Abnormal uterine bleeding in adolescents: Management

F.Tabatabaei

Pediatric Endocrinologist

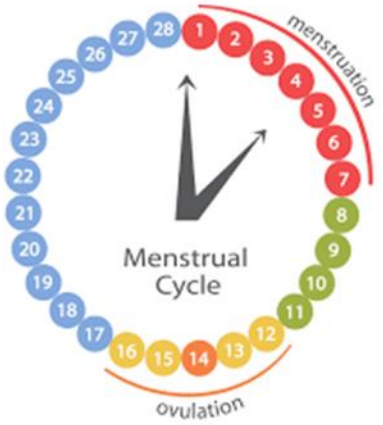
INTRODUCTION

- AUB are most frequent gynecologic complaints in adolescents.
- AUB refers to bleeding that is excessive or occurs outside of normal cyclic menstruation

INTRODUCTION

Abnormal uterine bleeding (AUB) is defined as bleeding from uterine corpus that is abnormal in :

- Duration
- Volume
- Frequency and/or
- Regularity



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Epidemiology

- About 10% of outpatients

- Common at extremes of reproductive life, but can occur at reproductive age:

- 50% at near menopause
- 20% in adolescents
- 30% at reproductive age

Normal Menstrual Cycles in Adolescents

- Menarche usually occurs in 12-13 yrs
- Normal cycle of adolescent every 21-45 days
- Bleeding lasting two and seven days
- Frequency of cycles decreases at higher postmenarchal ages.
- 60-80% of adolescents by third year postmenarche cycles are 21-34 days, similar to adults
- Average normal blood loss is 30-40 mL
- Use of 3-6 pads or tampons per day or 10-15 per cycle
- ❑ >50% of menstrual loss is an endometrial transudate
- ❑ 30-50% consists of whole blood components
- Chronic loss of ≥80 mL blood associated with anemia

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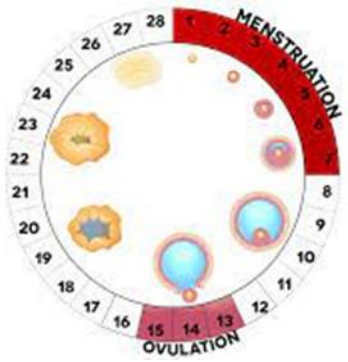
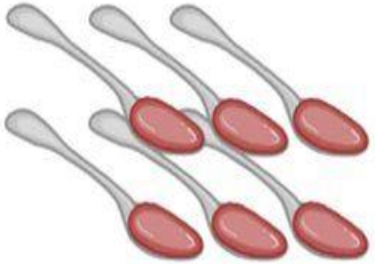


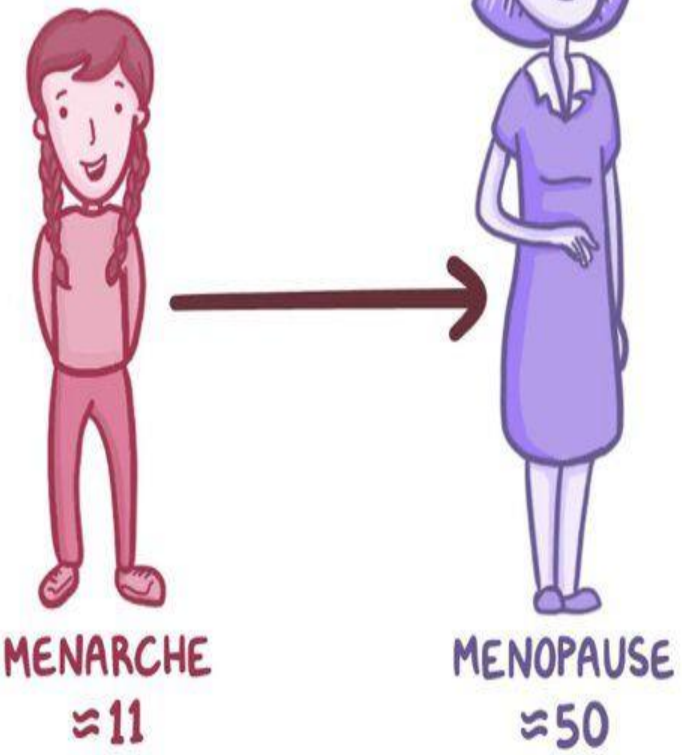
VAGINAL BLEEDING*

↳ FEMALES of REPRODUCTIVE AGE

* NORMAL = MENSTRUATION



- < 8 days
- < 80 mL (6 Tbsp)
- SHORTEST & LONGEST CYCLES don't VARY by > 9 days



Abnormal Uterine Bleeding

- The International Federation of Gynecology and Obstetrics (FIGO) recommends use of term AUB to describe any aberration of menstrual volume, regulation, duration and/or frequency
- FIGO also proposes to discard some definitions from accepted terminology, such as “menorrhagia”, “metrorrhagia”, “hyper/hypomenorrhea”, “polymenorrhea” and “dysfunctional uterine bleeding” as they are controversial, confusing and poorly defined
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Abnormal Uterine Bleeding

- Heavy menstrual bleeding (HMB) is most common clinical presentation of AUB.
  Formerly called “dysfunctional uterine bleeding”, DUB, refers to AUB which is not caused by structural lesions of the uterus

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Table 1. Abnormal uterine bleeding-The International Federation of Gynecology and Obstetrics recommendations for menstrual terminology

Category	Definition
Disorders in regularity	
Irregular menstrual bleeding	Variation > 20 days over a period of one year
Absent menstrual bleeding (amenorrhea)	No bleeding in a 90-day period
Disorders in frequency	
Infrequent menstrual bleeding (oligomenorrhea)	One or two episodes in a 90-day period
Frequent menstrual bleeding	More than four episodes in a 90-day period
Disorders in amount of flow	
Heavy menstrual bleeding	Excessive blood loss which interferes with the woman's physical, emotional, social and material quality of life and which can occur alone or with other symptoms
Heavy and prolonged menstrual bleeding	Excessive blood loss exceeding eight days
Light menstrual bleeding	Bleeding less than 5 mL in a period
Disorders of duration of flow	
Prolonged menstrual bleeding	Menstrual periods that exceed eight days on a regular basis
Shortened menstrual bleeding	Menstrual bleeding lasting less than two days

Abnormal Uterine Bleeding

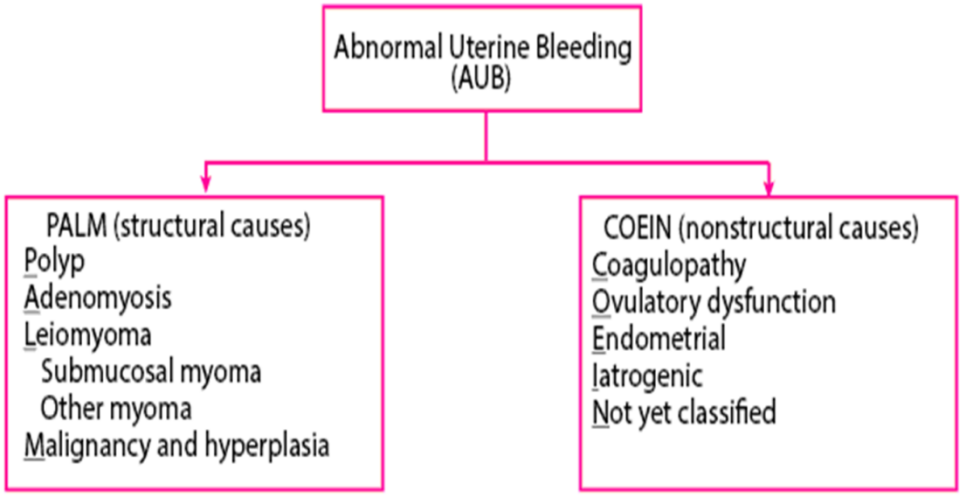
- FIGO defines etiology of AUB using PALM-COEIN classification:

➢ (structural causes)

❑ Polyp
❑ Adenomyosis
❑ Leiomyoma
❑ Malignancy

➢ (non-structural causes)

❖ Coagulopathy
❖ Ovulatory dysfunction
❖ Endometrial Hyperplasia
❖ Iatrogenic
❖ Not yet classified system



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Abnormal Uterine Bleeding

- AUB is very rarely due to structural problems (1.3-1.7%) in adolescents.
- Anovulatory cycles, manifest as amenorrhea, oligomenorrhea or HMB owing to immature hypothalamic-pituitary-ovarian axis are most common cause of AUB among adolescents.
- As another leading etiology, coagulopathy prevalence is reported to vary between 5% and 28% among hospitalized adolescents with HMB
- vWD was found to be 13% .

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Table 2. Differential diagnosis of heavy menstrual bleeding in adolescents

Endocrine causes	**Infections**
Anovulatory bleeding	Cervicitis
PCOS	Adenomyosis
Thyroid disease	**Disorders of the uterus**
Other	Myoma
Bleeding disorders	Intrauterine device
von Willebrand disease	Polyps
Platelet dysfunction	Cancer
Thrombocytopenia	**Medications**
Clotting factor deficiency	Depot medroxyprogesterone
Pregnancy	Anticoagulants
Abortion	**Trauma**
Ectopic pregnancy	**Foreign body**
Gestational trophoblastic disease	**Hemorrhagic ovarian cysts**

PCOS: polycystic ovary syndrome

Normal Cycles

- Occurrence of ovulatory menstrual cycles require regular interaction of hypothalamus, hypophysis, ovary and endometrium.
- GnRH pulses from hypothalamus induce FSH and LH secretion from hypophysis →induce development of a dominant follicle
- LH stimulates thecal cells to divide and produce androgens.
- FSH stimulates granulosa cells to divide and convert androgens to estradiol (E2) and E2 rise through follicular phase.
- When E2 exceeds a critical level (>200 pg/mL for two days) GnRH rises with positive feedback and causes an LH surge.
- LH surge activates proteolytic enzymes which leads to follicular rupture and causes luteinization of granulosa and theca cells, resulting in a marked increase in progesterone production.
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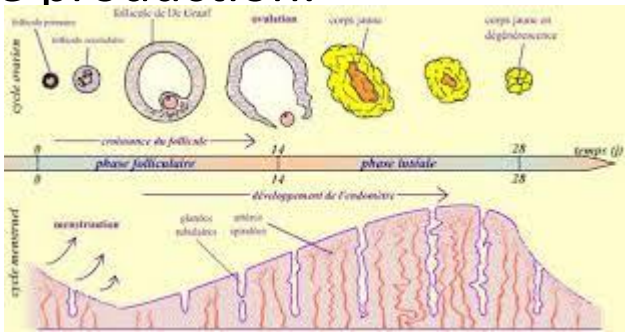

Normal Cycles

- E2 induces endometrial epithelial cell proliferation, gland growth and vascularization and production of both E2 and progesterone receptors thus preparing endometrium to respond to luteal production of progesterone.
- Progesterone stabilizes thickening endometrium by influencing production of key proteins such as matrix metalloproteinase 1, 3, and 9 which degrade extravascular and stromal matrix.
- Progesterone also stimulates production of tissue factor and plasminogen activator inhibitor 1, expediting coagulation and clot stabilization
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Anovulatory Cycles

- Pituitary potential to respond to GnRH stimulation and positive feed-back effect of E2 progressively improve after menarche.
- During first two postmenarchal years, approximately half of menstrual cycles are anovulatory.
- However, at five years post-menarche 75% of cycles are ovulatory and this increases further over next several years, reaching an 80% rate.
- Delayed or absent ovulation, either physiological or due to polycystic ovary syndrome (PCOS), results in lack of progesterone and excessive E2 production from ovarian follicles, causing endometrium to proliferate and to become prone to unpredictable menstrual bleeding in both timing and amount.
- For these reasons anovulatory cycles are leading cause of HMB during adolescence.
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Evaluation

- The focus of initial evaluation of a patient with HMB is to determine whether:

❖Bleeding is acute and causing hemodynamic instability

❖through careful history taking, PE, lab test and radiologic imaging

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Evaluation

- History should be taken both with and without parents because :

❖Some of questions difficult for patients to answer in presence of their parents, especially those relating to sexual activity,

❖While parents present may help to clarify details in some cases.

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Evaluation

- History should include:
- ➢ Menstrual history (age of menarche, regularity, duration, number of pads/tampons per day)
- ➢ Sexual history
- Past medical history :
- systemic illness
- current/recent medication
- Systemic review: (symptoms of systemic causes of HMB)
- obesity, PCOS, hypothyroidism, hyperprolactinemia, hypothalamic or adrenal disorder
- family history:
- Coagulopathy
- Hormone sensitive cancers
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Evaluation

- 1-Pelvic examination with a speculum or transvaginal ultrasonography may not be possible in sexually inexperienced adolescents.
- It is possible to postpone this exam until a trial of medical therapy has been attempted, as structural lesions in adolescents are very rare.
- 2-Pelvic ultrasonography provides non-invasive information about genital tract structural lesions, especially in adolescents in whom physical examination is limited.
- It also gives additional information about endometrial thickness and PCOS.
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Evaluation

- Minimum laboratory evaluation should include:

1. Human chorionic gonadotropin
2. CBC
3. Peripheral blood smear
4. Ferritin level
5. PT, PTT
6. Fibrinogen
7. The von Willebrand panel include:
   - Plasma von Willebrand factor (vWF) antigen
   - Functional tests for vWF
   - Factor VIII activity

- Blood type O have lower levels of vWF than A or B.
- vWF panel either before or 7 days after ceasing estrogen treatment
- Estrogen can increase plasma vWF antigen

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- Additional tests include:

1. Exclusion of infection in sexually active adolescents
2. Evaluation of thyroid functions in patients with hypothyroid symptoms
3. Significant bleeding history and non-diagnostic initial testing should referred to hematologist

Causes of abnormal vaginal bleeding in the nonpregnant adolescent

Causes of abnormal vaginal bleeding in the nonpregnant adolescent

Cause	Comments/associated clinical features
Causes of bleeding from the uterus	
Anovulatory uterine bleeding related to immature HPO axis at the onset of menarche*	Most common cause in adolescents; unpredictable timing of bleeding and variable amounts of flow
Other causes of ovulatory dysfunction	
PCOS* or other causes of hyperandrogenism (eg, adrenal tumor, CAH)	Hyperandrogenism (acne, hirsutism, clitoromegaly)
Thyroid disease	Weight loss or gain; heat or cold intolerance; fatigue
Hyperprolactinemia	Galactorrhea, vision change, headaches
Hypothalamic dysfunction	Stress, intense exercise, change in weight (loss or gain)
Estrogen-secreting ovarian tumor	Ovarian enlargement or mass
Hypercortisolism (Cushing syndrome)	Central obesity, proximal muscle weakness, purplish striae
Pituitary disease (tumor, infarction)	Impaired vision, headache, pituitary hormone deficiencies (eg, fatigue, cold intolerance, decreased appetite) or excess (eg, hyperprolactinemia)
Diabetes mellitus	Polyuria, polydipsia, nocturia
Primary ovarian insufficiency (premature ovarian failure)	Primary ovarian insufficiency in adolescents can be associated with chromosomal abnormalities (eg, Turner syndrome), thyroid or adrenal abnormalities, and fragile X syndrome. ¶[1]
Medications: Hormonal contraception Androgens Spironolactone Antipsychotics and antidepressants Corticosteroids Chemotherapeutic agents	

Infection	
Pelvic inflammatory disease*	Fever, mucopurulent discharge, lower abdominal or pelvic pain, pelvic organ tenderness (eg, cervical motion tenderness, adnexal tenderness), inflammation of the genital tract
Endometritis unrelated to pregnancy	Vague, crampy, lower abdominal pain Intrauterine foreign objects Uterine radiation
Endometriosis	Cyclic pain with menses that may progress to acyclic pain; bowel symptoms (rectal pain, constipation, painful defecation, rectal bleeding); bladder symptoms (dysuria, urgency, hematuria)
Bleeding disorders (coagulopathy)* Thrombocytopenia (eg, ITP, leukemia, aplastic anemia) Coagulation disorders (eg, von Willebrand disease, liver dysfunction, vitamin K deficiency) Associated with systemic disease (eg, systemic lupus erythematosus, liver disease, chronic renal disease) Associated with medications (eg, anticoagulants, platelet inhibitors)	Suggested by one of the following: [2] Heavy menstrual bleeding since menarche ≥1 of the following: Postpartum hemorrhage Surgery-related bleeding Bleeding associated with dental work ≥2 of the following: Bruising one to two times per month Epistaxis one to two times per month Frequent gum bleeding Family history of bleeding symptoms
Structural uterine problems Polyp Adenomyosis Leiomyoma (fibroid) Malignancy and hyperplasia Congenital uterine anomalies (eg, septate/arcuate, unicornuate, etc)	May be identified through imaging or histopathology
IUD-related bleeding	Intermenstrual: All IUDs Excessive volume: Primarily copper IUD Irregular bleeding: Primarily levonorgestrel IUDs Amenorrhea: Primarily IUDs containing 52 mg levonorgestrel

Causes of vaginal bleeding from sites other than the uterus
Ovary: Cyst, tumor
Cervix: Carcinoma, cervicitis, ectropion, hemangioma, polyp
Vagina: Carcinoma/sarcoma, foreign body (eg, retained tampon), trauma, vaginitis
Vulva: Trauma, sexually transmitted diseases (eg, ulcers), dermatologic conditions
Gastrointestinal tract: Hemorrhoids, infectious colitis, inflammatory bowel disease, vascular malformation, rectal prolapse
Urinary tract: Urinary tract infection, irritation of the urethral meatus, urethral trauma

HPO: hypothalamic-pituitary-ovarian; PCOS: polycystic ovary syndrome; CAH: congenital adrenal hyperplasia; ITP: immune thrombocytopenic purpura; IUD: intrauterine device.

* Most common causes in adolescents.

¶ Refer to UpToDate content on primary ovarian insufficiency for additional information.

CATEGORIES OF DYSFUNCTIONAL UTERINE BLEEDING

- **Estrogen Withdrawal Bleeding**

- This type of bleeding can occur after bilateral oophorectomy, radiation of mature follicles, chemotherapy for malignancy, or administration of estrogen to a castrated woman followed by discontinuation of therapy. Midcycle spotting can occur secondary to decrease in estrogen that precedes ovulation.

- **Estrogen Breakthrough Bleeding**

- This type of bleeding is a result of amount of estrogen that is stimulating the endometrium. Low levels of estrogen result in intermittent spotting that may be prolonged but is usually light in the amount of flow. High levels of estrogen for prolonged periods of time result in lengthy periods of amenorrhea followed by acute, often heavy, bleeding with excessive blood loss.

- **Progesterone Withdrawal Bleeding**

- Removal of corpus luteum, or administration and then discontinuation of progesterone or a nonestrogenic synthetic progestin result in endometrial desquamation. For progesterone withdrawal bleeding to occur, endometrium must first be proliferated by endogenous or exogenous estrogen. Progesterone withdrawal bleeding still occurs if estrogen therapy is continued after progesterone is withdrawn. Only increased estrogen levels of 10- to 20-fold delay progesterone withdrawal bleeding.

- **Progesterone Breakthrough Bleeding**

- This occurs with an abnormally high ratio of progesterone to estrogen. Continuous progesterone therapy without adequate estrogen results in bleeding of variable duration as seen in low-dose estrogen breakthrough bleeding. This is pattern of bleeding that can be seen with long-acting progestin-only contraceptive methods such as Norplant and Depo-Provera and progesterone-only birth control pill.
- Dysfunctional Uterine Bleeding Severino, M, Glob. libr. women's med., (ISSN: 1756-2228) 2011; DOI 10.3843/GLOWM.10294

SEVERITY CLASSIFICATION

Mild

- Menses >7 days or
- Cycles <24 days for ≥2 months
- Slightly or moderately ↑menstrual flow
- Hgb≥12 but may mild ↓ (10 to 12)

Moderate

- Menses>7 days or
- Frequent menses every 1-3weeks
- moderate to heavy menstrual flow
- Hgb ≥10

Severe

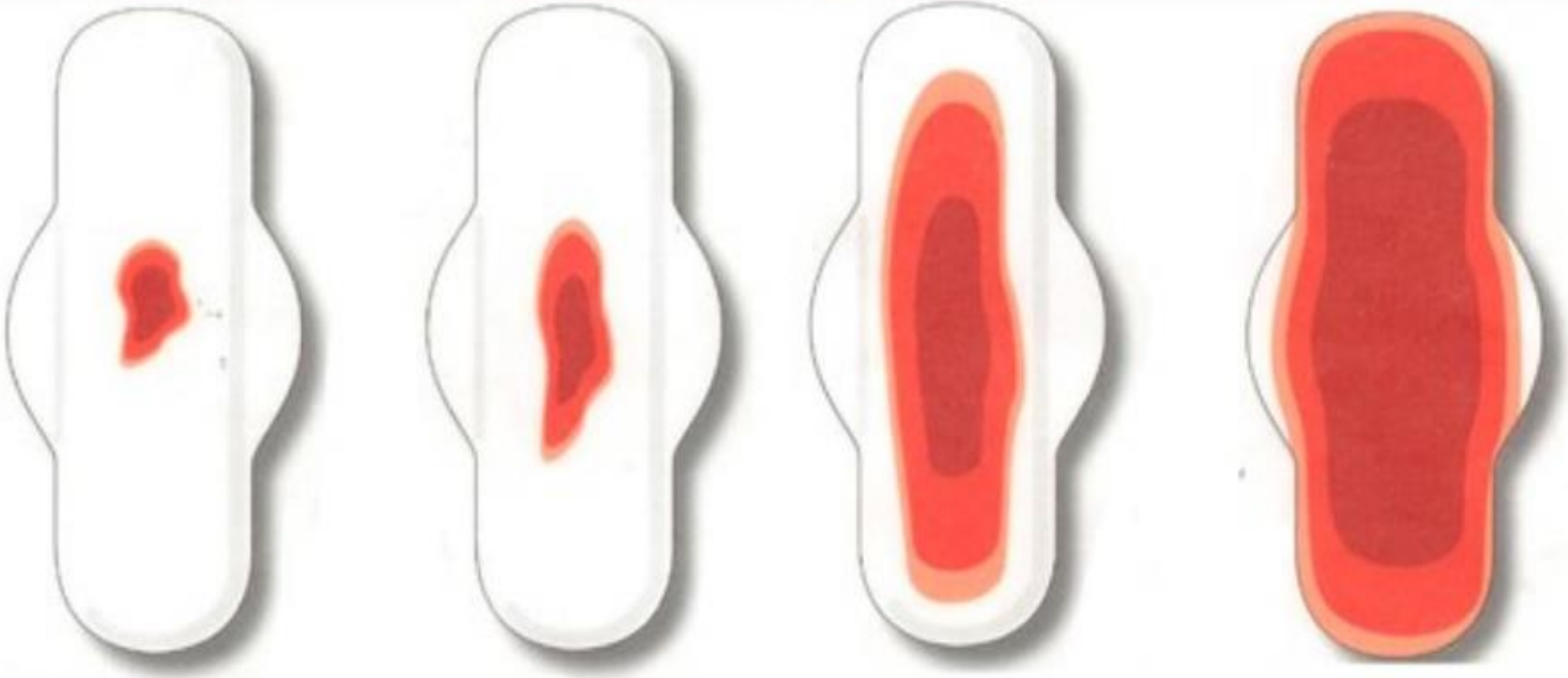
- Disruptive menstrual cycles with heavy bleeding that causes Hgb <10
- ± hemodynamic instability

Questions to ask to help quantify blood loss during menses

Questions to ask to help quantify blood loss during menses

How often do you change your sanitary pad/tampon during peak flow days?
How many pads/tampons do you use over a single menstrual period?
Do you need to change the pad/tampon during the night?
How large are any clots that are passed?
Has a medical provider told you that you are anemic?
Women with a normal volume of menstrual blood loss tend to:
Change pads/tampons at ≥3 hour intervals
Use fewer than 21 pads/tampons per cycle
Seldom need to change the pad/tampon during the night
Have clots less than 1 inch in diameter
Not be anemic

How much are you Bleeding?



Scant amount
Blood only on tissue when wiped or less than one-inch stain on maxi pad

Light amount
Less than four-inch stain on maxi pad within one hour.

Moderate amount
Less than six-inch stain on maxi pad within one hour.

Heavy amount
Saturated maxi pad within one hour.

GOALS OF MANAGEMENT

- Establishment ± maintenance of hemodynamic stability
- Correction of acute or chronic anemia
- Return to pattern of normal menstrual cycles
- Prevention of recurrence
- Prevention of long-term consequences of anovulation (eg, anemia, infertility, endometrial cancer)

Treatment

- Treatment options include:
  - Iron supplementation
  - Combined oral contraceptives (COCs)
  - Progesterone
  - Nonsteroidal anti-inflammatory drugs (NSAIDs)
  - Antifibrinolytics
  - Desmopressin
  - GnRH analogues
- Management is largely based on severity of bleeding and anemia.
- If an underlying cause is identified, specific treatment is given additionally.
- As HMB in adolescents is mostly due to anovulatory cycles, treatment is focused on anovulatory uterine bleeding.
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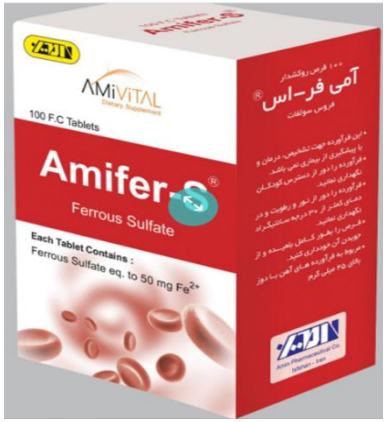
Pretreatment evaluation

Before initiating treatment of AUB important to exclude:

1. pregnancy
2. pelvic infections
3. Other causes of AUB and immature HPO axis based on clinical findings
4. Lab studies before initiation of hormone or blood transfusion

Management of iron deficiency

- Mild or moderate bleeding and mild, asymptomatic anemia (Hgb10 to 12)⟶ initiate 60 mg elemental iron per day.
- Severe bleeding⟶initiate 60 mg of elemental iron once or twice per day as soon as stable and able to take pills by mouth



Hormone effects

- In adolescents with anovulatory uterine bleeding and sustained acyclic estrogen secretion, bleeding occurs when endometrium proliferates beyond ability of endogenous estrogen to maintain integrity of endometrium.
- Administration of exogenous estrogen or progestin permits additional endometrial proliferation, which heals sites of endometrial bleeding, and provides hemostasis .
- Administration of progestin stabilizes endometrial lining .

Hormone effects

- Clinicians may be concerned that high doses of estrogen may cause premature closure of growth plates, reducing adult height.

➢ However, by time of menarche, most female adolescents undergone their growth spurt and achieved ~ ≥95 % of adult height.

➢ Oral contraceptive therapy has not been associated with reductions in expected height.

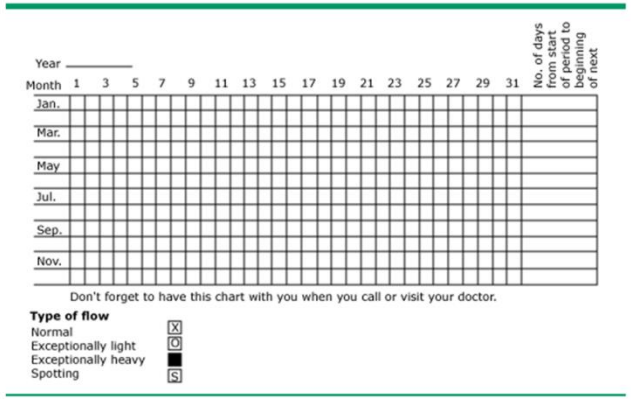
Monitoring response

- Adolescents who treated should maintain a menstrual calendar to monitor:

1) Response to therapy
2) Episodes of anovulatory uterine bleeding

- Several smart phone applications, or "apps," available at no cost, may facilitate recording and may be preferred by young teens over paper charting

Menstrual record chart



Menstrual record chart

Menstrual record chart

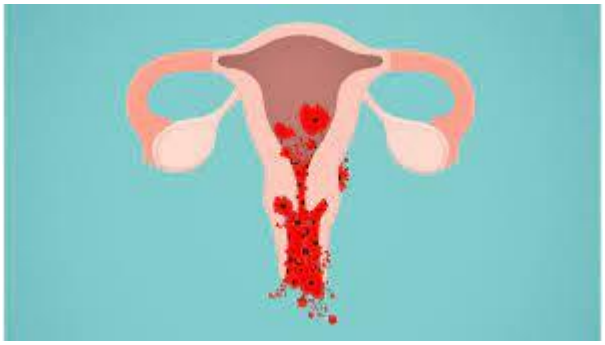
Year _____

Month	1	3	5	7	9	11	13	15	17	19	21	23	25	27	29	31	No. of days from start of period to beginning of next
Jan.																	
Mar.																	
May																	
Jul.																	
Sep.																	
Nov.																	

Don't forget to have this chart with you when you call or visit your doctor.

Type of flow

Normal	X
Exceptionally light	O
Exceptionally heavy	■
Spotting	S



MANAGEMENT

ACUTE MANAGEMENT OF MILD ANOVULATORY UTERINE BLEEDING

- Decisions individualized according to preferences of patient and guardian and need for contraception:

1-normal Hgb, and no desire contraception ,quality of life is not affected→

-observation and reassurance

2-Hgb 10 - 12→

-observation and reassurance or

-hormonal therapy to stabilize endometrial proliferation and promote cyclic shedding

-Iron supplementation

- Menstrual calendar or mobile phone "app" version
- Follow up in 3-6months ,unless bleeding more severe or prolonged
- We obtain a CBC in whose initial Hgb was <12 g/dL

ACUTE MANAGEMENT OF MODERATE ANOVULATORY UTERINE BLEEDING

- Usually manage in outpatient setting
- Treatment typically hormonal therapy to stabilize endometrial proliferation and shedding.
- Hormonal therapy regimen depends on:

1) Not currently bleeding
2) Currently bleeding

- Often have mild anemia (Hgb 10 to 12) should treat with iron

Not currently bleeding

Management are individualized according to preferences of patient and need for contraception

If not actively bleeding→ suggest either progestin-only hormone or combined OCP

Progestin-only regimen

- Norethindrone acetate 5 mg orally for first 5 to 10 nightly of each calendar month, or
- Oral micronized progesterone 200 mg nightly for first 12 days of calendar month

➢ Norethindrone is usually rapidly effective

➢ Oral micronized progesterone is chemical identical to endogenous progesterone

pills to start on first day of each calendar month is easy for teenagers to follow

Irregular spotting is common initially, but, if heavy vaginal bleeding occurs ,should discuss whether oral progestin is optimal regimen

- Combination OCP regimen
- Suggest monophasic OCP with min of 30 mcg EE, sufficient estrogen to prevent breakthrough bleeding
- Initiate pills according to usual schedule (one pill per day + pills that do not contain hormones)


Norethisterone
Tablets
For oral use
5mg
WOCKHARDT
30 tablets
Each tablet contains 5mg norethisterone
Dose: As directed by your doctor
Read the package leaflet before use
Contains lactose. Read the package leaflet for further information
Do not store above 25°C
Store in the original package
Keep out of the reach and sight of children

Suggested oral progestin/progesterone-only regimens for the acute management of anovulatory uterine bleeding and maintenance therapy after acute bleeding is controlled*

Suggested oral progestin/progesterone-only regimens for the acute management of anovulatory uterine bleeding and maintenance therapy after acute bleeding is controlled*

Preferred regimen for acute management	
Norethindrone acetate	5 or 10 mg orally nightly ¶ until bleeding stops and anemia resolves
Preferred maintenance regimens Δ	
Oral micronized progesterone	200 mg orally nightly for the first 12 days of each calendar month (if not allergic to peanuts) ◇
Norethindrone acetate	5 mg orally nightly for the first 5 to 10 days Δ of each calendar month ◇
Alternative maintenance regimen	
Medroxyprogesterone acetate	10 mg orally nightly for the first 10 days of each calendar month ◇

* For patients who do not desire contraception.

¶ May be administered up to four times per day if acute bleeding is severe.

Δ We suggest taking oral progesterone on the first 5 to 12 days of each calendar month because it is easier for adolescents to remember than other regimens.

◇ Discontinue if menstrual bleeding occurs while taking oral progesterone.

گشت به صفحه قبلی

Currently bleeding

Suggest combined estrogen-progestin OCP rather than progestin-only hormone therapy because estrogen provides hemostasis.

- Progestin-only therapy is an alternative for girls who cannot tolerate, dislike, or have a contraindication to estrogen therapy:

1. Migraine with aura
2. SLE
3. Arterial or venous thromboembolic disease
4. Estrogen-dependent tumors
5. Hepatic dysfunction or disease
6. Who object اعتراضto taking combination oral contraceptives

Treatment with tranexamic acid may be an option for girls decline hormonal options.

1300 mg orally up to three times per day for first 1-5 days of each menstrual cycle.

Cyclic tranexamic acid does not regulate menstrual cycles.

Antifibrinolytic agent

Currently bleeding

- Monophasic OCP with min of 30 mcg EE to ensure sufficient estrogen to prevent breakthrough bleeding.
- Randomized trials report 35 - 65 % reduction in blood loss
- For girls who are actively bleeding, following regimen :
  - •One pill every 8h until bleeding stops (usually 48 hours), then
  - •One pill every 12 hours for 2 days, then
  - •One pill once per day for a total of at least 21 days
- Close follow-up (in person or by phone) is essential while pills are being taken two or three times per day.

- High-dose estrogen therapy can cause nausea, →decreased adherence.

- Antiemetic therapy before each pill:

1) Promethazine 12.5 to 25 mg orally or per rectum
2) Ondansetron 4 to 8 mg orally

Currently bleeding

Patient and parent should call if patient has an increase in or continued heavy vaginal bleeding during taper or once taper is complete and patient is taking one pill per day.

Management of breakthrough bleeding following taper is individualized

- If hemodynamically stable, some clinicians discontinue hormon at least three days to permit shedding of endometrium
- However, possibility that withdrawal bleed may be very heavy must be weighed against risk of irregular vaginal bleeding if hormones are not discontinued.

- Another option, particularly for girls with anemia, is to revert to twice per day dosing, which may be necessary for full 21 days.
- Once anemia resolves, allowing a menses (by discontinuing hormon for at least three days) is optimal to prevent irregular vaginal bleeding.

ACUTE MANAGEMENT OF SEVERE ANOVULATORY UTERINE BLEEDING

- Control of severe anovulatory uterine bleeding may involve:

1. Hormonal therapy
2. Hemostatic agents
3. (rarely) surgical intervention

- Iron supplementation as soon as patient is stable and able to take pills by mouth
- Depending upon severity of iron deficiency, we use 60 mg of elemental iron once or twice per day

Treatment

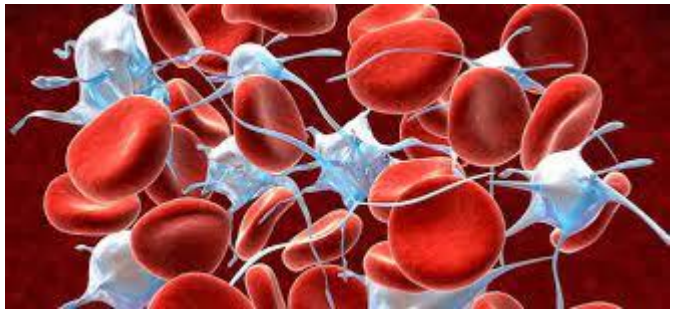
1) Hormonal therapy as initial intervention in severe anovulatory uterine bleeding that hospitalized or treated as outpatients.
2) Hemostatic agents →if bleeding is not controlled within 24 to 48 hours of hormonal therapy alone.
3) Surgical intervention →If bleeding is not controlled after hemostatic agents (dilation and curettage or uterine vacuum aspiration)

Indications for hospitalization

1. Hemodynamic instability (eg, tachycardia, hypotension, orthostatic vital signs)
2. Hgb<7 g/dL
3. <10 g/dL with active heavy bleeding
4. Symptomatic anemia (fatigue, lethargy)
5. Need for intravenous conjugated estrogen,(cannot take oral medications, continued heavy bleeding after 24 h of ocp therapy)
6. Need for surgical intervention

Additional evaluation

- In hospitalization should evaluation for bleeding disorder:
- 1-Pelvic ultrasonography to evaluate pelvic pathology (eg, polyps, ovarian tumors), particularly if do not respond to initial therapy .
- 2- Hospitalization or transfusion may be initial presentation of a coagulation disorder, particularly von Willebrand disease.



- Estimated up to 20 % of adolescents with HMB have:

➢ von Willebrand disease or

➢ platelet dysfunction

Additional evaluation

- lab evaluation for who require hospitalization for HMB includes:

1. Pregnancy
2. Hypothyroidism
3. CBC
4. PT
5. activated PTT
6. Von Willebrand factor (VWF) antigen
7. Plasma VWF activity (ristocetin cofactor activity)
8. Factor VIII activity
9. Blood group. O is associated with lower levels of VWF

- Lab evaluation should be before administration of blood products or estrogen (estrogen may elevate VWF).
- Consultation with a hematologist may be necessary to establish diagnosis

Combination therapy

- Combination OCP are first-line hormonal therapy for acute management
- Progestin-only and IV estrogen alternatives for who cannot take OCP

- In severe bleeding and anemia or who are at risk for anemia starting :

I. OCP with higher dose of estrogen (50 mcg EE)
II. Tapering according to regimen below:

●One pill every 4-6 h until bleeding subsides (usually within 24 hours), then
●One pill every 8 h for three days, then
●One pill every 12 h for up to two weeks, then
●one pill once per day.

- Once is weaned to one pill per day and anemia resolved, should allow to withdrawal bleed (by discontinuing hormones at least 3 days)
- if bleeding recurs during tapering →↑ dose to lowest dose that controls


Ovustop-H
210
F.C. Tablets
Ovustop-H
Contraceptive HD
Each Tablet Contains:
Levonorgestrel 0.25 mg
Ethinyl Estradiol 0.05 mg
Manufactured By: Iran Hormone Pharmac
اووستاپ-اچ
۲۱۰
قرص روکش دار
کنتراسپتیو اچ دی
هر قرص حاوی:
لووونورژسترل ۰/۲۵ میلی گرم
اتینیل استرادیول ۰/۰۵ میلی گرم
ساخت شرکت داروسازی ایران هورمون، ایران، تهران، تاسیس ۱۳۴۳

- OVCON 50
- 1 mg norethindrone and 0.05 mg EE

- Zovia 1/50E
- ethynodiol diacetate and EE

- Ogestrel 0.5/50 Pill
- EE0.05 mg / norgestrel 0.5 mg

Antiemetic therapy

- may be required for girls who are taking more than one pill per day

1. Promethazine 12.5 - 25 mg orally or per rectum or
2. Ondansetron 4 - 8 mg orally

Progestin-only pills

- Alternative to combination OCP in acute management in that estrogen is contraindicated :

A. Migraine with aura
B. SLE
C. Arterial or venous thromboembolic disease
D. Estrogen-dependent tumors
E. Hepatic dysfunction or disease
F. Refuse to take combination OCP

- we suggest norethindrone for acute bleeding.
- Norethindrone 5 to 10 mg can be given up to 4 times a day based on severity of bleeding
- Once bleeding has stopped, it can be tapered over several days

- Two commonly used tapering regimens are below:

1) ●Norethindrone 5 to 10 mg twice per day for7 days, followed by 5 to 10 mg once per day until maintenance therapy is initiated
2) ●Norethindrone 5 to 10 mg three times per day for 3 days, followed by 5 to 10 mg twice per day for 7 days, followed by 5 to 10 mg once per day until maintenance therapy is initiated.

- Management of hormonal therapy once bleeding is controlled and follow-up are below.

Intravenous estrogen is reserve for

1) unstable and cannot take oral medications .
2) if bleeding is not controlled after 24 hours of combination hormonal therapy.

- Dose of IV conjugated estrogen is 25 mg every 4-6 h until bleeding stops. No more than six doses
- Thromboembolism is a potential complication .
- Administration of antiemetics (promethazine 12.5 to 25 mg orally, transdermally , IV, or per rectum) one hour before each IV estrogen may need

- Bleeding usually subsides within 4 to 24 h of initiation of IV estrogen .
- Hemostatic therapy may be warranted if bleeding persists beyond 24 h .
- If bleeding lasts longer than 24 to 48 h after initiation of IV estrogen, oral progesterone should be added to stabilize endometrium
- Oral progesterone should be discontinued when oral contraceptive pills are initiated .

IV conjugated estrogen

- Successfully controlled bleeding in 72 % compared with 38 % of placebo.
- In most cases, bleeding diminished within three hours of initiating hormone therapy.

After bleeding subsides

- Patient should be switched to a taper of combination monophasic oral contraceptive.
- We use monophasic oral contraceptive that contains at least 50 mcg of estradiol and following schedule:
- ●One pill every 4-6 h until bleeding stops
- ●One pill every 8 h for three days, then
- ●One pill every 12 h for two weeks

- Multiple alternative tapering regimens are described in the literature

Addition of hemostatic therapy to hormonal therapy may be warranted for severe anovulatory uterine bleeding that :

1) Continues bleeding after 24 hours of hormonal therapy
2) Platelet dysfunction

- Classically used for von Willebrand disease .
- Prefer tranexamic acid unless patient has increased risks for thromboembolism
- Aminocaproic acid should be avoided in renal impairment

❑ ●Tranexamic acid is orally: 1300 mg three times per day for up to five days

❖ ●Aminocaproic acid may be administered orally or IV as follows:

❖ 1-Aminocaproic acid 5 g orally first hour, followed by continuous dose of 1 to 1.25 g per hour; treatment is continued for approximately eight hours or until bleeding controlled, or

❖ 2-Aminocaproic acid 4 to 5 g IV during first hour of treatment, followed by continuous infusion 1 g per hour; treatment is continued for approximately eight hours or until bleeding has controlled

➢ ●Desmopressin is administered IV as follows:

➢ •Desmopressin 0.3 mcg/kg IV over 15 to 30 minutes; dose may repeat in 48 h if no response

Refractory uterine bleeding

- In rare cases which hormones and antifibrinolytics fails→ additional evaluation to assess other causes :

A. Examination under anesthesia

B. Endometrial sampling

- Dilation and curettage (D&C) rarely for continue life-threatening bleeding despite other therapies
- Care must to prevent scarring of endometrial lining (Asherman syndrome)

LONG-TERM MANAGEMENT

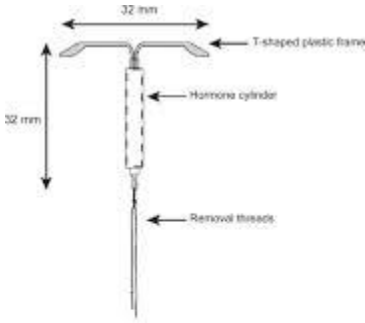
Maintenance therapy

After controlled acute bleeding and complete initial course of hormonal therapy is depends on :

1) Initial hormonal regimen
2) Patient's desire for contraception
3) Whether or not remains anemic

For girls who desire contraception or are unable to take pills effectively:

1) Levonorgestrel-releasing intrauterine device (IUD)
2) Depomedroxyprogesterone acetate (DMPA)



- May cause irregular and unpredictable bleeding for up to six months or longer

Initial control with estrogen-containing regimen and whose Hgb < 10 g/dL

- ●Hgb <10 g/dL –suggests monophasic combination OCP with at least 50 mcg EE once per day continuously (to avoid withdrawal menses) for at least three months (until Hgb ≥10 g/dL)
- Other experts may use different regimens (OCP with 30 to 35 mcg EE)

- We monitor Hgb monthly until it is ≥10 g/dL and then every 3-6 months until >12 g/dL.

- Patients should be counseled that breakthrough bleeding is common during first 3 months of continuous hormonal therapy and possibly longer.

- Maintenance of an accurate menstrual calendar will guide therapy.

After continuous therapy

- continuous OCP follow by cyclic therapy (21 days of hormone pills, 3-7 days of placebo or no pills to induce withdrawal bleeding) with OCP with 30 to 50 mcg of EE to complete a total of six months.

- In cyclic therapy, withdrawal bleeding begins 2-4 days after last pills and initial period may heavier than normal but should not last >7 day

- OCP can discontinued after six months if anemia has resolved →whether normal menstrual has been established.
- OCP may be continued in sexually active and adolescents who wish to continue.
- A menstrual calendar for monitor episodes of uterine bleeding.

After controlled acute bleeding with estrogen and whose Hgb ≥10 g/dL

- Suggest OCP with at least 30 mcg EE → cyclically (21 days, then 3-7days placebo or no pills to induce withdrawal bleeding) for three to six months.
- Monitor Hgb every 3-6 months until it is >12 g/dL.
- OCP can discontinue after three to six months →whether a normal menstrual has been established
- OCP may be continued in sexually active and adolescents who wish to continue.
- A menstrual calendar

Initial control with oral progestin do not desire contraception

- Suggest continuation of oral progestin-only for at least six months after bleeding is controlled
- After 6 month can be discontinued →whether a normal menstrual established

- Include cyclic norethindrone, oral micronized progesterone:

1) •Norethindrone 5 mg orally each night for first 5 to 10 days of each calendar month, or
2) •Oral micronized progesterone 200 mg each night for first 12 days of each calendar month

- pills on first 5 to 12 days of calendar month is easy to follow.

- With cyclic progesterone, bleeding usually begins 2-3 days after last progestin but may delay up to one week.
- If bleeding occurs during maintenance progesterone, should discontinue progesterone and allow menses to occur

- If patient not menses within one week after last progesterone, hormones should discontinue and pregnancy test.
- If is negative, endocrinology evaluation includes:

❑ FSH, LH , prolactin, DHEAS , 17-OH progesterone, free -total testosterone, TSH , FBS ,insulin

- A menstrual calendar
- Adolescents with cyclic progesterone should understand that it is not a method of contraception

Initial control with oral progestin who desire contraception

1) Depot medroxyprogesterone acetate
2) Progestin implants
3) levonorgestrel-releasing IUDs
4) Continuous progestin-only pills, but are not first choice, need to be with time of day, which may be difficult for adolescent

- A menstrual calendar should be maintained to monitor subsequent episodes of anovulatory uterine bleeding.

Follow-up schedule

- Frequency of follow-up varies depending on :

1) severity of bleeding
2) severity of anemia
3) type of treatment

Follow-up

- ●Mild anovulatory uterine bleeding who initiated hormonal or iron, should be followed three months after initial episode
- ●Mild anovulatory bleeding who initially observation and reassurance should follow up in three to six months to assess improvement in menstrual and/or need for hormonal therapy

Follow-up

- ●Moderate anovulatory uterine bleeding should be seen ~ three months after initial episode.
- If bleeding is not improved, hormonal therapy is adjusted, with follow-up every three to six months.

- Hormonal therapy adjustments may include:

1) Using a higher dose pill and/or
2) Addition of tranexamic acid

- If lack of compliance with pill, an alternative treatment may be warranted:

1. DMPA or
2. long-acting reversible contraception options

- Once menstrual are stable and treatment established, can be seen annually

Follow-up

- ●Severe anovulatory uterine bleeding who not hospitalization should be seen monthly until menstrual and treatments are stable and Hgb is >10
- ●Severe bleeding who hospitalization should seen two weeks after discharge and then at least monthly until menstrual and treatments are stable and Hgb >10 g/dL.

A. If irregular or heavy bleeding persists despite 3 month hormone therapy or
B. Normal menstrual not establish after discontinuation of hormonal therapy:

1) Endocrinology evaluation :FSH, LH, prolactin, DHEAS, 17-OH progesterone, free and total testosterone, TSH, and fasting insulin and glucose
2) Pelvic sonography for pelvic pathology (fibroids, polyps, ovarian tumors)

Long-term monitoring with a history of anovulatory cycles is essential

- Necessary to prevent potential sequelae of anovulatory uterine bleeding:

1) Chronic anemia
2) Infertility
3) Endometrial cancer

- Once hormonal therapy discontinued, who more than three months without a period (and not pregnant) should:

1) Undergo endocrine evaluation: FSH, LH, PRL, DHEAS, 17-OH progesterone, T , TSH, and fasting insulin and glucose
2) To induce withdrawal bleeding :

I. Oral micronized progesterone 200 mg nightly for 12 days per month.
II. Medroxyprogesterone 10 mg nightly for 10 to 12 days per month
III. Norethindrone acetate 5 to 10 mg nightly for 10 to 12 days per month.

- We instruct adolescent to induce menses at least every three months or to restart combined hormonal contraception .

Long-term monitoring

- Chronic anovulation (greater than two to three years) is associated with:

1) Endometrial hyperplasia
2) ↑ risk of endometrial carcinoma

- Concomitant obesity promotes peripheral conversion of androgens to estrogens, further endometrial growth.

- Endometrial biopsy may warranted in who with history of :

1) 2-3 yrs of untreated anovulatory bleeding
2) Particularly if obese or
3) Family history of endometrial, ovarian, breast, or colon cancer

PROGNOSIS

- Anovulatory uterine bleeding generally resolves with maturation of hypothalamic-pituitary-ovarian axis.

- Duration takes to attain maturity related to age of menarche
- In who begin menses at below age, 50 % of cycles are ovulatory by:

1) <12 years→ one year
2) 12 and 13 years→ three years
3) >13 years of age→ 4.5 years

- However, normal cycle length is not established until sixth gynecologic year, at average age of 19 years

- Long-term prognosis for AUB depends on underlying cause:

➢ Long history of anovulatory cycles and, particularly in PCOS, have an increased risk of later infertility and endometrial carcinoma