FOGSI Focus

Abnormal Uterine Bleeding

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Editor-in-Chief

Alpesh Gandhi

President, FOGSI

Editor

Laxmi Shrikhande

Chairperson Designate ICOG

CBS

CBS Publishers & Distributors Pvt Ltd

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ISBN: 978-93-89565-88-1

First Edition: 2020

Published by Satish Kumar Jain and produced by Varun Jain for

CBS Publishers & Distributors Pvt Ltd
4819/XI Prahlad Street, 24 Ansari Road, Daryaganj, New Delhi 110 002
Ph: 23289259, 23266861, 23266867 Fax: 011-23243014 Website: www.cbspd.com
e-mail: delhi@cbspd.com; cbspubs@airtelmail.in

Corporate Office: 204 FIE, Industrial Area, Patparganj, Delhi 110 092
Ph: 4934 4934 Fax: 4934 4935 e-mail: publishing@cbspd.com; publicity@cbspd.com

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  Ph: +91-22-24902340/41/42 Fax: +91-22-24902342 e-mail: mumbai@cbspd.com

Representatives

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• **Patna**	0-9334159340	• **Pune**	0-9623451994	• **Uttarakhand**	0-9716462459

Printed at Nutech Print Services, Faridabad, Haryana, India

Message

"The mother of excess is not joy but joylessness"—Friedrich Nietzsche

The above quote is apt for the topic chosen for this FOGSI Focus. The prevalence of Abnormal Uterine Bleeding (AUB) greatly varies anywhere between 3 and 30% in women and it is more prevalent around menarche and perimenopause. The causes for the condition are also varied. The management needs to be coordinated and an interdisciplinary approach is needed. AUB can be debilitating and may involve enormous direct and indirect costs.

The condition needs to be approached in a structured manner which will help in establishment of the cause. This will facilitate an accurate diagnosis and will lead on to an informed decision regarding the treatment options. The treatment needs to be individualised and should encompass impact of pressure symptoms, desire for fertility retention, contraceptive needs as well as improvement of quality of life.

This book has included the conditions which contribute to AUB relevant to our times. The chapters are authored by eminent gynaecologists with great clinical acumen. I thank the editor of this book, Dr Laxmi Shrikhande for taking the efforts to bring this book to realization.

I thank the coordinators Dr Ashok Kumar, Dr Charmila Ayyavoo and Dr Munjal Pandya for their efforts.

Take care and stay safe!!

Alpesh Gandhi

President, FOGSI

Message

It is my pleasure and privilege to write this message.

Women's health remains a priority and FOGSI and its members are doing all they can to meet the challenges to accomplish the goal of providing the best care to all our women. FOGSI is working on several fronts like advocacy with the government, training, continuing medical education and programs and projects to improve women's health and standardise quality of care.

AUB is a common and yet largely poorly understood problem. Starting from nomenclature to diagnosis and treatment, a lot needs to be elucidated and articulated. I hope that this important publication on this topic will serve to enlighten and guide who ever reads it and improve women's health in our country.

The Editor-in-Chief, Dr Alpesh Gandhi and the Editor, Dr Laxmi Shrikhande need to be congratulated for this publication.

Warm Regards.

Jaydeep Tank

Secretary General, FOGSI

Foreword

Abnormal Uterine Bleeding (AUB) is a persistent clinical problem in the life of any gynaecologist and one may wonder that will we ever be able to see the end of it!! Here I quote Robert H. Shuller who said "Problems are not stop signs, they are guidelines." This statement has been most appropriate in describing the pursuit of effective management of AUB. Over the last few decades, we have redefined this clinical entity not only by reclassifying its elements but also by approaching the diagnosis and management with a multipronged approach. It is therefore vital that the current practitioners are provided with a compendium of the recent advances in this area. It was heartening to see this edition of the "FOGSI Focus" dedicated to AUB with our FOGSI President, Dr Alpesh Gandhi as chief editor and Dr Laxmi Shrikhande as the editor.

The mysteries and advancements in the clinical understanding of AUB have been very skillfully unravelled through the chapters on the new FIGO classification and the emerging role of novel imaging modalities, endometrial sampling and management strategies. It is particularly notable that the importance of the age at presentation of AUB has been given importance by addressing the issue separately in adolescents, perimenopausal and postmenopausal groups. In this age of "women-centred care" every clinician has to understand that a single solution will not fit all and there is a need to revise individual management protocols taking the entire gamut of problems of a patient into consideration. It therefore becomes important to also look beyond pure gynaecological etiology and realise the importance of coagulopathies or bleeding disorders and systemic endocrine causes contributing to the pathophysiology of AUB.

The persistence of a clinical enigma, like AUB, has acted as a stimulus to recreate "protocols"(P), refine "practices"(P) along the basic "principles"(P) of clinical medicine. I congratulate the editors and authors of this FOGSI Focus on AUB for achieving the purpose of "P-P-P" meaningfully. The readers will benefit immensely with this compendium.

Happy Reading!!

S Shantha Kumari
MD, DNB, FICOG, FRCPI (Ireland), FRCOG (UK)
PRESIDENT ELECT FOGSI 2021

Preface

Abnormal Uterine Bleeding (AUB) continues to be one of the most common condition encountered by gynaecologists in contemporary practice. Keeping up with the rapid advancement of medical science, AUB has also undergone important revisions to its terminology, classification and management.

It gives me immense pleasure to present this dedicated FOGSI Focus on AUB. The entire gamut of AUB, right from adolescence to menopause, has been presented in a crisp, concise manner. All the authors have taken great efforts to provide you with up-to-date and clinically relevant information.

My sincere thanks to FOGSI President, Dr Alpesh Gandhi for entrusting me with this responsibility. Thanks to Dr Jaydeep Tank (Secretary General, FOGSI) for his guidance from time to time. I also thank the coordinators Dr Ashok Kumar, Dr Charmila Ayyavoo and Dr Munjal Pandya. My endeavour will be worthwhile if everyone incorporates these changes in their daily practice as—*"Change is the end result of all true learning."—Leo Buscaglia*

Laxmi Shrikhande

List of Contributors

Chaitanya Shembekar
MD, FICOG, FICMCH, Dip Pelviscopy
Chairman and Managing Director
Omega Hospital
Nagpur

Laxmi Shrikhande
MD, FICOG, FICMU, FICMCH
Consultant
Shrikhande Fertility Clinic
Nagpur

Kamini Patel
Director, Vani IVF Centre
Ahmedabad

Lipika Mohrana
MS (Ob/Gyn) (Utkal University)
Fellowship in Reproductive Medicine
Clinical Embryology, PCOS
Sexual Medicine and Ultrasound in Infertility
Member of ISAR SIG Sexual Medicine
Managing Committee Member of PCOS Society of India
Currently, Chief Consultant Fertility
PCOS and Sexual Medicine
Arogyam Clinics
Cuttack, Odisha

Kalpana Jetha
DNB
Consultant
Omega Hospital
Nagpur

Kausha Shah
MRCOG, DNB, FICOG, FCPS, DGO, DFP
Consultant
KK Maternity and Surgical Hospital
Mumbai
Ex-Assistant Professor
KEM Hospital and JJ Hospital
Mumbai

Mandakini Megh
MD, DGO, FICMCH, FICOG
Director and Consultant
Dr Megh's Gynae Care Clinic
Mumbai

Kirtan M Vyas
MS (Ob/Gy)
Sevak Maternity and Surgical Hospital
Ahmedabad

Neema Acharya
Professor and Head
Department of Obstetrics and Gynaecology
JNMC, DMIMSDU, Sawangi Meghe
Wardha

Niraj Jadav
MBBS, DGO
Sankalp Maternity Home
Rajkot

Sandhya Pajai
Professor
Department of Obstetrics
and Gynaecology
JNMC, DMIMSDU, Sawangi Meghe
Wardha

Parikshit Tank
MD, DNB, FCPS, DGO, DFP, FICOG, FRCOG
Consultant
Ashwini Maternity and Surgical
Hospital
Center for Endoscopy and
Assisted Reproduction

Seema Pandey
Consultant
Reproductive Medicine
Seema Hospital and EVA Fertility
and
IVF Center
Atraulia, Azamgarh

Parul Sharma Saoji
MS, DNB
Executive Director
Omega Hospital
Nagpur

Shobha N Gudi
MD, DNB, FICOG, CIMP
Professor and Head
Department of Obstetrics
and Gynaecology
St. Philomenas Hospital
Bengaluru

Prashant Gupta
MBBS, MD
Director
KC Hospital
Palwal, Haryana

Shraddha Agarwal
MBBS, DGO, FICOG
Director
KC Hospital
Palwal, Haryana

Rakhee Singh
DGO, DRM, DPE, FICOG, FIAOG
Director
Abalone Clinic and IVF Center
Noida

Vidya Thobbi
MBBS, MD, FICOG
Professor and Head
Department of Obstetrics and
Gynaecology
Al-Ameen Medical College
Bijapur, Karnataka

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Chapter 1

Overview

Mandakini Megh

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 quality of life, associated loss of productivity and major health care costs. Gynecologists encounter several challenges when delivering medical care to these women. The multiple etiologies of AUB, numerous available medical and surgical treatment options, and inconsistent measurement and reporting of treatment outcomes in studies contribute to the confusing nature of the body of literature on AUB. This has resulted in a body of literature that can be difficult to interpret and translate to clinical decision-making. This review addresses the causes and approach to assessment and general principles of management of AUB.

Definitions

AUB was redefined by Fédération International de Gynécologie et d'Obstétrique (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. It was hoped that this would facilitate ease of investigation and comparison of similar patient populations and thereby aid research and improve evidence-based care; this would also be a practical tool for assessing contributing etiologies.

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.

Suggested normal limits for menstrual parameters. Adapted from Fraser et al.

Clinical parameter	*Descriptive term*	*Normal limits (5–95th percentiles)*
Frequency of menses (days)	Frequent	<24
	Normal	24–38
	Infrequent	>38
Regularity of menses	Absent	No bleeding
Cycle to cycle (variation in days over 12 months)	Regular	Variation + 2–20 days
	Irregular	Variation >20 days
Duration of flow (days)	Prolonged	>8.0
	Normal	4.5–8.0
	Shortened	<4.5
Volume of monthly blood loss (ml)	Heavy	>80
	Normal	5–80
	Light	<5

With regard to volume, however, both the Royal College of Obstetricians and Gynecologists (RCOG) and American College of Obstetricians and Gynecologists (ACOG) prefer the patient-centric definition of HMB, "Excessive menstrual blood loss which interferes with a woman's physical, social, emotional and/or material quality of life" as an indication for investigation and treatment options. As such, objective measurements of volume are usually the preserve of research studies and surrogates such as pictorial blood loss assessment chart (PBAC) scores are not recommended in routine clinical practice.

FIGO CLASSIFICATION OF CAUSE: PALM-COEIN

Once bleeding is defined as being abnormal, the acronym PALM-COEIN is now being increasingly used for categorizing causes: Polyp, Adenomyosis, Leiomyoma, Malignancy (and hyperplasia), Coagulopathy, Ovulatory disorders, Endometrial, Iatrogenic and Not otherwise classified. The 'PALM' components are assessed visually (imaging and histopathology) and the 'COEIN' are non-structural components.

Polyps (AUB-P)

Endometrial polyps are epithelial proliferations arising from the endometrial stroma and glands. The majority are asymptomatic. The contribution of polyps to AUB varies widely ranging from 3.7 to 65%. The incidence of polyps, as with fibroids, increases with age and both pathologies may frequently co-exist, or suspected polyps visualized on transvaginal ultrasound scanning (TV-USS) may be mistaken for submucous fibroids and vice versa.

Adenomyosis (AUB-A)

The relationship between adenomyosis and AUB remains unclear particularly with regards to wide variations in the radiological and histopathological diagnostic criteria used. Typically, adenomyosis is associated with increasing age and may co-exist with fibroids. Furthermore, adenomyosis may be both focal and diffuse and it may be difficult to diagnose in the presence of co-existing fibroids.

Malignancy (AUB-M)

With the reclassification by the WHO from hyperplasia to endometrial intraepithelial neoplasia (EIN),

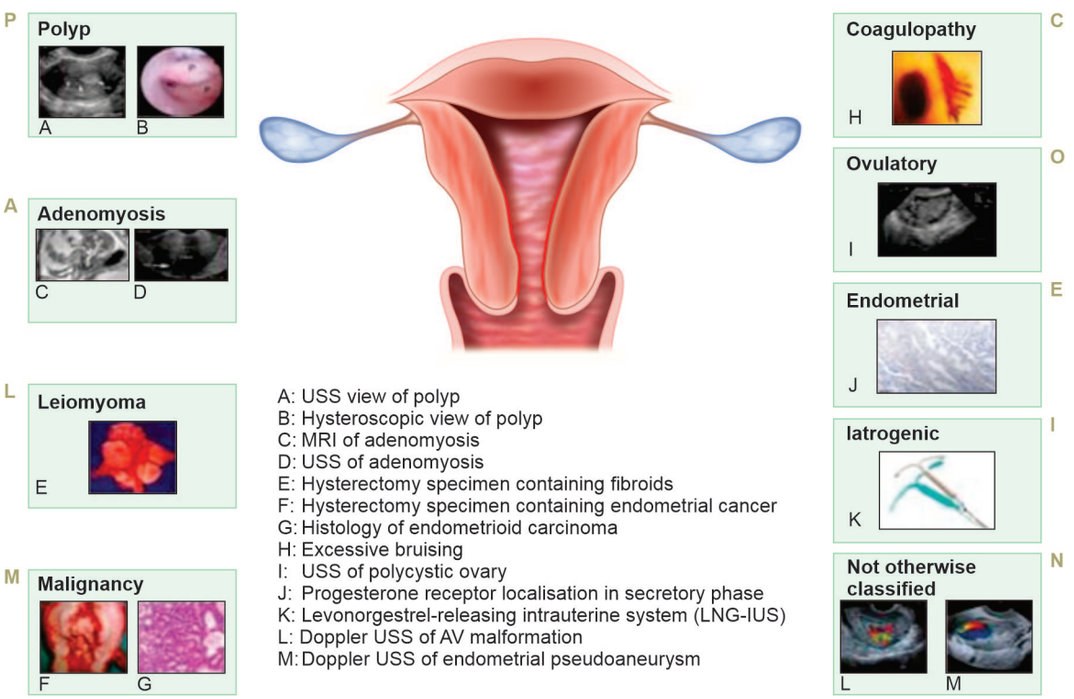

Fig. 1.1: FIGO classification of causes of AUB; 'PALM-COEIN'

the current prevalence of premalignant disease is unknown. The evaluation of the endometrium may be affected by distortion of the uterine cavity by fibroids, and co-existing pathologies may delay diagnosis.

The diagnosis of cervical cancer should be considered, particularly with persistent intermenstrual bleeding, and rarely ovarian cancer may present with AUB.

Uterine sarcoma has been reported as rare (3–7/100,000 in the USA) but is a cause of AUB-M. A recent meta-analysis reported that leiomyosarcomas are unexpectedly being diagnosed following surgery for anticipated 'benign' myomas in 2.94 per 1000 women (one in 340 women).

Interestingly, it was previously believed that a rapidly enlarging uterus would raise the suspicion of malignancy. This is now no longer considered to be true as benign fibroids can grow rapidly and sarcomas grow slowly. However, more objective investigations are still lacking. Both ultrasound scanning (USS) and magnetic resonance imaging (MRI) still do not have robust criteria to accurately predict differentiation between leiomyoma and leiomyosarcoma. The lack of a robust pre-surgical predictor/biomarker has recently altered surgical practice because morcellation of an unsuspected leiomyosarcoma increases dissemination of tumor cells.

If malignancy or premalignant lesion is found, then along with AUB classification, the pathology should be described and staged utilizing the appropriate FIGO systems.

Coagulopathy (AUB-C)

Coagulopathies are reported to affect 13% of the women presenting with HMB. Majority of these women suffer from von Willebrand disease. Systemic disorders of hemostasis may be identified in 90% of women using a structured history.

Ovulatory (AUB-O)

Anovulatory cycles may contribute to AUB by unopposed estrogen effects on the endometrium causing marked proliferation and thickening resulting in HMB along with an altered frequency of menstruation. This is observed at the extremes of reproductive age; however, impact on the HPO axis along with endocrinopathies may also be present. The latter include polycystic ovarian syndrome (PCOS), hyperprolactinemia, hypothyroidism as well as factors such as obesity, anorexia, weight loss, mental stress and extreme exercise. Typically, women in this group have menstrual cycles longer than 38 days or have a variation of >21 days. Drugs that affect dopamine levels, with their attendant effects on the HPO axis, also currently fall under this category rather than AUB-I. In women with fibroids, the co-existing ovulatory dysfunction may exacerbate menstrual loss.

Endometrial (AUB-E)

AUB that occurs in the context of a structurally normal uterus with regular menstrual cycles without evidence of coagulopathy is likely to have an underlying endometrial cause. Endometrial function in the context of menstruation and its disorders is still not fully understood and remains an area of active scientific enquiry, particularly the complexities of the sequence of events triggered by progesterone withdrawal (due to demise of the corpus luteum in the absence of pregnancy). Hypoxia, inflammation, hemostasis and angiogenesis all play crucial roles in the shedding and subsequent scarless repair of the functional upper layer of the endometrium. Disturbance of local glucocorticoid metabolism, aberrant prostaglandin synthesis and excessive plasminogen (resulting in premature clot lysis) have all been implicated in AUB.

Iatrogenic (AUB-I)

Iatrogenic causes of AUB include exogenous therapy that may lead to unscheduled endometrial bleeding. This is typically associated with continuous estrogen or progestin therapy (systemic or intrauterine delivery routes) or those interventions that act on ovarian steroid release such as gonadotropin-releasing hormone (GnRH) agonists and aromatase inhibitors. Selective estrogen receptor modulators (SERMs) and more rarely selective progesterone receptor modulators (SPRMs) may cause AUB through direct action on the endometrium.

The use of an intrauterine device (IUD) may cause a low-grade endometritis which may also contribute to AUB.

Not Otherwise Classified (AUB-N)

It is inevitable that there will be pathologies that are either rare or poorly defined that do not easily fit

within the categories described earlier. Examples include arteriovenous malformations, endometrial pseudoaneurysms, myometrial hypertrophy and chronic endometritis (not precipitated by an IUCD). All of these can co-exist with AUB-L.

The planned regular review of the FIGO PALM-COEIN classification system every 3–5 years through FIGO will allow reassessment, particularly of this category. Further areas considered for future sub-classification include AUB-P and AUB-A.

Structured Approach for Assessing the Patient Presenting with AUB

An accurate menstrual history and associated symptoms will identify a likely AUB-O cause. As described earlier, a structured screen for coagulopathies will identify 90% of those women with disorders of systemic hemostasis. Detailed history taking will also identify contributors to AUB-I.

Combined history and examination will suggest possible AUB-P/-A/-L and should be confirmed with subsequent imaging. TV-USS remains the most acceptable and validated first-line investigation. The increasing use of saline infusion ultrasonography (SIS) and selected hysteroscopy will improve sensitivity and specificity for diagnosis of polyps and SM fibroids. The optimal mode of imaging for suspected adenomyosis has yet to be established. Furthermore, women with fibroids may have them confused for focal adenomyosis and vice versa using conventional imaging. The increased use of one-stop clinics with access to outpatient hysteroscopy improves patient satisfaction and facilitates timely investigation and management.

MRI plays a role in selected patients with AUB and fibroids, also in the assessment of suitability for uterine artery embolization (UAE). As previously discussed, it is relatively poor at providing reassurance of the absence of sarcomatous change.

ENDOMETRIAL SAMPLING

In the UK, NICE guidelines recommend endometrial sampling in women with persistent inter-menstrual bleeding or aged ≥45 years with treatment failure.

History

Menstrual
- Menarche
- Last menstrual period
- Menses frequency, regularity, duration and volume
- International bleeding and postcoital bleeding

Symptoms of anaemia

Sexual and reproductive history
- Past pregnancies and mode of delivery
- Future fertility desire
- Subfertility
- Current contraceptive requirement
- Previous STIs
- Smear history

Associated symptoms
- Pain
- Discharge
- Bowel and bladder symptoms in particular pressure

Systemic
- Weight change
- Coagulopathy history
- PCOS, liver, renal, thyroid, pituitary and adrenal disease
- Drug history: Anti-platelet, anti-coagulant, tamoxifen, hormones, HRT, dopamine agonists

Family history: VTE, malignancy

Examination

Basic observations: BP, BMI

Pallor

Signs of systemic disease
- Thyroid disease
- Bruising, petechiae
- Cushing
- Hyperandrogenism

Palpable pelvic mass

Speculum and bimanual
If indicated: Smear, chlamydia screen, endometrial biopsy

Consider PR if appropriate

Investigation

Haemoglobin and consider ferritin
If indicated: TFTs, gonadotrophins, PRL, hCG, coagulopathy investigations

USS

MRI if required

Hysteroscopy if required

This has been highlighted in the RCOG guidelines with an exception of reducing the age of sampling in the context of treatment failure to 40. With the marked increase in endometrial cancer, the authors would encourage all gynecologists to continue to exercise their clinical judgement for those women aged <40 years with HMB who have risk factors for premalignant changes such as obesity and PCOS.

Approach to Management

Management of AUB-L should address fertility desire, impact of pressure symptoms, co-morbidities, and any other AUB contributors. Treatment should be individualized. No one-size-fits-all approaches are available for initial and subsequent treatment options, and there is a relative paucity of large robust clinical trials providing head-to-head data rather to placebo.

In women with other underlying AUB causes co-existing with fibroids, targeted treatment of these may ameliorate bleeding, and in the absence of pressure symptoms or sub-mucosal myoma-related infertility, all the treatments may be required.

Specific Treatment Options for Individual PALM-COEIN Causes of AUB

AUB sub-classification	*Specific treatment*
Polyp	Resection
Adenomyosis	Surgery: Hysterectomy; adenomyomectomy (not frequently performed)
Malignancy	Surgery +/− adjuvant treatment High-dose progestogens (if surgery not possible) Palliation (including radiotherapy)
Coagulopathy	Tranexamic acid DDVAP
Ovulation	Lifestyle modification Cabergoline (if hyperprolactinaemia) Levothyroxine (if hypothyroid)
Endometrial	Specific therapies await further delineation of underlying mechanisms
Iatrogenic	Refer to FSRH CEU guidance on problematic bleeding with hormonal contraception
Not otherwise classified	Antibiotics for endometritis Embolization of AV malformation

Otherwise, treatment should be tailored depending on the impact of related symptoms, fertility requirements and cavity distortion. It should be remembered that a conservative approach (incorporating oral iron replacement if indicated) may be an entirely acceptable treatment approach, particularly in the perimenopausal phase with amenorrhoea and imminent regression of fibroid size imminent.

Symptom-based Approach for Management of AUB in the Context of Fibroids

In AUB, in the absence of pressure symptoms, medical treatment may be more appropriate, particularly when fertility preservation is required. Tranexamic acid and NSAIDs (e.g. mefenamic acid) remain the only fully non-contraceptive medical options. Whilst the risk of expulsion of a levonorgestrel-releasing intrauterine system (LNG–IUS) is without doubt higher in the context of fibroids, there is still evidence for efficacy although cavity distortion may preclude the use of LNG–IUS.

The current Cochrane review for the SPRMs is limited to mifepristone and a future review incorporating other members of the SPRM class is underway. GnRH analogues are effective in reducing both size of fibroids and amelioration of bleeding, but their side effects and impact on bone density limit their long-term utility and rebound of symptoms is rapid on cessation of treatment. GnRH agonists often are beneficial as a short-term treatment prior to IVF or surgery.

With regards to interventional radiological (UAE) and surgical options, the anticipated outputs of the FEMME study will hopefully provide robust evidence for impact on symptoms and other qualitative measures between myomectomy and UAE. MR-guided focused ultrasound (MRgFUS) is not a widely available technique. Its role in the management of symptomatic fibroids remains to be established. Hysterectomy is a definitive treatment, and in the context of management options for HMB, it remains a therapeutic option with the highest patient satisfaction and cost-effectiveness for >5 years. Hysterectomy, however, is often a challenging surgery in women with high potential for blood loss and risk of ureteric injury due to anatomical distortion in the pelvis. With increasing obesity, the complexity of surgery is compounded. Whilst alternative treatment strategies are under development, for the

	Symptoms		
	AUB only	AUB with pressure symptoms; family complete and no desire to retain fertility	AUB symptoms and fertility desire/subfertility
No cavity distortion	LNG–IUS Tranexamic acid Mefenamic acid UPA GnRH analogue P	UPA GnRH analogue	Tranexamic acid Mefenamic acid UPA (short course) GnRH analogue (short course)
	UAE EA Hysterectomy	UAE (MRgFUS) Myomectomy Hysterectomy	Myomectomy UAE (evidence here needed) (MRgFUS)
Cavity distortion	Tranexamic acid Mefenamic acid UPA GnRH analogue P	UPA GnRH analogue	Tranexamic acid Mefenamic acid UPA (short course) GnRH analogue (short course)
	TCRF UAE Hysterectomy	UAE Myomectomy Hysterectomy	TCRF Myomectomy UAE (evidence here needed)

Medical treatment

Surgical treatment

LNG–IUS	Levonorgestrel-releasing—intrauterine system
UPA	Ulipristal acetate
GnRH analogue	Gonadotrophin-releasing hormone analogue
P	Systemic progestogens • Medroxyprogesterone acetate • Norethisterone • Depo-medroxyprogesterone acetate
EA	Endometrial ablation
UAE	Uterine artery embolisation
(MRgFUS)	MR-guided focused ultrasound—predominantly experimental at present
TCRF	Transcervical resection of fibroid

cohort of women whose fertility plans are complete, the most appropriate management will remain definitive surgery, that is, hysterectomy.

Conclusion

AUB is a common and debilitating condition with high direct and indirect costs. Symptoms of AUB frequently co-exist with fibroids, but the relationship between AUB and fibroids remains incompletely understood. In many women, fibroids may be an incidental innocent bystander in the underlying etiology of a menstrual bleeding complaint. A structured approach to establishing the cause using the FIGO PALM-COEIN classification system will facilitate accurate diagnosis and inform treatment options. Treatment must remain individualized and

encompass the impact of pressure symptoms, desire for retention of fertility and contraceptive needs, as well as address the management of their AUB in order to achieve improved quality of life.

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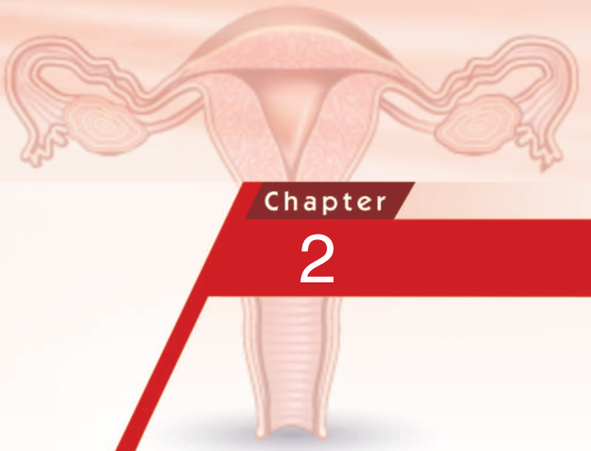


Chapter 2

FIGO Classification

Shraddha Agrawal, Prashant Gupta

Introduction

Abnormal uterine bleeding is a common problem in women of reproductive age and has great impact on quality of life of our women. The worldwide impact of abnormal uterine bleeding shows a prevalence of approximately 3–30% among reproductive aged women. The reported prevalence in India is around 17.9%. From a long time we were using the terms like menorrhagia, polymenorrhea, metrorrhagia, dysfunctional uterine bleeding to describe the abnormal bleeding in woman. These terms were quite confusing and categorization of patients for clinical trials as well as for investigations and treatment based on these features was difficult.

Background

A formal initiative was taken in International Workshop in Washington DC in 2005 where the discussion about confusing terminologies, definition and classification of abnormal uterine bleeding and its effect on quality of life were studied also the discussion about the cultural issues and controversies around investigations and management was conducted. After extensive discussion the trials were set up and use of an audience key responder system was suggested. These initial discussions and publications were followed by lectures, teleconferences and establishment of the **International Federation of Gynaecology and Obstetrics (FIGO) menstrual disorder working group**. Members of this group reviewed a series of recommendations in Capetown in Oct, 2009.

The multistage development process was adopted for menstrual symptoms and nomenclature using a modification of RAND/UCLA Delphi process. In this process a group of panelist (gynaecologist, reproductive endocrinologist, clinicians, researchers) was presented with a series of items which they rated anonymously and independently using a numerical scale. The aggregate ratings were then shared with the entire group and rerated at an inperson meeting. After discussion the process was used to develop the clinical guidelines for AUB. The goal of panel was to develop an agreed standard classification system with a nomenclature which can be used worldwide by researchers and clinicians investigating and treating woman of reproductive age with AUB.

There was general agreement that AUB was not restricted to just abnormally heavy uterine bleeding but also included bleeding that was abnormal in timing. Participants agreed that the term dysfunctional uterine bleeding should be discarded and there was common consensus on definition of abnormal reproductive tract bleeding. In Capetown respondents agreed that AUB was a suitable, overarching term for the symptoms of disturbed menstrual bleeding and also the term heavy menstrual bleeding should replace the term menorrhagia for the symptom of excess menstrual bleeding.

Article was published in journal of fertility and sterility in june 2011 by Malcolm G Munro, Hilary OD Critchley and Ion S Fraser. They suggested the following classification systems:

I. Acute, chronic, and intermenstrual AUB
II. FIGO classification system
    a. Polyps (AUB-P)
    b. Adenomyosis (AUB-A)
    c. Leiomyomas (AUB-L)
    d. Malignancy and premalignant conditions (AUB-M)
    e. Coagulopathy (systemic disorders of haemostasis) (AUB-C)
    f. Ovulatory disorders (AUB-O)
    g. Endometrial causes (AUB-E)

h. Iatrogenic (AUB-I)
i. Not classified (AUB-N)

This summary report describes the new PALM-COEIN classification for causes of abnormal bleeding developed by the FIGO menstrual disorders group (FMDG). The system was developed with contributions from an international group of both clinical and non-clinical investigators from 17 countries on six continents. A system for symptom nomenclature developed by the FMDG was described elsewhere in other publications that recommended standardized nomenclatures as well as abandonment of the terms menorrhagia, metrorrhagia, and dysfunctional uterine bleeding.

ACUTE, CHRONIC, AND INTERMENSTRUAL AUB

Acute AUB is defined as an episode of heavy bleeding that is sufficient in quantity to require immediate intervention to prevent further blood loss. Acute AUB may present in the context of existing chronic AUB or might occur without such a background history.

Chronic AUB is 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.

Intermenstrual bleeding (IMB) is defined as that which occurs between clearly defined cyclic and predictable menses and includes both randomly occurring episodes as well as those that manifest predictably at the same time in each cycle. This designation is designed to replace the word "metrorrhagia," which was one of the terms that the group recommended should be abandoned.

FIGO Classification System

The classification system is stratified into nine basic categories that are arranged according to the acronym PALM-COEIN [*pahm-koin*]: Polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory disorders, endometrium, iatrogenic, and not classified. In general, the components of the PALM group are discrete (structural) entities that are measurable visually, by use of imaging techniques, and/or by use of histopathology while the COEIN group is related to entities that are not defined by imaging or histopathology (non-structural). The categories were designed to facilitate the current or subsequent development of subclassification systems.

The system was constructed recognizing that any patient could have one or a spectrum of entities that could cause or contribute to the complaint of AUB and that definable entities such as adenomyosis, leiomyomas, and endocervical or endometrial polyps may frequently be asymptomatic and, therefore, not contributor to the presenting symptoms.

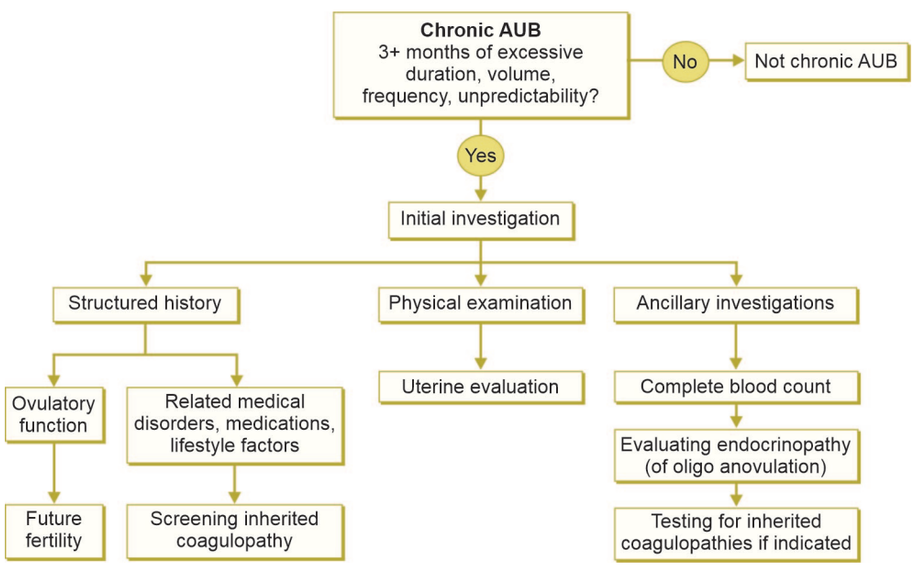


Fig. 2.1

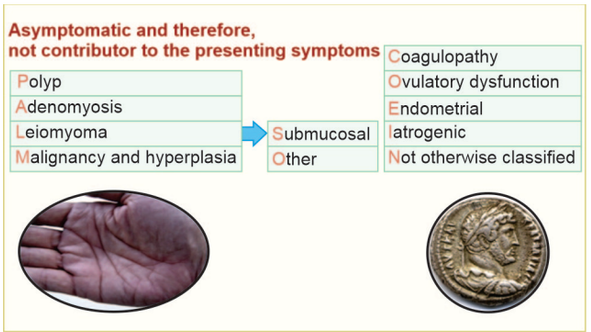


Fig. 2.2

The primary classification system reflects only the presence or absence of one or more leiomyomas, as determined by sonographic examination, regardless of the location, number, and size. In the secondary system, the clinician is required to distinguish myomas that involve the endometrial cavity (submucosal or SM) from others (O), because SM lesions are those that most likely contribute to the genesis of AUB. The root of the tertiary classification system is a design for subendometrial or submucosal leiomyomas originally submitted by Wamsteker et al that was subsequently adopted by the European Society for Human Reproduction and Embryology (ESHRE). The PALM-COEIN system adds categorization of intramural and subserosal myomas as well as a category that includes lesions ("parasitic") that appear to be detached from the uterus.

THE TWO FIGO SYSTEMS FOR NORMAL AND ABNORMAL UTERINE BLEEDING SYMPTOMS 2011

The International Federation of Gynecology and Obstetrics (FIGO) systems for nomenclature of symptoms of normal and abnormal uterine bleeding (AUB) in the reproductive years (FIGO AUB System 1) and for classification of causes of AUB (FIGO AUB System 2; PALM-COEIN) were first published together in 2011. The purpose was to harmonize the definitions of normal and abnormal bleeding symptoms and to classify and subclassify underlying potential causes of AUB in the reproductive years to facilitate research, education, and clinical care. The systems were designed to be flexible and to be periodically reviewed and modified as appropriate.

FIGO-AUB System 1

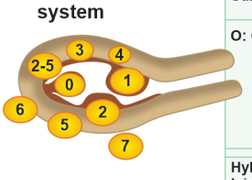
Munro et al described in the original publications terms such as menorrhagia, metrorrhagia, oligomenorrhea, and dysfunctional uterine bleeding have been abandoned. The specific changes in menstrual bleeding patterns that may be seen at each end of the reproductive spectrum (i.e. in adolescence or the perimenopause) have been mentioned.

FIGO-AUB System 2 (2011)

PALM-COEIN system as describe above.

Polyp		Coagulopathy
Adenomyosis		Ovulatory dysfunction
Leiomyoma	Submucosal	Endometrial
Malignancy and hyperplasia	Other	Iatrogenic
		Not otherwise classified

Leiomyoma subclassification system



SM: Submucosal	0	Pedunculated intracavitary
	1	<50% intramural
	2	≥50% intramural
O: Other	3	Contracts endometrium; 100% intramural
	4	Intramural
	5	Subserosal ≥50% intramural
	6	Subserosal <50% intramural
	7	Subserosal pedunculated
	8	Other (specify, e.g. cervical, parasitic)
Hybrid leiomyomas (impact both endometrium and serosa)	Two numbers are listed separated by a hyphen. By convention, the first refers to the relationship with the endometrium while the second refers to the relationship to the serosa. One example is below	
	2-5	Submucosal and subserosal, each with less than half the diameter in the endometrial and peritoneal cavities, respectively

Fig. 2.3: PALM-COEIN classification

The Revision of Two FIGO-AUB Systems in 2018

The previously published system was reviewed in 2018 by Munro et al.

Preparation of the present 2018 recommendations is the result of sequential reviews of the FIGO-AUB system 1 initially proposed in 2007 and 2009, and underwent slight modification for 2011. The current revisions represent deliberations in meetings held in 2012, 2015, and 2017. These reviews have included comment, detailed questioning, and recommendations from many clinicians from around the world but have only resulted in minor changes and refinement of definitions from the original systems.

Summary of changes to FIGO-AUB system 1 in 2018 (normal and abnormal uterine bleeding)

Parameter	*Change*
Frequency	Amenorrhea is now part of the frequency category
Regularity	Refined definition of regularity Normal variation (shortest to longest) 7–9 d Slight variance depends on age
Duration	Now only two categories for duration Normal: ≤8 d Prolonged: >8 d
Volume	Definition of the symptom of HMB NICE definition Bleeding volume sufficient to interfere with the woman's quality of life, intermenstrual bleeding Definition of the symptom of inter-menstrual bleeding Spontaneous bleeding occurring between menstrual periods Can be either cyclical, or random

Parameter	Normal	Abnormal	☑
Parameter	Absent (no bleeding) = amenorrhea		☐
	Infrequent (>38 days)		☐
	Normal (≥24 to ≤38 days)		☐
	Frequent (<24 days)		☐
Duration	Normal (≤8 days)		☐
	Prolonged (>8 days)		☐
Regularity	Normal or "Regular" (shortest to longest cycle variation:≤7–9 days)		☐
	Irregular (shortest to longest cycle variation:≥8–10 days)		☐
Flow volume (patient determined)	Light		☐
	Normal		☐
	Heavy		☐
Inter-menstrual bleeding (IMB) Bleeding between cyclically regular onset of menses	None		☐
	Random		☐
	Cyclic (predictable)	Early cycle	☐
		Mild cycle	☐
		Late cycle	☐
Unscheduled bleeding on progestin estrogen gonadal steroids (Birth control pills, rings, patches or injections)	Not applicable (not on gonadal steroid medication)		☐
	None (on gonadal steroid medication)		☐
	Present		☐

Fig. 2.4: FIGO-AUB system 1: Nomenclature and definitions of AUB symptoms

In this revision of FIGO-AUB System 1, the definition of regularity has been changed from one where the shortest to longest variation is up to 20 days, to variation of 7–9 days, depending upon age (18–25 years ≤9 days; 26–41 years ≤7 days; 42–45 years ≤9 days). For practical purposes, this normal variation in cycle length can be alternatively expressed as ±4 days. Formally included is the term HMB, a symptom (not a diagnosis), that has been defined (in clinical situations) by the National Institute for Health and Clinical Excellence as "excessive menstrual blood loss, which interferes with a woman's physical, social, emotional and/or material quality of life".

FIGO-AUB System 2 Revised (2018)

Revision of classification of underlying causes of AUB (PALM-COEIN) highlights of changes since the original publication in 2011 are summarized. The basic/core classification system is almost unchanged.

Summary of changes to FIGO-AUB system 2 causes or contributors to AUB in the reproductive years (PALM-COEIN)

System 2 category	*Change*
AUB-A	Refined sonographic diagnostic criteria
AUB-L	Inclusion of type 3 as a submucous leiomyoma Type definitions and distinctions Distinction between types 0 and 1; 6 and 7 Distinction between types 2 and 3; 4 and 5
AUB-C	No longer includes AUB associated with pharmacologic agents that impair blood coagulation which are now included in AUB-I
AUB-I	Now includes AUB associated with all iatrogenic processes including the use of pharmacological agents used for anticoagulation and those thought to interfere with ovulation
AUB-O	Diagnostic threshold changes based upon the revisions of system 1, described above. No longer includes ovulatory disorders associated with drugs known or suspected to interfere with ovulation
AUB-N	The name of the category has been changed from "Not Yet Classified" to Not Otherwise Classified there is a brief discussion of a potential new cause of AUB the so-called uterine "niche" or isthmocele following lower segment cesarean section

The only subclassification system ratified so far is the leiomyoma subclassification system which is unchanged since the initial 2011 publication. Distinguishing between type 0 and 1 and between type 6 and 7 is now accomplished by the stalk diameter to the mean diameter of the leiomyoma. Hysteroscopy has now been deemed the standard for distinguishing between type 2 and 3 leiomyoma. Differences between type 4 and 5 leiomyoma should be based on the distortion of the serosa by ultrasound or MRI.

The FIGO MDC is currently working on an international consensus for an imaging-based adenomyosis classification system designed to phenotype the disorder in a standardized fashion that should facilitate research, education, and clinical care. However, for diagnosis the use of transvaginal ultrasonography-based MUSA criteria for the diagnosis of adenomyosis for the purposes of FIGO-AUB system 2 is suggested.

Adenomyosis diagnostic criteria: Graphical depictions of the eight TVUS (transvaginal ultrasound) criteria proposed by the MUSA (morphological uterus sonographic assessment group) are presented. These include:

- Asymmetrical myometrial thickening
- Myometrial cysts
- Hyperechoic islands
- Fan-shaped shadowing
- Echogenic subendometrial lines and buds
- Translesional vascularity where present
- Irregular junctional zone and an interrupted junctional zone.

Identification and evaluation of the junctional zone may best be accomplished with three-dimensional ultrasonography. For the present at least, the presence of two or more of these criteria are highly associated with a diagnosis of adenomyosis.

Notation

After the patient has undergone appropriate investigation, an individual may be found to have one or multiple potential causes of or contributors to their complaint of AUB. Consequently, the system has been designed like the WHO TNM (tumor, node, metastasis) staging of malignant tumors, with each component addressed for all patients. Examples are

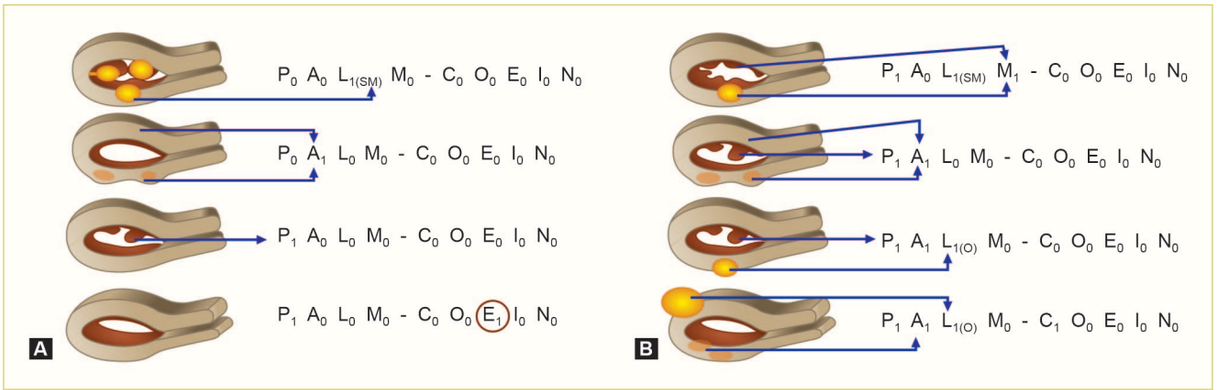


Fig. 2.5: FIGO classification notation: Notation for each case, the presence or absence of each criterion is noted, using 0 if absent, 1 if present, and "?" if not yet assessed. Each of these cases have one abnormality identified, from the top: at least one submucosal leiomyoma (L_{SM}); adenomyosis, both focal and diffuse (A); endometrial polyps (P); and an absence of any abnormality leaving endometrial causes (E) as a diagnosis of exclusion. (B) Each of these cases has more than one positive category. In the top panel, there is a submucosal leiomyoma (L_{SM}), as well as atypical endometrial hyperplasia (M) diagnosed by endometrial sampling. The second case is found to have both endometrial polyps (P) and adenomyosis (A). The next case is characterized by both a subserosal leiomyoma (L_O) and endometrial polyps (P); and the bottom case has a subserosal leiomyoma (L_O) as well as a coagulopathy determined by a positive screening test and subsequent biochemical confirmation of von Willebrand disease

shown below. Recognizing that, in clinical practice, the full notation like: AUB P_0 A_0 $L_{1(SM)}$ M_0-C_0 O_1 E_0 I_0 N_0 for a patient with disorder of ovulation, a type 2 leiomyoma might be considered to be cumbersome, so an option of abbreviation has been developed. The abbreviated FIGO description of this patient would be AUB-$L_{(SM)}$;-O.

FIGO-AUB SYSTEM 2 DIAGNOSTIC MATRIX

A simplified matrix system has been designed for the evaluation of patients with AUB in the reproductive years. FIGO encourages the use of this matrix by clinicians and investigators. This allows for the identification and documentation of the status of the investigation.

	Y	N	?
P			
A			
L			
M			
C			
O			
E			
I			
N			

	Y	N	?
P		X	
A		X	
L_O	X		
M		X	
C			X
O		X	
E			X
I		X	
N		X	

	Y	N	?
P		X	
A		X	
L_O	X		
M		X	
C		X	
O		X	
E	X		
I		X	
N		X	

System 1 (Symptom)

- Cycle length 14–60 days
- Regularity 14 days
- Duration: 2–22 days
- Volume: Normal to heavy
- Bleeding

System 2 (PALM-COEIN)

- Leiomyoma: Type 5
- Ovulatory disorder

	Y	N	?
P		X	
A		X	
L_O	X		
M		X	

C		X	
O	X		
E		X	
I		X	
N		X	

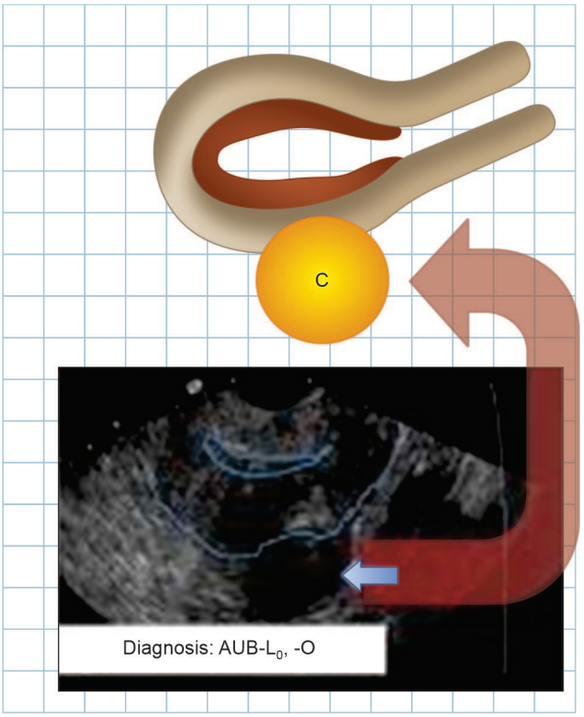


Fig. 2.6: Integration of system 1 and system 2 using matrix system

Conclusion

The only subclassification system ratified so far is the leiomyoma subclassification system, essentially unchanged since the initial 2011 publication as well as Fig. 2.4. The only subtle difference is for type 3 myomas, where contact with the endometrium is a feature shared by other submucous leiomyomas (types 0, 1, and 2), whereas intramural location, without focal distortion of the endometrial cavity, is a characteristic of types 4 and higher.

The FIGO MDC is currently working on subclassification systems for adenomyosis and endometrial polyps. The adenomyosis subclassification system is the most advanced and will be published soon in preliminary form with planned validation studies to follow.

The FIGO MDC is currently working on an international consensus for an imaging-based adenomyosis classification system designed to phenotype the disorder in a standardized fashion that should facilitate research, education, and clinical care.

The polyp system is being developed but a release date has not yet been determined. There is consideration for subclassification systems for AUB-C, -O, -E, and -I, but these initiatives are still in the very early stages of development.

It is important that clinicians recognize that these FIGO systems relate solely to assessment and management of nongestational AUB. There are other causes of genital tract bleeding and urinary tract or gastrointestinal bleeding that do not come from the uterus. These can usually be identified by an appropriate case history and physical examination.

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Chapter 3

Role of Imaging Modalities

Seema Pandey, Lipika Mohrana

Introduction

Abnormal uterine bleeding (AUB) describes any variation from normal bleeding patterns in non-pregnant women, beyond menarche, lasting for most part of last 6 months. It is a frequent reason for outpatient and emergency department visits in reproductive-aged women, may substantially affect quality of life.[1] The International Federation of Gynecology and Obstetrics (FIGO) systems 1 and 2 were created to provide clear terminology and nomenclature to globally facilitate the accurate diagnostic and effective treatment approaches to AUB.[2, 3]

The FIGO system 2(2011) acronym PALM-COEIN (polyp[s], adenomyosis, leiomyoma, malignancy, coagulopathy, ovulatory dysfunction, endometrial disorders, iatrogenic, and not yet classified) systematically defines the most common etiologies for AUB with structural (PALM) and nonstructural (COEIN) causes of AUB.[3] The FIGO classification for AUB refers to reproductive-aged, non-pregnant women, FIGO system 1 (2007) describes the 4 parameters of menstrual bleeding ***regularity, frequency, duration, and volume***. Normal menstrual bleeding is defined as cycles that occur every 24 to 38 days, with duration of bleeding up to 8 days.[2]

The first step is **to evaluate for pregnancy** and address whether a woman is **pre-menopausal and post-menarche.** In addition, **a thorough history** and **physical examination** will help distinguish gynecologic causes of bleeding from those with urinary or gastrointestinal etiologies (Table 3.1). The PALM-COEIN classification is used herein as a systematic approach to clarifying AUB, focusing on **role of imaging in diagnosis and management, *especially for the structural causes* of AUB.**[2, 3]

TABLE 3.1: Differential diagnosis of AUB

Organs	*Pathological causes*
Vagina	Benign growths, sexually transmitted infections, vaginitis, malignancy, trauma, foreign bodies
Cervix	Benign growths, sexually transmitted infections, malignancy
Fallopian tubes and ovaries	Pelvic inflammatory disease, malignancy, ectopic pregnancy (old ruptured), leakage of haematosalpinx in endometriosis
GI tract disease	Inflammatory bowel disease, Behçet syndrome
Urinary tract	Infections, malignancy, hematuria being misinterpreted
Pregnancy complications	Spontaneous abortion, ectopic pregnancy, placenta praevia

POLYPS

AUB may occur in up to 67% of premenopausal women with endometrial polyps**,** may be single or multiple, measuring from a few millimeters to centimeters, and may be sessile or pedunculated**.** The prevalence of polyps ranges from 7.8 to 34.9% of women and seems to increase with age. Endometrial polyps can be accurately diagnosed using **transvaginal ultrasound** (TVUS) (sensitivity, 91%; specificity, 90%), **saline infusion sonohysterography** (SIS) (sensitivity, 95%; specificity, 92%), diagnostic hysteroscopy (sensitivity, 90%; specificity, 93%), and hysterosalpingography (sensitivity, 98%; specificity, 35%)[1] (Fig. 3.1).

TVUS is an easily available, cheaper and non-invasive tool to diagnose and differentiate between different causes of AUB. Its significance goes higher if it is super added with SIS or color Doppler and or 3-D, 4-D.[4]

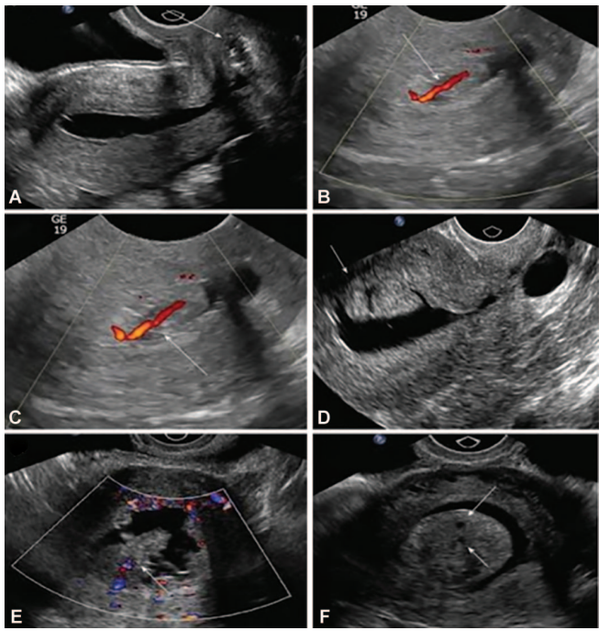

Fig. 3.1A to F: USG and Doppler image of a polyp showing a single feeding vessel

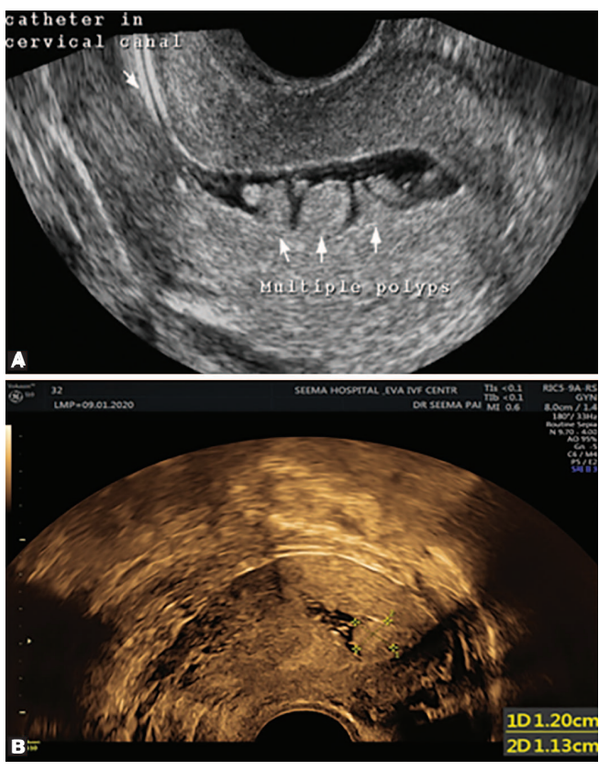

Fig. 3.2A and B: SIS image of multiple uterine polyps

Advantages of TVS

- One of the best screening imaging tools
- Non-invasive and cheap
- Clear visualization of endometrial interface and the entire cavity
- By being highly accurate in measuring endometrial thickness TVS saves women from undergoing unnecessary biopsies in around 40% cases (high negative predictive value).
- When combined with morphological parameters and Doppler velocimetry its diagnostic accuracy improves a lot.

SIS is an extension of TVUS, where we use normal saline instillation inside the endometrial cavity to delineate the cavity by separating the two layers of endometrium in an office setup under full aseptic precautions. If done with expertise, it performs better than transvaginal USG alone or almost at par with gold standard hysteroscopy in endometrial focal lesions of endometrium like polyp and sub-mucosal myomas. Despite high sensitivity and specificity for overall endometrial pathologies, it cannot replace hysteroscopy.

As per The American College of Obstetrics and Gynecology (ACOG) recommendations, sono-hysterography is superior to TVUS in detecting intracavitary lesions, such as polyps or submucosal leiomyomas. *(Level A Recommendation)*

- Some experts recommend TVUS as the initial screening test for AUB and MRI as second-line to be used when the diagnosis is inconclusive, further delineation would affect patient management, or coexisting uterine myomas are suspected.
- MRI may be useful to guide treatment of myomas, particularly when the uterus is enlarged, contains multiple myomas, or precise myoma mapping is clinically important. However, the benefits and costs must be weighed when considering its use.

ADENOMYOSIS

Adenomyosis is a disorder in which endometrial glands and stroma are present focally or globally through the uterine musculature, causing hypertrophy of the surrounding myometrium. Prevalence is predicted to be 5 to 70% of women. Most cases occur in multiparous women in the fourth to fifth decades of life. It can be *focal or diffuse and can co-exist with fibroids.*

Definitive diagnosis is by histologic examination at hysterectomy; however, specific TVUS and magnetic resonance imaging (MRI) criteria help establish the diagnosis.[1,5] **TVUS** may include echogenic striations, myometrial cysts, globular uterus configuration or asymmetrical thickening of the myometrium (Fig. 3.3) and heterogeneity of the myometrium leading to poor definition of the endometrial-myometrial interface (sensitivity, 89%; specificity, 89%) given that adenomyosis increases uterine vascularity, a pattern of penetrating vessels can be seen at color Doppler ultrasound.

TVS is the first-line imaging technique to diagnose adenomyosis. The sensitivity of TVS in detecting adenomyosis ranges from 65 to 81%, and specificity ranges from 65 to 100%. A recent meta-analysis, pooling results from eight studies, showed that two-dimensional TVS has a sensitivity and specificity of 83.8% and 63.9%, respectively, and that for three-dimensional TVS, pooled sensitivity and specificity for all combined imaging characteristics are 88.9% and 56.0%, respectively.

Recently, a uniform standardized reporting system of ultrasound findings of adenomyosis was made by using the morphological uterus sonographic assessment (MUSA) criteria (Fig. 3.4). According to those criteria, the typical ultrasound features to consider in order to make a diagnosis of adenomyosis are described in Fig. 3.4. The presence of two or more of these criteria are highly associated with a diagnosis of adenomyosis.[6]

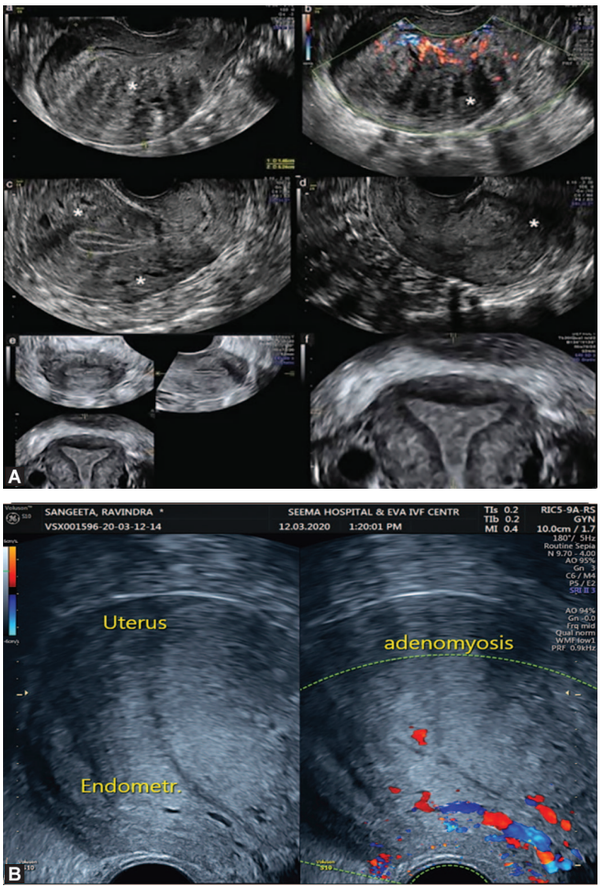

Fig. 3.3A and B: USG and Doppler image of adenomyosis uterus showing diffuse asymmetric thickening of uterine wall and increased myometrial vascularity

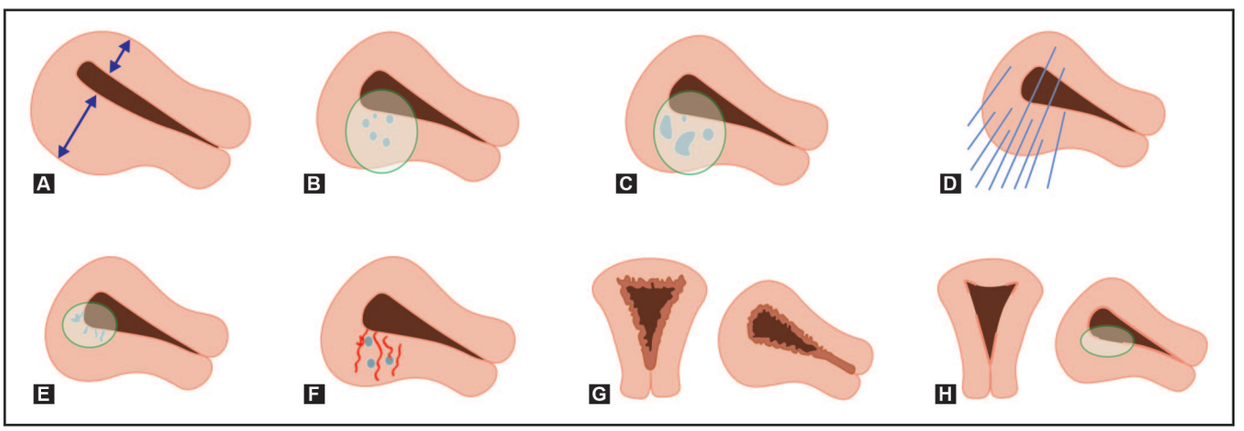

Fig. 3.4: MUSA diagnostic criteria to diagnose adenomyosis. (Graphical depictions of the eight TVUS criteria.) (A) asymmetrical myometrial thickening; (B) Myometrial cysts; (C) Hyperechoic islands; (D) Fan-shaped shadowing; (E) Echogenic sub-endometrial lines and buds; (F) Trans-lesional vascularity, where present; (G) Irregular junctional zone; and (H) An interrupted junctional zone

The new reporting system of adenomyosis, proposed by *Van den Bosch and de Bruijn et al*, is described in Table 3.2, and if applied by sonologists uniformly then would be a useful classification to standardize the description of adenomyosis. It has some limitations to be fully implemented in clinical practice though. *Another problem is the definition of severity of disease and identifying features which make the disease more severe.*

MRI diagnosis of adenomyosis is essentially done by looking at *the thickening of the JZ*, but it also looks at direct and indirect signs of the presence of endometrial glands within the myometrium and *smooth muscle cell hypertrophy*. Typical adenomyosis appears as an ***ill-demarcated low-signal-intensity area on T2-weighted images***, which represents the smooth muscle hyperplasia and the heterotopic endometrial tissue. T2-weighted sequences are of key importance for MRI diagnosis of adenomyosis as they highlight the *JZ*, which has commonly ***increased thickness***, at times, small high-signal-intensity areas denotes ectopic endometrium and also small ***intramyometrial cysts*** may be detected. Adenomyotic uterus looks as ***an enlarged, asymmetric***, where adenomyotic tissue is located mainly in the posterior wall or at the fundus.[6,8] The most frequent finding to diagnose adenomyosis is the thickening of JZ, and there are several criteria (*JZ of at least 8–12 mm, the maximum JZ/total myometrium ratio of over 40%, and a difference between the maximum and the minimum thickness of greater than 5 mm*); however, a ***thickness exceeding 12 mm*** seems to be *highly predictive* of adenomyosis but the JZ thickness varies as per the phase of menstrual cycle, post-menopause or if the lady is on a hormonal contraception. During menstruation, the uterus may present with a marked thickening of the JZ, mimicking adenomyosis; thus, ***MRI evaluations should preferably be carried out in the late proliferative phase.*** Furthermore, a common pitfall is transient uterine contractions that can mimic either T2-weighted hypointense bands perpendicular to the JZ or focal thickening of the JZ.[6,9] Adenomyosis may also be identified in the case of a poorly defined JZ or in the presence *of linear striations* of high T2 signal radiating from the endometrial zona basalis into the myometrium (Figs 3.5 and 3.6).

TABLE 3.2: Van den Bosch and de Bruijn system of USG reporting of adenomyosis

Disease location	Anterior, posterior, right/left lateral and fundal
Classification	Focal or diffused
Intra-lesional cyst	Present or absent
Myometrial layer involvement	JZ, myometrium, serosal
Disease extent	<25%, 25–50%, >50% of uterine volume affected

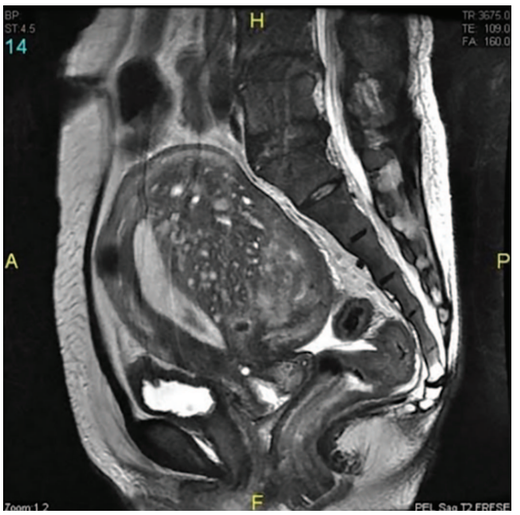

Fig. 3.5: Sagittal T2-weighted MRI of adenomyosis uterus showing asymmetric thickening of uterine wall and myometrial cysts

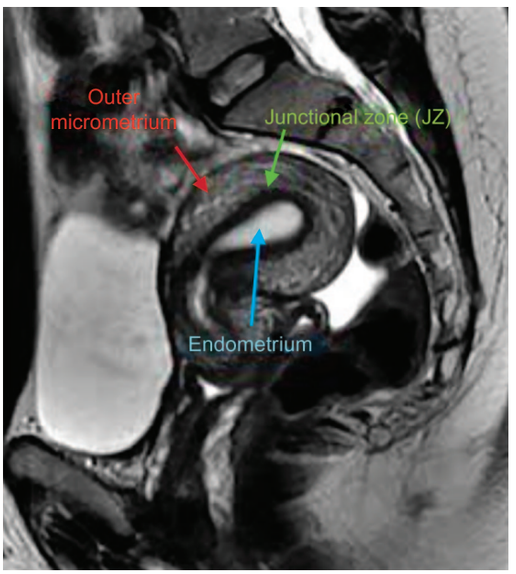

Fig. 3.6: A sagittal T2-weighted MRI image of adenomyosis showing thickening of junctional zone

In nonrandomized studies, uterine artery embolization **(UAE)** and MRI-guided focused ultrasound **(MgFUS)** seem to be promising treatments for adenomyosis Taran et al[10] reported improved symptoms in 50 to 90% of women in several small studies undergoing UAE followed for 1 or more years. Use of MgFUS resulted in a 25 to 66% reduction in bleeding over 12 months in women with adenomyosis.[12]

LEIOMYOMA

Clinical diagnosis may be based on results of pelvic examination (although normal findings do not exclude the presence of sub-mucosal leiomyoma as a cause of AUB), with **pelvic ultrasound** as the standard confirmatory test. The *FIGO classification* of leiomyoma location helps define the relationship of leiomyomas in reference to the endometrium or the visceral peritoneum (serosal layer). Submucous (subendometrial) or types 0, 1, and 2 leiomyomas can be diagnosed by using either **SIS** (Fig. 3.7), ultrasound (Fig. 3.8), or hysteroscopy. In addition**, MRI** (Fig. 3.9) can show *the relationship of leiomyomas* to both the endometrium and the visceral peritoneum. The use of **gadolinium** can identify devascularized (degenerated) leiomyomas, and MRI can also be used to determine whether uterine-sparing treatments are an option.[11] Although MRI may demonstrate features concerning for leiomyosarcoma, no preoperative testing can definitively rule out this rare malignancy.[11]

As per ACOG recommendations TVUS is the initial screening test for AUB and MRI as second-line to be used when the diagnosis is inconclusive, further delineation would affect patient management, or coexisting uterine myomas are suspected.

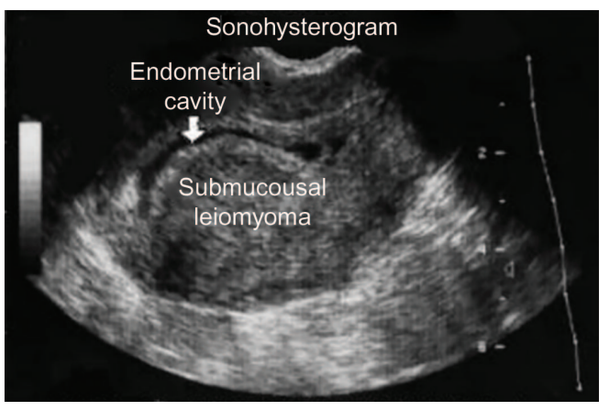

Fig. 3.7: SIS picture of submucous fibroid uterus

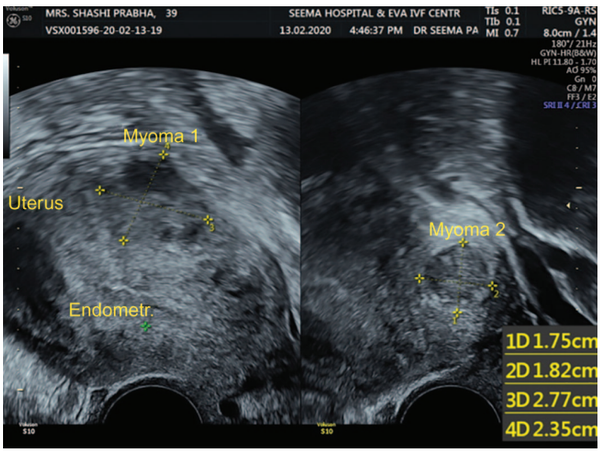

Fig. 3.8: Ultrasound image showing multiple myomas

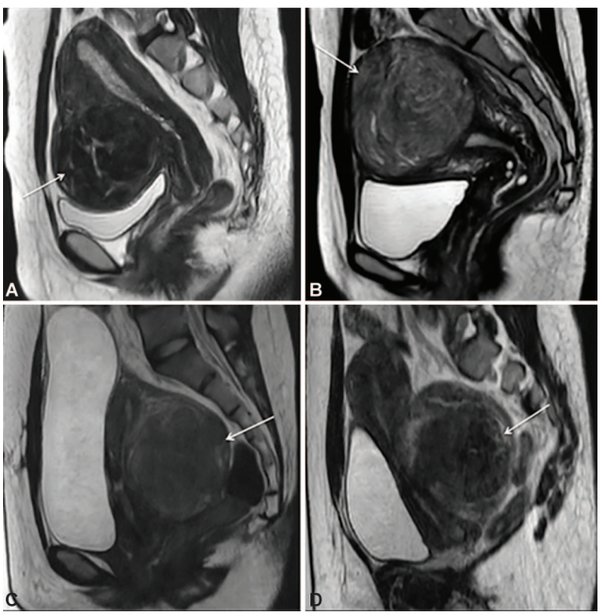

Fig. 3.9A to D: Sagittal T2-weighted MRI showing uterine fibroid

Fibroid typically looks as ***a well defined round lesion within the myometrium or attached to it, often showing shadows at the edge of the lesion and/or internal fan-shaped shadowing.*** The echogenicity varies and some hyper-echogenicity may be present internally. When we put color or power Doppler imaging, circumferential flow around the lesion is often visible. But, all fibroids do not exhibit such typical features, such fibroids are called *sonographically atypical fibroids.*

Uterine-sparing options include myomectomy, **UAE**, **MgFUS**, or laparoscopic radiofrequency ablation.[11] In comparing treatments, re-intervention risk after 36 months was 1.2% for abdominal myomectomy, 7.4% for UAE, 34.7% for high-intensity focused ultrasound **(HIFU)** (includes both MRI and ultrasound guided), and 3.2% for hysteroscopic myomectomy.[13]

MALIGNANCY AND PREMALIGNANT CONDITIONS

Malignancy of the vagina or uterus (including the cervix) can cause abnormal bleeding. Thus, it is important to discern the etiology of any AUB through examination of the vulva, vagina, and cervix with Pap test screening or tissue sampling.[14] In older premenopausal and menopausal women, AUB may be secondary to EIN (subtype: Simple or benign hyperplasia vs [the more worrisome] subtype: Atypical hyperplasia with progression to or concurrent with endometrial malignancy).[16]

Mostly patients present with postmenopausal bleeding or irregular bleeding patterns around menopause fortunately, 70% of cases are found at an early stage given that most women (75–90%) with malignancy present with AUB. They might present with normal to mildly enlarged uterus, however uterine size is not confirmatory of the benign or malignant nature of a lesion. **Ultrasound** may show thickened endometrium (>12 mm) in cases of endometrial hyperplasia or thickened and/or irregular endometrium and loss of endomyometrial junction in cases of endometrial malignancy. A endometrial biopsy for *histopathology reporting is the most confirmatory modality for further management.*

COAGULOPATHY

Inherited bleeding disorders, especially von Willebrand disease (vWF), are identifiable in 5 to 24% of women with HMB.[1] Coagulopathy should be considered in women with heavy, prolonged menses from an early reproductive age; a history of frequent bruising, epistaxis, gum/dental bleeding, postpartum hemorrhage, and severe surgical bleeding; and a family history of these issues. Heavy menses may be seen with factor deficiencies and platelet disorders. Management involves a *structured screen for history* and testing blood parameters, coagulation factors and liver function tests. No particular imaging modality is useful. **Ultrasound** scan reports are mostly normal or might show *haemorrhagic cysts* in the ovary.

OVULATORY DYSFUNCTION

Ovulatory dysfunction includes not ovulating on a regular basis or infrequently, which may lead to amenorrhea but more likely results in irregular bleeding. Anovulation occurs most commonly in the early reproductive years and later perimenopausal years. Episodes of bleeding range from light and infrequent for 2 or more months to episodes of unpredictable and extreme HMB.[1] Although there is no identifiable cause, ovulatory dysfunction can occur with polycystic ovarian syndrome, obesity, hypothyroidism, hyperprolactinemia, anorexia, extreme exercise, and significant weight loss.

In obese women, prolonged amenorrhea due to anovulation and exposure to unopposed endogenous estrogen increases the risk of EIN and endometrial cancer; consideration for endometrial sampling/assessment is important.[15] **Ultrasound** reveals features suggestive of PCOS and/or thickened endometrium (Fig. 3.10).

ENDOMETRIAL DISORDERS

AUB that occurs in context of a structurally normal uterus with regular menstrual cycles without the evidence of coagulopathy is likely to have an underlying endometrial cause. Endometrial disorders are due to primary dysfunction of local endometrial hemostasis. It is extremely important to rule out ***endometrial hyperplasia*** (Fig. 3.11), especially in the perimenopausal women. Endometrial lesions might present with inter-menstrual spotting and/or prolonged spotting. **On ultrasonography**, uterus is of normal size and there might be fluid in endometrial

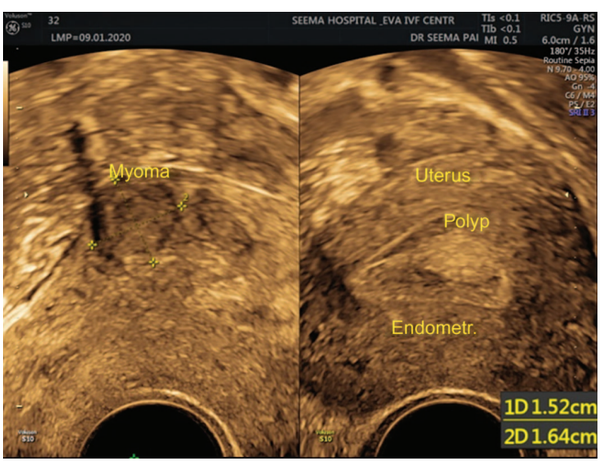

Fig. 3.10: AUB causes, a polyp co-existing with a fibroid

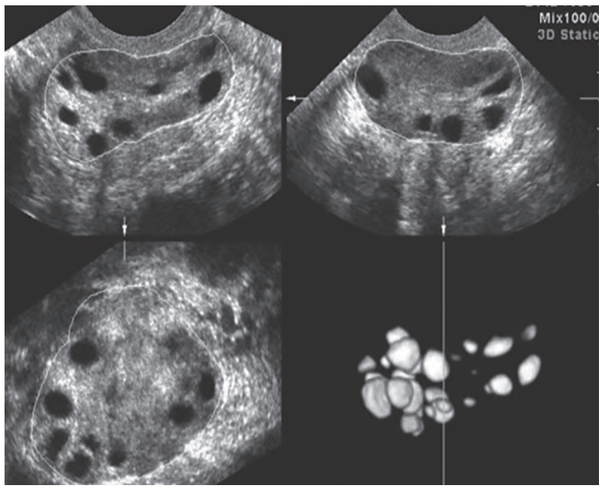

Fig. 3.11: USG image showing polycystic ovarian morphology

cavity. The ***morphology*** of the endometrium on ultrasound is the basis for suspicion of pathology. Histopathology and TVUS can help us confirm the presence and type of endometrial hyperplasia.[15]

IATROGENIC

The most common iatrogenic causes of AUB are due to hormone therapy such as OCPs or intramuscular, intrauterine, or sub-dermal contraceptives, which can cause BTB. Corticosteroid-related drugs that may cause BTB are GnRH agonists, aromatase inhibitors, SERMS, and SPRMs. Systemic agents (i.e. anti-depressants) that contribute to disorders of ovulation, such as those that interfere with dopamine metabolism or cause hyper-prolactinemia, may also lead to AUB. On **ultrasound** imaging, the uterus appears to be of normal size and the intrauterine device may be seen.

NOT OTHERWISE CLASSIFIED

This group of entities causing AUB is poorly defined, inadequately examined, and generally rare. They include arteriovenous malformation, myometrial hypertrophy, endometrial pseudo-aneurysms, chronic endometritis (not due to IUCD) and uterine isthmocele secondary to cesarean delivery scar defect. Imaging such as **TVUS (with Doppler**, especially for AVM**)** and **MRI** may be helpful.

The planned regular review of the FIGO PALM-COIEN classification system every 3–5 years through FIGO will allow reassessment, in particular, of this category. Further areas considered for future sub-classification include AUB-P and AUB-A.[17,19]

Conclusion

AUB is a common and debilitating condition with high direct and indirect costs. Symptoms of AUB frequently co-exist with fibroids (Fig. 3.12),[19] but the relationship is not completely understood.

An accurate menstrual history and associated symptoms and examination will suggest a likely cause and should be confirmed by blood tests, imaging, hysteroscopy, histopathology, etc. TVUS remains the most accepted and first-line investigation.[17] The increasing use of SIS and selected hysteroscopy will improve the sensitivity of diagnosing polyps and submucous fibroids. The optimal mode of imaging for adenomyosis is yet to be established. Table 3.3 summarizes the symptoms and findings on imaging.[20] The role of imaging modalities in diagnosis and management of AUB is mostly restricted to the structural causes.

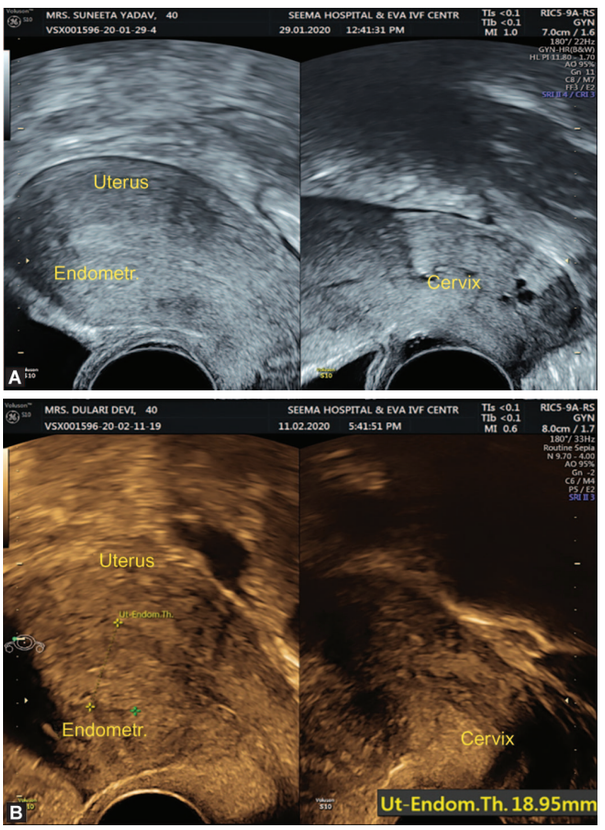

Fig. 3.12A and B: Ultrasound image showing normal triple line endometrium and endometrial hyperplasia

TABLE 3.3: Common symptoms and imaging features of abnormal uterine bleeding aetiologies

	Symptoms	*Signs*	*Imaging*
Polyp	Prolonged uncontrolled bleeding, inter-menstrual bleeding, pallor, infertility	Uterus is usually normal in size, if big, cervical os may be patulous, polyp extruding outside	Endometrium looks thickened, saline infusion sonography shows echogenic smooth intracavitary mass outlined by fluid
Adenomyosis	Heavy menstrual bleeding, marked dysmenorrhea	Uterus enlarged up to 12 weeks uniformly enlarged, globular may or may not be tender	Globular uterine enlargement up to 18 weeks (not due to leiomyoma) Thickening of uterine wall, which may be asymmetrical in focal disease Obscuring of endomyometrial junction; multiple hypoechoic halo zones of ≤12 mm thickness; heterogeneous texture of endometrium echogenic
Leiomyoma	Submucous—more prolonged uncontrolled bleeding, intramural variable amount of HMB, Subserous—may be asymptomatic	Uterus irregularly enlarged firm	Well-defined, solid masses with a whorled appearance; similar echogenicity to myometrium, occasionally hypoechoic alteration of the normal uterine contour of uterus 3D-USG—for exact location in selected patients MRI—fibroid mapping when indicated
Malignancy	Postmenopausal bleeding, irregular bleeding pattern at perimenopause	Normal to mildly enlarged uterus mobility may be restricted	US—endometrial hyperplasia—thickened endometrium >12 mm at premenopausal age Endometrial carcinoma—thickened endometrium, irregular endometrial lining, loss of endomyometrial junction
Coagulopathy	Puberty menorrhagia, heavy bleeding at menarche, history suggestive of bleeding diathesis, family history	Uterus normal size, pallor, easy bruisability, petechiae	Normal scan might have hemorrhagic cysts in ovary
Ovulatory disorders	Signs of anovulation—polycystic ovary syndrome oligomenorrhea signs of insulin resistance	Uterus normal size	Polycystic ovaries on ultrasound thickened endometrium
Endometrial	Inter-menstrual spotting Prolonged spotting	Discharge pervaginum Cervical erosion	Uterus normal size Fluid in endometrial cavity
Iatrogenic	History of medication intake copper T use	No abnormality	Uterus normal size copper T *in situ*
Not classified	HMB	Refer to PALM-COEIN	Ultrasound, Doppler, USG—for AVM

3D-USG: Three-dimensional ultrasonography; HMB: Heavy menstrual bleeding; MRI: Magnetic resonance imaging; AVM: Arteriovenous malformation

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Chapter 4

Role of Endometrial Sampling

Rakhee Singh

Endometrial sample is a frequent and easy, cost effective tool to evaluate the abnormal uterine bleeding. Endometrial biopsy is safe and well accepted valuable office based diagnostic tool. Transvaginal ultrasound is an effective first diagnostic step in the evaluation of bleeding disorders before the biopsy is done.

Dilatation and curettage (D and C) have been the standard procedure for evaluating suspicious endometrial lesions. The discomfort and injury caused by the D and C procedure, however, restrict its use as a screening method for early diagnosis of endometrial lesions.

There are several endometrial devices and methods proposed as screening tools for the collection of the endometrial sample by the aspiration devices on OPD basis to office hysteroscopy directed target sample collection.

Indications and Contraindications for Endometrial Biopsy[1]

Indication

- Abnormal uterine bleeding
- Evaluation of endometrial neoplasia/hyperplasia
- Evaluation of uterine response to hormone therapy
- Surveillance of previously diagnosed endometrial hyperplasia or cancer
- Postmenopausal bleeding

Contraindication

Absolute contraindication

- Pregnancy
- Acute PID
- Acute cervical/vaginal infection
- Cervical cancer

Relative contraindication

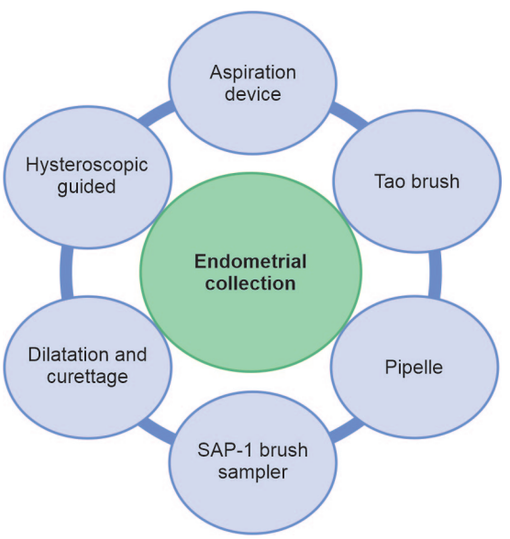
- Morbid obesity
- Cervical stenosis
- Coagulopathy

TRANSVAGINAL ULTRASONOGRAPHY

TVS can visualize the endometrium and the thickness of the endometrium can be measured with precision, also the endometrial-myometrial junction has a distinct halo-like appearance. TVS is highly sensitive and we can detect the polyps, and endometrial hyperplasia but also has high false-positive rates with low specificity for identifying endometrial carcinoma. When the endometrial thickness is of 4 mm for women less than 5 years since menopause and 3 mm for women more than 5 years since menopause, TVS had a 97.4% sensitivity, 75.7% specificity, and 99.7% negative predictive value.

TVS helps in detecting the thickness of the endometrium and any growth in the uterine cavity for the collection of the endometrial samples. Also, in the difficult cases like cervical stenosis, acutely anteverted or retroverted uterus ultrasound-guided biopsy do help.

Methods for the Collection of Endometrial Biopsy[6]



Ideal screening tool requirement

- It should collect as much endometrial specimen samples as possible including the uterine horns for the evaluation
- It should be able to reflect the uterine endometrial condition completely giving histological and cytological information to help in diagnosis and management
- It should be easily acceptable

Pipelle

The Pipelle endometrial sampler introduced in 1984, can be used without cervical dilatation in the outpatient department and causes minimum discomfort. Pipelle sampling should be reserved for those patients with only a minimal risk for endometrial carcinoma, hyperplasia, and polyps. The sensitivity and specificity of Pipelle in endometrial samplings were compared to fractional curettage in postmenopausal patients and found to be 87.5% and 100%, respectively.

Tao Brush

The Tao brush was introduced in 1993. To collect the endometrial cells, the sheath is pulled back, and then the brush is inserted at the level of the fundus through the cervical canal. The 3.5 cm brush is then rotated 360° 3–5 times to collect endometrial cells. The outer sheath is then pushed back to the tip, and the device is removed from the uterine cavity. The brush is cut-off and immersed into cell preservation liquids and sent for cytological assessment and diagnosis.

The Tao brush can be used in an outpatient setting, without the need for anaesthetic, as it is simple to use and appears to be well tolerated by women. There was less specimen insufficiency for diagnosis with the Tao brush (2%) than with the Pipelle (12%). Additionally, the Tao brush was significantly less painful than Pipelle. The disadvantage is not collecting enough endometrial cells of the uterine horns because of its round configuration of the brush.

SAP-1 Device

The SAP-1 device was introduced in 2001. The sheath of this sampler is approximately 3 mm in diameter and 25 cm in length. This protective sheath outside the loop can prevent contamination with cervical and vaginal cells. Sample is collected by rotating the loop in a clockwise direction for 15 circles. After collecting endometrial sample, the outer sheath is pushed up to avoid contamination and the device removed. There are not enough evidence of clinical trials and data.

Li Brush

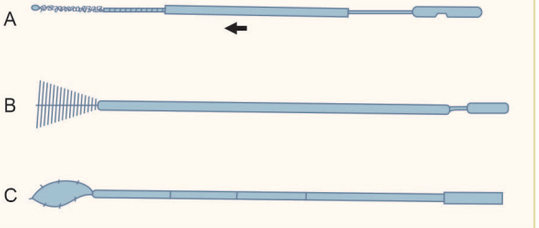
Li brush was patent in 2014. It was designed as an inverted cone, similar in shape to the uterine cavity. In theory, this brush can collect more endometrial cells than possible with other samplers, but there is no enough evidence of clinical trials and data in literature for its use.

Endometrial Sampler Aspiration Devices[5]

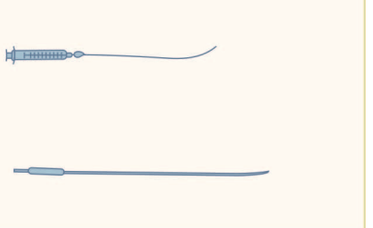
Endosampler is a low-pressure suction device, is a semirigid 3 mm curette with a single sharp slot in end having markings on it. Negative pressure is created by a syringe at the base of the device. There is a lock spring mechanism on syringe which prevents backflow of specimen. Karman cannula number 4 can also be used as a low cost on the other hand for the collection of the sample. It is a higher-pressure device and is a flexible cannula made of latex free polypropylene plastic. It is 24 cm in length and has 4 mm diameter. Suction is created by a 10 cc disposable syringe attached to the base of cannula.[5] Endosampler or the Karman cannula collects significantly more endometrial tissue as compared to Pipelle device.

DILATION AND CURETTAGE

D and C is a gold standard procedure for the endometrial biopsy, it works as a diagnostic and therapeutic procedure. It has been replaced by office-based endometrial biopsy using flexible aspiration devices with sensitivity and specificity rates of 90% and 95%.[4]



Endometrial cytology sample brushes: (A) Tao brush; (B) Li brush; (c) SAP-1 brush



Endometrial sample aspiration device

Fig. 4.1

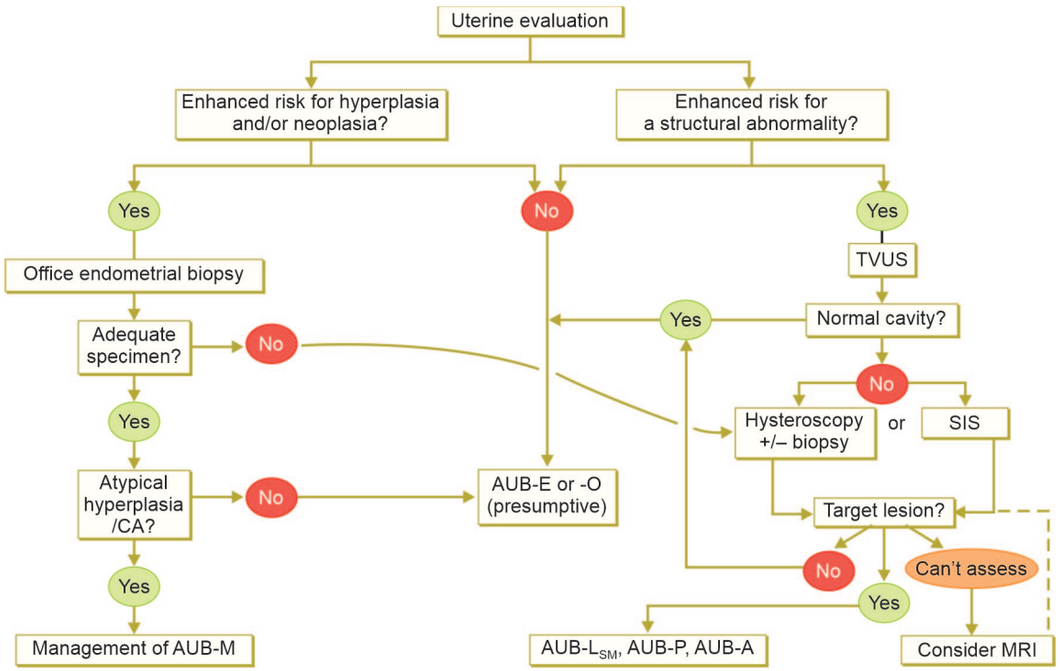


Fig. 4.2

D and C are used as a therapeutic procedure[4]

- Removal of retained products of conception
- Suction procedures for management of uterine haemorrhage
- Treatment and evaluation of gestational trophoblastic disease
- Haemorrhage unresponsive to hormone therapy
- In conjunction with endometrial ablation for histologic evaluation of the endometrium

Complications[4]

Possible complications while performing the procedure of D and C:

- Bleeding or haemorrhage
- Cervical laceration
- Uterine perforation
- Postprocedural infection
- Postprocedural intrauterine synechiae (adhesions)
- Anaesthetic complications

OFFICE HYSTEROSCOPY

Office hysteroscopy is indicated in any woman with abnormal uterine bleeding. Hysteroscopy unlike Pipelle or dilatation and curettage is not a blind procedure as it allows direct visualization and evaluation of the endometrial cavity and detection of the focal lesion and to obtain a targeted biopsy. Hence, a method to see and treat in the same sitting and there is no need for a separate scheduling of the procedure.

Office hysteroscope with reduced calibre scope and use of simpler distending media and availability of safer local infiltrative anaesthetics have all contributed to an increasing utilization of this technique in evaluation of the uterine cavity.

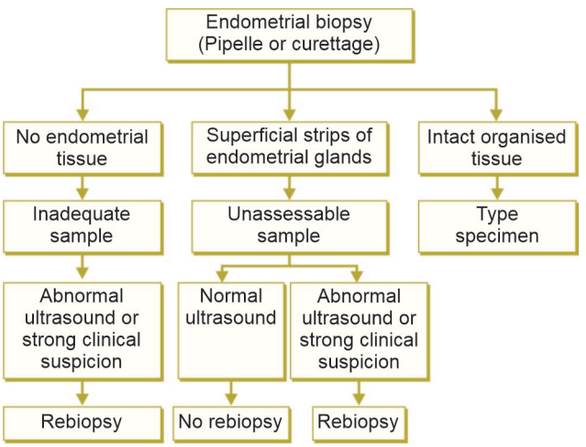
Hysteroscopy is contraindicated in the presence of active infection and intrauterine pregnancy. Active bleeding is a relative contraindication to office hysteroscopy only because blood interferes with vision if carbon dioxide is used as a distending medium. In patients who have severe medical problems, it is prudent to perform hysteroscopy in an OT setting where full monitoring and resuscitation facilities are available. Hysteroscopy directed biopsy is better for obtaining diagnosis from focal lesions.

When we compare office hysteroscopy to D and C, office hysteroscopy may provide a precise and accurate staging plan for the preoperative risk evaluation of patients with endometrial cancer. If during hysteroscopy we encounter a suspicious lesion of endometrial cancer, there is a need to take extra care ensuring that the cervix was overdilated and high flow and low pressure (<80 mmHg) were maintained in the uterus at all times.[3]

Fig. 4.3

REASON FOR OBTAINING INSUFFICIENT SAMPLE AND ASSESSMENT[7]

Algorithm for assessment of the adequacy of an endometrial biopsy specimen



Causes on insufficient sample

- Biopsy after the periods
- Atrophic or scared uterus
- Denuded endometrium
- Hypoestrogenic state
- Prolonged heavy bleeding

RISK AND COMPLICATIONS TO BE REPORTED AFTER THE PROCEDURE

- While an endometrial biopsy is safe, there is a chance of bleeding or spotting after the procedure. If bleeding persists for more than two days after the biopsy it needs to be looked at.
- The uterine wall perforation can occur while taking the sample, but this is very rare.
- Like other invasive procedures, there is a small risk of infection or there can be foul smelling discharge with fever or chills or severe pain in the lower abdomen.

Conclusion

Endometrial biopsy is an important step in the assessment of abnormal uterine bleeding to rule out endometrial carcinoma, so that medical management or conservative surgery can be offered and unnecessary surgery can be avoided. Various methods of endometrial sampling are used in practice, including invasive and non-invasive on an inpatient or outpatient basis. There are a number of techniques for endometrial sampling, but it is important that an adequate sample be obtained before the patient can be considered at low risk for a malignant neoplasm. Hysteroscopy and D and C are relatively invasive and costly nature in comparison with other endometrial aspiration devices but have the advantage of targeted biopsy.

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Chapter 5

AUB in Adolescents

Laxmi Shrikhande

Introduction

Abnormal uterine bleeding (AUB) is defined as any bleeding from uterus which is abnormal in duration, volume and frequency. It accounts for nearly half of the gynaecological consultations in adolescent population.[1]

Evaluation

A diagnostic evaluation should be performed before any treatment is initiated.[2] It is aimed at determining the severity of the bleeding and to find out the possible aetiology of AUB. Pathologies such as bleeding disorders, clotting abnormalities, pathology of the reproductive tract, genital injuries and drug use should be excluded in the differential diagnosis process. Pregnancy and pregnancy-related situations, such as ectopic pregnancy, should be promptly evaluated and excluded due to their high rates of morbidity and mortality. Bleeding disorders, which cause 20–33% of cases of prolonged and/or severe bleeding, should always be taken into consideration.[3]

Detail history taking is the first and most important part of evaluation. It 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, bruising should be taken. Family history of coagulopathy or hormone sensitive cancers should also be elicited.[4]

HMB is a subjective diagnosis. An adolescent might perceive 20 ml as heavy while another adolescent might perceive 120 ml as normal blood loss. It is desirable to use objective method of assessing blood loss (Fig. 5.1).

General examination is must to see for signs of pallor, hepatosplenomegaly, signs related to hormonal disorders like hirsutism, acanthosis nigricans.

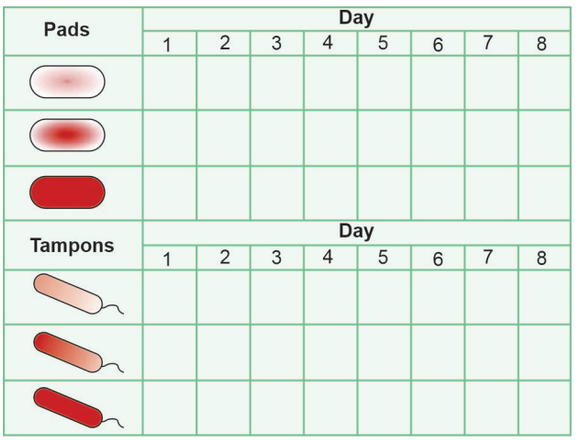

Fig. 5.1: Pictorial blood loss assessment chart. Each woman fills in on the chart how many pads or tampons she uses each day and to which degree they are soiled with blood[5]

Gynaecological examination is not needed unless some problem related to pregnancy pops out in the differential diagnosis.

Ultrasound is not mandatory as majority of these AUB are because of anovulatory cycles followed by bleeding disorders. Wherever it is needed USG should be done to rule out pelvic pathology. Transabdominal route is preferred in adolescent girls.

Laboratory Tests

The minimum laboratory evaluation should include; complete blood count, peripheral blood smear, ferritin level, prothrombin time, activated partial thromboplastin time and fibrinogen. Adolescents at risk of 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.[6]

It is important that the von Willebrand panel be obtained when the patient is not taking hormones, because exogenous estrogen may elevate vWF into the normal range.[3] Thus, the panel should be obtained at the time of presentation or after exogenous estrogen has been discontinued for seven days. It is also important to obtain blood group typing since blood group O is associated with lower levels of vWF, and to consult with a hematologist if the levels are low. If a bleeding disorder is considered, consultation with a hematologist is warranted.

TABLE 5.1: Differential diagnosis of AUB

Hematological	*Genital system pathologies*	*Pregnancy*	*Endocrine*	*Trauma*	*Drugs*	*Other*
vWF deficiency	Fibroid, myoma	Ectopic	Hyperprolactinemia	Sexual abuse	Antipsychotics	Excessive exercise
Thrombasthenia	Endometriosis	Implantation	Thyroid function disorders	Laceration	Anticoagulants	Eating disorders
Thrombocyte function disorder	Polyp	Placenta accreta	Adrenal diseases	Foreign body diseases	Platelet inhibitors	Systemic
Coagulation defects	Cervical dysplasia	Hormonal contraception	Polycystic ovary syndrome			Stress
Other factor deficiencies	Infections		Ovarian deficiency			Intrauterine device

International Journal of Women's Health and Reproduction Sciences, Vol. 5, No. 3, July 2017

Management

The first-line approach to AUB in the adolescent is medical management. The choice of treatment for management depends on clinical stability, overall acuity, suspected etiology of the bleeding, and underlying medical problems.

TABLE 5.2: AUB severity classification

Mild	Longer menses (>7 days) or shorter cycles (<3 weeks) for two months in succession, with slightly or moderately increased bleeding, a usually normal (≥12 g/dL) or mildly decreased Hb (10–12 g/dL)
Moderate	Moderately prolonged or frequent (every 1–3 weeks) menses, with moderate to heavy bleeding and a haemoglobin level of ≥10 g/dL
Severe	Heavy bleeding with a haemoglobin level of <10 g/dL

MILD AUB

Hormonal treatment is not considered. Non-steroidal anti-inflammatory drugs (NSAIDs) can be used. The patient should be followed up at 3-month intervals and should be instructed to keep a menstrual-cycle diary.

MODERATE AUB

These adolescents are managed on an outpatient basis. In addition to iron supplementation, hormonal therapy is necessary to stabilize endometrial proliferation and shedding. There is no consensus on whether to treat them with combined oral contraceptives (COCs) or progestin-only regimens.[7]

COCs are a better choice, as estrogen improves haemostasis. Monophasic COCs, containing at least 30 µg of ethinyl E_2, are preferred to prevent breakthrough bleeding. Dose is 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. 4–8 mg of ondansetron can be given if nausea occurs with high doses of E_2. At the end of 21 days, seven days of placebo or pause should be given. COCs treatment is continued for 3–6 months until the haemoglobin level reaches ≥12 g/dl.

Progestin-only hormone therapy can be an alternative to COCs for adolescents who are not currently bleeding or have a contraindication for estrogen therapy.[8] Progestin-only options are—micronized oral progesterone (200 mg/day), medroxyprogesterone (10 mg/day), norethindrone acetate (2.5–5 mg/day), depot medroxyprogesterone acetate (DMPA) or a levonorgestrel-releasing intrauterine device. The last two options are for those who need contraception or

cannot take pills. Micronized oral progesterone contains peanut oil and there must be caution for allergy. Also, there is no sufficient evidence to date to state that it is safer to use this progesterone than using synthetic progestin. However, micronized oral progesterone is chemically identical to endogenous progestin and this is more physiological. In some studies, it was also shown to have fewer side effects than synthetic progestin pills . Oral progestin is given for 12 days every month and bleeding occurs 2–7 days after cessation. If bleeding does not start within one week the patient should be re-evaluated.

Severe Bleeding or Haemodynamically Stable (Hb = 8–10 g/dl)

The use of OCPs, an approach that is similar to that for adolescents with moderate bleeding, is indicated if the family and the patient can comply with the treatment plan and follow-up. If there is no decrease in the severity of the bleeding following the first two doses of OCP treatment, the dose should be increased to three to 4 pills per day for 2 days; this dosage should be continued as needed 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 is important, and iron supplements should be prescribed.

All patients with severe anaemia due to menstrual bleeding must be assessed for bleeding disorders. Supplementation of 60–120 mg elemental iron must be started as soon as the patient is stable enough to take oral pills.

Severe Bleeding (Hb ≥7 g/dl) or Haemodynamically Unstable

The patient should be hospitalized and monitored. Preparations should be made for blood transfusions, as they may be required. Bleeding disorders must be eliminated before starting hormonal treatment.

The first treatment of choice is to prescribe OCPs containing high doses of oestrogen (35–50 µg ethinyl-oestradiol) because OCPs promote rapid endometrial regrowth to cover denuded epithelial surfaces. The use of pills containing 50 µg ethinyloestradiol is usually considered if there is no decrease in the severity of bleeding after the second dose of the 35 µg pills.[9]

The treatment with high-dose oestrogen 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. Anti-emetic therapy can be an added treatment for patients who experience high-dose oestradiol-induced nausea and vomiting. The therapy is maintained with pills containing 30–35 µg ethinyl-oestradiol. However, in cases where the bleeding is controlled with 50 µg high-dose ethinyloestradiol-containing pills, these are continued for about one or two cycles at the same dose (50 µg ethinyloestradiol); the treatment is then continued for 3–6 months with 35 µg ethinyloestradiol-containing pills.[9]

Intravenous (IV) conjugated oestrogen treatment (25 mg at intervals of 4–6 hours) may be considered for patients who cannot tolerate high-dose oral oestrogen therapy, if oral treatment is not possible due to a loss of consciousness or if the severity of bleeding does not decrease within 6–12 hours despite high-dose oral oestrogen.[10] The use of conjugated oestrogen treatment for more than 24 hours is not recommended due to potential side-effects.

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 haemostatic agents and surgery should be considered.[11]

High-dose progesterone is an alternative treatment choice in patients with severe bleeding, especially when the use of oestrogen is contraindicated. The progesterone reverses endometrial proliferation related to long-term estrogen exposure and induces endometrial maturation. Medroxyprogesterone acetate (MPA, 20–40 mg) and norethindrone acetate (NETA, 5–10 mg) are administered three times per day for 7 days.[6]

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 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 3.9–4 g/day in three doses for 4–5 days is an effective treatment for HMB and is more effective than placebo.[12] Although there is no evidence for increased incidence of thrombotic events associated with tranexamic acid, having a history of

TABLE 5.3: Medical treatment regimens for acute heavy menstrual bleeding

Drug	*Suggested dose*	*Dose schedule*
Conjugated equine estrogen	25 mg IV	Every 4–6 hours for 24 hours
Combined oral contraceptives	Monophasic combined oral contraceptive pills that contain 30–50 µg of ethinyl-oestradiol	Every 6–8 hours until cessation of bleeding
Medroxyprogesterone acetate	20 mg orally	Three times per day for 7 days
Tranexamic acid	1.3 g orally or 10 mg/kg IV (maximum 600 mg/dose)	Three times per day for 5 days (every 8 hours)

or active thromboembolic disease or an intrinsic risk for thrombosis are contraindications for tranexamic acid use. Concomitant usage of COCs increase the risk of thrombosis.[12]

If hormonal and hemostatic treatment fail to lessen bleeding in 24–36 hours, examination under anaesthesia, endometrial sampling and therapeutic curettage may be necessary.[3]

NON-HORMONAL TREATMENTS

Tranexamic Acid

Tranexamic acid, a lysine derivative, is bound to lysine in its fibrinogen structure. Tranexamic acid prevents the destruction of fibrin and decreases bleeding by 30–55%. However, it has no effect on the duration of bleeding or on the regulation of the menstrual cycle.[10] The recommended dose and duration are 3–4 doses of 1–1.5 g/d orally or 10 mg/kg intravenously (maximum 600 mg/ dose) per day for 5 days.[13]

Non-steroidal Anti-inflammatory Drugs

NSAIDs decrease bleeding by preventing prostacyclin formation. Adolescents with HMB and a possible history of bleeding disorders should be instructed to avoid NSAIDs due to decreased platelet aggregation by inhibiting thromboxane A_2 synthesis.

It has been reported that NSAIDs decrease bleeding 25–35% compared to placebos but that they are less effective when compared with other treatments (e.g. tranexamic acid, danazol and IUDs).[14] The recommended usage for mefenamic acid is 500 mg/dose at intervals of 3–5 hours on the first day and a 250- or 500-mg dose three to 4 times per day thereafter. The recommended dose for naproxen is 500–550 mg at intervals of 3–5 hours on the first day and 250–275 mg 4 times per day, while ibuprofen is recommended at 600–1200 mg/d following the start of menstrual bleeding. No difference in the effectiveness of naproxen versus ibuprofen has been demonstrated.

Desmopressin

Desmopressin is a synthetic analogue of arginine-vasopressin. It is used to control and to prevent bleeding episodes in patients with a coagulation disorder. Desmopressin increases the vWF and FVIII levels, as well as platelet adhesion, and its effects last for about 6 hours.[10] The literature contains various recommendations regarding dose and duration of desmopressin use. However, bleeding control is generally ensured in 80–92% of patients who take desmopressin nasally, 300 µg/d, divided into 2 or 3 doses in the first 2–3 days of the cycle.[15] Desmopressin combined with tranexamic acid is recommended as a good treatment option for adolescents.

Surgical Treatment

More than 90% of the severe bleeding that occurs in adolescents is controlled with medical treatment. However, surgery is required in the event of life-threatening bleeding, when medical treatment is unsuccessful and in situations where a histopathology evaluation is needed.

Follow-up

Follow-up visits depend on the severity of AUB. Each visit asks for compliance of the treatment, check menstrual diary, educate girl and family members. Patient education material in local language should be given to them to go through it at home.

Summary

- Evaluation of adolescent girls who present with heavy menstrual bleeding should include assessment for anaemia from blood loss, including serum ferritin, the presence of an endocrine disorder leading to anovulation, and evaluation for the presence of a bleeding disorder.
- Routine ultrasonography should not be obtained solely for the workup of heavy menstrual bleeding

in adolescents; however, it can be considered for patients who do not respond to initial management.

- The first-line approach to acute bleeding in the adolescent is medical management; surgery should be reserved for those who do not respond to medical therapy.
- Hormonal treatments can be safely used in adolescents; moreover, they have positive effects on school performance and on the social activities of this group by decreasing the number and severity of bleeding episodes without damaging the hormonal axis during the maturation process.[16]
- Adolescents who are hemodynamically unstable or actively bleeding heavily should be hospitalized for management.
- In the absence of contraindications to estrogen, hormonal therapy for acute heavy menstrual bleeding can consist of intravenous conjugated estrogen every 4–6 hours; alternatively, monophasic combined oral contraceptive pills (OCPs) (in 30–50 microgram ethinyloestradiol formulation) can be used every 6–8 hours until cessation of bleeding.
- Use of antifibrinolytics such as tranexamic acid or aminocaproic acid in oral and intravenous form may be used to stop bleeding.
- After correction of acute heavy menstrual bleeding, maintenance hormonal therapy can include combined hormonal contraceptives, oral and injectable progestins, and levonorgestrel-releasing intrauterine devices (LNG-IUDs).
- Iron replacement therapy should be provided for all reproductive-aged women with anaemia due to bleeding.
- Nonmedical procedures should be considered when there is a lack of response to medical therapy, if the patient is clinically unstable despite initial measures, or when severe heavy bleeding warrants further investigation, such as an examination under anaesthesia.
- Obstetrician and gynaecologists can provide important guidance to premenarchal and postmenarchal girls and their families about issues related to menses and should counsel all adolescent patients with a bleeding disorder about safe medication use and future surgical considerations.
- Adolescents in whom a bleeding disorder has been diagnosed should be reminded that products that prevent platelet adhesion, such as aspirin or nonsteroidal anti-inflammatory drugs, should be used only with the recommendation of a haematologist.

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Chapter 6

Medical Management in Reproductive Age

Sandhya Pajai, Neema Acharya

Abnormal uterine bleeding is a principal gynaecologic disorder having a negative impact on women's quality of life leading to the loss of working days, and treatment causes considerable costs on healthcare systems worldwide. During this decade the FIGO committee developed the acronym PALM-COEIN to rule out these causes while managing AUB in any age group. Once the cause is established the decision-making is easy in perimenopausal women but in younger women in reproductive age group where the aim is to preserve fertility every gynaecologist should be aware of management of AUB by medical method. It is also desirable to conserve uterus in perimenopausal women due to its added long-term benefits when diagnosis is not malignant or premalignant condition. Medical management becomes first-line of treatment or temporary method of treatment while we hope it to be therapeutic or want to buy time before surgical management. In this chapter we review various modalities of medical management of AUB in reproductive age group.

Complications of Pregnancy

During reproductive period when there is abnormal bleeding one should suspect pregnancy-related complications like threatened or spontaneous abortion, ectopic pregnancy, likelihood of retained products of conception and gestational trophoblastic disease. Investigations like pregnancy test and sonography will help in diagnosis and treatment.

Investigations

A detailed history of abnormality in uterine bleeding, onset, amount and duration of bleeding is recorded. Previous history of abortion, drug therapy, insertion of IUCD, pills use is to be noted.

Physical and general examination to note pallor, thyroid swelling, edema, weight, BP, hirsutism, acne should be noted systemic examination, abdominal, P/S and P/V examination should be done.[1, 3]

- Urine pregnancy test and ultrasonography to rule out the possibility that abnormal bleeding is due to complication of pregnancy.
- A complete blood count to diagnose anaemia and thrombocytopenia is advisable in women with abnormal bleeding.
- Thyroid-stimulating hormone level for thyroid disorder.
- Coagulation studies to rule out coagulopathies, in patients who have HMB since menarche and have a personal or family history suggesting a coagulation disorder (von Willebrand disease, factor deficiencies, and platelet function abnormalities).
- Pelvic ultrasonography: Transvaginal approach is best and can give good information regarding the location and size of uterine fibroids and favour suspicion for adenomyosis and endometrial pathology.
- Doppler ultrasonography: In suspected arteriovenous malformation, malignancy cases and to distinguish between fibroid and adenomyomas.
- Saline infusion sonography: If hysteroscopy is not available and intracavitary lesion is suspected.
- Intracavitary lesion or an abnormally thick or thin endometrium can be detected by ultrasonography.
- Magnetic resonance imaging: To differentiate between adenomyosis and leiomyoma and for uterine anatomy.
- Endometrial sampling: Age over 35 or 40 years an endometrial biopsy to rule out endometrial hyperplasia or cancer. In women with acute bleeding, dilatation and curettage can be performed as therapeutic and diagnostic procedure.

- When dilation and curettage is performed prior hysteroscopy to obtain targeted biopsies, hysteroscopy is also useful for diagnosis of submucous myoma and endometrial polyps.[2,3]

GENERAL MANAGEMENT

- Proper diet, adequate rest during menses.
- Oral iron or parental iron therapy. Vitamins and protein supplements may be prescribed.
- Blood transfusion for correction of anaemia.
- To relieve anxiety sedatives may be given when needed.
- To prevent pelvic congestion in between bleeding episodes normal activities are promoted.
- Menstrual calendar is maintained.[1,6]

TREATMENT OF ABNORMAL BLEEDING FROM SPECIFIC CAUSES

1. AUB-P (Endometrial Polyps)

Gonadotropin-releasing hormone agonists, progestins can be prescribed to relieve symptoms of polyp. These drugs are useful for short period. When the drugs are stopped usually symptoms will recur again.[5]

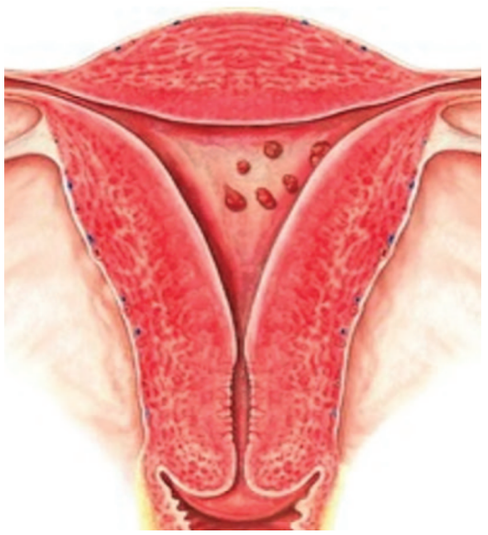

Fig. 6.1

2. AUB-A (Adenomyosis)

- **Nonsteroidal anti-inflammatory drugs (NSAIDs):** Mefenamic acid 150–600 mg daily started with onset of bleeding and given for 3–5 days.

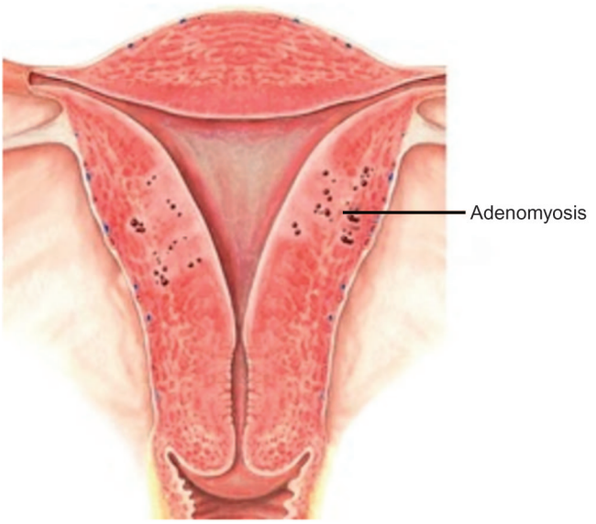

Fig. 6.2

- **Progesterone:** Dienogest in the dose of 2 mg daily for 5 months. It is contraindicated in thromboembolic diseases, hepatic disease and undiagnosed vaginal bleeding.
- **Combined oral contraceptive:** COC will induce amenorrhea when prescribed for prolonged period.
- **Danazol:** Danazol 200 to 400 mg is given daily continuously for 3 months. It is not indicated in presence of liver disease. Commonly not used due to androgenic side effects. Patients with adenomyosis may be treated with danazol loaded intrauterine device. Systemic side-effects are minimal. Reduction of blood loss is by 60%.

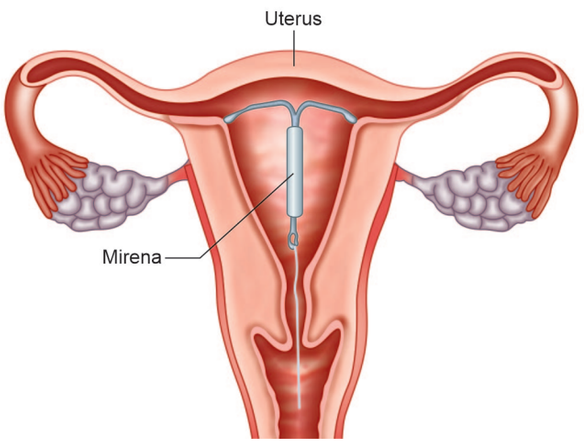

Fig. 6.3

- **LNG-IUS:** The levonorgestrel intrauterine system (LNG-IUS) will treat menorrhagia and dysmenorrhea. The LNG-IUS releases 20 µg levonorgestrel per day and there is definite reduction in menstrual blood loss in women with heavy menstrual bleeding. After 1 year of treatment 20% of the women using the LNG-IUS are amenorrhoeic. There is decidualisation of the endometrium followed by atrophic changes after use of the LNG-IUS. Due to this there is a definite decrease in menstrual blood loss. Levonorgestrel also acts directly on the adenomyotic deposits. It also acts as a contraceptive and its lifespan is 5 years.[3,6]

3. AUB-L (Leiomyoma)

- Treatment will depend on nature and severity of symptoms, the size, location, and multiplicity of myomas and desire for fertility.
- Tranexamic acid tab 500 mg 3 times a day for 4–7 days during menses. It is contraindicated in patients with history of thromboembolism.
- Nonsteroidal anti-inflammatory drugs (NSAIDs): Mefenamic acid 150–600 mg taken daily started with onset of bleeding and given for 3–5 days.
- Danazol administered daily in divided doses ranging from 200 to 400 mg for 3 months minimizes blood loss or even produce amenorrhea by its antigonadotropin and androgen agonist actions. It reduces the size of the tumour by 60%.
- GnRH agonists (leuprolide, buserelin, narfereline) can be used as injections, nasal spray, or implants. Injection leuprolide 3.75 mg monthly IM/SC for a period of three or six months. Buserelin injection SC/nasal spray 200–300 µg daily. They shrinks the volume and vascularity by 50 to 80%. There is increase in size of the fibroid after stoppage of the drug. Narfereline 200 µg intranasally daily for 6 months.
- GnRH antagonists (degarelix, ganirelix, cetrorelix)—depot cetrorelix shows quick response. Oral formulations are in phase III trial. Currently not available for daily practice.
  - Levonorgestrel: Releasing intrauterine system (LNG-IUS) reduces blood loss and uterine size. It is not inserted when the uterine size is >12 weeks or uterine cavity is distorted and there is submucous myoma.
  - Antiprogesterones: Mifepristone (RU 486) is useful to decrease fibroid size it also reduces bleeding. A daily dose of 25–30 mg is given for 3 months. 5 mg daily dose for five to six months is also useful. It shrinks myoma. With long-term therapy it causes endometrial hyperplasia so it is to be avoided.
  - Ulipristal acetate: Symptoms of uterine fibroids are decreased after treatment with ulipristal acetate which is a progesterone receptor antagonist. It is prescribed in the dose of 5 mg daily for three months which is followed by withdrawal bleeding for fibroids of 3 cm or more in diameter, and a haemoglobin level of 10 gm per litre or below up to four courses may be given. It reduces bleeding and size of fibroid. Currently it is banned in European countries for its liver toxicity.
  - Asoprisnil: It is selective progesterone receptor modulator. There is no endometrial hyperplasia with this treatment.[2,3,8]

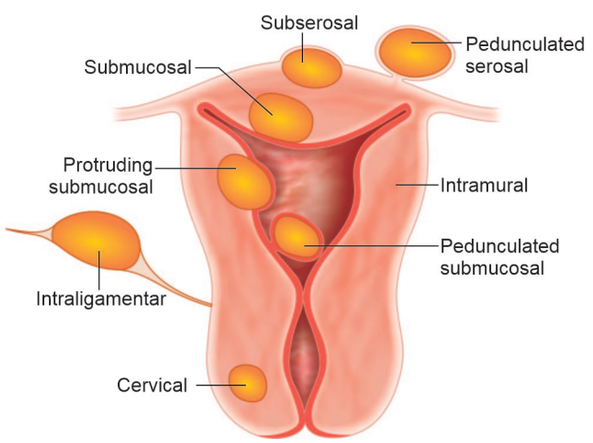

Fig. 6.4

4. AUB-M (Malignancy and Endometrial Hyperplasia)

- Endometrial hyperplasia without atypia has a low risk for progression to endometrial cancer.
  - In obese patient weight loss and if required tab metformin.
  - It can be treated by giving progestin treatment regimens. Cyclic progestin therapy medroxyprogesterone acetate (MPA) 10 mg or norethisterone 5–10 mg is used from 5th to 25th day of cycle for 3 cycles. Continuous progestogens are more effective than cyclical progestogens. Every six months endometrial sampling is advised.

Before stopping follow-up minimum two consecutive 6 monthly samples should be negative.

- Endometrial hyperplasia with atypia
  - Treatment with progestins cyclically or continuously for 6–9 months with 3 monthly endometrial sampling.
  - Levonorgestrel intrauterine system is other option for women who wants long-term contraception. As per RCOG guidelines LNG–IUS should be the first-line management. Regression rate is higher and side-effects are less.
  - Hysterectomy is advised in patients with persistent endometrial hyperplasia with atypia unresponsive to progestin regimens.
- The modalities of management of endometrial malignancy are hysterectomy, radiotherapy, chemotherapy, hormonal therapy.[1,2,6]

5. AUB-C (Coagulation Disorders)

- Tranexamic acid as primary option 10 mg/kg every eight hours may be used.
- Estrogen–progestin contraceptives or the levonorgestrel–intrauterine system also help to reduce the volume and duration of blood loss during menses in women with von Willebrand disease.
- Patients who are not responding to above medical and hormonal management, desmopressin is administered. There is rapid increase in coagulation factor VIII and von Willebrand factor that lasts 6–12 hours.

  Women with coagulation disorders with AUB with von Willebrand disease are treated with desmopressin in consultation with a haematologist. Desmopressin can be administered intravenously, subcutaneously, or by intranasal spray. For home and prophylactic treatment of von Willebrand disease the nasal spray is usually advised.
- Antifibrinolytic therapy: Tranexamic acid prevents clot dissolution, particularly in mucous membranes having naturally high fibrinolytic activity.
- Estrogen–progestin contraceptives or the LNG-IUS also help to reduce the volume and duration of menses in women with von Willebrand disease.[3]

6. AUB-O (Ovulatory) Dysfunction: Ovular Bleeding

- In ovular bleeding any low dose combined oral pills are beneficial when given from 5th to 25th day of cycle for 3 consecutive cycles. It causes endometrial atrophy. It suppresses the hypothalamo-pituitary axis more effectively so more beneficial compared to progesterone therapy. When there is normally functioning pituitary-ovarian-endometrial axis normal menstruation is likely to begin again. It reduces menstrual blood loss by 50%. It acts as a contraceptive.
- In patients with irregular ripening, irregular shedding of the endometrium and in ovular bleeding, when the patient desires pregnancy dydrogesterone 1 tab (10 mg) daily or twice a day from 15th to 25th days may be prescribed. It does not suppress ovulation. This regimen is less effective than 5th to 25th days course.
- Combined oral contraceptives can be used in ovulatory AUB.

Treatment of Anovulatory Bleeding

Progestin therapy

Endometrial thickness on ultrasound is in normal range or is thickened, anovulatory bleeding can be treated with high-dose progestin alone (medroxyprogesterone acetate 10–20 mg twice daily, megestrol acetate 20–40 mg twice daily, norethindrone 5 mg twice daily).

Cyclic progestogen preparation of medroxyprogesterone acetate (MPA) 10 mg or norethisterone 5 mg is used from 5th to 25th day of cycle for 3 cycles.

- To reduce the number of menstruations in a year to three monthly inj Depo-Provera is now prescribed three monthly. Number of menstrual cycles reduced to 4 in a year.
- Tab medroxyprogesterone acetate 10 mg thrice daily is given and treatment is usually continued for at least 90 days. It does not alter the serum lipid profile so it is better than norethisterone.
- Women who do not desire pregnancy the levonorgestrel-releasing intrauterine system is an helpful treatment for the long-term management of anovulatory bleeding.
- Estrogen–progestin therapy women with anovulatory bleeding who are not planning pregnancy are successfully treated with an estrogen–progestin contraceptive pill.

Estrogen therapy

- Parenteral conjugated equine oestrogens (CEE) can be administered in a dose of 12.5 mg IV to stop the bleeding and repeated after 12 hours if the bleeding is very heavy in anovulatory cycle not responsive to progestogens.

- Combined oral contraceptive is used for long-term treatment.[1]
- **Polycystic ovarian disease:** Patients with PCOS are advised weight reduction as a first-line approach. Tab metformin improves insulin sensitivity and currently remains drug of choice as an insulin-sensitizing agent for women with PCOS.
- Low dose combined oral contraceptives third generation containing 30 mg ethinyloestradiol and 150 mg desogestrel give excellent results. Combined oral contraceptives (COCs) are the most commonly utilized treatment approach for the menstrual abnormalities associated with chronic anovulation.
- Cyproterone acetate 2 mg the antiandrogen and ethinyloestradiol is useful in patients of PCOS with acne and hirsutism.
- The recent treatment is combination of oestradiol 30 mg with 3 mg of drospirenone.
- In women with PCOS and infertility in those with a history of resistance to clomiphene, letrozole 2.5 mg bd for 5 days should be considered as a first-line agent for ovulation induction.[1,6,4]

7. AUB-E (Endometrial)

Management of AUB-E

- Treatment with tranexamic acid combined with mefenamic acid.
- If patient does not respond to this then combined oral contraceptive pill if not contraindicated. Oral pills containing ethinyloestradiol 30 µg and levonorgestrel. They are given from 5th day of menstrual cycle for 21 days for 3–6 cycles.
- Levonorgestrel-releasing intrauterine system for women who cannot tolerate oral medications.

8. AUB-I (Iatrogenic Causes)

- With oral contraceptive use breakthrough bleeding occurs during first 1 to 3 months in around 30 to 40% of users. It is managed with reassurance as the frequency of breakthrough bleeding becomes less with next month of use.
- The use of a 5 to 7-day course of NSAIDs may result in decreased breakthrough bleeding.
- Antifibrinolytic agents and NSAIDs prescribed during menstruation for 4–5 days reduces blood loss by 70%, in patients with post-IUCD and post-sterilization menorrhagia.[5]

9. AUB-N (Not Defined)

- NSAIDs and tranexamic acid are useful. Treatment with combined oral contraceptives or levonorgestrel-releasing intrauterine system is advised for patients who desires of contraception.
- Gonadotropin releasing hormone agonists advised when other medical treatment has failed.

Medical Treatment of Acute Heavy Abnormal Uterine Bleeding (HMB)

- Take a history from the patient about amount duration of bleeding and is there any effect on her quality of life. On physical examination, signs for estimation of blood loss, pelvic examination to note trauma to genital tract and size of uterus.
- For most of the patients medical management should be the primary treatment, options include IV conjugated equine oestrogen, multi-dose regimens of COCs or oral progestins, and tranexamic acid. Choice of treatment will depend on the patient's medical history and contraindications to therapies.
- First line of medical therapy is hormonal for patients with acute AUB without known or suspected bleeding disorders
  - Admit the patient
  - Conjugated equine oestrogen (premarin) 25 mg IV every 4 hr, up to 3 doses, when bleeding is less. Oral premarine tablets are started or progestins are given for 10 days.
  - Combined oral contraceptive pills containing 30 µg ethinyloestradiol can also be prescribed if bleeding is heavy , two pill every 12 hours for 5 days and then 1 tablet per day for 15 days. Give antiemetics for controlling nausea.
  - As an alternative to high-dose estrogen therapy for acute HMB, high-dose medroxyprogesterone acetate 20 mg orally three times per day or norethisterone acetate 10 mg three times a day can be used.
  - Tranexamic acid IV dose is 10 mg/kg every 8 hours or 1000 mg IV. As bleeding decreases oral dose 500 mg three times a day. They usually reduce bleeding in these patients by 30–55%.
  - Desmopressin has been used successfully in the management of heavy menstrual bleeding in women with von Willebrand disease, beginning treatment with the onset of menses.[1,7]

Summary

AUB is a significant health issue affecting quality of life of women of all age groups.[9] Once the causes are established the decision-making is easy in perimenopausal women but in younger women in reproductive age group where the aim is to preserve fertility every gynaecologist should be aware of management of AUB by medical method. It is also desirable to conserve uterus in perimenopausal women due to its added long-term benefits when diagnosis is not malignant or premalignant condition.

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Chapter 7

Surgical Management in Reproductive Age

Chaitanya Shembekar, Parul Sharma Saoji, Kalpana Jetha

Introduction

Abnormal uterine bleeding (AUB) is one of the most common gynaecological disorders with incidence of approximately 10–35%.[1]

In India, the prevalence of AUB is around 17.9%.[2]

FIGO in 2011 standardized nomenclature of AUB with new system known by the acronym PALM-COEIN, with PALM describing structural causes and COEIN non-structural causes[3] (Fig. 7.1).

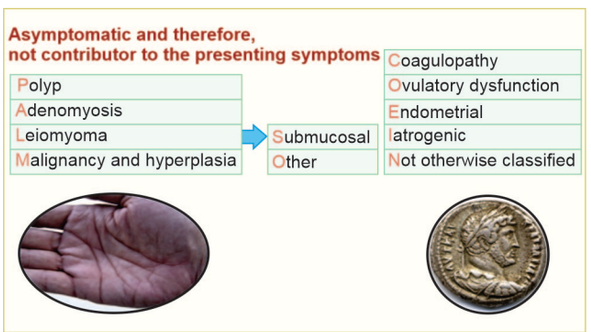


Fig. 7.1: PALM-COEIN classification

Women of reproductive age refers to all women aged 15–49 years.[4]

Challenges in this age group are vast. Aim of management is to treat the condition medically and if required surgically, with hysterectomy as the last resort.[5]

Following PALM-COEIN scheme, it would be prudent to evaluate the optimum and most recent surgical techniques to treat AUB in reproductive age group.

POLYPS

P in classification stands for polyps (Fig. 7.2). Rationale for treatment is focussed on relieving the symptoms of bleeding and obtaining histopathological diagnosis.

Polypectomy is a good option with respectable success rate.[6] The gold standard is hysteroscopy with see and treat policy.[7] Office hysteroscopy is gaining popularity with bipolar resection using saline as a medium, a safer option.

Polypectomy

Indications: Polyp with AUB, infertility and risk of malignant transformation.

Patient evaluation: Transvaginal sonography and saline infusion sonography.

Consent: Possibility of bleeding, fluid overload, gas embolism, perforation, infection and SOS laparoscopy or laparotomy.

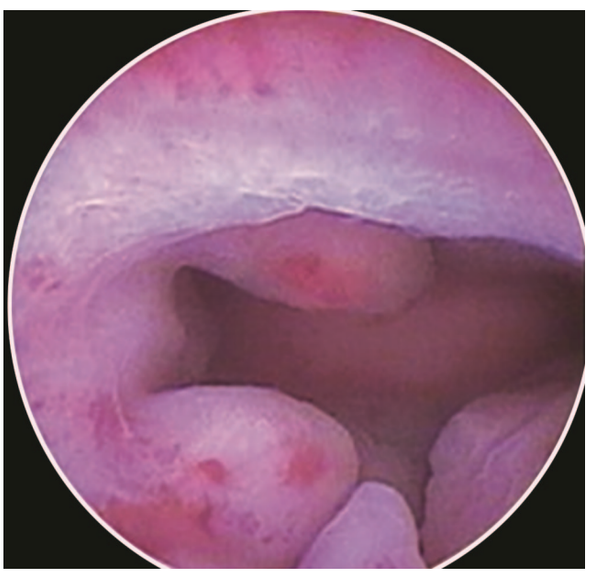


Fig. 7.2: Multiple polyps as seen on hysteroscopy

Patient preparation: Plan during post-menstrual phase. Vaginal tablet misoprostol 200 µg or IV drotaverine to facilitate dilatation. Preoperative antibiotics are not required (ACOG guidelines 2013).

Instruments: Resectoscope with 90° loop electrode. Intrauterine morcellator with hollow cannula attached to suction can be used for quick excision of polyps. Hysteromat is essential for fluid management.

Surgical steps

Anaesthesia and patient position: Local analgesia in office setting. In OR setup regional analgesia. Lithotomy position and Foley's catheter.

Media selection: Glycine for monopolar resectoscope. Saline for bipolar resection. Nowadays, normal saline and bipolar resectoscopes are preferred because of the risk of hyponatraemia with glycine.

Cervical dilatation: Required for 4 mm standard hysteroscope.

Resection: Start medium flow. Insert resectoscope under vision. Panoramic inspection to identify location and number of polyps. Electrosurgical current applied and loop is retracted towards cervix to cut the polyp from the base. Loop should always be in view. Polyp removed through cervix. Several passes of loop electrode required in large polyp. Start from the polyp tip or upper end and slowly go to the base. Uterus is not emptied after each pass. Resected segments are allowed to float in the cavity. At the end of procedure fragments are collected.

Haemostasis: Bleeding is controlled by same loop with coagulation current. Foley's catheter is used as a tamponade if bleeding is more than average.

Removal of instrument is followed by collection of the specimen for histopathology. Fluid calculation is a critical step and it should be followed throughout the procedure.

Postoperative: Recovery is rapid and without complications. Patient can be discharged same day.

In case of small polyps, hysteroscopic scissors without energy source can be used.

ADENOMYOSIS

First described by Rokitansky, adenomyosis, a benign condition characterized by myometrial invasion of endometrial glands and stroma in uterine muscle wall, diffuse or localized.[8]

No medical treatment allows conception. As a result, surgery plays a major role, even in a conservative scenario. In adenomyoma it is more difficult to expose the lesion, recognise clear margins and define exact extent of disease. Adenomyomectomy, laparoscopic or open, is thus challenging to the surgeon.[9]

Endometrial reduction, performed by uterine incision and wedge resection removing part of myometrium, has shown promising results. H-shaped variant of incision can give better results in terms of pregnancy rates (Fig. 7.3).

In case of perimenopausal women who have completed childbearing and have severe symptoms such as pain, menorrhagia, not responding to medical

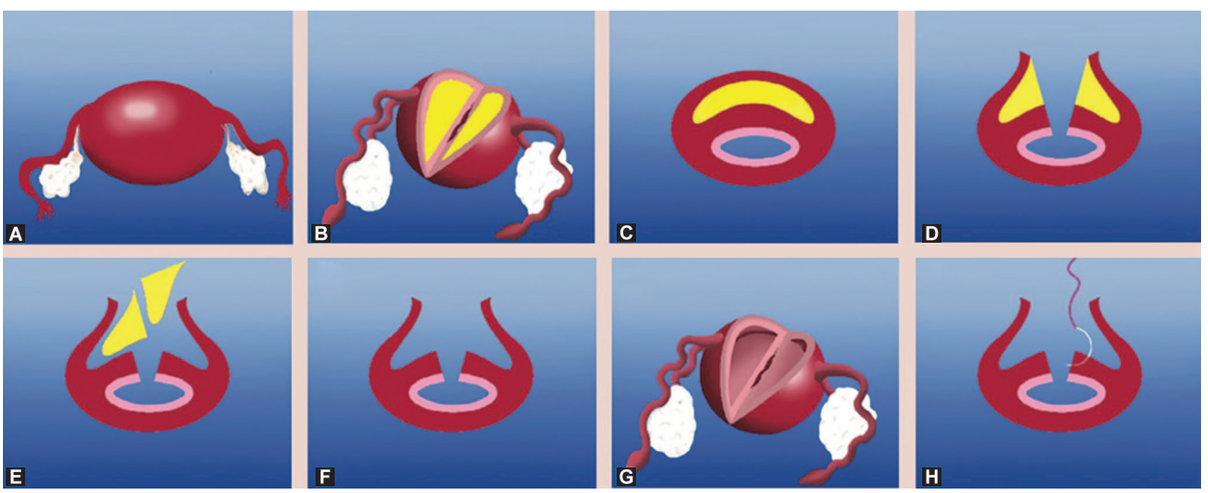
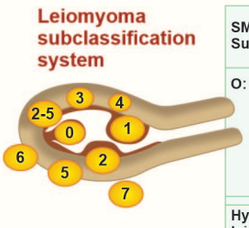


Fig. 7.3A to H: Adenomyomectomy procedures



SM: Submucosal	0	Pedunculated intracavitary
	1	<50% intramural
	2	≥50% intramural
O: Other	3	Contracts endometrium; 100% intramural
	4	Intramural
	5	Subserosal ≥50% intramural
	6	Subserosal <50% intramural
	7	Subserosal pedunculated
	8	Other (specify, e.g. cervical, parasitic)
Hybrid leiomyomas (impact both endometrium and serosa)	Two numbers are listed separated by a hyphen. By convention, the first refers to the relationship with the endometrium while the second refers to the relationship to the serosa. One example is below	
	2-5	Submucosal and subserosal, each with less than half the diameter in the endometrial and peritoneal cavities, respectively

Fig. 7.4: FIGO classification of leiomyomas

management, hysterectomy preferably laparoscopic, is the treatment of choice.[10]

LEIOMYOMA

FIGO classified leiomyoma as 0–8 depending upon the location of myoma (Fig. 7.4). Reproductive age group women with leiomyoma may present with AUB, pain, pressure symptoms or infertility. Management depends upon various factors like size, number, location of fibroids and symptoms associated with fibroids. Hysteroscopy and laparoscopic myomectomy are preferred over open method.

Intramural and subserous myomas especially when endometrial cavity is normal, should not cause symptoms and treatment plan will be decided on individualised basis. Submucous myomas are the cause of menorrhagia as well as infertility and they require hysteroscopic resection.[11]

Usually myoma bigger than 5 cm is considered not eligible for hysteroscopic myomectomy.[12]

Surgical Treatment

Hysteroscopic Myomectomy

Submucosal fibroids are best treated with hysteroscopic myomectomy (Fig. 7.5).

Most of the steps involved are same as that of hysteroscopic polypectomy.

Fibroid mapping plays a crucial role in myomectomy. This is possible with transvaginal and transabdominal sonography, saline sonography, 3D sonography and MRI in some cases.

The risk associated with procedure such as difficulty in removing FIGO L2 or ESGE type 2 fibroids, adhesions, perforation, fluid overload, Asherman's

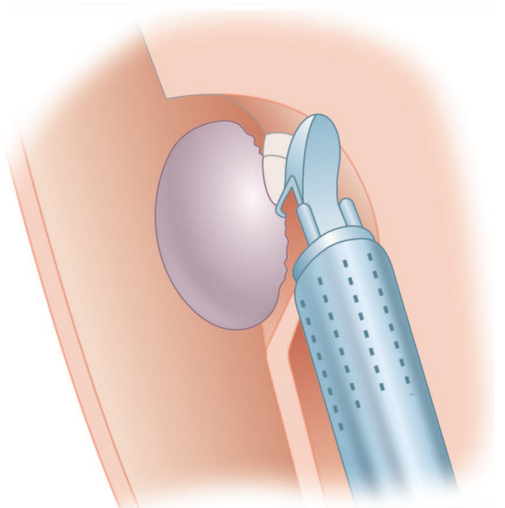


Fig. 7.5: Hysteroscopic myomectomy

syndrome and possibility of second sitting should be discussed while counselling regarding the treatment modality.

While resecting fibroids, avoid reinsertion. However, in large fibroids, a pause in resection may be required to remove pieces.

FIGO L2 fibroids, with less than 50% fibroids located in the cavity, are more difficult to resect and may require a two-stage procedure, especially if fibroid is more than 3 cm in size. When the resection reaches to the level of normal myometrium, a pause can help in delivering deeper portions.

Morcellators such as Myosure, Truclear work best in submucous fibroids. It is faster, with fewer complications and is easier to perform with shorter learning curve.

Since fibroids are highly vascular, special attention should be paid towards haemostasis.

Speed and skill of surgeon play an important role in myomectomy.

Myomectomy: Laparoscopy versus Laparotomy

Fibroids FIGO L3 and above and in some situations even large L2 fibroids are best removed by abdominal approach. The recovery with laparoscopic myomectomy is much better with less postoperative morbidity.

Step by Step Laparoscopic Myomectomy

Preoperative preparation: Preoperative GnRH analogue for 3 months can be given. However, recent studies indicate that there is difficulty in getting planes in case of preoperative treatment with GnRH analogues. Ulipristal acetate is a new kid on the block and PEARL trial proves the importance of three months preoperative treatment with ulipristal acetate to reduce the intraoperative blood loss and operative time.

A day prior to surgery bowel preparation helps in surgery.

Operative preparations: General anaesthesia is preferred over regional.

Standard lithotomy position with middle umbilical or higher trocar and two 5 mm trocars on each side is ideal placements of trocars.

Subserosal and intramural fibroids are first identified.

Technique involves 5 steps (Fig. 7.6A to I)

1. Infiltration of vasoconstrictive agents
2. Incision with monopolar hook
3. Enucleation of fibroid
4. Suturing
5. Morcellation

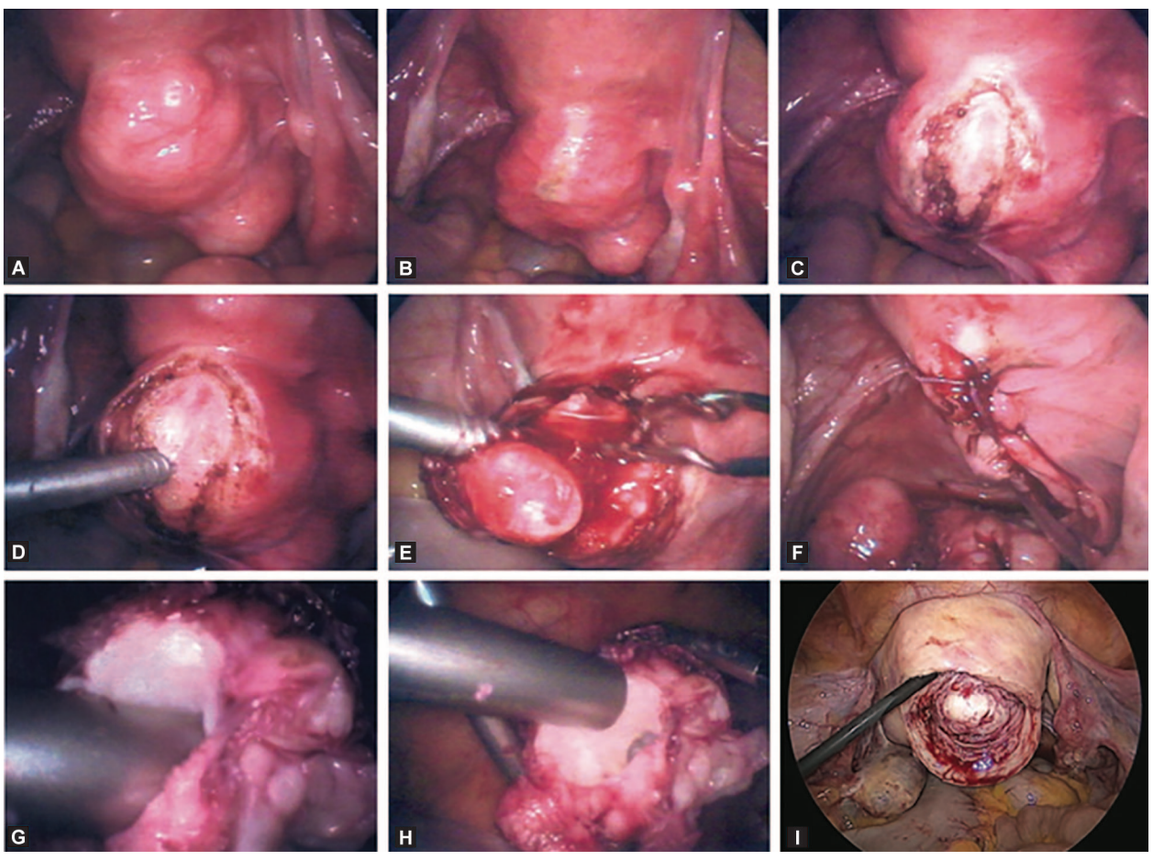


Fig. 7.6A to I: Steps of laparoscopic myomectomy

Pitressin is injected in diluted form, i.e. 20 units in 100 ml with the help of vasopressor injection needle. While using pitressin surgeon has to be careful and avoid vascular injection, as it may lead to sudden vasoconstriction.

Incision is made with the help of monopolar hook till the plane of cleavage is found.

Enucleation: In this step tenaculum and suction cannula are used for traction and countertraction.

Suturing with Quill, barbed or V-Loc sutures are more convenient. Baseball sutures are preferred.

Morcellation is the last step in myomectomy. The danger of dissemination can be taken care of by doing morcellation in bag.

Laparoscopic myomectomy is an art. It requires surgical skills and practice.

MALIGNANCY

Malignancy means AUB caused by endometrial transformation towards cancer or precancerous lesion.

Endometrial carcinoma and its precursor are characterised by hyperestrogenic condition with endometrial proliferation which explains symptoms of AUB. Sampling of endometrium prior to surgical intervention is a must. Once the diagnosis is confirmed, for endometrial carcinoma, total hysterectomy is the only surgical approach.

Women with PCO and endometrial carcinoma undergoing treatment for infertility, such as IVF may postpone hysterectomy while under treatment. This is possible with medical treatment in the form of progestins under strict surveillance.[13]

COEIN

All the diseases included in COEIN are usually not associated with organic or structural entities, so surgery could be less effective and is not the first choice of treatment.

Cases where medical treatment has failed, could benefit from surgical approach.

Endometrial ablation is one such treatment modality.

Special Treatment Modalities

Endometrial Ablation

Endometrial ablation is a treatment option for unexplained heavy bleeding when medical treatment is rejected, unsuccessful or poorly tolerated (Fig. 7.7).

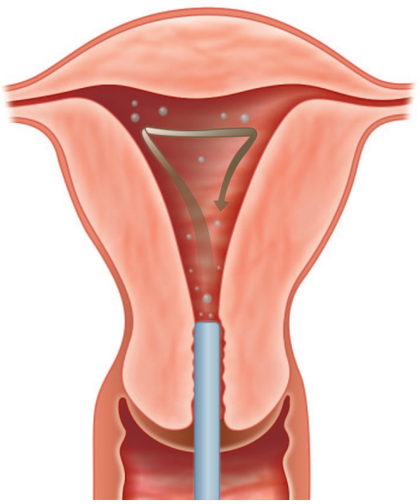


Fig. 7.7: Hysteroscopic thermal ablation

Wide variety of methods have been developed for ablation. It all started with transcervical resection of endometrium (TCRE) by urologist Smith based on his experience with transurethral resection of prostate. Hysteroscope with operating channel was used. Monopolar resectoscope with glycine as a media was preferred. Though the results were encouraging, it was associated with risks like fluid overload and perforation.

Though hysterectomy gives permanent solution to the problem, overall satisfaction rates with ablation are high.

Several additional techniques for endometrial ablation have been developed which include hydrothermal ablation with silicon balloon (Figs 7.8 and 7.9). Novasure, bipolar radiofrequency gold plated mesh electrode is one such technique which became popular in treatment of HMB (Fig. 7.10). Compared to traditional hysteroscopic methods, the blind techniques are technically easier to perform, take less time, are more likely to require only local anaesthesia, and achieve similar results, but equipment problems are more common (Fig. 7.11).[14] Although all methods are effective, there are reasons for choosing one method over another in individual women (Table 7.1).

Preoperative evaluation should include thorough examination with sonography and saline sonography to exclude polyps, myoma.

Best results of ablation can be achieved with thin and inactive endometrium. Several methods are described to achieve this, including curettage

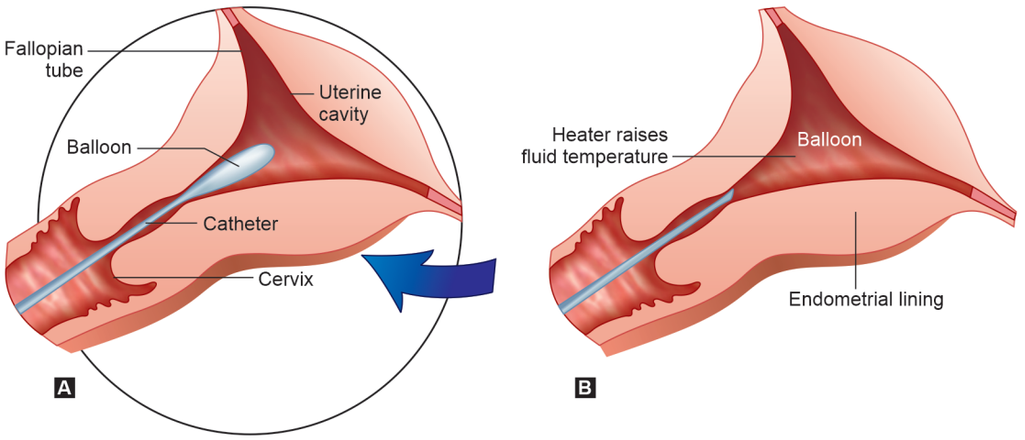


Fig. 7.8A and B: Cavaterm balloon

Fig. 7.9: Thermachoice III uterine balloon therapy system

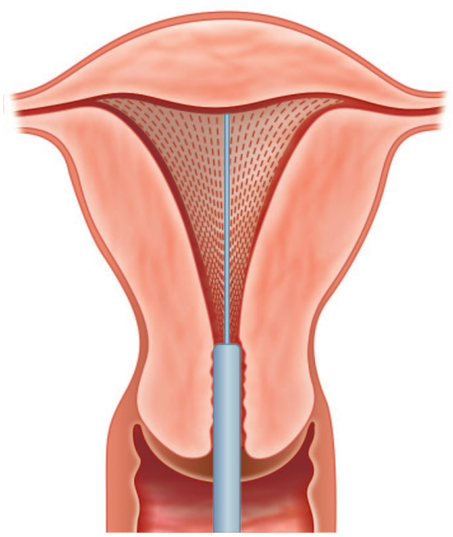


Fig. 7.10: Impedance controlled electrocoagulation

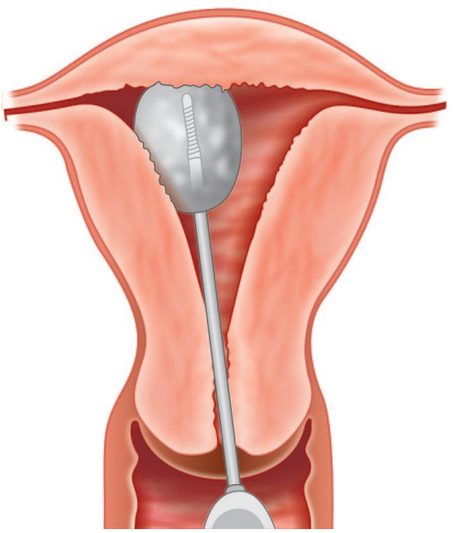


Fig. 7.11: Cryoablation

immediately prior to performing ablation and pre-operative treatment with progestins, OCPs, danazol or GnRH agonist.

For obvious reasons endometrial ablation is not an appropriate treatment for women who have not completed childbearing. Conversely, endometrial ablation is not a sterilization procedure. Although uncommon, pregnancy has been reported post-ablation and is associated with increased risk of complications such as miscarriage, preterm delivery and antepartum haemorrhage.

The legitimate concern in this treatment is that endometrial carcinoma might be inadvertently

TABLE 7.1: Advantages and disadvantages of various ablative techniques

Method	*Advantages*	*Disadvantages*
Cryoablation	Not completely blind Less pain than methods using heat energy Requires minimal or no anaesthesia	No outcomes data for women with intracavitary lesions
Thermal balloon ablation	First global technique approved for use Easy to learn	Not recommended for women with an abnormal uterine cavity (anomaly, enlarged, polyps, myomas, adhesions)
Hydrothermal ablation	Circulating hot water contacts all endometrial surfaces, regardless of shape	Not recommended for women with a uterus >10 cm Require 8 mm hysteroscope Hot water stimulates pain Risk for burns to vagina and perineum
Bipolar radiofrequency ablation	Short procedure time Easy to perform Requires no endometrial pretreatment	Not recommended for women with an enlarged or abnormal cavity
Microwave ablation	Applicable in women with large cavity or small myomas (<3 cm)	Requires pretreatment ultrasonography to document minimum 1 cm myometrial thickness in all areas Contraindicated for women with previous transmural myomectomy or classical cesarean section

managed by endometrial ablation. This observation emphasises the need for thorough preoperative evaluation, including endometrial biopsy. Although risk can never be completely avoided, endometrial ablation is not recommended for women at increased risk of endometrial cancer.

Other complications of endometrial ablation include haematometra, cervical stenosis, uterine perforation. Collection in the cavity can be drained after careful post-procedure follow-up.

Step by step TCRE

- Start with fundal and periosteal region
- Cornu and fundal region with roller ball
- 9 to 3′O clock position posterior wall with loop
- Similar fashion anterior wall
- Gentle movements under vision
- Anterior and posterior wall 2–3 layers
- Lateral wall single layer—care at uterotubal junction
- Where to stop? Till you see myometrium—2.5 to 3 mm
- Stop at internal os—to avoid cicatrix
- Endometrial chips removed with ovum forceps
- Roller ball used for coagulation

Step by step thermal ablation

- Lithotomy position
- PV examination
- Thorough curettage
- Check and insert catheter
- Check intrauterine volume—volume stabilization
- Heating time—3 to 4 minutes
- Therapy time—12 minutes
- Temperature—89–90°
- Follow instructions
- Remove catheter
- Heating and therapy time may vary depending on machine settings.

Uterine Artery Embolization

Described for the first time in 1995 by Ravina, this method is basically a treatment option for women with large fibroids who no longer desire fertility (Fig. 7.12).

MRI shows a transient ischaemia within the body of uterus and the endometrium, typically lasting for up to 72 hours after the procedure. This process is irreversible within fibroid tissue only and temporary in healthy uterine tissue. Nevertheless, this process raises concern regarding its effect on whole uterus and endometrial function. Uterine artery and ovarian artery show anastomosis on angiography in at least one side in 46% of women. Therefore, inadvertent embolization of ovarian tissue may result in premature ovarian failure. Given the current evidence base, UAE is not a treatment of choice for women with infertility and for those who desire pregnancy in future.

Magnetic Resonance–guided Focussed Ultrasound (MRgFUS)

This treatment modality is showing promising early results. MRgFUS involves application of MRI directed beams of ultrasound capable of heating an area of

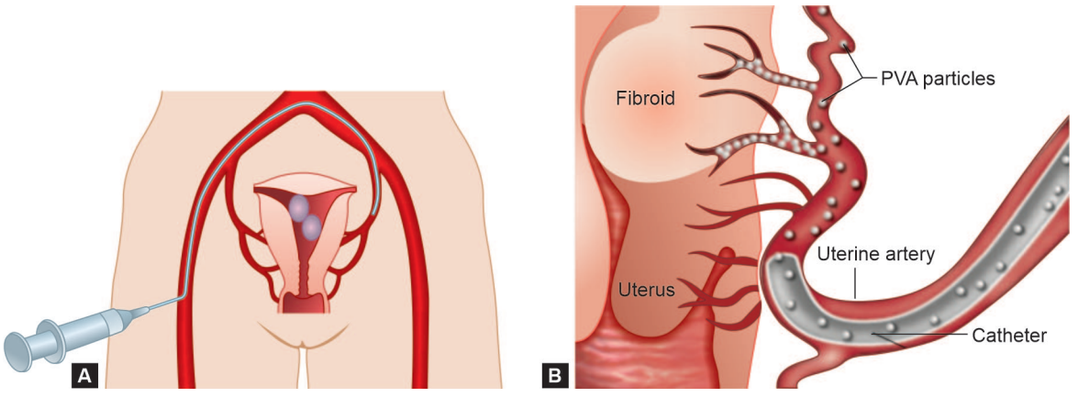


Fig. 7.12: (A) Embolisation through femoral artery; (B) Polyvinyl particles in arteries

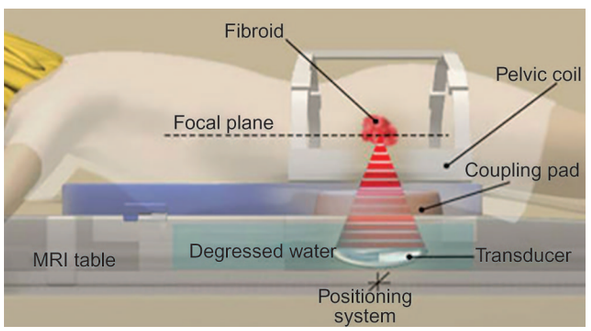


Fig. 7.13: MRgFUS

fibroid tissue up to 70°C and causing destruction through coagulative necrosis (Fig. 7.13).

Rabinovici et al reviewed all pregnancies following MRgFUS. Preliminary results are encouraging.[15]

Hysterectomy

Hysterectomy is the most common gynaecological procedure in the world for management of AUB. Over 60% patients with AUB end up having hysterectomy within 5 years from the diagnosis. About one-third of hysterectomies are avoidable. With newer modalities available, hysterectomy should be the last option. However, still hysterectomy is the treatment of choice in patients not responding to other forms of treatment, who have severe symptoms and have completed family.

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Chapter 8

Perimenopausal AUB

Kamini Patel

Introduction

Perimenopausal is the period before the onset of the menopausal phase of woman. It can usually start when the woman is in her 40s (exceptional cases it can start in 30s) and lasts till the menopause sets.[1] Perimenopause is the time period between premenopausal phases to menopausal phase. The median of perimenopausal period is approximately between 4 and 11 years.[2]

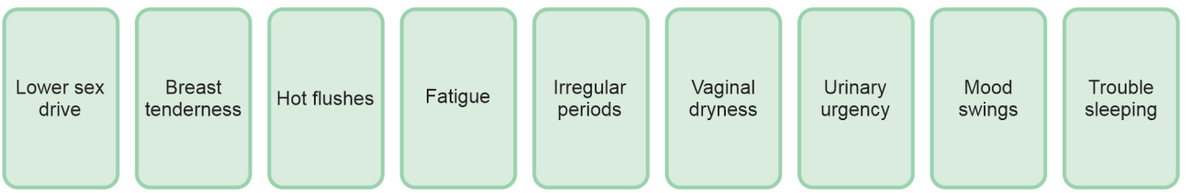

Fig. 8.1: Symptoms of perimenopausal phase

AUB: Abnormal uterine bleeding is defined as irregularity in bleeding in terms of volume, duration, regularity and/or frequency. AUB encompasses HMB (heavy menstrual bleeding) and IMB (intermenstrual bleeding) and is bifurcated into PALM and COEIN according to the FIGO classification. Assessment workflow of the AUB is starting with the general assessment which includes proper history taking and understanding the bleeding pattern. Physical, pelvic and speculum examination helps in diagnosis in a much better way. Taking the history will clarify our laboratory testing profile. Imaging techniques—TVS USG, endometrial biopsy and hysteroscopy adds to the final line of assessment in AUB.[3]

- General assessment
  - History and bleeding pattern
  - Physical, pelvic and speculum examination
- Laboratory tests including:
  - Full blood count, iron studies, thyroid, hCG
  - Disorders of hemostasis
- Determine ovulatory status
- Evaluate pelvic organs and endometrium
  - Role of transvaginal ultrasound
  - Role of endometrial biopsy

Fig. 8.2: Assessment of abnormal uterine bleeding

TREATMENT OF PERIMENOPAUSAL BLEEDING

Treatment of AUB in perimenopausal female depends on the diagnosis. Proper diagnosis is work half done. Treatment options must be selected based on the diagnosis done. After the options such as pregnancy and malignancy is ruled out, or woman with no anatomical abnormalities, or use of any contraceptive pills, adenomyosis or simply enlarged endometrium—variety of treatment options are available and can be explored.[4]

- Expectant
- Non-hormonal medical treatments
  - Non-steroidal anti-inflammatory drugs (NSAIDs)
  - Anti-fibrinolytic agents
- Hormonal medical treatments
  - Cyclical or long-acting progestogens
  - Combined oral contraceptives
  - GnRH analogs (fibroid-associated)
  - Selective progesterone receptor modulators (fibroid-associated)
- Levonorgestrel intrauterine system (LNG-IUS)
- Endometrial ablation
- Uterine artery embolization (fibroid-associated)
- Hysterectomy

Fig. 8.3: Treatment options for AUB

Pharmacological Therapy

Hormonal Therapy

After COCs, levonorgestrel intrauterine system (LNG-IUS) is the next best treatment option available to manage the AUB in perimenopausal female.[4] For female with the estrogen contraindications, progesterone therapy and LNG-IUS is used. LNG-IUS is better and helps in reduction of excessive menstrual bleeding (HMB).[5]

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs act on reduction of the prostaglandins (which are responsible for the abnormal uterine bleeding via aberrant neovascularization). NSAIDs play a major role in initial line of treatment—reducing the blood loss and menstrual cramps.[6]

Tranexamic Acid

Tranexamic acid is used routinely in the cases to reduce the HMB. Yet its use is contraindicated in the woman with the history of thromboembolism as it targets and binds to the lysine binding sites on plasminogen preventing plasmin and fibrin polymer interaction resulting in the fibrin degradation, stabilization of the clots thus reducing the blood loss.[7]

Non-medical Approaches to Abnormal Uterine Bleeding

Endometrial Ablation

Endometrial ablation is minimal invasive procedure and is usually chosen by the woman who wishes to avoid the definite surgical treatments like hysterectomy. Yet the drawback of the endometrial ablation is that it does not exclude the surgical risk and is followed by the hysterectomy after 4 years in about 40% of the cases.[8]

Treatment Option for AUB-related to Uterine Fibroids

Uterine fibroids are the causes of AUB in about 25% of the women presenting the complaint of AUB or HMB. Although surgical treatment, i.e. hysterectomy remains the first choice of option in this case—treatment options are chosen depending on the fibroid size, location and symptoms.

Non-surgical Treatment

There are no specific 'non-surgical treatment' method to curb fibroids but medical management helps in giving the symptomatic relief. Tranexamic acid, mefenamic acid, LNG-IUS and GnRh are the first-line treatment options for the small sized fibroids and symptomatic relief in the HMB.[9]

Radiological Treatment Options: Uterine Artery Embolism (UAE)

UAE is a little less invasive procedure and Cochrane review concluded this as safe and effective treatment option with minimal side effects. The major drawback related to UAE was the depletion of follicular reserve which may led to menopause.[10]

Surgical Treatment

Hysterectomy: Hysterectomy is the best and final source of management for the women no longer wishing to reproduce.

Myomectomy: Myomectomy is the treatment option for the woman who wishes to preserve her uterus.

Malignant and Premalignant Disease

Endometrial Polyps

Endometrial polyps are usually treated with the degree of malignancy potential. Endometrial polyps are also common symptoms present in the conditions like endometrial cancer, endometrial hyperplasia, and cervical cancer and less commonly in vaginal or vulva cancer.

Endometrial Hyperplasia

Endometrial hyperplasia of low potential should be handled by conservative method and with timely biopsy investigations to check regression. Atypical hyperplasia is usually treated with complete hysterectomy and bilateral salpingo-oophorectomy.

CORRELATION OF SONOGRAPHIC FINDINGS AND HISTOPATHOLOGICAL FINDINGS IN THE CASES OF AUB-PERIMENOPAUSAL WOMAN

There are several case studies conducted over the years to find out the etiological factors in perimenopausal patients presenting with AUB. These studies have found that about 67% of the patient were in the age group of 40–45 years. They also found a correlation between the parity and chances of AUB in the peri-menopausal phase.[12] According to the Table 8.1, it states clearly that women with 4 and more than 4 parity status had the chance of about 44% of AUB compared to 2–3 parity status women.[12]

TABLE 8.1: Correlation between parity and percentage chances of AUB according to the age[12]

Parity	*Years*			*Total (%)*
	40–45	*>45–50*	*>50*	
0	2	1	0	3 (2.91)
1	9	1	0	10 (9.70)
2	15	2	2	19 (18.44)
3	18	6	3	27 (26.21)
≥4	26	13	5	44 (42.71)
Total (%)	70 (67.97)	23 (22.33)	10 (9.70)	103 (100)

TABLE 8.2: Study showing the causes of AUB in perimenopausal female[12]

Diagnosis	*No (%)*
Fibroid uterus	47 (45.63)
Bulky uterus	30 (29.12)
Adenomyosis	11 (10.69)
Thickened endometrium	12 (11.65)
Endometrial polyp	2 (1.94)
Malignancy	1 (0.97)

In Table 8.2, it shows the percentage of aetiological factors responsible for the AUB. It shows that highest number of cases registered were because of fibroid uterus and menorrhagia.[12]

In Table 8.3, it shows the percentage of menstrual pattern and duration leading to AUB. Menorrhagia was found to be one of the main causes for the AUB in perimenopausal women (45%).[12]

Table 8.4 shows the study of endometrial biopsy histopathology—pathological findings in different groups.[13] Cystoglandular hyperplasia was seen in 1.8% cases and out of these 0.9% belonged to 40 to 49 years age group and 0.9% belonged to 50 to 59 years age group. Proliferative phase with chronic endometritis was also seen in 1.8% cases; out of these 0.9% belonged to 40 to 49 years age group and 0.9% belonged to 50 to 59 years age group. Complex hyperplasia without atypia and simple hyperplasia with atypia was seen only in one case that is 0.9% belonging to 40 to 49 years age group. Cystic atrophy of the endometrium and luteal phase defect was also found in one case (0.9%) that belonged to the age group of 50 to 59 years. Endometrial carcinoma was also reported in one case (0.9%) belonging to the age group of 50 to 59 years.

TABLE 8.3: Study showing the causes of AUB in terms of menstrual complaint and duration[12]

Complaints	*Months*				*Total (%)*
	1–3	*>3–6*	*>6–12*	*>12*	
Menorrhagia	8	28	5	4	45 (43.69)
Polymenorrhagia	3	7	2	2	14 (13.59)
Metrorrhagia	4	10	3	2	19 (18.45)
Menometrorrhagia	4	8	2	2	16 (15.54)
Postmenopausal	4	3	2	0	9 (8.73)
Total (%)	23 (22.33)	56 (54.37)	14 (13.60)	10 (9.70)	103 (100)

TABLE 8.4: Endometrial biopsy histopathology—pathological findings in different age groups[13]

	Age group					
	40–49 years		*50–59 years*		*Total*	
	Frequency	*Percent (%)*	*Frequency*	*Percent (%)*	*Frequency*	*Percent (%)*
Simple hyperplasia without atypia	11	10	1	0.9	12	10.9
Disorder proliferative phase	2	1.8	3	2.7	5	4.5
Secretory phase with chronic endometritis	4	3.6	0	0	4	3.6
Cystoglandular hyperplasia	1	0.9	1	0.9	2	1.8
Proliferative phase with chronic endometritis	1	0.9	1	0.9	2	1.8
Complex hyperplasia without atypia	1	0.9	0	0	1	0.9
Cystic atrophy of endometrium	0	0	1	0.9	1	0.9
Luteal phase defect	0	0	1	0.9	1	0.9
Simple hyperplasia with atypia	1	0.9	0	0	1	0.9
Endometrial carcinoma	0	0	1	0.9	1	0.9
Total/110	21	19.8	9	7.2	30	27

ALGORITHM FOR THE MANAGEMENT OF AUB IN PERIMENOPAUSAL FEMALE

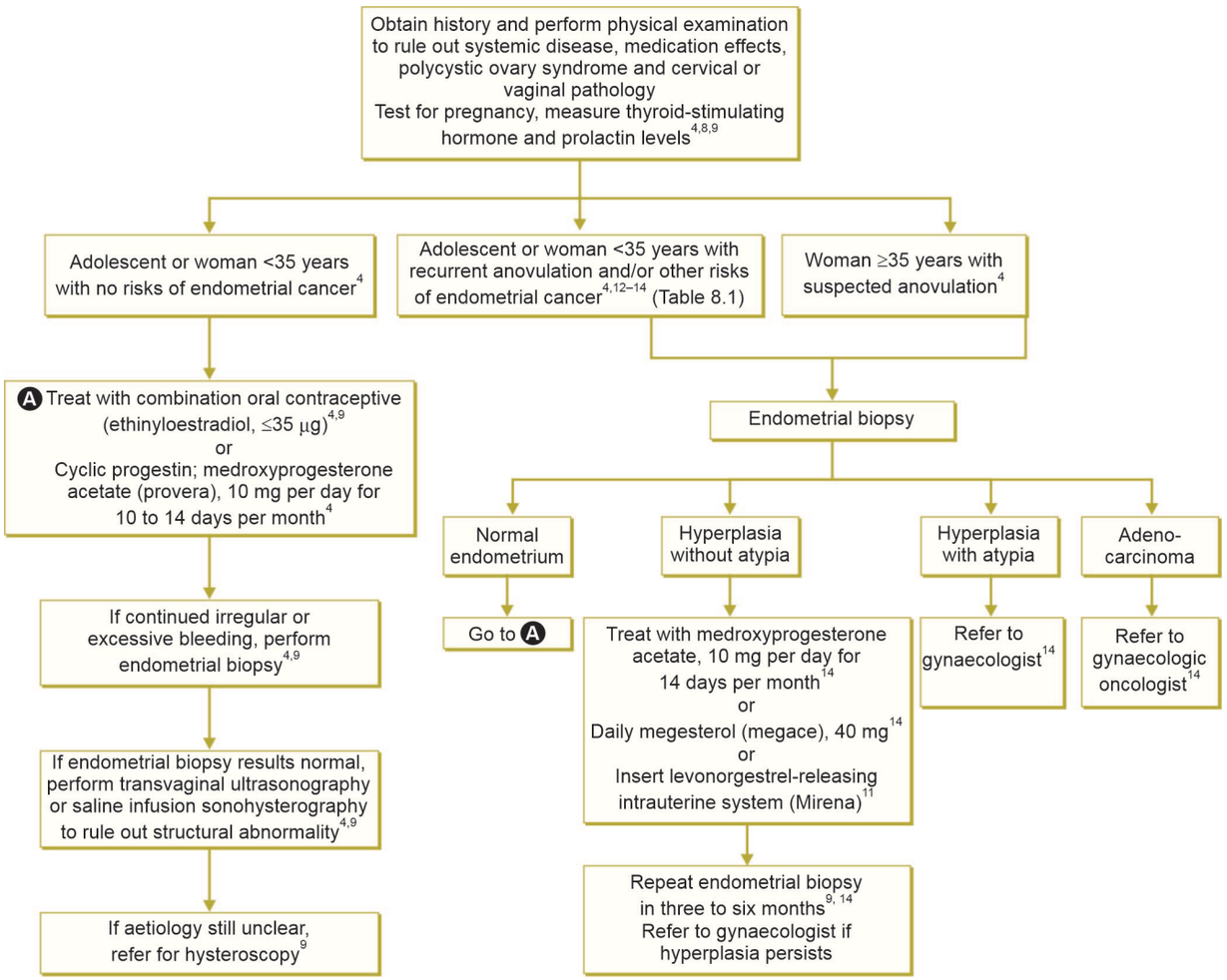

Fig. 8.4: Algorithm for the management of AUB patients[11]

Summary

- AUB is one of the most common causes (70%) detected in the gynaecological presentation in perimenopausal women.
- In perimenopausal women with AUB, TVS-USG should be the investigation of choice due to its convenience, accuracy and non-invasiveness. In patients with hyperplastic endometrium and/or endometrial thickness greater than 8 mm, a histopathological study of the endometrium is warranted to rule out atypical changes or endometrial malignancy.
- Dilatation and curettage is a diagnostic tool for patients with AUB.
- The primary indication for invasive methods like D and C should be in cases with abnormal thickness of endometrium >8 mm in order to obtain endometrial tissue to exclude precancerous lesion or endometrial cancer.
- Anaemia, and hypovolaemia can result in extreme conditions of significant blood loss.
- Endometriosis should be taken into consideration for one of the causes of AUB. This can help in removing major medical line of treatment.

- Surgery should be the last source of treatment unless we have a strong reason to do so. (Some uterine bleeding can be managed with first-line of treatment.)
- Therapeutic decisions should be taken considering patient's well-being.
- Many therapeutic modalities lead to a similar outcome, so be sure to discuss the risk, benefits and alternatives of available options.

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Chapter 9

Postmenopausal AUB

Vidya Thobbi

Menopause is defined as cessation of menstruation permanently for a period of more than one year, which is resulted from loss of ovarian activity. Postmenopausal bleeding (PMB) is defined as bleeding from the genital tract, more than 12 months after the last menstrual period in a woman not on hormone replacement (HRT).[9]

Women on continuous progesterone and oestrogen hormone therapy can expect to have irregular vaginal bleeding, especially for the first 6 months. This bleeding should cease after 1 year. Women on oestrogen and cyclical progesterone should have a regular withdrawal bleeding after stopping the progesterone.[8]

Postmenopausal bleeding (PMB) refers to any uterine bleeding in a menopausal woman (other than the expected cyclic bleeding that occurs in women taking cyclic postmenopausal hormone therapy). It accounts for approximately 5% of office gynaecology visits.[1]

All postmenopausal women with unexpected uterine bleeding should be evaluated for endometrial carcinoma since this potentially lethal disease will be the cause of bleeding in approximately 10% (range 1 to 25%, depending upon risk factors). However, the most common cause of bleeding in these women is atrophy of the vaginal mucosa or endometrium. In the early menopausal years, endometrial hyperplasia, polyps, and submucosal fibroids are also common etiologies.[1]

Incidence

Vaginal bleeding occurs in approximately 4 to 11% of postmenopausal women. The incidence of bleeding appears to correlate with time since menopause, with the likelihood of bleeding decreasing over time.[1]

Etiology

Abnormal bleeding noted in the genital area is usually attributed to an intrauterine source, but may actually arise from the cervix, vagina, vulva, or fallopian tubes, or be related to ovarian pathology. The origin of bleeding can also involve nongynaecologic sites, such as the urethra, bladder, anus/rectum/bowel, or perineum.

Causes of Postmenopausal Bleeding[6]

Cause of bleeding	*Frequency (%)*
Endometrial or cervical polyps	2–12
Endometrial hyperplasia	5–10
Endometrial cancer	10
Exogenous estrogens	15–25
Atrophic endometritis and vaginitis	60–80
Others (vaginal trauma, urethral curuncle, uterine sarcoma, cervical Ca, anticoagulants)	

Atrophy: Hypoestrogenism causes atrophy of the endometrium and vagina. In the uterus, the collapsed, atrophic endometrial surfaces contain little or no fluid to prevent intracavitary friction. This results in microerosions of the surface epithelium and a subsequent chronic inflammatory reaction (chronic endometritis), which is prone to light bleeding or spotting.

Classic vaginal findings of atrophy include a pale, dry vaginal epithelium that is smooth and shiny with loss of most rugation. If inflammation is present, additional findings may include patchy erythema, petechiae, blood vessels visible through the thinned out epithelium, friability, bleeding, and discharge.

Cancer: Approximately 6 to 19% of women with postmenopausal vaginal bleeding have endometrial cancer. The risk of endometrial cancer in the setting of postmenopausal bleeding increases with increasing

age after menopause. Age >55 years, history of recurrent bleeding episodes, and bleeding volume exceeding five pads per day were significantly associated with endometrial cancer.

Sarcomas of the uterus constitute only 3 to 5% of all uterine tumours and may present with postmenopausal bleeding. These cancers arise from the stroma of the endometrium (endometrial stromal sarcomas) or the myometrium. They may look and feel like benign leiomyomas. Endometrial histology may be normal; diagnosis requires a hysterectomy.

Fallopian tube or ovarian cancer can cause postmenopausal uterine bleeding. Cervical and vaginal cancers typically present with vaginal bleeding. Vulvar cancers are not associated with bleeding until they are advanced.

Choriocarcinoma is a rare cause of uterine bleeding in menopausal women.

Polyps: Polyps are benign endometrial growths of unknown aetiology that are a common cause of perimenopausal and early postmenopausal uterine bleeding. Growth of polyps can be stimulated by oestrogen therapy or tamoxifen.

Postmenopausal hormone therapy: Many postmenopausal women who take oestrogen therapy develop vaginal bleeding; the frequency depends upon the regimen used.

Endometrial hyperplasia: Endometrial hyperplasia may manifest clinically as uterine bleeding. Since postmenopausal women should be estrogen deficient, endometrial hyperplasia at this time is abnormal and requires an explanation. Endogenous estrogen production from ovarian or adrenal tumors or exogenous estrogen therapy are possible causes. Obese women also have high levels of endogenous estrogen due to the conversion of androstenedione to estrone and the aromatization of androgens to estradiol, both of which occur in peripheral adipose tissue.

Leiomyomata uteri: Leiomyomata uteri (fibroids) are the most common pelvic tumors in women. The prevalence in postmenopausal women is one-tenth that of premenopausal women, thus they are a potential, but uncommon, cause of uterine bleeding in menopausal women. The diagnosis of a uterine sarcoma should be considered in postmenopausal women with presumed uterine leiomyomas producing symptoms; the incidence of sarcoma is higher in this group, but is still small.

Disease in adjacent organs: Inflammation of neighbouring organs, such as diverticulitis, can occasionally cause a corresponding inflammation of the female upper genital tract. A ruptured sigmoid diverticulum may fistulize into the uterus and present as uterine bleeding, discharge, and endometritis.

Diseases of the urethra (e.g. urethritis), bladder (e.g. cancer or urinary tract infection), and bowel (e.g. inflammatory bowel disease or hemorrhoids) may cause bleeding that is mistaken for genital tract bleeding. These disorders should be considered and evaluated for in patients with bleeding in whom there is no obvious genital tract aetiology. A radiograph of the pelvis to rule out fracture should be considered when there is genital bleeding after trauma, especially in a postmenopausal woman with osteoporosis.

Post-radiation therapy: Vaginal bleeding can be a late effect of radiation therapy. Obliterative end arteritis and the vascular narrowing of aging and arteriosclerosis lead to devascularization of the radiated tissues. Tissue necrosis causes viscus perforation, tissue sloughing, and bleeding. Hemorrhagic cystitis and proctitis can lead to significant blood loss. Vaginal vault necrosis may cause uncontrolled bleeding and pain.

Anticoagulant therapy: Use of anticoagulants may cause uterine bleeding.

Herbal and dietary supplements: Soy and other phytoestrogens in large doses may be associated with stimulation of the endometrial lining.

Infection: Endometritis is an uncommon cause of postmenopausal bleeding. In the developing world, however, endometrial tuberculosis may present as postmenopausal bleeding.

DIAGNOSTIC EVALUATION

The primary goal in the diagnostic evaluation of postmenopausal women with uterine bleeding is to exclude malignancy since age is a significant risk factor for this disorder.

History and Physical Examination

Information that is important in the history includes the following:

- When did the bleeding start?
- Were there precipitating factors, such as trauma?
- What is the nature of the bleeding (temporal pattern, duration, postcoital, quantity)?

- Are there any associated symptoms such as pain, fever, or changes in bladder or bowel function?
- What is the medical history and are any medications being taken (e.g. hormones, anticoagulants)?
- Are any soy-containing herbal or dietary supplements being taken?
- Is there a family history of breast, colon, and endometrial cancer?[1]

The answers to these questions may help to direct the clinician toward one of the major categories of abnormal bleeding: Neoplasm; atrophy; medication; foreign body. Obesity (women with morbid obesity [body mass index (BMI) >30 have a high level of estrogen), diabetes mellitus, and use of tamoxifen are risk factors for endometrial cancer; vaginal dryness and soreness with dyspareunia and bleeding after intercourse suggest atrophy; and a foreign body may be the source of bleeding in a woman who uses a pessary.[1]

A general examination should be performed to look for signs of systemic illness (e.g. hepatitis, renal disease, splenomegaly).

SYSTEMIC EXAMINATION

Speculum Examination

Signs of atrophy: Pale, dry vagina sometimes with petechia (small red spots caused by submucosal bleeding). Prolapse with pressure sores, cervical carcinoma, vaginal discharge, cervicitis, endometrial polyp visible in vagina.

If possible perform a test for pre-stadia of cervical cancer like a human papillomavirus (HPV) test or a VIA; IUD thread.

PVE: Fibroids or pelvic masses? If you suspect advanced cervical carcinoma do a rectal examination. If you cannot find a plausible benign cause of postmenopausal blood loss the woman should undergo two tests: First an ultrasound to measure the thickness of the endometrium and to look for pelvic masses and secondly a test to exclude a premalignancy of the cervix (HPV or VIA).[3]

Thorough physical examination of the external and internal anatomy of the female genital tract is important. The focus of the evaluation is to determine the bleeding site; to note any suspicious lesions, lacerations, or foreign bodies; and to assess the size, contour, and tenderness of the uterus. Lower genital tract (vulva, vagina, ectocervix) causes of bleeding can usually be excluded by a normal physical examination.[1]

ENDOMETRIAL EVALUATION

Either endometrial biopsy or transvaginal ultrasound can be used as an initial test for evaluating the endometrium

TVS and Role of Colour Doppler[8]

The majority of women referred to outpatient gynaecological services have had pelvic ultrasound in order to evaluate the endometrial thickness and assess for pelvic pathology. Transvaginal ultrasound (TVUS) is considered an acceptable initial investigation in women with PMB.[2]

In this group of women, as distinct from women with an incidental finding of thickened endometrium or fluid without bleeding, an endometrial thickness of 4–5 mm typically correlates with low risk for endometrial disease. As the endometrial thickness increases to 20 mm so does the risk of endometrial cancer. It is important to remember that there is no accepted agreement on the cut-off for normal endometrial thickness and, thus, any women with risk factors and symptoms require endometrial sampling.

Transvaginal ultrasound examination is an acceptable initial test as an alternative to endometrial sampling in postmenopausal women who cannot tolerate office biopsy or in whom office endometrial sampling tissue was insufficient for diagnosis[2], and in women in whom evaluation for uterine pathology (e.g. polyp, leiomyoma) or of the adnexa is indicated. Endometrial cancer can reasonably be excluded by ultrasound in postmenopausal women with a thin (≤4 mm), homogeneous endometrium. Endometrial biopsy is required if:

- The endometrial lining is thicker than 4 mm
- The endometrium shows diffuse or focal increased echogenicity (heterogeneity)
- The endometrium is not adequately visualized on sonography
- The woman has persistent bleeding.

Persistent bleeding can be a sign of endometrial cancer even when the endometrial thickness is less than 4 to 5 mm since a thin or indistinct endometrial stripe does not reliably exclude type 2 endometrial cancer. Therefore, women with persistent bleeding should be evaluated further.

The measurement of endometrial thickness by transvaginal US is the most convenient, non-invasive method for the diagnosis of endometrial pathologies

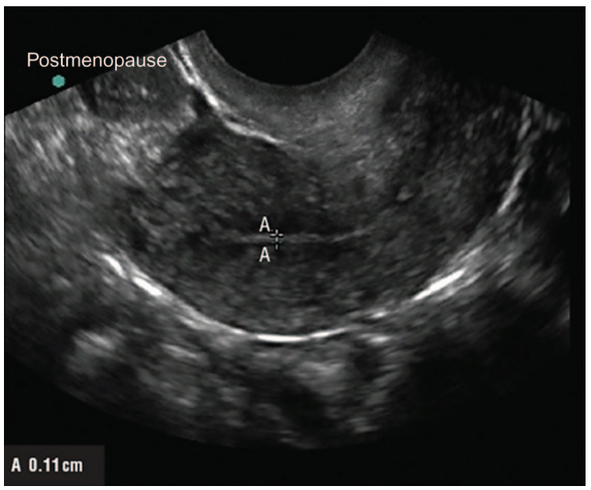

Fig. 9.1: Measurement of endometrial thickness. The endometrial thickness measures at its thickest portion as the distance between the echogenic borders (calipers) perpendicular to the midline longitudinal plane of the uterus

but it is a non-specific clinical evidence for endometrial malignancy.

Doppler analysis of uterine and myometrial arteries could be used in differentiation between benign and malignant uterine findings by significant difference in RI and PI of the uterine arteries, lower RI and PI in malignant lesions. The low RI is due to neovascularisation occurring within and around the tumour tissue distal to the point of sampling of the uterine artery.

Using the transvaginal approach, the accuracy of measurement is increased because of the small distance between the probe and the vessels under investigation and better identification of smaller vessels due to better resolution.[8]

Endometrial Biopsy

Endometrial biopsy can be done as the initial diagnostic test for women with postmenopausal bleeding due to its high sensitivity, low complication rate, and low cost. If a cause for the bleeding is determined, then further management depends upon the clinical diagnosis. However, endometrial biopsy is not a sensitive technique for diagnosing structural abnormalities, such as polyps.

An endometrial biopsy is considered the gold standard for evaluation of PMB.

Endometrial biopsy can be obtained with:

- Endometrial pipelle in the outpatient setting, or

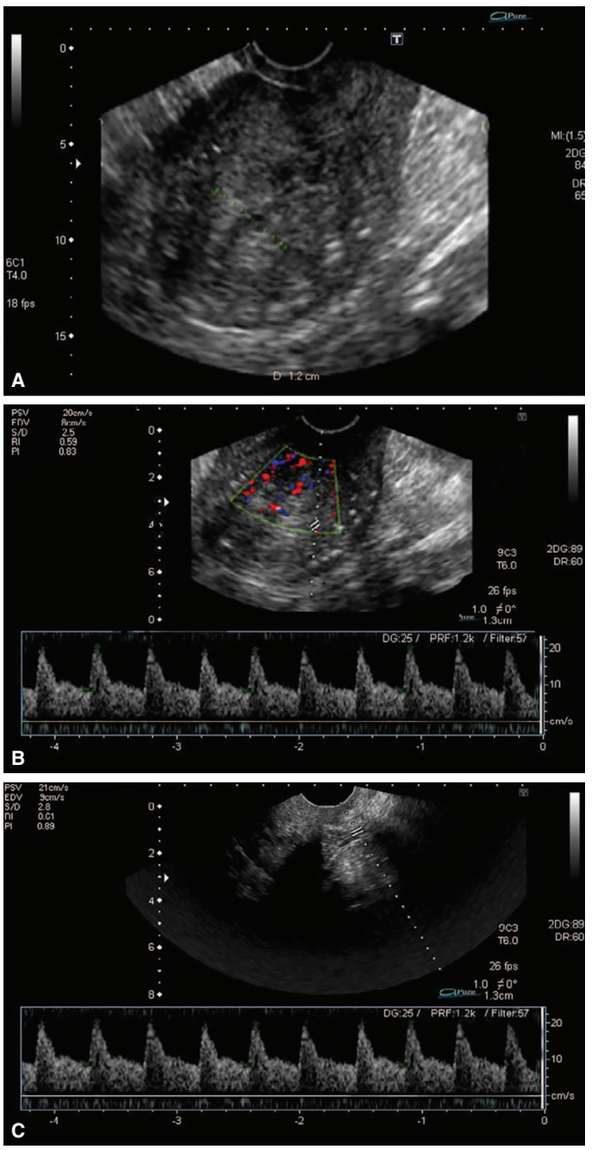

Fig. 9.2A to C: Endometrial hyperplasia with atypia: Thick and heterogeneous endometrium

- Hysteroscopy and curettage (with or without dilatation) in either the outpatient or inpatient setting.

Overall, the endometrial pipelle has been shown to adequately sample the endometrium. It is considered the more sensitive device in identifying hyperplasia or cancer compared to other sampling devices. It is important to remember pipelle sampling of the endometrium may miss pathology since less

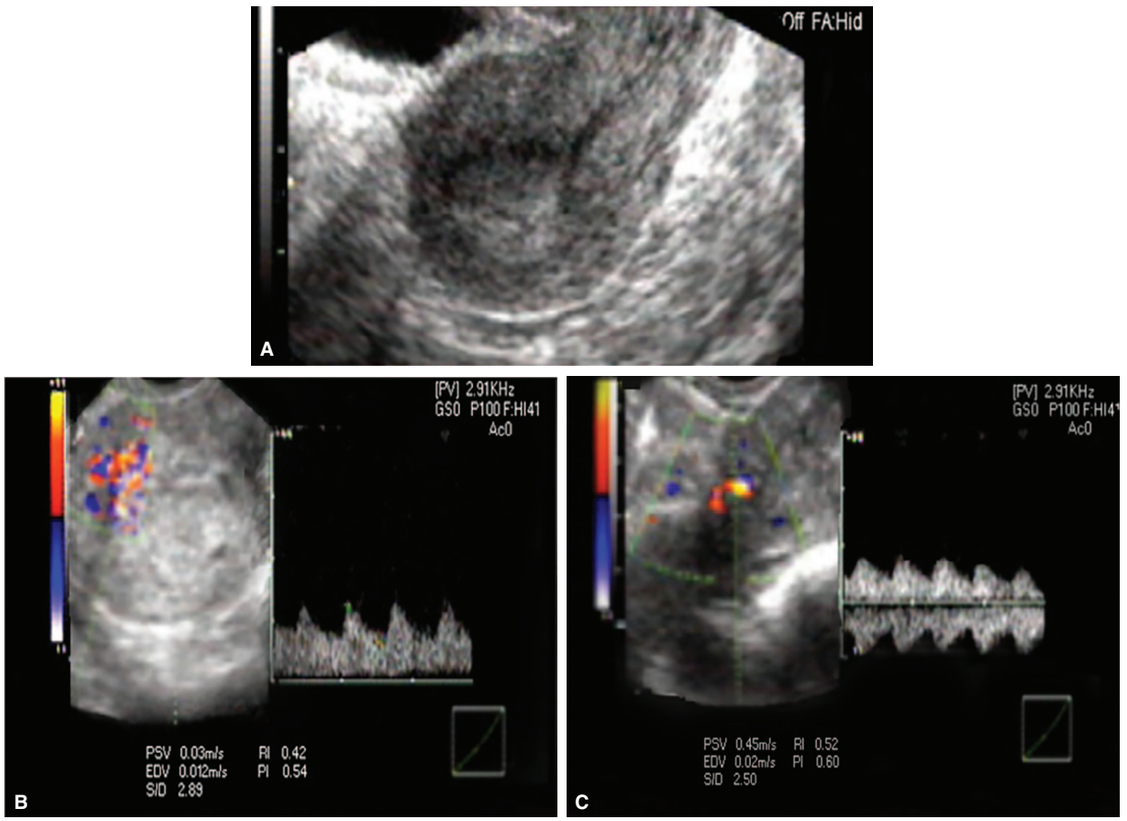

Fig. 9.3A to C: Endometrial carcinoma: Grossly thickened heterogeneous echogenic endometrium

than 50% of the endometrium is sampled, thus it is most useful when greater than 50% of the endometrium is involved with disease.

Potential complications of endometrial pipelle biopsy include uterine perforation and infection. Patients should be counselled regarding the possibility of insufficient or non-diagnostic sampling, which may necessitate further investigation.

Hysteroscopy and curettage is typically saved for cases where office sampling was insufficient or not possible owing to patient discomfort or cervical stenosis. The advantage to hysteroscopy is it provides the ability to see the entire endometrial cavity and is particularly useful in detecting and removing focal lesions such as polyps. Again, this can be performed on an outpatient basis, avoiding the complications of general anaesthesia. Complications include infection, bleeding, uterine perforation.

Endometrial sampling by suction curette device is an inexpensive, safe OPD procedure that appears to be a feasible alternative to more invasive procedures like D and C and hysteroscopy for evaluation of patients with abnormal uterine bleeding in peri- or postmenopausal patients. The endometrial sample so obtained is adequate for histology and shows well preserved architecture. However, a negative histology is no guarantee against the disease and warrants further evaluation by other modalities in patients with persistence of symptoms.

Women with recurrent PMB after an initial negative assessment should be reinvestigated because they may still have significant genital tract pathology.

Cervical cytology: The mean age of cervical cancer diagnosis is 52.2 years; the distribution of cases is bimodal, with peaks at 35 to 39 years and 60 to 64 years . All women need cervical cancer screening as part of the evaluation of abnormal bleeding, as it can be difficult to distinguish between endocervical and upper uterine bleeding. Any visible lesion needs to be biopsied, even if the cytology is normal.

Summary of Evaluation of PMB[7]

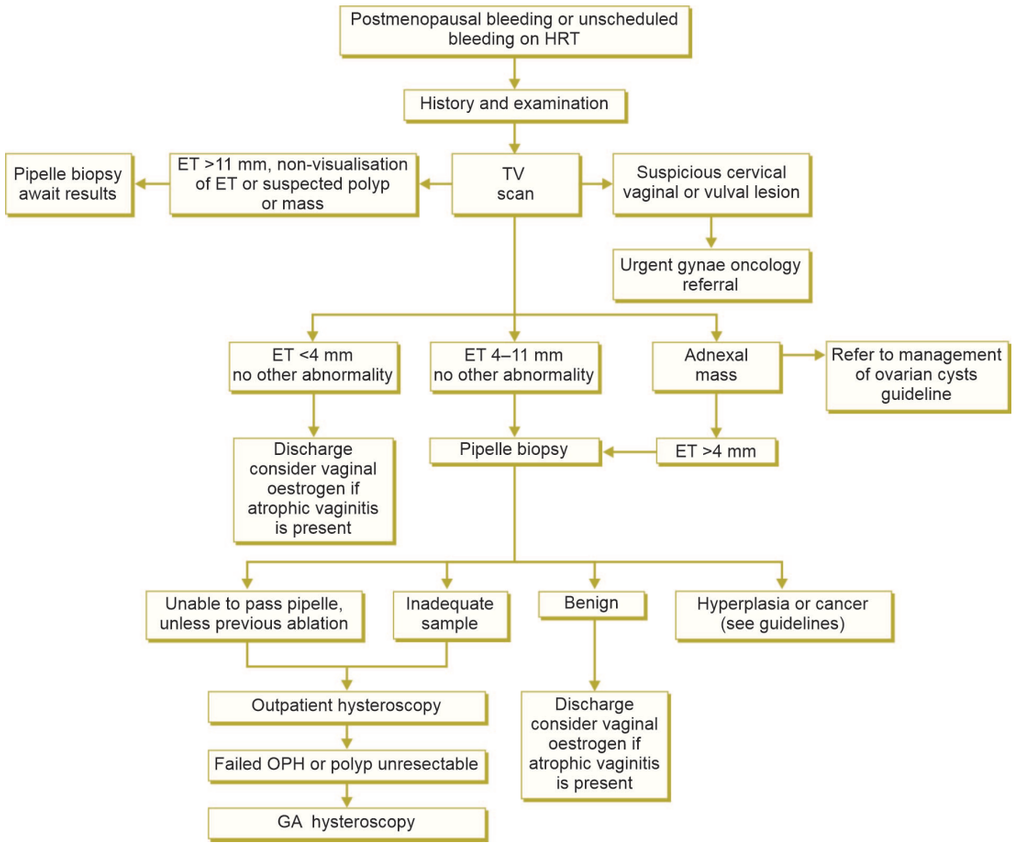

Fig. 9.4: Summary of evaluation of PMB[7]

Management

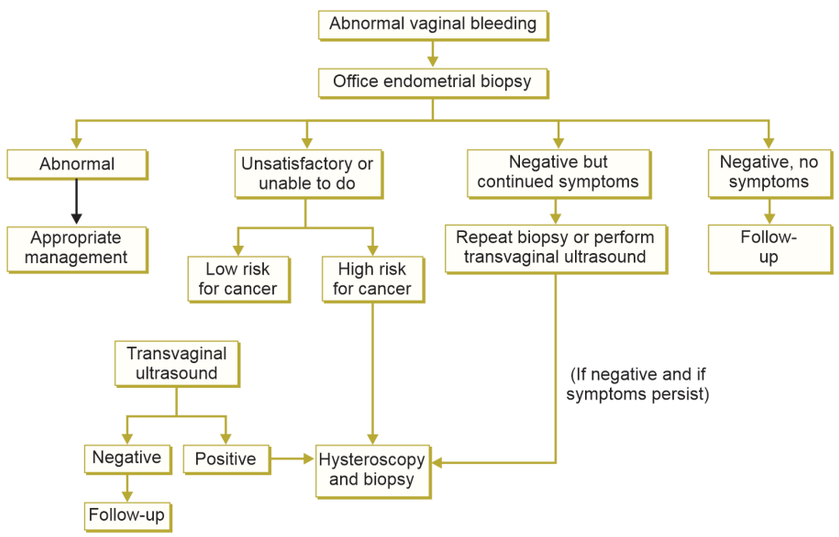

Fig. 9.5: Algorithm for the management of abnormal vaginal bleeding[8]

Summary

1. In postmenopausal women, uterine bleeding is usually light and self-limited. Exclusion of cancer is the main objective; therefore, treatment is usually unnecessary once cancer (or premalignant histology) has been excluded.
2. Further diagnostic evaluation is indicated for recurrent or persistent bleeding.
3. If a benign lesion is discovered, it can be treated, as appropriate, if symptoms are bothersome. Malignant lesions are evaluated and treated according to standard guidelines.
4. Endometrial malignancies almost always surgical with staging of disease. Hysterectomy with salpingo-oophorectomy and bilateral pelvic and para-aortic lymphadenectomy.
5. Hyperplasia with atypia needs a hysterectomy while hyperplasia without atypia can be best treated with a levonorgestrel (LNG)-IUD.
   - The LNG-IUS should be the first line medical treatment—has a higher disease regression rate, with fewer adverse effects with a more favourable bleeding profile than oral progestogens.
   - Second-best therapy is oral progestogens like medroxyprogesterone acetate (10 mg/day for 3 months). Cyclical progestogens should not be used because they are less effective in inducing regression of endometrial hyperplasia without atypia compared to continuous oral progestogens or LNG-IUS.
   - In both cases repeat the sampling of the endometrium after 3 months.
6. Polyps protruding through the cervix can be grasped with a sponge-holding forceps and you can twist them off. Endometrial polyp: Hysteroscopy-guided removal and histopathological examination of the specimen is mandatory to rule out cancerous changes. Hyperplastic polyps without atypia recur more frequently than benign ones so close and long follow-up is needed.
7. Atrophic endometritis: Systemic oestrogens can be given. The addition of progesterone is necessary.
8. Atrophy of the vagina can be treated with non-hormonal vaginal lubricants and moisturizers (first line), if no response to treatment, topical estrogen cream, for example estriol cream 2–3 times a week can be used. Should be continued as long as distressful symptoms remain. Progestogens are not indicated when low dose estrogen is administered for short period of time.
9. Cancer cervix usually treated with surgery along with surgical staging of the disease followed by radio- and chemotherapy.

PRACTICAL TIPS: THINGS TO KNOW ABOUT POSTMENOPAUSAL BLEEDING

1. Postmenopausal bleeding is never normal whether its light spotting or heavier flow.
2. There are several potential causes, but some are more serious than others.
3. Women are significantly more likely to have bleeding in the first year of menopause compared to later on.
4. The diagnostic process may involve multiple steps. A thorough evaluation in a case of postmenopausal bleeding is mandatory.

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Chapter 10

Acute AUB

Niraj Jadav, Kirtan M Vyas

Abnormal uterine bleeding may be acute or chronic. Although AUB is one of the commonest conditions, in most cases of AUB no apparent pathology is found. The bleeding is abnormal in frequency, duration, volume and regularity. Most cases of AUB are of chronic variety but Acute AUB is a severe variety of AUB that requires immediate intervention by the clinician to prevent any further bleeding for well-being of the patient.[1]

Types

Acute AUB may be spontaneous variety in which no prior episodes of AUB is present or it may be acute on chronic variety when AUB is present albeit in milder form for last 6 months or so. Thorough examination is required in patients with acute AUB to determine severity of hemorrhage, probable aetiology and accurate treatment for the patient. First important thing a clinician needs to evaluate for the acuteness and severity of hemorrhage is to watch for sign of hypovolemia and shock.[2]

Etiopathogenesis

Acute AUB, similar to chronic AUB can be multifactorial. As suggested by the menstrual disorders working group of the International Federation of Gynecology and Obstetrics and supported by ACOG—the causes can be broadly divided into AUB with uterine structural abnormalities and AUB without uterine structural abnormalities. This classification is popularly known as PALM-COEIN.[3]

Whatever the reason for acute AUB, proper history taking is very important to know the details of haemorrhagic episode, related symptoms, past medical/gynaecological history, any radiological or laboratory reports. It has been found that in almost 20% of women with acute AUB some form of coagulopathy is present.[5, 6]

Box 10.1: Clinical screening for an underlying disorder of haemostasis in the patient with excessive menstrual bleeding

Initial screening for an underlying disorder of haemostasis in patients with excessive menstrual bleeding should be structured by the medical history. A positive screening result comprises the following circumstances:

- Heavy menstrual bleeding since menarche
- One of the following conditions:
  - Postpartum haemorrhage
  - Surgery-related bleeding
  - Bleeding associated with dental work
- Two or more of the following conditions:
  - Bruising, one to two times per month
  - Epistaxis, one to two times per month
  - Frequent gum bleeding
  - Family history of bleeding symptoms

History and Examination

The clinician should obtain a detailed history from a patient who presented with complaints related to menstruation. Specific aspects of the history include:

- Menstrual history
  - Age at menarche
  - Last menstrual period
  - Menses frequency, regularity, duration, volume of flow
    - Frequency can be described as frequent (less than 24 days), normal (24 to 38 days), or infrequent (greater than 38 days)
    - Regularity can be described as absent, regular (with a variation of +/− 2 to 20 days), or irregular (variation greater than 20 days)
    - Duration can be described as prolonged (greater than 8 days), normal (approximately 4 to 8 days), or shortened (less than 4 days)

        - Volume of flow can be described as heavy (greater than 80 ml), normal (5 to 80 ml), or light (less than 5 ml of blood loss)
            - Exact volume measurements are difficult to determine outside research settings; therefore, detailed questions regarding frequency of sanitary product changes during each day, passage and size of any clots, need to change sanitary products during the night, and a "flooding" sensation are important[6]
    - Intermenstrual and postcoital bleeding
- Sexual and reproductive history
    - Obstetrical history including the number of pregnancies and mode of delivery
    - Fertility desire and subfertility
    - Current contraception
    - History of sexually transmitted infections (STIs)
    - Pap smear history
- Associated symptoms/systemic symptoms
    - Weight loss
    - Pain
    - Discharge
    - Bowel or bladder symptoms
    - Signs/symptoms of anaemia
    - Signs/symptoms or history of a bleeding disorder
    - Signs/symptoms or history of endocrine disorders
- Current medications
- Family history including questions concerning coagulopathies, malignancy, endocrine disorders
- Social history including tobacco, alcohol, and drug uses; occupation; impact of symptoms on quality of life
- Surgical history

The physical examination should include:

- Vital signs, including blood pressure and body mass index (BMI)
- Signs of pallor, such as skin or mucosal pallor
- Signs of endocrine disorders
    - Examination of the thyroid for enlargement or tenderness
    - Excessive or abnormal hair growth patterns, clitoromegaly, acne that could indicate hyperandrogenism
    - Moon facies, abnormal fat distribution, striae that could indicate Cushing's disease
- Signs of coagulopathies such as bruising or petechiae
- Abdominal examination to palpate for any pelvic or abdominal masses
- Pelvic examination: Speculum and bimanual
    - Pap smear if indicated
    - STI screening (such as for gonorrhoea and Chlamydia) and wet prep if indicated
    - Endometrial biopsy if indicated[5]

Investigations

Basic and specific laboratory investigations are required for further management of these patients. Endometrial sampling should be offered in a group of patients once haemorrhagic stability is attained. Pelvic USG is the gold standard for determining exact anatomical aspects of uterus and adnexae.

- Complete blood count
- Blood type and crossmatch
- Pregnancy test
- Partial thromboplastin time
- Prothrombin time
- Activated partial thromboplastin time
- Fibrinogen
- von Willebrand factor antigen
- Ristocetin cofactor assay
- Factor VIII
- Thyroid-stimulating hormone
- Serum iron, total iron binding capacity, and ferritin
- Liver function tests
- *Chlamydia trachomatis*

Treatment

Treatment of acute AUB depends upon haemodynamic stability of the patient, underlying cause, possible medical condition and future fertility perspective. The primary objective of treatment is to control ongoing haemorrhage and to regulate future menstrual cycles bleeding. Treatment is divided into medical and surgical.[7, 8.]

Haemodynamically unstable patients with uncontrolled bleeding and signs of significant blood loss should have aggressive resuscitation with saline and blood as with other types of haemorrhagic shock.

- Evaluate ABCs and address the priorities
- Initiate 2 large-bore intravenous lines (IVs), oxygen, and cardiac monitor

TABLE 10.1: Medical treatment regimens

Drug	*Source*	*Suggested dose*	*Dose schedule*	*Potential contraindications and precautions according to FDA labeling*[*]
Conjugated equine oestrogen	DeVore GR, Owens O, Kase N. Use of intravenous Premarin in the treatment of dysfunctional uterine bleeding—a double-blind randomized control study. Obstet Gynaecol 1982;59:285–91	25 mg IV	Every 4–6 hours for 24 hours	Contraindications include, but are not limited, to breast cancer, active or past venous thrombosis or arterial thromboembolic disease, and liver dysfunction or disease. The agent sould be used with caution in patients with cardiovascular or thromboembolic risk factors
Combined oral contraceptives[†]	Munro MG, Mainor N, Basu R, Brisinger M, Barreda L. Oral medroxyprogesterone acetate and combination oral contraceptives for acute uterine bleeding: A randomized controlled trial. Obstet Gynaecol 2006; 108–9	Monophasic combined oral contraceptive that contains 35 µg of ethinyl-oestradiol	Three times per day for 7 days	Contraindications include, but are not limited to, cigarette smoking (in women aged 35 years or older), hypertension, history of deep vein thrombosis or pulmonary embolism, known thromboembolic disorders, cerebrovascular disease, ischaemic heart disease, migraine with aura, current or past breast cancer, severe liver disease, diabetes with vascular involvement, valvular heart disease with complications, and major surgery with prolonged immobilization
Medroxyprogesterone acetate[‡]	Munro MG, Mainor N, Basu R, Brisinger M, Barreda L. Oral medroxyprogesterone acetate and combination oral contaceptives for acute uterine bleeding: A randomized controlled trial. Obstet Gynaecol 2006; 108:924–9	20 mg orally	Three times per day for 7 days	Contraindications include, but are not limited to, active or past deep vein thrombosis or pulmonary embolism, active or recent arterial thromboembolic disease, current or past breast cancer, and impaired liver function or liver disease
Tranexamic acid	James AH, Kouides PA, Abdul-Kadir R, Dietrich JE, Edlund M, Federici AB, et al. Evaluation and management of acute menorrhagia in women with and without underlying bleeding disorder: Consensus from an international expert panel. Eur J Obstet Gynaecol Reprod Biol 2011; 158:124–34.	1.3 g orally or 10 mg/kg IV (maximum 600 mg/dose)	Three times per day for 5 days (every 8 hours)	Contraindications include, but are not limited to, acquired impaired color vision and current thrombotic or thromboembolic disease. The agent should be used with caution in patients with a history of thrombosis risks), and concomitant administration of combined oral contraceptives needs to be carefully considered

Abbreviations: FDA indicates US Food and Drug Administration; IV, intravenously.

*The US Food and Drug Administration's labelling contains exhaustive lists of contraindications for each of these therapies. In treating women with acute abnormal uterine bleeding, physicians often must weigh the relative risks of treatment against the risk of continued bleeding in the context of the patient's medical history and risk factors. These decisions must be made on a case-by-case basis by the treating clinician.

[†]Other combined oral contraceptive formulations, dosages, and schedules also may be effective.

[†]Other progestins (such as norethindrone acetate), dosages and schedules also may be effective.

[‡]Other dosages and schedules also may be effective.

- If bleeding is profuse and the patient is unresponsive to initial fluid management, consider administration of IV conjugated oestrogen (Premarin) 25 mg IV every 4–6 hours until the bleeding stops.
- In women with severe, persistent uterine bleeding, an immediate dilation and curettage (D and C) procedure may be necessary.

Medical Treatment

This forms mainstay of treatment for acute AUB. Although choice of treatment is limited but IV conjugated equine oestrogen has found to be promising in study by US FDA. Conjugated equine oestrogen (CEE) is administered in dose of 25 mg IV every 6 hourly for 24 hours.[9, 10] This can be continued till 48 to 72 hours or till bleeding stops. It creates unopposed oestrogen environment in body and immediately arrests the bleeding. The efficacy of CEE in stopping the bleeding within first 8 hours is almost 72% compared to 38% in placebo. CEE is almost always combined with COC pills as the first line of treatment.[11] COC pills should be started in aggressive dose of 3 times a day for 7 days. The efficacy of COC pills has found to be 76% in controlling bleeding within 3 days of starting treatment. Medical eligibility criteria for COC pills should be reviewed before commencing this treatment. Antifibrinolytic agents like tranexamic acid and ethamsylate are extremely useful in controlling acute episode of bleeding. Although they are mainly used for post-partum haemorrhage or intra-operative haemorrhage, efficacy in acute AUB is 35 to 55%. [12.] Tranexamic acid can be started intravenous 1.5 gm per day in divided doses and patient can be switched over to oral therapy once acute episode is over. In resistant cases of acute AUB, 26F Foley's catheter may be used as an intrauterine temponade effectively. While using estrogen as the primary line of treatment certain contraindications should be kept in mind including possibility of breast and endometrial cancer, smoking, hypertension, migraine, cardiac disease, VTE to name a few.

Once the acute episode of bleeding is over, evaluation for detailed case history and treatment should be started as per individual causes. Most of these patients will require long-term use of COC pills in maintenance doses. Medroxyprogesterone acetate (MPA) 20 mg 12 hourly is advocated for at least 3 to 6 months.[13] Another alternative is DMPA injection intramuscular every 3 months.[14, 15] Dydrogesterone has a molecular structure similar to natural progesterone. The effect of 10 mg of dydrogesterone is comparable to the effect of 10 mg of medroxyprogesterone acetate. A study evaluated its use in women with excessive bleeding by comparing the use of 20 mg of oral dydrogesterone from the 15th day of the menstrual cycle for 10 days with the use of a 90 mg dose of vaginal micronized progesterone from days 17 to 27 of the menstrual cycle. It showed both treatments were similar in reducing the menstrual flow and regarding the presence of secretary endometrium at the end of the treatment. Satisfaction with the treatment and the presence of regular cycles after three months were also similar between the groups.[16] Haematologist opinion is sought for when patient is found to have any coagulation disorders. Patient with von Willebrand disease are started with desmopressin and recombinant factor 8 and von Willebrand factor are added in severe or resistant disease.

Surgical Treatment

The options of surgical management are dilatation and curettage (D and C), endometrial ablation, uterine artery embolism and hysterectomy. Patient's desire for future fertility plays an important role in deciding surgical line of treatment. D and C is one of the most popular and traditional methods used as diagnostic as well as therapeutic purpose. But that should be combined with hysteroscopy ideally to evaluate uterine cavity completely and to obtain endometrial tissue sampling from targeted areas.[17] LNG–IUS is very effective in patients with no uterine structural abnormalities. It releases fixed amount of progesterone to control subsequent cycles.[18] UAE, uterine ablation are treatment options in patients with no desire for future fertility while hysterectomy should be reserved in patients when all other treatments fail.[19, 20] In the presence of endometrial lesions such as endometrial polyps and submucosal leiomyomas, surgical treatment may be indicated.[21] The only definitive treatment for adenomyosis is hysterectomy, but the control of symptoms by medical drug treatment is not rare.[22, 23]

Summary of Management

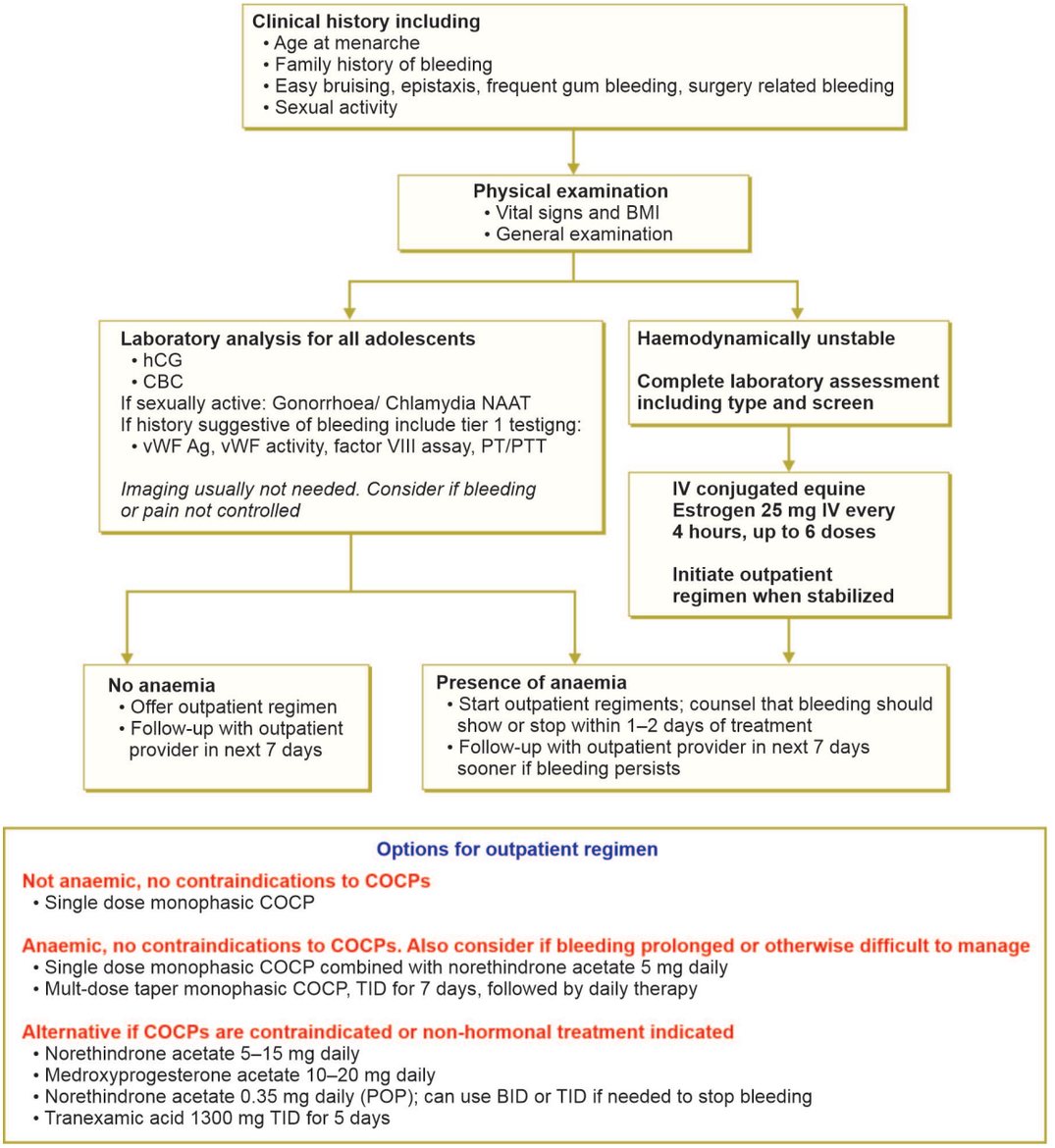

Fig. 10.1

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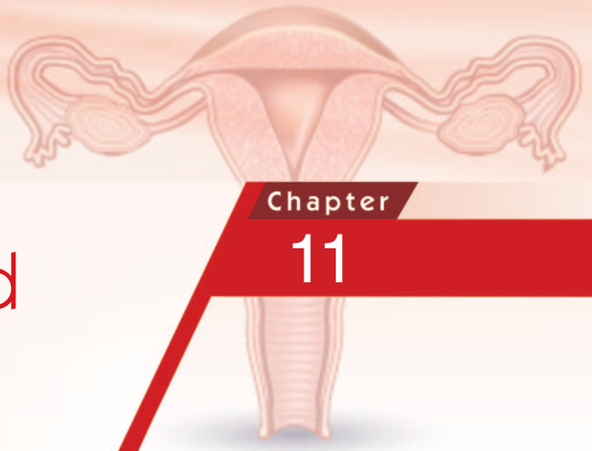

Chapter 11

AUB in Coagulopathy and Bleeding Dyscrasias

Shobha N Gudi

Abnormal uterine bleeding is a common problem in reproductive-age women. According to the PALM-COEIN classification AUB C is a condition of abnormal uterine bleeding due to disorders of haemostasis. AUB C,[1] is seen in about 5 to 10% of women with AUB.

Causes

1. **Thrombocytopenia:** Inherited/acquired causes, example, ITP (idiopathic thrombocytopenic purpura),[2] drug-induced, e.g. NSAID
2. Disorders of coagulation like von Willebrand disease, platelet function defects
3. Blood dyscrasias: Acute leukaemia
4. Women on anticoagulation or other medication, aspirin, NSAID, herbal preparations that could cause vitamin K deficiency
5. Women on chemotherapy
6. **Acquired von Willebrand syndrome:** Secondary to severe liver or renal disease, connective tissue disorders, hypothyroidism.

Clinical History

It is important to rule out other causes like fibroids, adenomyosis, polyps, endometrial hyperplasia and carcinoma. Identifying patients with AUB C starts with a structured history for risk factors for coagulation disorders.[3] Confirmation requires laboratory testing. The sites and character of bleeding help distinguish disorders of primary haemostasis (platelet function) from secondary haemostasis (coagulation factor function). Platelet and vascular disorders are generally characterized by mucosal bleeding, e.g. epistaxis, **petechiae, telangiectasias, bruises.** Coagulation factor disorders cause bleeding into muscles and joints.

1. **Menstrual history:** Heavy bleeding in periods since menarche and anaemia.
2. Endometriosis and haemorrhagic ovarian cysts may be seen in women with von Willebrand disease (vWD).[11]
3. **Post-partum or post-abortion haemorrhage:** In vWD, post-partum bleeding (24 to 28 hours after delivery) is more common than bleeding during pregnancy and labour as higher oestrogen levels/ pro-coagulatory changes increase vWF production.
4. Increased bleeding, diffuse oozing following surgery, trauma, dental treatment.
5. History of poor wound healing.
6. **Splenomegaly:** Indicates liver disease, lymphoma, or a myeloproliferative neoplasm. Related findings include jaundice, spider angiomata.

Family History

Severe bleeding requiring medical interventions (surgery, transfusions) may indicate hereditary condition.

von Willebrand disease (VWD)[4] is the most common inherited bleeding disorder, with low vWF levels in approximately 1% of the general population. It is autosomally inherited, only 1% of affected individuals will manifest with bleeding disorder of variable severity.

Acquired von Willebrand syndrome (avWS) may be due to reduced production, sequestration, or increased destruction of vWF.

Investigations

1. Directed to excluding other causes of AUB (AUB O, AUB L, AUB E, AUB M, etc.): This includes imaging, endometrial biopsy, etc.
2. Laboratory tests for precise diagnosis of a bleeding disorder, the extent and sequence of testing are tailored to the likely cause.

Initial tests: CBC complete blood count, that includes platelet count and morphology.

Tests for primary haemostasis (platelet and vascular function defects): When menorrhagia is associated with mucocutaneous bleeding.

1. **Testing for platelet function defects:** To assess platelet number/platelet function, or both. These tests are poorly standardized and not reproducible. For drug-induced cause, change or discontinue the drug and in case of uraemia, myeloproliferative disorder, cardiopulmonary bypass, treat the underlying disorder and re-evaluate.
   - **Platelet aggregation studies**
   - **Bleeding time (BT):** Not sensitive and is operator-dependent. It is prolonged in vWD, thrombocytopenia, and disorders of vascular contractility.
   - **PFA-100:** The platelet function analyzer (PFA-100) measures the time it takes for blood flow to stop under shear stress in a capillary tube containing a membrane impregnated with collagen Col/Epi or Col/ADP.
   - **Genetic testing:** For known platelet function disorders.
2. Testing fibrinolytic defects with a suspected bleeding disorder who has a normal PT, aPTT, and platelet count.

Tests for Secondary Haemostasis

1. Prothrombin time (PT) to test the extrinsic pathway.
2. Activated partial thromboplastin time (aPTT) to test the intrinsic pathway.
3. **The international normalized ratio (INR):** This is used to monitor therapy with warfarin or other vitamin K-dependent antagonists.
4. **Thrombin time and reptilase time:** They measure the final step in the clotting cascade (cleavage of fibrinogen to fibrin).

PT and aPTT both prolonged—suggest a deficiency/inhibitor in a common pathway factor (e.g. factor X, V, II [prothrombin], or fibrinogen).

The situations are: Iatrogenic with high doses of warfarin/heparin, acquired factor inhibitor of factors X, V, II, or fibrinogen as seen in pregnancy, malignancy, or connective tissue disorder, amyloidosis.

PT prolonged (aPTT normal)—suggests a deficiency or inhibitor in the extrinsic pathway (e.g. factor VII) or early phase of DIC, vitamin K deficiency, warfarin use, or liver disease, because factor VII has the shortest half-life.

aPTT prolonged (PT normal)—suggests a deficiency or inhibitor in the intrinsic pathway (e.g. factors VIII, IX, or XI).

Positive bleeding history and normal initial testing (PT, aPTT, platelet count): The classic example is von Willebrand disease (vWD).[5] aPTT is prolonged only if the factor VIII level is significantly reduced.

Thrombocytopenia—due to increased binding between vWF and platelets that causes increased platelet clearance, may worsen with desmopressin (DDAVP), so caution is necessary.

vWD screening tests[6]**—**three screening tests are recommended by the national heart, lung, and blood institute (NHLBI).

- vWF antigen (vWF Ag)
- vWF activity (ristocetin cofactor) functional assays
- Factor VIII activity

These tests are performed on plasma as baseline tests. They are acute phase reactants increase during exercise, stress, infections and with estrogen exposure (e.g. COC, HRT, pregnancy).

Diagnosis of vWD: The diagnosis of vWD is clinical and laboratory

- **vWF <30%, positive personal or family history:** Confirmed
- **vWF 30 to 50%, positive personal or family history—**should have repeat testing with baseline samples.

In AUB C referral to haematologist is needed in following situations

- Abnormal initial testing that persists upon retesting, especially with family history
- Test results consistent with a specific haematologic disorder (e.g. von Willebrand disease [vWD], immune thrombocytopenia [ITP])
- Concern about a bleeding disorder and upcoming surgery.

Management of AUB C: It is centered around effective medication to manage an acute phase of menorrhagia, managing underlying cause and maintenance therapy to prevent relapse.

Managing HMB due to **von Willebrand's disease**.

1. **Antifibrinolytic tranexamic acid:** To stabilize the clot, useful in areas of high fibrinolytic activity such as uterine endometrium. It is effective alone or with hormonal therapy. Dosage is 25 mg/kg per dose orally every 6 to 8 hours or 10 mg/kg intravenously 3 times per day up to 5 days.
2. **Hormonal therapy:** This is described in detail in section on management of AUB related to chemotherapy.
3. **Desmopressin (DDAVP):** Helps more often in mild to moderate cases of bleeding. It can be given for three to five days and acts by release of endogenous vWF from storage sites in endothelial cells. It can be started at onset of menses.

   Intravenous: 0.3 µg/kg (maximum dose, 20 µg) in 50 ml saline over 20 minutes or nasal spray: 150 to 300 µg (1 spray in each nostril). Close monitoring is needed to pick up tachyphylaxis and hyponatraemia.
4. In refractory cases, vWF concentrates, IVIG, recombinant activated factor VII (rFVIIa) may be added.

Monitoring the therapy: The clinical status, vWF activity, factor VIII activity, and CBC with platelet count at least once per day during treatment.

Blood component therapy: Needed in addition to drugs in certain situations of AUB C:

- **Platelet transfusions** preferably single donor units are used in women with severe active menorrhagia to raise the platelet count to 50,000/µl and in impaired platelet function.
- **Vitamin K** injections.

Fibrinogen concentrate (or cryoprecipitate) to maintain the fibrinogen level above 100 mg/dl.

AUB C following chemotherapy: Due to thrombocytopenia or DIC (e.g. acute promyelocytic leukaemia).[8]

Primary prevention of menorrhagia in women scheduled for chemotherapy: Injection leuprolide acetate, a GnRH agonist, one-month earlier to expected thrombocytopenia,[9] will induce amenorrhoea prior to the start of chemotherapy. In the first two weeks breakthrough bleeding will happen and is to be managed with counselling and blood product administrations if severe.

Management of menorrhagia during chemotherapy: Women with moderate to severe menorrhagia need to be administered with blood products. Non-hormonal and hormonal therapy, and inducing amenorrhoea in those at risk of future chemotherapy-induced thrombocytopenia. Evidence is based on only small observational studies.

Non-hormonal medications: These drugs are contraindicated in patients with a history of venous thrombosis, tranexamic acid as described above.

Hormone therapy

1. High dose oestrogen, oestrogen–progestin preparation, high-dose progestins.[8,9]
2. For recurrent menorrhagia: A GnRH agonist is a good option.
3. **High-dose oestrogen:** Women who have been bleeding heavily for a prolonged period of time (≥2 weeks) have an atrophic, denuded endometrial lining. Estrogen promotes rapid regrowth of endometrium over the denuded epithelial surface, stabilizes lysosomal membranes, and stimulates proliferation of ground substance. The adverse effect of nausea and vomiting adds to side effect of chemotherapy. An antiemetic is often required (e.g. promethazine 12.5 to 25 mg per rectum, as needed).

Options for oestrogen therapy include:

- Conjugated oestrogen (e.g. premarin) 1.25 mg orally two or three times per day, OR
- Oestradiol 2 mg orally two or three times per day, OR
- Conjugated oestrogen 25 mg intravenously every six hours for 24 hours

Preferably only 24 hours for the IV therapy, to follow with oestrogen–progestin contraceptive pills.

High-dose oestrogen–progestin: Oral contraceptive pills (OC) at high doses, taken two to four times per day with an antiemetic medication will control severe bleeding in 48 hours. This regimen is less effective than oestrogen, better in terms of convenience and compliance.[10]

Contraindications

For high-dose oestrogen–progestin regimens

- Smokers
- Previous thromboembolic event or stroke
- Known inherited thrombophilia

- History of an oestrogen-dependent tumour
- Ischaemic heart disease
- Active liver disease
- Known hyperlipidemias
- Poorly controlled hypertension
- Migraine headaches with aura
- Diabetes mellitus with vascular disease.

High-dose progestin: Progestin-only regimens are less successful than oestrogen–progestin regimens, useful when oestrogen is contraindicated, progestin-only options include any one of the following for 5 to 10 days.

Norethisterone acetate: 5 to 10 mg twice or thrice a day.

Medroxyprogesterone acetate (20 to 40 mg per day in divided doses).

After the bleeding stops, lower dose progestin therapy continued.

Levonorgestrel intrauterine device: The LNG 52/5 is a highly effective well evaluated and easy to use treatment option for AUB C. It may be used as a first-line option for treatment of HMB in women who do not desire pregnancy. 71 to 95% of women using the LNG 52/5 respond, the efficacy is higher than other medical treatments and comparable to that of endometrial ablation. Local uterine pathologies like fibroid, adenomyosis will make it less effective and patient selection is important. It is a good option for maintenance therapy once the acute bleeding phase is controlled. When used for contraception, the LNG 52/5 is replaced every five years, when LNG 52/5 is used to treat HMB, more frequent replacement is needed.

Endometrial ablation: In rare cases, endometrial ablation can be performed if all other methods of haemostasis have failed and other pathologies including malignancy is excluded. It is minimally invasive and successful ablation avoids chronic use of medications. Endometrial ablation is the surgical destruction of the uterine lining. This can be accomplished under hysteroscopic visualization, using rollerball ablation.[11] It can also be performed with a non-resectoscopic ablation device, which is inserted into the uterine cavity and delivers energy to uniformly destroy the uterine lining, e.g. balloon endometrial ablation, radiofrequency method, microwave and cryoablation.[12] Endometrial resection is contraindicated in AUB C.

Women who have completed childbearing are suitable for this method since fertility cannot be guaranteed after the procedure. However, unintended pregnancies are possible after ablation and effective contraception should be in place.

Contraindications

- Complex or atypical endometrial hyperplasia or cancer
- Desire to preserve fertility
- Active pelvic infection
- Previous uterine surgery
- Uterine cavity length that is greater than 10 to 12 cm

Antibiotic prophylaxis is necessary. Cefazolin in the non-leukopenic patient, and the combination of ampicillin, gentamicin, and clindamycin is a reasonable option in leukopenic patients.

Uterine curettage after antibiotic prophylaxis and prior to ablation improves the success and ensures histopathologic evaluation.

Anaesthesia: Resectoscopic ablation is usually performed with regional or general anaesthesia. Non-resectoscopic endometrial ablation can be performed using local, regional, or general anaesthesia.

Complications

Uterine perforation, haemorrhage, haematometra, fluid overload: Very rare about 0.5 to 2%.

Results: 70 to 80% success rate, the training required for resectoscopic method is higher, however, the cost of procedure is lower than the non-resectoscopic method.

Summary and Key Points

1. AUB C (coagulopathy) is rare and challenging and the relief from HMB mainly depends on the control of underlying disease, mainly coagulation disorders and chemotherapy induced bleeding through multidisciplinary approach.
2. Adequate evaluation of these conditions through appropriate tests is important to achieve good results for therapy.
3. The other causes of AUB P, A, L, M, O, E, L should be ruled out as additional causes.
4. Correction of factor deficiencies, component replacements, hormonal and hemostatic management of

the acute bleeding phase is followed by maintenance therapy to prevent recurrence.

5. A suitable alternative to long-term oral oestrogen–progestin or only progestin hormone intake is insertion of LNG–IUS into the uterine cavity, this method is finding higher acceptance in women suffering from these severe conditions.[13]

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Chapter 12

AUB in Endocrine Disorders

Parikshit Tank, Kausha Shah

Introduction

The phenomenon of heavy and/or irregular bleeding has been described by various terminologies over the years. Abnormal uterine bleeding is one of them. Typically, it has been used to describe abnormal uterine bleeding in the absence of a tumor, infection or pregnancy.[1] There have been many aetiological classifications of the problem. The FIGO has given a two-system method for the classification of this disorder.[2] FIGO AUB System 1 deals with the nomenclature and FIGO AUB System 2 covers the classification of causes. As per the revised FIGO AUB System 1, amenorrhoea and irregular periods are also included as AUB. FIGO AUB System 2 is also commonly called the PALM-COEIN classification. The letter "O" in this classification stands for "ovulatory dysfunction" and this is the basis of endocrine factors causing AUB.

Mechanism of Endocrine Factors Causing AUB

The mechanism of endocrine factors causing AUB is through ovulatory dysfunction. This has been termed AUB-O in the PALM-COEIN classification. This results in changes in altered endometrial behaviour and consequent AUB. The changes in the endometrium are usually related to hyperplasia and hypertrophy which occur due to excess and/or unopposed oestrogen stimulation of the endometrium. However, irregular shedding, atrophy and malignant change may also present as AUB from the underlying ovulatory dysfunction. Therefore, there is a possibility of an overlap between the AUB from endometrial causes and those from ovulatory dysfunction.

There are a number of sources of endocrine ovulatory dysfunction which may originate from the ovary or outside. These are classified in Table 12.1.

TABLE 12.1: Common endocrine disorders leading to AUB-O

Ovarian	*Extra-ovarian*
Polycystic ovarian syndrome (PCOS)	Thyroid dysfunction (hypothyroidism)
Low ovarian reserve or premature ovarian failure	Hyperprolactinemia
	Obesity
	Hypothalamopituitary dysfunction (eating disorders, athletes)

Clinical Manifestations and Diagnosis

When a woman presents with AUB, there should be a routine evaluation by history and systemic evaluation for the possibility of endocrine factors being the underlying cause. Some pointers in the clinical evaluation are outlined in Table 12.2. If these features are present, the woman should be evaluated for the relevant endocrine dysfunction. It may not be prudent to subject every woman to a complete endocrine profile especially if there are obvious other aetiological factors such as an anatomical cause. Women who present with AUB due to endocrine disorders may also have other gynaecological and general issues. The management of a particular woman should be individualized and should encompass the range of disorders that need attention. This chapter focuses exclusively on the AUB aspect of the clinical presentation.

AUB IN PCOS

PCOS is probably the most common endocrine factor leading to AUB. It manifests as early as menarche. PCOS is the most common reason for AUB in the adolescent age group and is also responsible for anaemia and hospitalizations.[3] The bleeding pattern is usually of delayed menses ranging from 45 days to amenorrhoea. The woman usually responds to

TABLE 12.2: Clinical evaluation pointers towards endocrine factors and relevant tests

	History	*Examination*	*Tests to be prescribed*
PCOS	Irregular cycles since menarche, excess hair growth. May present with infertility	High BMI, hirsutism, acanthosis nigricans	Ultrasound for ovarian morphology, tests for insulin resistance, DHEA
Low ovarian reserve or POF	Irregular cycles with reduced bleeding of recent origin. May present with infertility	Usually unremarkable	Ultrasound for antral follicle counts. FSH, LH, AMH
Hypothyroidism	Weight gain, constipation, edema of the legs and around eyes, somatic symptoms	High BMI, myxedema, goitre	Thyroid function tests and anti-thyroid antibodies
Hyperprolactinemia	Breast secretions and milk discharge, breast tenderness		Galactorrhoea, serum prolactin
Obesity	Weight gain	High BMI	Tests for co-morbidities, glycaemic status and lipid profile
Hypothalamopituitary dysfunction	Profession, interests, hobbies, eating habits	Abnormal BMI	Psychological evaluation

progesterone as a withdrawal challenge when there is amenorrhoea. When the duration of amenorrhoea is prolonged, there is endometrial hyperplasia and the subsequent period is heavy, often with passage of clots and tissue. The tissue is called an endometrial cast. On history taking, the woman may mistake this for a complete abortion. It is important to clarify this aspect of the history with a negative urine pregnancy test which can be done at home. Occasionally, a woman may remain under the false impression of having had an abortion. She may later present with a history of "recurrent miscarriage".

The management of women with PCOS irrespective of their desire for fertility should include lifestyle modifications and BMI correction as a primary step. This is an ongoing process and needs sustained motivation and focused interventions. Ovulation may get restored and AUB could abate from this alone. Various drugs (insulin sensitizers) that reduce insulin resistance have been used in the management of PCOS. They also work by restoring ovulation and avoiding the endometrial disturbances. Some drugs such as metformin and combinations of metformin and inositol have given promising results.[4] However, this study was directed towards infertile women undergoing ovulation induction. At present, there are no studies which have looked at a primary endpoint of treating AUB with insulin sensitizers in PCOS. This is a potential area for research.

AUB IN LOW OVARIAN RESERVE AND POF

In the reproductive age group, ovarian reserve may diminish early. The changes leading to menopause may manifest before 40 years of age and if they lead to a menopause, the condition is known as a premature ovarian failure (POF). The changes in the endometrial behaviour mimic perimenopause and the same mechanisms are at play.[5] The cycles become anovulatory. This leads to a prolonged follicular phase and prolonged exposure to oestrogen. The luteal phase is insufficient and the endometrial shedding is irregular. Ultimately this manifests as irregular and heavy menstrual bleeding.

For women with low ovarian reserve, fertility may be an important consideration in the reproductive age group. This should be assessed and if so, therapy should be directed accordingly. If fertility is not desired, hormonal medications as outlined below are useful methods of managing the condition. For women with premature ovarian failure, hormone replacement should be considered as it has important implications for long-term bone and cardiovascular health.

AUB IN HYPOTHYROIDISM

Both hypothyroidism and hyperthyroidism can cause menstrual disturbances.[6] Hypothyroidism is a much more common clinical entity. Hypothyroidism affects the pulsatile release of GnRH. This is required for the normal secretion of FSH and LH and consequently, there is an ovulatory dysfunction. Women usually present with prolonged cycles or amenorrhoea and subsequent heavy menstrual bleeding. The most common differential diagnosis is PCOS. They may also co-exist in 15% of women with

PCOS. On the other hand, hyperthyroidism results in an increased sensitivity to GnRH and subsequently increased LH and SHBG. This usually manifests as delayed and scanty menstrual cycles.

The management of the thyroid dysfunction by appropriate medical therapy is usually adequate to allow a resolution of the AUB symptoms. It should be emphasized to the woman that thyroid disorders are chronic and therapy is also needed on a long-term basis. Appropriate monitoring is required for dose adjustments. These may change in the course of the disorder. There is a therapeutic benefit from BMI management in women with hypothyroidism. This should again, be looked upon as a long-term endeavour.

AUB IN HYPERPROLACTINAEMIA

Hyperprolactinaemia is one of the most common endocrine disorders associated with ovulatory dysfunction that results in menstrual irregularities.[7] Prolactin is a stress hormone and levels fluctuate to a significant with time of blood collection, collection technique, mental status, physical illness, menstrual cycle phase, sexual activity, etc. Abnormally high levels or pathological causes of hyperprolactinaemia may originate from the pituitary. The most common reason is a microprolactinoma. This is essentially a hypertrophy of some of the prolactin secreting cells. Occasionally, there may be a tumour which results in mass effects. This is called a macroprolactinoma. High levels of prolactin may be seen in association with hypothyroidism.

Clinical presentation is often with galactorrhoea. Other causes of galactorrhoea, most commonly antipsychotic drugs and antacids should be looked for. An enquiry should be made about vision and headaches for every patient so that a gross neurological problem is not missed.

The treatment of hyperprolactinaemia has been simplified greatly in recent times with the availability of cabergoline. This is the drug of first choice as it allows for weekly dosing and has very side effects as compared to its predecessor, bromergocriptine. Women should be assessed for associated endocrine disorders such as PCOS and hypothyroidism and treatment should be directed in a wholesome manner.[8]

AUB IN OBESITY

Obesity is an independent risk factor for AUB in the absence of PCOS and thyroid dysfunction. Obesity may contribute to AUB causation with other endocrine factors too.[9] The mechanism of obesity leading to AUB is multifold:

- Obesity results in increased conversion of androgens to oestrogens in the peripheral fat. This is a weaker form of oestrogen (oestriol). However, the quantity of conversion is significant when BMI is high. The high oestrogen level influences the endometrial behaviour as it is largely unopposed.
- Obesity causes a reduction in the SHBG. This leads to higher free androgens and consequently ovulatory dysfunction.

The evaluation of obesity should be holistic and should consider other metabolic parameters. This is best done in conjunction with a physician. The management is a long-term plan of reducing BMI as mentioned earlier. It requires discipline, motivation and sustained effort.

AUB IN HYPOTHALAMOPITUITARY DYSFUNCTION

In this broad category of endocrine disturbances, the common ones are anovulation resulting from eating disorders and anovulation secondary from excessive physical exercise. The former is generally pathological, while the latter may be considered physiological in athletes, sportswomen and women in professions where there are excessive demands of physical training such as the armed forces and the police.

Eating disorders are seen disproportionately more common in women who belong to professions where body image is an important component such as media, modeling, actors, dancers, etc. The disorder may alternate from starvation to binge eating. It results in fluctuating BMI and consequently, a disturbance in the GnRH pulsatility. This leads to anovulation and subsequent AUB.

The management of such situations calls for a multispeciality approach and may require hospitalization, parenteral nutrition and psychiatric intervention.[10]

Management of AUB from Endocrine Factors

The management of AUB from endocrine factors should be essentially directed towards the underlying endocrine disturbance. In addition to this, BMI correction plays an important role in most of the endocrine disorders. Other medications are useful as symptomatic measures in managing the AUB. They do not correct the basic endocrine problem but are useful adjuncts in patient care.

Non-hormonal drugs such as NSAIDs and tranexamic acid reduce menstrual flow by 25%. They also reduce dysmenorrhoea. These are to be used only during the menstrual bleeding phase. These medications enjoy a high degree of compliance and are useful measures for adolescents, women seeking fertility and in women where hormonal therapy is contraindicated. The disadvantage is the low efficacy and possibility of gastrointestinal disturbances.[11]

For an acute episode of AUB, probably the most effective intervention is a course of hormonal medications. Progesterone, especially norethisterone in a dose of 10 to 15 mg per day is the medication of choice. It usually results in control of bleeding in 2 to 3 days. Therapy should be continued for at least 15 days to reduce endometrial hyperplasia and achieve some menstrual control. Going further, hormonal medications should be directed according to the fertility seeking status of the woman. For those who desire fertility, cyclical progesterone, preferably dydrogesterone in the latter part of the cycle is acceptable. For those women who do not seek fertility or are actively seeking contraception, the options available are progesterone, oral contraceptive pills, depot medroxyprogesterone acetate injections, GnRH agonist depot injections and the levonorgestrel intrauterine system.[11] The levonorgestrel intrauterine system is the most efficacious, sustainable, cost-effective option amongst these, especially for a woman seeking a long-term solution.[12]

Operative interventions such as endometrial curettage and endometrial ablation are also possible therapeutic options. In the absence of clinical improvement, one may resort to a hysterectomy in women who have completed their childbearing. However, this should be used sparingly with the options of LNG–IUS and endometrial ablation being available in a woman with endocrine factors causing AUB.

Conclusion

AUB due to endocrine factors is multifactorial. Clinical assessment and prudently advised investigations lead to an accurate diagnosis. Management should be holistic including the other gynaecological complaints that a woman presents with. It should be directed towards the correction of the primary endocrine factor. Symptomatic management with non-hormonal and hormonal medications is useful in the clinical care of these women.

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