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Menstrual Disorders

Paula K. Braverman, MD* and Steven J. Sondheimer, MD†

> **IMPORTANT POINTS**
> 1. The median age of menarche in the United States is 12.77 years.
> 2. Ninety percent of females achieve menarche by the time they reach Tanner stage 4 breast and pubic hair development.
> 3. A lack of pubertal development by age 13 years warrants investigation.
> 4. Turner syndrome is characterized by short stature, webbed neck, widely spaced nipples, shield chest, high arched palate, congenital heart disease, renal anomalies, and autoimmune disorders.
> 5. Polycystic ovary syndrome is the most common cause of persistent irregular menses.
> 6. Primary dysmenorrhea is caused by prostaglandins; secondary dysmenorrhea is associated with pelvic pathology.

Introduction

One of the major milestones during pubertal development in females is menarche. Although most adolescent women pass through this transition with relative ease, menstrual disorders such as amenorrhea, dysfunctional uterine bleeding, and dysmenorrhea are common complaints that present to the primary care physician.

Menarche and The Menstrual Cycle in Adolescents

The median age of menarche in this country, according to the National Health Examination Survey, is 12.77 years, with African-American females reaching menarche a few months before Caucasian females. Although almost 90% of females have achieved menarche by the time they reach Tanner stage 4 breast and pubic hair development, there is a mean of slightly more than 2 years (range, 0.5 to 5.75 years) between the onset of breast development and menarche. The normal menstrual cycle lasts between 21 and 35 days (mode, 28), with fewer than 0.5% of women having cycles shorter than 21 days and fewer than 1% having cycles lasting more than 35 days. Most women bleed for 3 to 7 days and experience approximately 30 to 40 mL of blood loss. Cycles lasting 8 to 10 days and/or having more than 80 mL of blood loss are considered abnormal. Estimating the number of soaked pads or tampons used during a 24-hour period sometimes is helpful in determining the amount of menstrual flow. Although it is somewhat difficult to obtain an accurate pad or tampon count, using five to six soaked pads per day is clearly of less concern than completely soaking one pad per hour.

Defining terminology with the patient is crucial in obtaining an accurate menstrual history. Many patients do not understand the concept of a regular 28-day cycle. When questioned about how often their menstrual cycle occurs, many begin counting the number of days from the *end* of their last menses rather than from the first day of bleeding. Another commonly held belief is that menses should begin on the same date each month. Variability in the menstrual start date, depending on the length of the month, or the possibility of having menses twice during the same calendar month are difficult concepts.

Regular ovulatory menstrual cycles do not develop for 1 to 1.5 years after menarche: 55% to 82% of cycles are anovulatory during the first 2 years after menarche, and approximately 10% to 20% of cycles can remain anovulatory up to 5 years after menarche. Women who have anovulatory cycles are at increased risk for having heavier and longer cycles. It is very common for adolescents to experience irregular menstrual bleeding patterns, which can include several consecutive months of amenorrhea, especially during the first year after menarche.

Normal Menstrual Cycle

Ovulation leads to normal repetitive menstrual bleeding. The menstrual cycle is divided into three phases: the follicular (proliferative) phase, ovulation, and the luteal (secretory) phase (Figure). During the follicular phase, pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates the pituitary gland to secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which in turn stimulate ovarian follicular growth. The growing follicle predominantly secretes estrogen, which induces proliferation (cell division) within the endometrium. Approximately 7 days before ovulation, a dominant follicle is present. As estrogen levels peak, the pituitary gland releases increased amounts of LH and ovulation occurs approximately 12 hours after the midcycle surge in LH.

The luteal phase, which follows ovulation, is characterized by the presence of the corpus luteum, which is formed by luteinization of the follicular cells. It is within the corpus luteum that cholesterol is converted to progesterone and estrogen, the key hormones produced during this part of the cycle. The presence of progesterone counteracts the estrogenic effects on the endometrium, inhibiting proliferation and producing the glandular changes that make the lining receptive to implantation by the fertilized ovum. Without fertilization and the subsequent production of human chorionic gonadotropin (HCG), the corpus luteum cannot survive. Regression of the corpus luteum results in a decrease in both progesterone and estradiol, triggering synchronous sloughing of the endometrial lining (menstruation) approximately 14 days after ovulation.

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Amenorrhea

Amenorrhea can be categorized as either primary or secondary. Primary amenorrhea is the absence of menarche by age 16. However, breast development, which is the initial sign of puberty in most females, should begin by the age of 13. The lack of pubertal development by age 13 is considered delayed and warrants investigation. The mean time between the onset of breast development and menarche is slightly more than 2 years. A lack of menses within 2 to 2.5 years of initiating puberty, especially if the individual has reached Tanner stages 4 or 5, should raise concern.

Secondary amenorrhea is the absence of three consecutive menstrual cycles or 6 months of amenorrhea. The definition of secondary amenorrhea can be applied only to those who already have established regular cyclic menstrual periods. It should not be used in cases of amenorrhea presenting in the immediate postmenarchal period when regular ovulatory cycles have not begun.

The same clinical entity can be associated with either primary or secondary amenorrhea, depending on the relationship between the onset of the particular disease and the timing of pubertal development. Rather than simply discussing primary or secondary amenorrhea, a more useful approach would be to divide amenorrhea into the following categories: amenorrhea with pubertal delay, amenorrhea with normal pubertal development, genital tract abnormalities, and hyperandrogenic anovulation (polycystic ovary syndrome).

AMENORRHEA WITH PUBERTAL DELAY

Amenorrhea associated with pubertal delay can be divided into hypergonadotropic hypogonadism and hypogonadotropic hypogonadism to differentiate between abnormalities at the level of the ovary and those involving the hypothalamic-pituitary axis.

### Hypergonadotropic Hypogonadism

The term hypergonadotropic hypogonadism indicates a hypoestrogenic state due to ovarian failure in which levels of gonadotropins are elevated because of the lack of negative feedback of estradiol on the hypothalamic-pituitary axis. An elevated FSH level is sufficient to make this diagnosis.

Turner syndrome and XY gonadal dysgenesis are two syndromes associated with ovarian failure and a lack of pubertal development. Of the two, Turner syndrome is by far the most common. Individuals who have Turner syndrome have streak gonads associated with the absence of one of the X chromosomes. Usually the chromosomal pattern will be pure XO, although 40% to 50% of individuals have either a structurally abnormal X chromosome or a mosaic chromosomal pattern (46XX/45XO). Because women who have Turner syndrome do not have appropriate levels of estradiol, they do not initiate puberty or proceed through the proper sequence of events, including uterine growth and development. The classic features associated with this syndrome are short stature, webbed neck, widely spaced nipples, shield chest, high arched palate, congenital heart disease, renal anomalies, and autoimmune disorders such as thyroiditis and Addison disease. However, especially in cases of mosaicism, this diagnosis may not be suspected until adolescence, when there is pubertal delay and amenorrhea.

Of the other conditions listed in Table 1, ovarian failure resulting from oophoritis due to autoimmune phenomena and ovarian damage
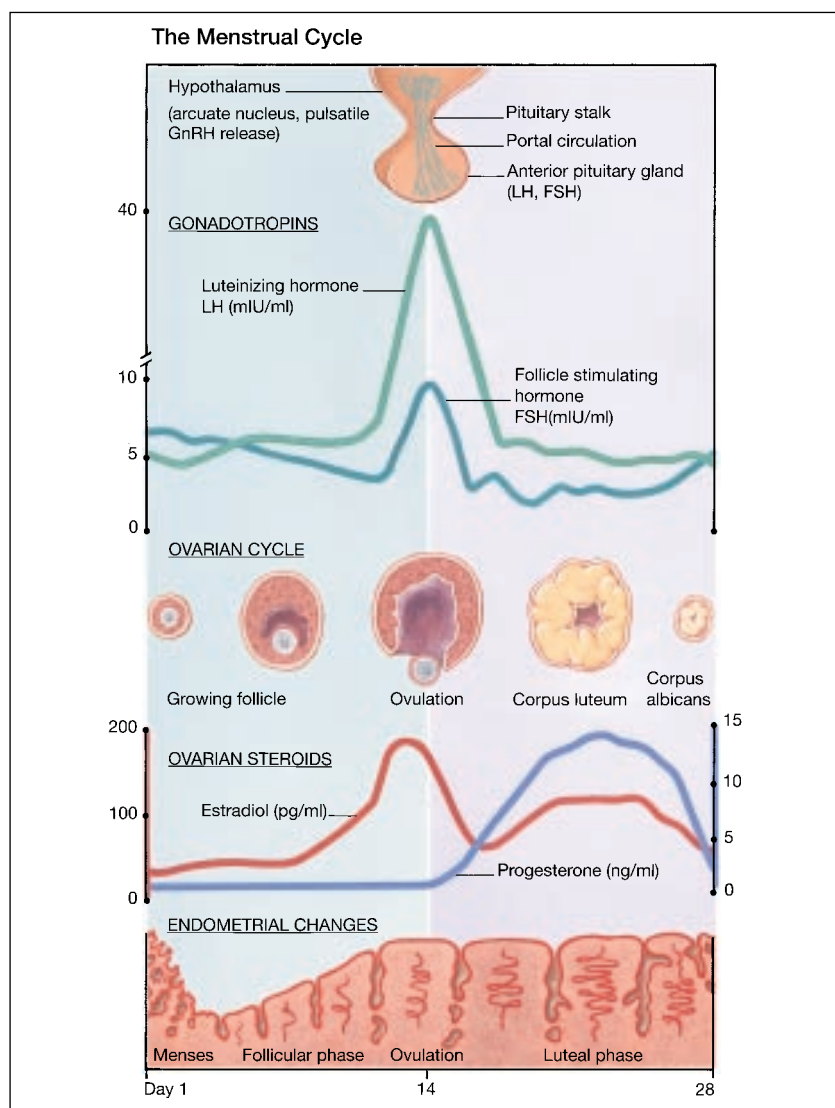
FIGURE. The normal menstrual cycle, with relationships among levels of gonadotropins, physiologic activity in the ovary, levels of ovarian steroids, and changes in the endometrium.

TABLE 1. Differential Diagnosis of Amenorrhea

- Pregnancy

- Hormonal contraception

- Hypothalamic-related
  — Chronic or systemic illness
  — Stress
  — Athletics
  — Eating disorder
  — Obesity
  — Drugs
  — Tumor

- Pituitary-related
  — Hypopituitarism
  — Tumor
  — Infiltration
  — Infarction

- Ovarian-related
  — Dysgenesis
  — Agenesis
  — Ovarian failure
  — Resistant ovary

- Outflow tract-related
  — Imperforate hymen
  — Transverse vaginal septum
  — Agenesis of the vagina, cervix, uterus
  — Uterine synechiae

- Androgen excess
  — Chronic anovulatory hyperandrogenism (PCO)
  — Adrenal tumor
  — Adrenal hyperplasia (classic and nonclassic)
  — Ovarian tumor

- Other endocrine causes
  — Thyroid disease
  — Cushing syndrome

Adapted from Emans JS, Goldstein DP. **Pediatric and Adolescent Gynecology.** *3rd ed. Boston, Mass: Little, Brown and Company; 1990.*

ible, with remissions and the resumption of regular ovulatory cycles. Ovarian damage from radiation and chemotherapy is most likely to occur when high doses and alkylating agents are being used. Children and adolescents appear to preserve ovarian function better than adult women, and prepubertal girls seem to be the least affected by chemotherapeutic agents.

Hypogonadotropic Hypogonadism
Hypogonadotropic hypogonadism represents dysfunction at the level of the hypothalamus or the pituitary gland with low or normal levels of LH and FSH. Decreased estradiol levels may be present because of inadequate stimulation of the gonads. Although this discussion will focus on abnormalities of the pituitary and hypothalamus, other endocrinopathies such as thyroid disease and Cushing syndrome may present with pubertal delay and low gonadotropin levels.

Amenorrhea due to problems at the level of the pituitary gland may be secondary to congenital hypopituitarism, tumor (pituitary adenoma), or infiltration (hemochromatosis). The most common pituitary tumor is the prolactin-secreting tumor pituitary adenoma (prolactinoma). Prolactinomas classically present with galactorrhea, headache, and visual fields cuts. Amenorrhea results from prolactin-induced inhibition of GnRH secretion. Although patients who have pituitary adenomas have elevated prolactin levels, galactorrhea is not a universal sign, and its absence does not preclude the presence of the tumor. Tumors smaller than 1 cm, microadenomas, will not impinge on the optic nerve and may present only with galactorrhea and amenorrhea.

Craniopharyngioma is another tumor commonly found in the region of the sella turcica that affects hypothalamic-pituitary function, presenting with pubertal delay and amenorrhea.

Prolactinomas are not the only cause of galactorrhea and amenorrhea. Hypothyroidism increases prolactin release through excessive production of thyrotropin-releasing hormone; breast stimulation or suck-

ling, stress associated with trauma or surgery, and certain drugs, particularly phenothiazines and substances of abuse such as opiates, suppress the activity of hypothalamic prolactin-inhibiting factor.

Abnormalities at the level of the hypothalamus include hypothalamic suppression and deficiency in the pulsatile release of GnRH. Laurence-Moon-Biedl, Prader-Willi, and Kallmann syndromes are associated with hypothalamic dysfunction and pubertal delay. Laurence-Moon-Biedl and Prader-Willi classically present with obesity; individuals who have Kallmann syndrome have anosmia. The defect in Kallmann syndrome has been traced to a problem in the migration of olfactory and GnRH neurons. The ovaries in these individuals are normal and will respond appropriately to exogenous gonadotropins.

The most common causes of hypothalamic suppression are stress, competitive athletics, and inadequate nutrition associated with chronic or systemic illness and eating disorders. Patients who have eating disorders, especially those who have anorexia nervosa, most commonly experience hypothalamic suppression and amenorrhea when weight loss reaches levels less than 15% of ideal body weight. However, some patients actually experience amenorrhea very early in the course of this illness; in some cases, amenorrhea may be the presenting symptom of anorexia nervosa. Strenuous exercise, which is characteristic of many patients who have anorexia, probably contributes to the hypothalamic suppression. Because anorexic women commonly have low estradiol levels, they are at increased risk of osteoporosis and stress fractures. Although gonadotropin secretion resumes with weight gain, menses may be the last physiologic event to normalize. Bulimia nervosa can be associated with amenorrhea, but menstrual disturbance is much less common because these individuals maintain a relatively normal body habitus and weight.

Competitive athletes, especially those participating in ballet and long-distance running, are particularly prone to hypothalamic suppression and amenorrhea. Amenorrhea is

resulting from exposure to radiation or chemotherapy are most common. Autoimmune oophoritis may be associated with other autoimmune diseases. It also is interesting to note that this condition may be revers-

related to the intensity of exercise as well as to body weight and percent body fat. Neurotransmitters such as endorphins appear to play a role in the hypothalamic suppression, and a level of 22% body fat is considered necessary to maintain regular menses. Reducing the intensity of exercise can result in a resumption of menses even without weight gain or change in body fat. If strenuous athletics begin prior to menarche, each year of training actually delays the onset of menarche by 5 months.

with the use of OCS, depot medroxy-progesterone acetate (DMPA, Depo-Provera®), and less frequently with implantable levonorgestrel (Norplant®). Amenorrheic adolescents should be asked about the use of hormonal contraception because many are unlikely to volunteer this information without prompting. The amenorrhea associated with hormonal contraceptives is due to the progestational effect of these hormones, is not dangerous, and does not require intervention. However, a pregnancy test always is a wise precaution.

Pregnancy always must be considered in the differential diagnosis of a pubertally mature woman who has amenorrhea.

AMENORRHEA WITH NORMAL PUBERTAL DEVELOPMENT

Pregnancy always must be considered in the differential diagnosis of a pubertally mature women who has amenorrhea. Denial of sexual activity does not eliminate the need to rule out pregnancy. If the individual is sexually active prior to the onset of menses and the first cycle is ovulatory, it is possible to become pregnant rather than experiencing the onset of menarche. Unfortunately, the history may not always be reliable because adolescents may have concerns about confidentiality and feel uncomfortable revealing that they are sexually active, even when asked privately.

Because some disease processes discussed previously may begin at any point during pubertal development, they often cause amenorrhea, even in women whose pubertal development is normal. Clinical entities applicable to both categories include acquired ovarian failure (oophoritis, damage from radiation and chemotherapy), acquired abnormalities of the pituitary gland (prolactinoma and infiltration), thyroid disease, and hypothalamic suppression (stress, athletics, eating disorders, chronic or systemic illness). In addition, conditions such as polycystic ovarian disease, which often are associated with irregular bleeding, can present with amenorrhea.

Amenorrhea has been associated

Uterine synechiae (Asherman syndrome) should be considered in the postpartum or postabortional woman who has amenorrhea, especially if she required curettage. Sheehan syndrome, pituitary infarction, occurs in the setting of intrapartum bleeding and hypotension.

GENITAL TRACT ABNORMALITIES

Genital tract abnormalities include obstruction of an otherwise normal outflow tract or the presence of a müllerian abnormality such as absence of the vagina or uterus. Imperforate hymen is recognized as a membrane covering the area where one normally would expect to find a vaginal opening. The membrane may be bulging or have a bluish hue from blood retained within the obstructed outflow tract. A history of cyclic abdominal pain may be elicited, and a midline abdominal mass might be palpated if the patient has been having menses for a period of time. If the mass is large enough, an individual might present with urinary tract obstruction. A transverse vaginal septum would have a similar presentation but may be more easily missed because a speculum examination may be necessary for identification.

One of the most common müllerian tract abnormalities is agenesis of the vagina, Mayer-Rokitansky-

Küster-Hauser syndrome. Agenesis of the vagina appears as a blind-ended pouch that does not proceed further than a few centimeters from the external vaginal opening. These individuals have normal pubertal development with respect to breast and pubic hair but never achieve menarche because of müllerian agenesis resulting in the absence of the vagina and usually the uterus. The key to making this diagnosis is recognition that the individual began puberty in a timely manner but failed to complete an otherwise normal progression of events.

Another common cause of vaginal agenesis is androgen insensitivity (testicular feminization). In the complete form, the individual would be recognized as having pubertal development that was incomplete and out of sequence. Breast development is accompanied by a growth spurt, but with little if any pubic or axillary hair. These women have an XY chromosomal pattern with intra-abdominal or inguinal testes that produce testosterone, but they are unable to respond because of an X-linked inherited defect at the level of the androgen receptor. In utero, the lack of response to androgens prevents the development of male external genitalia, producing an XY individual who is born with female-appearing external genitalia. The presence of müllerian inhibitory factor suppresses development of a uterus and vagina. During puberty, breast development occurs via aromatization of androgens to estrogens. Pubic and axillary hair do not develop because of the tissue insensitivity to androgens.

The testes in these patients are at increased risk for developing gonadal tumors and must be removed. Based on the low incidence of tumors prior to puberty, some published recommendations suggest preserving endogenous hormones and waiting until there is adequate height and breast development before removing the gonads. However, others *strongly* recommend removal at the time of diagnosis because tumors have been reported in prepubertal children. Hormone replacement therapy should be initiated at the time of

gonadectomy in a pubertal adolescent or at the appropriate age to initiate puberty in a younger child.

HYPERANDROGENIC ANOVULATION (POLYCYSTIC OVARY SYNDROME)

The most common cause of persistent irregular menses is the so-called polycystic ovary syndrome (PCO). The name is misleading to the patient and not particularly helpful to the treating physician. Although clear-cut polycystic ovaries are found in many patients, the appearance of normal ovaries on ultrasonography does not rule out this diagnosis, especially in younger women. Chronic hyperandrogenic anovulation is probably a more accurate name, reflecting the most common symptoms—anovulation that leads to either irregular periods or intervals of amenorrhea. The hyperandrogenism, whose extent varies among affected women, may present as hirsutism, acne, or rarely clitoromegaly. Obesity occurs in about 50% of these individuals and often is associated with metabolic problems, including insulin resistance, glucose intolerance, and lipid abnormalities, all of which increase the risk of early onset atherosclerotic cardiovascular disease. It is important to note that obesity independent of PCO also may cause anovulation and amenorrhea, which are reversible with weight loss.

History is the most important diagnostic tool. Irregular menses beginning with menarche and persisting through adolescence is the primary symptom. Increased facial hair, midline hair over the sternum and lower abdomen, or in a male, abdominal escutcheon pattern, indicates a hyperandrogenic effect. If the patient has severe hirsutism or evidence of virilization (frontal balding, deepening of the voice, or clitoromegaly), an ovarian and adrenal tumor or adrenal enzyme deficiency may be present. Mood changes, fatigue, weakness, weight gain accompanied by moon facies, and truncal obesity may indicate Cushing syndrome.

Some of the obese women have acanthosis nigricans, a thickening and increased pigmentation of the skin in the nape of the neck, as well

as insulin resistance representing an insulin receptor defect that is independent of androgen excess. Controlling the androgen excess will not improve insulin resistance, but weight loss will decrease insulin levels, occasionally restoring ovulation and improving androgen excess to some extent.

The etiology of chronic hyperandrogenic anovulation is not understood completely. In fact, given the variability of clinical presentations, these patients may have multiple causes or variation in penetration. PCO most likely is an autosomal recessive disorder that affects steroidogenesis in the ovary. Although not necessary to make the diagnosis, an elevated LH-to-FSH ratio may be found, which is reflective of the abnormal feedback between the ovary and hypothalamic pituitary axis.

If the anatomy is normal with or without complete pubertal development, LH, FSH, and estradiol will help distinguish between ovarian failure and a problem at the hypothalamic level. High FSH and LH levels and a low estradiol level indicate ovarian failure from gonadal dysgenesis (Turner syndrome, XY gonadal dysgenesis), autoimmune oophoritis (anti-ovarian antibodies), or other causes. Normal or low LH, FSH, and estradiol levels indicate hypothalamic suppression, a central nervous system tumor, or an endocrine problem such as hypothyroidism.

If the individual is mature pubertally, it is essential to rule out pregnancy and to determine that amenorrhea cannot be explained by the normal developmental immaturity of the hypothalamic pituitary axis seen after menarche. Many clinicians rou-

> *Evidence of elevated androgen levels on physical examination, such as hirsutism or acne, suggest androgen excess and polycystic ovary syndrome (PCO).*

The adolescent who has chronic anovulation and elevated androgen levels presents with special needs. The initial goal is to explain the problem, recognizing that this is a chronic condition that she will not outgrow, but that the symptoms can be managed successfully. Ovulation occasionally can occur spontaneously so that amenorrhea secondary to pregnancy always must be considered.

EVALUATION

A complete history and physical examination should be performed to determine if there is evidence of a chronic or systemic illness, eating disorder, or drug use, including hormonal contraception, and to perform Tanner staging. A pelvic examination and possibly pelvic ultrasonography are essential in determining the presence of normal anatomy. An imperforate hymen or transverse vaginal septum can be corrected surgically. If the uterus, vagina, or both is absent, a chromosomal analysis can determine if the karyotype is XX or XY and help differentiate between müllerian agenesis and androgen insensitivity.

tinely check T4, TSH, and prolactin levels regardless of symptomatology to rule out these treatable causes of amenorrhea. If the prolactin level is elevated, then magnetic resonance imaging with sella views would be used to evaluate for the presence of a prolactinoma.

Evidence of elevated androgen levels on physical examination, such as hirsutism or acne, suggest androgen excess and PCO. Total testosterone and dehydroepiandrosterone sulfate (DHEAS) levels help rule out ovarian and adrenal tumors. Levels of testosterone greater than 200 ng/dL and DHEAS greater than 700 μg/dL require further investigation to rule out a tumor. Measurement of a morning 17-hydroxyprogesterone level screens for nonclassic adrenal hyperplasia (adult onset). A 17-hydroxyprogesterone level above 2 ng/mL should be followed by an adrenocorticotropic hormone (ACTH) stimulation test to diagnose 21-hydroxylase deficiency. An elevated LH-to-FSH ratio is common with PCO but not required for the diagnosis. Similarly, although not a necessary diagnostic criterion, an

ultrasonographic examination would be helpful in determining the presence of polycystic ovarian changes. Individuals who have acanthosis nigricans should be screened for insulin resistance; those who have android obesity (ie, increased waist-to-hip ratio) should be screened for diabetes and elevated fasting lipid levels. These baseline tests help guide response to nutritional and exercise programs.

TREATMENT

Anovulation and, therefore, the lack of progesterone secretion increases the risk of endometrial hyperplasia and eventually endometrial cancer. These risks can be eliminated with regular exposure to a progestational agent such as oral medroxyprogesterone, norethindrone, or oral contraceptives (OCs). Oral progestins can be given cyclically for 12 days every month or even every third month. OCs provide the additional advantage of contraception and frequently are begun after a progestin-induced withdrawal bleed.

For patients who have PCO, OCs serve the dual role of regulating menses and decreasing blood levels of free active androgens and ovarian androgen production through increased levels of sex hormone-binding globulin. The decrease in androgen levels has a beneficial effect on both hirsutism and acne.

Unfortunately, control of hirsutism in patients who have PCO is difficult and may require electrolysis or the use of antiandrogens such as the potassium-sparing diuretic spironolactone as adjunctive therapy. It may take up to 6 months for OCs to decrease effectively the frequency of shaving or the need for plucking hair. Spironolactone can decrease the rate of hair growth markedly as well as change the character of body and facial hair at a dosage of 50 mg three times a day. Because its effects on the developing fetus are unknown and to maximize its benefit, spironolactone should be used in conjunction with an OC.

Patients who are hypoestrogenic and anovulatory due to hypothalamic suppression (eg, anorexia, stress, or strenuous athletics) should be given calcium and hormonal replacement therapy (OCs) to reduce the long-term risks of osteoporosis. Patients who have Turner syndrome or ovarian failure require hormonal replacement therapy beginning with gradually increasing doses of estrogen and a progestational agent until pubertal development is satisfactory, at which time they can be switched to an OC for hormone replacement.

Dysfunctional Uterine Bleeding

The term dysfunctional uterine bleeding (DUB) has been used to describe conditions in which there is an excessive amount of bleeding or a prolonged number of days of bleeding with or without shortened cycles. Menorrhagia (normal intervals with excessive flow), metrorrhagia (irregular intervals with excessive flow), and menometrorrhagia are the terms used traditionally to distinguish between different types of excessive bleeding. Some gynecologists prefer to use of the term abnormal vaginal bleeding rather than DUB as a more accurate representation of the problem; this terminology will be used throughout the remainder of this article.

The most common cause of abnormal vaginal bleeding in adolescence is anovulation. Abnormal bleeding patterns frequently are seen in young adolescents within the first 1 to 2 years after menarche when, because of the immaturity of the hypothalamic-pituitary axis, anovulatory cycles are common. As discussed previously, there are many causes of anovulation, including suppression of the hypothalamic-pituitary axis and PCO. Regardless of the etiology, anovulation can present as either amenorrhea or irregular vaginal bleeding.

When anovulatory cycles occur, the endometrium experiences estrogen stimulation that is unopposed by progesterone. Growth of the vascular and glandular elements is not accompanied by the stromal support usually provided by progesterone. Eventually the endometrial lining begins breaking down, and although endogenous estrogen may produce homeostasis in one particular area, estrogen stimulation of the lining is still unopposed. The endometrial lining continues to build up, even as multiple areas of asynchronous breakdown occur in the lining, preventing adequate hemostasis. Bleeding becomes prolonged, irregular, and sometimes profuse.

Although many adolescents experience anovulatory cycles at the onset of menarche, relatively few develop significant problems with abnormal vaginal bleeding. This is because most adolescents exhibit negative feedback of estradiol on the hypothalamic-pituitary axis. This feedback causes a decrease in estradiol levels and subsequent withdrawal bleeding that is sufficient to prevent irregular bleeding even though ovulation and a mature menstrual cycle do not occur. It is postulated that adolescents who develop abnormal vaginal bleeding may not have developed the negative feedback mechanism and, therefore, do not benefit from the periodic sloughing that occurs when estrogen levels fall.

The differential diagnosis of abnormal vaginal bleeding is listed in Table 2. Pregnancy and pregnancy-related complications always should be considered. Traumatic causes of bleeding can include forceful sex or rape. Sexually transmitted diseases (STDs) and pelvic inflammatory disease (PID) also should be considered because sexually active adolescents have the highest rate of STDs of any sexually active age group. In addition, an adolescent is much more likely to develop PID than is a women in her twenties. Although cervical carcinoma is rare in adolescents, there have been increasing rates of cervical dysplasia due to the epidemic of human papillomavirus infection. Vaginal tumors, uterine carcinoma, and uterine myomas also would be rare in adolescents. Common foreign bodies causing bleeding include retained tampons or a contraceptive sponge. In these situations, the adolescent may forget that the foreign body is in the vagina or simply have difficulty with removal. The sponge now is off the market and should become an infrequent problem. Use of intrauterine devices (IUDs) by adolescents is uncommon, but they may cause heavier menstrual periods.

Abnormal vaginal bleeding occasionally is the initial presentation of a blood dyscrasia or coagulation defect, and von Willebrand disease

TABLE 2. Differential Diagnosis of Abnormal Vaginal Bleeding (Dysfunctional Uterine Bleeding)

- Pregnancy-related
  — Ectopic pregnancy
  — Abortion
- Hormonal contraception
- Hypothalamic-related
  — Chronic or systemic illness
  — Stress
  — Athletics
  — Eating disorder
  — Obesity
  — Drugs
- Pituitary-related
  — Prolactinoma
- Outflow tract-related
  — Trauma
  — Foreign body
  — Vaginal tumor
  — Cervical carcinoma
  — Polyp
  — Uterine myoma
  — Uterine carcinoma
  — Intrauterine device
- Androgen excess
  — Chronic anovulatory hyperandrogenism (PCO)
  — Adrenal tumor
  — Ovarian tumor
  — Adrenal hyperplasia (classic and nonclassic)
- Other endocrine causes
  — Thyroid disease
  — Adrenal disease
- Hematologic-related
  — Thrombocytopenia
  — Abnormalities of clotting factors
  — Abnormalities of platelet function
  — Anticoagulant medications
- Infectious causes
  — Pelvic inflammatory disease
  — Cervicitis

Adapted from Emans JS, Goldstein DP. **Pediatric and Adolescent Gynecology.** *3rd ed. Boston, Mass; Little, Brown and Company; 1990.*

is one of the common coagulopathies. Von Willebrand may be unrecognized previously because there is no history of a substantial insult that would have caused uncontrolled bleeding prior to menarche. However, it always should be considered when there is abnormal vaginal bleeding at menarche or a history of consistently long and/or heavy periods.

Hormonal contraceptive use, including OCs, depot medroxyprogesterone acetate, or implantable levonorgestrel, frequently is overlooked when obtaining a history from a patient who has abnormal vaginal bleeding. Breakthrough bleeding is more common with progestin-only formulations compared with combined OCs, and this bleeding usually resolves within the first 3 months of initiating OC use. However, with adolescents, it is important to determine that the patient is not forgetting to take the pills and, therefore, experiencing bleeding due to hormonal withdrawal. Users of depot medroxyprogesterone acetate commonly experience amenorrhea by the end of the first year, but prior to that time a significant proportion will have irregular, unpredictable bleeding patterns. Of all of the hormonal methods, implantable levonorgestrel is associated most commonly with frequent and irregular bleeding. The lack of estrogen stimulation of the endometrial lining with the progestin-only contraceptives can result in a very thin endometrium that is prone to breakdown. The bleeding associated with these hormonal contraceptive methods, however, almost never is associated with a drop in hematocrit and usually is not described as profuse hemorrhagic flow. Intermenstrual bleeding in a previously well-regulated OC user may be a marker for chlamydial infection.

EVALUATION

The evaluation of irregular vaginal bleeding should include a thorough history and physical examination, including the age of menarche, menstrual pattern, amount of bleeding, symptoms of hypovolemia, history of sexual activity, genital trauma, and any symptoms to suggest an endocrine abnormality or systemic illness. Postural vital signs should be obtained as objective evidence of hypovolemia, and a pelvic examination should be performed to rule out abnormal anatomy, trauma, infection, foreign body, and possibly a pregnancy-related complication. Pelvic ultrasonography can be used to clarify pelvic anatomy further.

Laboratory evaluation always should include a pregnancy test and complete blood count. If there is a history of a very heavy period with menarche or repeated prolonged or heavy menses, bleeding disorders should be investigated. Evaluation of prothrombin time/partial thromboplastin time will provide a screen for bleeding abnormalities; a bleeding time and von Willebrand screening panel can be used to identify more specific coagulation disorders. Signs of androgen excess would indicate a need to investigate PCO. A chronic history of irregular vaginal bleeding also warrants investigation of other causes of anovulation, including prolactinoma and endocrine abnormalities such as thyroid disease.

TREATMENT

If the history and examination are consistent with prolonged bleeding or shortened cycles but there is a normal hematocrit, normal physical and pelvic examinations, and no hemodynamic compromise, a conservative approach can be followed. A menstrual calendar frequently is helpful in assessing the menstrual pattern, especially if the bleeding is close to the time of menarche and/or the history is unclear.

If mild anemia is accompanied by stable vital signs, estrogen, and progesterone or progesterone alone can be used to stop the bleeding in the outpatient setting. Combined OCs are a convenient way to administer these hormones, beginning with a daily multiple pill regimen followed by a tapering dosage. The estrogen in combined OCs provides hemostasis; the progesterone stabilizes the endometrial lining. Many clinicians would continue cycling the patient on low-dose OCs for 3 to 4 months before allowing the individual to resume normal cycles. The

initial regimen should use a 35 to 50 mcg monophasic pill to ensure a steady tapering dose. The type of OC used during the subsequent 3 to 4 months of cycling is not as crucial and can be either a triphasic or monophasic formulation because only one pill is administered daily. There are many ways to use OCs in the treatment of abnormal vaginal bleeding. One suggested regimen is shown in Table 3. Iron therapy should be included in all therapeutic regimens to correct the anemia.

If the hematocrit is very low (ie, 7 or 8 mg/dL) or vital signs are unstable, hospitalization usually is recommended. When rapid cessation of bleeding is required, intravenous conjugated estrogens (Premarin®) in a dose of 25 mg IV every 4 to 6 hours for 24 hours usually is sufficient to stop the bleeding quickly. Conjugated estrogen therapy is followed immediately by OCs to provide the progesterone necessary to stabilize the endometrium. As in the case of outpatient hormonal treatment, iron therapy is required to help the patient replace iron stores and correct the anemia. Blood transfusion is unnecessary unless the patient is symptomatic. Many have recovered quickly from a hemoglobin as low as 5 to 6 mg/dL simply by stopping the bleeding with hormonal therapy and providing oral iron. Dilatation and curettage is used as a last resort and seldom is necessary in adolescents.

Sometimes cyclic progestins are used alone to treat abnormal vaginal bleeding, especially if the use of estrogen is contraindicated or the patient experiences extreme nausea and vomiting and cannot tolerate the estrogen component of the OC. Long-acting injectable progestins such as depot medroxyprogesterone acetate are best avoided in treating acute or chronic abnormal vaginal bleeding.

Antiprostaglandin medications (prostaglandin synthetase inhibitors) appear to diminish menstrual blood loss significantly. These drugs favor substances that promote platelet aggregation and vasoconstriction rather than those that have antiaggregating and vasodilator effects. Antiprostaglandins can be used alone in mild cases of abnormal vaginal bleeding and as adjunct therapy in more severe cases.

Dysmenorrhea

One of the most common complaints presenting to a primary care physician is dysmenorrhea. More than 50% of adolescents experience dysmenorrhea, and school attendance is affected in more than 10% of cases. In considering possible etiologies, dysmenorrhea has been divided into the categories of primary and secondary.

PRIMARY DYSMENORRHEA

Primary dysmenorrhea is crampy lower abdominal and pelvic pain during menses that can radiate to the back and thighs but is not associated with pelvic pathology. This is the most common form of dysmenorrhea and is caused by prostaglandins, which are produced during ovulatory cycles. The decrease in progesterone levels at the end of the luteal phase permits lysosomal membranes to become unstable, releasing lysosomal enzymes that in turn release

phospholipid A_2, converting phospholipids to arachidonic acid and then to PGE_2 and $PGF_{2\alpha}$ via cyclic endoperoxidase and prostaglandin synthetase. Endometrial prostaglandin levels increase during the luteal and menstrual phases of the cycle, causing uterine contractions along with headache, nausea, vomiting, and diarrhea, when released into the systemic circulation. The association of prostaglandin production with ovulation explains why primary dysmenorrhea usually first begins 6 months to 1 year after menarche once menstrual cycles become ovulatory. The symptoms tend to be most severe during the first few days of the menstrual cycle when prostaglandin levels are highest. Women who have more severe dysmenorrhea seem to produce more prostaglandins and have excessive uterine contractions in response to these hormones.

SECONDARY DYSMENORRHEA

Secondary dysmenorrhea is painful menses associated with pelvic pathology. Examples of pelvic pathology would be genital tract obstruction such as a bicornuate uterus with partial obstruction, endometriosis, PID, uterine fibroids and polyps, cervical stenosis, ovarian neoplasms, and the presence of an IUD. Typically, secondary dysmenorrhea occurs at a later age than primary dysmenorrhea and can be associated with anovulatory cycles or symptoms that persist after menses have finished. If an adolescent has severe dysmenorrhea, especially from the onset of menarche, obstructing lesions of the genital tract should be considered. Endometriosis is not just found in older adolescents or adult women. Laparoscopic studies of adolescents who have chronic pelvic pain have found endometriosis to be the most common diagnosis—present in almost 50% of subjects. In the Boston Children's study, 12% of those who had endometriosis were between 11 and 13 years of age and 28% were between 14 and 15 years. A history of progressively worsening dysmenorrhea is consistent with the diagnosis.

TABLE 3. Outpatient Regimen for Treatment of Abnormal Vaginal Bleeding With Oral Contraceptives

- One pill QID × 4 days
- One pill TID × 3 days
- One pill BID × 7 days
- One pill QD × 7–14 days**
- Stop all pills for 7 days and then begin cycling on low dose OCP

Initial 3 to 4 weeks of therapy should be with a monophasic 35 to 50 mcg OC. Monophasic or triphasic OC can be used for cycling once bleeding is controlled.
**Length of therapy depends on level of anemia and amount of time required to reach an adequate hemoglobin level for resumption of menstruation.*

EVALUATION

All patients who have dysmenorrhea should undergo a complete medical history, including a gynecologic history that addresses the relationship of the pain to the menstrual cycle, sexual activity, and the extent to which the cramps interfere with daily activities. If the pain is mild, easily relieved by prostaglandin synthetase inhibitors, and the patient has a normal physical examination including the hymen, a speculum examination is not necessary. Pain that is more severe, especially if it interferes with daily living, warrants a pelvic examination. The examination will help detect a genital tract obstruction, adnexal and/or uterosacral pain suggestive of endometriosis, evidence of STD or PID, and an adnexal or uterine mass. Ultrasonography and MRI are useful techniques for evaluating potential genital tract abnormalities or obstruction.

TREATMENT

The first line of treatment for dysmenorrhea usually includes drugs that inhibit prostaglandin synthesis (Table 4). Drugs in the phenylpropionic acid group such as ibuprofen and naproxen act by inhibiting synthesis of prostaglandins. Those in the fenamate group such as mefenamic acid also prevent the action of prostaglandins by binding to prostaglandin receptor sites. Gastric irritation is a common side effect of these medications, so patients should be advised to take them on a full stomach. Therapy should begin with the onset of bleeding and need only

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

be continued for as long as pain lasts. A trial of medication usually is given for a few months before does not appear to be adequate. Approximately 90% of women experience subjective relief. OCs are effective because they prevent ovulation and, therefore, the cascade of events leading to the synthesis of switching to another antiprosta-glandin preparation. These medications are effective in 75% to 90% of cases.

OCs are very useful and can be added if antiprostaglandin medicine prostaglandins. They also reduce the size of the endometrial lining, limiting the amount of prostaglandin production. It actually is the progestin part of the OC that is effective in treating dysmenorrhea; thus, depot medroxyprogesterone acetate and implantable levonorgestrel also are useful. It is important to remember that there are many noncontraceptive advantages to the use of hormonal contraception, including protection from endometrial and ovarian cancer, a decreased risk of symptomatic PID, reduction in iron deficiency anemia, and possibly the prevention and slowing of the progression of

endometriosis. Sometimes both adolescent patients and their parents are resistant to prescription of OCs. Reminding them of their noncontraceptive benefits sometimes is helpful. In addition, explaining that the OCs are being used as a medication may make the decision more palatable. Finally, pharmacists have been willing to repackage the pills in a regular medication bottle to eliminate the need to use a standard pill pack.

Individuals who have severe dysmenorrhea and do not respond to antiprostaglandin therapy or the OC/antiprostaglandin combination may require ultrasonography, MRI, or a laparoscopy to investigate possible causes of secondary dysmenorrhea, including endometriosis.

SUGGESTED READING

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PIR QUIZ

9. Joy is a 15-year-old girl who complains about recurrent heavy vaginal bleeding since menarche. She feels healthy otherwise and says she is not sexually active. In arriving at a diagnosis, it would be *essential* to test for:
   A. Blood dyscrasia.
   B. Fibroid tumors.
   C. Malignancy.
   D. Pelvic inflammatory disease.
   E. Systemic lupus erythematosus.

10. Diane is a 16-year-old girl who complains of persistent irregular menses since menarche at age 14. She does not complain of discomfort with her periods and does not believe she has unusually heavy bleeding. She feels healthy and is on the gymnastic team, although she has complained about persistent acne and increasing amounts of facial hair. She says she is not sexually active. The *most* likely cause of her irregularity is:
    A. Athletics.
    B. Eating disorder.
    C. Polycystic ovary syndrome.
    D. Sexually transmitted disease.
    E. Thyroid disorder.

11. Ann is a 15½-year-old girl who has complaints of prolonged bleeding with her periods. She says her periods last 8 or 9 days but does not believe bleeding is excessive. She feels well otherwise, and her appetite is normal. She says she is not sexually active. Her hemoglobin is 9 g/dL. The *best* treatment for her disorder is:
    A. Dilatation and curettage.
    B. Exploratory surgery.
    C. Intravenous conjugated estrogens.
    D. Long-acting injectable progestin.
    E. Oral contraceptives.

12. Andrea is a 17-year-old girl who complains of cramping lower abdominal and pelvic pain associated with her menstrual periods. The pain radiates to her back. The discomfort began about 1 year after menarche and varies somewhat from period to period. She says that she is not sexually active. The *first* line of treatment for her discomfort is:
    A. Acetylsalicylic acid with bed rest.
    B. Acetaminophen.
    C. Ibuprofen.
    D. Irradiation.
    E. Oral contraceptives.

13. Patricia is a 15½-year-old girl who has not had a menstrual period since menarche at age 13½ years. Breast development was noted at about 12 years of age. She says that she feels well but thinks she is overweight and pays very strict attention to her diet. She feels this is necessary to help her maintain her place on the gymnastics team. Her weight is about 5 pounds less than normal for her height. With this history, you should direct specific attention to:
    A. Anorexia nervosa.
    B. Autoimmune oophoritis.
    C. Polycystic ovary syndrome.
    D. Thyroid disorder.
    E. Turner syndrome.

IN BRIEF

Marijuana

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Uncommonly used by adolescents prior to the 1960s, marijuana experienced a dramatic increase in popularity among teenagers over the next 2 decades. At its peak, approximately 60% of high school seniors reported some lifetime use of marijuana. Although use declined during the 1980s, the past few years have witnessed a resurgence in popularity among adolescents in the United States. Currently, approximately 40% of high school seniors report some lifetime use of marijuana, with 35% reporting use during the past year, and nearly 5% using on a daily basis. Approximately 20% of 8th graders has had some lifetime experience with marijuana, with 75% of these young students reporting use during the past year.

Marijuana is derived from the hemp plant (cannabis sativa). The psychoactive compound within marijuana, delta-9-tetrahydrocannabinol (THC), is found in differing concentrations within the plant and, in particular, the leaves and flowering shoots. Hashish, containing a much higher concentration of THC, is derived from a resinous exudate found on the tops of female plants.

Although products containing THC may be ingested or injected, adolescent use primarily is limited to smoking marijuana cigarettes or "joints". When smoked, marijuana's euphoric effects may be appreciated within seconds of inhalation because cannabinoids are transported rapidly from the lungs to the brain. Peak effects are achieved within minutes, with blood levels falling rapidly over the ensuing half hour.

Because cannabinoids are distributed widely to tissues throughout the body, subtle impairments of function may persist for long periods after smoking, and laboratory testing may confirm the use of marijuana for days and even weeks after use. In general, urine testing remains posi-

Menstrual Disorders

Paula K. Braverman and Steven J. Sondheimer

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