DISORDERS OF MENSTRUATION

Four compartments: useful algorithm for differential diagnosis; compartment 1 — uterus and outflow tract; compartment 2 — ovary; compartment 3 — anterior pituitary; compartment 4 — everything above pituitary; fluctuations in luteinizing hormone, follicle-stimulating hormone (FSH), estrogen (E), and progesterin (P) known of before radioimmunoassay; follicular and luteal phases of cycle refer to ovary; proliferative and secretory phases refer to endometrium; endometrium must be primed by E before P can produce withdrawal bleed

Menstrual cycle as vital sign: patient with abnormal menstrual history requires evaluation; most classic studies done using middle-class white women, so results may not apply to others; evaluate patients with no menses and no signs of secondary sexual characteristics by 14 yr of age, patients with no menses by 16 yr of age regardless of other findings, and women without menses for duration equivalent to 3 cycles (in absence of pregnancy); ask about length and regularity of cycles and whether bleeding heavy or light

Normal menses: duration — normal bleeding episode lasts 2 to 8 days, but 4 to 6 days usual; normal blood loss 30 mL; ovulation — woman with 35-day cycle ovulates on approximately day 21; ovulation occurs ±14 days before onset of next period; patient with 32-day cycle ovulates on day 18, not day 16; luteal phase fixed at 13 to 15 days, but length of follicular (proliferative) phase varies; endometrium — in ovulatory woman, self-limited cycle occurs with dominance of E and then P, followed by withdrawal; endometrium structurally stable, behaves in synchronized fashion, and does not break down randomly due to fragility; events that start menstruation also stop it; vasoconstriction, clotting factors, and progestins result in ischemia and sloughing, and prevent exsanguination; orderly sequence of events observed within each cycle; breakdown of tissue, clearance of debris, and restructuring of endometrium related to effect of sex steroids on lysoenzymes of endometrial cells

Endometrial responses to hormones: E withdrawal bleeding — withdrawal of endogenous or unopposed E produces bleeding; midcycle spotting usually related to increased E at that time; E breakthrough bleeding — occurs in anovulatory women with high-E state; often produces light spotting; however, if endometrium thickened due to continuous exposure to high levels of E, endometrium asynchronous, with resulting heavy and disorderly withdrawal bleeding; polycystic ovary syndrome (PCOS) most common E; breakthrough bleeding also seen in teenagers ovulating intermittently and in late perimenopause; P withdrawal — occurs in E-primed endometrium after removal of hemorrhagic corpus luteum, or after erratic administration of E, then P, followed by withdrawal of both, as seen with hormone replacement therapy or oral contraceptives (OCs); P breakthrough bleeding — occurs when E insufficient to produce proliferation of endometrium; endometrium thin and atrophic; observed in patients using levonorgestrel implant (Norigest) or injectable medroxyprogesterone acetate (MPA; Depo-Provera, depo-subQ provera 104)

Abnormal bleeding: includes amenorrhea, regular but abnormal bleeding, and irregular bleeding; amenorrhea either primary or secondary; regular but abnormal bleeding often due to mechanical problem, such as fibroid or polyp; irregular bleeding anovulatory

Compartment 1 causes of amenorrhea: primary amenorrhea — associated with abnormalities of Mullerian development, such as absence of uterus; causes of absent uterus include agenesis of uterus (Mayer-Rokitansky-Kuster-Hauser syndrome); disorders with XY karyotype — include androgen insensitivity syndrome (lack of androgen receptors), 5α-reductase deficiency (testosterone [T] not converted to dihydrotestosterone), vanishing testes syndrome, and defective gene for testis-determining factor; Mullerian agenesis — anatomic defects can occur along entire Mullerian tract and within testes; genetic origins of Mullerian agenesis unclear; daughters of women with uterine agenesis (conceived with in vitro fertilization and gestational carriers) have normal uterus; uterine agenesis probably genetic condition without high penetrance; congenital defects of urogenital sinus manifested by improper development of cervix or structures below it; most common disorder imperforate hymen; transverse vaginal septum — upper vagina of Mullerian origin and lower vagina of cloacal origin; caused by errors of fusion and cannulation; patients present with severe cyclic abdominal pain; secondary amenorrhea — causes include Asherman syndrome and tuberculosis

Hypothalamic causes: after PCOS, second most common cause of secondary amenorrhea starvation or exercise-induced amenorrhea; congenital deficiency of gonadotropin-releasing hormone (Kallmann syndrome) — Kallmann midline defect associated with anosmia

Less common causes of secondary amenorrhea: inflammatory and infiltrative diseases, including brain tumor (eg, craniopharyngioma); injury to pituitary stalk; traumatic brain injury; other genetic syndromes

Educational Objectives

The goal of this program is to improve diagnosis and treatment of menstrual disorders. After hearing and assimilating this program, the clinician will be better able to:

1. Outline the causes of primary and secondary amenorrhea relative to each of 4 compartments.
2. Select relevant laboratory tests for a patient with a disorder of menstruation based on her history and physical examination.
3. Use medical therapy to manage secondary amenorrhea.
4. Design a treatment plan for a patient with dysmenorrhea.
5. Diagnose and manage premenstrual syndrome.

Faculty Disclosure

In adherence to ACCME Standards for Commercial Support, Audio-Digest requires all faculty and members of the planning committee to disclose relevant financial relationships within the past 12 months that might create any personal conflicts of interest. Any identified conflicts were resolved to ensure that this educational activity promotes quality in health care and not a proprietary business or commercial interest. For this program, Dr. Ginsburg and the planning committee reported nothing to disclose. In her lecture, Dr. Ginsburg presents information related to the off-label or investigational use of a therapy, product, or device.

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OBSTETRICS/GYNECOLOGY

Recorded at the Annual Comprehensive Obstetrics & Gynecology Review Course, sponsored by the State University of New York Downstate Medical Center, Brooklyn
Pituitary causes: hyperprolactinemia due to prolactinoma most common; other causes — pituitary meningioma and pituitary infarction (including postpartum Sheehan syndrome); impaired lactation earliest sign of Sheehan syndrome; empty sella syndrome produced by herniation of meninges into sella (pituitary compressed)

Ovarian causes: primary or secondary ovarian failure; Turner syndrome most common cause of primary ovarian failure; secondary failures probably genetic, but gene not yet identified

Significance of secondary sexual characteristics: ≈30% of girls with primary amenorrhea have breast development; of those, one-third have Mullerian agenesis, and one-third have androgen insensitivity; patients with androgen insensitivity have no pubic hair, but those with Mullerian agenesis do; distinguished via T level and karyotype; in women with Y component, gonads must be removed to prevent malignancy; in women with androgen insensitivity, remove gonads after pseudopuberty that produces breast development and growth; in others, remove gonads immediately; imperforate hymen probably underreported because usually handled in primary care setting; in girls without breast development, one-third have 46,XX karyotype with missing portion of X chromosome; others have 46,XY or other abnormal karyotype; women with 46,XX karyotype have high FSH, but patients with androgen insensitivity syndrome have low FSH because they produce T; assess FSH and karyotype in women with primary amenorrhea; one-third of patients with no breast development and low FSH have constitutional delay of puberty

More on secondary amenorrhea: evaluation of gonadotropins — most patients with secondary amenorrhea have low to normal FSH; category includes patients with PCOS, hypothryroidism, Cushing syndrome, pituitary tumors, empty sella syndrome, and Sheehan syndrome; patients with high FSH have premature ovarian failure (POF); average age at menopause 50 yr of age, but 40 yr of age at low end of normal range; genetic cause likely in younger women with elevated FSH (obtain karyotype in women <30 yr of age to look for partial Y chromosome); additional causes — high prolactin; Asherman syndrome; hyperandrogenic states caused by ovarian tumors; nonclassical congenital adrenal hyperplasia; idiopathic

Karyotypes: among patients with elevated gonadotropins, most of those with secondary amenorrhea have 46,XX karyotype, but 30% to 40% of those with primary amenorrhea have gonadal dysgenesis (45,XO in 50%; mosaicism in 25%; 46,XX in 25%)

Primary ovarian failure: fragile X syndrome — most common inherited cause of mental retardation and autism; characterized by abnormal expansion of unstable trinucleotide (cytosine-guanine-guanine repeat sequence) in FMR1 gene on long arm of X chromosome; early ovarian aging often observed in family; one-third of women with fragile X syndrome have early menopause; prevalence of premutations 14% in women with familial POF; and 1% to 7% in sporadic cases of POF; test patients with POF for fragile X so that family may undergo testing; other causes — chemotherapy; unexplained POF often associated with multiple autoimmune endocrinopathies

Disorders of anterior pituitary: prolactinoma most common cause of amenorrhea in this compartment; treat adenomas ≥1 cm (macroadenomas) with bromocriptine; surgical intervention has high rate of failure, so postoperative radiation therapy often required; remove adenoma that does not decrease in size with treatment; treat microadenomas only when breast discomfort, infertility, or galactorrhea present; if patient hypoestrogenic, OCs or hormone replacement therapy may be prescribed; nonsecreting adenomas possible

Acute Abnormal Uterine Bleeding (AUB)

Terminology: AUB refers to women of reproductive age; heavy menstrual bleeding referred to as AUB/HMB, and intermenstrual bleeding as AUB/IMB; structural causes — denoted by PALM (polyps, adenomyosis, leiomyoma, including submucosal [AUB/LSM] and other leiomyoma [AUB/LO], and malignancy); nonstructural causes — denoted by COEIN (coagulopathy, ovulatory dysfunction, endometrial dysfunction, iatrogenic, and not yet classified)

Evaluation: for hemorrhage, perform complete blood count, type and crossmatch blood, and obtain pregnancy test; in emergency setting, check for disseminated intravascular coagulation using partial thromboplastin time (PTT), prothrombin time, activated PTT, and fibrinogen; after patient stable, look for coagulopathy (von Willebrand factor, ristocetin cofactor, or factor VIII); check thyrotropin (TSH); levels of iron, total iron-binding capacity, and ferritin may reveal duration of problem; assess liver function and test for Chlamydia trachomatis; perform endometrial sampling in women >45 yr of age and in younger women with long duration of exposure to unopposed E (those with, eg, PCOS) or persistent bleeding despite medical management; use transvaginal ultrasonography to find polyps and fibroids; no biopsy required if endometrial thickness ≤4 mm

Management: hormonal — recent studies support use of OCs instead of intravenous (IV) conjugated E (eg, Cenestin, Enjuvia, Premarin); also consider MPA; 88% of women stop bleeding when combination OCs given for 1 wk; however, 76% stop bleeding with MPA, possibly with fewer side effects; avoid IV conjugated E in patients of perimenopausal age with hypertension, diabetes, obesity, or other comorbidities associated with thromboembolic events; tranexamic acid — first nonhormonal product approved for treatment of HMB; synthetic derivative of lysine that inhibits conversion of plasminogen to plasmin; prevents fibrinolysis and breakdown of clots; women taking 3.9 g/day have significantly decreased menstrual blood loss and increased health-related quality of life; common adverse effects include menstrual discomfort, headache, and back pain; serious reactions include thromboembolism and renal thrombosis; avoid in women for whom E contraindicated; may give 1300 mg 5 times daily for maximum of 5 days; surgical management — for exsanguinating patient, may consider intravenous tamponade with 26F catheter infused with saline, dilatation and curettage with hysterectomy, uterine artery embolization, endometrial ablation, or hysterectomy

Irregular bleeding: has hormonal cause; requires evaluation for PCOS, including TSH, prolactin, T, and FSH; assess glucose levels with 2-hr screen, hemoglobin A1c, or fasting ratio of glucose to insulin; medical management usually adequate; when medical management fails, reevaluate for structural or neoplastic cause of bleeding

Disorders of hemostasis: screen patients with postpartum hemorrhage or bleeding related to surgical or dental procedures; screen patients with ≥2 risk factors (ie, bruising, epistaxis, frequent gingival bleeding, or family history of bleeding)

Practical points: primary objective of treatment to restore universal synchronous endometrial events, structural stability, and vasomotor rhythmicity; begin with intensive E and P (give OCs 3 times daily for 7 days, then cycle for 3 mo on low-dose OCs, after which patient may be observed); alternatively, give MPA 10 mg daily for 10 days/mo; MPA may be given every other month, especially in teens, who may establish regular cycle with time; restart treatment if patient has no bleeding for 2 mo

Dysmenorrhea

Primary dysmenorrhea: caused by contractions of myometrium induced by prostaglandins in secretory endometrium

Secondary dysmenorrhea: associated with pathology such as endometriosis, adenomyosis, or leiomyoma; look for secondary cause in adult women who develop pain

Pelvic congestion syndrome: pain, burning, or throbbing, worse at night and after standing; at laparoscopy, reduce intraabdominal pressure to see vasocongestion; can be treated with selective embolization (performed cautiously in young patients)

Treatment: prostaglandin F2α causes symptoms by stimulating contractions of uterus; prostaglandin E2 inhibits contractions;
women with dysmenorrhea have higher levels of prostaglandins; OCS — induce atrophy in decidualized endometrium, which decreases synthesis of prostaglandins; nonsteroidal anti-inflammatory drugs (NSAIDs) — relieve symptoms in 80% of women; equally effective when begun before or at onset of menses; decrease quantity of blood loss; other options — if medical treatment not effective, perform laparoscopy to rule out endometriosis; for medical management, injectable MPA or levonorgestrel-containing intrauterine device (Mirena) may be used

**Premenstrual syndrome (PMS)**

**Background:** condition has genetic and cultural components; diagnosis requires luteal symptoms, so use of menstrual diary necessary ("mood swings" on day 12 of cycle not consistent with PMS because patient not in luteal phase); probably related to serotonergic regulation; women with PMS have better response to selective serotonin reuptake inhibitors (SSRIs) than to noradrenergic antidepressants (however, some patients with PMS do not respond to SSRIs); definition of luteal phase dysphoric disorder, or severe PMS, proffered by American Psychiatric Association; speaker recommends treatment of all nonfunctional patients, but stresses importance of distinguishing PMS from psychiatric disorders (study found concomitant psychiatric disorder in 60% of women with PMS); clinical symptoms variable, and significant placebo effect observed

**Treatment:** supportive therapy reasonable but not well studied; ineffective treatments include aerobic exercise, calcium, vitamin E, high-carbohydrate beverages, evening primrose oil, and vitamin B₆; SSRIs drugs of choice for mild or severe PMS; OCS also used to treat PMS, since patients without luteal phase should not have PMS

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### Suggested Reading

1. Which of the following patients should undergo evaluation for a disorder of menstruation?
   (A) A 16-year old with secondary sexual characteristics who has not menstruated
   (B) A 12-year old without secondary sexual characteristics
   (C) An obese 20-year old who has missed a menstrual period
   (D) A 15-year old with an imperforate hymen

2. A patient with untreated polycystic ovary syndrome and heavy bleeding is experiencing:
   (A) Estrogen withdrawal bleeding
   (B) Estrogen breakthrough bleeding
   (C) Progestin withdrawal bleeding
   (D) Progestin breakthrough bleeding

3. Disorders of menstruation associated with the 46,XY karyotype include all the following, except:
   (A) 5-α-reductase deficiency
   (B) Androgen insensitivity
   (C) Vanishing testes syndrome
   (D) Mayer-Rokitansky-Kuster-Hauser syndrome

4. The most common cause of primary ovarian failure is:
   (A) Chemotherapy
   (B) Turner syndrome
   (C) Kallmann syndrome
   (D) Autoimmune endocrinopathy

5. The majority of girls who never experience breast development have which of the following karyotypes?
   (A) 46,XX
   (B) 45,XO
   (C) 46,XY

6. The most common inherited cause of mental retardation and autism is:
   (A) Fragile X syndrome
   (B) Turner syndrome
   (C) Mosaicism
   (D) Gonadotropin deficiency

7. First-line treatment for a symptomatic microadenoma is:
   (A) Surgical resection
   (B) Bromocriptine
   (C) Radiation therapy
   (D) Observation

8. Tranexamic acid is approved for treatment of
   (A) Intermenstrual bleeding
   (B) Progestin breakthrough bleeding
   (C) Heavy menstrual bleeding
   (D) Dysmenorrhea

9. Treatments for dysmenorrhea include all the following, except:
   (A) Selective embolization of uterine artery
   (B) Laparoscopy to rule out endometriosis
   (C) Oral contraceptives
   (D) Nonsteroidal anti-inflammatory medications

10. The initial treatment of choice for premenstrual syndrome is:
    (A) Aerobic exercise
    (B) Psychiatric evaluation
    (C) Oral contraceptives
    (D) Selective serotonin reuptake inhibitors

Answers to Audio-Digest Obstetrics/Gynecology Volume 60, Issue 22: 1-C, 2-A, 3-A, 4-D, 5-C, 6-C, 7-B, 8-D, 9-D, 10-B

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