

PediatricsⁱⁿReview[®]

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Pediatrics in Review 2013;34;6

DOI: 10.1542/pir.34-1-6

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<http://pedsinreview.aappublications.org/content/34/1/6>

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Menstrual Disorders

Susan Hayden Gray, MD*

Author Disclosure
Dr Gray has disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Practice Gap

1. Dysmenorrhea, amenorrhea, and abnormal vaginal bleeding affect the majority of adolescent females, impacting quality of life and school attendance. Patient-centered adolescent care should include searching for, assessing, and managing menstrual concerns.
2. Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in young adult women, and pediatricians should recognize, monitor, educate, and manage their patients who fit the medical profile for PCOS based on any/all of the three sets of diagnostic criteria.

Objectives

After reading this article, readers should be able to:

1. Define primary and secondary amenorrhea and list the differential diagnosis for each.
2. Recognize the importance of a sensitive urine pregnancy test early in the evaluation of menstrual disorders, regardless of stated sexual history.
3. Know that polycystic ovary syndrome is a common cause of secondary amenorrhea in adolescents and may present with oligomenorrhea or abnormal uterine bleeding.
4. Recognize that eating disordered behaviors are a common cause of secondary amenorrhea and irregular bleeding, and treatment of the eating disordered behavior is the best recommendation to ensure resumption of regular menses and long-term bone health.
5. Know the differential diagnosis of abnormal uterine bleeding and describe the preferred treatment, recognizing the central importance of iron replacement.
6. Understand the prevalence of primary dysmenorrhea and its role in causing recurrent school absence in young women, and describe its evaluation and management.
7. Understand the need for discussion of menstrual and reproductive health with young women who have special health-care needs and their families.

The onset of menstruation in young women is a milestone with personal, cultural, and medical ramifications. Menarche heralds the onset of fertility, which can be cause for both celebration and trepidation for the patient, her family, and clinicians. It behooves both general and specialist pediatricians to be comfortable discussing what is normal and what is not normal about menstruation. Young women who have special health-care needs and their families deserve particular attention. Both the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists encourage pediatricians to think of menstruation as a “vital sign” for women. (1)(2) Irregular, absent, or overly painful periods should be evaluated, closely monitored, and managed proactively.

Patient-Centered Care of Menstrual Disorders

In both the evaluation and treatment of menstrual disorders, it is critical to keep in mind the patient’s perspective on her symptoms. It is extremely valuable to hear from the patient

Abbreviations:

AIS:	androgen insensitivity syndrome
DHEAS:	dehydroepiandrosterone-sulfate
FSH:	follicle stimulating hormone
GnRH:	gonadotropin-releasing hormone
IUD:	intrauterine device
LH:	luteinizing hormone
MRKH:	Mayer-Rokitansky-Küster-Hauser syndrome
NSAID:	nonsteroidal anti-inflammatory drug
OCP:	oral contraceptive
PCOS:	polycystic ovary syndrome
TSH:	thyroid stimulating hormone

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what her expectations of menses are, and where she has derived these expectations. In conditions ranging from polycystic ovary syndrome (PCOS) to endometriosis, the patient's quality of life has been shown to be much more strongly linked to her own perception of her symptoms than to her doctors' assessment of their severity. Periods perceived as heavy, painful, or abnormal can be a significant cause of school absence and decreased work productivity. What many patients and families desire as much as relief from menses or menstrual pain is predictability. Setting realistic expectations from the onset of medical treatment goes a long way in improving quality of life.

The presence of menses can be a challenge to the families of young women who have special health-care needs, and particular sensitivity is warranted. The onset of menstruation may raise what can be uncomfortable questions about fertility and sexual activity (voluntary or otherwise) for the families of these young women. Patients and families appreciate and deserve the opportunity to talk openly about these subjects.

Epidemiology/Normal Menses

The median age of menarche in the United States is 12.4 years, with African-American girls experiencing menarche slightly earlier on average than non-Hispanic white and Mexican-American girls, as determined in the third National Health and Nutrition Evaluation Survey. (3) The usual sequence of events leading up to menarche includes thelarche (Tanner [sexual maturation rating] stage 2 breast development) at a median age of 10.2 years and pubarche (Tanner stage 2 pubic hair) at a median age of 11.6 years, but recent studies have revealed that girls are developing breasts and pubic hair earlier than in past generations although the age of menarche has remained more constant. (4) Some girls, particularly African-American girls, may experience pubarche before thelarche. Early pubarche, especially accompanied by obesity and insulin resistance, is associated with later development of PCOS.

The definition of precocious puberty remains controversial because of mixed data about how ethnicity and adiposity affect development. Generally, the presence of breast development or pubic hair before age 8 years is considered precocious, although girls whose BMI is greater than 85% or who are African-American or Mexican-American may have earlier development. In one study, 27% of African-American girls had signs of pubertal development at age 7 years, compared with 7% of white girls. (5) Menarche occurring after age 14.1 years occurs in only 5% of girls in the United States; the definition of primary amenorrhea is failure to achieve menarche by age 15 years. Failure to progress from thelarche to menarche within 3 years is also cause for concern.

It was thought previously that hypothalamic axis immaturity in the first gynecologic year was common, and therefore menstrual irregularity was to be expected. More current data indicate that even in the first gynecologic year, amenorrhea for more than 3 months is uncommon in healthy girls in the United States and should be investigated if there are other issues apparent, or if the pattern persists into the second year. A normal menstrual cycle (counting from the first day of one menstrual period to the first day of menses of the next cycle) is 21 to 35 days in adults but has a slightly wider range of normal in adolescents during the first 2 years after menarche. A normal period lasts from 3 to 7 days. Bleeding lasting 8 or more days is considered prolonged.

Review of Menstrual Physiology

The menstrual cycle is divided commonly into three phases: follicular (proliferative), ovulation, and luteal (secretory) (Figure). The follicular phase may vary in length, but the luteal phase is 14 days during normal ovulatory cycles. Ovulation is the event that defines regular cycles and triggers the prostaglandin cascade, which is associated with primary dysmenorrhea.

Gonadotropin-releasing hormone (GnRH) secretion in the hypothalamus is pulsatile and stimulates the pituitary gland to secrete luteinizing hormone (LH) and follicle stimulating hormone (FSH), which stimulates follicle growth in the ovary. A dominant follicle in the ovary secretes increasing amounts of estrogen, which causes the endometrial lining to proliferate. A feedback loop develops in which increasing amounts of estrogen result in decreasing LH and FSH levels; but above a certain estrogen level, the negative feedback is reversed and LH release from the pituitary is stimulated. This "LH surge" triggers ovulation.

After ovulation, the remaining follicular cells in the ovary luteinize and become the corpus luteum. This corpus luteum secretes estrogen and progesterone, which has the effect of stabilizing the endometrium and causing differentiation into glandular tissue to produce the spongy lining needed for implantation of a fertilized ovum. If fertilization and implantation do not occur, human chorionic gonadotropin is not produced, and the corpus luteum involutes. The withdrawal of progesterone (and estrogen) levels derived from the corpus luteum is the trigger for the shedding of the endometrial lining, or menses. In anovulatory girls, menstrual periods occur from a proliferative endometrium because of waxing and waning of estrogen levels.

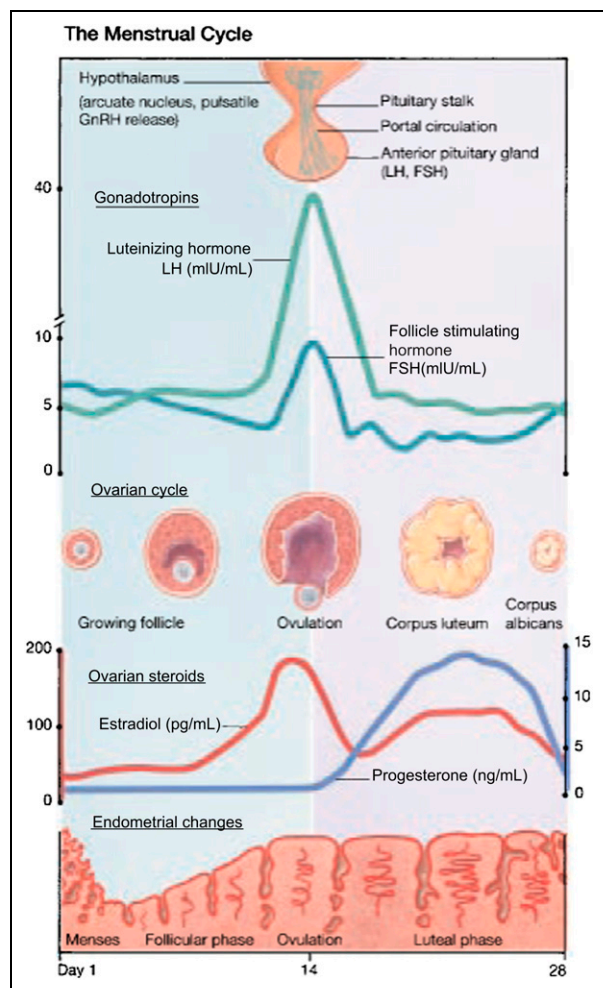


Figure. The normal menstrual cycle, with relationship among levels of gonadotropins, physiologic activity in the ovary, levels of ovarian steroids, and changes in the endometrium. Reprinted with permission from Braverman PK, Sondheimer SJ. Menstrual disorders. *Pediatr Rev.* 1997;18(1):18.

Amenorrhea

Primary amenorrhea is clinically defined as the lack of menses by the age of 15 years or by more than 3 years after the onset of secondary sexual development. Lack of any secondary sexual characteristics by age 13 years also is abnormal and should be investigated. Secondary amenorrhea is defined as 3 months of amenorrhea after the achievement of menarche. Underlying conditions may overlap in primary and secondary amenorrhea (Table 1). Careful history and physical examination are crucial to diagnosis. It cannot be overstated, however, that a sensitive pregnancy test must be part of the initial evaluation of any patient with amenorrhea, regardless of the reported sexual history. Besides pregnancy, disordered

eating patterns and weight changes are among the most common reasons for amenorrhea. Review of a growth chart is important in considering the possible causes.

The differential diagnosis of primary amenorrhea includes genital tract abnormalities, as well as endocrine causes (which also may cause secondary amenorrhea), including hypothalamic/pituitary, ovarian, thyroid, or adrenal abnormalities. The assessment of the patient should include a detailed history and physical examination, laboratory testing, and radiologic imaging in some cases.

The patient and parent should be asked about a past medical history of chronic illness, tempo of any pubertal development, weight gain or loss, exercise habits, and stressors. Family history should focus on any potential endocrine disorders in first-order relatives, including thyroid disease, diabetes, PCOS, and infertility. The parent should be asked also about any family history of constitutional delay of menses. Sexual history should be obtained confidentially, because pregnancy is a rare but possible cause of primary amenorrhea and the most common cause of secondary amenorrhea.

Social stressors may contribute to primary or secondary amenorrhea, and asking about academic pressure, family conflict, mood disorders, body image, and eating behaviors is important. Clinicians should ask about history of medication use, including any antipsychotic medication, contraceptive use (adolescents often forget or deny use unless asked specifically), and illicit drug use. The review of systems should include discussion of acne or unwanted hair growth, weight changes, mood changes, disordered eating attitudes and behavior, change in bowel habits, abdominal pain, headaches, visual changes, galactorrhea, and vaginal discharge.

The review of a growth chart identifies patients who are overweight or underweight for height. Girls who are overweight for height and not growing appropriately are more likely to have an endocrinopathy (hypothyroidism, Cushing syndrome), whereas patients underweight for height may have a deficit of calories (eating disorder or bowel disease such as inflammatory bowel disease or celiac disease).

The patient who has exceptionally short stature (final height predicted to be less than 5 ft in the patient who has normal parental heights), with or without other features such as webbed neck, widely spaced nipples, shield chest, and high arched palate, and primary amenorrhea raises concerns about Turner syndrome (45,X) or mosaicism (46,XX/45,X). Consultation with a geneticist or endocrinologist may be warranted.

Physical examination should include assessment of height, weight, and BMI in addition to routine vital signs. The clinician should examine the patient's skin thoroughly. Peripheral visual fields should be checked by confrontation and the fundi examined. The clinician should

Table 1. Differential Diagnosis of Amenorrhea

	Primary Amenorrhea	Secondary Amenorrhea
Central (hypothalamus/pituitary; hypogonadotropic hypogonadism with low FSH)	Constitutional delay ^a Chronic illness ^a Functional hypothalamic amenorrhea ^a Kallmann syndrome Laurence–Moon–Biedl and Prader–Willi syndromes Tumors (craniopharyngioma and prolactinoma) Infiltration (hemochromatosis) Infarction Iatrogenic (radiation, surgery) Congenital hypopituitarism	Functional hypothalamic ^a amenorrhea Chronic illness Tumors (prolactinoma)
Ovarian (hypergonadotropic hypogonadism with high FSH)	Turner syndrome ^a Gonadal dysgenesis Primary ovarian insufficiency Oophoritis Galactosemia Tumor Radiation, chemotherapy	Primary ovarian insufficiency Oophoritis Radiation, chemotherapy
Genital outflow tract	Imperforate hymen ^a MRKH ^a Transverse vaginal septum Vaginal agenesis Androgen insensitivity Intersex disorders	Uterine synechiae (Asherman syndrome)
Other	Pregnancy PCOS (uncommon) Thyroid disease Cushing syndrome Addison disease	Pregnancy ^a PCOS ^a Contraceptive use Hyperprolactinemia due to medication or illicit drug use Thyroid disease Late-onset congenital adrenal hyperplasia Cushing syndrome Addison disease

^aMost common diagnosis in each category; the other diagnoses are not listed in order of prevalence.

test for, or at least ask about, the presence of smell (anosmia is associated with Kallmann syndrome). The thyroid gland should be palpated for enlargement. Tanner staging should be recorded and tracked over time, and breast examination should verify whether there is any galactorrhea. Abdominal palpation should be performed to detect constipation or the presence of any masses.

An external genital evaluation should be performed to detect clitoromegaly (clitoral glans wider than 0.5 cm) and patency of the introitus. All that is necessary for an internal examination in virginal patients may be passage of a saline moistened cotton-tip swab to assess the depth of the vagina (7–8 cm is average for a postpubertal young

woman). If there is any question of an anatomic abnormality, pelvic ultrasonography should be performed at a center experienced with prepubertal patients.

Genital Outflow Tract Anomalies

The range of congenital abnormalities includes external anomalies such as imperforate hymen and transverse vaginal septum with normal müllerian structures, as well as müllerian anomalies such as uterine and vaginal agenesis. Appropriate and consistent visual examination of the vaginal introitus in the newborn and at health maintenance visits should prevent the late diagnosis of imperforate hymen. Early detection can help avoid the “classic”

presentation of imperforate hymen in a postpubertal young woman: cyclic abdominal pain, midline abdominal mass, and purplish bulging seen at the introitus of the vagina (a hematocolpos, which may be remarkably large). Such late-found cases require gynecologic intervention in an operating room or controlled setting, as opposed to a simpler procedure when the patient is diagnosed as a newborn.

Transverse vaginal septum presents similarly but may be harder to identify because the external examination may appear normal. A swab cannot be passed a normal length in the presence of a low transverse septum, but a high septum may not be detected without direct visualization or pelvic imaging.

Vaginal agenesis rarely occurs as an isolated finding and usually is associated with other müllerian anomalies. Mayer-Rokitansky-Küster-Hauser syndrome (MRKH) includes vaginal agenesis and, usually, uterine and fallopian tube agenesis as well. On external examination, the vaginal opening ends in a blind pouch. Girls with MRKH go through puberty at the usual tempo because they have normal ovaries, but they do not attain menarche. Because they have normal ovaries, they can have children by oocyte retrieval, fertilization of the egg in vitro, and a gestational carrier.

Young women born with androgen insensitivity syndrome (AIS) are genetically males (46,XY), but their androgen receptors do not respond to testosterone in the usual way. They have serum levels of testosterone comparable with adolescent males, but do not have body hair and do have breast development due to peripheral aromatization to estrogen. Because they are 46,XY, they possess müllerian inhibitory substance, which inhibits formation of the uterus and vagina. Although they have female-appearing external genitalia, they possess testes, which most patients elect to have surgically removed after puberty because of the increased risk of cancer. There are rare, partial forms of AIS in which female patients present as somewhat virilized.

Patients with vaginal agenesis are able to create a vagina with the use of manual dilators with expert coaching and education. The young woman must be able to choose whether she wants to and, if so, at which age she wishes to begin. Although there are surgical procedures such as bowel vaginas and other complex approaches, the drawbacks are excess vaginal discharge and the need for ongoing dilatation. Online resources and support groups, such as at www.youngwomenshealth.org, may provide a needed source of information and emotional support for girls with MRKH, AIS, and other rare conditions.

Other Causes of Amenorrhea

For girls with primary amenorrhea unrelated to outflow tract anomalies, the diagnostic evaluation is similar to that

for girls who experience secondary amenorrhea. Because pregnancy is a common cause for secondary amenorrhea, the first test to perform is a sensitive urine pregnancy test. The next steps are to obtain levels of FSH, LH, thyroid stimulating hormone (TSH) or free thyroxine, and prolactin. Other laboratory tests to consider include levels of androgen (total and free testosterone and dehydroepiandrosterone-sulfate [DHEAS]) to screen for hyperandrogenism, and possibly pelvic ultrasonography. Free testosterone levels should only be drawn if the laboratory is known to provide high quality results. Elevated levels of FSH indicate hypergonadotropic hypogonadism, whereas low levels indicate hypogonadotropic hypogonadism.

Hypergonadotropic hypogonadism implies ovarian insufficiency, and the most common cause is gonadal dysgenesis, most frequently due to Turner syndrome. Turner syndrome usually presents with delayed puberty and primary amenorrhea, but secondary amenorrhea is possible, especially in patients born with a mosaic chromosome pattern. Other causes of ovarian insufficiency include autoimmune and radiation- or chemotherapy-induced oophoritis, as well as galactosemia. Autoimmune oophoritis may be associated with other autoimmune conditions, such as diabetes mellitus, adrenal insufficiency, thyroid disease, celiac disease, and vitiligo.

Hypogonadotropic hypogonadism implies that either the hypothalamus or the pituitary gland is the root of the problem. The most common cause of hypogonadotropic hypogonadism is functional hypothalamic amenorrhea, but this is a clinical diagnosis, and a diagnosis of exclusion, so diagnostic evaluation, including levels of FSH, LH, TSH, and prolactin, is warranted as well as screening for eating disorders and sometimes for celiac diseases.

Although rare, tumors may impinge on the pituitary, so it is important to ask all patients about the occurrence of headaches, visual changes, and galactorrhea, and to check for galactorrhea on examination. The most common pituitary tumor is a prolactinoma. A craniopharyngioma also can present with poor growth and amenorrhea, as can pituitary infiltration by hemochromatosis.

Laurence-Moon-Biedl and Prader-Willi syndromes present with obesity, developmental delay, and amenorrhea due to hypothalamic dysfunction. Kallmann syndrome presents as amenorrhea with anosmia. Kallmann syndrome is a disorder of neuronal migration, whereby GnRH neurons do not migrate to the hypothalamus; thus, the olfactory bulbs also do not develop properly.

Functional hypothalamic amenorrhea, or secondary amenorrhea due to suppression of GnRH pulsatility in which no anatomic or organic disease is known, can be

caused by stress, weight loss, or exercise. This condition may result in a low estrogen state, which places young women at risk for failure to achieve peak bone mass. This disorder is often, but not always, associated with being underweight and with eating disorders. Secondary amenorrhea may precede significant weight loss in anorexia nervosa, and weight gain beyond the point where menses were lost frequently is required for resumption of menses. Normal-weighted bulimic patients who are purging frequently also may experience amenorrhea.

Female athletes are at risk for developing the “female athlete triad,” consisting of energy insufficiency, amenorrhea, and low bone density. Use of oral contraceptives (OCs) can induce withdrawal bleeding but has not been shown to be effective at increasing bone density in athletes or in those with anorexia nervosa.

The role of leptin is being investigated actively, because leptin administration recently has been demonstrated to promote resumption of menses. Trials of androgens and estrogens together and transdermal estrogen alone have demonstrated promising effects in small studies. Increased energy availability, meaning weight gain in most cases, has been shown to have long-term and significant positive effects on bone density.

Because of the serious long-term sequelae for bone health, young women with prolonged functional hypothalamic amenorrhea who do not or will not increase their energy availability should be referred for multidisciplinary assessment to a nutritionist, a mental health professional, and a health-care provider who are well versed in eating disorders and bone health. (6)

PCOS is the most common endocrinopathy in young adult women; some researchers estimate that the condition affects up to 10% of American women of reproductive age. Young women with PCOS present with amenorrhea or oligomenorrhea and signs of hyperandrogenism, including hirsutism and acne. They are often, but not always, overweight.

There are three sets of criteria for diagnosis of PCOS: the 1990 National Institutes of Health consensus criteria, the 2003 Rotterdam criteria, and the 2006 Androgen Excess Society criteria. (7)(8)(9) The National Institutes of Health criteria include patients with anovulatory menses and clinical or biochemical evidence of hyperandrogenism, with or without polycystic ovaries on ultrasonography, in whom other diagnoses (eg, late-onset congenital adrenal hyperplasia and thyroid disease) have been excluded. The Androgen Excess and PCOS Society guidelines also include those patients who experience normal menses but have biochemical or clinical hyperandrogenism and also polycystic ovaries on ultrasonography. Most

pediatric clinicians use one of these two definitions, with clinical or biochemical hyperandrogenism being *sine qua non*.

Evaluation for PCOS includes measuring LH, FSH, TSH, and prolactin levels to exclude other disorders, as well as obtaining serum levels of testosterone (a normal total testosterone excludes a testosterone-producing tumor), free testosterone (elevated in most patients with PCOS), and DHEAS.

In patients with virilization (eg, clitoromegaly, deep voice, notable hirsutism), a first morning 17-hydroxyprogesterone to rule out late-onset congenital adrenal hyperplasia and evaluation for a tumor is warranted. Pelvic ultrasonography may be a useful adjunct to laboratory testing, although ideally the procedure should be performed in a center with pediatric expertise. In the case of significantly elevated concentrations of DHEAS or total testosterone, other androgen levels, such as androstenedione and dehydroepiandrosterone, may be drawn, and consultation with an endocrinologist is suggested. In rare situations of high testosterone levels combined with genital anomalies, chromosome studies should be considered to rule out intersex conditions.

PCOS is associated with abnormal LH pulsatility and secretion beginning in the premenarchal period, ultimately resulting in increased androgen production from the ovaries and adrenal glands, as well as anovulation. Because anovulation leads to irregular buildup of the endometrial lining, the initial presentation of PCOS may be as heavy (previously known as dysfunctional) uterine bleeding.

PCOS is associated with insulin resistance in more than one half of patients and is an independent risk factor for later development of type II diabetes and the metabolic syndrome. Current recommendations are that patients who have PCOS and an elevated BMI should undergo lipid testing and an oral glucose tolerance test every 1 to 2 years.

Because of prolonged periods of unopposed estrogen stimulation and endometrial proliferation resulting from anovulation, older women with PCOS also are at increased risk of endometrial cancer. This risk can be reduced through early detection and treatment to ensure more regular endometrial shedding. Lifestyle modification including exercise and weight loss can improve menstrual regularity in some women.

Pharmacologic treatment for PCOS includes three options: cyclic use of progestins to induce withdrawal bleeding; use of estrogen-containing contraceptives (pills, transdermal patch, or vaginal ring) to reduce ovarian androgen production and increase steroid hormone binding globulin; and use of metformin to lower circulating

insulin levels and reduce ovarian steroid hormone production.

It is important to note the potential reproductive ramifications of these therapies. Estrogen-containing contraceptives are the best option for sexually active young women who do not desire a pregnancy and those with hirsutism and acne; metformin use is particularly helpful for those with glucose intolerance. Metformin promotes ovulation, so this drug should not be the sole therapy in sexually active teenagers. Some young women choose to use both therapies. Spironolactone often is used as an adjunct treatment to reduce androgen effects on the hair follicle in girls with hirsutism; spironolactone's use as monotherapy is not recommended because it is teratogenic and causes menstrual irregularity unless used in conjunction with an estrogen-containing contraceptive.

Abnormal Vaginal Bleeding

Abnormal vaginal bleeding is reported commonly during adolescence. Pediatric practitioners must know what is normal in order to assess patients accurately. A normal period usually lasts 3 to 7 days. Bleeding that lasts 8 days or longer is considered abnormal. The normal interval between menses in adolescents may be between 21 and 45 days in young adolescents, although 21 to 35 days is more common.

Menorrhagia means a large quantity of bleeding, metrorrhagia means irregular bleeding, and menometrorrhagia means heavy and irregular bleeding. When patients say that they have "heavy" bleeding, however, it is important to ask them whether they mean bleeding that is in large quantity, frequent, or associated with pain, because these symptoms have different implications. Studies reveal that both adolescent patients and their clinicians can significantly underestimate as well as overestimate the amount of vaginal bleeding, so it is important to obtain objective evidence of blood loss regardless of the history (eg, complete blood count).

The differential diagnosis of abnormal vaginal bleeding is broad (Table 2). The term "dysfunctional uterine bleeding" has been replaced by "abnormal uterine bleeding." Abnormal uterine bleeding refers to irregular and sometimes heavy bleeding due to a delay in maturation of the negative feedback loop whereby rising estrogen levels suppress FSH secretion. This maturational delay results in a constantly proliferative endometrium with irregular shedding. Abnormal uterine bleeding is the most common cause of abnormal bleeding in adolescents, but it is a diagnosis of exclusion, and the differential diagnosis also should include pregnancy (including complications

such as ectopic pregnancy and miscarriage), bleeding disorders, pelvic infection, and endocrinopathies such as PCOS and thyroid disease.

In evaluating the patient with abnormal vaginal bleeding, it is important to consider the possibility of pregnancy first, because pregnancy complications presenting with bleeding, such as ectopic pregnancy, can be life threatening. All patients should be asked privately whether they have ever had sex, coerced or voluntary, but pregnancy testing should be obtained universally because patients may fear the consequences of disclosure. Patients who have ever had sex should be asked specifically about contraceptive use and about history of any sexually transmitted infections, and should be tested for gonorrhea and *Chlamydia trachomatis* infection by using simple urine nucleic acid amplification tests. Regardless of stated history, pediatricians should have a low threshold for performing these tests for unexplained bleeding because the prevalence of *Chlamydia* is so high in adolescent women.

The patient's menstrual history can then help narrow down other possibilities. Patients should be asked about the date of menarche and the pattern of bleeding since that time. For patients who have had heavy flow from the time of initial menses, a bleeding disorder such as von Willebrand disease is more likely. Regular cycles accompanied by premenstrual symptoms and dysmenorrhea usually imply ovulatory bleeding. Regular, cyclic, but heavy flow is suggestive of a hematologic cause. Irregular cycles suggest anovulatory cycles, which may be due to an underlying endocrinopathy such as PCOS or hypothyroidism, a condition that causes functional hypothalamic amenorrhea. Intermenstrual bleeding suggests anatomic disease (cervicitis due to sexually transmitted infections must be ruled out) or breakthrough bleeding associated with use of hormonal contraception.

The review of symptoms should include questions about weight changes, exercise habits, bleeding tendencies, acne, hirsutism, headaches, visual changes, chronic illness, bowel habits, and urinary symptoms (younger patients may confuse hematuria with vaginal bleeding). Family history of bleeding tendencies (especially during childbirth and surgical procedures), endocrinopathies, and infertility should be elicited. Patients should be asked specifically (and confidentially) about contraceptive use, including intrauterine devices (IUDs). Clinicians also should ask about antipsychotic and antiepileptic medications that may cause irregular bleeding, and aspirin and other anti-coagulants, which may worsen bleeding.

Physical examination should include orthostatic vital signs for those with heavy bleeding. Young women

Table 2. Differential Diagnosis of Abnormal Vaginal Bleeding in the Adolescent Girl

Abnormal uterine bleeding	Cervical problems
Pregnancy-related complications	Cervicitis (including cystic fibrosis)
Threatened abortion	Polyp
Spontaneous, incomplete, or missed abortion	Hemangioma
Ectopic pregnancy	Carcinoma or sarcoma
Gestational trophoblastic disease	Uterine problems
Complications of termination procedures	Submucous myoma
Infection	Congenital anomalies
Pelvic inflammatory disease	Polyp
Endometritis	Carcinoma
Cervicitis	Use of intrauterine device
Vaginitis	Breakthrough bleeding associated with hormonal contraceptives
Bleeding disorders	Ovulation bleeding
Thrombocytopenia (eg, idiopathic thrombocytopenic purpura, leukemia, aplastic anemia, hypersplenism, chemotherapy)	Ovarian problems
Coagulation disorders (eg, von Willebrand disease, other disorders of platelet function, liver dysfunction, vitamin K deficiency)	Cyst
Endocrine disorders	Tumor (benign, malignant)
Hypo- or hyperthyroidism	Endometriosis
Adrenal disease	Trauma
Hyperprolactinemia	Foreign body (eg, retained tampon)
PCOS	Systemic diseases
Primary ovarian insufficiency	Diabetes mellitus
Vaginal abnormalities	Renal disease
Carcinoma or sarcoma	Systemic lupus erythematosus
Laceration	Medications
	Hormonal contraceptives
	Anticoagulants
	Platelet inhibitors
	Androgens
	Spironolactone
	Antipsychotics

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may be remarkably tolerant of severe anemia and show no signs other than resting tachycardia or orthostatic hypotension. Providers should examine the skin for acne, hirsutism, and acanthosis nigricans suggestive of PCOS as well as petechiae or bruising to suggest bleeding disorders. The thyroid gland should be palpated. Palpation of the abdomen should begin in the epigastric area and progress downward, assessing for a uterine fundus that would suggest undetected pregnancy. Pelvic and bimanual examination is indicated for sexually active patients to screen for cervicitis and pelvic inflammatory disease. In virginal patients who have longstanding ongoing

bleeding or bleeding resulting in anemia, assessment can be managed by external genital examination with passage of a cotton-tip swab to assess vaginal patency, as well as transabdominal pelvic ultrasonography.

Laboratory testing should consist initially of a urine pregnancy test and a complete blood count, including platelet and reticulocyte count, and TSH level. In both the initial evaluation and in follow-up treatment, for girls who have normal hemoglobin level and hematocrit, the content of hemoglobin in the reticulocyte is a sensitive indicator of iron deficiency and can give clinicians more information about the tempo of bleeding or recovery of

iron stores. Other laboratory testing may be indicated depending on the severity and nature of the symptoms.

For those patients with hemorrhage from menarche or serious bleeding at any time, coagulation studies including prothrombin time/international normalized ratio, partial thromboplastin time, and Von Willebrand panel are indicated. For those patients with previous amenorrhea or irregular bleeding, screening for endocrinopathies should be conducted by measuring FSH, LH, TSH, and possibly prolactin, as well as androgen levels for girls with signs of hyperandrogenism on examination. For girls presenting with focal pain or a pelvic mass, abdominal ultrasonography also is warranted.

Treatment of abnormal vaginal bleeding is based largely on the severity of anemia, in addition to management of any comorbid conditions. The preferred treatment of vaginal bleeding in adolescence is medical; surgical intervention rarely is indicated. All treatment of vaginal bleeding resulting in anemia must include iron replacement, although this therapy can be overlooked easily during the acute presentation and management.

The general goal of treatment is to stabilize the endometrium by providing estrogen for initial hemostasis and progestins for endometrial stability. The most convenient and effective option in most cases is treatment by using combined OCPs (Table 3). Sudden withdrawal of either estrogen or progestin may trigger ongoing bleeding, so treatment for several months usually is warranted. Long-term follow-up for conditions predisposing to abnormal bleeding, such as PCOS, is necessary as well.

For adolescents who have contraindications to the use of estrogen, such as a history of blood clot, uncontrolled hypertension, migraine with aura, immobility, or chronic illness, management of abnormal bleeding with cyclic progestins often is possible, although sometimes more challenging. Progestin-eluting IUDs may be an option in some cases.

Menstrual suppression by using GnRH analogs is desirable in some conditions, but because of the initial agonist phase, withdrawal bleeding often occurs at 3 weeks before amenorrhea is established. For this reason, prophylactic use is better than use in an acute emergency. Antifibrinolytics such as tranexamic acid interfere with the breakdown of blood clots and thus stop or slow down bleeding; these agents may be an option in some adolescents with bleeding disorders; consultation with a hematologist is suggested.

Dysmenorrhea

Dysmenorrhea is common in young women worldwide and occurs in the majority of adolescents. Primary, or

functional, dysmenorrhea is pain that occurs in the absence of pelvic disease, whereas secondary dysmenorrhea is secondary to a pathologic process. Primary dysmenorrhea is more common than secondary dysmenorrhea, but clinicians should be familiar with “red flags” on history and examination that should lead them to pursue a diagnosis other than functional pain.

Primary dysmenorrhea usually presents in the second or third gynecologic year, when ovulation becomes more regular. Pain may be reported in the lower abdomen, back, or upper thighs. The pain may be associated with headache, nausea, or diarrhea. The symptoms are caused by prostaglandin E₂ and F_{2a} secretion in the uterus after an ovulatory cycle, resulting in increased uterine contractility and upregulation of pain receptors.

Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and naproxen, inhibit cyclooxygenase, an enzyme necessary for prostaglandin synthesis. NSAIDs are used commonly to treat dysmenorrhea and have been shown to be effective in randomized controlled trials. It is important to know that acetaminophen does not act on this pathway and is much less effective for the treatment of primary dysmenorrhea. Traditional recommendations for rest, exercise, and proper nutrition have not been shown to be effective.

Primary dysmenorrhea may result in significant school absence and lost productivity, so aggressive and evidence-based treatment is warranted. If appropriate doses of NSAIDs (Table 4) do not control symptoms after two to three cycles, a trial of OCPs may be indicated. OCPs reduce menstrual pain by eliminating ovulation and by thinning the endometrial lining; when ovulation does not occur and the endometrial lining is thinner, the synthesis of prostaglandins is reduced. In severe cases, extended cycle OCP regimens (eg, 84 active pills, followed by 7 placebos) may be used to eliminate menses. Young women with dysmenorrhea often try over-the-counter medications, including ibuprofen and naproxen, and complementary therapies such as vitamins and herbal remedies. Pediatric clinicians should therefore ask specifically about previous treatments before prescribing additional medications.

Before assuming a patient has primary dysmenorrhea, the clinician should consider possible causes of secondary dysmenorrhea. Patients who continue to experience significant pain despite 3 to 6 months of OCP use have a significantly higher risk of endometriosis (presence of endometrial tissue outside the uterus) and should be referred to a pediatric gynecologist for evaluation. Laparoscopy is the only definitive way to diagnose endometriosis, but often it is difficult to recognize this condition in pediatric patients.

Table 3. Suggested Combined OCP Regimens for Abnormal Bleeding

Use a monophasic OCP such as:

- Norgestrel 0.3 mg/ethinyl estradiol 30 μ g (Lo/Ovral, Low-Ogestrel, Cryselle).^a
- Levonorgestrel 0.15 mg/ethinyl estradiol 30 μ g (Nordette, Levlen, Levora, Portia).^a

For all patients:

- Advise the patient to keep a menstrual calendar.
 - Ensure iron stores are addressed. Patients typically need several months of oral iron supplementation to replete iron stores, and then should be instructed in maintenance of iron needs.
 - If OCPs are used for treatment and then discontinued, consider cyclic progestin therapy to prevent recurrences.
- A. For mild bleeding—menses slightly prolonged or cycle slightly more frequent, without anemia (Hgb normal):
- May be observed for several cycles and provided treatment with iron and NSAIDs such as ibuprofen or naproxen sodium.
 - Consider treatment with OCP or progestin.
 - If choose to treat with OCP: 1 pill daily for 21 d, followed by 1 wk of placebo pills or 1 hormone pill continuously for 84-day cycles or longer.
 - Continue this regimen for 3–6 mo.^b
- B. For moderate bleeding—menses lasting >7 d or cycle frequency <3 wk and mild anemia (Hgb 10–11 g/dL):
- If the patient is not bleeding significantly at the time of the visit, is not already on hormonal therapy, and anemia is mild: 1 pill a day for 21 d is a reasonable first step.
 - If patient is bleeding moderately at time of visit: 1 pill twice a day until bleeding stops, followed by 1 hormonal pill a day for at least 21 d is a reasonable first step.
 - If bleeding is under control, continue cyclic 21 day or may elect extended cycles for 3–6 mo.^b
 - Follow serial Hgbs, as needed; if bleeding persists, may need to continue twice-daily pill for a short interval.
- C. For severe bleeding with moderate anemia (Hgb 8–10 g/dL)
- Consider inpatient admission unless patient's bleeding is slowing and family is reliable, has transportation, and is reachable by phone.
 - For severe bleeding: 1 pill four times a day for 2–4 d, with antiemetic as needed 2 h before each pill; followed by 1 pill three times a day for 3 d; and then 1 pill twice a day for at least 2 wk. (For this regimen, prescribing OCPs "four times a day" should be written as "1 pill every 6 hours" and "3 times a day" as "1 pill every 8 hours" in order to maintain hormonal concentrations.)
 - For bleeding that is slowing and Hgb >9 g/dL: 1 pill twice a day can be initiated as a first step.
 - Follow closely with serial Hgb; if anemia or bleeding persists, may need to continue twice-daily hormonal pill and eliminate pill-free interval until Hgb has returned to normal.
 - Once Hgb has normalized, cycle using 21 once-daily pills and 5–7 d of placebo or extended cycles for 6 mo.^b
- D. Severe bleeding with severe anemia (Hgb \leq 7 g/dL, orthostatic vital signs):
- Admit for inpatient management. Transfusion needs are individualized on the basis of Hgb, orthostatic symptoms, amount of ongoing bleeding, and the ability to gain control of the bleeding.
 - Most patients can be treated with OCPs: 1 pill every 4–6 h until bleeding slows (usually takes 24–36 h), with antiemetics as needed; 1 pill four times a day for 2–4 d; 1 pill three times a day for 3 d; 1 pill twice a day until hematocrit is >30%.
 - Occasionally intravenous conjugated estrogens (Premarin) 25 mg every 4 h for 2–3 doses are used in severe acute hemorrhage. It is very important to remember that the estrogen will stop the bleeding but if a progestin is not added, a re-bleed from estrogen withdrawal will occur when the IV estrogen is discontinued.
 - Consider antifibrinolytic therapy.
 - Once Hgb has normalized, cycle using 21 once-daily pills and 5–7 d of placebo or use extended cycles for 6–12 mo.^b

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^aMention of brand name does not imply endorsement of a particular product.

^bIt is important to reconsider a patient's need for birth control before discontinuing OCP therapy.

Other red flags include pelvic pain or bleeding that occurs midcycle and pain associated with vaginal discharge, all of which may be associated with pelvic infections. Clinicians should have a low threshold for sending nucleic acid amplification testing for gonorrhea and *C trachomatis* and doing a speculum and bimanual examination to screen for pelvic inflammatory disease. Pelvic examination also may

reveal evidence of an IUD; non-hormone-containing IUDs may increase menstrual pain significantly. Again, urine pregnancy testing is always worthwhile because adolescents may mistake bleeding in early pregnancy for a period.

In adolescents who have dysmenorrhea from menarche that progresses steadily, genital tract abnormalities with obstruction should be considered, as well as endometriosis.

Table 4. Medications Used to Treat Dysmenorrhea

Propionic Acid Group:	
• Ibuprofen	400–600 mg Q 4–6 H
• Naproxen sodium	550 mg load, then 275 mg Q 6 H
• Naproxen	500 mg load, then 250 mg Q 6–8 H
Fenamate Group:	
• Mefenamic acid	500 mg loading dose, then 250 mg Q 6 H

Reprinted with permission from Braverman PK, Sondheimer SJ. Menstrual disorders. *Pediatr Rev.* 1997;18(1):25.

Other causes of pelvic pain not associated with menstrual problems are beyond the scope of this review.

Young Women With Special Health-Care Needs

Young women with special health-care needs and their families may need particular care with respect to normal menstruation as well as menstrual disorders. When possible, the patient's concerns should be expressed privately and remain confidential. It is important that pediatric practitioners not assume that young women with disabilities, cognitive or otherwise, are not sexually active. Patients' ability to consent to sexual activity should be assessed and discussed openly with parents when appropriate. Many parents have fears about their daughters' vulnerability to coerced sex and deserve the opportunity to discuss these concerns.

Normal menses may cause problems of hygiene for girls with limited cognitive skills or limited mobility. Painful menses cause unnecessary suffering, and some conditions (eg, seizures, headaches) may be triggered or worsened by menstrual changes. Treatments to decrease, eliminate, or make bleeding more predictable should be "safe, minimally invasive, and nonpermanent" according to the 2009 American Congress of Obstetricians and Gynecologists Committee Opinion on menstrual manipulation for adolescents with disabilities. (10) Total amenorrhea may be difficult to obtain, and some patients and families may decide that it is easier to manage bleeding that is predictable but potentially longer, rather than bleeding that is sporadic and irregular.

NSAIDs may play a useful role in reducing pain and bleeding, as may combined OCPs, used traditionally or in extended or continuous regimens. For young women with limited mobility, the potential increased risk of deep vein thrombosis with estrogen use should

be weighed, although the absolute risk is low. Transdermal contraceptive patches may have a higher associated risk of blood clot. Medroxyprogesterone injection also may be of limited use in these patients due to the potential additive risk of low bone density with immobility, as well as weight gain that may further limit mobility.

Progestin implants offer long lasting and reversible contraception and sometimes can result in amenorrhea but carry a risk of unpredictable bleeding, as do progestin eluting IUDs, and both may require placement under anesthesia. Hysterectomy and endometrial ablation are more likely to result in amenorrhea but would be recommended only in very unusual circumstances.

Summary

- The presence of normal menses in young women should be considered a vital sign; heavy, painful, absent, or irregular menses should be investigated. (Based on some research evidence as well as consensus.) (1)(2)
- Patients who are pregnant usually present with secondary amenorrhea but may present with irregular or heavy menstrual bleeding. A sensitive urine pregnancy test should be performed early in the evaluation of these complaints, regardless of stated sexual history. (Based on expert opinion.)
- Menstrual complaints such as heavy bleeding and dysmenorrhea are a frequent cause of school absence in girls and should be evaluated and treated. (Based on some research evidence as well as consensus.) (1)(2)
- Polycystic ovary syndrome (PCOS) is a frequent cause of secondary amenorrhea or oligomenorrhea but also can present with anovulatory and frequent menses. (Based on expert opinion.)
- Functional hypothalamic amenorrhea is associated commonly with stress, weight change, chronic illness, and intense athletic activity. Patients with eating disorders have an energy deficit, as do many of those experiencing intense athletic activity, and are at risk for hypothalamic amenorrhea.
- The morbidity associated with prolonged amenorrhea is low bone density due to inadequate estrogen production. Use of oral contraceptives (OCPs) alone appears not to restore bone density in girls with anorexia nervosa. The best recommendation is increased energy intake and weight gain when underweight. (Based on some research evidence as well as consensus.) (6)
- Young women with special health-care needs need assessment and counseling about sexuality and reproductive health. Clinicians should be aware of how cognitive or mobility issues affect menstrual hygiene and should present options for medical management of menses to improve quality of life. (Based on expert opinion.) (10)

ACKNOWLEDGEMENTS. The author wishes to thank Ms Alison Clapp for her assistance with review of the literature, as well as Drs S. Jean Emans and Gregory F. Hayden for their helpful suggestions regarding this article.

References

1. Diaz A, Laufer MR, Breech LL; American Academy of Pediatrics Committee on Adolescence; American College of Obstetricians and Gynecologists Committee on Adolescent Health Care. Menstruation in girls and adolescents: using the menstrual cycle as a vital sign. *Pediatrics*. 2006;118(5):2245–2250
2. ACOG Committee on Adolescent Health Care. ACOG Committee Opinion No. 349, November 2006: Menstruation in girls and adolescents: using the menstrual cycle as a vital sign. *Obstet Gynecol*. 2006;108(5):1323–1328
3. Chumlea WC, Schubert CM, Roche AF, et al. Age at menarche and racial comparisons in US girls. *Pediatrics*. 2003;111(1):110–113
4. Sun SS, Schubert CM, Chumlea WC, et al. National estimates of the timing of sexual maturation and racial differences among US children. *Pediatrics*. 2002;110(5):911–919
5. Herman-Giddens ME, Slora EJ, Wasserman RC, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. *Pediatrics*. 1997;99(4):505–512
6. Gordon CM. Clinical practice. Functional hypothalamic amenorrhea. *N Engl J Med*. 2010;363(4):365–371
7. Zadański J, Dunaif A. *Diagnostic Criteria for Polycystic Ovary Syndrome: Towards a Rational Approach*. Oxford, England: Blackwell Scientific Publications; 1992
8. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod*. 2004;19(1):41–47
9. Azziz R, Carmina E, Dewailly D, et al; Androgen Excess Society. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. *J Clin Endocrinol Metab*. 2006;91(11):4237–4245
10. American College of Obstetricians and Gynecologists Committee on Adolescent Health Care. ACOG Committee Opinion No. 448: Menstrual manipulation for adolescents with disabilities. *Obstet Gynecol*. 2009;114(6):1428–1431

Suggested Reading

Braverman PK, Sondheimer SJ. Menstrual disorders. *Pediatr Rev*. 1997;18(1):17–25, quiz 26

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1. A mother brings in her daughter because of a concern that she has never menstruated. The patient is thin, athletic, and has a normal physical examination (including genital inspection). At what minimum age does this concern warrant further investigation?
 - A. 13 years.
 - B. 14 years.
 - C. 15 years.
 - D. 16 years.
 - E. 17 years.
2. A 14-year-old girl comes in with a history of monthly cyclical abdominal pain. On examination, you note midline tenderness in the area below the umbilicus, and a purplish bulging at the vaginal introitus. Of the following, the most likely diagnosis is:
 - A. Androgen insensitivity syndrome.
 - B. Chlamydial infection.
 - C. Crohn disease.
 - D. Hematocolpos.
 - E. Ovarian torsion.

3. A 15-year-old girl comes in for evaluation of infrequent menstrual periods. On examination, you note a BMI of 35 and acne. Otherwise, her examination is unremarkable. Of the following, what is the most likely laboratory abnormality associated with this patient's presentation?
 - A. Elevated follicular stimulating hormone (FSH).
 - B. Elevated free testosterone.
 - C. Elevated gonadotropic releasing hormone (GnRH).
 - D. Elevated prolactin.
 - E. Elevated thyroid stimulating hormone.

4. A 16-year-old girl is seen with a complaint of excessive bleeding with menses (menorrhagia). Of the following, which component of the history and examination most suggests von Willebrand disease?
 - A. Anovulatory cycles.
 - B. Heavy flow from time of initial menses.
 - C. Breakthrough bleeding in between periods.
 - D. Previous oral contraceptive use.
 - E. Tenderness on bimanual examination.

5. Of the following, which is the most appropriate first-line therapy for primary dysmenorrhea?
 - A. Acetaminophen.
 - B. Ibuprofen.
 - C. Metronidazole.
 - D. Oral contraceptive trial.
 - E. Relaxation techniques.

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Susan Hayden Gray
Pediatrics in Review 2013;34;6
DOI: 10.1542/pir.34-1-6

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