

Adolescent heavy menstrual bleeding and dysmenorrhoea

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Introduction

Menstrual disorders are common conditions in adolescents, with Heavy Menstrual Bleeding (HMB) having a prevalence of 37% in adolescents compared to 10-20% in adults, and dysmenorrhoea accounting for approximately 15% of adolescent complaints.¹

Menstrual disorders have serious effects on quality of life due to school absenteeism and limitation of sport or social activity participation.

Abnormal Uterine Bleeding (AUB) is the preferred term to describe abnormality of menstrual volume, regulatory, frequency and duration according to International Federation of Gynaecology and Obstetrics (FIGO).^{2,3}

Several studies have confirmed a racial difference in the age of menarche, with African girls experiencing menarche earlier and Caucasian girls experience it later. It has been postulated that increasing body mass index (BMI) and weight are factors in the earlier menarche; however studies have not been consistent in demonstrating that to be the case.^{4,5,6}

According to the World Health Organization (WHO), an adolescent is referred to as an individual between the ages of 10-19 years of age.

Normal Menstruation

The mean age of the menarche is 12-13 years, occurring 2-3 years after onset of breast development.^{1,9} Menstruation should occur every 21-45 days, as even when there is some irregularities in the first several years following menarche, 90% of the cycles still fall within this range. Bleeding usually lasts 7 days with an average pad/tampon change of 3-6 / days.¹⁰

HMB is defined as loss >80ml of blood per menstrual cycle or bleeding for more than 7 days.¹⁰ It may also be identified on the basis of increased menstrual blood flow that impedes the well-being and quality of life of an individual.²

Challenges in HMB

The diagnosis of HMB in adolescents is often challenging because the condition is overlooked as an abnormality by the adolescent, and delays often occur in making the correct diagnosis. Possible reasons for delay can be related to the difficulty in obtaining menstrual history due to inconsistency in disclosure, variety in feminine hygiene products, cycle to cycle variability, recall difficulty, so information pertaining to

one cycle is not generalisable. It is also crucial to note that children may have undiagnosed bleeding disorders due to hemostatic challenges until menarche.¹¹ Accurate data on the frequency of HMB, the last menstrual period, volume and pattern should be collected at each visit. The importance of tracking the cycle, either using calendars or electronic applications should be stressed.

Diagnosis of HMB

FIGO, supported by the American College of Obstetrics and Gynaecology (ACOG) provided a schematic flowchart for the aetiology of AUB utilising standardised terminologies, known as the PALM-COEIN classification (Fig 1).¹² This classification outlines AUB as either HMB or intermenstrual bleeding. The aetiologies are divided into two categories, those related to structural abnormalities (polyps, adenomyosis, leiomyomata, malignancy and hyperplasia) and those related to non structural causes (coagulopathies, ovulatory dysfunctions, endometrial reasons, iatrogenic, and "not yet classified"). In adolescents, the most common aetiologies are nonstructural, with anovulatory bleeding being the most common cause due to the immature hypothalamic-pituitary-ovarian axis;^{13,14} however this is a diagnosis of exclusion. The other common cause of anovulatory bleeding is Polycystic Ovarian Syndrome (PCOS) and this condition is infrequently diagnosed in adolescents. It should be highly considered in adolescents with signs of PCOS such as obesity, hirsutism, acne and acanthosis nigricans.¹⁵ The classical presentation of anovulatory bleeding is often with disordered bleeding patterns.

Bleeding disorders are rare in the general population, with Von Willenbrand's disease (vWD) having a prevalence of 1%.¹ Other bleeding disorders include clotting factor deficiencies, immune thrombocytopenia, platelet function defects and fibrinolytic pathway defects.¹⁶ The incidence of the bleeding disorders are disproportionately increased to occur in up to 30% of adolescents with HMB.^{17,18}

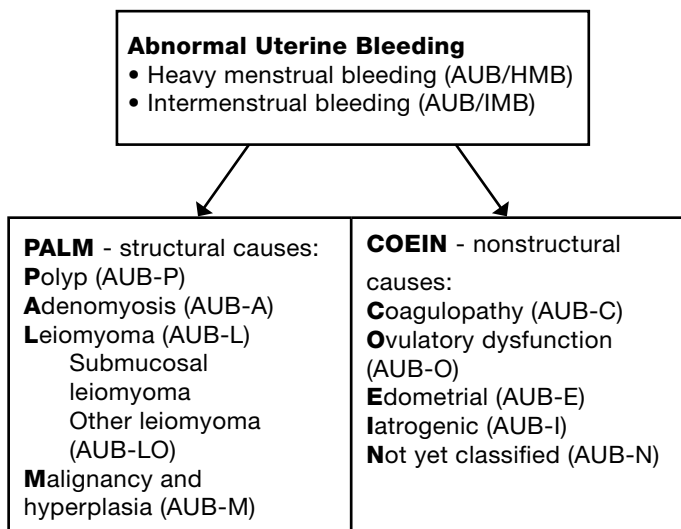
Pregnancy and sexually transmitted infections should not be forgotten in adolescents. Hereditary collagen disorders such as Ehlers-Danlos and benign joint hypermobility syndromes have been associated with bleeding abnormalities, thus history of HMB with joint hyperflexibility, dislocations, hyperextensive skin or abnormal scarring warrants further investigations in adolescents presenting with HMB. Medication such as anticoagulants and hormonal contraceptives can lead to HMB. A rare but not to be forgotten causes are polyps and leiomyomas. Although leiomyomas are rare in adolescents, they should be suspected where pelvic pain or a pelvic mass is present and thus warrants further investigation.^{19,20}

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Fig 1. PALM-COEIN classification of aetiologies of AUB in nonpregnant woman of reproductive age.



Approach to adolescent with HMB

History

Initial step in evaluation and assessment is to determine if bleeding in HMB is acute or chronic in origin using history, physical examination, relevant investigations and radiological testing. Focused history on the quality and quantity of bleeding should be elicited and also ascertain if symptoms of anaemia or hemodynamic instability is present. Sexual and reproductive history is important. Symptoms associated with systemic causes such as PCOS, hyperprolactinaemia, hypothyroidism, hypothalamic or adrenal disorders and obesity.

Significant family history suggestive of HMB such as hysterectomy at a younger age or history suggestive of

Table 1: Red flags in patients with heavy menstrual bleeding^{3,10}

Prolonged bleeding from trivial wounds lasting > 15 min
Heavy, prolonged, or recurrent bleeding after surgery
Heavy, prolonged, or recurrent bleeding after dental procedures or tooth extraction
Bruising with minimal or no trauma, especially resulting in a lump 1 - 2 times/month
Nose bleeds lasting > 10 min or requiring medical attention 1 - 2 times/month
Unexplained bleeding from gastrointestinal tract
Anemia requiring iron therapy or transfusions
Heavy menstrual bleeding
Family history of bleeding disorders such as van Willebrand disease or hemophilia
Family history of hysterectomy at a young age
Postpartum hemorrhage

coagulopathies, thromboembolic events, or hormone sensitive cancers and medications such as hormonal contraceptive, SSRI, anticoagulants, antipsychotics, tamoxifen, and herbal products containing ginseng is important. Certain red flags of bleeding disorders must be elicited from history and physical examination as listed in Table 1.

Physical examination

Physical examination should entail assessment for acute blood loss and assess if the patient is haemodynamically stable. It is essential to exclude genital trauma as a course of acute HMB, however performing a vaginal or bimanual examination might not be possible in adolescents and thus it may be difficult to exclude upper vaginal trauma or cervical causes. In adolescents, the most common causes of HMB are the non-structural causes in the COEIN classification.

Laboratory

A tiered approach to laboratory testing for evaluation allows for the assessment of acute and chronic blood loss resulting in anaemia as well as investigation of potential aetiologies of HMB. If the first tier results are normal then the second tier testing may be considered. The first tier testing includes: pregnancy tests, haematological tests, endocrine tests, evaluation for bleeding disorders, gynaecological tests (such as PCOS and sexually transmitted infection screening), while the second tier includes evaluation for bleeding disorders, gynaecological tests (such as ultrasound, if not responding to medical therapy) and liver function tests. An expansive list is provided in Table 2.

Management

Acute Treatment

A variety of treatment options for the cessation of bleeding in HMB have been described for acute management. It is important to take note of whether the patient is hemodynamically stable or not and whether the patient will require admission into hospital. The first line treatment beyond blood transfusion usually involves estrogen containing hormonal treatment where intravenous conjugated equine estrogen or oral estrogen can be administered.²³ Intravenous treatment can be administered in 25mg doses every four to six hours in patients who are haemodynamically unstable or unable to tolerate oral therapy.²⁴ This is continued for 24 hours or until cessation of bleeding which can be followed by gradual tapering down to maintenance dosages. A high dose 50µg combination contraceptive pill can be used in patients who can tolerate oral therapy. This option has been shown to be effective in stabilising the endometrium and resulting in bleeding cessation within the first 24 hours of commencing treatment in most cases. A transition from high dose estrogen therapy to a lower dose maintenance treatment is necessary, thus tapering regimens may start from initial combined estrogen pills every six hours down to eight hours for three to seven days, then twelve hourly for another three to seven days until one tablet daily; thereafter until it is safe to cycle in controlled fashion (Table 3).

Progesterone only preparations are available for patients with contraindications to estrogen. The two most commonly used oral progestin therapy in adolescents are medroxyprogesterone acetate (MPA) and norethindrone acetate. Tapering protocols for these therapies are available ranging from administration of pills every eight hours then to every twelve hours followed by every 24 hours to a daily pill. A challenge with progesterone only therapy is that strict compliance is required to prevent breakthrough bleeding.²¹ Some patients will require augmentation of hormonal therapy

Table 2: First and second tier testing for evaluation of heavy menstrual bleeding²¹

First tier	Pregnancy test Hematologic test: CBC, reticulocyte count Iron profile or ferritin level Blood type and screen Endocrine tests: TSH, free T4 Bleeding disorder evaluation von Willebrand panel - von Willebrand factor antigen, factor VIII, ristocetin cofactor activity Platelet function defects - platelet aggregation or PFA-100 Coagulation studies: PT/INR, aPTT, fibrinogen Gynecologic tests (if indicated by patient history): PCOS screening - FSH, LH, testosterone, DHEA-S Sexually transmitted infection screening - <i>Chlamydia trachomatis</i> , <i>Neisseria gonorrhoea</i>
Second tier	Bleeding disorder evaluation (in consultation with hematologist): Repeat von Willebrand disease testing (regardless of initial results), multimer analysis Repeat platelet aggregation (if initial results are abnormal) Dysfibrinogenemia panel - thrombin time, fibrinogen antigen, reptilase time (if thrombin time or fibrinogen abnormal) Coagulant factor assays - Factor XI, Factor IX, Factor VII, Factor XIII Fibrinolysis testing - euglobin clot lysis time, α -2 antiplasmin, plasminogen activator-1 activity Platelet glycoprotein expression/flowcytometry (based on platelet aggregation testing) Electron microscopy - platelet granules (based on platelet aggregation testing) Gynecologic test: Pelvic ultrasound - if not responding to medical therapy PCOS screening - if not already performed Liver function tests: ALT, bilirubin (if prolonged PT)

to normalise bleeding volumes. Antifibrinolytic agents are an exceptional option in this situation when patients have been unresponsive to hormones alone.

There are two options approved by U.S Food and Drug Administration which are tranexamic acid and aminocaproic acid. These can be given orally or via i.v route. Aminocaproic acid is less potent and has more side effects hence its use is not preferred as first option.²⁵ Haematological medication that can be used such as 1-deamino-8-D-arginine vasopressin or factor replacement may be indicated for patients with type I

Table 3. Medication details.

Therapy	Dose	Route	Initial Frequency
Conjugated estrogen	25 mg	IV	Every 4-6 hours
50 µg ethinyl estradiol combined pill	1 tablet	Oral	Every 6 hours
30 - 35 µg ethinyl estradiol combined pill	1 tablet	Oral	Every 6 hours
Medroxyprogesterone	10 - 20 mg (maximum 80 mg/d)	Oral	Every 6-12 hours
Norethindrone acetate	5 - 10 mg	Oral	Every 6 hours
Tranexamic acid	10 mg/kg	IV	Every 6-8 hours
Aminocaproic acid	100 - 200 mg/kg (maximum 30 g/d)	IV or Oral	Every 4-6 hours

vWD, haemophilia and in women with a prolonged bleeding time without a bleeding disorder. It is best to consult with a haematologist prior to administration (Table 3).²⁶

Maintenance treatment

There are varieties of maintenance therapy available for adolescents. These range from combination oral contraceptives, patches, vaginal rings, progesterone alone treatments including cyclic progesterone, injectable formulations, implantable devices or intrauterine devices. They have been shown to effectively reduce menstrual blood flow and result in fewer missed days from school due to HMB, increase iron levels and haemoglobin, and increase the quality of life.

Long term maintenance option includes etonorgestrel subdermal implant and the levonorgestrel-releasing intrauterine device (LNG-IUD). This can only be considered if menstrual bleeding has been normalised. The implant is effective for three years and can result in amenorrhea in 24% of patients; however the most common sideeffect is irregular bleeding which leads to high rate of discontinuation. Alternatively the LNG- IUD is a device that can be placed in the uterine cavity for five years. Many studies demonstrated the superiority of the LNG-IUD over oral MPA, norethindrone acetate, DMPA, and COCs, as there is greater reduction in HMB and improved quality of life.³⁰ Gonadotropin-releasing hormone agonists (GnRH-a) such as depoleuprolide have rarely been used in severe cases of chronic HMB due to hematologic or oncologic-related causes, but it is not reliable for use in acute HMB. GnRH-a results in endometrial atrophy and amenorrhea within 3-4 weeks of administration. Its known side effects include vasomotor symptoms, and loss of bone mineral density and thus to prevent these side effects, an add-back hormonal therapy is recommended.

NSAIDs have been shown to decrease HMB in

premenopausal women; however they are not as effective as other medical therapies. This should be avoided in patients with suspected bleeding disorders as they can exacerbate HMB.²¹ The more invasive therapies such as hysterectomy and uterine ablation are avoided unless absolutely needed in case of life threatening emergencies .

Dysmenorrhoea in Adolescents

Menstrual pain (dysmenorrhoea) is defined as menstrual cramps that occur during menstruation and it is the most common gynaecological complaint in young women of reproductive age. It is classified as primary if there is no underlying attributed pathology, or secondary if a specific pathology is identified and this should be suspected usually in older women.⁷ Primary dysmenorrhoea usually presents 6 to 12 months after the menarche with a peak prevalence occurring in the late teens or early twenties.^{7,8}

Symptoms and Risk factors

Lower abdominal pain is the most common symptom of dysmenorrhoea and many adolescents suffer from menstrual associated symptoms such as headaches, nausea, bloatedness and vomiting. Fifty five percent of adolescents with dysmenorrhoea will present with nausea and 24% will present with vomiting, with onset at the beginning of menstruation or may occur within a few hours before or after the onset of menstrual flow and last for the first 24-48 hours.²⁸

The severity of symptoms correlates with onset of ovulatory cycles and with increased duration and amount of menstrual flow. Cigarette smoking may increase the duration of dysmenorrhoea most likely due to the nicotine induce vasomotor constriction.²⁹ Low fish consumption has been correlated with severe dysmenorrhoea in some studies.³⁰

Pathophysiology of Primary Dysmenorrhoea

In adolescent the most common cause of dysmenorrhoea is of primary origin, and this is associated with normal ovulatory cycles and no pelvic pathology or aetiology and usually has a clear physiologic aetiology. Following ovulation, there is a build-up of fatty acids in the phospholipids of the cell membranes. After the initiation of progesterone withdrawal before menstruation, these omega 6- fatty acids, particularly arachidonic acids are released and a cascade of prostaglandins (PG's) and interleukins (LT's) are initiated in the uterus. These PG's and LT's induce an inflammatory response which leads to both cramps and systemic symptoms such as headaches, nausea, vomiting and bloating.

Prostaglandin F_{2α}, cyclo-oxygenase (COX) are metabolites of arachidonic acid which cause potent vasoconstriction and myometrial contraction leading to uterine ischemia and pain.³¹ Other documented mechanism attributing to dysmenorrhoea is uterine contractility and relaxation. Circulatory vasopression has been attributed to inducing uterine contraction and has been reported in women with dysmenorrhoea, however the pathogenesis of primary dysmenorrhoea remains controversial.³²

Nitric oxide is known to induce myometrial contractions and vasoconstrictions which can play a role in generating dysmenorrhoea.³³

Pathophysiology of secondary Dysmenorrhoea

Secondary dysmenorrhoea accounts for 10% of dysmenorrhoea in adolescents and it is most likely to be associated with chronic pelvic pain, mid-cycle pain, dyspareunia and HMB. Endometriosis, which is defined as the presence and growth of uterine stroma and glands outside of the uterine cavity is the most common cause of secondary

dysmenorrhoea in adolescents.

In adolescents with early onset of severe dysmenorrhea nonresponding to first line treatment, obstructive anomalies should be suspected. Adhesions, PID, leiomyomata, adenomyosis, endometrial polyps, ovarian cysts and neoplasms have all been described as rare causes of menstrual pain in adolescents.

Approach to Adolescents with Dysmenorrhoea

Obtaining history confidentially should be the paramount initial evaluation of adolescents with dysmenorrhoea. History should entail the age of menarche, menstrual pattern, onset and character of menstrual cramps, menstrual associated symptoms, response to analgesics, sexual history, history of sexual abuse, contraception use, condom use, previous STI, vaginal discharge, school performance and absenteeism and family history of first degree relative with endometriosis. Psychological aspect of dysmenorrhoea and sequel of chronic pelvic pains should be explored at all times. In non-sexually active persons where the history is suggestive of primary dysmenorrhoea, pelvic examination should be deferred and only be performed if the adolescent is sexually active or has no improvement on first line therapy.

Pelvic and rectal examinations should be performed in patients thought to have secondary dysmenorrhoea in whom you suspect endometriosis which can present with uterine, adnexal or recto-vaginal tenderness.

Counseling is important including explaining the physiology of the menstrual cycle, the symptoms and the pathophysiology of dysmenorrhoea. Girls who smoke should be encouraged to stop smoking as it associated with prolonged dysmenorrhoeic symptoms. They should also be encouraged to increase dietary intake rich in omega-3- polyunsaturated fatty acids. Treatment response is an important component of evaluation because NSAIDs will not improve dysmenorrhoea secondary to endometriosis.³⁴

Management of Primary Dysmenorrhoea

Therapeutic dosage of NSAIDs is the preferred initial treatment and should be tried for at least three menstrual periods. This is most effective if started two days before onset of menses, however adolescents who cannot predict when menstruation will start, should be advised to start as soon as menstrual blood begins or when experiencing menstrual associated symptoms. It is justified to add a second NSAID preparation if the symptoms are not relieved by mono-therapy and adolescents should be given strict instructions on how to take NSAID with meals and increased fluid intake in order to prevent gastric and renal side effects respectively.

COX-2 inhibitors can be administered in patients with history of gastric bleeding or ulcer, adolescents requiring high dose NSAIDs, gastro-intestinal adverse effects on NSAIDs and in patients with coagulation deficiencies. COCs can be offered for three months if NSAIDs are not effective. In adolescence where the dysmenorrhoea does not respond to 6 months of NSAIDs and COC diagnosis of secondary dysmenorrhoea should be explored.

Management of Secondary Dysmenorrhoea

Low dose monophasic contraceptives given in a non-cyclical fashion are the initial medical treatment in adolescents with suspected endometriosis. The aim of this therapy is to prevent endometrial proliferation and avoid endometrial implants from bleeding because it is the endometrial implants that cause pain, scarring and infertility.

GNRH-a such as leuprolid or nafarelin can be administered for 6 months in order to induce a hypo-estrogenic state

however treatment is associated with bothersome side effects such as; hot flushes, emotional liability and headaches, thus add back therapy should be added if long treatment with GNRH-a is planned. Danazole is not recommended due to its high rates of severe adverse side effects. LNG- IUD can also be used in the management of secondary dysmenorrhoea. Laparoscopy should be advocated in patients with severe dysmenorrhoea not responding to medical treatment or deep infiltrating endometriosis.

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