FOGSI - ICOG

Good Clinical Practice Recommendations GCPR on

Management of Abnormal Uterine Bleeding

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From the Desk of Prof. Hrishikesh D Pai

Trustee FIGO Asia-Oceania (2023-25)
President Federation of Obstetric and Gynecological Societies of India (FOGSI) (2023)

It is with great pride and enthusiasm that I present to you this well-researched and scholarly Good Clinical Practice Recommendations (GCPR) on "Abnormal Uterine Bleeding" developed under my leadership as President of FOGSI (2023). This endeavor represents a significant milestone in our ongoing commitment to improving women's healthcare across the nation.

The formulation of this GCPR has been a collaborative effort, bringing together the collective wisdom and expertise of some of the brightest minds in our field. As President of FOGSI, I had the honor of overseeing this ambitious project, and I am deeply grateful for the dedication and hard work of everyone involved.

Our Advisors, past presidents of FOGSI, Dr. Sanjay Gupte and Dr. Hema Diwakar, provided invaluable guidance and support throughout the process. The National Coordinators- Dr. CN Purandare, Dr. Rishma Pai, Dr. Nandita Palshetkar, and Dr. Jaydeep Tank, played a crucial role in coordinating efforts and ensuring the smooth progress of this project.

A pivotal role was played by Dr. Surekha Tayade, Chairperson of the Clinical Research Committee of FOGSI. As the Coordinator of the GCPR, she ensured that each step of the development process was meticulously followed. Her tireless dedication and attention to detail have been truly commendable.

I thank the Convenor, Dr Shyjus P, Chairperson of Midlife Management Committee, FOGSI, and the Co-convenor, Dr Shobha Gudi, Governing Council Member, ICOG, who toiled for the development of this GCPR.

This GCPR was developed through a rigorous process. A drafting committee comprising 6-7 renowned experts in the field reviewed all existing literature and evidence to formulate the initial draft, which was presented to a team of 10-12 experts who reviewed it and provided feedback. Multiple meetings were organized to review and incorporate these suggestions, ensuring the latest evidence and best practices were incorporated.

We believe this good practice recommendation will be an invaluable resource for healthcare practitioners, enabling them to provide the highest standard of care to women across India and beyond.

Warm regards,

Hrishikesh D Pai
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Fogsi Good Clinical Practice Recommendations

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EXECUTIVE SUMMARY OF RECOMMENDATIONS

Based on what parameters is menstrual bleeding labeled as abnormal?

Menstrual bleeding is labeled as abnormal based on the frequency of menses, regularity of menses, duration of flow, and the volume of flow.

How do we categorize abnormal uterine bleeding?

Once labeled as abnormal, abnormal uterine bleeding (AUB) is categorized with the PALM-COEIN classification.

The PALM-COEIN is the acronym for Polyp (AUB-P), Adenomyosis (AUB-A), Leiomyoma (AUB-L), Malignancy (AUB-M) (and hyperplasia)-Coagulopathy (AUB-C), Ovulatory disorders (AUB-O), Endometrial (AUB-E), Iatrogenic (AUB-I), and Not otherwise classified (AUB-N).

In a patient diagnosed to have AUB, which points in history indicates an underlying coagulopathy?

History of heavy bleeding starting at menarche, postpartum hemorrhage, surgery-related bleeding, bleeding associated with dental work, episode of bruising, epistaxis, frequent gum bleeding, and a family history of bleeding manifestations points to an underlying coagulopathy (Grade B; Level 4).

Which are the laboratory tests required while evaluating a case of AUB?

A complete blood count (CBC), a sensitive urine pregnancy test when indicated, bleeding time, platelet count, prothrombin time and partial thromboplastin time (in all with a positive screen for coagulopathies), and a thyroid-stimulating hormone (TSH) testing.

Testing for von Willebrand disease, ristocetin cofactor activity, factor VIII activity, and von Willebrand factor antigen is recommended in consultation with a hematologist in those with a positive screen for coagulopathies (Grade A; Level 1).

What is the role of imaging studies in the diagnosis of AUB?

Ultrasonography is mandatory in AUB to evaluate uterus, adnexa, and endometrial thickness (Grade A; Level 1).

Addition of a Doppler may be indicated in suspected arteriovenous malformation, suspected malignancies, and to differentiate between fibroids and adenomyomas (Grade B; Level 3).

Three-dimensional (3D)-ultrasound imaging is used in the evaluation of myometrial lesions such as fibroids/adenomyomas and saline infusion sonography is used in case of a suspected intracavitary lesion (Grade B; Level 4).

What medications are recommended to manage an acute heavy episode of AUB?

Options include multidose regimens of combined oral contraceptives (COCs) or oral progestins and tranexamic acid. Oral progestins, either medroxyprogesterone acetate 20 mg orally three times per day or norethisterone acetate 10 mg three times a day is generally the preferred hormonal therapy for managing an episode of acute heavy AUB. The other option is COCs. Combined oral contraceptive pills containing 30 µg ethinylestradiol, two pills every 12 hours for 5 days and then 1 tablet per day for 15 days is the schedule for control of an acute episode (Antiemetics can be co-prescribed for controlling nausea). Tranexamic acid intravenously or orally is the nonhormonal agent used, alone or in combination with hormonal therapy, for managing an acute episode of heavy bleeding. Intravenous (IV) dose used is 10 mg/kg every 8 hours (maximum 600 mg/dose). As bleeding decreases, switch over to an oral dose 500 mg three times a day is done (Grade A; Level 1).

How would you manage a case of AUB-P?

Hysteroscopic polypectomy is recommended for younger women, who wish to preserve fertility (Grade A; Level 1).

In women with multiple endometrial polyps and not desirous of fertility, hysteroscopic polypectomy followed by levonorgestrel-releasing intrauterine system (LNG-IUS) insertion after the confirmation of a benign lesion on histopathology is suggested (Grade A; Level 2).

What are the options to manage AUB-A?

The available options for medical management include nonsteroidal anti-inflammatory drugs (NSAIDs), progestogens, combined oral contraceptive pills (OCPs), Dienogest, LNG-IUS, and gonadotropin-releasing hormone (GnRH) agonists.

For those desirous of preserving fertility but not immediately planning for conception, LNG-IUS is an effective option. In case of failure/non-tolerance/refusal of medical management, hysterectomy is indicated (Grade A; Level 1).

What are the ways of managing AUB-L?

Treatment for AUB-L should be individualized based on many variables such as age, parity, symptoms, fertility desires and size, location, and the multiplicity of myomas.

The options for the medical management of fibroids (of any grade) include tranexamic acid, NSAIDs, GnRH agonists/antagonists, LNG-IUS, mifepristone, and ulipristal acetate.

Surgical treatment options for submucous myomas (Grade 0-1) include hysteroscopic resection (for those <4 cm diameter) or laparoscopic/abdominal myomectomy (for those >4 cm diameter) (Grade B; Level 4).

For Grade 2–6 myomas, laparoscopic approach at myomectomy provides the advantages of earlier recovery and lesser postoperative morbidity compared to an open approach (Grade B; Level 3).

In women above 40 years of age, not desirous of fertility, hysterectomy is the definitive treatment option (Grade B; Level 1).

For the short-term management (up to 6 months), GnRH agonists with add-back therapy is an option in perimenopausal women, prior to myomectomy or for the correction of anemia (Grade A; Level 1).

How do we manage AUB-M with atypical hyperplasia?

In those who do not wish to preserve fertility, a total hysterectomy is advised because of the high risk of underlying malignancy or progression to cancer (Grade A; Level 1).

Women wishing to retain their fertility should be counseled about the risks of underlying malignancy and subsequent progression to endometrial cancer.

What are the medical management options and how do we follow up these women?

The first-line medical management is LNG-IUS, continuous oral progestogens being the other option if LNG-IUS is not applicable. Endometrial surveillance in these women should include endometrial biopsy, every 3 months until two consecutive negative biopsies are obtained. For those in whom medical management fails, and in those with persistent atypical hyperplasia, hysterectomy is the definitive treatment (Grade B; Level 2).

How do we manage AUB-M with endometrial hyperplasia without atypia?

These women should be informed that the risk of progressing to endometrial cancer is less than 5% over 20 years and that the majority of cases of endometrial hyperplasia without atypia will regress spontaneously during follow-up.

LNG-IUS should be the first-line medical treatment because compared with oral progestogens it has a higher disease regression rate with a more favorable bleeding profile and is associated with fewer adverse effects (Grade A ; Level 1).

How long should we treat women with AUB-M with endometrial hyperplasia without atypia?

Treatment with oral progestogens or the LNG-IUS should be for a minimum of 6 months in order to induce the histological regression of endometrial hyperplasia without atypia. Endometrial surveillance should be arranged at a minimum of 6-monthly intervals and at least two consecutive 6-monthly negative biopsies should be obtained prior to discharge (Grade B; Level 2).

Is hysterectomy indicated in women with AUB-M with hyperplasia without atypia?

Hysterectomy is indicated in women not wanting to preserve their fertility when:

- progression to atypical hyperplasia occurs during follow-up, or
- there is no histological regression of hyperplasia despite 12 months of treatment, or
- there is relapse of endometrial hyperplasia after completing progestogen treatment, or
- there is persistence of bleeding symptoms, or
- the woman declines to undergo endometrial surveillance or comply with medical treatment.

How is AUB-C managed?

In patients with AUB-C, nonhormonal treatment with tranexamic acid is the first option. Hormonal treatment with COCs/LNG-IUS are the other options recommended, in consultation with a hematologist (Grade A; Level 2).

For patients with uncontrolled uterine bleeding, in spite of the above medical management, specific factor replacement or desmopressin are to be considered.

How do we manage AUB-O?

In women not desirous of conception, COCs can be used as the first-line therapy for 6–12 months. Norethisterone/Medroxyprogesterone acetate can also be used from D5–D25 of the cycle for up to 3 cycles (Grade A; Level 1).

How do we manage AUB-E?

The initial treatment options are tranexamic acid combined with mefenamic acid and COCs, though LNG-IUS remains the most effective option (Grade B; Level 3).

How do we approach a case of AUB in adolescents?

A diagnostic evaluation should be performed before any treatment is initiated, aimed at determining the severity of the bleeding and to find out the possible etiology of AUB. Pathologies, such as bleeding disorders and clotting abnormalities, and pathologies of the reproductive tract, genital injuries, and drug use, should be excluded in the differential diagnosis.

How do we manage an acute heavy menstrual bleeding episode in adolescents?

The first-line approach to managing AUB in the adolescents is medical management, the choice of treatment depending on the clinical stability, overall acuity, suspected etiology of the bleeding, and underlying medical problems. In mild AUB, nonhormonal therapy with NSAIDs would suffice in most cases. In moderate AUB, hormonal therapy is necessary to stabilize endometrial proliferation and shedding, either with progestin-only regimens or with COCs.

INTRODUCTION

Menstrual disorders are the most common gynecologic conditions in the general population. Abnormal uterine bleeding (AUB) can mean both heavy and irregular menstrual bleeding, and many patients experience a combination of both.

The substantial impact of AUB lies not only in its prevalence, but its effect on the quality of life, associated loss of productivity, and major health care costs.[1]

AUB was redefined by the Fédération International de Gynécologie et d'Obstétrique (International Federation of Gynaecology and Obstetrics) (FIGO) in 2009 by the FIGO Menstrual Disorders Group (FMDG). This was in order to standardize the definition, nomenclature, and the underlying categories of etiology.

Acute AUB refers to an episode of heavy bleeding that, in the opinion of the clinician, is of sufficient quantity to require immediate intervention to prevent further blood loss. Chronic AUB was defined as 'bleeding from the uterine corpus that is abnormal in volume, regularity and/or timing that has been present for the majority of the last 6 months. Values outside the accepted 5–95th percentiles indicated abnormality **(Table 1)**.

Table 1 International Federation of Gynaecology and Obstetrics (FIGO) system for abnormal uterine bleeding: Suggested "normal" limits for menstrual parameters for uterine bleeding

Clinical dimensions of menstruation and menstrual cycle	*Descriptive tersm*	*Normal limits (5th to 95th percentiles)*
Frequencey of menses (days)	Frequent Normal Infrequent	<24 24–38 >38
Regularity of menses (cycle to cycle variation over 12 months; in days)	Absent Regular Irregular	— Variation ± 2 to 20 days Variation greather than 20 days
Duration of flow (days)	Prolonged Normal Shortened	>8.0 4.5–8.0 <4.5

Contd...

Contd...

Clinical dimensions of menstruation and menstrual cycle	*Descriptive tersm*	*Normal limits (5th to 95th percentiles)*
Volume of monthly blood loss (mL)	Heavy Normal Light	>80 5–80 <5

Based primarily on [23–25].

ETIOLOGY AND NOMENCLATURE OF ABNORMAL UTERINE BLEEDING

Once bleeding is defined as being abnormal, the acronym PALM-COEIN is now being increasingly used for categorizing causes: Polyp (AUB-P), Adenomyosis (AUB-A), Leiomyoma (AUB-L), Malignancy (AUB-M) (and hyperplasia)-Coagulopathy (AUB-C), Ovulatory disorders (AUB-O), Endometrial (AUB-E), Iatrogenic (AUB-I), and Not otherwise classified (AUB-N) **(Table 2)**. The 'PALM' components are assessed visually (imaging and histopathology) and the 'COEIN' are nonstructural components[2] **(Fig. 1)**.

Table 2 PALM-COEIN classification for the etiologies of abnormal uterine bleeding proposed by the International Federation of Gynaecology and Obstetrics (FIGO)

AUB causes	*Subclass*	*Characteristics*	
Structural causes	Polyps (**AUB-P**)	• Present in endometrial and endocervical canal • Categorized as absent or present	
	Adenoma (**AUB-A**)	• The genesis is controversial but minimal criterion is identification on ultrasound testing	
	Leiomyoma (**AUB-L**)	0: Submucosal types, do not impact endometrial cavity Others: 1: <50% intramural 2: ≥50% intramural 3: Totally extracavitary but lean on the endometrium, 100% intramural 4: Intramural leiomyomas that are entirely within the myometrium 5: Subserosal and at least 50% intramural	6: Subserosal and <50% intramural 7: Subserosal and attached to serosa by stalk 8: Do not involve the myometrium include cervical lesions, lesions that exist in the round or broad ligaments without direct attachment to the uterus, and parasitic lesions
	Malignancy & hyperplasia (**AUB-M**)	• May occur because of ovulatory disorder • Subclassification according to the WHO or FIGO system	
	Coagulopathy (**AUB-C**)	• Coagulopathy represents both inherited and acquired • Most common is inherited von Willebrand disease	
	Ovulatory dysfunction **(AUB-O)**	• Can lead to amenorrhea or heavy menstrual bleeding	
Non-structural causes	Endometrial (AUB-E)	• Likely to occur when other abnormalities are excluded in the presence of normal ovulatory function	
	Iatrogenic (AUB-I)	• Breakthrough bleeding during use of single or combined gonadal steroid therapy, intrauterine systems, or devices, systemic agents that interfere with dopamine metabolism, or anticoagulant drugs	
	Not classified (AUB-N)	• Rare or ill-defined conditions: Chronic endometritis, arteriovenous malformations, and myometrial hypertrophy	

METHODOLOGY OF FRAMING RECOMMENDATIONS

A systemic review of literature was conducted to collect the best of evidence for the good clinical practice recommendations (GCPRs). Existing guidelines, meta- analyses, cross-sectional studies, systemic reviews, and key-cited articles related to AUB were reviewed by a group of experts. The expert committee considered the recommendations from the existing guidelines of the Fédération International de Gynécologie et d'Obstétrique (FIGO), National Institute for Health and Care Excellence (NICE), American College of Obstetricians and Gynecologists (ACOG), and Royal College of Obstetricians and Gynaecologists (RCOG), and identified variability in the reproductive profile of Indian women compared to the Western countries. This variability may probably be due to the differences in the racial, socioeconomic, and cultural background of Indian and Western populations. Therefore, there is a need to formulate recommendations in the Indian context.

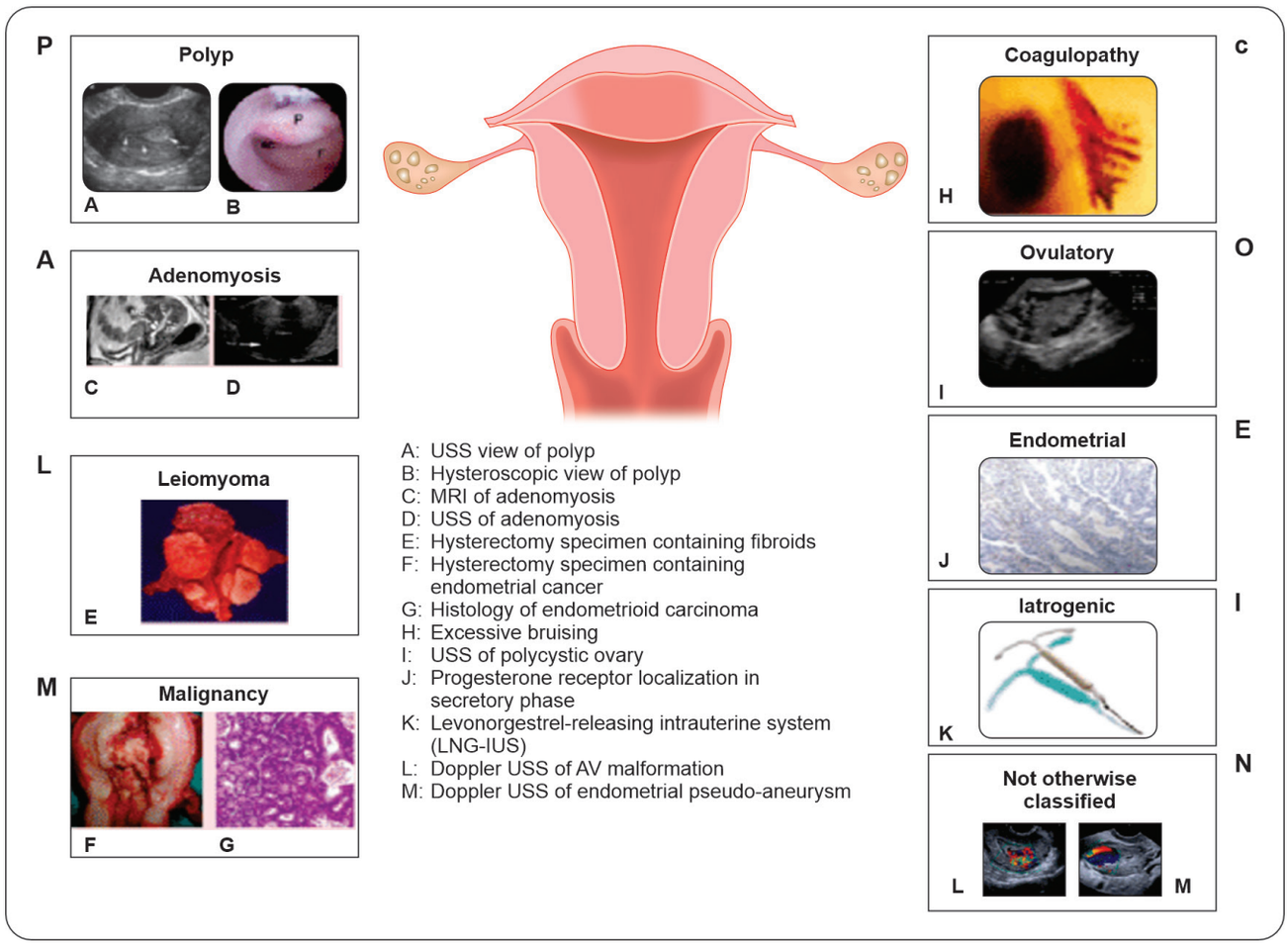


Fig. 1: PALM-COEIN classification

The draft recommendations were framed by the committee and discussed during an Expert Panel meeting held in May 2023. The Expert Panel discussed the draft recommendations on the basis of clinical evidences, from India and abroad, and framed the final version. Where evidence is limited, the Expert Panel relied on their vast experience and clinical judgement.

Recommendations are organized etiology-wise, according to the PALM- COEIN system. They are based on clinical importance and graded (A, B, C, and D), coupled with four intuitive levels of evidence (1, 2, 3, and 4) based on the quality of supporting evidence.

DIAGNOSIS OF ABNORMAL UTERINE BLEEDING

History and Initial Examinations

Recommendations regarding obtaining patient history and performing initial examination:

- It is suggested to abandon the old terminology and to use PALM-COEIN classification for the diagnosis AUB (Grade A; Level 4).[2]
- It is recommended to obtain a thorough history and to conduct a physical examination to direct the need for further investigations and treatment (Grade A; Level 4).
- It is recommended to obtain information about the concomitant use of any medications, which may likely be the cause AUB (Grade B; Level 4).
- In patients with AUB, any of the following criteria should be considered a positive screen for coagulopathies (Grade B; Level 4) **(Table 3)**.

  - History of heavy bleeding starting at menarche
  - One of the following:
    - Postpartum hemorrhage
    - Surgery-related bleeding
    - Bleeding associated with dental work
  - At least two of the following symptoms:
    - At least one episode of bruising per month o At least one episode of epistaxis per month o Frequent gum bleeding
    - Family history of bleeding symptoms
- ***Examination:*** Including the assessment of weight, pallor, thyroid, breasts, acne, hirsutism scoring (if present), abdominal, P/S & P/V examination (Grade A, Level 4).

Table 3 Screening instrument for coagulopathies in women with the symptom of heavy menstrual bleeding.[a,b]

Initial screening for an underlying disorder of hemostasis in patients with excessive menstrual bleeding should be by a structured history. A positive screening result comprises any of the following:[c]
• Heavy menstrual bleeding since menarche
• One of the following: – Postpartum hemorrhage – Surgical related bleeding – Bleeding associated with dental work
• Two or more of the following symptoms: – Bruising 1–2 times per month – Epistaxis 1–2 times per month – Frequent gum bleeding – Family history of bleeding symptoms

[a]Reproduced with permission
[b]This structured history-based instrument is 90% sensitive for the presence of a coagulopathy in women with the symptom of heavy menstrual bleeding.
[c]Patients with a positive screening result should be considered for further evaluation including consultation with a hematologist and/or testing of von Willebrand factor and ristocetin cofactor.

INVESTIGATIONS

Laboratory Testing

Recommendations on laboratory testing:
- A complete blood count (CBC) is recommended for women with AUB.
- It is recommended to perform a sensitive urine pregnancy test whenever indicated, or if pregnancy is suspected.
- Bleeding time, platelet count, prothrombin time, and partial thromboplastin time are recommended in all adolescents and in adults with a positive screen for coagulopathies. Further testing for von Willebrand disease, ristocetin cofactor activity, factor VIII activity, and von Willebrand factor antigen is recommended in consultation with a hematologist.
- Thyroid-stimulating hormone (TSH) testing is recommended for all women with AUB.

Imaging

Recommendations on imaging:
- Ultrasonography is mandatory in AUB to evaluate uterus, adnexa, and endometrial thickness (Grade A; Level 1).
- Transvaginal ultrasound is the most accepted first-line imaging study in the evaluation of AUB, except may be in a young girl.
- Addition of a Doppler may be indicated in suspected arteriovenous malformation, suspected malignancies, and to differentiate between fibroid and adenomyomas (Grade B; Level 3).
- 3D ultrasound imaging may be used in the evaluation of myometrial lesions such as fibroids/adenomyomas (Grade B; Level 4).
- Saline infusion sonography is used in the evaluation of a suspected intracavitary lesion (Grade A; Level 1).

- Hysteroscopy is used as an added tool in the diagnosis of intrauterine abnormalities such as endometrial polyps and submucous fibroids (Grade A;Level 1).

MANAGEMENT OF PATIENTS WITH ABNORMAL UTERINE BLEEDING

Management of Acute Heavy Abnormal Uterine Bleeding (HMB)

- For most of the patients, medical management should be the primary treatment, options include oral progestins or multidose regimens of combined oral contraceptives (COCs), and tranexamic acid (Grade A; Level 1).[3]
- Though the use of intravenous (IV) conjugated estrogen is mentioned in most textbooks and review articles for control of an acute episode, it is hardly ever used in clinical practice.
- Choice of treatment will depend on the patient's medical history and contraindications to therapies (Grade B; Level 2).
- First line of medical therapy is hormonal, for patients with acute AUB without known or suspected bleeding disorders (Grade A; Level 1).
- Oral progestins, either medroxyprogesterone acetate 20 mg orally three times per day or norethisterone acetate 10 mg three times a day is generally the preferred hormonal therapy for managing an episode of acute heavy AUB (Grade A; Level 1).
- The other option for hormonal therapy of an acute episode is combined oral contraceptive pills (OCPs) containing 30 µg ethinylestradiol, two pills every 12 hours for 5 days and then 1 tablet per day for 15 days is the schedule for the control of an acute episode (Antiemetics can be coprescribed for controlling nausea) (Grade A; Level 1).
- Tranexamic acid intravenously or orally is the nonhormonal agent used, alone or in combination with hormonal therapy, for managing an acute episode of heavy bleeding. IV dose used is 10 mg/kg every 8 hours (maximum 600 mg/dose). As bleeding decreases, switch over to an oral dose 500 mg three times a day (Grade B; Level 2).
- Desmopressin has been used successfully in the management of heavy menstrual bleeding (HMB) in women with von Willebrand disease, with treatment started with the onset of menses (Grade C; Level 3).[4]

AUB-P (Polyps)

Recommendations for the management of AUB-P:

- Hysteroscopic polypectomy is recommended for younger women, who wish to preserve fertility (Grade A; Level 1).
- In women with multiple endometrial polyps and not desirous of fertility, it is suggested to perform hysteroscopic polypectomy followed by levonorgestrel-releasing intrauterine system (LNG-IUS) insertion after the confirmation of a benign lesion on histopathology (Grade A; Level 2).
- Polyp should always be sent for histopathology.
  If histopathology suggests malignancy, further management should be as AUB-M (Grade A; Level 2).

AUB-A (Adenomyosis)

Recommendations for the management of AUB-A:

- For managing AUB-A, it is suggested to consider the age, symptomology (pain and/or infertility) and association with other conditions (leiomyomas, polyps, and endometriosis) (Grade B; Level 3).
- In women with AUB-A, the available options for medical management include nonsteroidal anti-inflammatory drugs (NSAIDs), progestogens, combined OCPs, Dienogest, LNG-IUS, and gonadotropin-releasing hormone (GnRH) agonists.
- In women with AUB-A, desirous of preserving fertility but not immediately planning for conception, LNG-IUS is an effective option, whereby good symptom control can be achieved with the avoidance of systemic side effects of progesterone (Grade A; Level 1).
- In patients with AUB-A, when other medical therapies fail or are not tolerated, GnRH agonists is recommended as a second-line therapy (Grade A; Level 1).
- In case of failure/nontolerance/refusal of medical management, hysterectomy is indicated (Grade A; Level 1).[5]

AUB-L (Leiomyoma)

Recommendations for AUB-L: Treatment for AUB-L should be individualized based on many variables such as age, parity, symptoms, fertility desires and size, location, and multiplicity of myomas.

Various options can be generalized as follows:

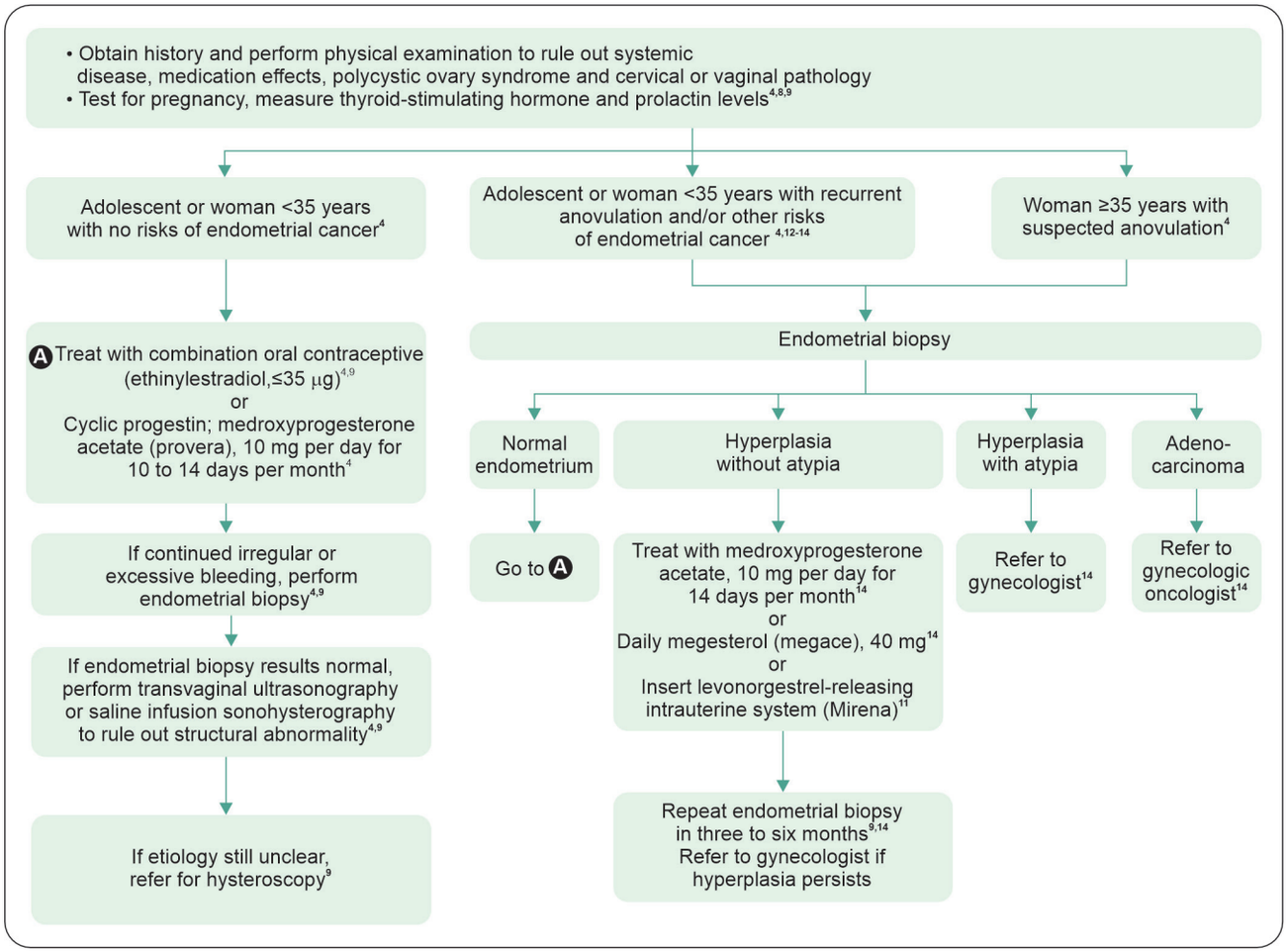
- Women with myomas, which are purely submucosal or have a significant submucous component (Grade 0–1), are more likely to have symptoms such as excessive bleeding at menses, pain at menses, infertility, and hence are more likely to need treatment (Grade A; Level 2).
- Women with myomas, which are predominantly/purely intramural or those with subserosal myomas (Grade 2–6), generally do not have much symptoms, and if so, may not need any treatment (Grade B; Level 2).
- The options for the medical management of fibroids (of any grade) include tranexamic acid, NSAIDs, GnRH agonists/antagonists, LNG-IUS, mifepristone, and ulipristal acetate.
- Surgical treatment options for Grade 0–1 myomas include hysteroscopic resection (for those <4 cm diameter) or laparoscopic/abdominal myomectomy (for those >4 cm diameter) (Grade B; Level 4).
- For Grade 2–6 myomas, when myomectomy is indicated, it should be done preferably by a laparoscopic approach, considering its advantages of earlier recovery and lesser postoperative morbidity compared to an open approach (Grade A; Level 3).
- In women above 40 years of age, not desirous of fertility, hysterectomy is the definitive treatment option; however, medical management including LNG-IUS may be tried in small fibroids (<4 cm diameter) before undergoing definitive surgery (Grade B; Level 3).
- For the short-term management (up to 6 months), GnRH agonists with add-back therapy is an option in perimenopausal women, prior to myomectomy or for the correction of anemia (Grade A; Level 1) **(Flowchart 1)**.

AUB-M (Malignancy and Endometrial Hyperplasia)

Recommendations for AUB-M:

- In AUB-M with endometrial malignancy, standard protocol for the management of malignancy should be followed (Grade B; Level 4).
- In AUB-M with endometrial hyperplasia with atypia, who do not wish to preserve fertility, should undergo a total hysterectomy because of the high risk of underlying malignancy or progression to cancer.
- Women wishing to retain their fertility should be counseled about the risks of underlying malignancy and subsequent progression to endometrial cancer. Pretreatment investigations should aim to rule out invasive endometrial cancer or coexisting ovarian cancer. Histology, imaging, and tumor marker results should be reviewed in a multidisciplinary meeting and a plan for management and ongoing endometrial surveillance formulated.[6]
- First line in medical management is LNG-IUS, continuous oral progestogens being the other option, if LNG-IUS is not applicable.
- Endometrial surveillance in these women should include endometrial biopsy. Review intervals should be every 3 months until two consecutive negative biopsies are obtained.[7]
- For those in whom medical management fails, and in those with persistent atypical hyperplasia, hysterectomy is the definitive treatment (Grade B; Level 2).[8]
- Women with endometrial hyperplasia without atypia should be informed that the risk of progressing to endometrial cancer is less than 5% over the next 20 years and that the majority of cases of endometrial hyperplasia without atypia will regress spontaneously during follow-up.
- Both continuous oral and local intrauterine (LNG-IUS) progestogens are effective in achieving the regression of endometrial hyperplasia without atypia.
- LNG-IUS should be the first-line medical treatment because compared with oral progestogens it has a higher disease regression rate, with a more favorable bleeding profile and is associated with fewer adverse effects.
- Progestogens should be used continuously (medroxyprogesterone 10–20 mg/day or norethisterone 10–15 mg/day) in women who decline the LNG-IUS.[8]
- Cyclical progestogens should not be used because they are less effective in inducing the regression of endometrial hyperplasia, compared with continuous oral progestogens or the LNG-IUS (Grade A; Level 1).
- Treatment with oral progestogens or the LNG-IUS should be for a minimum of 6 months, in order to induce the histological regression of endometrial hyperplasia without atypia.
- If adverse effects are tolerable and fertility is not desired, women should be encouraged to retain the LNG-IUS for up to 5 years, as this reduces the risk of relapse, especially if it alleviates AUB symptoms.
- Endometrial surveillance with an outpatient endometrial biopsy is recommended, in women with a diagnosis of hyperplasia without atypia.

Flowchart 1: Algorithm for management of abnormal uterine bleeding in perimenopausal women



- Endometrial surveillance should be arranged at a minimum of 6-monthly interval.
- Follow up should continue till at least two consecutive 6-monthly endometrial biopsies are negative.
- Women should be advised to seek a further referral if abnormal vaginal bleeding recurs after the completion of treatment, because this may indicate disease relapse.
- In women at a higher risk of relapse, such as women with a body mass index (BMI) of 35 kg/m^2 or more or in those treated with oral progestogens, 6-monthly endometrial biopsies are recommended. Once two consecutive negative endometrial biopsies have been obtained, then the long-term follow-up should be considered with annual endometrial biopsies.
- Hysterectomy is indicated in women not wanting to preserve their fertility when: (i) progression to atypical hyperplasia occurs during follow-up, or (ii) there is no histological regression of hyperplasia despite 12 months of treatment, or (iii) there is relapse of endometrial hyperplasia after completing progestogen treatment, or (iv) there is persistence of bleeding symptoms, or (v) the woman declines to undergo endometrial surveillance or comply with medical treatment.

AUB-C (Coagulopathy)

Recommendations specific to AUB-C:

- In patients with AUB-C, nonhormonal treatment with tranexamic acid is the first option. Hormonal treatment with COCs/LNG-IUS are the other recommended options, in consultation with a hematologist (Grade A; Level 2).

- For patients with uncontrolled uterine bleeding, in spite of the above medical management, specific factor replacement or desmopressin should be considered (Desmopressin can be administered intravenously, subcutaneously, or as an intranasal spray).[9]
- In these women, NSAIDs are contraindicated as they can alter platelet function and interact with drugs that might affect the liver function and the production of clotting factors.
- Injectables (e.g. GnRH agonists) are also avoided in this group of patients, except in those with mild coagulation abnormalities [When administered, prolonged pressure should be applied at injection site (Singh et al., 2013)].

AUB-O (Ovulatory Dysfunction)

Recommendations specific to AUB-O:

- Oral progestins are generally the first line of management (Grade A; Level 1).
- Norethisterone/Medroxyprogesterone acetate can be used from D15 - D25 of the cycle for upto 3 cycles (Grade B; Level 4).
- Women who are not desirous of pregnancy can be managed with COCs or an LNG-IUS.
- It is suggested to assess response after 1 year of medical management and judge whether to continue/discontinue the ongoing therapy (Grade B; Level 4).[9]
- Surgical intervention is not recommended unless, there is evidence of persistent AUB or failure of medical management to alleviate the condition (Grade A; Level 4).
- In adolescents with AUB-O, both hormonal and nonhormonal therapies can be prescribed (Grade A; Level 4).

AUB-E (Endometrial)

Recommendations specific to AUB-E:

- Initial treatment options available for these women are tranexamic acid combined with mefenamic acid, oral progestins, and COCs.
- LNG-IUS is an extremely effective option in this group.

AUB-I (Iatrogenic causes)

Recommendations specific to AUB-I:

- The breakthrough bleeding that occurs with the use of combined OCPs during the first 1–3 months, is managed with reassurance, as the frequency of breakthrough bleeding becomes lesser in the future cycles.
- The use of a 5 to 7-day course of NSAIDs may be used to reduce the volume of breakthrough bleeding.
- The breakthrough bleeding or intermenstrual bleeding is generally noted in the first 6 months of LNG-IUS insertion and counseling regarding this entity is crucial prior to LNG-IUS insertion.[9]
- NSAIDs and tranexamic acid are considered as the first-line therapy options in LNG-IUS-related bleeding/spotting. Tranexamic acid is more effective than NSAIDs in cases of spotting and vice-versa in cases of significant bleeding. NSAIDs should be considered as the first-line therapy also in those cases where bleeding is associated with pain. Addition of an oral estrogen or a COC for the initial months, is the other option when the first-line management fails.
- Post intrauterine contraceptive device (IUCD) and post sterilization patients with bleeding can also be managed with a combination of antifibrinolytic agents and NSAIDs.
- Bleeding in women who are on anticoagulant therapy is managed with oral progestins/depot medroxyprogesterone acetate or an LNG-IUS.

Antifibrinolytics and COCs (which contain estrogen) have traditionally been considered contraindicated in this group of women with a probable history of thrombosis, though most studies have not been able to show any significant increase in venous thromboembolism (VTE) with their use. A switch over to another anticoagulant preparation, with a lesser risk of causing abnormal bleeding may also be considered, along with the hormonal therapy.[10]

AUB-N (Not defined)

Recommendations for AUB-N:

- In patients with idiopathic AUB and desiring effective contraception, LNG-IUS is recommended as the first-line therapy to reduce menstrual bleeding (Grade A; Level 1).

- In patients with AUB-N, desirous of continued fertility and in whom LNG-IUS is contraindicated, the use of COCs are recommended as the second-line therapy (Grade A; Level 1).
- For the management of abnormal uterine bleeding that are mainly cyclic or predictable in timing, nonhormonal options, such as NSAIDs and tranexamic acid, are recommended (Grade A; Level 1).[10]

AUB-COEIN: General management guidelines

Recommendations of AUB-COEIN:

- Tranexamic acid is the first-line therapy alone or in combination with NSAIDs (Grade B; Level 1).[10]
- In women desiring effective contraception, LNG-IUS is recommended (Grade A; Level 1).
- Cyclic oral progestins (from day 5–25) are recommended as the second-line therapy (Grade B; Level 1).
- COCs are recommended in patients desiring effective contraception, but unwilling or unsuitable for LNG-IUS (Grade A; Level 4).
- Centchroman is an option when steroidal hormones and other medical options are not suitable (Grade B; Level 3).
- Use of cyclic luteal-phase progestins is not recommended as a specific therapy for managing AUB (Grade A; Level 4).
- GnRH agonists are recommended as a last resort when medical or surgical treatments for AUB have failed or are contraindicated (Grade B; Level 4).[10]
- Conservative surgeries, such as ablation, are less often used these days, with increasing popularity of LNG-IUS as a medical ablative therapy.

ABNORMAL UTERINE BLEEDING IN ADOLESCENTS

- A diagnostic evaluation should be performed before any treatment is initiated which is aimed at determining the severity of the bleeding and to find out the possible etiology of AUB **(Tables 4 and 5)**.[11]
- Pathologies, such as bleeding disorders and clotting abnormalities, and pathologies of the reproductive tract, genital injuries, and drug use, should be excluded in the differential diagnosis.
- Pregnancy and pregnancy-related situations, such as ectopic pregnancy, should be promptly evaluated and excluded.
- Bleeding disorders which cause 20–33% of cases of prolonged and/or severe bleeding, should always be taken into consideration.
- A detailed history should be taken both with and without parents (with parents to know the details of the problem and without parents to know the sexual history).
- Detail menstrual history, history of prolonged bleeding after surgery or tooth extraction, epistaxis, gum bleeding, and bruising should be taken.
- Family history of coagulopathy or hormone sensitive cancers should also be elicited.
- Since HMB is a subjective diagnosis, it is desirable to use an objective method of assessing blood loss, especially in this age group **(Figs. 2 and 3)**.
- General examination is must to see for the signs of pallor, hepatosplenomegaly, signs related to hormonal disorders such as hirsutism and acanthosis nigricans.
- Gynecological examination is not necessary, unless a pregnancy-related cause is suspected.
- Ultrasound too is not mandatory as majority of these AUB are due to anovulatory cycles (When needed, USG should preferably be by the transabdominal route).
- The minimum laboratory evaluation should include a complete blood count (CBC), peripheral blood smear, ferritin level, prothrombin time and activated partial thromboplastin time.
- Adolescents suspected to have bleeding disorders should undergo testing for vWD (The von Willebrand panel should include plasma for von Willebrand factor (vWF) antigen and functional tests for vWF and factor VIII activity).[12]
- The first-line approach to managing AUB in the adolescent is medical management, the choice of treatment depending on the clinical stability, overall acuity, suspected etiology of the bleeding, and underlying medical problems.
- In mild AUB, nonhormonal therapy with NSAIDs would suffice in most cases (A follow-up at 3-month intervals with a menstrual-cycle diary is advised).
- In moderate AUB, hormonal therapy is necessary to stabilize endometrial proliferation and shedding, either with COCs or progestin-only regimens.
- Oral progestin therapy is generally the first choice to arrest an acute episode of HMB.

Table 4 Suggested treatment options for abnormal uterine bleeding based on PALM-COEIN etiology

Etiology	*Treatment*
Polyp	Hysteroscopic surgical removal Multiple polyps or polypoidal endometrium and fertility is not desired– LNG-IUS can be combined with surgical removal
Adenomyosis	LNG-IUS, if LNG-IUS is not accepted – GnRH agonists with add-back therapy; if it fails OCP, NSAIDs, progestogens
Leiomyoma	Intramural or subserosal myomas (Grade 2–6) Tranexamic acid or COCs or NSAIDs, LNG-IUS, if treatment fails myomectomy depending on location In women >40 years of age, fertility is not desired, for small fibroids (<4–5 cm) – medical management followed by hysterectomy Short-term management (up to 6 months) – GnRH agonists with add-back therapy followed by myomectomy Long-term management – LNG-IUS Newer medical options: Ulipristal acetate or low-dose mifepristone, currently not available in India Submucosal myoma (Grade 0–1) hysteroscopic (< 4 cm) or abdominal(open or laparoscopic for > 4 cm)
Malignancy	Atypical endometrial hyperplasia – surgical treatment Continued fertility not desired – hysterectomy Hyperplasia without atypia LNG-IUS followed by oral progestins or PRMs
COEIN	LNG-IUS or tranexamic acid, NSAIDs, followed by COCs or cyclic oral progestins Medical or surgical treatment failed or contraindicated: GnRH agonists with add-back hormone therapy When steroidal and other options unsuitable: Centchroman

Table 5 Strength of recommendation and scale of scientific support

Strength of Recommendation	
A	Strongly recommended
B	Intermediate
C	Weak
D	Not-Evidence based, Panel recommended
Scale of Scientific Support	
1	Meta-analysis of randomized controlled trials (RCTs)
2	Meta-analysis of nonrandomized prospective or case-controlled trials, nonRCTs, prospective cohort study, and retrospective case-control studies
3	Cross-sectional studies, surveillance studies (registries, surveys, epidemiologic studies, retrospective chart reviews, mathematical modeling of database), consecutive case series, single case reports
4	Opinion/consensus by experts or preclinical study

- Options of oral progestin therapy include medroxyprogesterone (5–10 mg three times a day) or norethisterone acetate (2.5–5 mg three times a day) to stop an acute episode of heavy bleed and then tapering it to a twice daily dosing for the next 2 weeks.
- COCs are the other option. Monophasic COCs, containing at least 30 µg of ethinyl E2, are preferred to prevent breakthrough bleeding.
- One pill every 8–12 hours until the bleeding stops, then to continue with one pill per day for a total of at least 21 days. If bleeding starts again dosing may be increased to twice a day for a total 21 days (Antiemetics like 4–8 mg of ondansetron can be given if nausea occurs with high doses of E2).[13]
- After allowing for withdrawal bleeding, COCs treatment is continued for 3–6 months until the hemoglobin level reaches ≥12 g/dL.
- Depot medroxyprogesterone acetate (DMPA) or a levonorgestrel-releasing intrauterine device are only used in those girls, who need contraception or those who cannot take pills.
- With severe AUB in a hemodynamically stable girl (Hb = 8–10 g/dL), the use of OCPs is similar to those with moderate bleeding. If there is no decrease in the severity of the bleeding following the first 2 doses of OCP treatment, the dose

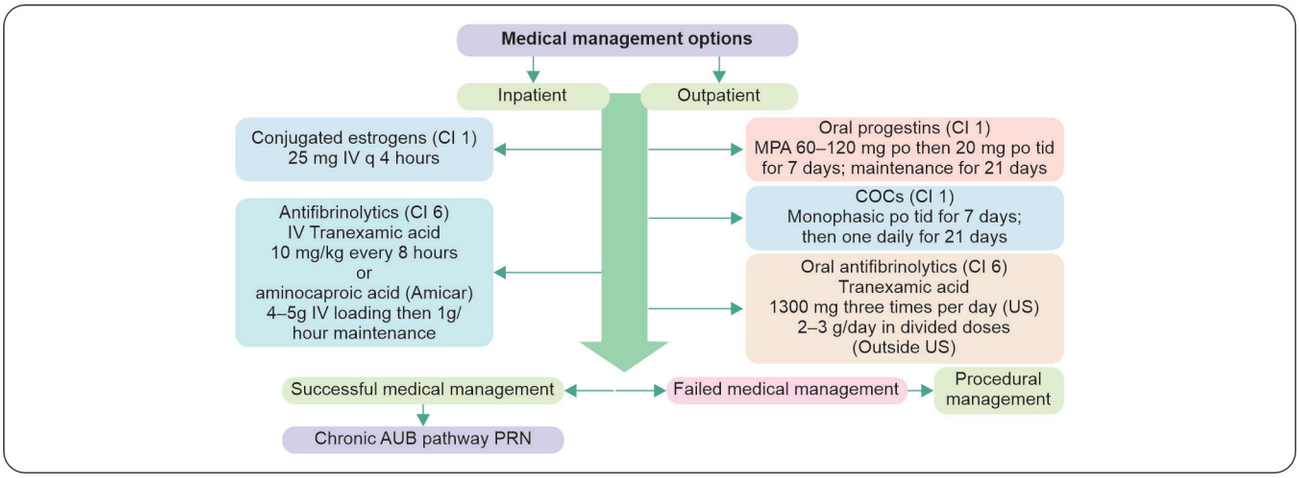


Fig. 2: Medical management of acute heavy menstrual bleeding

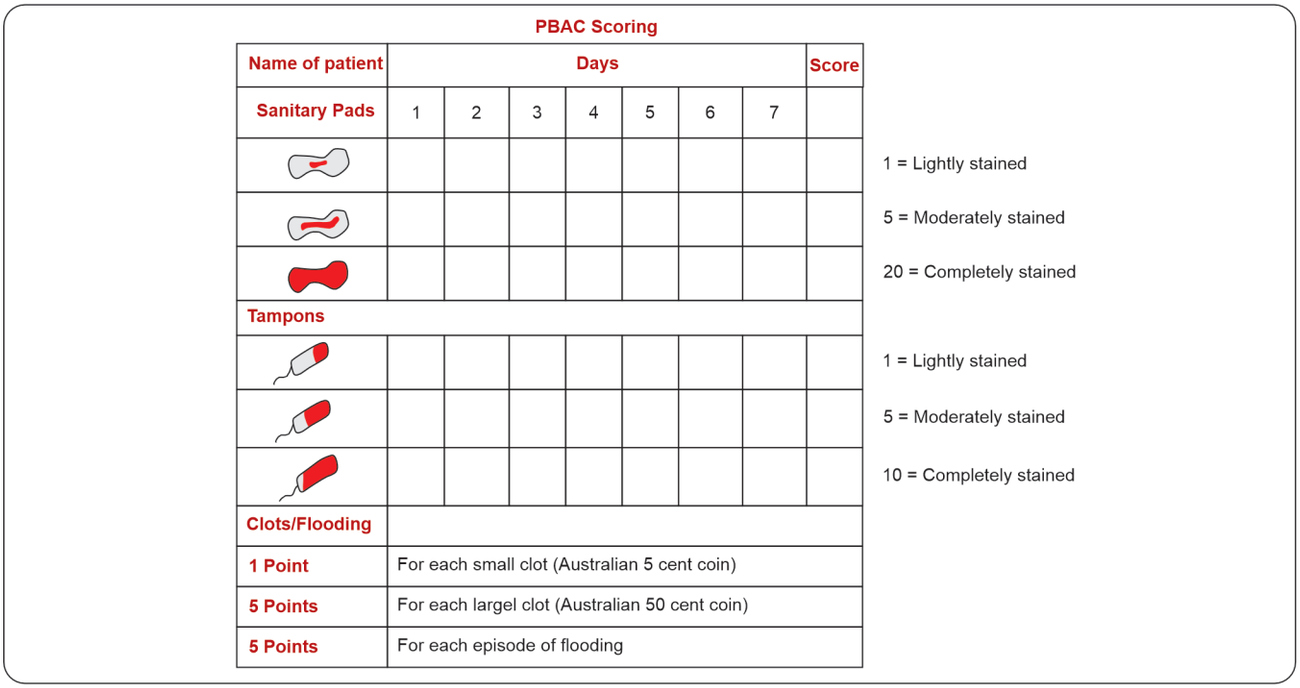


Fig. 3: Pictorial Blood Assessment Chart (PBAC) scoring for uterine bleeding

should be increased to 3–4 pills per day for 2 days and this dosage should be continued until the bleeding stops. The OCP treatment is continued at a dose of 4 pills per day for 4 days and then one pill per day for a minimum of 3–6 months.

- Close monitoring and iron supplements should be prescribed in these patients.
- In a case of severe AUB in a hemodynamically unstable girl, the patient should be hospitalized and monitored. Preparations should be made for blood transfusion, as it may be required. Bleeding disorders must be ruled out before starting hormonal treatment.
- The first treatment of choice is high-dose oral progestin therapy, with either medroxyprogesterone (20–40 mg/day) or norethisterone acetate (10–15 mg/day) to stop an acute episode of heavy bleed and then tapering it to a twice daily dosing for the next 2 weeks.[13]

- The progesterone reverses endometrial proliferation related to long-term estrogen exposure and induces endometrial maturation.
- OCPs containing high doses of estrogen (35–50 µg ethinylestradiol) are the other option. Estrogen in these OCPs also promotes rapid endometrial regrowth to cover denuded epithelial surfaces. The use of pills containing 50 µg ethinylestradiol is usually considered, if there is no decrease in the severity of bleeding after the second dose of the 35 µg pills. The treatment with high-dose estrogen is continued at 6-hour intervals until the severity of the bleeding decreases. The dose is then decreased within 1 week as follows: One pill every 6 hours for 2 days, then every 8 hours for 2 days, then every 12 hours for 2 days, and finally 1 pill daily for a minimum of 6 months (Antiemetic therapy can be an added treatment for patients who experience high-dose estradiol-induced nausea and vomiting).[14]
- The therapy is maintained with pills containing 30–35 µg ethinylestradiol. However, in cases where the bleeding is controlled with 50 µg high-dose ethinylestradiol containing pills, these are continued for about one or two cycles at the same dose (50 µg ethinylestradiol); the treatment is then continued for 3–6 months with 35 µg ethinylestradiol-containing pills.
- The bleeding is usually controlled within 24 hours with OCP treatment. If the bleeding continues for more than 24–48 hours without any decrease in severity, the addition of hemostatic agents should be considered.
- Another recommended treatment for acute HMB is depot MPA (150 mg), administered intramuscularly and followed by MPA (20 mg) orally every 8 hours for 9 doses. When the bleeding stops, the progesterone dose is decreased to every 12 hours for 2 weeks. Thereafter, therapy is maintained with the cyclic use of MPA (10 mg/d) and norethindrone acetate (NETA) (5 mg/d) for 12 days per month and between the same dates in every month. There may be a need for hemostatic agents, such as tranexamic acid, aminocaproic acid, and desmopressin, if bleeding exceeds 24 hours despite high dose COCs or there is a known platelet dysfunction. Tranexamic acid 3–4 g/day in three doses for 4–5 days is an effective treatment for HMB and/or active thromboembolic disease or an intrinsic risk for thrombosis are contraindications for tranexamic acid use. The concomitant usage of COCs increases the risk of thrombosis.
- If hormonal and hemostatic treatment fail to lessen bleeding in 24–36 hours, examination under anesthesia, endometrial sampling, and therapeutic curettage may be necessary.

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