# Progestins in The Management of AUB-O

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# INTRODUCTION

- The worldwide impact of abnormal uterine bleeding (AUB) in the reproductive years is substantial, with a prevalence of approximately 3%–30% among reproductive aged women.

- In 2011, recognizing the international need created by the impact of AUB, the International Federation of Gynecology and Obstetrics (FIGO), published a pair of systems and a set of clinical recommendations.

# FIGO Classification

- This 2011 manuscript introduced the PALM-COEIN classification based on clinical- and imaging-based stratification of causes into “structural” pathologies that can be “imaged” and/or defined histopathologically (PALM).
- The remaining causes were categorized as “non-structural”, in that they cannot be imaged, but clinical assessment with detailed history and appropriate physical examination, sometimes supported by laboratory testing, can largely imply or make a diagnosis of cause (COEIN).

# ACUTE VERSUS CHRONIC NONGESTATIONAL AUB

- Chronic nongestational AUB is defined as bleeding from the uterine corpus that is abnormal in duration, volume, frequency, and/or regularity, and has been present for the majority of the preceding 6 months.
- Acute AUB, on the other hand, is defined as an episode of heavy bleeding that, in the opinion of the clinician, is of sufficient quantity to require immediate intervention to minimize or prevent further blood loss.
- Acute heavy menstrual bleeding may present in the context of existing chronic AUB or can occur in the absence of such a background history.

# FIGO-AUB SYSTEM 1

| Parameter | Normal | Abnormal | ☑ |
|---|---|---|---|
| Frequency | 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 | | ☐ |

| | | | |
|---|---|---|---|
| **Intermenstrual Bleeding (IMB)** Bleeding between cyclically regular onset of menses | None | | ☐ |
| | Random | | ☐ |
| | Cyclic (Predictable) | Early Cycle | ☐ |
| | | Mid 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 | ☐ |

# Heavy Menstrual bleeding

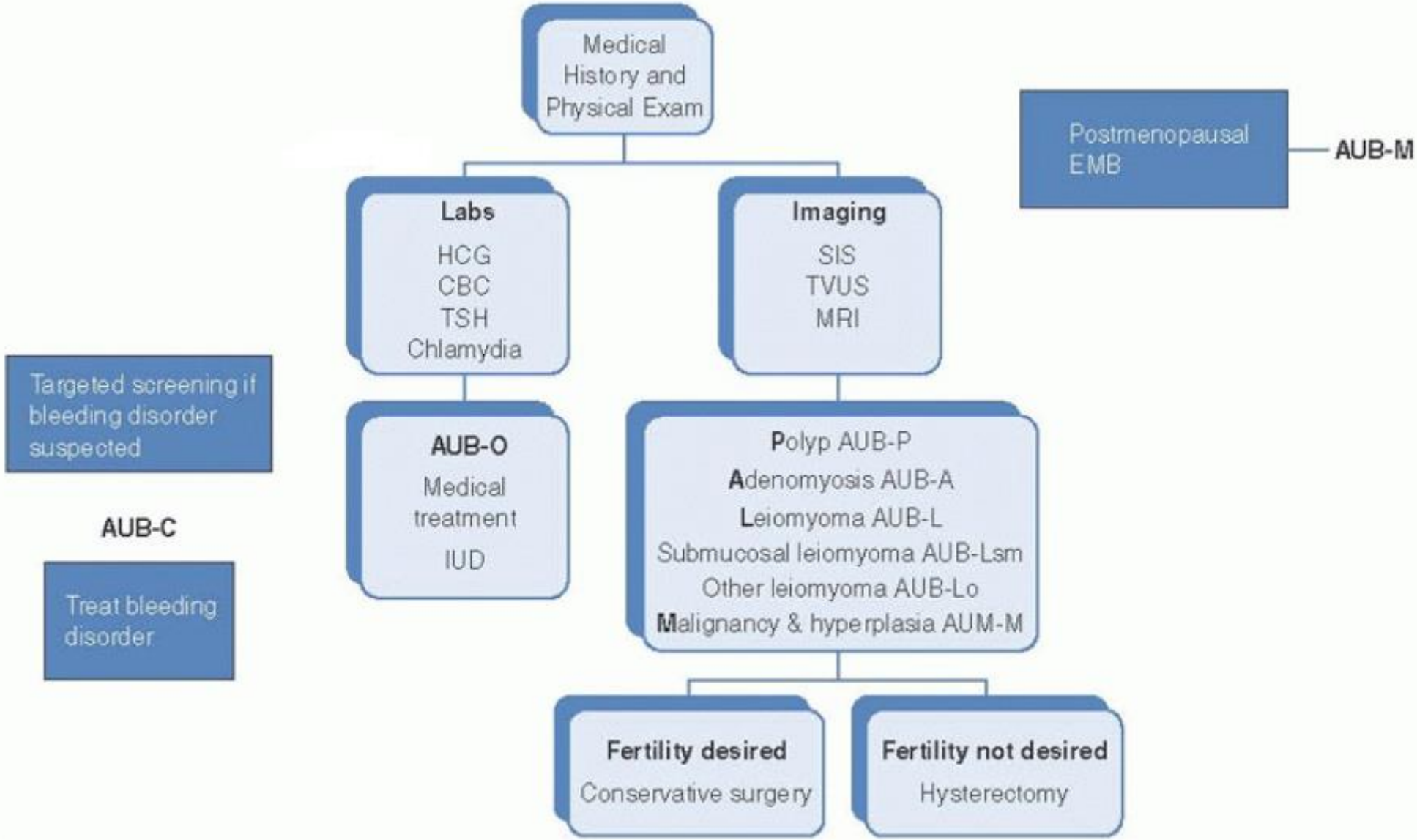
- For clinical purposes, the definition of HMB proposed by the UK National Institute for Health and Care Excellence has been adopted – “Excessive menstrual blood loss which interferes with a woman’s physical, social, emotional, and/or material quality of life”.

- Terms such as menorrhagia, metrorrhagia, oligomenorrhea, and dysfunctional uterine bleeding have been abandoned.

# FIGO AUB SYSTEM 2

| |
|---|
| **P**olyp |
| **A**denomyosis |
| **L**eiomyoma |
| **M**alignancy & hyperplasia |

| |
|---|
| **C**oagulopathy |
| **O**vulatory dysfunction |
| **E**ndometrial |
| **I**atrogenic |
| **N**ot otherwise classified |

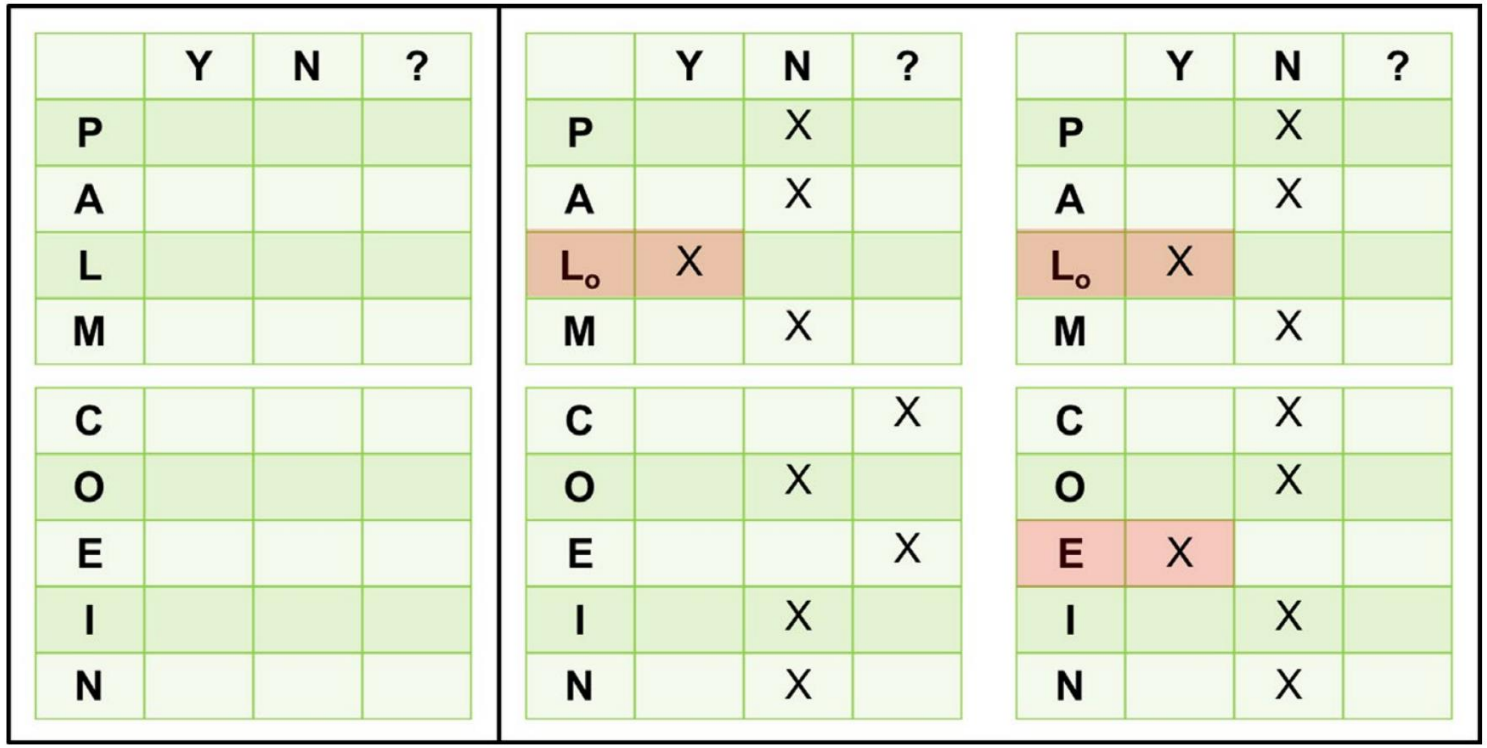

Medical History and Physical Exam
Postmenopausal EMB
AUB-M
Labs
HCG
CBC
TSH
Chlamydia
Imaging
SIS
TVUS
MRI
Targeted screening if bleeding disorder suspected
AUB-O
Medical treatment
IUD
Polyp AUB-P
Adenomyosis AUB-A
Leiomyoma AUB-L
Submucosal leiomyoma AUB-Lsm
Other leiomyoma AUB-Lo
Malignancy & hyperplasia AUM-M
AUB-C
Treat bleeding disorder
Fertility desired
Conservative surgery
Fertility not desired
Hysterectomy

# RECOMMENDATIONS FOR CLINICAL INVESTIGATION

- This approach has been designed following the example of the WHO TNM staging of malignant tumors, with each component addressed for all women investigated for AUB symptoms using the two FIGO AUB Systems.

- For example, if an individual was suspected to have a disorder of ovulation, a type 2 leiomyoma, and no other anomalies, they would be categorized as follows in the context of a complete evaluation: AUB P0 A0 L1(SM) M0 - C0 O1 E0 I 0 N0.

# FIGO AUB System 2 diagnostic matrix



| | 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 | |

# Example 1

**System 1 (Symptoms)**

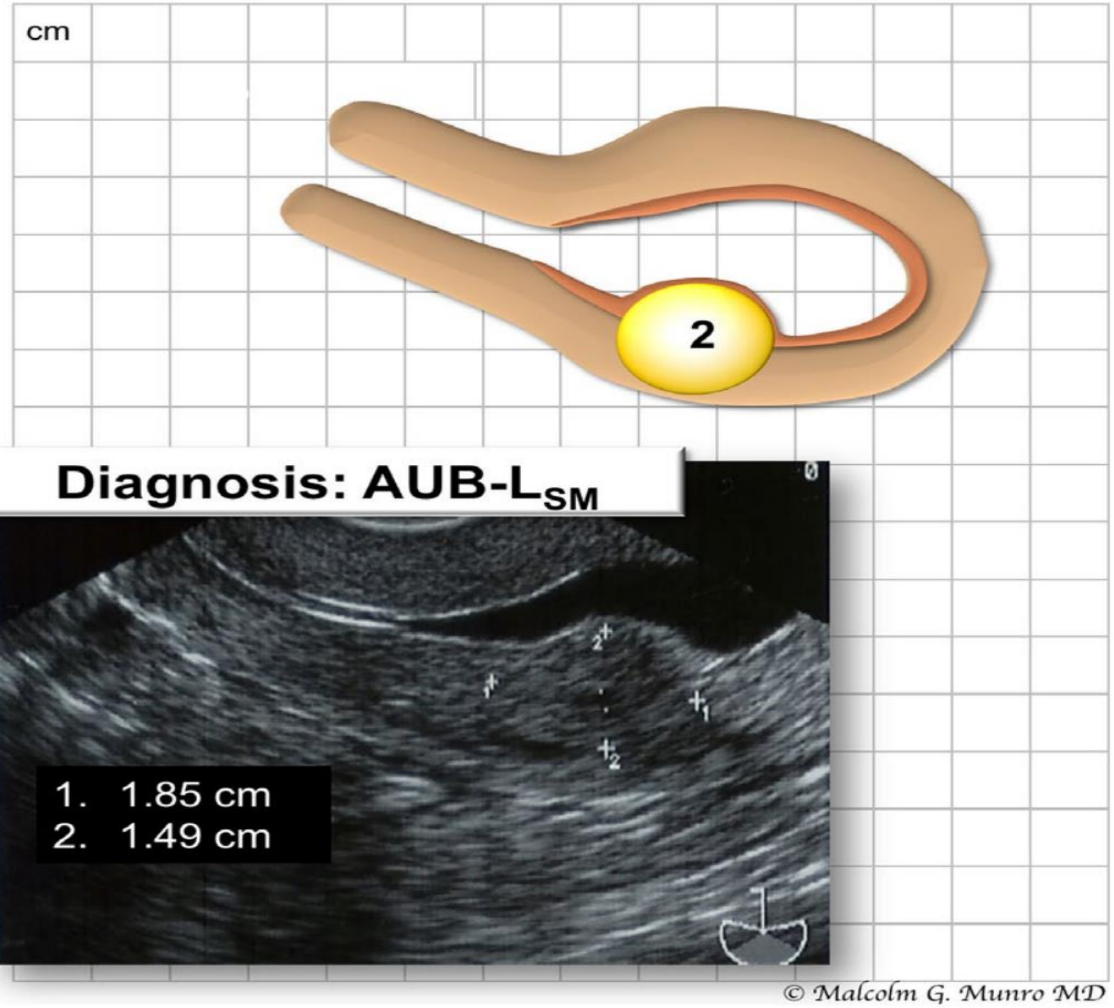
- Cycle Length: 30 days
- Regularity: ±2 days
- Duration: 10 days
- Volume: Heavy
- Intermenstrual Bleeding: -

**System 2 (PALM-COEIN)**

- Leiomyoma: Type 2

| | Y | N | ? |
|---|---|---|---|
| P | | X | |
| A | | X | |
| $L_{sm}$ | X | | |
| M | | X | |

| | | | |
|---|---|---|---|
| C | | X | |
| O | | X | |
| E | | X | |
| I | | X | |
| N | | X | |



# Example 2

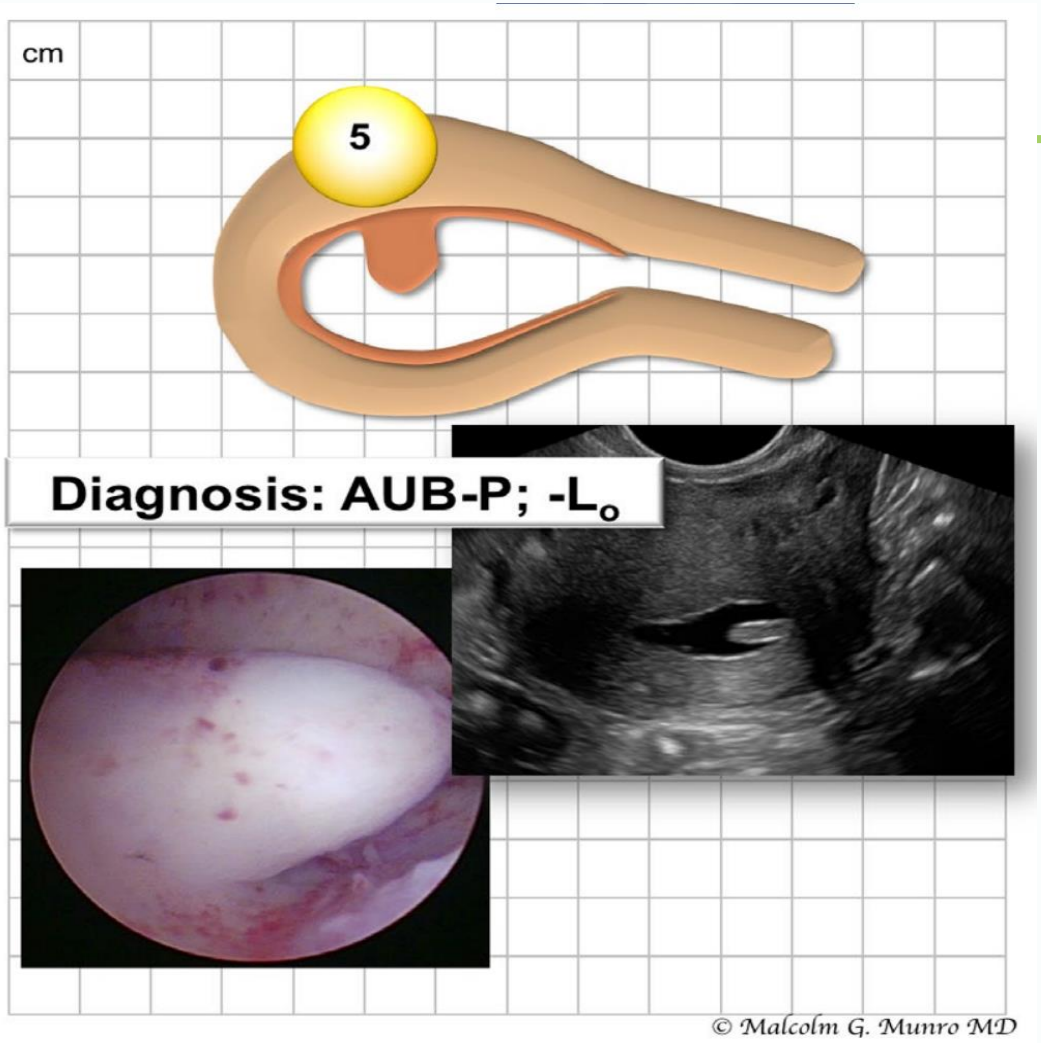
**System 1 (Symptoms)**

- Cycle Length: 31 days
- Regularity: ±3 days
- Duration: 4 days
- Volume: Normal
- Intermenstrual Bleeding: +

**System 2 (PALM-COEIN)**

- Polyp: Endometrial
- Leiomyoma: Type 5

| | Y | N | ? |
|---|---|---|---|
| P | X | | |
| A | | X | |
| $L_o$ | X | | |
| M | | X | |
| C | | X | |
| O | | X | |
| E | | X | |
| I | | X | |
| N | | X | |



# Determination of ovulatory status

- Predictable cyclic menses every 24–38 days are usually (but not always) associated with ovulation whereas bleeding associated with ovulatory disorders is typically irregular in timing and flow, and often interspersed with episodes of amenorrhea.
- If there is uncertainty regarding ovulatory status, measurement of serum progesterone, timed to the best estimate of mid-luteal phase, may be useful for confirming ovulation in the current cycle.
- Whereas endometrial biopsy is not recommended as a method for determination of ovulatory status, when performed and appropriately indicated—to evaluate for the presence of premalignant or malignant endometrial change—histopathological findings reflecting secretory change may confirm that ovulation has occurred.

**Box 1. Causes of Anovulation** ⇦

***Physiologic***

- Adolescence
- Perimenopause
- Lactation
- Pregnancy

***Pathologic***

- Hyperandrogenic anovulation (eg, polycystic ovary syndrome, congenital adrenal hyperplasia, or androgen-producing tumors)
- Hypothalamic dysfunction (eg, secondary to anorexia nervosa)
- Hyperprolactinemia
- Thyroid disease
- Primary pituitary disease
- Premature ovarian failure
- Iatrogenic (eg, secondary to radiation or chemotherapy)
- Medications

# Evaluation of the endometrium

- Endometrial sampling is not required for all patients with AUB, so it is necessary to identify the women for whom endometrial biopsy is appropriate.
- Selection for endometrial sampling is based on a combination of risk factors for the presence of premalignant or malignant changes, comprising some combination of age, personal, and genetic risk factors, and TVUS screening for endometrial echocomplex thickness.
- Most suggest that endometrial sampling be considered for all women over a certain age, usually 45 years.
- It is also evident that obesity contributes significantly to the risk of premalignant and malignant change in the endometrium, a feature that increases the risk of endometrial neoplasia even in young women in the third and fourth decades of life.

- Regardless of the clinical guideline, when AUB is persistent and either unexplained or inadequately treated, endometrial sampling is necessary.

# Women who should undergo evaluation for endometrial hyperplasia or endometrial cancer

- Postmenopausal women – Any uterine bleeding, regardless of volume (including spotting or staining). Pelvic ultrasound to evaluate endometrial thickness is an alternative to endometrial sampling in appropriately selected women. A thickened endometrium should be further evaluated with endometrial sampling.
- Age 45 years to menopause – In any woman, bleeding that is frequent (interval between the onset of bleeding episodes is <21 days), heavy, or prolonged (>8 days). In women who are ovulatory, this includes intermenstrual bleeding.
- Younger than 45 years – Any abnormal uterine bleeding in obese women (BMI ≥30). In non-obese women, abnormal uterine bleeding that is persistent and occurs in the setting of one of the following: chronic ovulatory dysfunction, other exposure to estrogen unopposed by progesterone, failed medical management of the bleeding, or women at high risk of endometrial cancer (eg, Lynch syndrome, Cowden syndrome).

# Treatment Approach

- AUB Tx depends on:
  - Woman's age
  - Severity of Bleeding
  - Medical risk factors
  - Need for contraception
  - Desire for future fertility

  AUB-O is an endocrinologic  abormality.

# Management of Abnormal Bleeding in reproductive ages

  - Cyclic progestin
- COC-LD: in healthy women, not smoker, with no cardiovascular risk factors.
- Levonorgestrel  IUD
- Cyclic hormone therapy
- GnRH agonists

# Progestational agents have many important functions, including

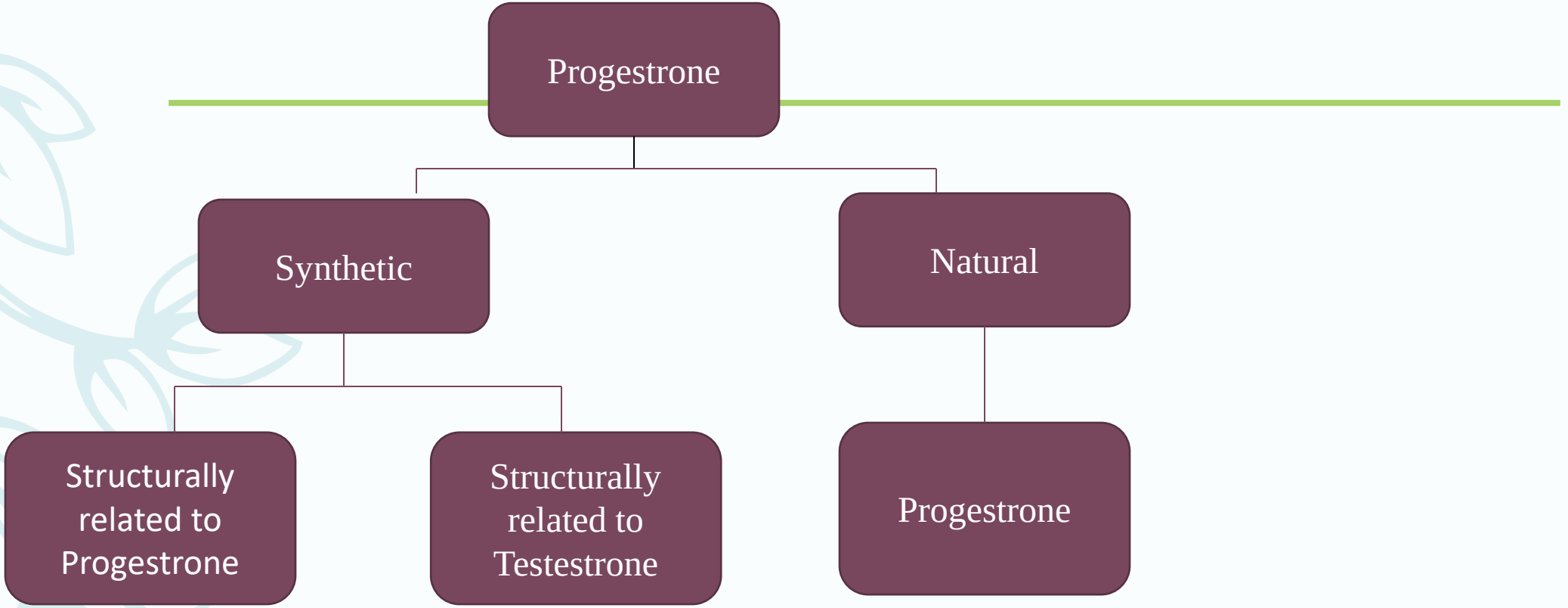
- *regulation of the menstrual cycle*
- *treatment of dysfunctional uterine bleeding*
- *prevention of endometrial cancer and hyperplastic precursor lesions*
- *contraception*

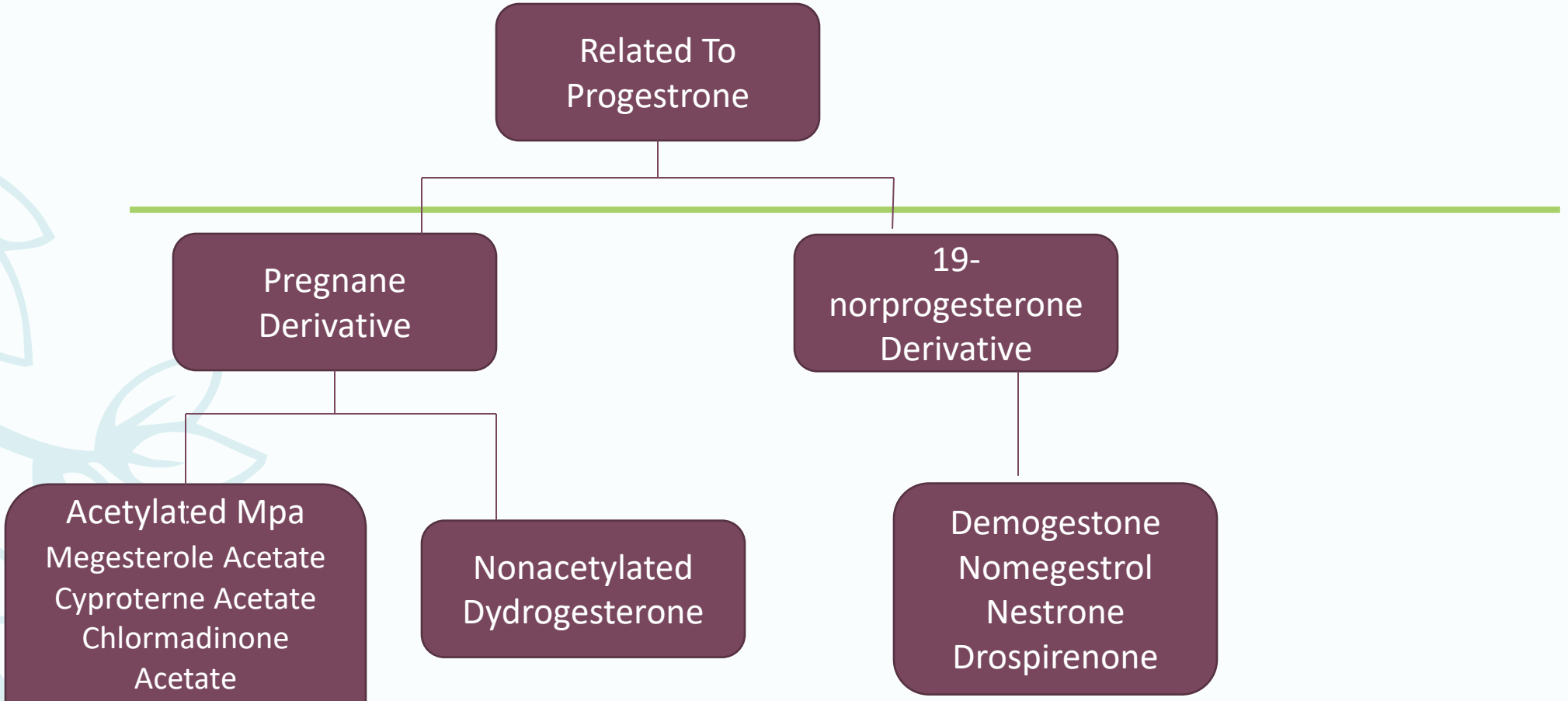
# Progesterone

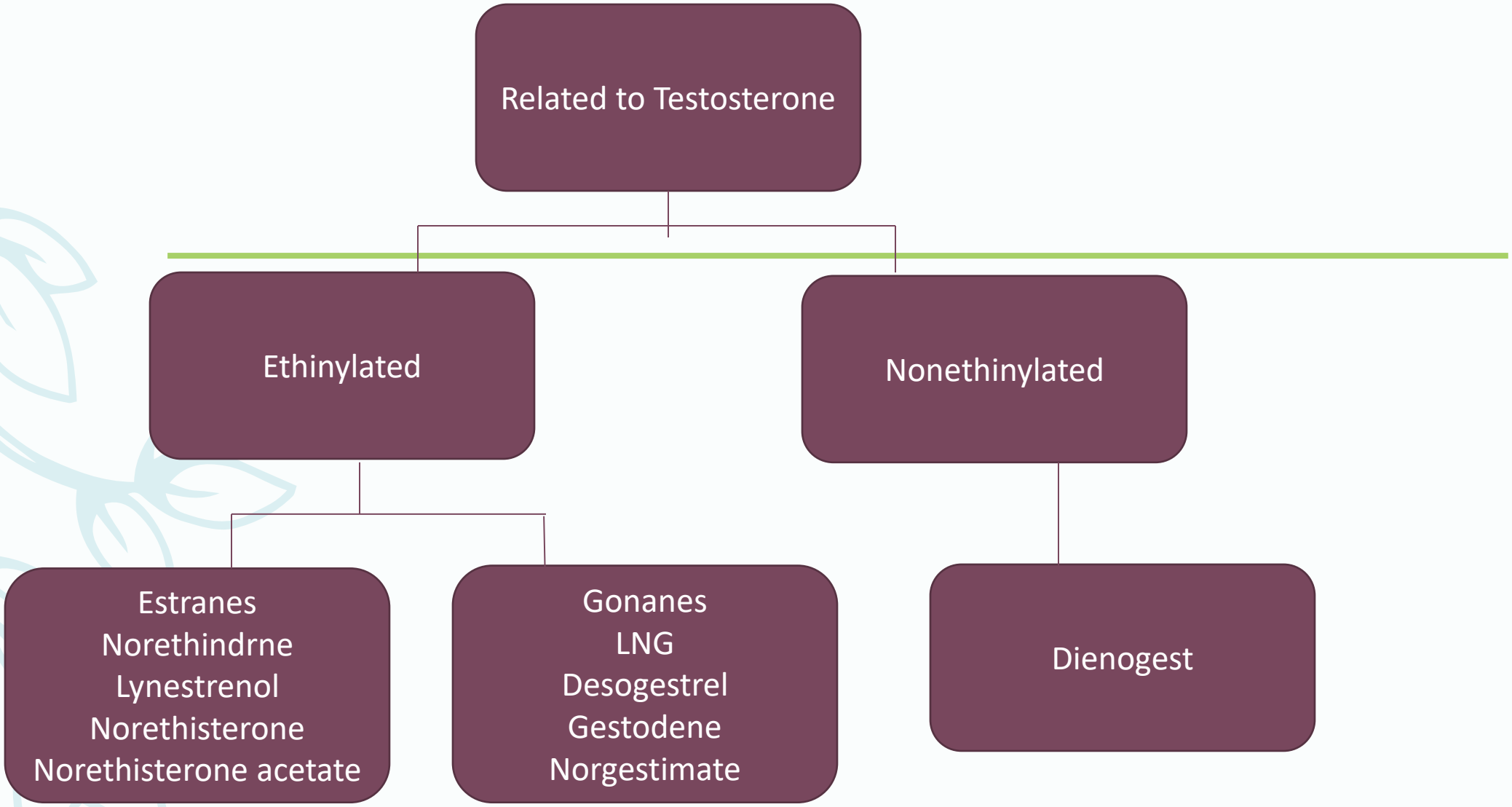
- Secreted by:
  - *corpus luteum*
  - *Placenta(from 2nd trimester till term )*
  - *Adrenal cortex*
- Metabolised:
  - rapidly by the liver
- Excreted:
  - 20% in the urine as sodium pregnanediol glucuronide.

# Types of Progestins

# Classification




Related To Progestrone
Pregnane Derivative
19-norprogesterone Derivative
Acetylated Mpa
Megesterole Acetate
Cyproterne Acetate
Chlormadinone Acetate
Nonacetylated Dydrogesterone
Demogestone
Nomegestrol
Nestrone
Drospirenone


Related to Testosterone
Ethinylated
Nonethinylated
Estranes
Norethindrne
Lynestrenol
Norethisterone
Norethisterone acetate
Gonanes
LNG
Desogestrel
Gestodene
Norgestimate
Dienogest

# Medroxyprogesterone acetate

- **Abnormal uterine bleeding:**
- Oral: 5 or 10 mg daily for 10 to 14 days starting on day 16 or 21 of menstrual cycle. A suggested dose of 10 mg daily for 10 days starting on day 16 of the cycle induces optimum secretory transformation of the endometrium when adequately primed with endogenous or exogenous estrogen.
- Withdrawal bleeding may be expected within 3 to 7 days after discontinuing medroxyprogesterone. Planned menstrual cycling may benefit patients with a history of recurrent episodes of abnormal uterine bleeding.

# Medroxyprogesterone acetate

- **Abnormal uterine bleeding, acute (off-label):** Oral: 20 mg three times a day for 7 days.

- **Amenorrhea, secondary:** Oral: 5 or 10 mg daily for 5 to 10 days. Therapy may be started at any time . Withdrawal bleeding may be expected within 3 to 7 days after discontinuing.
- No contraceptive activity.

# Dydrogesterone

- Dydrogesterone is an established oral retroprogesterone approved for the treatment of threatened and recurrent miscarriage (associated with proven progesterone deficiency), and infertility due to luteal phase insufficiency.
- Compared with progesterone, dydrogesterone has a greater affinity for the progesterone receptors and can be used at lower oral doses to promote endometrial proliferation, owing to its better bioavailability and to the progestogenic activity of its metabolites .

# Dydrogesterone

- Dydrogesterone also appears to have no affinity for androgenic, estrogenic, glucocorticoid or mineralocorticoid receptors , demonstrating a favorable safety and tolerability profile in pregnancy, both to the mother and child.

- Oral: 10 mg twice daily for 14 days starting on day 11 of menstrual cycle

# Levonorgestrel intrauterine device

- The LNg is a highly effective and easy to use treatment option for AUB. Most women using the LNg52/5 develop scant bleeding or amenorrhea. The LNg52/5 is approved by the US FDA for treatment of HMB.
- LNg52/5 has been found to reduce menstrual blood loss in women with HMB by 71 to 95 percent, an efficacy higher than for other hormonal and nonhormonal medical treatments and comparable to that of endometrial ablation .
- In studies of women with HMB, three months after IUD placement, the most common bleeding pattern is spotting. At six months, menstrual suppression is substantially greater, with the majority of patients experiencing amenorrhea or infrequent bleeding, and median hemoglobin and ferritin levels increase 7.5 and 68.8 percent from baseline, respectively.
- Serum progestin concentrations produced by LNg52/5 do not inhibit ovulation in most women. The high local progestin concentration results in a thinning of the endometrium.

# Take home massages

- Compelet evalution of AUB based on FIGO classification.
- Determine the possible causes of AUB.
- Consider endometrial sampling in high risk patients.
- AUB-O is an endocrinologic  abnormality, so it should be treated medically at first.
- Progestins are good options for AUB-O.

# THANKS FOR YOUR ATTENTION