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How best to manage dysfunctional uterine bleeding

Irregular or unusually heavy periods are a common complaint. Most often, the condition is benign and can by managed conservatively.

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PRACTICE RECOMMENDATIONS

› *Assess postmenopausal women for cancer by endometrial biopsy, transvaginal ultrasound, or saline infusion sonohysterogram.* (A)

› *Treat mild dysfunctional uterine bleeding (DUB) with nonsteroidal anti-inflammatory drugs, levonorgestrel intrauterine device (IUD), or danazol.* (A)

› *Treat moderate DUB with oral contraceptive pills* (C)*, levonorgestrel IUD, danazol, or tranexamic acid.* (A)

› *Treat severe DUB with the same agents used for moderate DUB, or with IV estrogen followed by oral contraceptive pills.* (C)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence
(B) Inconsistent or limited-quality patient-oriented evidence
(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

Test your skills: How would you treat these 3 patients?

CASE 1 Casey is a 14-year-old with a normal body mass index who has had heavy vaginal bleeding for 10 days. For the last 3 days, the bleeding has been so heavy she has been soaking more than 15 pads a day. She feels tired and is light-headed and dizzy when she stands up. Casey had her first period 13 months ago. Since then, her periods have varied in length from 18 to 40 days, with heavy bleeding for 7 to 14 days. She tells you she is not taking any prescription or herbal medications or over-the-counter supplements, and does not have any other medical problems. She is not sexually active. Her physical examination was remarkable only for pale skin and a positive tilt test. She feels frustrated and wants something done immediately.

CASE 2 Sarah is a 35-year-old obese woman whose chief complaint is irregular periods. For the past 3 years, she has had only 3 to 6 periods per year, each period lasting for 3 to 10 days. Her most recent period was 4 months ago. Sarah has a moderate amount of acne and facial hair.

CASE 3 Joan is a 53-year-old postmenopausal woman who has never been pregnant. She has a history of type 2 diabetes mellitus, hypertension, and obesity. She has come to your office for a routine physical examination. She tells you that her periods were regular until she stopped menstruating 4 years ago. But for the past 6 to 8 months she says she's had irregular bleeding every 30 to 45 days, each period of bleeding lasting for 3 to 7 days. Her previous Pap smears and mammograms were normal. She has no family history of breast, gastrointestinal, or genital tract cancer. Her physical examination, including her pelvic examination, is negative.

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To quantify blood loss, find out how many pads or tampons the patient uses and how often she changes them, the size of clots, and whether she has to get up at night to change pads.

These 3 women are fairly typical patients in a family medicine practice. Most women experience episodes of abnormal uterine bleeding (AUB) at some point in their reproductive lives. The condition occurs in approximately 1 in every 3 women of reproductive age and 1 in 10 postmenopausal women, and the impact on quality of life is often substantial.[1,2] Abnormal bleeding can be divided into 4 major categories: genital tract pathology, systemic disease, exposure to medication or radiation, and dysfunctional uterine bleeding (DUB). Specific conditions within each category are listed in **TABLE 1**. The focus of this article will be on DUB, the category that remains after the other possibilities are excluded.

First, find out what your patient means by "abnormal"

A normal menstrual cycle varies in length between 24 and 35 days, with menstrual flow lasting 2 to 7 days. Blood loss of 30 to 80 cc per cycle is considered normal.[3-5] To quantify blood loss, ask the patient how many pads or tampons she uses each period (<21 would be normal), how often she has to change pads (every 3 hours is usual), the size of clots (less than 1 cm is normal), and whether she has to get up at night to change pads.[6] If blood loss is sufficient to cause anemia, the condition is always considered abnormal and requires further evaluation. When your patient's description leaves you in doubt about whether her bleeding is abnormal, base your evaluation and treatment on her perception of a change in her menstrual cycle.

Stages of the reproductive life cycle

The meaning of abnormal bleeding varies with your patient's stage in her reproductive life cycle. Uterine bleeding in a premenarchal child or a postmenopausal woman is always abnormal and must be evaluated.[7-9]

Premenarchal children with vaginal bleeding should be evaluated for trauma, sexual or physical abuse, foreign bodies, signs of precocious puberty, and possible infectious etiologies.[7] If the cause of the bleeding is not obvious, these patients should be immediately referred to a pediatric gynecologist.

TABLE 1
Abnormal uterine bleeding: A typology[3,5,17,18,22-24,30]

Genital tract pathology
Vulva
Cancer
Lichen sclerosis
Sexually transmitted diseases (STDs)
Vagina
STDs
Trauma
Foreign body
Cancer
Cervix
STDs
Cervicitis
Cancer
Uterus
Endometritis
Hyperplasia
Cancer
Polyps
Leiomyomas
Systemic disease
Crohn's disease
Von Willebrand's disease
Thrombocytopenia
Acute leukemia
Advanced liver disease
Hyper/hypothyroidism
Chronic renal disease
Pituitary disease
Emotional or physical stress
Medication/iatrogenic cause
Tamoxifen
Corticosteroids
Chemotherapy
Anticoagulants
Warfarin
Aspirin
Clopidogrel
Antipsychotics
Hormonal therapy
Oral contraceptives
Medroxyprogesterone acetate
Intrauterine devices
Herbal supplement
Black cohosh
Soy supplements
Radiation
Dysfunctional uterine bleeding
Anovulatory (90%)
Hypothalamic suppression
Pituitary adenoma
Eating disorders
Thyroid disorders
Adrenal disorders
Primary ovarian disorders (such as polycystic ovarian syndrome)
Ovulatory (10%)
Structural anomalies

Postmenopausal bleeding is defined as any bleeding that occurs more than 1 year after the last menstrual period.[8] Cancer is the primary concern in these women and must always be excluded. (More on that, in a bit.)

History may reveal underlying pathology

The initial approach to evaluating abnormal bleeding is a thorough history and physical. Ask about stress, dietary habits, exercise, medications, radiation exposure, visual disturbances, headache, weight loss or gain, galactorrhea, palpitations, abdominal symptoms, jaundice, or excessive hair growth. Your patient's answers to these questions may point to pathologies that underlie the abnormal bleeding, as listed in **TABLE 1**.

In postmenopausal women, rule out cancer

The initial work-up for a postmenopausal patient should begin with a pelvic examination, followed by an assessment of her endometrial cavity by transvaginal ultrasound (TVUS), saline infusion sonohysterogram (SIS), or biopsy. An SIS, in particular, is often superior to TVUS in screening for anatomic anomalies.[10] If a sonogram shows an endometrial thickness greater than 5 mm or the patient has risk factors for endometrial neoplasia, an endometrial biopsy for histologic diagnosis will be needed.[11] Risk factors for endometrial cancer include age older than 40, infertility, diabetes mellitus, hypertension, obesity, and estrogen medication. Repeat the sampling if the biopsy is inadequate. If the patient continues to have uterine bleeding, further evaluation with hysteroscopy by a gynecologist should be considered.[12-14]

Evaluating bleeding in women of child-bearing age

Bleeding in this age group is most often related to pregnancy, so the diagnostic work-up should begin with a urine pregnancy test.[3,15] If pregnancy is ruled out, most etiologies in these women are benign, respond to conservative therapy, and can often be managed exclusively by family physicians.

After excluding pregnancy, look for genital tract pathology, including infection, polyps, uterine fibroids, and signs of cancer; iatrogenic causes such as medications or radiation; and systemic illnesses. In teenagers, look for inherited clotting disorders such as Von Willebrand's disorder. If cervical cancer screening is not up to date, do a Pap smear.[16] Cervical dysplasia generally does not cause heavy vaginal bleeding, but can cause postcoital bleeding.[17] A complete blood count and a thyroid-stimulating hormone (TSH) level will allow you to rule out anemia, leukemia, thrombocytopenia, and thyroid disorders.[11]

Dysfunctional uterine bleeding (DUB): A diagnosis of exclusion

Once you have ruled out genital tract pathology, systemic disease, and iatrogenic causes, you are left with a diagnosis of dysfunctional uterine bleeding. DUB occurs most commonly at the onset of regular menstrual cycles or when menstruation is coming to an end during menopause.

The menstrual cycle in a woman with DUB may be ovulatory or anovulatory. Women who have ovulatory cycles usually know the characteristics of their menses and are often aware of minor variations in the timing or flow. A patient with an anatomic problem who has ovulatory cycles will usually present with complaints of menorrhagia.

Anovulatory cycles are more typical, occurring in 90% of patients with DUB.[18] In anovulatory cycles, the corpus luteum is not produced and the ovaries do not secrete progesterone. In the absence of progesterone, constant estrogen stimulation produces a proliferative endometrium that is not sustainable. As 1 area of bleeding heals, another site begins to slough, and the result is an irregular and prolonged bleeding pattern that is unpredictable. The clinical result in this scenario is varying cycle lengths and differing amounts of menstrual blood loss.

Treatment depends on the etiology

Cervical and endometrial cancer should be ruled out early, because early diagnosis and treatment may improve survival. If the source of abnormal bleeding is an anatomic abnor-

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Uterine bleeding in a premenarchal child or postmenopausal woman is always abnormal and must be evaluated.

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TABLE 2

Medical treatment for dysfunctional uterine bleeding

Mild (bleeding is minimal and symptoms limited)
• NSAIDs, mefenamic acid 500 mg TID for 3-5 days[28,29,31]
• Medroxyprogesterone acetate 10 mg/d for 7-10 days each month[28,29,31]
• Monophasic OCPs 35 mcg each day of the month, including inactive pills[28,29,31]
• Levonorgestrel IUD[28,29,31]
• Danazol 200-400 mg/d[32-35]
Moderate (moderate amounts of bleeding, mild anemia, and mild orthostatic symptoms or fatigue)
• Medroxyprogesterone acetate 10 mg/d for 7-10 days each month[28]
• OCPs BID for 5-7 days (flow should decrease in 24-48 hours), followed by 1 pill/d for the rest of the cycle for the next 3-6 months. Warn patients that flow will be heavy after the first pill pack, will decrease by 60% toward end of treatment period. Use an antiemetic with increased OCP dose[28]
• Levonorgestrel IUD[1]
• Danazol[32-35]
• Antifibrinolytic agents (tranexamic acid, 1-1.5 g 3 to 4 times per day)[32-34,36]
Severe (heavy bleeding, moderate to severe anemia, significant orthostatic symptoms)
• OCPs as for moderate bleeding, with antiemetic for increased dose[28]
• IV estrogen, 25 mg IV q 4 to 6 hours until bleeding stops or for 24 hours, followed by OCPs. Use with antiemetic medication[2]
• Levonorgestrel IUD[1]
• Danazol[32-35]
• Antifibrinolytic agents (tranexamic acid 1-1.5 g 3 to 4 times per day)[32-34,36]

IUD, intrauterine device; NSAIDs, nonsteroidal anti-inflammatory drugs; OCPs, oral contraceptive pills.

In women of childbearing age, bleeding is most often related to pregnancy; most other etiologies are benign.

mality such as an endometrial polyp, removing the polyp under hysteroscopic guidance should alleviate the problem. If the bleeding is due to medication exposure or a systemic disease such as hypothyroidism, withdrawing the offending agent or treating the systemic disorder will generally alleviate the problem.

For patients with DUB, hormonal (medroxyprogesterone acetate, oral contraceptive pills [OCPs], levonorgestrel intrauterine device [IUD]) and nonhormonal treatment (nonsteroidal anti-inflammatory drugs, tranexamic acid, danazol) decisions are based on the age of the patient, severity of bleeding and symptoms, and the patient's hematocrit.[19] Patients with persistent bleeding despite medical treatment require a complete reevaluation and referral to a gynecologist if an explanation is not found or if surgical treatment is required.

CASE 1 ▸ Casey

Where does Casey fit in this typology? She is in the perimenarchal stage of her reproductive life cycle, when anovulatory bleeding is common. For the first 18 to 24 months after menarche, the immature hypothalamic-pituitary-ovarian axis may fail to respond to estrogen and progesterone stimulation, resulting in anovulation and irregular, often heavy bleeding. Her urine test rules out pregnancy. Blood tests confirm the anemia her pallor and fatigue suggest. Her initial, empiric treatment would be iron supplementation for anemia and cyclic medroxyprogesterone acetate or OCPs (**TABLE 2**) to regulate her periods. If these conservative measures are not sufficient, further evaluation would be indicated.

Blood dyscrasias (5%-20% incidence in teenagers) and systemic disorders, including Von Willebrand's disease, idiopathic thrombocytopenic purpura, and leukemia, are the major diseases to consider.[20-23] An endometrial biopsy is not indicated, because the incidence of endometrial cancer in Casey's age group is less than 1 in 100,000.[24]

CASE 2 ▸ Sarah

How can you explain Sarah's irregular periods? A negative urine test rules out pregnancy, and her responses to questions about diet, exercise, and stress rule out hypothalamic sup-

pression. She doesn't complain of headaches, visual field changes, or galactorrhea, which would exclude a pituitary microadenoma. She does not exhibit symptoms of a thyroid disorder and her TSH is normal. Complaints of frequent urination, thirst, or weight loss could be indications of diabetes mellitus, but Sarah does not present with these symptoms. Her facial hair and acne suggest androgen excess originating from the adrenal glands or ovaries.

Sarah's history of infrequent and heavy menses, as well as an absence of breast tenderness, bloating, or mittelschmerz, indicate she is not ovulating. The most likely explanation for her failure to ovulate is polycystic ovarian syndrome (PCOS), and you can initiate treatment immediately. The major treatment options for this disorder are observation, medroxyprogesterone acetate, and OCPs (**TABLE 2**).

If Sarah does not respond to hormonal therapy, a thorough reevaluation is indicated, including additional laboratory tests and a pelvic sonogram to evaluate the uterus and ovaries. Other tests to consider include prolactin, fasting blood sugar, early morning 17-hydroxy-progesterone, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S), testosterone, and cortisol. For an extensive review of PCOS and its relationship with endocrine, metabolic, and reproductive disorders, as well as cardiovascular disease and obstructive sleep apnea, see the excellent review by Ehrmann.[25] If hormonal therapy is unsuccessful, a hysteroscopy with endometrial ablation could then be offered. In refractory cases, a hysterectomy can be performed.

Although Sarah is only 35, her prolonged exposure to unopposed estrogen (>3 years, according to her history) warrants an endometrial biopsy. The presence of other endometrial cancer risk factors (obesity, chronic anovulation, nulliparity) supports this decision. The incidence of endometrial cancer is 2.3 cases per 100,000 patients in 30- to 34-year-old women, 6.1 cases per 100,000 patients in 35- to 39-year-old women, increasing to 36.5 cases per 100,000 in women ages 40 to 49 years.[24]

If Sarah is troubled by her infertility, consider referring her to a specialist. Treatment options for her infertility would include weight loss, insulin-lowering medications, and clomiphene citrate to induce ovulation.

CASE 3 ▸ Joan

Uterine bleeding in a postmenopausal patient like Joan is always abnormal. In 5% to 10% of cases, such bleeding indicates endometrial cancer.[26,27] An endometrial biopsy to rule out cancer is the first order of business. If the biopsy is nondiagnostic or reveals endometrial polyps or submucosal fibroids, the next step would be a diagnostic hysteroscopy. Alternatively, Joan's endometrium could first be evaluated with a TVUS. If the sonogram showed an endometrium 5 mm in thickness or more, an endometrial biopsy could be performed then.[26-29]

If these tests rule out a cancer diagnosis, your next step would be to try low-dose cyclic OCPs or medroxyprogesterone acetate (**TABLE 2**) to control the bleeding. If hormonal therapy is not effective or Joan doesn't want to try it, an endometrial ablation in conjunction with a hysteroscopy performed by a gynecologist is another option. But if Joan's bleeding is light, it may be due simply to her postmenopausal hypoestrogenic state, and can be left untreated as long as Joan is comfortable with this option.

Lessons learned

Patients like Casey, Sarah, and Joan can be successfully managed by the family physician. A thorough history, physical examination, and basic laboratory tests will usually suffice to rule out anatomic, systemic, or iatrogenic explanations. Pregnancy, the most common explanation for abnormal uterine bleeding, can be ruled out with a urine pregnancy test. Patients like Sarah and Joan, who have some of the risk factors for endometrial cancer, require an evaluation of the endometrium to rule out that possibility. When none of these etiologies is the culprit, your working diagnosis is DUB, and medical treatment for it is well within your competence. JFP

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Anovulatory cycles, in which the corpus luteum is not produced and the ovaries do not secrete progesterone, occur in 90% of women with dysfunctional uterine bleeding.

Decisions about treatment for dysfunctional uterine bleeding are based on age, severity of bleeding and symptoms, and the patient's hematocrit.

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