Abnormal Uterine Bleeding

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Continuing Medical Education

AMERICAN ACADEMY OF FAMILY PHYSICIANS

STRONG MEDICINE FOR AMERICA

Disclosure Statement

Dr Weismiller has nothing to disclose.

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Learning Objectives

1. Formulate evaluation and treatment plans related to various high-risk conditions and reproductive complications, including dysfunctional uterine bleeding and potential cancers.
2. Clarify the appropriate diagnostic strategies for evaluating abnormal bleeding.
3. Assess training needs for procedures used to evaluate and treat abnormal uterine bleeding.
4. Formulate a treatment plan for women with abnormal uterine bleeding including dysfunctional uterine bleeding, menorrhagia, and amenorrhea.

1. When considering abnormal uterine bleeding, which of the following statements is true?

A. Up to 20% of women (at any age) presenting with heavy bleeding will have an underlying bleeding disorder (disorder of hemostasis).

B. Between the ages of 40 and menopause, pregnancy is one of the common etiologies.

C. Measurement of endometrial thickness in premenopausal women is exceedingly helpful in the evaluation.

D. Hirsutism associated with PCOS is best treated with metformin.

E. Bleeding associated with the endometrium under minimal estrogen stimulation (too thin) is best treated with progestins.

1. When considering abnormal uterine bleeding, which of the following statements is true?

17% ✓ A. Up to 20% of women (at any age) presenting with heavy bleeding will have an underlying bleeding disorder (disorder of hemostasis).

17% B. Between the ages of 40 and menopause, pregnancy is one of the common etiologies.

14% C. Measurement of endometrial thickness in premenopausal women is exceedingly helpful in the evaluation.

34% D. Hirsutism associated with PCOS is best treated with metformin.

18% E. Bleeding associated with the endometrium under minimal estrogen stimulation (too thin) is best treated with progestins.

Definition

Menstrual flow outside of normal volume, duration, regularity, or frequency

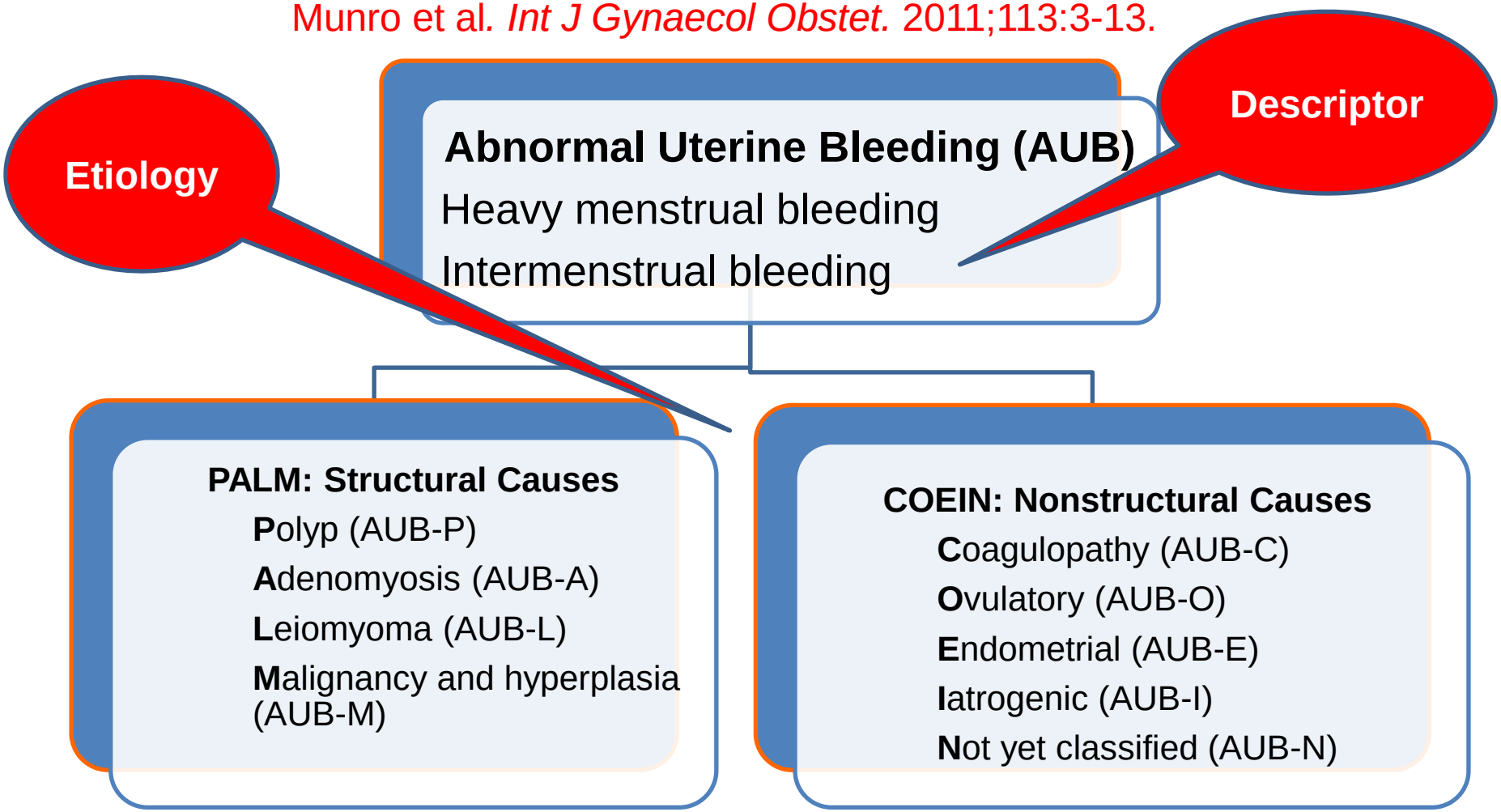
Nomenclature

2011 International Federation of Gynecology and Obstetrics

- New classification scheme
- Standardize terminology
- Abnormal Uterine Bleeding (AUB)
  - Paired with descriptive term
    - Heavy menstrual bleeding (instead of menorrhagia)
    - Intermenstrual bleeding (instead of metrorrhagia)
  - Paired with etiology or etiologies

Basic PALM-COEIN Classification System for the Causes of Uterine Bleeding in Non-pregnant Women of Reproductive Age

Munro et al. *Int J Gynaecol Obstet.* 2011;113:3-13.



Nomenclature

2011 International Federation of Gynecology and Obstetrics

- New classification scheme
- Standardize terminology
- Abnormal Uterine Bleeding (AUB)
  - Paired with descriptive term
    - Heavy menstrual bleeding
    - Intermenstrual bleeding
  - Paired with etiology or etiologies
- Recommend discontinuation of the term DUB

Pathophysiology

- Why do we have abnormal uterine bleeding?
  - Structural (PALM)
  - Systemic (both inherited and acquired)
  - Ovulatory AUB
    - Hypothalamic-pituitary-ovarian axis intact
    - Steroid hormone profiles are normal.
    - Once regular menses has been established during adolescence, ovulatory AUB account for most cases
      - Abnormal prostaglandin synthesis and receptor upregulation
      - Increased local fibrinolytic activity
      - Increased tissue plasminogen activator activity
  - Ovulatory dysfunction AUB
    - Spectrum of disorders ranging from amenorrhea to irregular heavy menstrual periods
    - Typically result of endocrinopathy – eg, PCOS
    - Mechanisms of abnormal bleeding related to unopposed estrogen

Diagnosis

- Medical history
  - Family history of AUB or other bleeding problems
    - Up to 20% of women (at any age) presenting with heavy bleeding will have an underlying bleeding disorder (disorder of hemostasis).

Clinical Screening for an Underlying Disorder of Hemostasis

- Initial screening structured by medical history; (+) screen comprises any of the following:
  - Heavy menstrual bleeding since menarche
  - One of the following:
    - Postpartum hemorrhage
    - Surgery-related bleeding
    - Bleeding associated with dental work
  - Two or more of the following:
    - Bruising 1-2x/month
    - Epistaxis 1-2x/month
    - Frequent gum bleeding
    - Family history of bleeding symptoms
- (+) Screen
  - Further evaluation to include:
    - Testing of:
      - von Willebrand factor
      - Ristocetin cofactor
    - Consultation with hematologist

Diagnosis

- Medical history
  - Family history of AUB or other bleeding problems
    - Up to 20% of women (at any age) presenting with heavy bleeding will have an underlying bleeding disorder (disorder of hemostasis)
  - Medication or herb remedies
    - Warfarin
    - Heparin
    - NSAID
    - Motherwort
    - Hormonal contraceptives
    - Gingko
    - Ginseng

Diagnosis

- Physical findings
  - Weight
  - Signs of PCOS
    - Hirsutism
    - Acne
  - Signs of thyroid disease
  - Signs of insulin resistance
    - Acanthosis nigricans on the neck

Acanthosis Nigricans

Diagnosis

- Physical findings
  - Weight
  - Signs of PCOS
    - Hirsutism
    - Acne
  - Signs of thyroid disease
  - Signs of insulin resistance
    - Acanthosis nigricans on the neck
  - Look at the vagina and cervix − lesions

Laboratory Tests

- Pregnancy test (blood or urine)
- CBC
  - Anemia
  - Thrombocytopenic bleeding
- Screening for bleeding disorders (Level A)
  - CBC with Plts, PT/PTT; fibrinogen and thrombin time are optional; bleeding time neither sensitive or specific – do not need.
    - All adolescents with heavy menstrual bleeding
    - Adult patients with (+) screen
- TSH (Level B)
- *Chlamydia trachomatis* (Level B)
- Pap – if needed

Imaging

- Transvaginal US
- TVUS images are not adequate or further evaluation of cavity is necessary
  - Saline infusion sonohysterography (Level A)
  - Hysteroscopy
- MRI is NOT a primary imaging modality for AUB.

Who Needs Imaging with AUB?

- Literature is unclear. Some suggestions:
  - Abnormal physical exam, eg, enlarged or globular uterus on bimanual
  - Symptoms persist despite treatment in the setting of normal pelvic exam (Level C); TVUS, or biopsy, or both
  - Clinical suspicion for polyps or submucosal leiomyomas
    - Sonohysterography
    - Hysteroscopy
      - **Numerous recent studies have demonstrated that DH had a significantly better diagnostic performance than SH and TVUS and was significantly more precise in the diagnosis of intracavitary masses. Hysteroscopy not only has increased accuracy for identifying the etiology of AUB, compared with D&C, but also offers the possibility of in-office use.**
  - NO measurement of endometrial thickness in premenopausal women – not helpful

Endometrial Tissue Sampling

- Primary role: Carcinoma or premalignant lesions present
- AUB and:
  - > 45 years (Level C)
    - First-line test
  - < 45
    - History of unopposed estrogen
      - Obesity
      - PCOS
    - Failed medical management
    - Persistent AUB

2. In considering the results of an endometrial biopsy, which of the following statements is true?

A. Secretory endometrium is normal in the follicular phase.
B. Proliferative endometrium is normal in menopause.
C. Atrophic endometrium is seen in women on Depo-Provera.
D. Hyperplasia is the advanced effect of unopposed progestin.

2. In considering the results of an endometrial biopsy, which of the following statements is true?

32% A. Secretory endometrium is normal in the follicular phase.

7% B. Proliferative endometrium is normal in menopause.

46% ✓C. Atrophic endometrium is seen in women on Depo-Provera.

16% D. Hyperplasia is the advanced effect of unopposed progestin.

EMB
Results

- Proliferative – normal in the follicular phase
  - When associated with abnormal bleeding, confirms anovulation and the effect of unopposed estrogen
- Secretory/menstrual – confirms ovulation has occurred
- Hyperplasia – advanced effect of unopposed estrogen atypia = premalignant
- Atrophic – seen in menopause or effect of OCPs, Depo-Provera, and continuous ERT

Aged-Based Common Differential Diagnosis

13-18

- Persistent anovulation
  - Immaturity of HPO axis and represents normal physiology
  - Hormonal contraceptive use
  - Pregnancy
  - Pelvic infection
  - Coagulopathies
  - Tumors

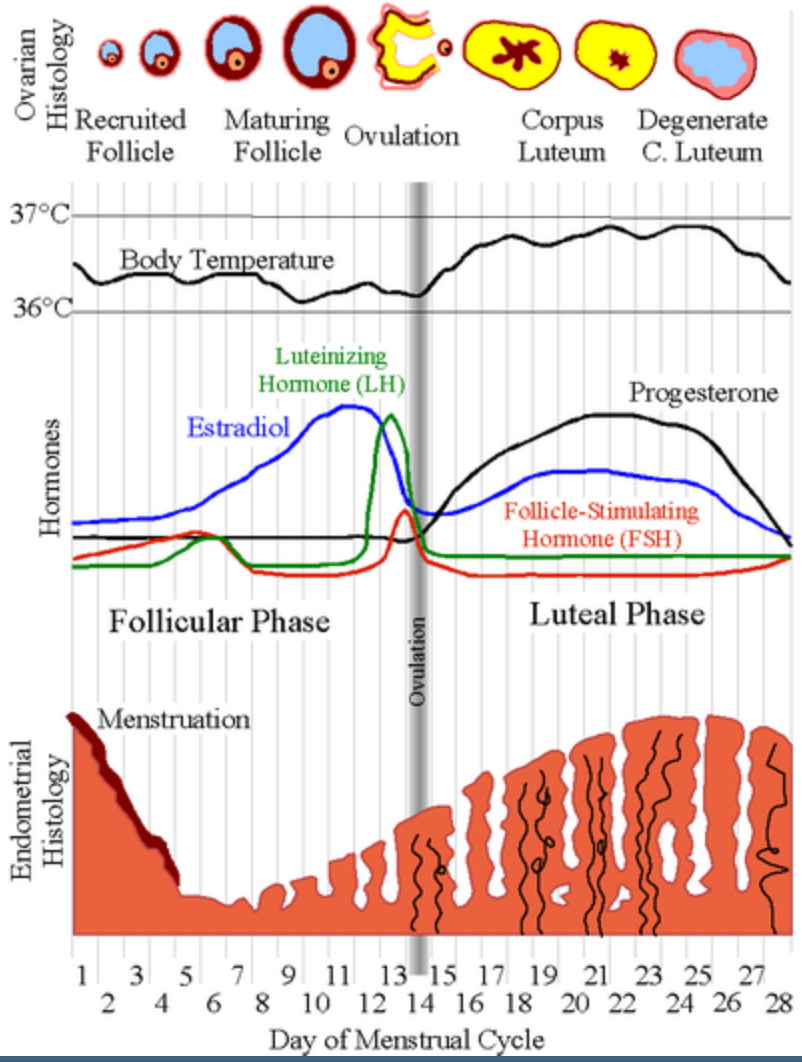
19-39

- Pregnancy
- Structural lesion
  - Leiomyoma
  - Polyp
- Anovulatory cycles
  - PCOS
- Hormonal contraceptive use
- Endometrial hyperplasia

Age-Based Common Differential Diagnosis

- 40 Years to Menopause
- Anovulatory
  - Represents normal physiology in response to declining ovarian function
- Endometrial hyperplasia
- Endometrial carcinoma
- Endometrial atrophy
- Leiomyomas

Endometrial Axis



Source: Wikimedia

At What Point in the Evaluation Is Therapy Appropriate?

- Lower risk – empiric trial of therapy
  - < 45
  - Adolescent
  - No enhanced risk of endometrial hyperplasia, neoplasia, structural abnormality
- Higher risk – initiation of therapy only after complete diagnostic evaluation
  - > 45
  - Prolonged anovulatory cycles
  - Persistent bleeding despite therapy

Treatment of *Thick* Endometrium

- What is the therapy?
  - Goal is to reduce the thickness of the endometrium.
  - Progestins or OCPs

Who Has *THICK* Endometrium?

- Women who:
  - Are obese
  - Have chronic anovulation
  - Have PCOS
  - Are taking unopposed estrogen (uncommon)

AUB

Emergency Management

Isn't TOO much Estrogen what one is trying to correct? Why give MORE?

- IV conjugated estrogen – 25 mg q 4 hours until bleeding slows for 12 hours
  - Believed to be a stimulus for clotting at the capillary level
  - Promotes rapid growth of endometrium to cover denuded endometrial surface and stop bleeding
  - 75% will be controlled in 6 hours.
- Oral conjugated estrogen 10 mg/day in four divided doses can be substituted for IV estrogen.
- Start OCPs or 10 days of monthly progestin (cyclic) after bleeding stops to prevent recurrence.

AUB

Non-Emergency Management

- One combined hormonal OCP for 7 days
  - If the flow stops within12-24 hours, the diagnosis of DUB can be confidently made.
  - Stop combined OCPs for 7 days after one week of therapy.
  - Begin regular OCPs for the next 3-6 months.
- *Alternative*
  - *Cyclic administration of progesterone for 3 months*

When the Endometrium Is Too *Thin* Because of Heavy Continuous Bleeding

- The endometrium is shed and minimal.
- It may have previously been “too thick.”
- Treatment
  - Estrogen followed by progestin

Endometrium Is "*Too Thin*" Typically Associated with…

- Endometrium has minimal estrogen stimulation.
  - High progestational OCP
    - e.g. LoOvral, Nordette
  - Progestin-only contraception
    - Depo-Provera, Minipill, IUD
- Endometrium becomes thinner and potentially atrophic.
- **Treatment**
  - Add estrogen, change from minipill to combination OCP or change OCP.
  - General rule: Using progestins when the endometrium is *too thin* makes a bad situation worse.

Who Has *THIN* Endometrium?

- Women who:
  - Have heavy continuous uterine bleeding
  - Are using a progestin-dominant OCP, IUD, Depo-Provera, or minipill (progestin only)
  - Are excessively thin or have low body fat – may be hypoestrogenic
    - Eating disorders
    - Elite athletes
      - Marathon runners, gymnasts, skaters

Treatment of AUB
(Cochrane Review)

- **Medical**
  - NSAIDs − ↓ prostacyclin (platelet anti-aggregating vasodilator)
    - Decrease blood flow 20%-50%.
    - Mefenamic acid 500 mg po TID
  - Tranexamic acid (Lysteda)
  - Danazol − 200 mg po q day
    - Anti-estrogen
    - Decrease blood flow 50%.
    - Side effects limit use.
  - OCPs
  - Continuous OCPs
  - Oral continuous progestins (d 5-26)
  - Levonorgestrel IUS
    - 80% decrease in blood loss
- **Surgical**
  - Myomectomy
  - Hysterectomy
  - Ablation
    - 1st generation: Resection (laser, rollerball)
    - 2nd generation:
      - Cryoablation*
      - Laser Intrauterine thermotherapy
      - Radiofrequency ablation*
      - Thermal balloon ablation
      - Microwave ablation*

Endometrial Ablation Methods

- Rule out preinvasive and invasive endometrial lesions before procedures.
- Must have completed childbearing and tolerate some menstrual bleeding.

Treatment of AUB
Cochrane 2005

- Endometrial ablation significantly more effective with fewer side effects than medical therapies
- No significant differences between levonorgestrel IUD and any surgery in satisfaction rates or quality of life
  - > 64% of women scheduled for hysterectomy canceled the surgery after Mirena.
- Hysterectomy has high satisfaction rates but risks of major surgery.

Society of Gynecologic Surgeons

- Systematic Review Group (SRG) of the Society of Gynecologic Surgeons
  - Tradeoffs between treatment effectiveness and the risk of serious adverse events between hysterectomy, ablation, and the LNG-IUS
  - SRG was able to conclude ONLY that there was moderate strength of evidence supporting the statement that bleeding is better controlled following hysterectomy than following ablation.
  - Three studies found statistically significant differences in validated dimensions of the SF-36 questionnaire favoring hysterectomy for pain, general health, vitality, and social function over ablation.

Wheeler TL II, Murphy M, Rogers RG, et al; Society of Gynecologic Surgeons Systematic Review Group. Clinical practice guidelines for abnormal uterine bleeding: hysterectomy versus alternative therapy. *J Minim Invasive Gynecol.* 2012;19(1):81–87.

3. Which of the following statements is true when considering a patient with amenorrhea?

A. Amenorrhea is rarely associated with PCOS.
B. It is unusual to find a positive pregnancy test in the patient presenting with amenorrhea.
C. The relative estrogen status can be evaluated with a progestin challenge test.
D. A TSH is not necessary in the evaluation.

3. Which of the following statements is true when considering a patient with amenorrhea?

4% A. Amenorrhea is rarely associated with PCOS.

4% B. It is unusual to find a positive pregnancy test in the patient presenting with amenorrhea.

90% ✓C. The relative estrogen status can be evaluated with a progestin challenge test.

1% D. A TSH is not necessary in the evaluation.

Amenorrhea
Systematic Approach

- Focus on the signs and symptoms that suggest an underlying cause.
  - Thyroid disease: Hypo- or hyperthyroidism
  - Estrogen deficiency: Menopause
  - Androgen excess: Tumor, PCOS
  - Pituitary tumors: Prolactinoma

Steps in Evaluation

Step 1 – Rule out pregnancy.

Step 2 – TSH to evaluate for hypo- or hyperthyroidism
Prolactin to evaluate for pituitary tumor
(fasting, no breast stimulation)

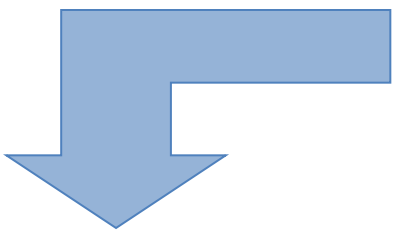
Step 3 − Determine the relative estrogen status.

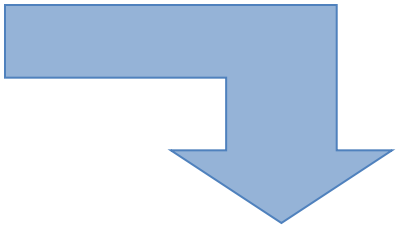
Relative Estrogen Status
Progestin Challenge Test

- 5-10 mg medroxyprogesterone acetate po q day x 10 days
- Any bleeding within 2-7 days is *"positive."*

Amenorrhea

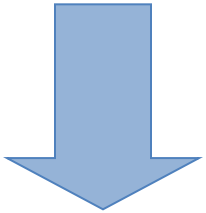
TSH
Prolactin
Progestin challenge

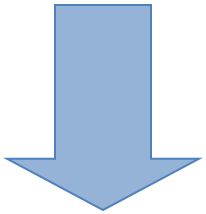




Elevated TSH or prolactin

(+) Withdrawal bleed





Hypothyroidism
Pituitary disease

Normal TSH and prolactin

Anovulation

Anovulatory Amenorrhea

- Amenorrheic women with adequate estrogen ([+] Progestin challenge test)
- Anovulatory, frequently obese, +/− PCOS
  - Progesterone is NOT being adequately produced in luteal phase.
  - Unopposed estrogen stimulation
    - Risk of endometrial cancer is increased.
    - Treatment
      - Progestin 10 mg q day 7-10 days every month or OCPs

Amenorrhea

TSH (nl),
prolactin (nl),
and
progestin challenge

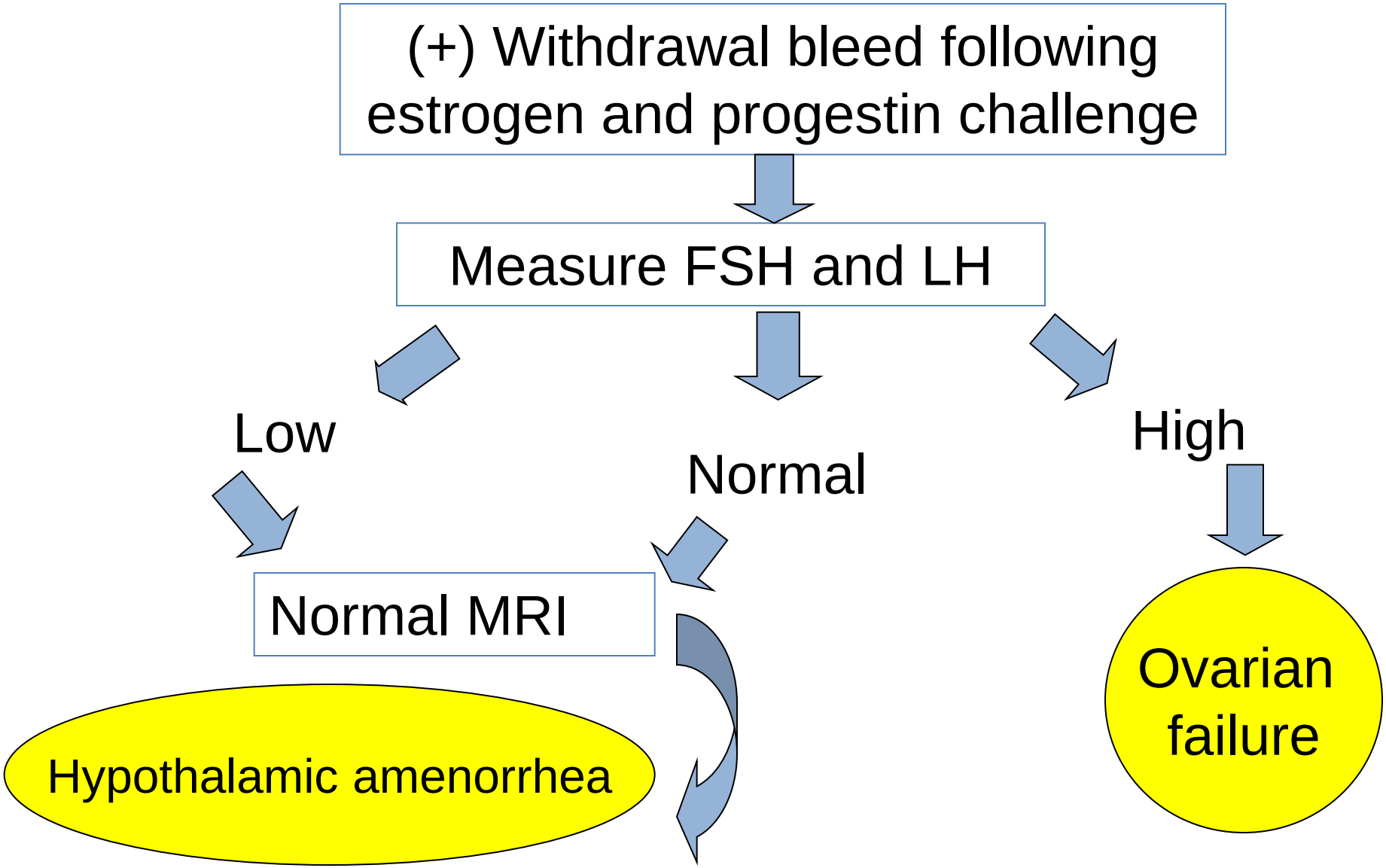
(−) withdrawal bleed

Estrogen and progestin challenge test

No withdrawal bleed

Outflow tract obstruction
(Asherman's, Mullerian agenesis)

Amenorrhea


(+) Withdrawal bleed following estrogen and progestin challenge
Measure FSH and LH
Low
Normal
High
Normal MRI
Hypothalamic amenorrhea
Ovarian failure

Hypothalamic Amenorrhea
Hypogonadotropic Hypogonadism

- Low or normal FSH/LH, normal prolactin, low levels of endogenous estrogen, normal MRI of sella
- *(+) Withdrawal bleed* following estrogen-progestin challenge test
- Usually diagnosed by exclusion of pituitary lesions
- Anorexia/bulimia, stress, high-intensity exercise, chronic illness

Hypothalamic Amenorrhea

Amenorrheic Women with Inadequate Estrogen

- Risk of decreased bone density (10%-20%)
  - Cannot be completely overcome with supplemental calcium or *weight-bearing exercise*
  - *? Rate of fractures*
- Although OCPs improve lumbar and total bone mineral, effect on fractures unknown
- *Increase BMI > 20* to restore menses
- Decrease intensive exercising.

Ovarian Failure
High FSH/LH

- Premature ovarian failure
  - < 40 not always reversible
  - Autoimmune, genetic, chemotherapy, mumps
- Postmenopausal ovarian failure
- Absence of secondary sex characteristics
  - Gonadal dysgenesis
    - Turner syndrome (most common form)

4. Which of the following drugs is not uncommonly used in the management of PCOS?

A. Rifampin
B. Clomiphene
C. Insulin
D. Naprosyn
E. Megace

4. Which of the following drugs is not uncommonly used in the management of PCOS?

12% A. Rifampin

57% ✓ B. Clomiphene

12% C. Insulin

9% D. Naprosyn

11% E. Megace

What Is Polycystic Ovary Syndrome?

Consensus

- Infrequent or no ovulation, infertility
  - Oligomenorrhea or amenorrhea
- Hyperandrogenism
  - Presence of hirsutism or biochemical hyperandrogenemia
- Polycystic ovaries on ultrasound
  - Presence of one polycystic ovary is sufficient to provide diagnosis.
- Appears between puberty and mid-20s

Suggested Evaluation
Physical

- BP
- BMI
  - > 30 = obese
- Waist circumference to determine body fat distribution
  - > 35 inches = abnormal
- Stigmata of hyperandrogenism and insulin resistance
  - Acne, hirsutism, androgenic alopecia, acanthosis nigricans

PCOS

Diagnosis (AES 2009)

- Androgen excess (clinical and/or biochemical)
- Ovarian dysfunction (oligo-anovulation and/or polycystic ovarian morphology)
- Exclusion of other causes of androgen excess and ovulatory disorders

Suggested Evaluation
Laboratory/Imaging

- Documentation of biochemical hyperandrogenemia
  - Total testosterone and sex hormone-binding globulin or
  - Bioavailable and free testosterone
- Exclusion of other causes of hyperandrogenism
  - TSH
  - Prolactin
  - 17-hydroxyprogesterone (non-classical congenital adrenal hyperplasia due to 21 hydroxylase deficiency)
    - Random normal level < 4 ng/mL or
    - Morning fasting level < 2 ng/mL
  - Consider screening for Cushing syndrome and other rare disorders such as acromegaly.
- Transvaginal pelvic ultrasound

Diagnostic Evaluation of Abnormal Uterine Bleeding—*Imaging Evaluation*

- Saline infusion sonohysterography (SH)
  - Superior to TVUS in the detection of intercavitary lesions (eg, polyps, submucosal leiomyomas
  - Can distinguish between focal versus uniform thickening of the endometrium and structural abnormalities
- Transvaginal ultrasonography (TVUS)
  - Helpful for evaluating the myometrium itself
  - Sensitivity and specificity for evaluating intracavitary pathology are low.
- Diagnostic hysteroscopy (DH)
  - **Numerous recent studies have demonstrated that DH had a significantly better diagnostic performance than SH and TVUS and was significantly more precise in the diagnosis of intracavitary masses. Hysteroscopy not only has increased accuracy for identifying the etiology of AUB, compared with D&C, but also offers the possibility of in-office use.**
- MRI - May be useful to guide the treatment of myomas

Suggested Evaluation
Laboratory

- Evaluation for metabolic abnormalities
  - 2-hour glucose tolerance test
- Fasting lipid and lipoprotein level

Hyperinsulinemia

- Insulin sensitivity DECREASES.
- Insulin release and circulating insulin INCREASE; normal glucose tolerance unless there is metabolic syndrome present.
- 45% of PCOS patients will have impaired glucose tolerance of type 2 diabetes.
- Practical world: fasting glucose, Hgb A1c

Insulin Resistance

- Insulin resistance stimulates ovarian androgen production leading to anovulation.
  - Prolonged anovulation can lead to development of enlarged ovaries with multiple cysts that were first seen on US, thus the name of the syndrome.
- Hyperinsulinemia and hyperandrogenemia interfere with the secretion of gonadotropins from the pituitary gland, resulting in changes to the mid-cycle LH surge and its diurnal variation.

Management of PCOS

Oligomenorrhea and amenorrhea

- OCPs[#] (combination pill, low dose)
- Monthly progesterone

Hirsutism

- OCPs
- Spironolactone[*]
- Finasteride

Insulin resistance

- Metformin

Infertility

- Clomiphene[^]
- Metformin
- ? Pioglitazone

Cochrane 2007.
* Farquhar et al. Cochrane 2004.
^ Farquhar et al. Cochrane 2005.

Key Points

- Improving insulin sensitivity with insulin-sensitizing drugs is associated with decrease in circulating androgen levels, improved ovulation rate, and improved glucose tolerance.
- Metformin or clomiphene alone or in combination are first-line treatment for ovulation induction.
  - No success – add exogenous gonadotropins or laparoscopic ovarian surgery.

ACOG Practice Bulletin 108: Polycystic Ovary Syndrome. *Obstet Gynecol*. 2009;114(4):936-949.
Radosh L. Drug treatments for PCOS. *Am Fam Physician.* 2009;79(8):671-676.

Perimenopausal Bleeding *(Endometrial Biopsy First)*

- Progestins – Provera 5-10 mg for 12 days/month
  - Prevents endometrial hyperplasia
- OCPs (agent of choice if nonsmoker – *expert opinion*)
  - Regulate cycles and control bleeding, contraception
- Levonorgestrel IUD (Mirena)
  - Induces amenorrhea, may cause atrophy
- HRT – sequential more effective than continuous
  - Prevents hyperplasia but NO contraception

Triage Guidelines
Reproductive Age Women

- No cytologic atypia
  - Simple EMHP with abnormal bleeding
    - Progestin withdrawal for 6 months, then re-biopsy
  - Complex (adenomatous) EMHP
    - Progestin withdrawal, then re-biopsy
- Cytologic atypia
  - High-dose progestins, Megace, or Depo-Provera for 3 months, then re-biopsy

What Are We Looking For on the Biopsy?

- Cytologic atypia is the SINGLE most important histologic finding.
- Only ATYPICAL hyperplasia has a significant risk of developing into endometrial cancer.
  - 29% progresses to invasion.
  - Need to rule out cancer if atypia is present.
- Endometrial hyperplasia is a BENIGN condition, not a cancer precursor.

Transvaginal Ultrasound?

Saline infusion sonohysterography is more sensitive and specific for the detection of endometrial abnormalities than transvaginal ultrasonography (SOR C).

5. A 55-yo postmenopausal woman presents with 2 days of vaginal bleeding (spotting). She initiated HRT 10 months ago because of significant nocturnal hot flashes. Which of the following statements is most accurate?

A. Irregular bleeding is uncommon after HRT is initiated.
B. Postmenopausal women on hormone therapy for > 4 months who experience bleeding require prompt evaluation.
C. Postmenopausal women on HRT for <12 months who experience bleeding may be observed for one year before diagnosing abnormal uterine bleeding.
D. The sensitivity of endometrial biopsy for the detection of endometrial abnormalities is 50%.

5. A 55-yo postmenopausal woman presents with 2 days of vaginal bleeding (spotting). She initiated HRT 10 months ago because of significant nocturnal hot flashes. Which of the following statements is most accurate?

3% A. Irregular bleeding is uncommon after HRT is initiated.

53% B. Postmenopausal women on hormone therapy for > 4 months who experience bleeding require prompt evaluation.

36% ✓C. Postmenopausal women on HRT for <12 months who experience bleeding may be observed for one year before diagnosing abnormal uterine bleeding.

9% D. The sensitivity of endometrial biopsy for the detection of endometrial abnormalities is 50%.

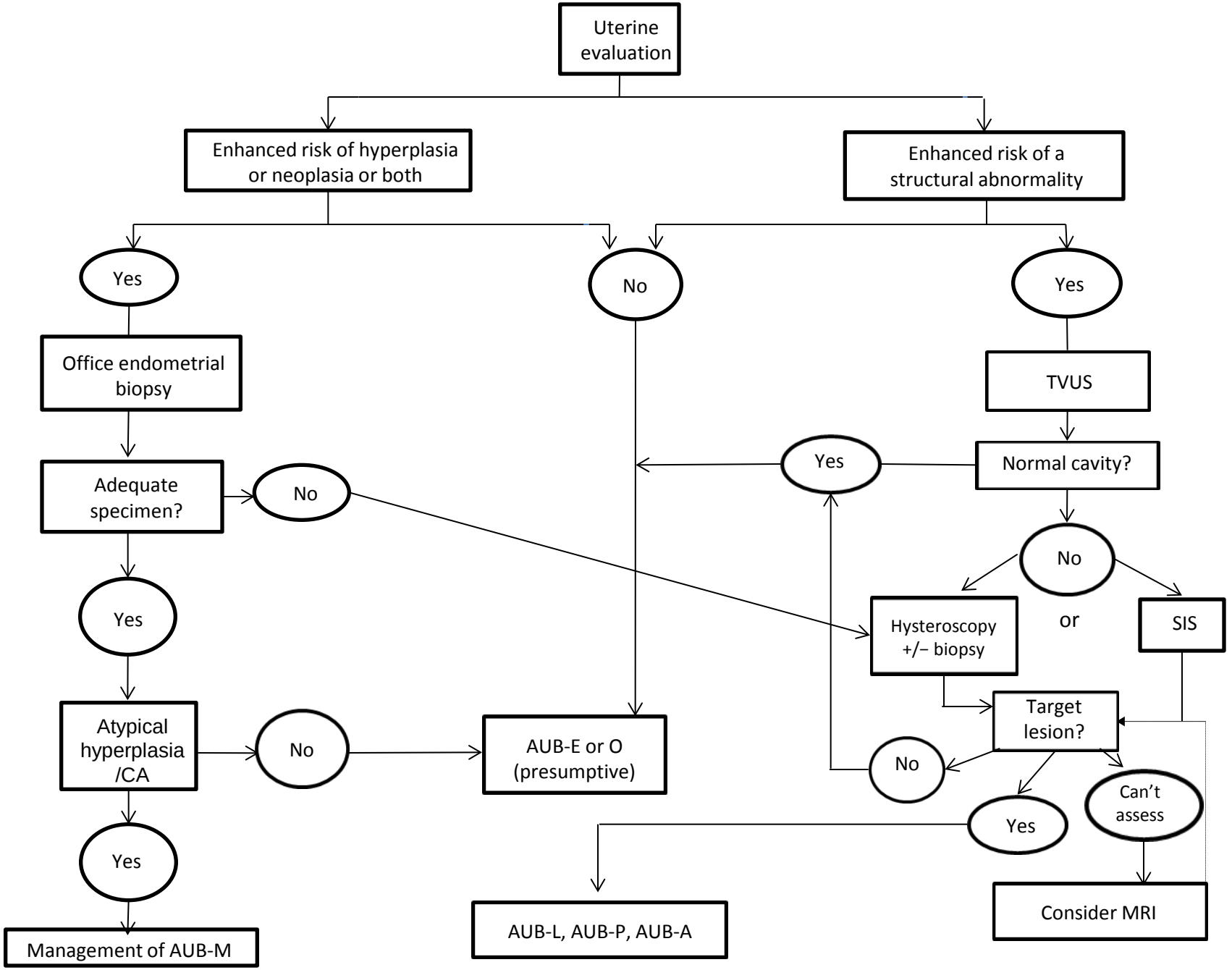
Postmenopausal Bleeding

- Irregular bleeding is common after HRT is initiated and improves within 6-12 months for most women.
- **Evaluate**
  - **Cyclic HRT**, experience unusually prolonged or heavy bleeding that occurs near the end of the progestogen phase of the cycle, or breakthrough bleeding that occurs at any other time.
  - **Continuous HRT**, experience bleeding that persists > 6-12 months or that occurs after amenorrhea has been established.
  - **HRT < 12 months** may be observed for 1 year before diagnosing abnormal uterine bleeding.
  - **Postmenopausal on no HRT or HRT > 12 months** with bleeding

Practice Recommendations

- Screen all women with postmenopausal vaginal bleeding for endometrial cancer [SOR:A].
- Use transvaginal ultrasound for the initial study for patients at low risk for endometrial cancer, and endometrial biopsy for those at higher risk [SOR:B].
- Use saline infusion sonography as a second step in the evaluation of postmenopausal bleeding if the diagnosis remains unclear after a biopsy or the bleeding persists despite a normal initial workup [SOR:B].

SUMMARY


Uterine evaluation
Enhanced risk of hyperplasia or neoplasia or both
Enhanced risk of a structural abnormality
Yes
No
Yes
Office endometrial biopsy
TVUS
Adequate specimen?
No
Yes
Normal cavity?
Yes
No
Hysteroscopy +/− biopsy
or
SIS
Yes
Target lesion?
Atypical hyperplasia /CA
No
AUB-E or O (presumptive)
No
Can't assess
Yes
Yes
Consider MRI
Management of AUB-M
AUB-L, AUB-P, AUB-A

Pharmacologic Treatment of Abnormal Uterine Bleeding—*Summary*

Type/Medication
Anovulatory bleeding • Combination contraceptives • MPA (Provera)
Endometria hyperplasia without atypia • MPA (Provera) • Megestrol (Megace) • Levonorgestrel IUS
Ovulatory Bleeding • Levonorgestrel IUS • MPA (Provera) • NSAIDS • Tranexamic acid (Lysteda)

SORT Key Recommendations for Practice—*Summary*

- Adolescents with excessive uterine bleeding should be evaluated for bleeding disorders, such as von Willebrand disease *(SOR C).*
- Saline infusion sonohysterography is more sensitive and specific for the detection of endometrial abnormalities than transvaginal ultrasonography *(SOR C).*
- The levonorgestrel-releasing intrauterine system (Mirena) is an effective treatment for menorrhagia, with patient satisfaction scores similar to endometrial ablation and hysterectomy *(SOR A).*
- NSAIDs are effective in reducing heavy menstrual blood flow. There is no evidence that one NSAID is more effective than another *(SOR B).*

Answers

1. A
2. C
3. C
4. B
5. C

Supplementary Slides

References

- ACOG Practice Bulletin 128. Diagnosis of Abnormal Uterine Bleeding in Reproductive-Aged Women. *Obstet Gynecol.* 2012;120(1):197-206.
- Sweet, MG, Schmidt-Dalton TA, and Weiss PM. Evaluation and Management of Abnormal Uterine Bleeding in Premenopausal Women. *Am Fam Physician.* 2012;85(1):35-43.

6. Which of the following is a true statement regarding natural menopause?

A. An FSH > 20 IU/mL is the most accurate biologic marker for menopause.
B. Postmenopause is defined as the period after menopause and begins following 6 months of spontaneous amenorrhea.
C. There appear to be no cultural differences in the reporting or experiencing of hot flashes.
D. Healthy women > 40 years of age who are nonsmokers can safely use combination estrogen-progestin contraceptives.

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✓ D. Healthy women > 40 years of age who are nonsmokers can safely use combination estrogen-progestin contraceptives.

Vasomotor Instability
"Hot Flashes"

- Probably hypothalamic origin
  - Menopause
  - Thyroid disease
  - Panic or anxiety disorder
  - Insulinoma
  - Autoimmune disorders
  - Pheochromocytoma
  - Carcinoid syndrome
  - Tamoxifen and raloxifene

Influences on Hot Flashes

- **Cultural**
  - More prevalent in African American and Latin American women than in white women
  - Less common in Chinese and Japanese women
- **Other variables associated with increased reporting of hot flashes**
  - Cigarette smoking
  - Potential risk factors with inconsistent association
    - Maternal history
    - Early age of menarche and menopause onset
    - History of irregular menses
    - Higher BMI
    - Alcohol use
    - Hot/humid weather

Treatment of Hot Flashes

All oral, transdermal, topical gel, and emulsions estrogen/testosterone preparations are FDA-approved.

Organization	Recommendation
North American Menopause Society (NAMS) 2007	Treatment of moderate to severe hot flashes is the primary indication for oral estrogen therapy.
ACOG	Primary indication for hormone replacement therapy (HRT)
Cochrane 2006	HRT significantly reduces the frequency and severity (75%) of hot flashes.
AHRQ – March 2005	Studies on reduction of vasomotor symptoms are conclusive ONLY for estrogen.

Hot Flashes:
Other Hormonal Therapies

OCPs	• Highly effective • Known contraindications
Androgen-estrogen therapy (Estratest)	• Approved for treatment of moderate to severe flashes not improved by estrogen alone • Data are lacking.
Custom hormone preparations (Compounding pharmacist)	• Not adequately studied for any indication • *No data they are safer than conventional therapy*

Atrophy of Vagina (Dryness)

- *Suckling et al. Cochrane 2006*
- Local estrogens equally effective
- Vaginal estradiol ring (worn 90 days) – preferred
- Vaginal estradiol tablets
- Vaginal cream (Premarin)
  - More uterine bleeding, breast pain than tablets
  - Significantly more endometrial stimulation than estradiol ring

7. Which of the following is true regarding combination estrogen-progesterone hormone replacement therapy (HRT)?

A. HRT reduces the risk of osteoporosis.
B. HRT increases the risk of colon cancer.
C. HRT decreases the risk of breast cancer.
D. HRT has no effect on the risk of stroke.

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HRT

*Women's Health Initiative Study**

- Proven benefits
  - Reduced risk of osteoporosis and related fractures (34%)
  - Decreased colon cancer risk (37%)
  - Improvement of vasomotor symptoms
- Increases the risk of the following:
  - Breast cancer (26%)
  - CVA (41%)
  - MI (29%)
  - Venous thromboembolic events*

• *Previous thromboembolic disease is the only **ABSOLUTE** contraindication to HRT. Heart disease, breast cancer, and endometrial cancer are **RELATIVE** contraindications.*

* Writing Group for the Women's Health Initiative. JAMA. 2002;288:321-333.

USPSTF 2005: *Chemoprevention for Combination HRT in Postmenopausal Women*

- Recommends AGAINST routine use of combined HRT for prevention of chronic conditions in postmenopausal women

Androgen Therapy

- The FDA has not approved any use of androgens alone for symptoms that may be attributable to androgen deficiency (which may also be attributable to estrogen deficiency).
  - Low libido
  - Decreased sexual response
  - Decreased sense of well-being
  - Poor concentration
  - Fatigue
- Use of androgens is considered off-label.
- Adverse effects with use at supraphysiological levels
  - Acne
  - Hirsutism
  - ↓ HDL

Testosterone Therapy
Cochrane 2006

- Addition of testosterone to HRT regimens improved sexual function scores in postmenopausal women.
  - Significant adverse effect: HDL reduction
- Conclusion: Limited number of trials – cannot conclude efficacy and safety

8. A 52-yo patient currently takes no prescribed or over-the-counter medications and declines estrogen replacement therapy.

Which <u>one</u> of the following would be most effective for relieving this patient's menopausal symptoms?

A. Venlafaxine (Effexor)
B. Black cohosh
C. Soy protein
D. Vitamin E

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Hot Flashes
Other Therapies

- Significant reduction
  - Gabapentin – 100 mg/d
  - Clonidine − 0.1 mg/d
  - Venlafaxine (SSRI) − 37.5-75 mg/d
- Some reduction
  - Methyldopa – 500 mg/d (frequent side effects)
- No better or only slightly better than placebo
  - Vitamin E
  - Soy protein
  - Red clover
  - Black cohosh