Amenorrhea: Evaluation and Treatment

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A thorough history and physical examination as well as laboratory testing can help narrow the differential diagnosis of amenorrhea. In patients with primary amenorrhea, the presence or absence of sexual development should direct the evaluation. Constitutional delay of growth and puberty commonly causes primary amenorrhea in patients with no sexual development. If the patient has normal pubertal development and a uterus, the most common etiology is congenital outflow tract obstruction with a transverse vaginal septum or imperforate hymen. If the patient has abnormal uterine development, müllerian agenesis is the likely cause and a karyotype analysis should confirm that the patient is 46,XX. If a patient has secondary amenorrhea, pregnancy should be ruled out. The treatment of primary and secondary amenorrhea is based on the causative factor. Treatment goals include prevention of complications such as osteoporosis, endometrial hyperplasia, and heart disease; preservation of fertility; and, in primary amenorrhea, progression of normal pubertal development.

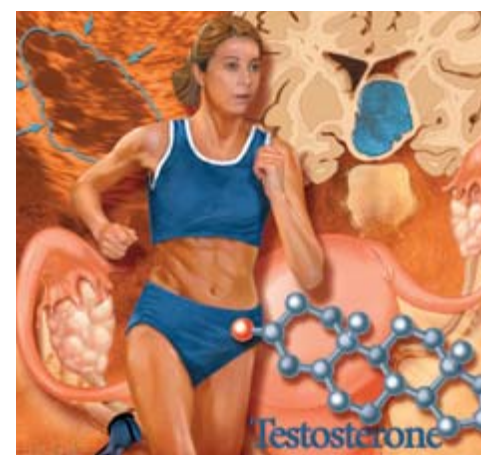


ILLUSTRATION BY JOAN BECK

▶ **Patient information:** A handout on amenorrhea, written by the authors of this article, is provided on page 1387.

Primary amenorrhea can be diagnosed if a patient has normal secondary sexual characteristics but no menarche by 16 years of age. If a patient has no secondary sexual characteristics and no menarche, primary amenorrhea can be diagnosed as early as 14 years of age. Secondary amenorrhea is the absence of menses for three months in women with previously normal menstruation and for nine months in women with previous oligomenorrhea. Secondary amenorrhea is more common than primary amenorrhea.[1-3]

Pubertal changes typically occur over a three-year period and can be measured using Tanner staging.[4] The normal progression of female puberty is illustrated in *Table 1*.[4,5] The normal menstrual cycle involves a complex interaction between the hypothalamic-pituitary-ovarian axis and the outflow tract. Any disruption in this interaction can cause amenorrhea.

Evaluation

Physicians should conduct a comprehensive patient history and a thorough physical examination of patients with amenorrhea *(Table 2*[2,6-8]*)*. Many algorithms exist for the evaluation of primary amenorrhea; *Figure 1*[1,7,9,10] is one example. Laboratory tests and radiography, if indicated, should be performed to evaluate for suspected systemic disease. If secondary sexual characteristics are present, pregnancy should be ruled out. Routine radiography is not recommended, however.[7]

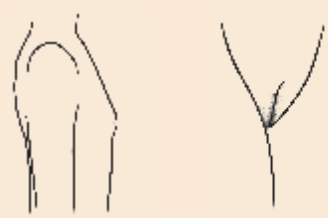
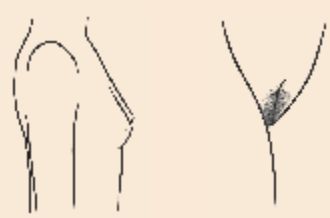
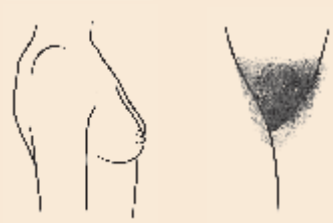
Figure 2[1-3,6] is an algorithm for the evaluation of secondary amenorrhea. The most common cause of secondary amenorrhea is pregnancy. After pregnancy is ruled out, the initial work-up should be based on patient history and physical examination findings. Prolactin levels should be checked in most patients. The risk of amenorrhea is lower with subclinical hypothyroidism than with overt disease. However, the effects of subclinical hypothyroidism on menstruation and fertility are unclear, and abnormal thyroid hormone levels can affect prolactin levels; therefore, physicians should consider measuring thyroid-stimulating hormone (TSH) levels.[3,11,12] A study[13] of 127 women with adult-onset amenorrhea showed that

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
A female patient with primary amenorrhea and sexual development, including pubic hair, should be evaluated for the presence of a uterus and vagina.	C	1, 18
Women with secondary amenorrhea should receive pregnancy tests.	C	1-3, 6
Women with polycystic ovary syndrome should be tested for glucose intolerance.	C	21

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 1313 or http://www.aafp.org/afpsort.xml.

TABLE 1
Normal Female Pubertal Development

		Tanner stage	
Developmental stage (age in years)	*Anatomic drawing*	*Breast development*	*Pubic hair development*
Initial growth acceleration (8 to 10)	Elevation of papilla only; no pubic hair	1	1
Thelarche (9 to 11)	See adrenarche for stage 2 development	2	1
Adrenarche (9 to 11)		2	2
Peak growth (11 to 13)		3	3
Menarche (12 to 14)		4	4
Adult characteristics (13 to 16)		5	5

Illustrations by Renee Cannon.

Information from references 4 and 5.

7.5 percent of participants had abnormal prolactin levels and 4.2 percent had abnormal TSH levels.

If TSH and prolactin levels are normal, a progestogen challenge test *(Table 3[3,14])* can help evaluate for a patent outflow tract and detect endogenous estrogen that is affecting the endometrium. A withdrawal bleed usually occurs two to seven days after the challenge test.[3] A negative progestogen challenge test signifies an outflow tract abnormality or inadequate estrogenization. An estrogen/progestogen challenge test *(Table 3[3,14])* can differentiate the two diagnoses. A negative estrogen/progestogen challenge test typically indicates an outflow tract obstruction. A positive test indicates an abnormality within the hypothalamic-pituitary axis or the ovaries.

TABLE 2
History and Physical Examination Findings Associated with Amenorrhea

Findings	*Associations*
Patient history	
Exercise, weight loss, current or previous chronic illness, illicit drug use	Hypothalamic amenorrhea
Menarche and menstrual history	Primary versus secondary amenorrhea
Prescription drug use	Multiple, depending on medication
Previous central nervous system chemotherapy or radiation	Hypothalamic amenorrhea
Previous pelvic radiation	Premature ovarian failure
Psychosocial stressors; nutritional and exercise history	Anorexia or bulimia nervosa
Sexual activity	Pregnancy
Family history	
Genetic defects	Multiple causes of primary amenorrhea
Pubic hair pattern	Androgen insensitivity syndrome
Infertility	Multiple
Menarche and menstrual history (mother and sisters)	Constitutional delay of growth and puberty
Pubertal history (e.g., growth delay)	Constitutional delay of growth and puberty
Physical examination	
Anthropomorphic measurements; growth chart	Constitutional delay of growth and puberty
Body mass index	Polycystic ovary syndrome
Dysmorphic features (e.g., webbed neck, short stature, widely spaced nipples)	Turner's syndrome
Rudimentary or absent uterus; pubic hair	Müllerian agenesis
Striae, buffalo hump, significant central obesity, easy bruising, hypertension, or proximal muscle weakness	Cushing's disease
Tanner staging (Table 1)	Primary versus secondary amenorrhea
Thyroid examination	Thyroid disease
Transverse vaginal septum; imperforate hymen	Outflow tract obstruction
Undescended testes; external genital appearance; pubic hair	Androgen insensitivity syndrome
Virilization; clitoral hypertrophy	Androgen-secreting tumor
Review of systems	
Anosmia	Kallmann syndrome
Cyclic abdominal pain; breast changes	Outflow tract obstruction or müllerian agenesis
Galactorrhea; headache and visual disturbances	Pituitary tumor
Hirsutism or acne	Polycystic ovary syndrome
Signs and symptoms of hypothyroidism or hyperthyroidism	Thyroid disease
Vasomotor symptoms	Premature ovarian failure

Information from references 2 and 6 through 8.

Evaluation of Primary Amenorrhea

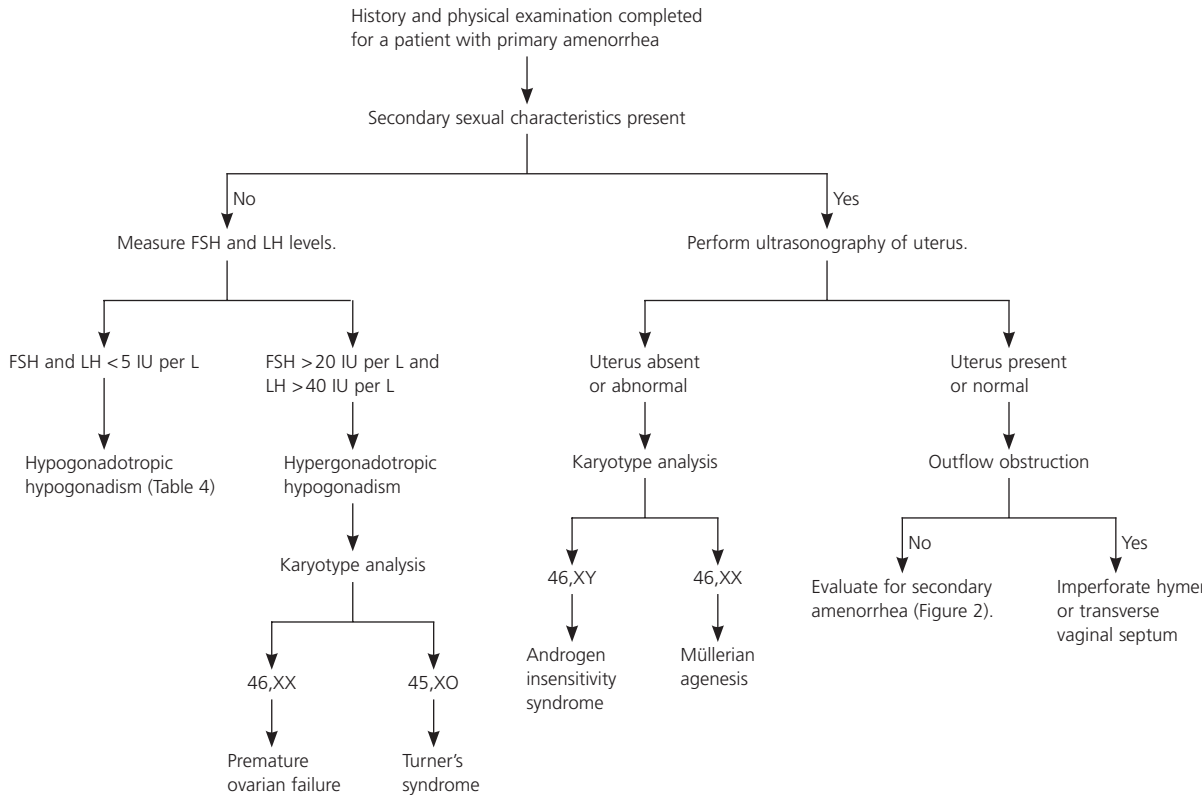


Figure 1. Algorithm for the evaluation of primary amenorrhea. (FSH = follicle-stimulating hormone; LH = luteinizing hormone.)

Information from references 1, 7, 9, and 10.

Gonadotropin levels can further help determine the source of the abnormality. Elevated follicle-stimulating hormone (FSH) or luteinizing hormone (LH) levels suggest an ovarian abnormality (hypergonadotropic hypogonadism). Normal or low FSH or LH levels suggest a pituitary or hypothalamic abnormality (hypogonadotropic hypogonadism). Magnetic resonance imaging (MRI) of the sella turcica can rule out a pituitary tumor. Normal MRI indicates a hypothalamic cause of amenorrhea.[3]

Differential Diagnosis of Primary Amenorrhea

Causes of primary amenorrhea should be evaluated in the context of the presence or absence of secondary sexual characteristics. *Table 4*[3,6,15] includes the differential diagnosis of primary amenorrhea.

PRESENCE OF SECONDARY SEXUAL CHARACTERISTICS

If a patient with amenorrhea has breast development and minimal or no pubic hair, the usual diagnosis is androgen insensitivity syndrome (i.e., patient is phenotypically female but genetically male with undescended testes). A karyotype analysis is needed to determine proper treatment. If testes are present, they should be removed because of the high risk of malignant transformation after puberty.[1]

If a patient has normal secondary sexual characteristics, including pubic hair, the physician should perform MRI or ultrasonography to determine if a uterus is present. Müllerian agenesis (the congenital absence of a vagina and abnormal uterine development [usually rudimentary]) causes approximately 15 percent of primary amenorrhea.[16] The etiology is thought to involve embryonic activation of the antimüllerian hormone, causing malformation of the female genital tract.[7,17] Patients may have cyclic abdominal pain if there is endometrial tissue in the rudimentary uterus, mittelschmerz, or breast tenderness. An absent or truncated vagina and an abnormal adult uterus confirm müllerian agenesis. Karyotype analysis should be performed to determine if the patient is genetically female.[8]

If the patient has a normal uterus, outflow tract obstruction should be considered. An imperforate hymen or a transverse vaginal septum can cause congenital outflow tract obstruction, which typically is associated with cyclic abdominal pain from blood accumulation in the uterus and vagina.[1] If the outflow tract is patent, the

Evaluation of Secondary Amenorrhea

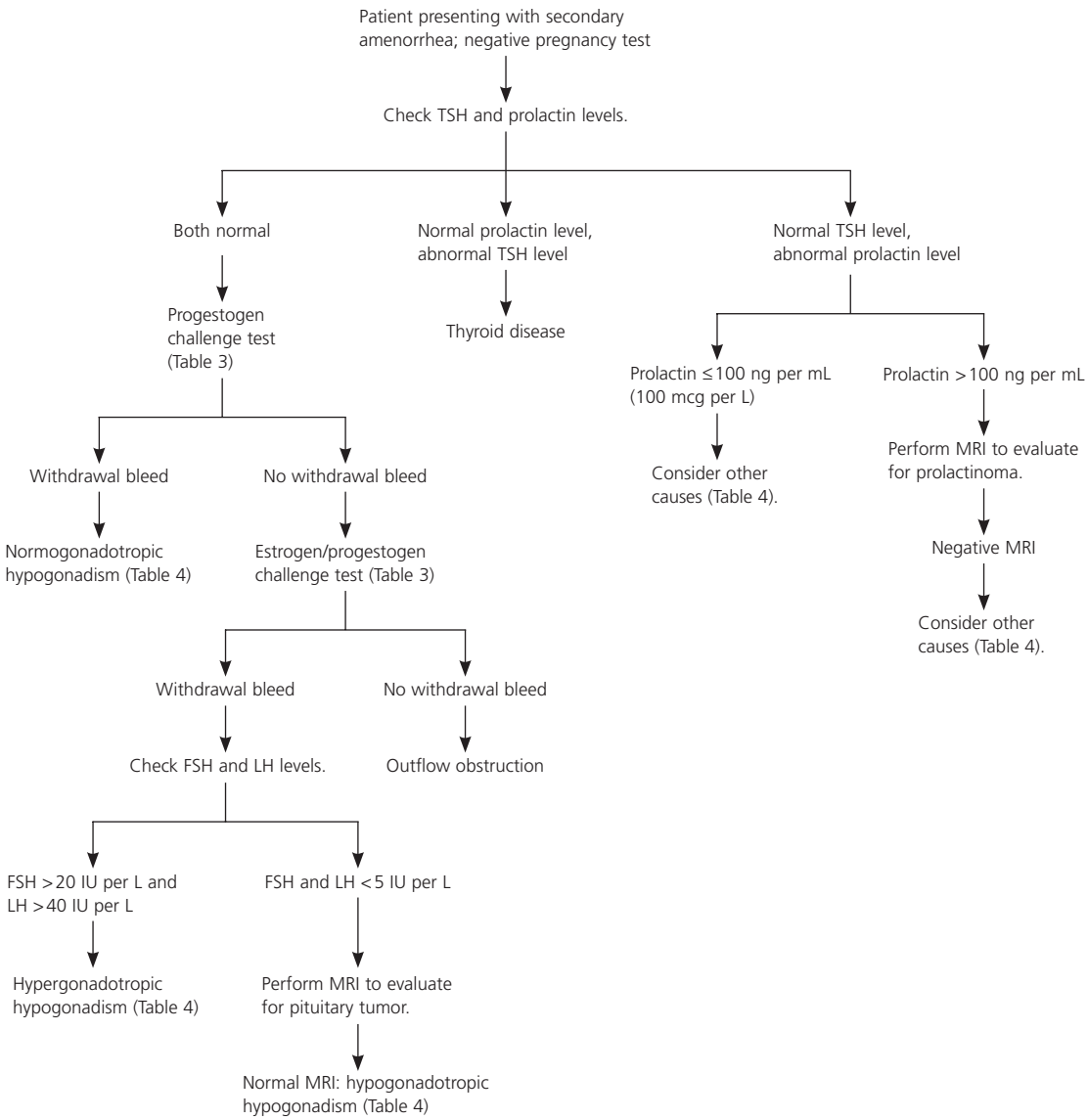


Figure 2. Algorithm for the evaluation of secondary amenorrhea. (TSH = thyroid-stimulating hormone; MRI = magnetic resonance imaging; FSH = follicle-stimulating hormone; LH = luteinizing hormone.)

Information from references 1 through 3 and 6.

physician should continue an evaluation similar to that for secondary amenorrhea *(Figure 2*[1-3,6]*)*.[1]

ABSENCE OF SECONDARY SEXUAL CHARACTERISTICS

Diagnosis of patients with amenorrhea and no secondary sexual characteristics is based on laboratory test results and karyotype analysis. The most common cause of hypogonadotropic hypogonadism (low FSH and LH levels) in primary amenorrhea is constitutional delay of growth and puberty.[16,17] A detailed family history also may help detect this etiology, because it often is familial. Hypogonadotropic hypogonadism associated with constitutional delay of growth and puberty is indistinguishable from that associated with hypothalamic or pituitary failure.[10] Watchful waiting is appropriate for constitutional delay of growth and puberty. Kallmann syndrome, which is associated with anosmia, also can cause hypogonadotropic hypogonadism.[18]

Hypergonadotropic hypogonadism (elevated FSH and LH levels) in patients with primary amenorrhea is caused by gonadal dysgenesis or premature ovarian failure. Turner's syndrome (45,XO karyotype) is the most common form of female gonadal dysgenesis. Characteristic physical findings include webbing of the neck, widely

TABLE 3
Guidelines for Progestogen and Estrogen/Progestogen Challenge Tests

Drug	*Dosing*	*Duration*
Progestogen challenge test		
Medroxyprogesterone acetate (Provera)	10 mg orally once per day	Seven to 10 days
Norethindrone (Aygestin)	5 mg orally once per day	Seven to 10 days
Progesterone	200 mg parenterally once per day	Single dose
Progesterone micronized	400 mg orally once per day	Seven to 10 days
Progesterone micronized gel (4 or 8%)	Intravaginally every other day	Six applications
Estrogen/progestogen challenge test		
Conjugated equine estrogen (Premarin)	1.25 mg orally once per day	21 days
or		
Estradiol (Estrace)	2 mg orally once per day	21 days
followed by		
Progestational agent	As noted above	As noted above

Information from references 3 and 14.

spaced nipples, and short stature. Mosaicism occurs in approximately 25 percent of patients with Turner's syndrome.[19] These patients often have a more normal phenotype with spontaneous onset of puberty and menarche. Other rare causes of pure gonadal dysgenesis can occur with a 46,XY or XX karyotype.[7]

Differential Diagnosis of Secondary Amenorrhea

After pregnancy, thyroid disease, and hyperprolactinemia are eliminated as potential diagnoses, the remaining causes of secondary amenorrhea are classified as normogonadotropic amenorrhea, hypogonadotropic hypogonadism, and hypergonadotropic hypogonadism; each is associated with specific etiologies *(Table 4[3,6,15])*.

HYPOTHYROIDISM

Other clinical signs of thyroid disease are usually noted before amenorrhea presents. Mild hypothyroidism is more often associated with hypermenorrhea or oligomenorrhea than with amenorrhea. Treatment of hypothyroidism should restore menses, but this may take several months.[12]

HYPERPROLACTINEMIA

A patient with markedly elevated prolactin levels, galactorrhea, headaches, or visual disturbances should receive imaging tests to rule out a pituitary tumor. Adenomas are the most common cause of anterior pituitary dysfunction.[15] A prolactin level more than 100 ng per mL (100 mcg per L) suggests a prolactinoma, and MRI should be performed. If tumor is excluded as the cause, medications (e.g., oral contraceptive pills, antipsychotics, antidepressants, antihypertensives, histamine H_2 blockers, opiates) are the next most common cause of hyperprolactinemia. Medications usually raise prolactin levels to less than 100 ng per mL.[15] When hyperprolactinemia is not related to tumor, physicians should identify and treat or eliminate the underlying cause. *Table 4*[3,6,15] lists common etiologies of hyperprolactinemia.

If asymptomatic microadenomas (smaller than 10 mm) are found on MRI, repeat prolactin measurements and imaging should be performed to monitor for progression. Microadenomas are slow growing and rarely malignant. Treatment of microadenomas should focus on management of infertility, galactorrhea, and breast discomfort. A dopamine agonist can help improve symptoms and fertility. Bromocriptine (Parlodel) is effective, but cabergoline (Dostinex) has been shown to be superior in effectiveness and tolerability.[20] Macroadenomas may be treated with dopamine agonists or removed with transsphenoidal resection or craniotomy, if necessary.

NORMOGONADOTROPIC AMENORRHEA

Two common causes of normogonadotropic amenorrhea are outflow tract obstruction and hyperandrogenic chronic anovulation. The most common cause of outflow obstruction in secondary amenorrhea is Asherman's syndrome (intrauterine synechiae and scarring, usually from curettage or infection).[3] Hysterosalpingography, hysteroscopy, or sonohysterography can help diagnose Asherman's syndrome. Other causes of outflow tract obstruction include cervical stenosis and obstructive fibroids or polyps.

Polycystic ovary syndrome (PCOS) is the most common cause of hyperandrogenic chronic anovulation. The National Institutes of Health diagnostic criterion for PCOS[21] is chronic anovulation and hyperandrogenism

TABLE 4
Causes of Amenorrhea

Hyperprolactinemia
- Prolactin ≤100 ng per mL (100 mcg per L)
  - Altered metabolism
    - Liver failure
    - Renal failure
  - Ectopic production
    - Bronchogenic (e.g., carcinoma)
    - Gonadoblastoma
    - Hypopharynx
    - Ovarian dermoid cyst
    - Renal cell carcinoma
    - Teratoma
  - Breastfeeding
  - Breast stimulation
  - Hypothyroidism
  - Medications
    - Oral contraceptive pills
    - Antipsychotics
    - Antidepressants
    - Antihypertensives
    - Histamine H_2 receptor blockers
    - Opiates, cocaine
- Prolactin >100 ng per mL
  - Empty sella syndrome
  - Pituitary adenoma

Hypergonadotropic hypogonadism
- Gonadal dysgenesis
  - Turner's syndrome*
  - Other*
- Postmenopausal ovarian failure
- Premature ovarian failure
  - Autoimmune
  - Chemotherapy
  - Galactosemia
  - Genetic
  - 17-hydroxylase deficiency syndrome
  - Idiopathic
  - Mumps
  - Pelvic radiation

Hypogonadotropic hypogonadism
- Anorexia or bulimia nervosa
- Central nervous system tumor
- Constitutional delay of growth and puberty*
- Chronic illness
  - Chronic liver disease
  - Chronic renal insufficiency
  - Diabetes
  - Immunodeficiency
  - Inflammatory bowel disease
  - Thyroid disease
  - Severe depression or psychosocial stressors
- Cranial radiation

Hypogonadotropic hypogonadism *(continued)*
- Excessive exercise
- Excessive weight loss or malnutrition
- Hypothalamic or pituitary destruction
- Kallmann syndrome*
- Sheehan's syndrome

Normogonadotropic
- Congenital
  - Androgen insensitivity syndrome*
  - Müllerian agenesis*
- Hyperandrogenic anovulation
  - Acromegaly
  - Androgen-secreting tumor (ovarian or adrenal)
  - Cushing's disease
  - Exogenous androgens
  - Nonclassic congenital adrenal hyperplasia
  - Polycystic ovary syndrome
  - Thyroid disease
- Outflow tract obstruction
  - Asherman's syndrome
  - Cervical stenosis
  - Imperforate hymen*
  - Transverse vaginal septum*

Other
- Pregnancy
- Thyroid disease

**—Causes of primary amenorrhea only.*

Information from references 3, 6, and 15.

with no other identified secondary cause. The primary etiology of PCOS is unknown, but resistance to insulin is thought to be a fundamental component.[21]

The diagnosis of PCOS is primarily clinical, although laboratory studies may be needed to rule out other causes of hyperandrogenism *(Table 5*[6,21]*)*. Significantly elevated testosterone or dehydroepiandrosterone sulfate levels indicate a possible androgen-secreting tumor (ovarian or adrenal). Levels of 17-hydroxyprogesterone can help diagnose adult-onset congenital adrenal hyperplasia. Cushing's disease is rare; therefore, patients should only be screened when characteristic signs and symptoms (e.g., striae, buffalo hump, significant central obesity, easy bruising, hypertension, proximal muscle weakness) are present.[21,22]

Patients with PCOS have excess unopposed circulating estrogen, increasing their risk of endometrial cancer threefold.[21] The insulin resistance associated with PCOS increases a patient's risk of diabetes mellitus two- to fivefold; therefore, testing for glucose intolerance should be considered.[21-24]

The primary treatment for PCOS is weight loss through diet and exercise. Modest weight loss can lower androgen levels, improve hirsutism, normalize menses, and decrease insulin resistance. It may take months to see these results, however.[21] Use of oral contraceptive pills or cyclic progestational agents can help maintain a normal endometrium. The optimal cyclic progestin regimen to prevent endometrial cancer is unknown, but a monthly 10- to 14-day regimen is recommended.[21] Insulin sensitizing agents such as metformin (Glucophage) can reduce insulin resistance and improve ovulatory function.[21,25,26]

HYPERGONADOTROPIC HYPOGONADISM

Ovarian failure can cause menopause or can occur prematurely. On average, menopause occurs at 50 years of age and is caused by ovarian follicle depletion. Premature

TABLE 5
Laboratory Evaluation of Hyperandrogenism

Findings	*Indications*
Serum testosterone (normal: 20 to 80 ng per dL [0.7 to 2.8 nmol per L])	
≤200 ng per dL (6.9 nmol per L)	Consider hyperandrogenic chronic anovulation*
>200 ng per dL	Evaluate for androgen-secreting tumor
Serum dehydroepiandrosterone sulfate (normal: 250 to 300 ng per dL [0.7 to 0.8 µmol per L])	
≤700 ng per dL (1.9 µmol per L)	Consider hyperandrogenic chronic anovulation*
>700 ng per dL	Evaluate for adrenal or ovarian tumor
Serum 17-hydroxyprogesterone (normal: <2 ng per mL (6.1 nmol per L])†	
>4 ng per mL (12.1 nmol per L)	Consider adrenocorticotropic stimulation test to diagnose congenital adrenal hyperplasia
Dexamethasone suppression test (if clinically indicated)††	
Morning cortisol level > 5 µg per dL (138 nmol per L)§	Evaluate for Cushing's disease

**— These values are not specific for diagnosis of hyperandrogenic chronic anovulation.*

†—Morning level during follicular phase of menstrual cycle.

††—For an overnight dexamethasone suppression test, the physician should administer a 1-mg dose of dexamethasone orally between 11 p.m. and midnight and draw a single blood sample for serum cortisol testing at 8 a.m. the following day.

§—Morning cortisol level in a healthy patient with an intact hypothalamic-pituitary axis. There is some variability in the cutoff values that can affect sensitivity and specificity of the test. Patients should receive further testing to confirm Cushing's disease.

Information from references 6 and 21.

ovarian failure is characterized by amenorrhea, hypoestrogenism, and increased gonadotropin levels occurring before 40 years of age and is not always irreversible[27] (0.1 percent of women are affected by 30 years of age and one percent by 40 years of age).[28] Approximately 50 percent of women with premature ovarian failure have intermittent ovarian functioning[29] with a 5 to 10 percent chance of achieving natural conception.

Women with premature ovarian failure have an increased risk of osteoporosis and heart disease.[29-31] The condition also can be associated with autoimmune endocrine disorders such as hypothyroidism, Addison's disease, and diabetes mellitus.[27,29] Therefore, fasting glucose, thyroid-stimulating hormone (TSH), and, if clinically appropriate, morning cortisol levels should be measured. Other laboratory testing should be determined based on the individual patient.[32] Approximately 20 to 40 percent of women with premature ovarian failure will develop another autoimmune disorder; therefore, if initial laboratory tests are normal, periodic screening should be considered. Patients younger than 30 years should receive a karyotype analysis to rule out the presence of a Y chromosome and the need for removal of gonadal tissue.[29] Ovarian biopsy and antiovarian antibody testing have not been shown to have clinical benefit.[27,29]

HYPOGONADOTROPIC HYPOGONADISM

Hypothalamic amenorrhea is associated with abnormalities in gonadotropin-releasing hormone (GnRH) secretion and disruption of the hypothalamic-pituitary-ovarian axis. The condition often is caused by excessive weight loss, exercise, or stress. Other causes are listed in *Table 4*.[3,6,15] The mechanism of how stress or weight loss affects GnRH secretion is unknown.[33-35] Treatment of hypothalamic amenorrhea depends on the etiology. Women with excessive weight loss should be screened for eating disorders and treated if anorexia nervosa or bulimia nervosa is diagnosed. Menses usually will return after a healthy body weight is acheived.[35]

Young athletes may develop a combination of health conditions called the female athlete triad that includes an eating disorder, amenorrhea, and osteoporosis. Menses may return after a modest increase in caloric intake or a decrease in athletic training. Similar to patients with eating disorders, athletes with continued amenorrhea are at risk of bone loss. In adolescent athletes, the bone loss occurs during peak bone mass development and may not be reversible.[36,37] Weight-bearing exercise may partially protect against bone loss.[38]

In patients with amenorrhea caused by eating disorders or excessive exercise, the use of oral contraceptive pills or menopausal hormone therapy may decrease bone turnover and partially reverse bone loss; however, neither therapy has been shown to significantly increase bone mass.[38] Bisphosphonates, traditionally used to treat postmenopausal osteoporosis, are possible teratogens and have not been studied as a therapy in women of reproductive age. Adequate calcium and vitamin D intake are recommended for these patients.

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REFERENCES

1. The Practice Committee of the American Society for Reproductive Medicine. Current evaluation of amenorrhea. Fertil Steril 2004;82(suppl 1): S33-9.
2. American College of Obstetricians and Gynecologists. Amenorrhea (ACOG Technical Bulletin 128). Washington, D.C.: ACOG, 1989.
3. Speroff L, Fritz MA. Amenorrhea. In: Clinical gynecologic endocrinology and infertility. 7th ed. Philadelphia, Pa.: Lippincott Williams & Wilkins, 2005;401-64.
4. Marshall WA, Tanner JM. Variations in patterns of pubertal changes in girls. Arch Dis Child 1969;44:291-303.
5. Speroff L, Glass RH, Kase NG. Normal and abnormal sexual development. In: Clinical gynecologic endocrinology and infertility. 6th ed. Baltimore, Md.: Lippincott Williams & Wilkins, 1999:339-79.
6. Kiningham RB, Apgar BS, Schwenk TL. Evaluation of amenorrhea. Am Fam Physician 1996;53:1185-94.
7. Pletcher JR, Slap GB. Menstrual disorders. Pediatr Clin North Am 1999;46:505-18.
8. Reindollar RH, Byrd JR, McDonough PG. Delayed sexual development: a study of 252 patients. Am J Obstet Gynecol 1981;140:371-80.
9. McIver B, Romanski SA, Nippoldt TB. Evaluation and management of amenorrhea. Mayo Clin Proc 1997;72:1161-9.
10. Albanese A, Stanhope R. Investigation of delayed puberty. Clin Endocrinol (Oxf) 1995;43:105-10.
11. Arojoki M, Jokimaa V, Juuti A, Koshinen P, Irajala K, Anttila L. Hypothyroidism among infertile women in Finland. Gynecol Endocrinol 2000; 14:127-31.
12. Kalro B. Impaired fertility caused by endocrine dysfunction in women. Endocrinol Metab Clin North Am 2003;32:573-92.
13. Laufer MR, Floor AE, Parsons KE, Kuntz KM, Barbieri RL. Hormone testing in women with adult onset amenorrhea. Gynecol Obstet Invest 1995;40:200-3.
14. Warren MP, Biller BM, Shangold MM. A new clinical option for hormone replacement therapy in women with secondary amenorrhea: effects of cyclic administration of progesterone from the sustained–release vaginal gel Crinone (4% and 8%) on endometrial morphologic features and withdrawal bleeding. Am J Obstet Gynecol 1999;180(pt 1):42-8.
15. Pickett CA. Diagnosis and management of pituitary tumors: recent advances. Prim Care 2003;30:765-89.
16. Folch M, Pigem I, Konje JC. Müllerian agenesis: etiology, diagnosis, and management. Obstet Gynecol Surv 2000;55:644-9.
17. Seldmeyer IL, Palmert MR. Delayed puberty: analysis of a large case series from an academic center. J Clin Endo Metab 2002;87:1613-20.
18. Traggiai C, Stanhope R. Delayed puberty. Best Pract Res Clin Endocrinol Metab 2002;16:139-51.
19. Simpson J, Rajkovic A. Ovarian differentiation and gonadal failure. Am J Med Genet 1999;89:186-200.
20. Webster J, Piscitelli G, Polli A, Ferrari CI, Ismail I, Scanlon MF, et al. A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. N Engl J Med 1994;331:904-9.
21. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists: number 41, December 2002. Obstet Gynecol 2002;100:1389-402.
22. Solomon CG. The epidemiology of polycystic ovary syndrome. Prevalence and associated disease risks. Endocrinol Metab Clin North Am 1999;28:247-63.
23. Chang RJ, Katz SE. Diagnosis of polycystic ovarian syndrome. Endocrinol Metab Clin North Am 1999;28:397-408, vii.
24. Mather KJ, Kwan F, Corenblum B. Hyperinsulinemia in polycystic ovary syndrome correlates with increased cardiovascular risk independent of obesity. Fertil Steril 2000;73:150-6.
25. Velazquez E, Acosta A, Mendoza SG. Menstrual cyclicity after metformin therapy in polycystic ovary syndrome. Obstet Gynecol 1997;90:392-5.
26. Kolodziejczyk B, Duleba AJ, Spaczynski RZ, Pawelczyk L. Metformin therapy decreases hyperandrogenism and hyperinsulinemia in women with polycystic ovary syndrome. Fertil Steril 2000;73:1149-54.
27. Anasti JN. Premature ovarian failure: an update. Fertil Steril 1998;70:1-15.
28. Kalantaridou S, Naka KK, Papanikolaou E, Kazakos N, Kravariti M, Calis KA, et al. Impaired endothelial function in young women with premature ovarian failure: normalization with hormone therapy. J Clin Endocrinol Metab 2004;89:3907-13.
29. Kalantaridou S, Davis SR, Nelson LM. Premature ovarian failure. Endocrinol Metab Clin North Am 1998;27:989-1006.
30. van der Schouw Y, van der Graaf Y, Steyerberg EW, Eijkemans JC, Banga JD. Age at menopause as a risk factor for cardiovascular mortality. Lancet 1996;347:714-8.
31. Jacobsen BK, Nilssen S, Heuch I, Kvale G. Does age at natural menopause affect mortality from ischemic heart disease? J Clin Epidemiol 1997;50:475-9.
32. Kim TJ, Anasti JN, Flack MR, Kimzey LM, Defensor RA, Nelson LM. Routine endocrine screening for patients with karyotypically normal spontaneous premature ovarian failure. Obstet Gynecol 1997;89(5 pt 1):777-9.
33. Miller KK, Parulekar MS, Schoenfeld E, Anderson E, Hubbard J, Klibanski A, et al. Decreased leptin levels in normal weight women with hypothalamic amenorrhea: the effects of body composition and nutritional intake. J Clin Endocrinol Metab 1998;83:2309-12.
34. Welt CK, Chan JL, Bullen J, Murphy R, Smith P, DePaoli AM, et al. Recombinant human leptin in women with hypothalamic amenorrhea. N Engl J Med 2004;351:987-97.
35. Mitan LA. Menstrual dysfunction in anorexia nervosa. J Pediatr Adolesc Gynecol 2004;17:81-5.
36. Drinkwater BL, Nilson K, Ott S, Chesnut CH III. Bone mineral density after resumption of menses in amenorrheic athletes. JAMA 1986;256:380-2.
37. Robinson TL, Snow-Harter C, Taaffe DR, Gillis D, Shaw J, Marcus R. Gymnasts exhibit higher bone mass than runners despite similar prevalence of amenorrhea and oligomenorrhea. J Bone Miner Res 1995;10:26-35.
38. Hergenroeder AC, Smith EO, Shypailo R, Jones LA, Klish WJ, Ellis K. Bone mineral changes in young women with hypothalamic amenorrhea treated with oral contraceptives, medroxyprogesterone, or placebo over 12 months. Am J Obstet Gynecol 1997;176:1017-25.