36. ABNORMAL UTERINE BLEEDING

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I. **Classification of abnormal uterine bleeding.** Normal menstrual bleeding is defined as cyclic menstruation every 21–35 days that lasts fewer than 8 days with 20–80 mL of blood loss. For practical purposes, any patient who complains of a change in her previously established menstrual pattern may be considered to have abnormal uterine bleeding.
   A. **Definitions**
      1. Polymenorrhea is uterine bleeding at intervals of fewer than 21 days.
      2. Oligomenorrhea is uterine bleeding at intervals of more than 35 days.
      3. Hypermenorrhea (menorrhagia) is excessive bleeding at regular intervals.
      4. Metrorrhagia is bleeding at irregular intervals.
      5. Menometrorrhagia is heavy, irregular bleeding.
      6. Intermenstrual bleeding is bleeding between regular menses.
   B. **Differential diagnosis.** The causes of abnormal uterine bleeding may be categorized as either **organic** or **nonorganic**. Organic causes can be further classified as reproductive tract disease, systemic disease, trauma, and pharmacologic alterations. The diagnosis of nonorganic cause, or **dysfunctional uterine bleeding**, is assumed when an organic cause cannot be found (Table 36-1).

Organic causes	Reproductive tract disorders
	Complications of pregnancy (ectopic pregnancy, miscarriage)
	Benign disease—fibroids, polyps, infections, endometrial hyperplasia
	Malignancy—endometrial, cervical cancer
	Trauma or foreign body
	Systemic diseases
	Coagulation disorders
	Endocrinopathies—hypothyroidism, hyperprolactinemia
	Liver failure
	Obesity
	Iatrogenic/pharmacologic causes
	Psychotropic medications
	Hormonal contraception/replacement
Nonorganic	Dysfunctional uterine bleeding
	Anovulation (more common)
	Ovulation

TABLE 36-1. DIFFERENTIAL DIAGNOSIS OF ABNORMAL UTERINE BLEEDING

II. **Evaluation.** To determine the cause of a patient's abnormal uterine bleeding, a complete workup must be performed, including history, physical examination, laboratory evaluation, possible imaging studies, and possible tissue sampling (Table 36-2).

Hemodynamic stabilization	Vital signs, orthostatics, general appearance
History	Duration, frequency, severity of bleeding
	Associated pain, discharge, abdominal symptoms
	Contraceptive history, medical history, obstetric-gynecologic history, medications
Physical examination	Vital signs, abdominal examination, pelvic examination
Laboratory tests	β-hCG level, CBC, PT/aPTT, LFTs, TFTs, prolactin level
Imaging studies	Ultrasonography, CT scan, SHG
Tissue sampling	D & C, endometrial biopsy, hysteroscopically directed biopsy

aPTT, activated partial thromboplastin time; β-hCG, human chorionic gonadotropin, β-subunit; D & C, dilation and curettage; LFTs, liver function tests; PT, prothrombin time; SHG, sonohysterography; TFTs, thyroid function tests.

TABLE 36-2. COMPLETE EVALUATION

   A. **History.** The history must include a qualification of the abnormal bleeding, specifically determining the onset, duration, frequency, amount, and pattern of the bleeding. In addition, the degree of associated pain, vaginal discharge, fever, nausea, and vomiting should be clarified. Other sources of the bleeding, such as from the GI or urinary tract, should be ruled out. For women of childbearing age, sexual and contraceptive history should be explored to help determine likelihood of pregnancy. Menopausal symptoms should be explored in appropriate patients. Any change in the patient's diet, weight, and exercise pattern is relevant. The patient's age, parity, hormonal contraception or hormone replacement history, past medical history, gynecologic and obstetric history, and medication regimen are pertinent to the evaluation. Family history of diseases, including gynecologic cancer or bleeding disorders, should be discussed.
   B. **Physical examination.** The patient should first be evaluated to ensure that she is hemodynamically stable. If the patient does not require immediate resuscitative intervention, attention should be directed to the abdomen and pelvis. Examination of the abdomen can determine if the patient has an acute or surgical abdomen that requires urgent surgical intervention. Inspection of the vaginal vault can demonstrate the degree of current bleeding, source of the bleeding, discharge suggestive of infection, or evidence of trauma, lesions, polyps, tissue, or masses. A bimanual examination should be performed to establish the status of the internal os, presence of cervical motion tenderness, presence of any palpable masses or lesions, size and contour of uterus and adnexa, and presence of any tenderness on manipulation of any of the pelvic organs. Finally, more specific physical findings can be associated with abnormal uterine bleeding caused by systemic diseases (see sec. **III.C**).
   C. **Laboratory studies.** To establish the acuteness and severity of the abnormal vaginal bleeding, the patient's hemoglobin level or hematocrit or both should be determined. Any patient of childbearing age must be assumed to be pregnant until proven otherwise; therefore, a urine level of human chorionic gonadotropin, b-subunit (b-hCG) must be obtained. Other laboratory tests that may be of interest include a Pap smear (if the patient is not actively bleeding) to evaluate for cervical dysplasia; WBC to look for other evidence of infection; platelet count, prothrombin time, and partial thromboplastin time to rule out a coagulation disorder; liver function tests to assess for hepatic disease; and thyroid function tests to investigate the possibility of thyroid disorders. A

perimenopausal patient may need hormonal assays to evaluate her current hormonal state (follicle-stimulating hormone, estradiol).

D. **Imaging studies.** Depending on the differential diagnosis, various imaging studies may be necessary.
   1. **Ultrasonography.** Ultrasonography is useful to evaluate for the presence of benign reproductive tract conditions such as fibroids, possible polyps, intrauterine pregnancy, and ectopic pregnancy. In the workup for possible malignant processes, sonography can be used to search for a thickened endometrial stripe and masses within the uterus, adnexa, or cervix.
   2. **Sonohysterography (SHG).** SHG involves the instillation of a sterile solution (usually crystalloid) into the uterine canal during ultrasonography. SHG is the most sensitive noninvasive method of diagnosis for endometrial polyps and submucous myomata; its sensitivity approaches that of hysteroscopy.
   3. **CT scanning.** CT imaging is used primarily in patients in whom the suspicion for malignancy is high. The CT scan can be used to help evaluate the location and extent of the disease.

E. **Tissue sampling.** Assessment of the endometrium is almost never needed for patients younger than 30 years (unless for endometrial dating). Endometrial sampling may be indicated in patients aged 30–40 years with risk factors for carcinoma. In premenopausal patients older than 40 years, the endometrium should be assessed if abnormal bleeding occurs. Postmenopausal bleeding must be assumed to be due to a malignancy until proven otherwise by tissue sampling.
   1. **Office biopsy.** Office sampling using a Novak curette or a Pipelle or Vabra aspirator is simple, safe, and cost effective. Complications are extremely rare.
   2. **Office hysteroscopy and biopsy.** Hysteroscopy can be used to visualize the endometrial cavity directly to look for lesions or pathology and to perform a directed biopsy. Complications are rare (less than 1%).
   3. **Dilation and curettage (D & C).** D & C is a simple procedure. Performing the procedure, however, incurs the cost of an expensive operating room and carries the inherent risks of anesthesia.

III. **Diagnosis and treatment**

A. **Benign reproductive tract disease**
   1. **Complications of pregnancy.** Any patient of childbearing age must be assumed to be pregnant until proven otherwise.
      a. **Diagnosis.** A positive result on a urine b-hCG test is the definitive indicator of pregnancy. If findings of the urine b-hCG test are positive, a careful pelvic examination must be performed and an ultrasonographic study obtained to determine if the patient has an ectopic pregnancy or a threatened, inevitable, incomplete, or missed abortion. A quantitative serum b-hCG test may be helpful.
      b. **Treatment.** Any patient who is hemodynamically unstable, bleeding heavily, or septic requires surgical intervention, such as a D & C for an early intrauterine pregnancy or abdominal surgery for an ectopic pregnancy.
   2. **Leiomyomata.** Leiomyomata **(fibroids)** are the most common uterine neoplasm. These benign smooth muscle tumors are found in 20–30% of patients older than 30 years and are uncommon in younger patients. The most common bleeding pattern associated with leiomyomata is hypermenorrhea. (See Chap. 33 for diagnosis and treatment.)
   3. **Polyps.** Endometrial polyps are generally benign lesions that are found in fewer than 2% of premenopausal patients who undergo D & C. Benign cervical polyps are found in up to 4% of patients undergoing routine speculum examination. Although cervical polyps are often asymptomatic, associated symptoms most commonly include intermenstrual bleeding and postcoital spotting.
      a. **Diagnosis.** Polyps can be diagnosed by a sonogram, hysterosalpingogram, or hysteroscopy.
      b. **Treatment.** Polyps can be treated by simple polypectomy. Hypermenorrhea associated with endometrial polyps may respond to hormonal therapy.
   4. **Infection.** Abnormal bleeding is not a common presenting symptom of either endometritis or cervicitis. If present, bleeding associated with endometritis is most commonly intermenstrual, and bleeding associated with cervicitis is postcoital.
      a. **Diagnosis.** Endometritis is diagnosed by fundal tenderness and fever. Any recent history of instrumentation of the uterus adds to the suspicion of endometritis. Cervicitis is diagnosed by clinical examination and results of cervical cultures.
      b. **Treatment.** Endometritis and cervicitis should be treated with antibiotics. (See Chap. 24.)
   5. **Typical endometrial hyperplasia**
      a. **Diagnosis.** An endometrial tissue sample, either from an endometrial biopsy or a D & C, is required to make the diagnosis of typical endometrial hyperplasia.
      b. **Treatment.** In the absence of attempts at conception, these patients should probably be maintained on a regimen of cyclic monthly progestin withdrawal or oral contraceptive pills to prevent recurrence. An endometrial biopsy should be repeated if abnormal bleeding persists during treatment or recurs after therapy. Treatment should be continued for 4–6 months, at which time an endometrial biopsy should be performed to confirm regression of the hyperplasia.
   6. **Atypical endometrial hyperplasia**
      a. **Diagnosis.** Diagnosis of atypical hyperplasia requires an endometrial tissue sample.
      b. **Treatment.** Treatment is always required, because in approximately 25% of cases, atypical hyperplasia progresses to carcinoma. Hysterectomy is an acceptable first-line treatment. As many as 25% of uteri removed in the treatment of atypical hyperplasia harbor a focus of well-differentiated carcinoma. For patients who wish to retain their fertility, progestational therapy is an acceptable approach. Continuous regimens of megestrol acetate (20–40 mg twice daily) may achieve an adequate response. Preliminary data suggest that even lower dosages may be effective. Treatment is continued for 6 months, with endometrial biopsies performed at 3 and 6 months. Dosing is increased if regression is not observed. Progesterone withdrawal regimens are not consistently effective and should not be used in the treatment of atypical hyperplasia; they may, however, be useful in preventing recurrence. (See Chap. 44.)

B. **Malignant reproductive tract disease**
   1. **Endometrial cancer.** Endometrial carcinoma is rare in patients younger than 40 years and uncommon in the perimenopausal years. Postmenopausal bleeding, however, should be assumed to represent endometrial cancer until proven otherwise. (See Chap. 44.)
      a. **Diagnosis.** In a postmenopausal woman not receiving HRT, the presence of a thickened endometrial stripe (larger than 5 mm) on ultrasonography can be suggestive, but an endometrial tissue sample taken by D & C or endometrial biopsy is required for diagnosis.
      b. **Treatment.** Total abdominal hysterectomy with bilateral salpingo-oophorectomy and staging is the standard therapy. The need for postoperative radiation therapy is dependent on the stage and risk of recurrence.
   2. **Cervical cancer.** Cervical carcinoma is a disease of both the relatively young and the old. Although it is rarely the cause of abnormal bleeding, it must be considered in the differential diagnosis. Almost all cervical lesions that cause abnormal bleeding are visible on examination. The most common bleeding patterns associated with cervical carcinoma are intermenstrual and postcoital bleeding. (See Chap. 43 for additional discussion of diagnosis and treatment.)
      a. **Diagnosis.** Patients are screened for cervical cancer with routine Pap smears. Abnormal smears can be followed by colposcopy. Lesions warrant biopsy.
      b. **Treatment.** Depending on the stage of the cervical cancer, the patient may require surgical resection, chemotherapy, radiation, or a combination of these.
   3. **Ovarian cancer.** Estrogen-producing ovarian tumors, such as a granulosa-theca cell tumor, can produce endometrial hyperplasia and abnormal uterine bleeding. (See Chap. 45.)
      a. **Diagnosis.** Diagnosis usually involves a sonographic finding or a tissue diagnosis after resection.
      b. **Treatment.** Ovarian cancer is treated by resection with or without adjuvant therapy.

C. **Systemic disease or disorder**
   1. **Disorders of coagulation.** Coagulopathies may lead to abnormal uterine bleeding, often by exacerbating another underlying mild abnormality such as fibroids. Coagulopathies, however, are a relatively rare cause of abnormal uterine bleeding. **von Willebrand's disease** is the most common inherited bleeding disorder in women (occurring in up to 1 in 1000 patients). Other entities such as idiopathic thrombocytopenic purpura, hypersplenism, and hematologic malignancy (e.g., leukemia) may also be associated with abnormal uterine bleeding.
      a. **Diagnosis.** Menorrhagia during adolescence should be attributed to a coagulation disorder until proven otherwise. Blood tests to evaluate the platelet count, prothrombin time, and partial thromboplastin time are indicated. Bleeding from multiple sites (nose, gingiva, intravenous sites, GI and genitourinary tracts) can be suggestive of a coagulopathy.
      b. **Treatment.** Therapy usually involves treating the underlying cause and may require administration of blood products.
   2. **Endocrinopathies** that cause anovulation. Anovulation can create an environment of unopposed estrogen. In the absence of progestin, the endometrium eventually breaks down, which may or may not lead to the formation of hyperplasia. **Hypothyroidism** and **hyperprolactinemia** are common disorders that can lead to anovulation.
      a. **Diagnosis.** Signs and symptoms of hypothyroidism (fatigue, weight gain, cold intolerance, goiter, myxedema, delayed reflexes) and hyperprolactinemia (galactorrhea or visual changes from mass effect) should be reviewed and examined. Laboratory studies are diagnostic; therefore, thyroid function tests (measurement of levels of thyroid-stimulating hormone and free thyroxine) and measurement of prolactin level are indicated.
      b. **Treatment.** Thyroid replacement therapy may be necessary for hypothyroidism. Bromocriptine mesylate or surgical resection of any macroadenoma of the pituitary, or both, may help relieve symptoms of hyperprolactinemia. Oral contraceptive pills (OCPs) or progestin may help eliminate the bleeding resulting from anovulation.
   3. **Liver failure.** Decreased metabolism of estrogen and decreased clotting factor synthesis may lead to endometrial glandular and stromal breakdown,

which may or may not produce endometrial hyperplasia. Anovulation may also ensue. Menometrorrhagia is common.

a. **Diagnosis.** Liver function tests are necessary to make the diagnosis. Physical examination findings of jaundice, ascites, hepatosplenomegaly, palmar erythema, pruritus, and spider hemangiomata are suggestive of liver failure.
b. **Treatment.** If possible, the underlying cause of the liver disease should be treated. If the patient is coagulopathic and is hemorrhaging from her disorder, administration of fresh frozen plasma may be indicated. Progesterone therapy may also be beneficial.

D. **Pharmacologic alterations.** Various medications may cause abnormal uterine bleeding. Any medication that acts on the hypothalamic-pituitary axis can lead to anovulation and abnormal bleeding.

1. **Psychotropic medications.** Certain medications used in the treatment of psychiatric patients can affect the hypothalamic-pituitary axis and interfere with ovulation. **Antidepressants** are among the commonly used medications associated with anovulation. The **antipsychotics** can also interfere with the normal menstrual cycle.
2. **Hormonal manipulation**
   a. **Levonorgestrel implants.** Sixty percent to 80% of patients experience irregular bleeding during the first year of levonorgestrel implant (Norplant) use.
   b. **Medroxyprogesterone acetate.** Approximately 30% of patients taking medroxyprogesterone (Depo-Provera) experience irregular bleeding during the first year. After the first year, 75% of patients on medroxyprogesterone are amenorrheic.
   c. **Combination oral contraceptive preparations.** Intermenstrual (breakthrough) bleeding is experienced by 10–30% of patients during the first month of OCP use, and by 1–10% during the subsequent 2 months. With long-term use, abnormal bleeding may result from endometrial atrophy. Abnormal bleeding for longer than 6 months requires further evaluation.
   d. **Progestational agents.** High doses of progesterone often are used in the treatment of abnormal uterine bleeding and endometrial hyperplasia. Prolonged use of these agents may result in endometrial atrophy, which itself often can cause abnormal uterine bleeding.
3. **Anticoagulants.** If the dosage of anticoagulants is too high, the patient can experience abnormal uterine bleeding.
4. Other drugs that may cause abnormal uterine bleeding include digitalis, phenytoin, and corticosteroids.

E. **Intrauterine devices.** Inert and copper-containing intrauterine devices can frequently cause heavy and irregular bleeding secondary to local inflammation and increased endometrial fibrinolytic activity. Such bleeding is often treated successfully with nonsteroidal anti-inflammatory agents.

F. **Dysfunctional uterine bleeding (DUB).** DUB is defined as abnormal uterine bleeding without a demonstrable organic cause and is found in approximately one-third of all patients evaluated. Treatment is directed toward stabilizing the endometrium and balancing the hormonal alterations. Medical therapy can include nonsteroidal anti-inflammatory agents, antifibrinolytic agents, high-dose estrogens, progestins, OCPs, danazol, and gonadotropin-releasing hormone agonists.

1. **Anovulation.** The predominant cause of DUB is anovulation. By definition, this anovulation is not secondary to a demonstrable organic cause. Anovulation is multifactorial and related to alterations of the hypothalamic-pituitary-ovarian axis. Anovulation associated with **polycystic ovary disease** and other forms of hyperandrogenism lacks a discrete organic cause, and associated bleeding abnormalities may be considered to be DUB. **Morbid obesity** can also cause DUB. Peripheral conversion of androstenedione to estrone occurs in adipose tissue. Elevated estrogen levels may lead to anovulation, which causes unopposed estrogen exposure and DUB.
2. **Ovulation.** Occasionally, DUB may be associated with ovulatory cycles. A persistent corpus luteum that does not regress in 12–14 days may result in DUB.

IV. **Acute vaginal hemorrhage** Occasionally, patients experience severe vaginal bleeding. These patients usually present to the emergency department. Under such circumstances, endometrial sampling is inappropriate.

A. **History and physical examination.** An abbreviated history and physical examination is performed. Particular attention is paid to menstrual history and reproductive tract disease, as pregnancy and leiomyomata are by far the most common offenders. It is also necessary to look for vaginal tears from coitus or trauma and rectal bleeding, which are other common causes of acute hemorrhage.

B. **Laboratory studies.** A pregnancy test should be performed, and CBC, prothrombin time, and activated partial thromboplastin time should be obtained.

C. **Treatment.** Intravenous fluid resuscitation should be initiated immediately. If anemia is severe or symptomatic and bleeding persists, blood transfusion should be initiated.

1. **Endometrial atrophy.** Patients on chronic megestrol acetate therapy occasionally present with vaginal hemorrhage. Patients bleeding from endometrial atrophy may be treated with conjugated equine estrogens (Premarin), 25 mg intravenously every 2–4 hours (up to four doses). Antiemetics also should be administered to alleviate nausea associated with high-dose estrogen therapy. Patients may continue to take oral Premarin or OCPs. After 2 weeks of Premarin therapy, progestin should be added. An OCP taper also may be used as the primary therapy.
2. **Endometrial hyperplasia.** Often, morbidly obese patients present with signs and symptoms of endometrial hyperplasia. An OCP taper or high-dose continuous progestin therapy should be initiated. Megestrol 20 mg can be given twice each day and should be continued for at least 1 month. An endometrial sample should be obtained after the bleeding is controlled.
3. **Unclear etiology or suspected myoma.** An OCP taper usually controls the bleeding. No data suggest a superiority of any available formulation or taper regimen. A common approach is to administer four tablets/day for 4 days, three tablets/day for 4 days, two tablets/day for 4 days, then one tablet/day for a total of 2 months (omitting placebo pills). Patients are then continued on OCP therapy with normal monthly withdrawal for at least 4 months. Intravenous Premarin is an acceptable alternative for patients who cannot tolerate oral medication. Bleeding usually is controlled within 48 hours.
4. **Pregnancy.** Acute vaginal hemorrhage associated with previable pregnancy usually is caused by incomplete abortion. Such hemorrhage in first or second trimester pregnancies is best treated with suction curettage or evacuation. Antimicrobial prophylaxis (e.g., doxycycline 100 mg before the procedure) is warranted. If any signs of infection are present, broad-spectrum coverage with intravenous cefotetan disodium and doxycycline or triple antibiotics should be initiated.
5. **Bleeding requiring surgical intervention.** Surgical intervention is indicated if blood loss cannot be replaced with transfusion or if bleeding shows no signs of abating after 48 hours. D & C should be performed, although it may provide only temporary attenuation and should be followed by hormonal therapy. The patient should provide informed consent for hypogastric artery ligation and hysterectomy, which are the next lines of therapy should D & C fail. If available, hypogastric/uterine artery embolization may be considered as an alternative to ligation.