In the name of GOD

IRAN UNIVERSITY
--------- oF----------
MEDICAL SCIENCE

The role of progesterone and progestogens in the management of abnormal uterine bleeding (AUB)

Dr. Mojgan Javedani masroor

Associated professor Of Iran University

In this section explores the role of progesterone and progestogens in the management of abnormal uterine bleeding (AUB)

- In addition, overall, up to 38% of the women who underwent a hysterectomy were never offered an alternative treatment option. Therefore, it is crucial to review the medical options available and to reduce the reliance on major surgical interventions, when possible.

- Among women in whom medical therapies have failed, who do not desire future fertility, and who do not desire a hysterectomy, endometrial ablation can be considered.

Uptodate 2021

➢SAFETY, ACCEPTABILITY, EFFICACY

of progesterone and progestogens in the management of abnormal uterine bleeding

Uptodate 2021

History of progestins and their classification

- Progesterone was first isolated in 1934
- From 1942 to the mid-1970s, unopposed oestrogen was used in HRT.
- from 1975 onwards showed that unopposed oestrogen increased the risk of endometrial cancer
- Research in the early 80s showed that the addition of progestogen had a protective effect against endometrial cancer.

Uptodate 2021

Progestational agents have many important functions , including:

- Regulation of menstural cycle
- Treatment of dysfunctional uterine bleeding
- Prevention of endometrial cancer and hyperplastic precursor lesions
- contraception

Uptodate 2021

Progesterone plays a pivotal role in the management of abnormal uterine bleeding.

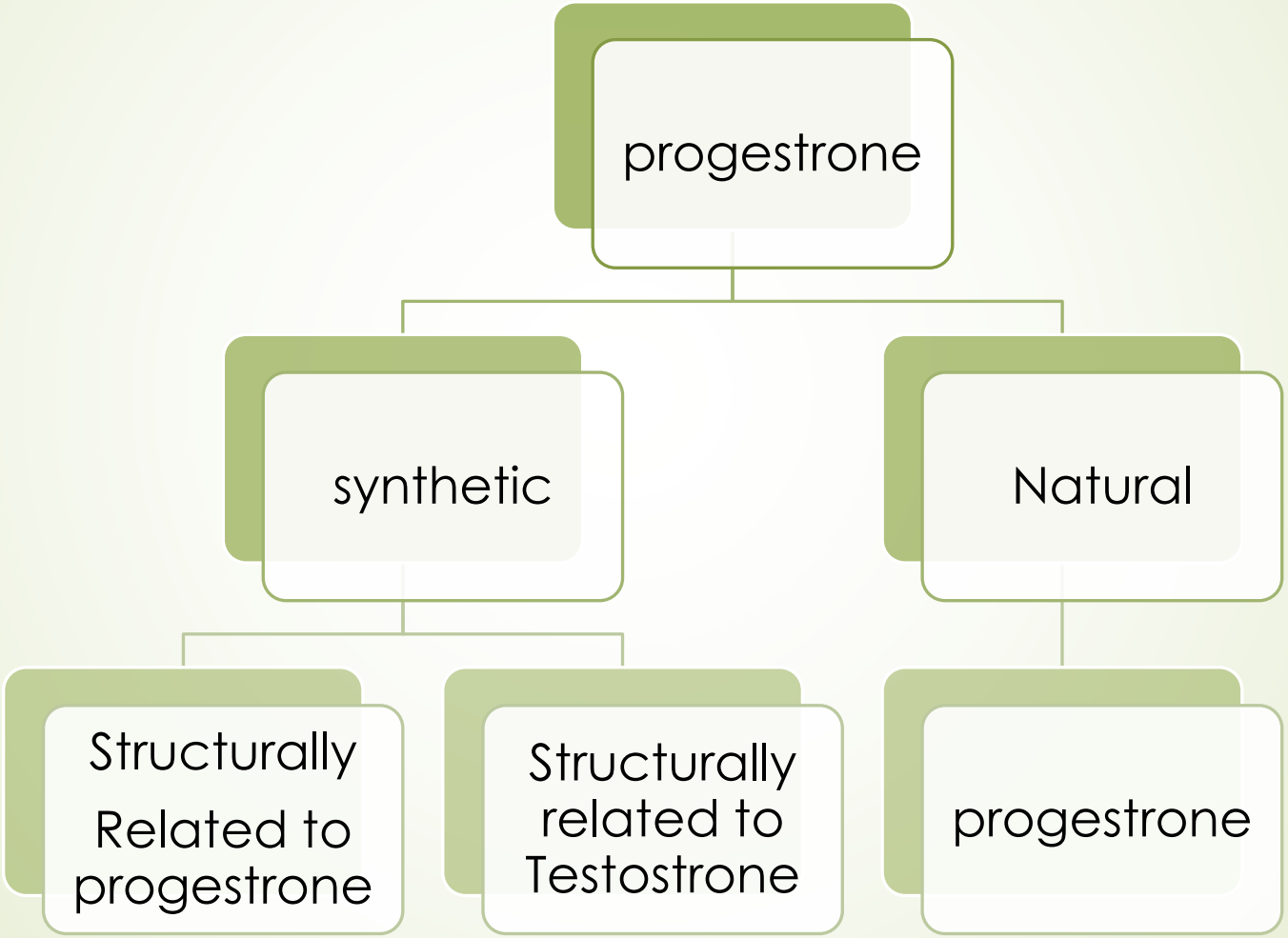
- Its role is diverse and encompasses :
- the reduction of excessive menstrual bleeding
- the cessation of excessive menstrual bleeding
- the endometrial protection and
- treatment of endometrial hyperplasia.
- The preparation of progestin can be extremely important in hormone replacement therapy,
- but the route of administration is also important in both the treatment o
AUB and endometrial hyperplasia

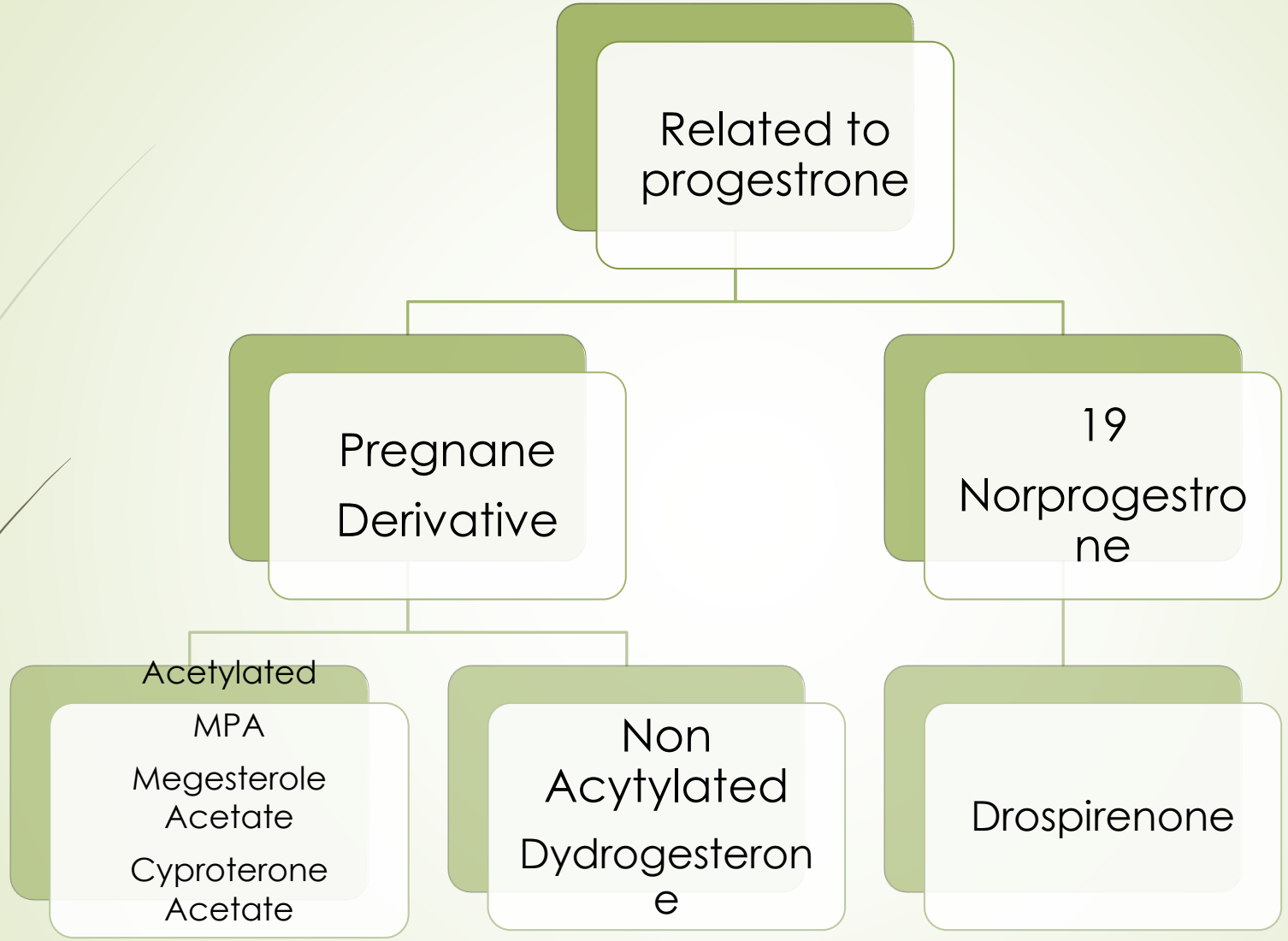
- Progestin selection can be challenging, but should be determined by the mechanisms of action, bioavailability, drug interactions and safety profile , age.

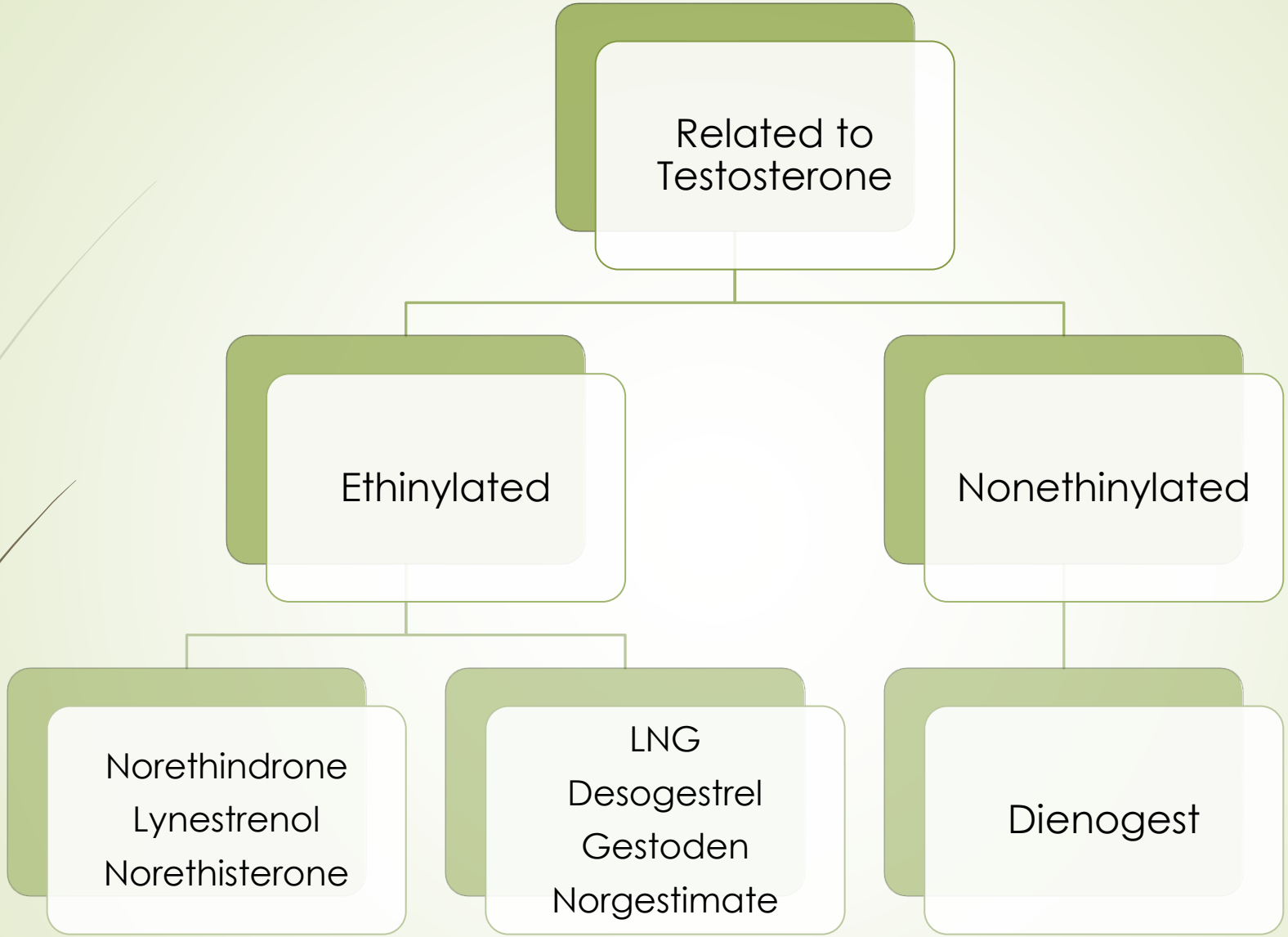
- Their bioavailability depends on multiple factors , including the administration route, metabolism, protein binding and affinity to other steroid receptors (android, glucocorticoid and mineralocorticoid).

Uptodate 2021

Classification




Related to progestrone
Pregnane Derivative
19 Norprogestrone
Acetylated
MPA
Megesterole Acetate
Cyproterone Acetate
Non Acytylated
Dydrogesteron e
Drospirenone


Related to Testosterone
Ethinylated
Nonethinylated
Norethindrone
Lynestrenol
Norethisterone
LNG
Desogestrel
Gestoden
Norgestimate
Dienogest

- Progesterone should refer to the natural hormone or when micronized,

- progestogen is the umbrella term to include progesterone and synthetic progestogens

- Vaginal administration was developed followed by micronized progesterone as the absorption of the hormone through the skin is difficult, unlike oestradiol.

- Progestins also combine with other receptors such as glucocorticoid, mineralocorticoid and androgen, which results in different effects . However, they all decidualise the endometrium, and their potency is judged by their ability to achieve this .

Uptodate 2021

- women's age is thought to be an important consideration in prescribing the safety profile.

- Aging changes pharmacokinetics through various mechanisms including declining hepatic and renal function. Cytochrome P450 metabolism of progestins declines with age and the ability of the liver to conjugate steroid hormones reduces, which can result in altered metabolism and clearance of progestins

Uptodate 2021

ogestogens	Progestational activity	Androgenic activity	Antiandrogenic activity	Levels of SHBG ↓
Progesterone	1	–	+	–
cyproterone acetate	4	–	+++	–
medroxy progesterone	4	+	–	+
norethosterone	4	+	–	–
norgestimate	4	+	–	–
Drospirenone	4	–	+	–
Dienogest	4	–	+	–
nomegestrol	5	–	+	–

Activity of Progestin Agents

Generation	Progestin	Estrogenic	Progestational	Androgenic
First	Norethindrone	++	++	++
	Ethynodiol diacetate	++	+++	+
	Norgestrel	–	+++	+++
	Norethindrone acetate	++	++	++
Second	Levonorgestrel	–	++++	++++
Third	Norgestimate	–	++	++
	Desogestrel	+/–	++++	++
Fourth	Drospirenone	–	+/–	–

Abnormal uterine bleeding (AUB) and its management

- AUB is an umbrella term encompassing heavy menstrual bleeding (HMB) and intermenstrual bleeding.

- Prolonged AUB can lead to anaemia, investigations for malignancy, social isolation and relationship breakdown

- AUB is exceedingly common at the extremes of reproductive years, puberty and perimenopausal, and accounts for 70% of gynaecology clinic attendances in the perimenopausal and menopausal period.

- As such, the management of AUB is a core gynaecological skill

Abnormal Bleeding Categories

- **Brain Dysfunction**
- Brain dysfunctions include hypothalamic and pituitary problems.
- Stress, both physical and emotional
- Inadequate body fat (as in some professional athletes)
- Excess body fat
- Eating disorders
- Serious illness of another nature
- Certain drugs, including some steroids and hormones
- Other alterations with your endocrine system, such as hyperthyroid disease
- Brain injury or malformation
- Primary Unspecified Dysfunction, which is one of the most common causes for anovulation (failure to ovulate) and is frequently not understood.

Abnormal Bleeding Categories

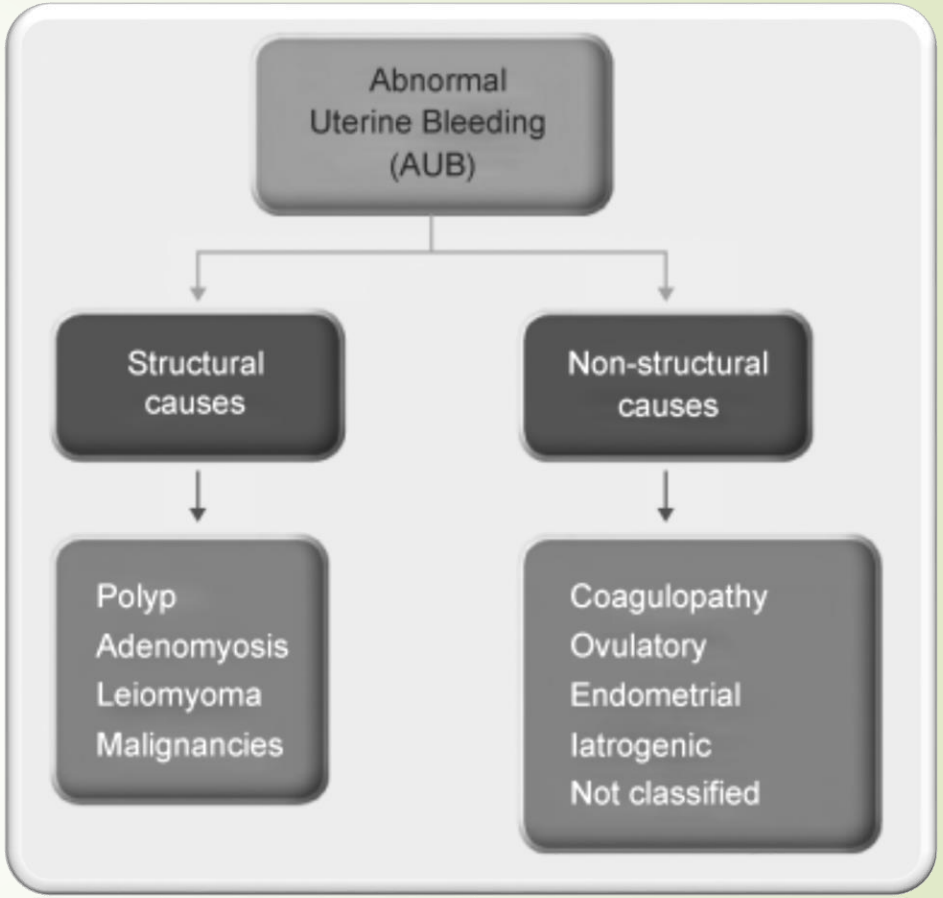
- **Ovarian Dysfunction**
- Some of the reasons an ovary might not ovulate are as follows:
- Abnormally developed ovaries
- Polycystic ovarian syndrome (also called PCO or PCOS)
- Perimenopause
- Menopause
- Ovarian cysts (but not all cysts, not all the time)
- Extensive pelvic adhesions
- Tumors and cancer
- Other disorders of the function of the ovarian follicle and corpus luteum.
-

Even when the brain and ovaries are working normally, it is possible for a problem in the uterus to cause abnormal bleeding.

- Some of these problems are:
- Polyps
- Fibroids
- Adenomyosis
- Uterine malformation
- Scars (such as the uterine scar after a C-section)
- Cervical stenosis (narrowing)
- Oral hormones.

The causes of AUB are divided into 2 groups: those related to uterine structural abnormalities and those unrelated to such abnormalities. The first group consists of polyps, adenomyosis, leiomyoma, malignancy and hyperplasia and the second consists of coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not otherwise classified .

The goals of this new classification system are to provide a uniform and clear communication modality for physicians, scientists, and patients and to facilitate optimal patient care by fostering a common language for research.

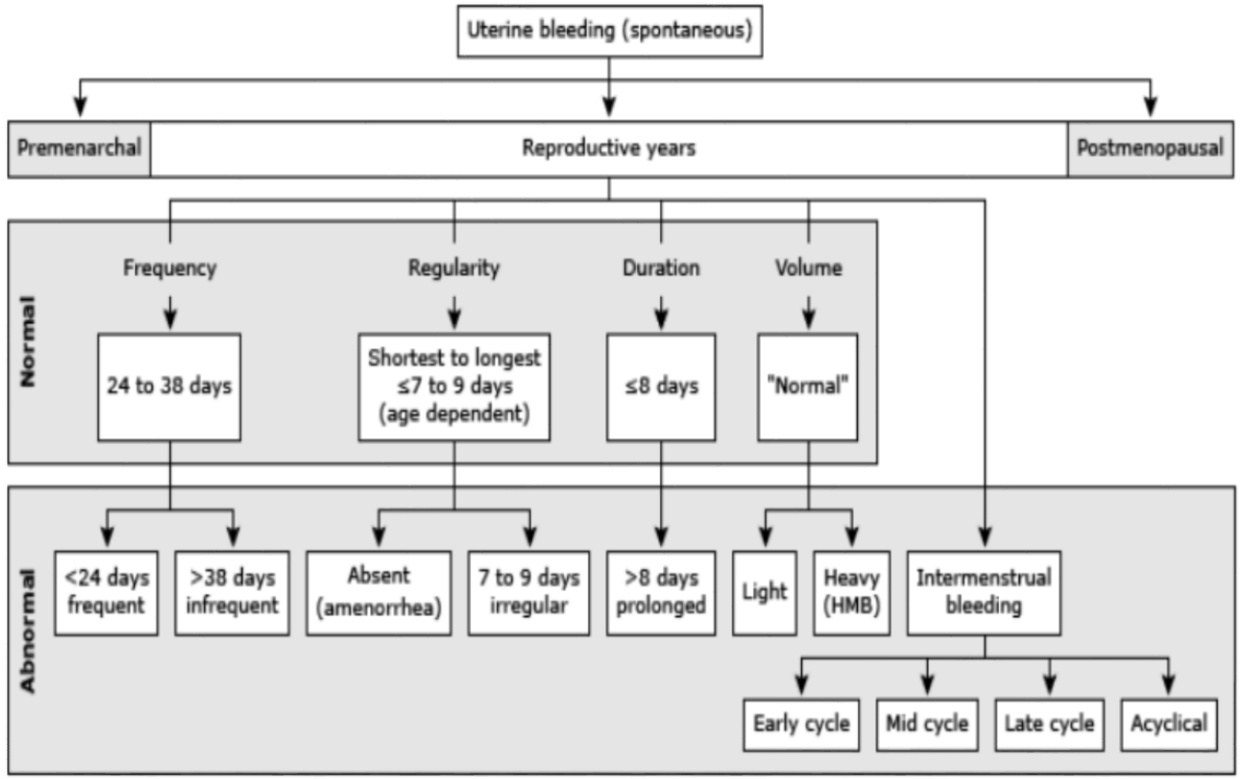


International Federation Of Gynecology &Obstetrics 2011

- In the treatment of women with abnormal uterine bleeding, once a thorough history, physical examination, and indicated imaging studies are performed and all significant structural causes are excluded, medical management is the first-line approach.

Uptodate 2021

ormal and abnormal uterine bleeding patterns in reproductive-age women



polyps

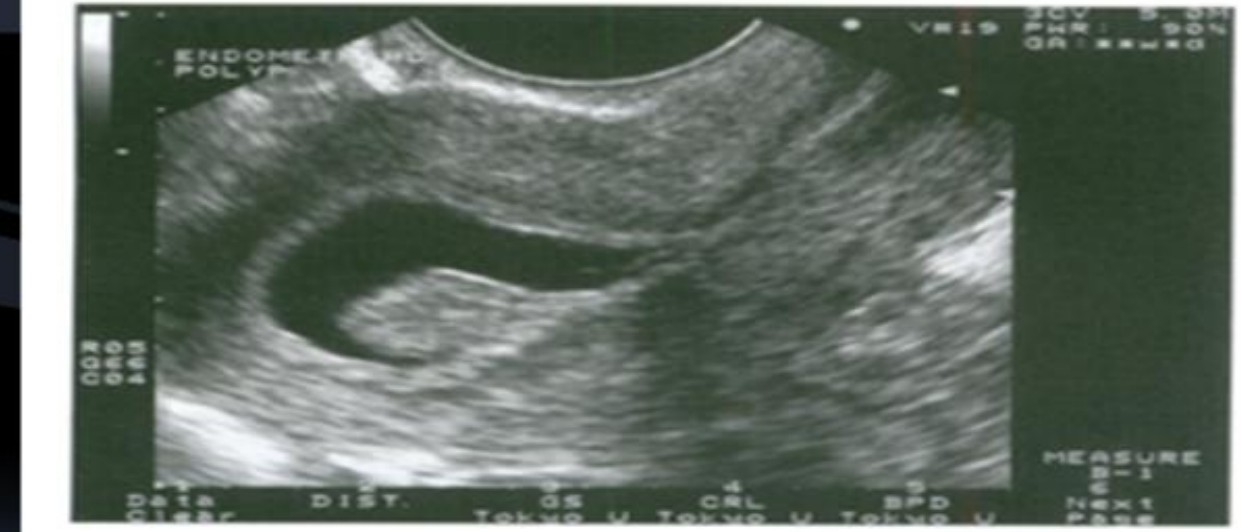


Figure 2 A transvaginal ultrasound scan of the uterus of an infertile patient with irregular menstrual bleeding, after injection of isotonic saline. Note the area of increased endometrial thickening representing a polyp

Treatment of Abnormal Uterine Bleeding of Structural Cause (PALM)

- **Polyp**
- In the presence of an endometrial polyp causing AUB, hysteroscopic polypectomy is an effective and safe option for the diagnosis and treatment, with rapid recovery and early return to activities.
- Small polyps (< 0.5 cm) can be removed in the ambulatory setting using 5-Fr mechanical instruments (sharp scissors and/or grasping forceps) primarily for cost reasons.
- Larger polyps (> 0.5 cm) can be removed en bloc (by resection of the base of the implantation injury with a monopolar or bipolar electrode) or, alternatively, sectioned into fragments.

Uptodate 2021

The role of progesterones in the treatment of polyps

- Clinical data suggest that the antiestrogenic effect of progestins hormone to prevent the development of endometrial polyps and hyperplasia in women on oestrogen replacement therapy and Tamoxifen.

- Post hysteroscopic progesterone hormone therapy has favorable clinical effect in treating endometrial polyps as it can effectively prevent the recurrence of endometrial polyps, relieve the level of hemoglobin and reduce endometrial thickness.

Uptodate 2021

Mechanism of PAIN in ENDOMETRIOSIS

- There are three main mechanisms suggested for the pain in endometriosis:
- The effect of active bleeding from the endometriotic lesions;
- The overexpression of the growth factors and pro-inflammatory cytokines in the ectopic endometrium;
- The irritation or direct invasion of pelvic nerves.

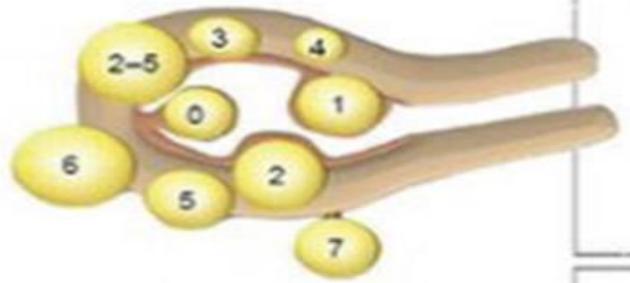
Uptodate 2021

The role of progesterones in the treatment of endometriosis

- The progestins stimulate atrophy or regression of endometrial lesions. The effectiveness of progestins for treating endometriosis is not just related to its growth inhibiting actions, but also to its induction of anovulation, inhibition of blood vessel growth and anti-inflammatory actions

Speroff Clinical Gynecologic Endocrinology and Infertility (9 thEdition)

Leiomyoma



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

Figure 1.

FIGO Leiomyomas subclassification system.

Myoma

- Myoma About 30% of the patients with leiomyomas will require treatment because of the presence of symptoms, including AUB.

- Pharmacological treatment can be used in the presence of symptoms, and it has as alternatives the same drugs available for the reduction of non-structural bleeding.

- IUD , This option is for women with fibroids that do not distort the inside of the uterus. It reduces heavy and painful bleeding but does not treat the fibroids themselves.

Journal of Clinical Medicine

MDPI

J Clin Med. 2020 Dec; 9(12): 3948.
Published online 2020 Dec 5. doi: 10.3390/jcm9123948

PMCID: PMC7762035
PMID: 33291422

Uterine Fibroids and Progestogen Treatment: Lack of Evidence of Its Efficacy: A Review

Jacques Donnez[1,2]

▸ Author information ▸ Article notes ▸ Copyright and License information Disclaimer

Neither was able to demonstrate any significant reduction in bleeding or myoma size in most cases. Indeed, no individual study has established that progestogens have a beneficial effect on the different pathogenetic mechanisms involved in fibroid related HMB.

- Drug therapy is an option for some women with fibroids. Medications may reduce the heavy bleeding and painful periods that fibroids sometimes cause. They may not prevent the growth of fibroids. Surgery often is needed later.

- Surgical approach should be considered if there is no response to the clinical treatment. The path and type of approach will depend on the number, location, and size of the leiomyoma, as well as on the future desire of conception.

Speroff Clinical Gynecologic Endocrinology and Infertility (9 thEdition)

Adenomyosis

- Adenomyosis Often associated with bleeding and dysmenorrhea, adenomyosis is usually treated with a hysterectomy.

- However, studies show that symptoms can be controlled with suppressive therapies similar to those used for AUB without structural change, such as combined contraceptives, progestogens, and the levonorgestrel-releasing intrauterine system (LNG-IUS), especially when there is a desire to maintain the reproductive capacity.

Uptodate 2021

Isthmocele

- The increasing prevalence of isthmocele, thus its gynecological and obstetric complications, led by the rising number of CS deliveries performed worldwide is alarming.
- Postmenstrual spotting, pelvic pain, and secondary infertility are common complaints in gynecologist practice, and isthmocele should figure as a differential diagnosis in women with previous CS deliveries, especially in those with risk factors of multiple previous CSs and retroflexed uterus..

- Diagnosis of isthmocele by TVUS and especially by SIS are cost-effective and have good specificity and sensitivity. Treatment should be offered according to the presence of symptoms, secondary infertility, defect size, and plans for childbearing.

- The defect can be minimally invasively repaired with sparing techniques by hysteroscopy for small defects, and by vaginal approach, laparoscopy, and combined laparoscopy and hysteroscopy for larger defects.

Uptodate 2021

KEY POINTS

- 1) Safety , Accepability , Efficacy
- 2) Progesterone plays a pivotal role in the management of abnormal uterine bleeding
- 3)Progestin selection can be challenging
- 4) women's age is thought to be an important consideration in prescribing the safety profile
- 5)medical management is the first-line approach
- 6) PATIENT SELECTION in MEDICAL TREATMENT for uterine structural abnormalities

.

با تشکر از همه ی شما عزیزان