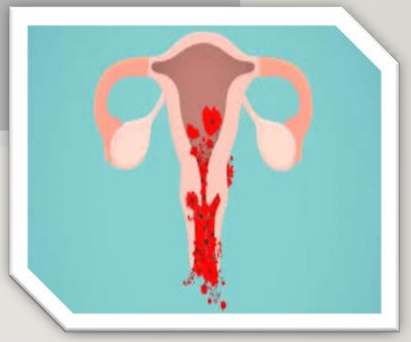
'' Menstrual Abnormality in Thalassemia ''



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- Beta-thalassemia (BTM) major , the most common hemoglobin disorder worldwide
- High prevalence in people of Mediterranean / Arab / Asian origin
- The carriers of BTM , ***1.5%*** of the global population (80–90 million people)
- The total annual incidence of symptomatic individuals , ***1 / 100,000***

Thalassemia diseases

- Transfusion-dependent thalassemia (TDT)
- Non- transfusion-dependent thalassemia (NTDT)

Advances in the primary care of BTM major

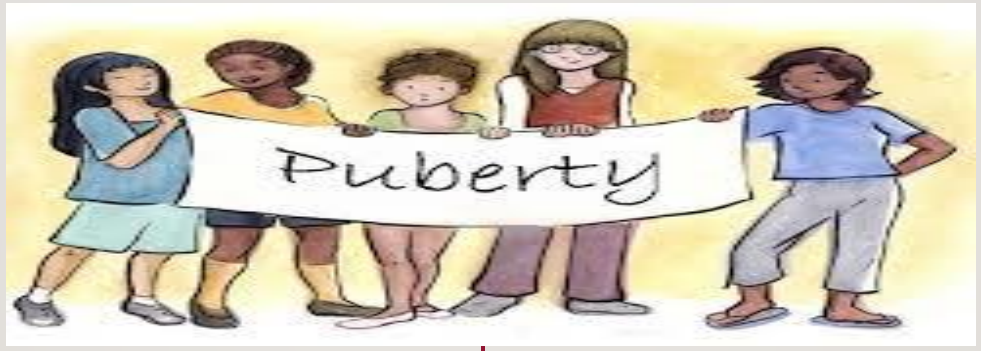
- Optimal blood transfusion → Improved quality of life
- Chelation RX → Improved survival rates

Iron overload → Iron-related organ toxicity → Involvement of the heart, liver, & **endocrine glands**

The accumulation of hemosiderosis in the hypothalamus & pituitary gland may cause **hypogonadotropic hypogonadism**

Normal Pubertal Development

Process of sexual maturation requires approximately 4 years



- Growth acceleration
- Breast development **Thelarche**
- Pubic hair development **Pubarche**
- Maximum growth rate
- **Menarche**
- Ovulation

Normal Pubertal Development

- Timing of puberty, menarche, and menstrual patterns are considered indicators of overall health

- **The difference may result**
  - BMI
  - genetic factors
  - environmental factors
  - socioeconomic conditions
  - nutrition
  - access to preventive health care
  - **chronic illness**

Chronic disease

+

Iron overload

Acquired hypogonadotropic hypogonadism

particularly in poorly controlled patients

Delayed puberty

Late menarche

Arrested puberty

Primary & secondary Amenorrhea

Chronic disease

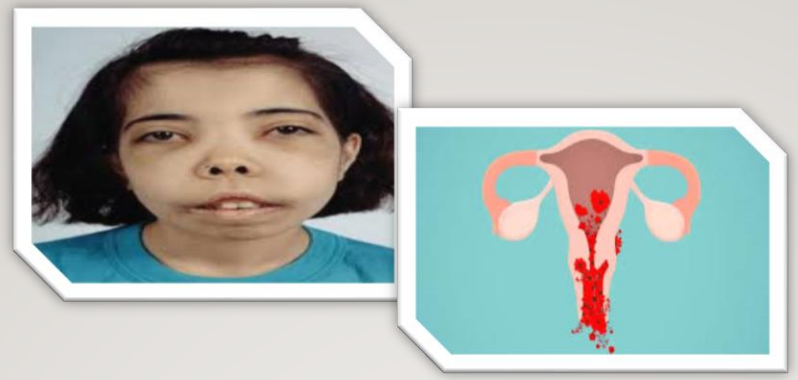
+

Iron overload

Hypothyroidism

GH deficiency

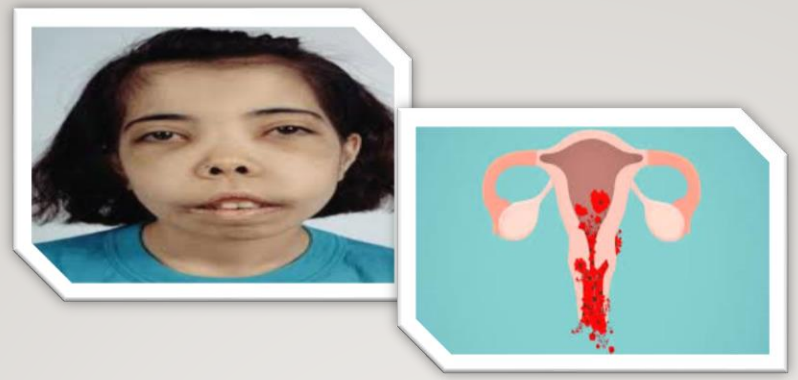
particularly in poorly controlled patients



Late menarche in patients with TDT

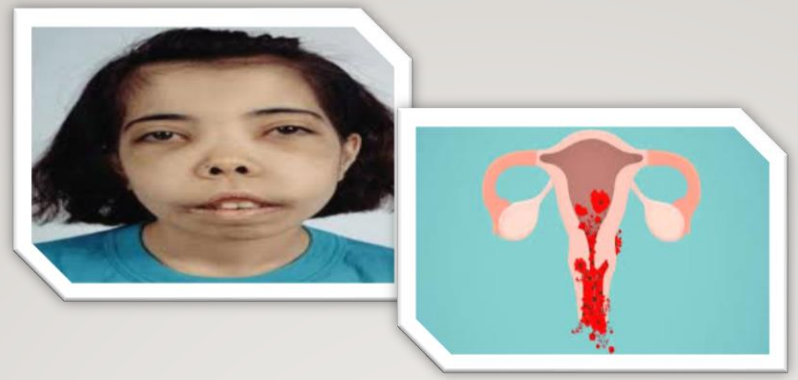
- Chronic illness (Thalassemia)
- Gonadotoxicity (Iron overload)
- **Functional Hypogonadotropic hypogonadism**
- Poly Cystic ovarian SX ,…..

The importance of regular & constant ICT should be conscious that even short periods of interruption / irregular adherence to ICT can have late deleterious effects on the H-P-G axis /pubertal & menstrual abnormalities



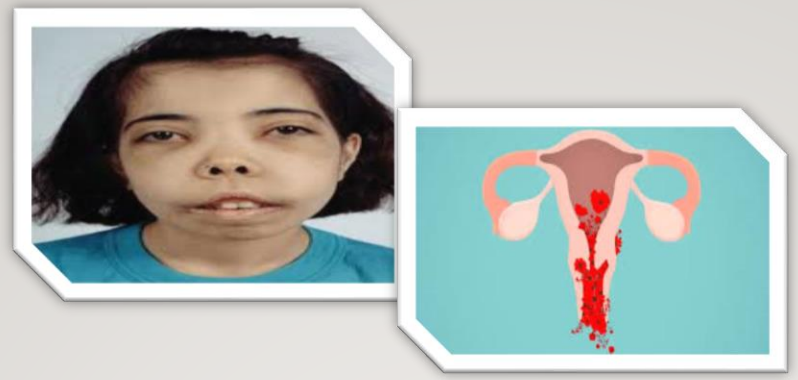
Hypogonadotropic hypogonadism

- The most common endocrinopathy in thalassemia patients(40-91%)
- It leads to **delay puberty , AUB , sexual dysfunction , subfertility , Psychologic impact**
- Hypothalamo-pituitary damage is usually irreversible
- It still appears to be common, despite advances in chelation regimens



Diagnostic Evaluation :

- FSH
- LH
- TSH
- Estradiol
- Prolactin
- MRI of Pituitary
- Ferritin
- Bone Age Assessment



The importance of regular & constant ICT should be conscious that even short periods of interruption / irregular adherence to ICT can have late deleterious effects on the H-P-G axis /pubertal & menstrual abnormalities

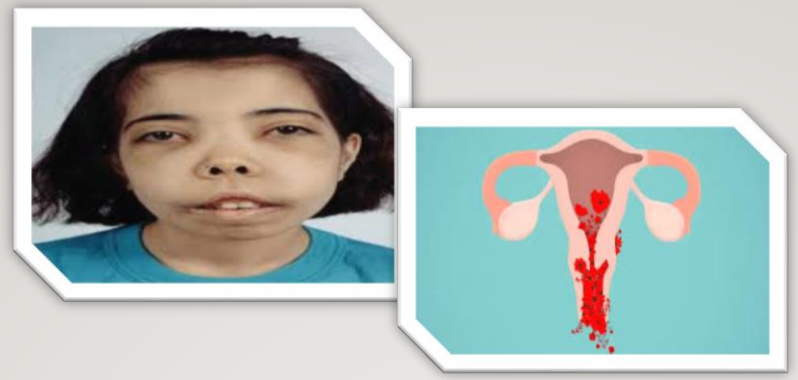
- Ovarian reserve is preserved in the majority of TM, despite a low follicle count & reduced ovarian volume

- AFC , affected by the low gonadotropin secretion & cannot accurately reflect ovarian reserve

- AMH the better marker for determination of reproductive stage

- HH & amenorrhea due to hemosiderosis of the hypothalamus & pituitary gland are common in BTM

- The effect of iron load on the ovaries is unclear



- 3 iron chelators are available to treat iron overload:
  - desferrioxamine (DFO)
  - deferiprone (DFP)
  - deferasirox (DFX)

- **Hormonal replacement therapy**

(to avoid the secondary effects of low estrogen, delay puberty , low bone density)

- **The kinds of hormonal therapy :**

1- estrogen–progestin sequential RX

2- oral contraceptives

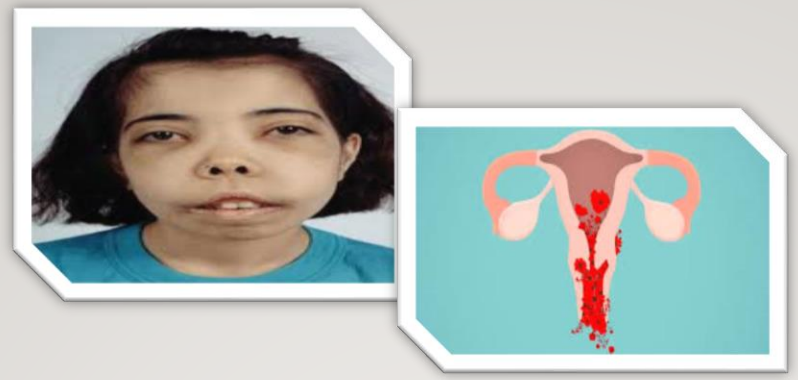
To mimic the physiological menstrual cycle

- The appropriate chelation regimens
- The role of antioxidant supplementation.

Early diagnosis & treatment are essential to achieve normal puberty, target height, and reduce the risk of long-term infertility & sexual dysfunction

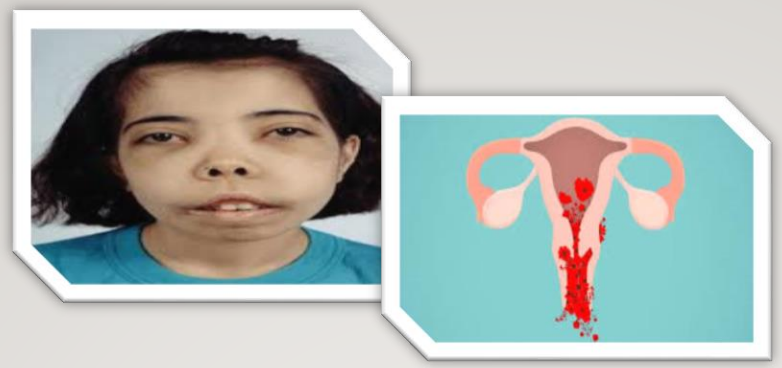
well-managed chelation RX & its early initiation, allowing good control of iron overload, reduce the risk of hypogonadism.

in order to optimize the pubertal development & possibility of fertility, measures must be taken starting from childhood & this would involve the collaboration of **hematologists, endocrinologists & gynecologists**



- **Menstrual disorders** & AUB are among the most frequent gynecologic concerns in adolescents with thalassemia

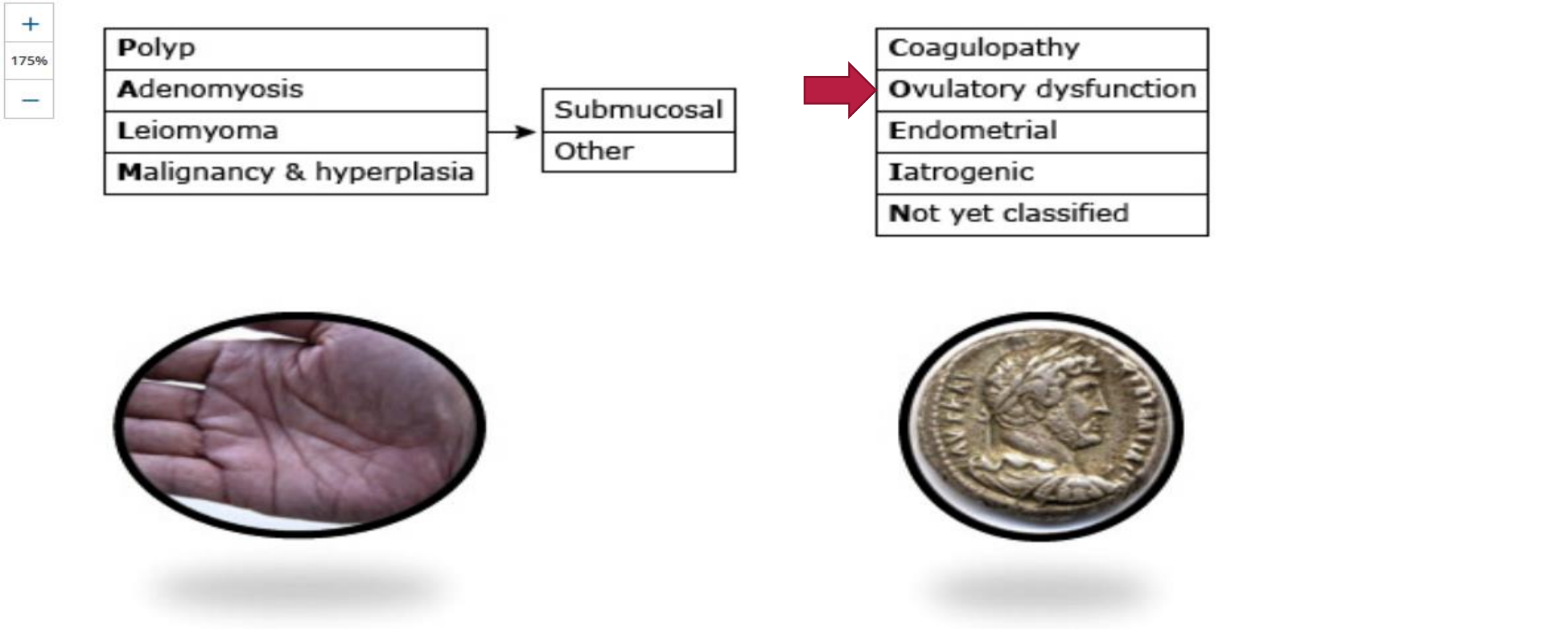
- Regularity patterns include three main dimensions:
  - **frequency**
  - **duration**
  - **intensity**



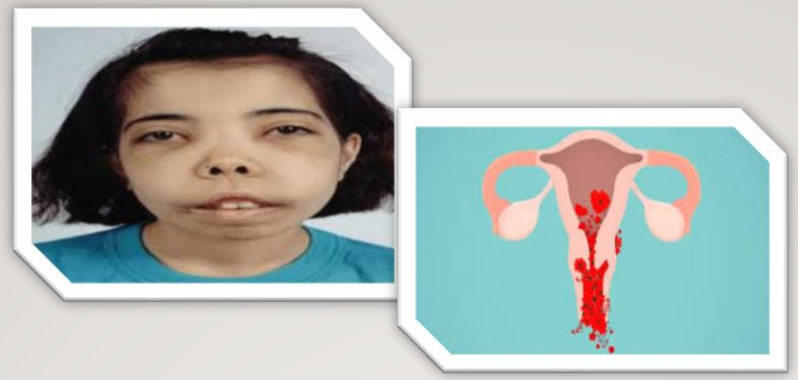
- **PRETREATMENT EVALUATION :**

  - Exclude pregnancy & pelvic infections
  - Evaluate for other causes of abnormal uterine bleeding (**PALM- COIN CLASSIFICATION**)

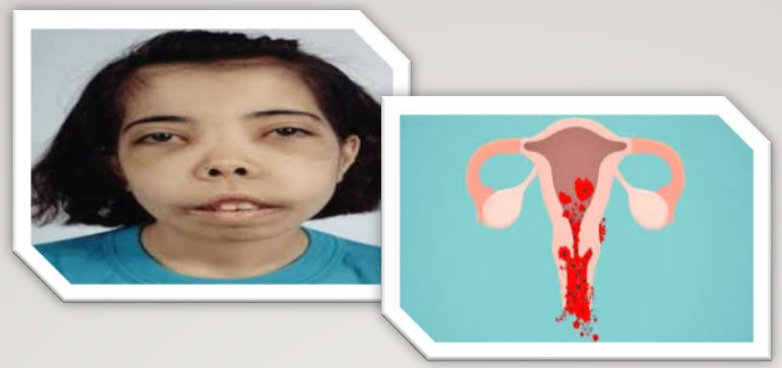
PALM-COEIN classification system for abnormal uterine bleeding in nongravid reproductive-age women



Basic classification system. The basic system comprises four categories that are defined by visually objective structural criteria (PALM: polyp, adenomyosis, leiomyoma, and malignancy and hyperplasia), four that are unrelated to structural anomalies (COEI: coagulopathy, ovulatory dysfunction, endometrial, iatrogenic), and one reserved for entities that are not otherwise classified (N). The leiomyoma category (L) is subdivided into patients with at least one submucous myoma (L_{SM}) and those with myomas that do not impact the endometrial cavity (L_O). In the 2018 version, the words "submucosal" and "other" do not appear and the phrase "not yet classified" has been changed to "not otherwise classified."



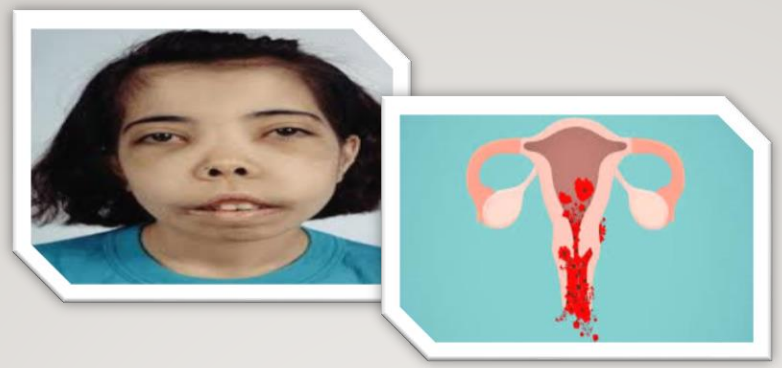
- **Anovulatory uterine bleeding** is a subset of AUB , a diagnosis of exclusion (Palm - Coin Classification) .
- Anovulatory uterine bleeding is characterized by noncyclic menstrual blood flow that occurs when sex steroid production is not synchronized.
- It can present with oligomenorrhea / amenorrhea / prolonged bleeding
- Immaturity of the hypothalamic-pituitary-ovarian (HPO) axis is the most common cause of anovulatory uterine bleeding in adolescents



- **Not currently bleeding**
- **If contraception is not desired :**

  - Progestin-only regimens
  - Combined estrogen-progestin regimens

Equally appropriate choices

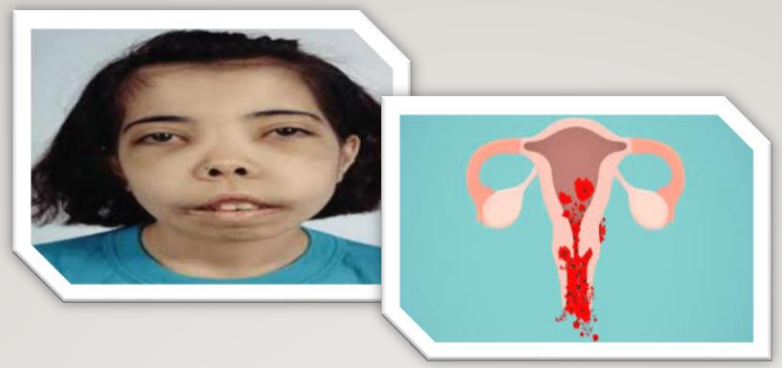


- **If contraception is desired**
- Estrogen is **not contraindicated**

  - combined estrogen-progestin contraceptive (cyclic – continues)

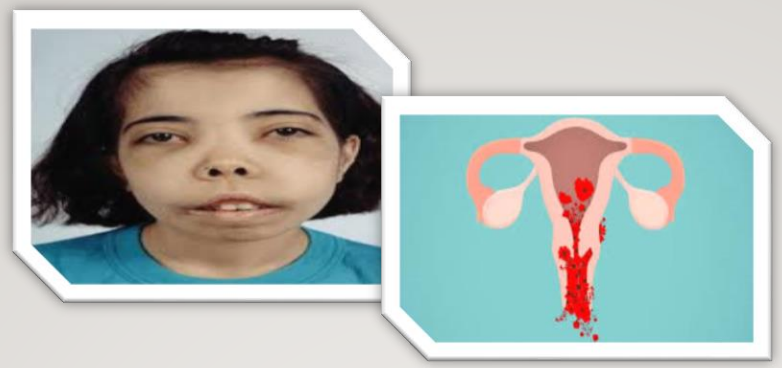
  - contraceptive patch

  - Vaginal ring



- **If contraception is desired**
- If estrogen is **contraindicated**
  - Daily progestin-only contraceptive regimen
  - Hormonal intrauterine device (IUD)
  - Depot medroxyprogesterone

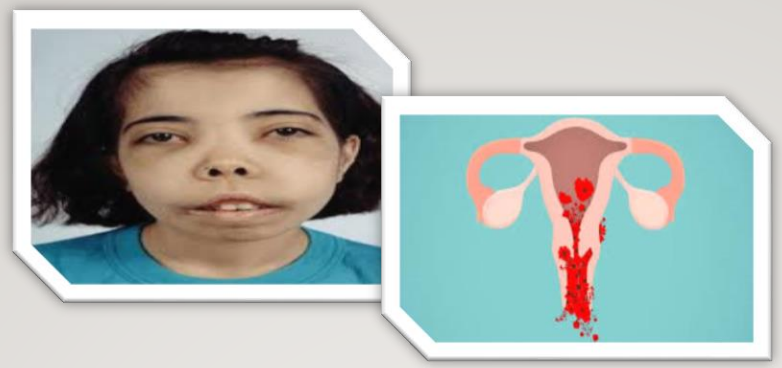
- migraine with aura
- SLE
- antiphospholipid antibodies SX
- arterial / venous thromboembolic disease
- estrogen-dependent tumors
- hepatic dysfunction / disease



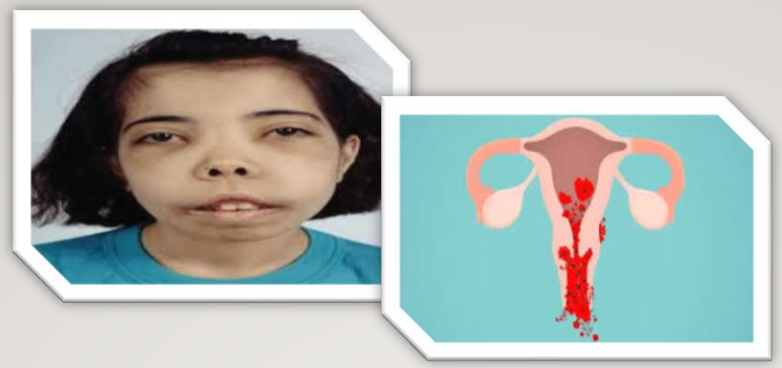
- **Oral progestin-only options**

-Norethindrone 0.35 mg once daily(effective for contraception when taken consistently)

-Drospirenone 4 mg once daily for 24 days followed by an inactive pill once daily for four days



- **Cyclic options** **(no contraceptive efficacy)**
- -Norethindrone acetate 5 mg daily for the first 5 - 10 days of each calendar month
- -Micronized progesterone 200 mg daily for the first 12 days of each calendar month
- -Medroxyprogesterone acetate 10 mg daily for the first 10 days of each calendar month



- **Currently bleeding**

- Combined estrogen-progestin oral contraceptives as <u>first-line therapy</u>

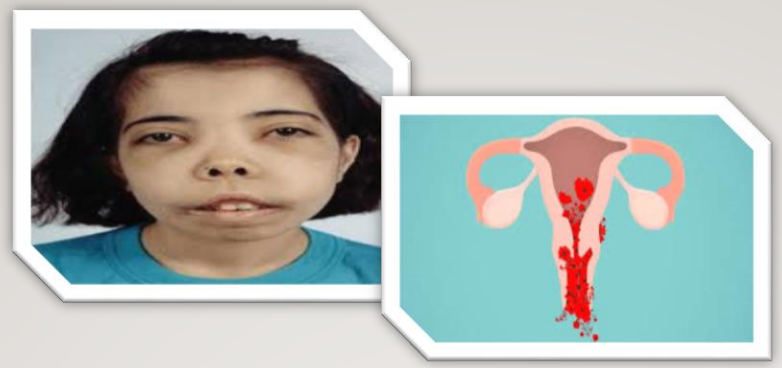
(the estrogen component, ethinyl estradiol dose of 30 - 35 mcg , provides greater hemostasis than progestin alone)

- Progestin-only therapy

(an alternative for patients who cannot tolerate or have a **<u>contraindication</u>** to estrogen)

- 52 mg <u>levonorgestrel</u> (LNG) IUD

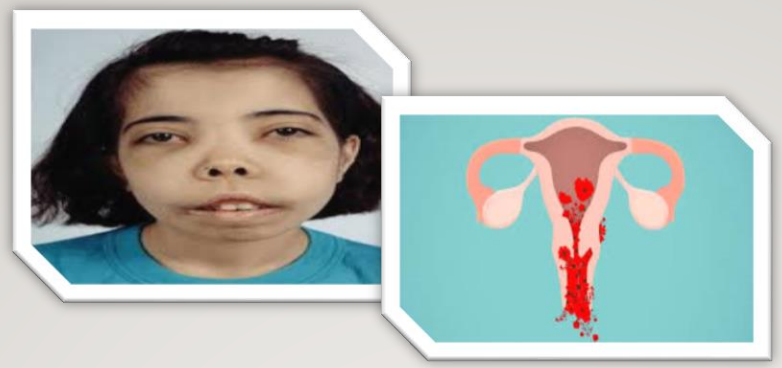
(both contraception & stabilization of bleeding)



- The first follow-up visit is scheduled 3 months after the initial episode of bleeding to assess bleeding patterns & response to hormonal therapy.

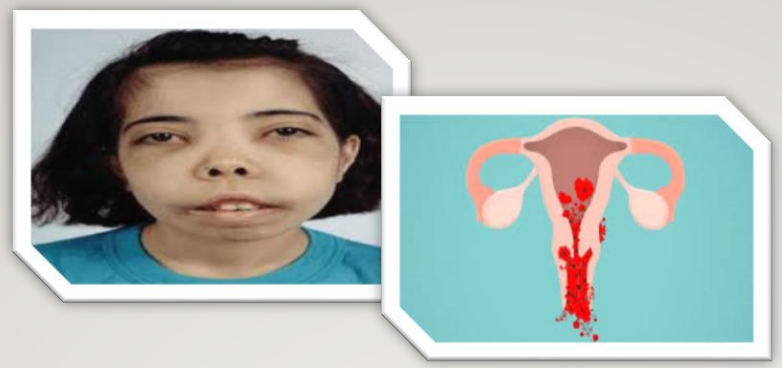
- Once the bleeding pattern is stable, patient follow-up visits are scheduled annually

- **Tranexamic acid (TXA)** is an option for patients who decline all hormonal treatments
- The dose is 1300 mg orally, 3 times per day during the first 1-5 days of each menstrual bleed
- The very low risk of thromboembolism in patients who are taking concurrent COCs and TXA



- **Estrogen-containing oral option**

- **The tapering regimen:**
  - One pill every eight hours until the bleeding stops (usually within 48 hours)
  - One pill every 12 hours for 2 days
  - One pill daily for 21 days
- Once endometrial shedding has occurred and if the patient desires a cyclic bleed or needs contraception transition to a cyclic oral progestin-only regimen or a daily oral progestin-only contraceptive

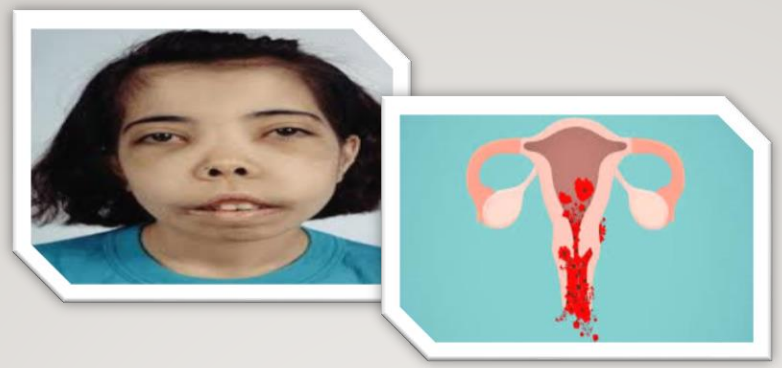


- A planned withdrawal bleed allows for shedding of a dyssynchronous proliferated endometrium.

- Following the withdrawal bleed, continue the next cycles of pill- taking

- The high doses of estrogen used during the taper often cause nausea:
  - **ondansetron** 4 to 8 mg orally
  - **promethazine** 12.5 to 25 mg orally or per rectum.

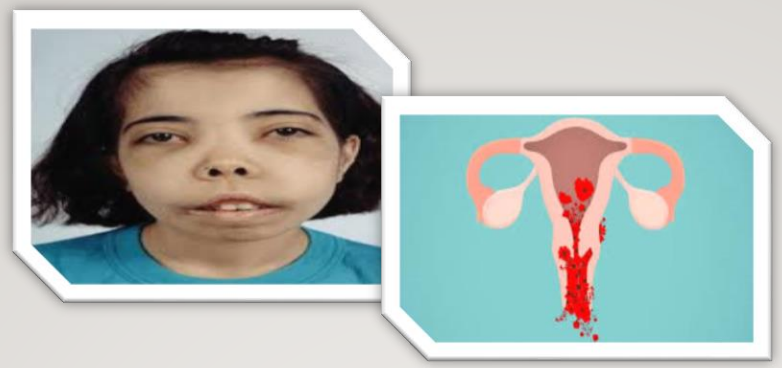
  The antiemetic should be taken one hour before each dose of hormone



- **Progestin-only options**
  - 5 to 10 mg of oral **norethindrone acetate** daily until the bleeding stops & HB≥12 g/Dl
  - 5 to 40 mg of oral **medroxy progesterone acetate** daily until the bleeding stops & HB≥12 g/Dl

- Once the bleeding is controlled, 5-7 day pause of hormones to permit the shedding of the endometrium.

- Once endometrial shedding has occurred and if the patient desires a cyclic bleed or needs contraception transition to a cyclic oral progestin-only regimen or a daily oral progestin-only contraceptive



- **Cyclic Progestin-only options**

-Norethindrone acetate 5 mg daily for the first 5 to 10 days of each calendar month

-**Micronized progesterone** 200 mg daily for the first 12 days of each calendar month

-Medroxyprogesterone acetate 10 mg orally for the first 10 days of each calendar month

- •Daily options **with contraceptive efficacy**

-Norethindrone 0.35 mg once daily; effective for contraception when taken consistently

-Drospirenone 4 mg once daily for 24 days followed by inactive pill once daily for four days

SEVER VAGINAL BLEEDING

- **Choice of therapy**
- **combined oral contraceptive (COC) pills**

- containing 30 to 35 mcg of ethinyl estradiol , as the first line of hormonal therapy

- **Progestin-only therapy**
- **, 0.3 mg norgestrel , 0.4 to 1 mg norethindrone**

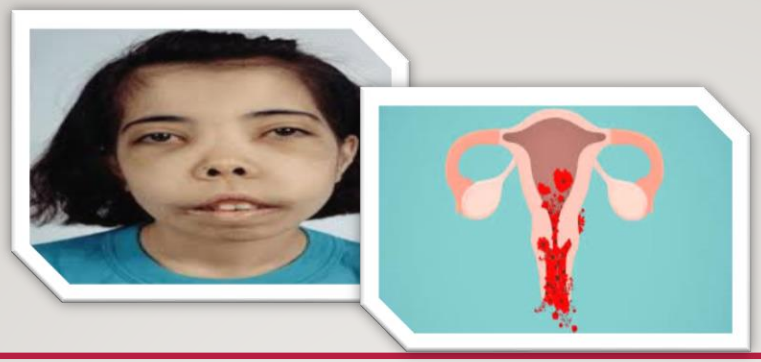
- **IV conjugated estrogen**

SEVER VAGINAL BLEEDING

- **Choice of therapy**
- **combined oral contraceptive (COC) pills**

-containing 30 to 35 mcg of ethinyl estradiol , as the first line of hormonal therapy

- **(Tapering regimen of COC)**
- ●One pill every 4-6 hours until the bleeding subsides (usually within 24 hours)
- ●One pill every 8 hours for 3 days
- ●One pill every 12 hours for up to 2 weeks
- ●One pill once per day until maintenance therapy is initiated



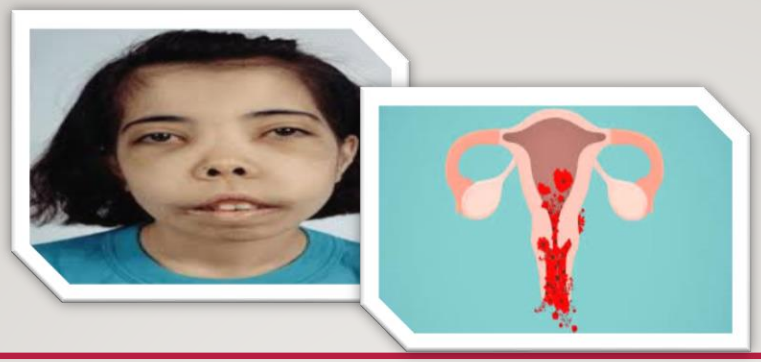
- The **norethindrone** dose (5 to 10 mg, , up to 4 times per day)

- Once bleeding subsides, the number of tablets can be tapered over several days.

- **Two commonly used tapering regimens :**

-One tablet 2 per day for 7 days, followed by one tablet daily until maintenance therapy is initiated

- One tablet 3 times per day for 3 days, followed by one tablet 2 per day for 7 days, followed by one tablet daily until maintenance therapy is initiated

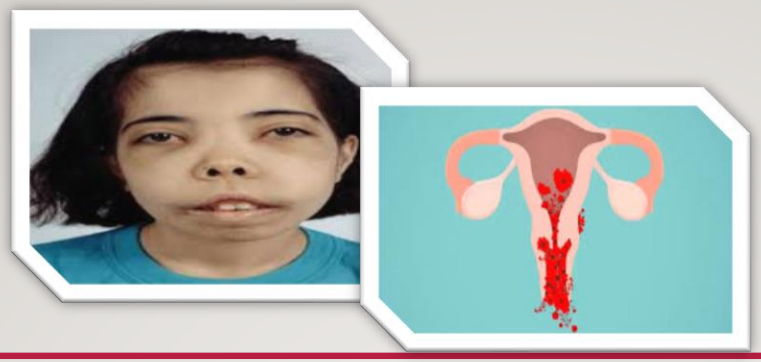


- **IV estrogen**

reserved for patients with severe anovulatory uterine bleeding who are :

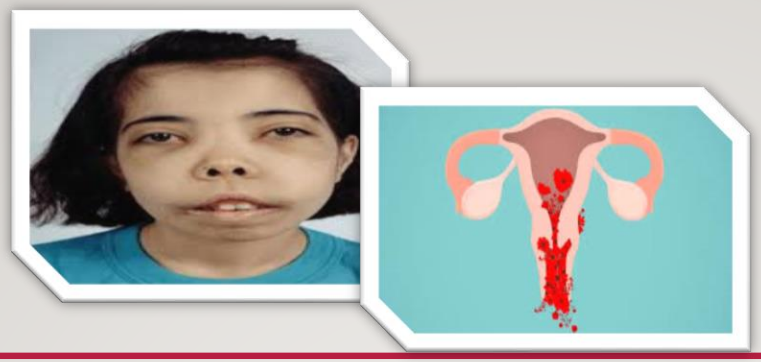
- unstable & cannot take oral medications
- heavy bleeding continues after 24 hours of oral estrogen-progestin combination RX

- 25 mg of IV **conjugated estrogen** every 4 to 6 hours for 24 hours.
- Bleeding usually subsides within 4 to 24 hours of initiating IV estrogen
- Thromboembolism is a potential complication , **NO** more than 6 doses should be administered



- **Inadequate response to IV estrogen therapy**
- add hemostatic therapy when severe anovulatory uterine bleeding does not improve after 24 hours of IV estrogen therapy

- **tranexamic acid (TXA)** 1300 mg 3 times per day for up to 5 days
- **aminocaproic acid** 5 g orally during the first hour, followed by a continuous dose of 1 - 1.25 g per hour (**NOT** be used in patients with kidney function impairment)



- **Management of refractory uterine bleeding**
- additional evaluation (,examination under anesthesia, endometrial sampling, pelvic ultrasound) may be necessary to evaluate for other causes of abnormal uterine bleeding.

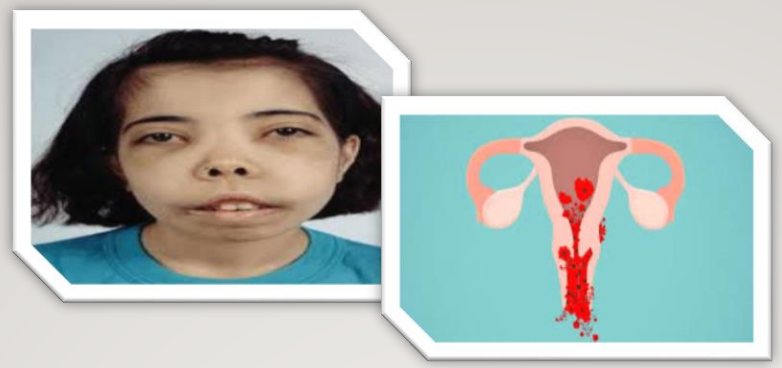
(the presence of clots within the uterus may hamper uterine contractions and require evacuation)

- Suction curettage/ (D&C)

- a therapeutic D&C procedure is rarely required in adolescents with anovulatory uterine bleeding

(suction curettage is preferred to sharp curettage)

Thanks for your attention



- **If a cyclic pattern has not been established or flow is not reduced**
- change the progestin to one that has more progestational activity **(norgestrel or LNG)**
- increase the number of COC pills per day to the lowest dose that controls bleeding.

- **If the menstrual pattern has not improved because the patient has difficulty taking a daily pill**
- 52 mg LNG IUD
- Depot medroxyprogesterone acetate (DMPA)