به نام خدا

Title:AUB

Dr.Afsaneh Mohammad Zadeh Asst.Prof.

Fellowship in Reproductive Endocrinology &Infertility

Zahra Jamalpour /MD

Fellowship assistant of Infertility

“AVICENNA” research institute and infertility center

Part 1: Physiology of Normal Menstruation

Part 2: Pathophysiology and Classification

Part 3: structural and Non-structural Causes of aub

Part 4: Clinical Diagnostic Approach

Part 5: Management and Treatment

Normal Menstruation:The Foundation for Understanding AUB

· Menstruation is the result of an organized sequence of endocrine signals within the hypothalamic-pituitary-ovarian **(HPO)** axis.

· This hormonal order provides menstruation with regularity, predictability, and consistency.
· Without **ovulation and hormonal order**, the menstrual pattern becomes disrupted.

Endometrial Cycle and Hormones

Follicular (Proliferative) Phase: Rising estrogen stimulates the regeneration and growth of the functional layer of the endometrium.

Luteal (Secretory) Phase: The corpus luteum secretes estrogen and, more importantly, **progesterone**, preparing the endometrium for implantation.

Mechanism of Menstrual Bleeding Onset

· If pregnancy does not occur, the corpus luteum undergoes programmed cell death **(apoptosis).**

· Estrogen and progesterone levels fall simultaneously (withdrawal).

· This hormonal withdrawal removes functional support from the endometrium, initiating menstruation.

Hormonal **Sequence**; The **Secret** to a **Stable Endometrium**

· From the endometrium's perspective, the **sequence of hormones** is **more important** than their **quantity**:

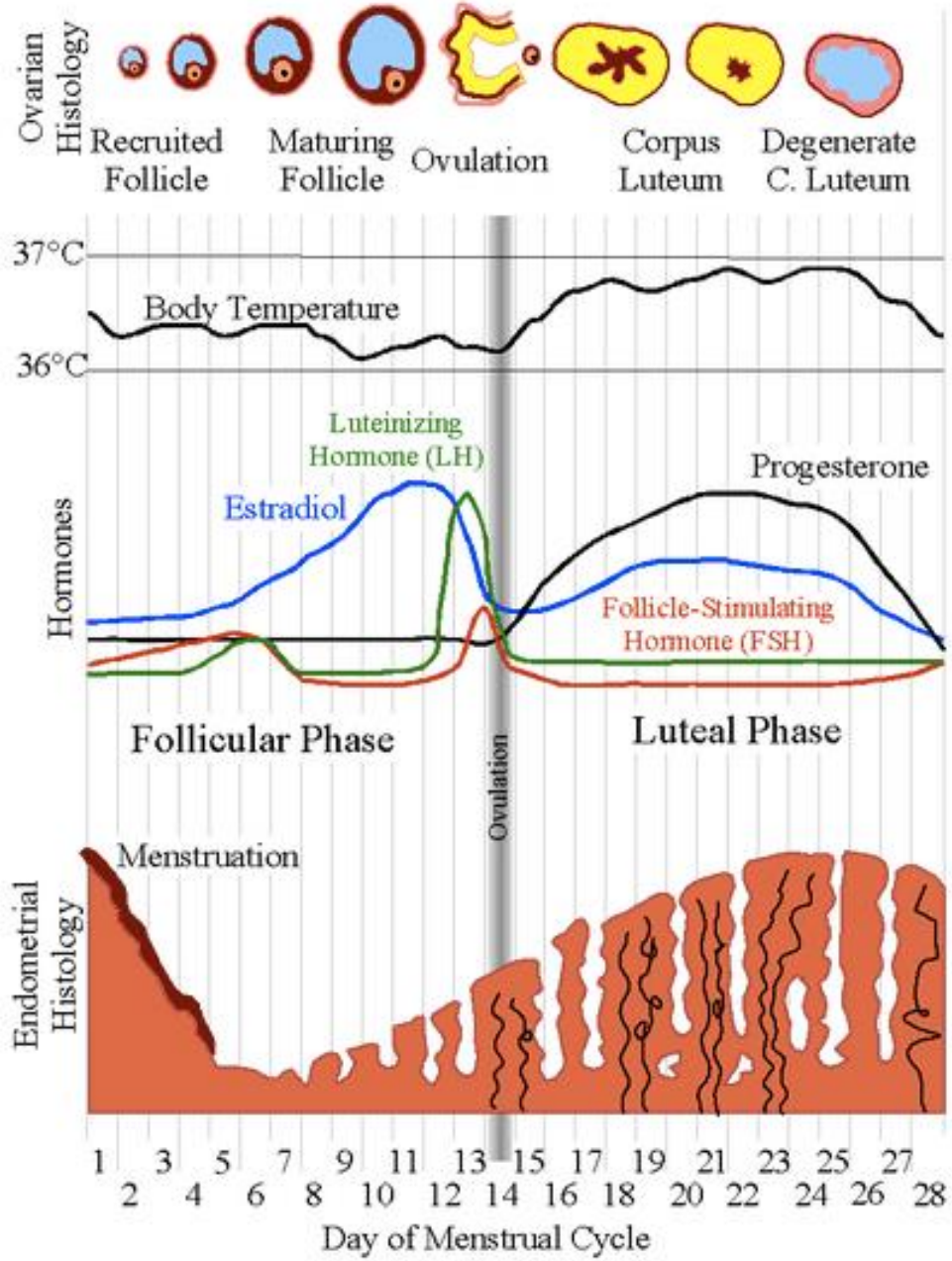
estrogen, followed by **estrogen + progesterone**, followed by the **withdrawal of both.**

· Estrogen-progesterone stimulation produces the most **stable** endometrium, and their **combined withdrawal** yields the most consistent bleeding.

the population-based norms are wider than the generally accepted norms for menstrual:

frequency :(24–35 days)
regularity :(±5 days variation)
and duration: (2–7 days) among ovulatory women.

Normal volume 2_80cc(average:30cc)



(Average values. Durations and values may differ between different females or different cycles.)

Mechanisms of Cessation of Normal Bleeding **(Hemostasis)**

Enzymatic degradation of the endometrium (by lysosomal enzymes and MMPs) initiates bleeding.

· Bleeding cessation depends on **coagulation, spiral arteriole vasoconstriction**, and epithelial repair.

· **Endometrial shedding** occurs uniformly and synchronously throughout the uterine cavity.

Part 2: Pathophysiology and Classification

Pathophysiology of Anovulatory Bleeding

· In the absence of ovulation, **no corpus luteum** forms, and **no progesterone** is produced.
· The endometrium is exposed only to continuous **estrogen** (unopposed estrogen) and **overgrows (hyperplasia).**

Why Does the Endometrium Become Fragile in Anovulation?

· The endometrium becomes **so thick** that it outgrows its own blood supply.

· **Without** the limiting effect **of progesterone**, the **supportive stromal** structure weakens.

· **Focal areas** undergo **necrosis** and **breakdown**, leading to irregular and prolonged bleeding.

The Role of Abnormal Blood Vessels in AUB

· In persistent proliferative endometrium, blood vessels increase in **number** and become **dilated.**

· These vessels have a fragile structure and are prone to spontaneous rupture.

Introduction to the Standard FIGO System (PALM-COEIN)

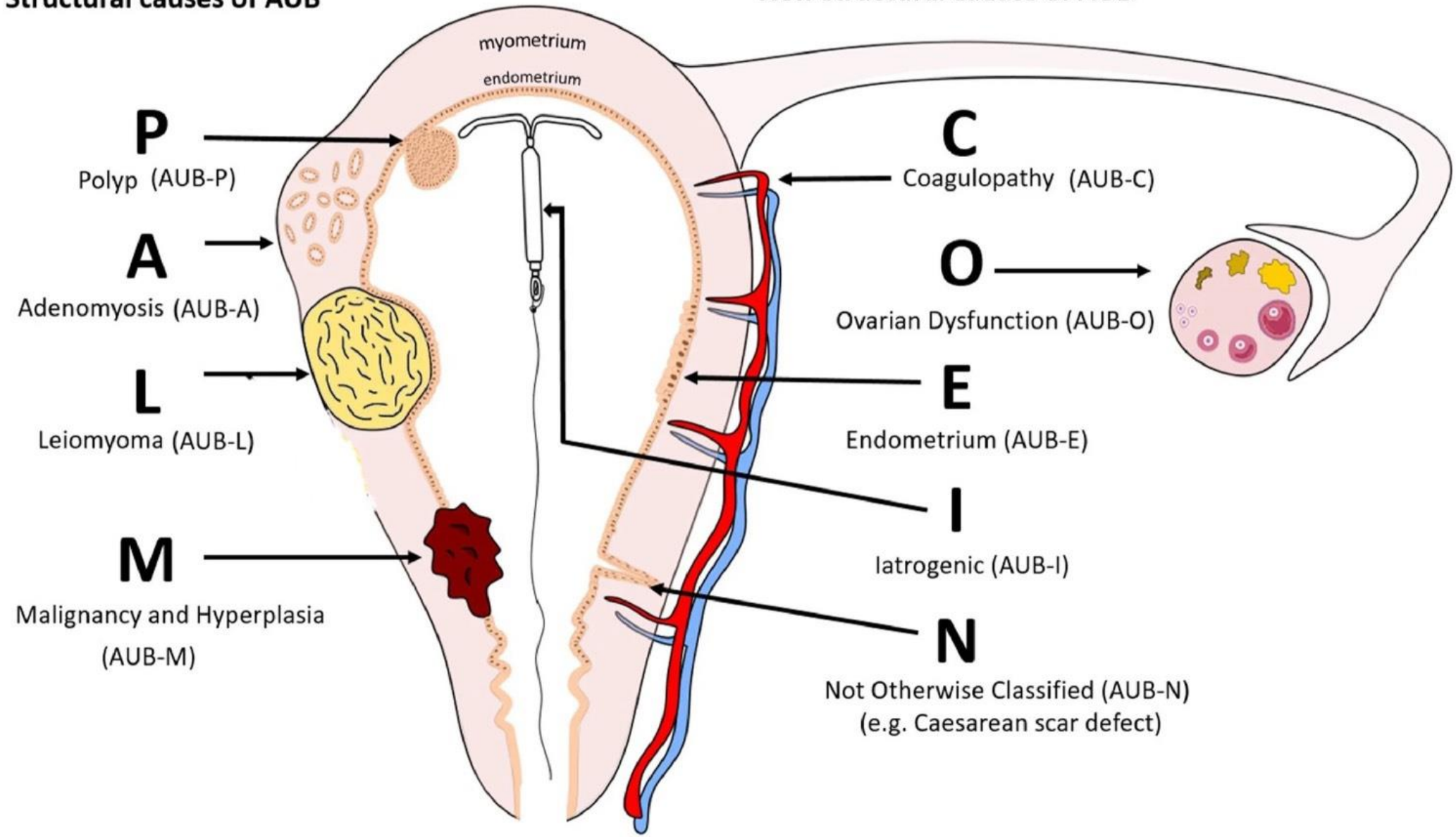
· A new system was introduced to eliminate the confusion of old terminology.

· **Goal:** A universal language for diagnosis and treatment.

· Divided into two main categories: Structural causes **(PALM)** and Non-structural causes **(COEIN).**

"PALM"
Structural causes of AUB

"COEIN"
Non-structural causes of AUB



Structural Causes (PALM):

· P (Polyp): Endometrial polyp
· A (Adenomyosis): Adenomyosis
· L (Leiomyoma): Uterine fibroid
· M (Malignancy & Hyperplasia): Malignancy and hyperplasia (neoplasia)

Non-structural Causes (COEIN):

. C (Coagulopathy): Coagulation disorders·
. O (Ovulatory dysfunction): Ovulatory dysfunction
· E (Endometrial): Endometrial causes
· I (Iatrogenic): Iatrogenic/medication causes
· N (Not yet classified): Not yet classified (rare and unclear cases)

Part 3: structural and Non-structural Causes

Polyps and Adenomyosis:

· **Polyp:** Premenstrual spotting or intermenstrual bleeding. **Treated** with **hysteroscopy.**

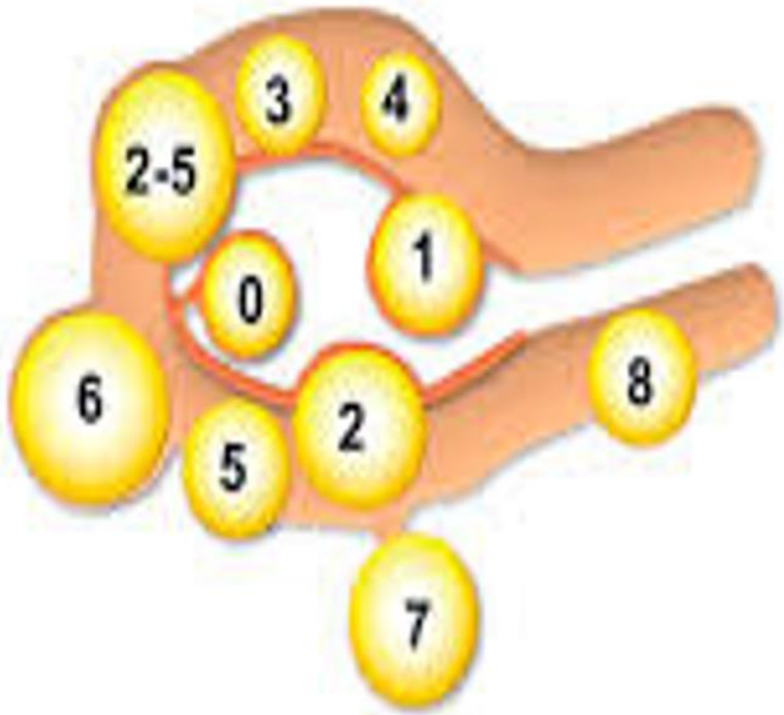
· **Adenomyosis:** Invasion of endometrium into the myometrium. Causes an enlarged uterus, heavy menses, and dysmenorrhea (pain).

Leiomyoma (AUB-L):

·The **most common form** of AUB in these patients: Heavy Menstrual Bleeding

Clinical Note:

Fibroids are very common and **should not** be assumed as the definitive cause of bleeding solely based on **ultrasound findings** (especially if not submucosal).



Type	Location
0	100% intracavity
1	>50% intracavity
2	<50% intracavity
3	Contact endometrium, 100% intramural
4	100% intramural
5	<50% subserosa
6	>50% subserosa
7	100% subserosa
8	Others (cervical, broad ligament, parasitic, etc.)

Endometrial Hyperplasia and **Malignancy (AUB-M):**

· The result of chronic exposure to **unopposed estrogen.**
· Important risk factors: **Obesity, PCOS, advanced age, history of long-term estrogen use.**

· Hyperplasia **without atypia**: Low risk of cancer, treated with progestins.
· Hyperplasia **with atypia**: A precancerous lesion (10-30% risk) requiring more aggressive treatment (e.g., hysterectomy).

Non-structural Causes

Coagulation Disorders (AUB-C)

· In adolescents with heavy bleeding **since menarche**, a coagulopathy should be suspected.

· The most common disorder: **von Willebrand** disease **(vWD).**

· A history of bleeding after surgery, tooth extraction, or easy bruising raises our suspicion.

Ovulatory Dysfunction (AUB-O)

· The most common cause of AUB in **reproductive age** and adolescence.

· **Clinical pattern:** Irregular, unpredictable bleeding with variable volume and duration.
· Absence of premenstrual molimina (PMS symptoms) is common in these patients.

Iatrogenic and Endometrial Causes (AUB-I and AUB-E)

· **Iatrogenic (I):** Copper IUD (heavy bleeding), progestins (spotting), anticoagulants.

· **Endometrial (E):** Heavy bleeding in a healthy uterus with normal ovulation (defect in local hemostasis: defect in prduce PG & MMPs).

AUB-N (Not Yet Classified)

· A vague category containing rare cases.

· Includes arteriovenous malformations (AVMs)
. chronic endometritis (chronic endometrial inflammation diagnosed by biopsy).

Part 4: Clinical Diagnostic Approach

Step 1 - Detailed History

Must determine:
onset, duration, interval, volume, and bleeding pattern.

· **Key questions:**
Is there intermenstrual spotting?
Is there pain?
Is she taking specific medications?
· Family history of bleeding disorders.

Step 2 - **Physical Examination**

· Check vital signs (hypotension in severe bleeding).

· Pelvic exam: Assess uterine size, presence of masses, and examine the vagina and cervix.

· Assess for signs of **hyperandrogenism or thyroid disorders**

Step 3 - **Initial** Laboratory Tests

· **Most important test:** Pregnancy test (β-hCG)
- must always be ruled out in reproductive age.

· **Second test:** CBC (to evaluate for anemia and thrombocytopenia).

Step 4 - Assessment of Ovulation

· Does the patient ovulate?

· If history is insufficient: **Serum progesterone** measurement in the luteal phase (**days 22-24 of the cycle).**

· A progesterone level greater than **3 ng/mL** indicates recent ovulation.

Step 5 - **Imaging (Ultrasound)**

· Transvaginal Ultrasound (TVS):
Assess uterine size, fibroids, and endometrial thickness.

· Sonohysterography (SIS): Excellent for detailed evaluation of the uterine cavity and intracavitary lesions (like polyps).

When to Perform Endometrial Biopsy?

· In women with AUB, if the history indicates long-term exposure to unopposed estrogen (e.g., obesity or anovulation), endometrial biopsy is indicated even if the endometrial thickness is **normal** (between 5 and 12 mm).

· If the endometrium on ultrasound is thick (greater than 12 mm).

When is Biopsy NOT Necessary?

· If the endometrium is very thin **(less than 4 mm),** especially in **postmenopausal** women, the risk of hyperplasia/cancer is very low, and biopsy is usually not required.

· In women with regular cycles and completely normal ultrasound, biopsy is often unnecessary.

Diagnostic Summary (Functional vs. Structural Causes)

· **History and physical examination** provide the most information to differentiate functional causes (like anovulation) from **structural causes.**

· **Irregular and unpredictable** bleeding leans more towards anovulation.

· Regular but heavy bleeding leans more towards structural causes (like fibroids) or coagulopathies.

Part 5: Management and Treatment

General Principles of AUB Management

· **Goals:**
Stop **acute** bleeding
prevent **recurrence**
treat **anemia** and improve quality of life.

· Treatment choice **depends on**:
the **cause of AUB**, **age**, desire for **pregnancy**, and **severity** of bleeding.

Treatment of Hyperplasia:

without Atypia: Cyclic or continous progestin (e.g., MPA 5-10 mg/day for 14 days/month) for 3-6 months or **LNG-IUS.**
Repeat biopsy in **3 months**.

· **Atypical Hyperplasia**: **Hysterectomy** is the **first** line (if no fertility desire).
For fertility-sparing: **High-dose progestin** (e.g., Megestrol acetate 80 mg twice daily) for 3-6 months + close surveillance and Repeat biopsy
.LNG-IUS is highly effectiv

Treatment of Anovulatory Bleeding (AUB-O):

· Goal: Restore **normal endometrial growth and shedding** (Progestins are the mainstay).
· Cyclic Progestin (For women not seeking pregnancy/**not sexually active**): e.g., Medroxyprogesterone acetate (MPA) 5-10 mg/day for 10-14 days each month. (Induces predictable withdrawal bleeding).
· **Combined Oral Contraceptives** (For **sexually active** women not seeking pregnancy): Regulates cycles and reduces bleeding volume.
· **LNG-IUS:** Excellent long-term option for women **not seeking pregnancy**.
· **(Note: Cyclic progestin is NOT contraceptive).**

Approach to the Patient with Acute Heavy Bleeding

· Initial Assessment: Determine **hemodynamic status** (Stable vs. Unstable).
· **Unstable Patient:** Requires hospitalization, fluid resuscitation, blood transfusion, and emergency intervention.

· **Stable Patient:** Assess endometrial thickness to choose the appropriate medical therapy.

Medical Treatment for Acute Bleeding with a **Thick** Endometrium

· If the patient is **stable** and the endometrium is **thick**:
High-dose **estrogen-progestin** (**High-dose COC**) or High-dose **progestin** (e.g., Megestrol or Medroxyprogesterone).

· Goal: Uniform shedding of the endometrium and cessation of bleeding.

Medical Treatment for **Acute Bleeding with a Thin Endometrium**

· In patients with a **thin** endometrium and severe bleeding, **estrogen** (alone) is the **best initial choice**, not progestin.

· Unstable patient with a thin endometrium: Use Intravenous Estrogen (25 mg of conjugated equine estrogen every 4 hours, up to 24 hours).

· This method controls bleeding within **4 to 8 hours** in more than 70% of patients.

Mechanical Measures in Acute Bleeding

· When medical therapy is insufficient or the patient is unstable, the use of **intrauterine tamponade** (such as a balloon/Foley catheter) is **highly effective** for mechanical control of bleeding.

· Dilation and Curettage (D&C): For acute bleeding control and diagnosis, but it should not be the gold standard (it can **miss focal lesions**).

It is best **combined with hysteroscopy.**

The Role of **LNG-IUS** in **Long-term** Management

· An excellent option for long-term management of AUB (especially in adenomyosis and fibroids).
· Reduces bleeding by 75% to 95%.
· Highly suitable for women who have not responded to pills or cannot take them

Non-hormonal Medications:

· NSAIDs (e.g., Ibuprofen): 20% to 40% reduction in bleeding, excellent for dysmenorrhea.
· Tranexamic Acid: Antifibrinolytic, 35% to 60% reduction in blood volume. Used **only during bleeding** days.

Surgical Treatment for Structural Lesions

· Polyp: Removal via hysteroscopy.
· Fibroid: Myomectomy (**for fertility preservation**) or hysterectomy (if **no desire for fertility**).

· Adenomyosis: **Hysterectomy** in cases resistant to medical therapy.

Endometrial Ablation

· A procedure to destroy the **inner lining** of the uterus.
· For women with **heavy bleeding**, failed medical therapy, and **no desire** for future pregnancy.
· Reduces bleeding by 80% to 90%.

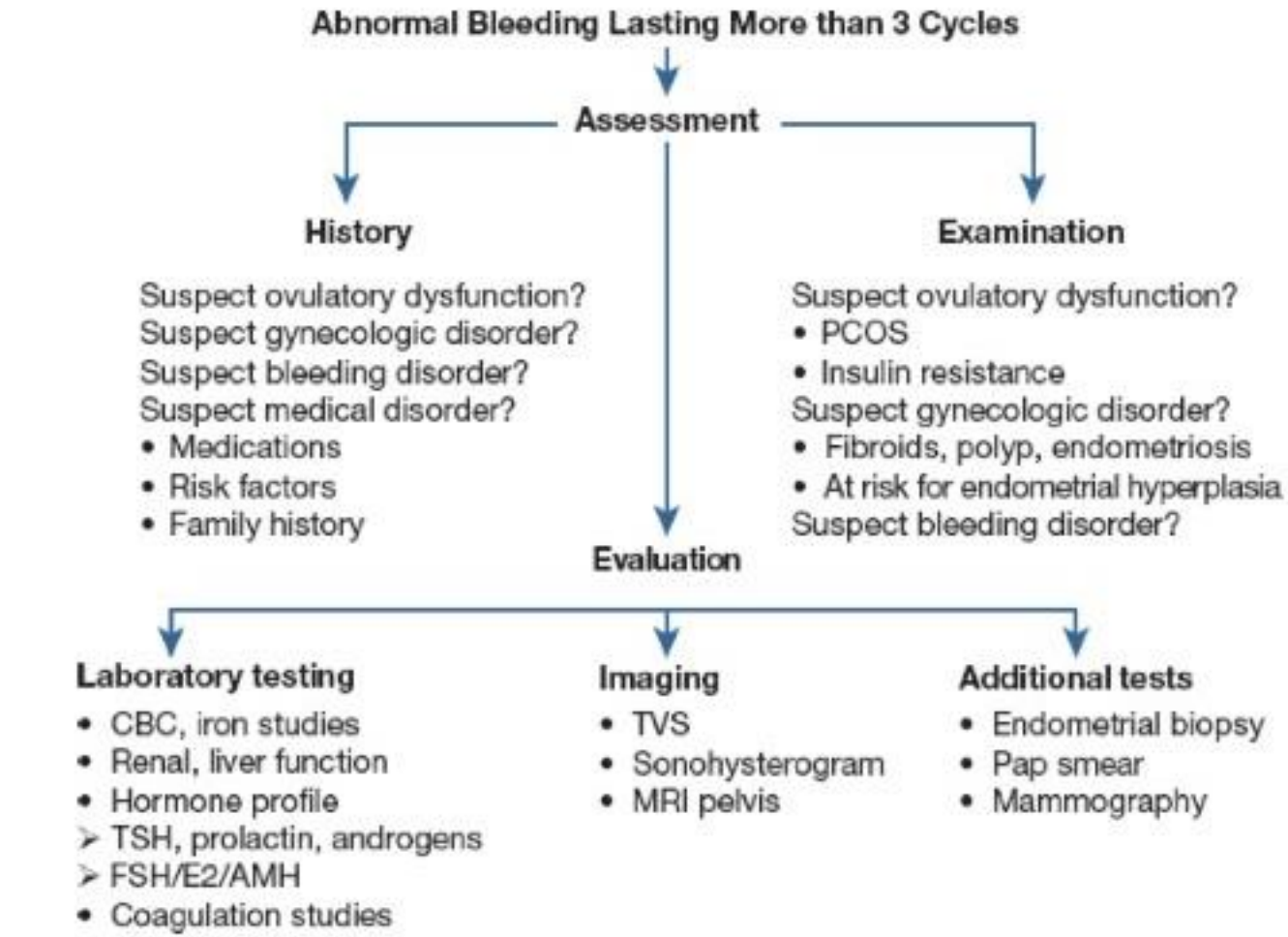

Abnormal Bleeding Lasting More than 3 Cycles
Assessment
History
Suspect ovulatory dysfunction?
Suspect gynecologic disorder?
Suspect bleeding disorder?
Suspect medical disorder?
• Medications
• Risk factors
• Family history
Examination
Suspect ovulatory dysfunction?
• PCOS
• Insulin resistance
Suspect gynecologic disorder?
• Fibroids, polyp, endometriosis
• At risk for endometrial hyperplasia
Suspect bleeding disorder?
Evaluation
Laboratory testing
• CBC, iron studies
• Renal, liver function
• Hormone profile
➢ TSH, prolactin, androgens
➢ FSH/E2/AMH
• Coagulation studies
Imaging
• TVS
• Sonohysterogram
• MRI pelvis
Additional tests
• Endometrial biopsy
• Pap smear
• Mammography

FIGURE 15.7

Clinical Case (1)

· History: A 35-year-old woman with **irregular cycles** for 6 months, no pain. Ultrasound: Endometrial thickness 17 mm, normal uterus.
· Question: What is the next step?
· Answer: **Endometrial biopsy** to rule out **hyperplasia** (given the increased thickness and irregular cycles).

Clinical Case (2) - Acute Bleeding

· History: A 30-year-old woman with severe and active vaginal bleeding, hemodynamically unstable. Ultrasound: Thin endometrium (3 mm).
· Question: What is the best initial treatment?
· Answer: Hospitalization, administration of **Intravenous Estrogen** (to stabilize the thin endometrium). If unresponsive, use an intrauterine **balloon** for mechanical control.

Key Takeaways

· AUB is a **symptom,** NOT a diagnosis.

· Always rule out **pregnancy** first.

· Use the **PALM-COEIN** system to organize your clinical thinking.

· Treatment is **based on hemodynamic status** and endometrial **thickness**:

Thin endometrium = Estrogen

Unstable patient = IV Estrogen/Tamponade

Thick endometrium = Progestin/COC

Thank you for your attention