Dysfunctional Uterine Bleeding

Shirley Uy, MD, Clinical Professor of Medicine, David Geffen School of Medicine at the University of California, Los Angeles

Menstrual cycle: includes follicular phase that varies in length, ovulation, and luteal phase, lasting 12 to 16 days; hypothalamic secretes gonadotropin-releasing hormone (GNRH); GNRH acts on pituitary, which secretes follicle-stimulating hormone (FSH); positive feedback of estrogen (E) from dominant follicle to hypothalamus leads to surge of luteinizing hormone (LH) from pituitary, which initiates ovulation; follicle ruptures, releases ovum, and transforms into corpus luteum; CL; secretes E and progesterone (P); if no pregnancy occurs, CL disintegrates and cycle repeats

Menstruation: proliferative phase of endometrium corresponds to follicular phase of ovary; secretory phase and menstruation follow; menses cease due to unopposed E from follicle; at ovulation, P from CL antagonizes effect of E, which halts growth of endometrium and promotes secretory tissue to support fertilized ovum; if no pregnancy occurs, levels of prostaglandin rise in endometrium, which leads to vasospasm of spiral arteries and sloughing

Normal patterns: first menses occur at mean of 12.5 yr of age (range 9-16 yr of age); normal cycles may take 5 yr to develop; menopause occurs at mean of 51 yr of age (range 45-55 yr of age); typical interval between menses 21 to 35 days; duration of menses 4 days (range 2-7 days); normal volume 35 mL (range 20-80 mL)

Definitions: menorrhagia or hypermenorrhagia — prolonged, excessive, cyclic bleeding; metrorrhagia — irregular but frequent bleeding; menometrorrhagia — prolonged, excessive, and irregular bleeding; polymenorrhea — cycles <21 days in length; oligomenorrhea — cycles >35 days in length

Organic causes of uterine bleeding: endocrine — hyper- and hypothyroidism; elevated prolactin; adrenal dysfunction; systemic — include hepatic or renal disease, diabetes mellitus (DM), lupus, sarcoid, tuberculosis, and blood dyscrasias (eg, von Willebrand disease, leukemia, idiopathic thrombocytopenic purpura, aplastic anemia); hepatic disease produces coagulopathy; trauma — includes abrasions, lacerations, abuse or assault, and foreign bodies such as intrauterine devices (IUDs) and pessaries; iatrogenic — includes E, P, androgens, tamoxifen, GNRH agonists, corticosteroids, antidepressants, antipsychotics, anticonvulsants, anticoagulants, aspirin, and chemotherapeutic agents; gynecologic — most common etiology; includes neoplasms in reproductive tract, metastases from gastrointestinal or genitourinary tract, cervical polyps or erosions, fibroids, adenomyosis, cervicitis, endometritis, salpingitis, abortion, ectopic pregnancy, and trophoblastic disease; dysfunctional uterine bleeding (DUB) — diagnosis of exclusion; most cases anovulatory, but 10% relate to impaired hemorrhage in endometrium; physiologic DUB occurs at extremes of reproductive life; puberty — hypothalamic-pituitary axis and positive feedback mechanism that triggers ovulation immature; ovaries make E, which thickens endometrium; however, negative feedback intact, so endometrium breaks down when E level falls; perimenopause — ovaries do not make enough E to trigger ovulation; irregular bleeding occurs as E levels fall

Pathologic bleeding: occurs with excess E, hypothalamic dysfunction, and polycystic ovary syndrome (PCOS); hypotalamic dysfunction — seen with extreme exercise and in women with physical stress, illness, chronic disease, uncontrolled DM, emotional stress, and anorexia; in complete hypothalamic failure, serum E <40 pg/mL, but irregular bleeding occurs before amenorrhea; PCOS — secretion of GNRH and LH increased; ratio of LH to FSH often >2; excess androgens converted to E in fat; may present with DUB, oligomenorrhea, amenorrhea, obesity, hirsutism, acne, insulin resistance, or DM; due to excess E, endometrium proliferates, outgrows blood supply, and sloughs irregularly; patients at risk for adenomatous hyperplasia, atypical hyperplasia, and cancer; other causes — midcycle spotting due to falling E level, short follicular phase, luteal phase deficiency, or problem with function or production of prostaglandins that affects hemorrhage in endometrium

Evaluation of heavy bleeding: predictable bleeding pattern suggests structural lesion; look for proptosis suggesting hypothyroidism or ecchymoses related to disorder of hemorrhage; rule out pregnancy; perform other tests based on clinical suspicion (eg, Papanicolaou test, complete blood count, coagulation parameters)

Endometrial biopsy: performed if patient >35 yr of age or at risk for cancer due to chronic anovulation, PCOS, obesity, or uncontrolled DM; may be done during active bleeding; proliferative tissue suggests exposure to unopposed E and anovulation; secretory tissue confirms ovulation and presence of P; hyperplasia advanced effect of unopposed E; atypical premalignant; menopausal women or those treated with P (oral contraceptive, injectable medroxyprogesterone acetate [MPA; Depo-Provera, depo-subQ provera 104], or hormone replacement therapy) may have atrophic endometrium

Other tests: endometrial lining <4 or 5 mm on transvaginal ultrasonography (TVUS) suggests nonmalignant condition; use saline infusion sonohysterography or hysteroscopy to assess cavity; hysterosalpingography rarely used

Educational Objectives

The goals of this program are to improve diagnosis and treatment of dysfunctional uterine bleeding and uterine cancer. After hearing and assimilating this program, the clinician will be better able to:

1. Diagram the organs and hormones governing the menstrual cycle.
2. Diagnose and treat a patient with dysfunctional uterine bleeding.
3. Describe the epidemiology and types of uterine cancers.
4. Recommend surgical and adjuvant treatment for a patient with uterine cancer based on the type, grade, and stage of her tumor, and other patient characteristics.
5. Establish a follow-up plan for a patient previously treated for uterine cancer.

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, the faculty and planning committee reported nothing to disclose.
Adolescents: most women with DUB anovulatory; ≈20% of those who present to emergency department (ED) with heavy bleeding have coagulopathy; biopsy not usually necessary; observe for 6 mo unless severe anemia present or bleeding persists; treat with 10 mg MPA for 10 days/mo or combined oral contraceptives (OCs); options for heavy bleeding — conjugated equine E (CEE), tapered when effective, and followed by P for 7 days (after withdrawal bleed, cycle with MPA, OC, ring, or patch); ethinyl E/norgestrel (Ovral), then cycle; in ED, 25 mg intravenous (IV) CEE administered every 4 hr, but IV route not superior to oral

Young women: OCs reduce bleeding by 50%; other options — cyclic P; levonorgestrel IUD (Mirena), which reduces bleeding by 90%; injectable MPA; P helpful for inadequate luteal phase; clomiphene (Clomid, Serophene) used if pregnancy desired

Perimenopause: ≈10% of perimenopausal women with abnormal bleeding have cancer; tissue diagnosis important, but TVUS can be done initially; hormonal treatment — if no organic disease found, cyclic P, low-dose OC, or levonorgestrel IUD used; for ovulatory patients, hormonal therapy, OC, IUD, or continuous norethindrone may be used; danazol may cause weight gain, acne, or hirsutism; GNRH agonists cause climacteric symptoms; nonhormonal treatment — nonsteroidal anti-inflammatory drugs such as mefanamic acid (Ponstel), ibuprofen, and naproxyn reduce bleeding by 30% to 50%; anti-fibrinolytics inhibit plasminogen activators, thus promoting clotting in endometrium; tranexamic acid (Lysteda) indicated for cyclic heavy bleeding (reduces bleeding by 34% to 59%); contraindicated in patients with thromboembolic disease; OCs must be combined cautiously due to thrombogenicity; surgical treatment — dilation and curettage (D&C) controls heavy bleeding but does not prevent recurrence; hysteroscopy used to treat intrauterine lesions or ablate endometrium; hysterectomy treatment of last resort

Update on Uterine Cancer

Tana Shah Pradhan, DO, Assistant Professor of Obstetrics and Gynecology, New York Medical College, Valhalla

Incidence: fourth most common cancer, but eighth leading cause of death from cancer in US women; cancer related to obesity

Histology: epithelial or mesenchymal; endometrioid adenocarcinoma accounts for 87%; papillary serous and clear cell carcinoma aggressive; mesenchymal tumors (ie, carcinosarcoma, leiomyosarcoma, endometrial stromal sarcoma, and adenosarcoma) account for 6%

Risk factors: obesity most important; fat cells make unopposed E; others — increasing age; tamoxifen; exogenous E; PCOS; Stein-Leventhal syndrome; anovulation; DM; hypertension; gall bladder disease; thyroid disease; metabolic syndrome

Types of cancers: type 1 — E-dependent; common in whites and younger patients; associated with endometrial hyperplasia; includes well-differentiated endometrioid cancers; responsive to surgery; recurrence rate low; type 2 — E-independent tumors; occur in older women; includes aggressive histologies such as papillary serous and clear cell; can occur in atrophic endometrium with 1- to 2-mm lining; spread similar to that of ovarian cancers (distant metastases more common and mortality rate higher)

Screening: no evidence supports routine screening (no good screening test); hereditary nonpolyposis colorectal cancer syndrome — screening recommended for affected patients, who may present at early age with colorectal or endometrial cancer; associated with ovarian, gastric, small bowel, pancreatic, and biliary tract cancers; genetic testing should be considered in patients <55 yr of age with endometrial cancer or those with significant family history (screen with annual biopsy starting at 35 yr of age)

Race: most uterine cancers more common in whites than blacks, but mortality rate 2 times higher in blacks due to higher incidence of aggressive subtypes and less access to care

Diagnosis: presentation abnormal vaginal bleeding in 90%; 3% to 20% of postmenopausal patients with bleeding have cancer (hyperplasia in 5%-15%); only biopsy can rule out cancer; negative predictive value of endometrial stripe ≤4 mm nearly 100%; biopsy options — suction curette (eg, Pipelle), aspirator (eg, Vabra), or D&C; D&C gold standard, but not needed if sufficient tissue obtained in office

Endometrial hyperplasia: with simple hyperplasia, glands swollen but have normal architecture; abnormal architecture with many mitotic figures concerning; use “penny, nickel, dime, quarter” to recall rates of progression of hyperplasias to cancer (1% for simple; 3%-5% for complex; 8%-10% for simple with atypia; 25%-29% for complex with atypia [if childbearing completed, hysterectomy recommended]; 40% of such patients have occult cancer; consultation with gynecologic oncologist and frozen section advised)

Tamoxifen: antagonist in breast and agonist in uterus; risk low, and most cancers stage 1; women >50 yr of age at highest risk; benefits of tamoxifen for breast cancer outweigh risks; screening unnecessary, but biopsy needed if bleeding

Women with cancer: assess comorbidities, lymph nodes (LNs), and cervical or paravaginal involvement; obtain chest x-ray; in advanced cases, evaluate bladder and colon, do computed tomography (CT) to assess nodes and extruterine spread, and use magnetic resonance to see invasion of myometrium; CA-125 reasonably sensitive marker of extruterine disease

Treatment: total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), pelvic washings, and LN dissection (LND); if disease limited to uterus, use minimally invasive approach; patients with cervical involvement may need radical hysterectomy; vaginal hysterectomy with BSO alternative in many patients and beneficial in women with comorbidities, obesity, or stage I disease in which LND not necessary; with aggressive histology, do extended staging with infracolic omentectomy and peritoneal biopsies; LND required for extrauterine disease, grade 3 tumor, nonendometrioid histology, >50% myometrial invasion, tumor >2 cm, or cervical involvement; LND not needed for grade 1 cancer without myometrial invasion; medical management — possible if patient premenopausal and tumor grade 1; repeat biopsy after 6 mo of MPA or megestrol (Megace); for young patient with complex atypical hyperplasia and poor surgical candidates, opt P or levonorgestrel IUD

Stage and grade: IA — <50% of myometrium invaded; IB — ≥50% of myometrium invaded; II — cervical stroma invaded; IIIA — uterine serosa or adnexae involved; IIIB — vagina or parametria involved; IIC — positive pelvic or periaortic LNs; IIIC1 — positive pelvic LNs; IIIC2 — positive periaortic LNs; IVA — invasion of mucosa of bladder or bowel; IVB — distant or inguinal metastases; results of washings do not alter stage; grade 1 — has appearance similar to glands; grade 3 — more solid in appearance

Adjuvant treatment: stage and grade most important factors; other factors depth of myometrial invasion, LN status, lymphovascular invasion, and histology; adjuvant therapy used for type 2 cancers; increasing age poor prognostic factor; molecular features, ethnicity, and comorbidities used to guide therapy; brachytherapy (BT) delivered intravaginally after hysterectomy; other treatments include external-beam radiotherapy (EBRT), hormonal therapy, cytotoxic chemotherapy, and combination therapy in women with advanced disease and high-risk histology; discuss lifestyle changes with obese women

Radiotherapy: used for low-stage, high-grade disease; pelvic RT controls local disease but does not change survival; causes side effects in small bowel and bladder; trial of EBRT vs BT in early-stage disease with high-risk features found no difference in survival; intravaginal BT more widely used than EBRT; for advanced cancer, chemotherapy more effective than RT; carboplatin and paclitaxel standard of care

Recurrence: all patients need postoperative surveillance; intravaginal RT often used in comprehensively staged women; all
cancers require gynecologic oncologist; combination chemotherapy used for advanced disease and preferable to whole-abdominal RT; low-risk patients followed every 3 to 6 mo for 1 yr, then every 6 mo, then annually for 5 yr; history and examination used to detect recurrence; vaginal Papancicolau test not helpful; bloating or bowel problems may prompt imaging, but no data support routine imaging; if recurrence suspected, best imaging modality unclear (positron emission tomography/CT or CT often used); utility of CA-125 unclear; RT treatment of choice for recurrence at cuff or women with no previous RT; surgical treatment of isolated lesion possible; 15% to 30% respond to P; response rates to other treatments lower; P used for E-responsive tumors; chemotherapy used for widespread recurrence, disease in chest, or large tumor burden.

**Sarcomas:** mortality rates exceed 98%; most common type sarcomatosis, followed by leiomyosarcoma, endometrial stromal sarcoma, and Mullerian adenocarcinoma; criteria for leiomyosarcoma — ≥2 of 3 factors (coagulative tumor cell necrosis, >10 mitoses/high-power field, and atypia); endometrial stromal sarcomas — related to hormonal stimulation; Mullerian adenosarcoma — rare; optimal treatment unknown; staging — traditional schema used for carcinosarcoma; leiomyosarcoma has different staging system based on size and extent of tumor.

Nodal metastases: carcinosarcoma (mixed Mullerian tumor) commonly metastasizes to pelvic and paraaortic LNs; comprehensive staging with LND improves survival; leiomyosarcoma rarely spreads to LNs and does not require LND if found incidentally.

Treatment: TAH-BSO standard treatment; prognosis poor and no effective adjuvant treatment available; incidence of leiomyosarcoma in rapidly enlarging uterus only 0.6%; postoperative RT often used to decrease pelvic recurrence of carcinosarcoma; chemotherapy may be used for advanced or recurrent disease.

**Suggested Reading**


**Acknowledgements**

Dr. Uy was recorded at the *Office Gynecology/Women's Health for Primary Care*, sponsored by the David Geffen School of Medicine and the UCLA Department of Family Medicine, and held August 1-4, 2013, in Anaheim, CA. Dr. Pradhan spoke at the *Comprehensive Obstetrics and Gynecology Review Course*, presented by the State University of New York Downstate Medical Center, and held May 17-19, 2013, in Brooklyn, NY. For information on continuing medical education courses from the David Geffen School of Medicine, please go to cme.ucla.edu. To learn about upcoming obstetrics and gynecology review courses from SUNY Downstate, please visit downtowntecobyn.com. The Audio-Digest Foundation thanks the speakers and the sponsors for their cooperation in the production of this program.

**Accreditation:** The Audio-Digest Foundation is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

**Designation:** The Audio-Digest Foundation designates this enduring material for a maximum of 2 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

The American Academy of Physician Assistants (AAPA) accepts certificates of participation for educational activities designated for AMA PRA Category 1 Credits™ from organizations accredited by ACCME or a recognized state medical society. Physician assistants may receive a maximum of 2 Category 1 CME credits for each Audio-Digest activity completed successfully.

Audio-Digest Foundation is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center’s (ANCC) Commission on Accreditation. Audio-Digest designates each activity for 2.0 CE contact hours, including 0.5 pharmacology CE contact hours. Audio-Digest Foundation is accredited as a provider of continuing education by the American Academy of Nurse Practitioners (AANP) Provider number 030904. Audio-Digest designates each activity for 2.0 CE contact hours, including 0.5 pharmacology CE contact hours.

The California State Board of Registered Nursing (CA BRN) accepts each activity for 2.0 CE contact hours, including 0.5 pharmacology CE contact hours. Audio-Digest accepts certifiable credits for 3 years from the date of publication.

**Cultural and linguistic resources:** In compliance with California Assembly Bill 1195, Audio-Digest Foundation offers selected cultural and linguistic resources on its website. Please visit this site: www.audiodigest.org/CLCResources.

**Estimated time to complete the educational process:**

- **Review Educational Objectives on page 1**: Take pretest 5 minutes
- **Take pretest**: 10 minutes
- **Listen to audio program**: 60 minutes
- **Review written summary and suggested readings**: 35 minutes
- **Take posttest**: 10 minutes
1. Which of the following is characterized by menstrual cycles <21 days apart?
   (A) Hypermenorrhea  (B) Polymenorrhea  (C) Menorrhagia  (D) Endometrial polyp

2. Most women with dysfunctional uterine bleeding are anovulatory.
   (A) True  (B) False

3. Complete hypothalamic failure is associated with:
   (A) Midcycle spotting  (B) Follicular phase defect  (C) Ratio of luteinizing hormone to follicle-stimulating hormone >2  (D) Serum estradiol <40 pg/mL

4. Tranexamic acid is contraindicated in patients with:
   (A) Hirsutism  (B) Diabetes  (C) Thromboembolic disease  (D) Perimenopausal bleeding

5. The histology of which of the following uterine tumors is mesenchymal?
   (A) Papillary serous  (B) Clear cell  (C) Endometrioid  (D) Endometrial stromal

6. Which of the following is the most important risk factor for uterine cancer?
   (A) Age  (B) Diabetes  (C) Obesity  (D) Anovulation

7. A lymph node dissection is not required for patients with uterine cancer and:
   (A) Extrauterine disease  (B) Diagnosis of leiomyosarcoma  (C) Grade 3 tumor  (D) Nonendometrioid histology

8. A woman with uterine cancer and positive pelvic lymph nodes has stage _______ disease.
   (A) IIIB  (B) IIIC  (C) IVA  (D) IVB

9. Which of the following is recommended for detection of a recurrence of uterine cancer?
   (A) Papanicolaou test  (B) Positron emission tomography  (C) Magnetic resonance imaging  (D) History and physical examination

10. The most common type of uterine sarcoma is:
    (A) Carcinosarcoma  (B) Leiomyosarcoma  (C) Mullerian adenosarcoma

Answers to Audio-Digest Obstetrics/Gynecology Volume 61, Issue 04: 1-B, 2-A, 3-D, 4-C, 5-B, 6-A, 7-D, 8-A, 9-C, 10-D