂, ethinyl-estradiol; FIGO, International Federation of Gynaecology and Obstetrics; HMB, heavy menstrual bleeding; ICD, International Statistical Classification of Diseases and Health Related Problems; LNG-IUS, levonorgestrel-releasing intrauterine system; MMAS, Menorrhagia Multi-Attribute Scale; NSAIDs, nonsteroidal anti-inflammatory drugs.

Disclosures

The authors declare that they have no disclosures.

Disclaimer

This report contains the collective views of two international experts, and does not necessarily represent the decisions or the stated policy of the World Health Organisation.

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