Learning Objectives

1. Assess the etiologies of abnormal vaginal bleeding
2. Clarify the appropriate diagnostic strategies for evaluating abnormal bleeding
3. Review the major etiologies of dysfunctional uterine bleeding (DUB)
4. Discuss the various therapeutic interventions for the management of DUB and menorrhagia
5. Define a diagnostic and therapeutic approach to the patient with amenorrhea.

1. Which of the following is true regarding Dysfunctional Uterine Bleeding (DUB)?

A. The diagnosis of DUB is associated with malignancies of the genitourinary tract
B. Diagnosis is excluded if the bleeding is NOT controlled with estrogen and/or progestin
C. A pregnancy test is typically NOT needed in the evaluation of DUB
D. Hypothyroidism is a common cause of DUB

Dysfunctional Uterine Bleeding (DUB) is ANOVULATORY Uterine Bleeding
• Absence of pathology or medical illness
• Diagnosis is excluded if the bleeding is NOT controlled with estrogen and/or progestin
• Search for other etiologies if hormones DO NOT correct the problem

DUB Is a Diagnosis of Exclusion:
• Adolescence
• Perimenopause
  – Rule out cancer
• PCOS (70%)
• Hypothalamic anovulation
  – Anorexia (10%)
• Hyperprolactinemia
• Hypothyroidism
• Premature ovarian failure
• Iatrogenic
  – Radiation, chemotherapy
• Hyperthyroidism
• Coagulation disorders
• Genital injury or foreign object
• Benign tumors (fibroids) and endometrial polyps
• Cancers of the reproductive tract
• Pregnancy and pregnancy-related disorders

DUB is a diagnosis made AFTER exclusion of these conditions!
DUB

**Laboratory Evaluation**
- Pregnancy test
- Pap smear
- CBC
- +/- CMP
- Platelets
- Coagulation studies
- U/L
- Midluteal progesterone level (>3ng/mL)
- Prolactin
- TSH
- FSH
- LH
- Testosterone
- DHEA-S

Next – Endometrial Evaluation

**Endometrial Biopsy**
- Exclude Endometrial Cancer
- Risk Factors
  - History of Anovulatory cycles
  - Obesity
  - Nulliparity
  - History of tamoxifen use
  - Diabetes mellitus

DUB

**Endometrial Biopsy**
- Age > 35 or < 25 if risk factors (PCOS, obese)
- Best time is when patient is bleeding
- Combination of intrauterine lidocaine plus oral naproxen sodium significantly decreases pain with endometrium sampling (LOE=1b)


**Endometrial Axis**

- 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

2. Which of the following is considered the first-line treatment of DUB?
   A. Dilation and Curettage
   B. Combined Oral Contraceptive Pill
   C. Danazol
   D. Cyclic estrogen for 10-14 days per month
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DUB

**Therapeutic Agents**

- Recommendations based on good evidence
  - Treatment of choice for anovulatory bleeding (DUB) is medical therapy with OCPs
  - Cyclic progestin is also effective
    - Medroxyprogesterone acetate (MPA) 10 mg po for 10-12 days each month
  - Recommendations based on expert opinion
    - IV Conjugated estrogen therapy for acute DUB is “effective” in controlling bleeding
    - Oral estrogen + MPA or high-dose OCPs to stop bleeding - then cycle on combination OCPs.
    - IV conjugated estrogen 25 mg q 4-6 hours
      - IV route more costly; no advantage over oral route for speed or efficacy
    - No mention of D&C


**The Dilemma in Treatment**

- Is the endometrium too Thick?
- Is the endometrium too Thin?
- Some patients can be managed with hormonal therapy before diagnostic testing
  - Age < 35

**When the Endometrium is too Thick…**

- Estrogen-stimulated withdrawal bleeding
  - Continuous unopposed estrogen stimulation
  - Endometrium attains an abnormally thick height and bleeding is common

- This is the issue with DUB!

Who Has **THICK** Endometrium?

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

Treatment of **Thick** Endometrium

- What is the therapy?
  - Goal is to reduce the thickness of the endometrium
    - Progestins or OCPs
<table>
<thead>
<tr>
<th>DUB</th>
<th>DUB</th>
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<tbody>
<tr>
<td><strong>Emergency Management</strong></td>
<td></td>
</tr>
<tr>
<td>• IV conjugated estrogen – 25 mg q 4 hours until bleeding slows for 12 hours</td>
<td></td>
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<tr>
<td>– Believed to be a stimulus for clotting at the capillary level</td>
<td></td>
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<tr>
<td>– Promotes rapid growth of endometrium to cover denuded endometrial surface and stop bleeding</td>
<td></td>
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<tr>
<td>– 75% will be controlled in 6 hours</td>
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<tr>
<td>• Oral conjugated estrogen 10 mg/day in four divided doses can be substituted for IV estrogen</td>
<td></td>
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<tr>
<td>• Start OCPs or 10 days of monthly progestin (cyclic) after bleeding stops to prevent recurrence</td>
<td></td>
</tr>
<tr>
<td><strong>Non-Emergency Management</strong></td>
<td></td>
</tr>
<tr>
<td>• One combined hormonal OCP for 7 days</td>
<td></td>
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<tr>
<td>– If the flow stops within 12-24 hours, the diagnosis of DUB can be confidently made</td>
<td></td>
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<tr>
<td>– Stop combined OCPs for 7 days after one week of therapy</td>
<td></td>
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<tr>
<td>– Begin regular OCPs for the next 3-6 months</td>
<td></td>
</tr>
<tr>
<td>• Alternative</td>
<td></td>
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<tr>
<td>– Cyclic administration of progesterone for 3 months</td>
<td></td>
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</tbody>
</table>

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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

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Endometrium Is **“too Thin”** Typically Associated with...

• Endometrium has minimal estrogen stimulation
  – High progestational OCP
    • Lo/Ovral, Norlute
  – 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.

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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

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3. A 32 yo female presents to the office with a complaint of very heavy periods that occur at regular intervals. She complains, “I soak a box of pads the first two days of my menses.” Her past medical history is unremarkable and her physical exam reveals no abnormalities. The clinical presentation is most consistent with which of the following diagnoses?

- A. Metrorrhagia
- B. Menorrhagia
- C. Polymenorrhea
- D. Hypomenorrhea

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Patterns of Bleeding

- Menorrhagia: Cyclic prolonged and/or excessive bleeding
- Metrorrhagia: Bleeding at irregular and frequent intervals
- Polymenorrhea: Cycles < 21 days
- Oligomenorrhea: Cycles > 35 days
- Amenorrhea: Absence of menses > 6 months
- Hypomenorrhea: Cyclic light flow

So Where Are We…

- We have been discussing anovulatory bleeding = DUB!
- Is there an entity related to ovulatory bleeding?

Yes - Menorrhagia

DUB with OVULATORY Cycles

- Much less common
- Physiologic: mid-cycle spotting result of small drop in estrogen prior to ovulation
- Shortened follicular phase or luteal phase (polymenorrhea)
- Abnormality in endometrial prostaglandin production leading to loss of endometrial hemostasis (Menorrhagia)

What Is Menorrhagia?

- Prolonged or excessive menstrual bleeding that occurs at regular intervals (loss of > 80 mL or lasts more than 7 days).
- “I soak a box of pads the first two days of menses.”
- Consider uterine fibroids or endometrial polyps
- Consider coagulopathies (rare)
- Exclude endometrial cancer

4. Which of the following is considered a suitable medical treatment for menorrhagia?

A. NSAIDs
B. SSRIs
C. Gabapentin
D. Testosterone
4. Which of the following is considered a suitable medical treatment for menorrhagia?

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Alternate Medical Therapies

- NSAIDs: ↓ prostacyclin (platelet anti-aggregating vasodilator)
  - Decrease blood flow 20-50%
  - Mefenamic acid 500 mg po TID
- Danazol – 200 mg po qD
  - Anti-estrogen
  - Decrease blood flow 50%
  - Side effects limit use
- GnRH agonists – limited by climacteric symptoms and osteoporosis
- Antifibrinolytic agents – GI side effects, ? Thrombosis
- LNG-IUS – 80% decrease in blood loss

Endometrial Ablation Methods

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

Treatment of Menorrhagia (Cochrane Review)

- Medical
  - NSAIDs
  - Danazol
  - OCPs
  - Continuous OCPs
  - Oral continuous progestins (d 5-26)
  - Levonorgestrel IUD
- Surgical
  - Hysterectomy
  - Ablation
    - 1st generation
      - Resection
        - Laser
        - Rollerball
    - 2nd generation
      - Cryoablation
      - Laser Intrauterine Thermotherapy
      - Radiofrequency ablation*
      - Thermal balloon ablation
      - Microwave ablation

Treatment of Menorrhagia 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 cancelled the surgery after Mirena
- Hysterectomy has high satisfaction rates but risks of major surgery

5. 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
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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

- 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
      - Progesterin 10 mg q day 7-10 days every month or OCPs

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Amenorrhea

- TSH (nl)
- Prolactin (nl)
- and Progestin Challenge

Outflow Tract Obstruction (Asherman’s, Müllerian agenesis)

(-) withdrawal bleed

Estrogen and Progestin Challenge Test

No withdrawal bleed

Amenorrhea

(+ ) withdrawal bleed following Estrogen and Progestin challenge

Measure FSH and LH

Low

Normal

High

Hypothalamic amenorrhea

Ovarian Failure

Hypothalamic Amenorrhea

Hypogonadotrophic 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, Kallmann’s syndrome, 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)

6. Which of the following statements is true regarding Polycystic Ovarian Syndrome?

A. The serum FSH and LH are frequently abnormal
B. Hyperandrogenism is an unusual finding with the syndrome
C. It is one of the least common endocrinopathies seen in women
D. Metformin is recommended as a first-line agent for anovulatory women with PCOS and insulin resistance
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Pathophysiology

- Multiple genetic variants
- Environmental factors (diet, obesity, toxins)
- Excess LH secretion
- Deficient progesterone
- Increased free testosterone
- Functional androgen excess

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

- 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

- 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 (nonclassical congenital adrenal hyperplasia due to 21 hydroxylase deficiency)
      - Random normal level < 4ng/mL, or Morning fasting level < 2ng/mL
      - Consider screening for Cushing syndrome and other rare disorders such as acromegaly
    - Transvaginal pelvic ultrasound

What Is Polycystic Ovarian 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

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

**Expected Values for PCOS**
- FSH: Normal to mildly elevated
- LH: Generally moderately elevated
  - Dependent on timing of sample to last menstrual period
- Prolactin: Normal to mildly elevated
- Testosterone: normal to moderately elevated
- Normal serum estradiol, increased serum estrone concentrations

**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 DM
- 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

**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 clomiphine alone or in combination are first-line treatment for ovulation induction
  - No success – add exogenous gonadotropins or laparoscopic ovarian surgery

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7. 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

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 black 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

"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

8. Which of the following is true regarding combination estrogen-progesterone hormone therapy (HT)?

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

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*


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 supraphysiologic levels
  - Acne
  - Hirsutism
  - ↓ HDL
Testosterone Therapy

Cochrane 2006

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

9. A 52-year-old patient currently takes no prescribed or over-the-counter medications and declines estrogen replacement therapy...

Which one of the following would be most effective for relieving this patient’s symptoms?

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

Hot Flashes

Other Therapies

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

Bleeding

- Perimenopausal
- Postmenopausal

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
- HT – sequential more effective than continuous
  - Prevents hyperplasia but NO contraception

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10. A 55 yo postmenopausal woman presents with two days of vaginal bleeding (spotting). She initiated hormone therapy 14 months ago because of significant nocturnal hot flashes. Which of the following statements is most accurate?

A. Irregular bleeding is uncommon after HT is initiated
B. Postmenopausal women on hormone therapy for > 6 months who experience bleeding require prompt evaluation
C. Postmenopausal women on HT 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%

Postmenopausal Bleeding

• Irregular bleeding is common after HT is initiated and improves within 6-12 months for most women
• Evaluate
  – Cyclic HT, 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 HT, experience bleeding that persists > 6-12 months or that occurs after amenorrhea has been established
  – HT <12 months may be observed for 1 year before diagnosing abnormal uterine bleeding
  – Postmenopausal on no HT or HT >12 months with bleeding

Answers

1. B
2. B
3. B
4. A
5. C
6. D
7. D
8. A
9. A
10. C