Menstrual Disorders in the Adolescent: Amenorrhea

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This is the first of a two-part article about menstrual disorders in the adolescent. The second part, on dysmenorrhea and dysfunctional uterine bleeding, will appear in the March 1992 issue of Pediatrics in Review. *R.J.H.*

FOCUS QUESTIONS

1. What is the difference between primary and secondary amenorrhea?
2. What are the symptoms of hypothalamic amenorrhea and how are they treated?
3. What is the appropriate laboratory evaluation of secondary amenorrhea?
4. What is the diagnostic approach to patients who have primary amenorrhea?

The menstrual history is an integral part of the evaluation of the adolescent female. Abnormal menstrual flow or timing may be the first sign of systemic illness or sexually transmitted disease. Amenorrhea may signal an endocrine or genetic disorder or may suggest structural abnormalities of the genital tract. Most importantly, any abnormality in menstruation should alert the clinician to the possibility of pregnancy.

Normal Menstrual Cycle

The average age of menarche in the United States is 12.8 years and ranges from 9 to 16 years. Menarche usually occurs 2 to 2.5 years after breast budding and 1 year after the growth spurt. Consequently, the absence of menarche at 15 years of age may be normal in an adolescent who just passed her growth spurt but abnormal in an adolescent who completed puberty 2 years earlier. Most early menstrual cycles are anovulatory. As a result, menses in the young adolescent often are irregular and may be prolonged or heavy. Dysmenorrhea and premenstrual symptoms tend to accompany ovulatory cycles and, therefore, are more common in the older adolescent.

Regular ovulatory cycles usually are established within 1 to 2 years of menarche. Although normal cycle length ranges from 21 to 45 days, the length for a given individual is fairly constant. Normal menstrual flow lasts 2 to 7 days and usually is heaviest on the first and second days. The average blood loss during a normal menstrual period is 30 to 40 mL.

Primary Amenorrhea

Primary amenorrhea, or delayed menarche, is defined as any one of the following: 1) the absence of menarche by 16 years of age in the presence of normal pubertal growth and development; 2) the absence of menarche by 14 years of age in the absence of normal pubertal growth and development; or 3) the absence of menarche 2 years after completed sexual maturation.

INITIAL EVALUATION

A complete history and physical examination is the most important step in evaluating the adolescent who has primary amenorrhea. Particular attention should be focused on pubertal milestones. The history should include questioning about maternal age

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at menarche, gestational complications and medications, childhood development, chronic systemic illness, nutrition, and family history of genetic anomalies. Physical examination should be meticulous and include charting of height, weight, and sexual maturation rating; complete neurologic examination, including the cranial nerves; examination of the skin, hair, and genitalia for signs of hirsutism or virilization; palpation of the thyroid; and palpation of the abdomen and groin for masses.

Pelvic examination, if done in a sensitive manner, need not be a traumatic experience. At absolute minimum, a careful examination of the external genitalia must be performed. Use of the speculum should be preceded by digital vaginal examination to avoid injuring the patient with an absent vagina or an outflow obstruction. If a normal vagina and cervix are present, microscopic examination of the cervical mucus may help clarify the degree of estrogen stimulation. Bimanual examination, followed by ultrasonographic examination of the pelvis, if necessary, will establish the presence or absence of a uterus and ovaries.

DIFFERENTIAL DIAGNOSIS AND MANAGEMENT

Patients who have primary amenorrhea can be divided into four groups, depending on pubertal maturation and internal genitalia (Figure 1).

No breast development—Intact uterus

These individuals lack ovarian estrogen but have normal development of the Mullerian system during fetal life. The differential diagnosis includes gonadal dysgenesis, hypothalamic-pituitary disorder, and genetic defects in ovarian steroid production. Measurement of the serum levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH) will differentiate patients who have gonadal (ovarian) dysgenesis and abnormal steroid production from those who have hypothalamic or pituitary disorders. Chromosomal analysis is indicated when FSH and LH levels are high.

Gonadal dysgenesis is the most common cause of primary amenorrhea. It usually is due to Turner syndrome (45,XO karyotype) or some other abnormality in X chromosome structure or number. The ovaries fail to develop, leaving remnant fibrous bands called gonadal streaks. Patients who have gonadal dysgenesis are sexually immature, amenorrheic, and have high FSH and LH levels (hypergonadotropic hypogonadism). Individuals who have Turner syndrome often have other stigmata, such as short stature, webbed neck, or chest and limb abnormalities. Patients who have mosaic Turner syndrome or other X chromosome abnormalities may be phenotypically normal except for sexual immaturity.

Gonadal dysgenesis also may occur in individuals who have normal

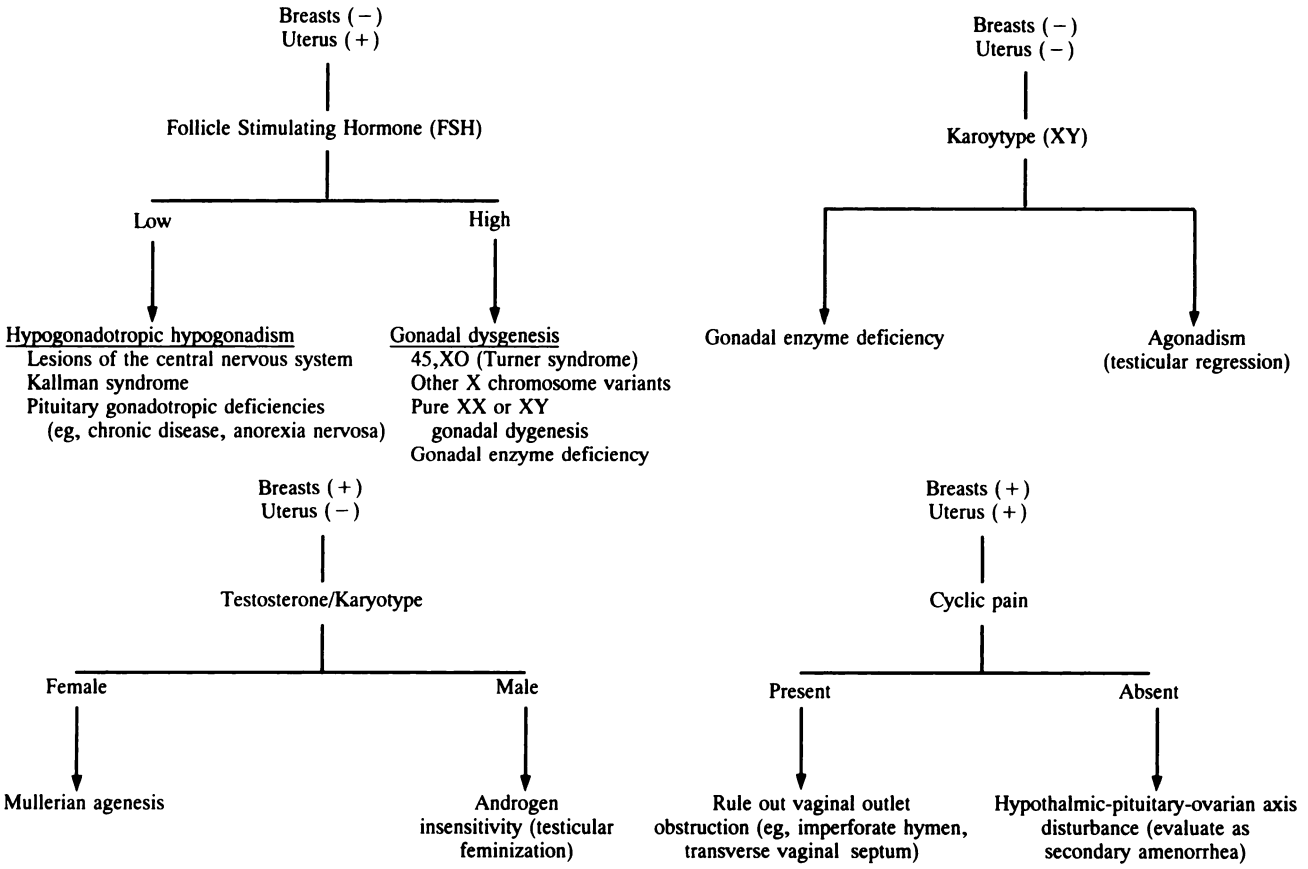

FIGURE 1. Diagnostic approach to patients who have primary amenorrhea. Adapted from Maschak CA, Kletzky OA, Davajan V, Mishell DR Jr. Clinical and laboratory evaluation of patients with primary amenorrhea. Obstet Gynecol. *1981;57:719. Reprinted with permission from the American College of Obstetrics and Gynecology.*

Any abnormality in menstruation should alert the clinician to the possibility of pregnancy.

karyotypes. Genetic males and females who have gonadal dysgenesis will be phenotypically female because, in the absence of testosterone, gender development is female. In the genetic male, the gonadal streaks must be removed because of the risk of malignancy.

Individuals who have gonadal dysgenesis are almost universally sterile, and hormonal replacement should be initiated during early adolescence. However, these patients do have intact uteri and may be able to bear children after donor oocyte implantation and hormonal support.

Patients who have primary amenorrhea due to hypogonadotropic hypogonadism have normal ovaries but lack hypothalamic or pituitary stimulation of the ovaries. FSH and LH levels will be low or low-normal. These patients are genetically and phenotypically female but are sexually immature. Care must be taken to exclude both tumors of the central nervous system (CNS) and congenital defects in the production of gonadotropin releasing hormone (GnRH). The most common CNS tumors producing primary amenorrhea are pituitary adenomas and craniopharyngiomas. Hypothalamic defects in GnRH production may occur as the result of abnormal hypothalamic development. When this occurs in association with anosmia and facial abnormalities, it is called Kallmann syndrome. Hypogonadotropic hypogonadism also may be associated with systemic disease, exercise, psychological stress, or anorexia nervosa. (These diagnoses are discussed in detail in the section on secondary amenorrhea.)

Abnormal steroidogenesis due to 17-alpha-hydroxylase deficiency is a rare disorder that results in the inability of the ovary to produce estrogen. It occurs in chromosomally normal females with structurally normal ovaries and uterus. These patients also have a defect in adrenal steroid production resulting in hypertension and hypokalemia. The diagnosis should be considered in patients who have hypergonadotropic hypogonadism, normal female karyotypes, and normal female genitalia.

Normal breast development—Absent uterus

Individuals in this category are phenotypically female. Pelvic examination, however, reveals an absent or shortened vagina and an absent uterus. The diagnosis at this point is either androgen insensitivity (testicular feminization) or Mullerian agenesis.

Patients who have testicular feminization are chromosomally male (XY) and have normal male gonads that produce normal male levels of testosterone, yet they appear phenotypically female. This is due to a genetic X-linked defect in androgen-receptor function with resultant end-organ insensitivity to androgen. The Wolffian ducts fail to develop, and the external genitalia develop as female in the absence of testosterone stimulation. Because the male gonad is still able to produce Mullerian inhibiting factor, the Mullerian ducts regress and female internal genitalia do not develop. Internally, these individuals have normal male gonads and fibrous Mullerian remnants. The low levels of endogenous gonadal and adrenal estrogens, unopposed by androgen, result in breast development. Because of target end-organ androgen insensitivity, axillary and pubic hair is sparse or absent. Confirmatory laboratory studies include male levels of serum testosterone and male chromosomes. The gonads, which may be either intraabdominal or inguinal, should be removed because there is a 20% incidence of malignancy. Estrogen replacement should be initiated following surgery.

Approximately 15% of cases of primary amenorrhea are due to Mullerian agenesis (Rokintansky-Kuster-Hauser syndrome). These patients are chromosomally and phenotypically female but have anomalous development of the Mullerian system. Consequently, the vagina and uterus fail to develop normally. Ovaries are present; breast development, steroid production, axillary hair, and pubic hair are normal. Renal anomalies occur in 15% to 40% of patients, and skeletal abnormalities occur in 12%. Cardiac and other congenital abnormalities also are increased in frequency. Chromosomal studies should be performed to confirm the normal XX chromosomal complement and to exclude rare forms of incomplete androgen insensitivity or pseudohermaphroditism. Once the diagnosis is made, a functioning vagina usually can be created by the use of vaginal dilators or by vaginoplasty. Hormonal therapy is not necessary.

No breast development—Absent uterus

This rare combination occurs in genetic males (XY) whose gonads produce Mullerian inhibiting factor but insufficient testosterone to induce the development of male internal and external genitalia. Phenotypic gender, therefore, is female. The lack of testosterone is due to a gonadal enzyme deficiency or to early gonadal regression ("vanishing testes"). Laboratory evaluation reveals a male karyotype, low androgen levels, and high gonadotropin levels. Treatment includes surgical removal of the gonads and estrogen replacement.

Normal breast development—Intact uterus

Individuals in this category are phenotypically normal females who undergo normal Mullerian development and normal pubertal progression. They can be presumed to have normal female karyotypes. The causes of the amenorrhea include vaginal outlet obstruction (eg, imperforate hymen, transverse vaginal septum) and disturbances in the hypothalamic-pituitary-ovarian axis. The management of patients in this latter group is identical to that of patients who have secondary amenorrhea.

Secondary Amenorrhea

Secondary amenorrhea is defined as the absence of menstruation for at least three cycles or at least 6 months

in females who have already established menstruation. Although menses often are irregular in young adolescents, they should stabilize within 1 to 2 years of menarche. Amenorrhea occurring more than 18 months after menarche should be considered abnormal and warrants investigation.

Pregnancy always must be included in the differential diagnosis of secondary amenorrhea. Sensitive questioning need not imply inherent distrust or disbelief of the adolescent who denies sexual activity. Instead, it acknowledges the strong sociocultural pressures that may lead an adolescent to give an inaccurate sexual history.

Once pregnancy has been excluded, evaluation of secondary amenorrhea focuses on the hypothalamic-pituitary-ovarian axis. This begins with a complete history and physical examination (Figure 2).

INITIAL EVALUATION

Maintenance of normal menses requires adequate body fat composition. Because weight loss or failure to gain weight is a common sign of illness during adolescence, secondary amenorrhea may be an indication of poor nutrition, stress, or systemic illness. Common diseases presenting during adolescence that may be associated with secondary amenorrhea include anorexia nervosa, inflammatory bowel disease, diabetes mellitus, thyroid disease, and pituitary adenomas. The history, therefore, should include questioning about caloric intake, dieting, weight fluctuation, bowel habits, exercise, medication and drug use, headache, visual change, and galactorrhea. Family history of menstrual irregularities, eating disorders, diabetes, and thyroid disease also may be helpful.

The physical examination should begin with measurement of height and weight and an assessment of body habitus. Common stigmata of anorexia nervosa include cachexia, lanugo, parotid enlargement, bradycardia, hypotension, and hypothermia. Fundoscopic examination, gross visual fields, and examination of the cranial nerves should be done as part of an initial screening for a pituitary lesion. Breast examination should include an attempt to elicit galactorrhea. If light microscopy of the

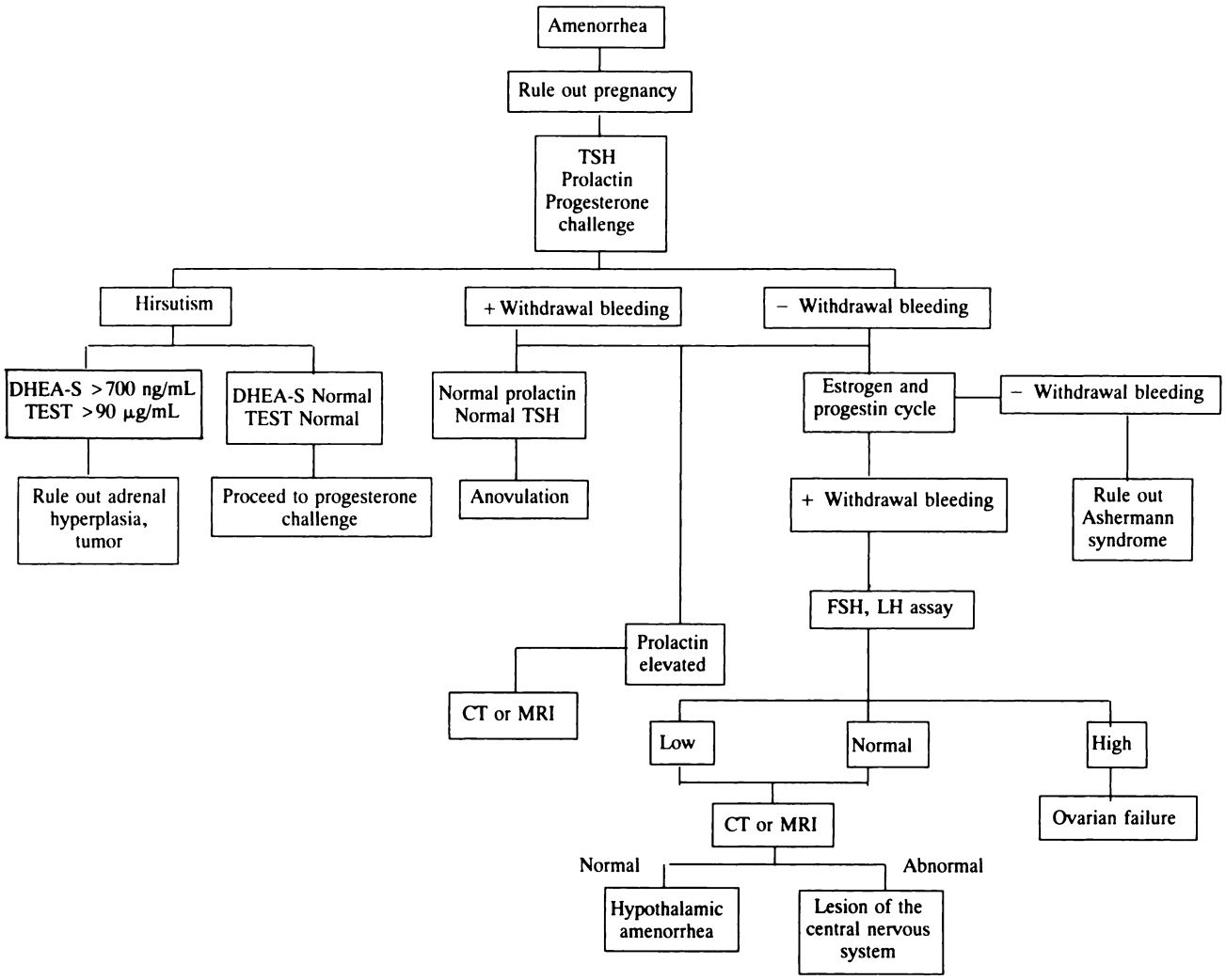

FIGURE 2. Evaluation of secondary amenorrhea. CT, computed tomography; DHEA-S, dehydroepiandrosterone sulfate; LH, luteinizing hormone; MRI, magnetic resonance imaging; TEST, testosterone; TSH, thyroid stimulating hormone. Modified from Speroff L, Glass RH, Kase NG. Clinical Gynecologic Endocrinology and Infertility. *4th ed. Baltimore, MD: Williams and Wilkins; 1989:178*

expressed fluid reveals fat lobules, it confirms that the discharge is breast milk and suggests stimulation of the breast by high prolactin levels. The hair, skin, and external genitalia should be inspected for evidence of androgen excess (eg, hirsutism, clitoromegaly, male escutcheon). The abdomen should be palpated for tenderness, masses, or signs of pregnancy. A rectal examination for fissures, fistulae, skin tags, or occult blood also should be done.

On pelvic examination, the vaginal mucosa and cervical mucus may help define the degree of estrogen stimulation. Estrogenic mucus is clear, watery, distensible, and reveals fern-ing on light microscopy. Bimanual and rectovaginal examination should be done in all patients presenting with unexplained secondary amenorrhea to evaluate uterine and ovarian size and to screen for pelvic masses.

The minimum laboratory evaluation of secondary amenorrhea includes a pregnancy test (serum or urine level of human chorionic gonadotropin), thyroid function studies, and serum prolactin level. Prolactin should be measured even in the absence of galactorrhea because only one third of patients who have elevated levels will have galactorrhea. It is estimated that 5% to 10% of patients who have both amenorrhea and elevated serum prolactin levels have pituitary adenomas, while 25% of those with amenorrhea, galactorrhea, and high prolactin levels have adenomas. It should be remembered that mild elevations in the serum prolactin level usually are due to medication, breast stimulation, stress, hypothyroidism (due to stimulation of the pituitary by thyroid releasing hormone), or other extraneous factors. The first elevation should be evaluated by comparison with a second sample drawn in a relaxed, fasting state. Persistently high prolactin levels (>100 ng/mL) are associated with tumors and mandate radiologic evaluation of the pituitary via computed tomography or magnetic resonance imaging.

If the physical examination reveals signs of androgen excess, serum levels of dehydroepiandrosterone sulfate (DHEA-S) and testosterone should be measured. The differential diagnosis of hirsutism-virilization and oligomenorrhea includes polycystic ovarian syndrome (PCOS), ovarian tumors, congenital adrenal hyperplasia (C-21 hydroxylase deficiency), adrenal tumors, and Cushing syndrome. DHEA-S levels >700 ng/mL and testosterone levels >90 μg/mL require further investigation. This may include measurement of a serum 17-hydroxyprogesterone level, adrenal suppression testing, and computed tomography or magnetic resonance imaging of the abdomen and pelvis.

Menses often are irregular during early adolescence but should stabilize within 2 years of menarche.

PROGESTERONE CHALLENGE

After excluding pregnancy, hypothyroidism, and pituitary adenoma as the cause of secondary amenorrhea, the next step in the evaluation is administration of a progesterone challenge. The purpose of this is twofold. First, withdrawal bleeding following exposure to exogenous progesterone establishes the presence of a normal uterus. Second, withdrawal bleeding indicates that the endometrium has been primed by endogenous estrogen and, thus, implies ovarian function. Oral medroxyprogesterone acetate is administered in a dose of 5 to 10 mg daily for 5 to 10 days. If compliance is of concern, 200 mg of progesterone suspended in oil can be given as a single intramuscular injection.

Positive withdrawal bleeding

The occurrence of bleeding, however minimal, 2 to 7 days after concluding the progesterone regimen constitutes positive withdrawal bleeding and establishes the presence of anovulation. The most common cause of anovulation in a postmenarchal adolescent is PCOS. This disorder is characterized by amenorrhea or oligomenorrhea, hirsutism, infertility, and often obesity. When spontaneous bleeding occurs in association with PCOS, it tends to be unpredictable and often is prolonged or heavy (ie, dysfunctional uterine bleeding). Oligomenorrhea or secondary amenorrhea is variable in its onset and duration.

The fundamental defect characterizing PCOS probably is not located in the ovary. Instead, it is probably the result of inappropriate signals along the hypothalamic-pituitary-ovarian axis. It has been suggested that exaggerated adrenarche and obesity, resulting in high levels of extraglandular estrogen, lead to positive feedback on LH secretion and negative feedback on FSH secretion. This is reflected in a high LH-to-FSH ratio (>2). The elevated LH level leads to hyperplasia of the ovarian stroma and theca cells and increased ovarian production of androgens. Peripheral aromatization of the androgens to estrogens then perpetuate the anovulation.

Treatment of PCOS attempts to interrupt this cycle. Use of a combined estrogen-progestin oral contraceptive helps control hirsutism, regulates menses, and is well-tolerated by most adolescents. Although a strong oral progestin formulation (ie, levonorgestrol) is useful in controlling dysfunctional uterine bleeding, a lower strength, nonandrogenic progestin formulation (ie, norothindrone) should be considered for long-term use in the hirsute patient. If the adolescent prefers not to use an oral contraceptive, progesterone should be administered every 3 months in the absence of spontaneous menses to protect against the long-term risk of endometrial hyperplasia.

The hirsutism associated with PCOS also may respond to anti-androgens such as spironolactone. The effectiveness of spironolactone is related to dosage. An initial dose of 150 to 200 mg daily is recommended, with subsequent tapering to a maintenance dose of 25 to 50 mg.

Oral contraceptives containing gestodene and norgestimate are expected to be approved by the FDA in 1992. These nonandrogenic, potent proges-

tins may prove to be the optimal formulation for the hirsute patient with PCO.

Negative withdrawal bleeding

If the patient fails to bleed after the progestin challenge, either the uterus is abnormal or there has been insufficient endogenous estrogen to prime the endometrium. A combined oral estrogen-progestin regimen should result in bleeding if the endometrium is normal.

If no bleeding occurs after the estrogen-progestin regimen, Asherman syndrome may have occurred as a result of uterine instrumentation, trauma, or infection. The resulting formation of intrauterine scarring (synechiae) causes amenorrhea.

In the adolescent who has a normal vagina and uterus and no risk factors for intrauterine scarring, the estrogen-progestin challenge can be eliminated and a hypoestrogenic state can be presumed to exist. Serum gonadotropin levels then should be measured. High serum levels of gonadotropins (FSH and LH) indicate ovarian failure (hypergonadotropic hypogonadism). Karyotype testing should be performed on patients with presumed ovarian failure to rule out Turner mosaicism or other chromosomal abnormalities. The presence of any portion of a Y chromosome mandates gonadectomy to eliminate the risk of malignant transformation of the gonad. Ovarian failure also may result from autoimmune disease, chemotherapy, or radiation.

Low serum levels of gonadotropins point to a defect in the hypothalamus or pituitary (hypogonadotropic hypogonadism or hypothalamic amenorrhea). Although the incidence of pituitary tumors is low in the absence of galactorrhea or an elevated serum prolactin, radiologic evaluation should be considered in cases where no obvious cause for hypothalamic dysfunction can be found. Hypothalamic amenorrhea comprises a heterogeneous group of disorders as discussed previously, including systemic illness, anorexia nervosa, exercise-induced amenorrhea, and stressful situations (eg, going away to school). It is believed that stress leads to alterations in hypothalamic GnRh secretion, possibly due to elevated beta-endorphin levels. Short-term treatment includes reassurance, counseling, and watchful waiting. If the amenorrhea persists, estrogen replacement is indicated. This is best accomplished with a combined estrogen-progestin oral contraceptive. An alternative regimen for the adolescent who is not sexually active is a conjugated estrogen (0.625 to 1.25 mg daily on days 1 to 25) and medroxyprogesterone acetate (10 mg daily on days 16 to 25). Menses usually occurs at the end of each cycle.

Exercise-induced amenorrhea probably is due to a complex interplay of decreased body fat and stress. Athletes who have body fat below the tenth percentile for age are likely to develop amenorrhea. High-energy output and stress may act independently of body fat in inducing amenorrhea because menses often return during nontraining intervals, even when body fat remains unchanged. Elevated prolactin levels also have been observed in some amenorrheic athletes during peroids of intense exercise. The simplest way to treat exercise-induced amenorrhea is to decrease the amount of exercise. If the amenorrhea persists, estrogen replacement therapy should be instituted.

Anorexia nervosa is a special case of hypothalamic amenorrhea. Although the mechanisms of amenorrhea are similar to those of exercise-induced amenorrhea (ie, low body fat, stress, beta-endorphin release), the complex psychological and medical problems associated with anorexia nervosa are difficult to manage. A team approach employing psychiatric counseling, close medical supervision, nutritional consultation, and hormonal replacement provides the best outcome.

There is increasing evidence that osteoporosis associated with chronic estrogen deficiency may begin during the adolescent years. For this reason, estrogen replacement therapy should not be delayed until adulthood in the patient who has well-established hypogonadism. Progesterone should be administered with the estrogen to minimize the risk of endometrial carcinoma. When such a combined regimen is used, the benefits appear to far outweigh the risks.

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