Concise Review for Primary-Care Physicians

Evaluation and Management of Amenorrhea

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All women who enter menopause experience amenorrhea unless they receive hormone replacement therapy. In younger women, amenorrhea unrelated to pregnancy and lactation can be a distressing symptom. In addition to its psychologic morbidity, amenorrhea may be the manifesting feature of a wide array of anatomic and endocrine abnormalities. Amenorrhea results in impaired fertility. When estrogen levels are low, changes in mineral, glucose, and fat metabolism accompany amenorrhea. These metabolic changes affect bone and cardiovascular health, increasing the risk of osteoporosis and coronary heart disease in later life. Amenorrhea with hyperandrogenism, most commonly caused by the polycystic ovarian syndrome, may cause endometrial hyperplasia and increases the risk of endometrial adenocarcinoma. Because of the broad differential diagnosis of amenorrhea, establishing an accurate diagnosis can prove challenging. In this article, we outline one approach to the assessment of patients with amenorrhea and to the management of its common causes and consequences.

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DHEA-S = dehydroepiandrosterone sulfate; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; PCOS = polycystic ovarian syndrome; TSH = thyroid-stimulating hormone

Disorders of menstruation are among the most common reasons that women seek medical attention. Amenorrhea, the failure of menstrual function, affects all women who reach menopause unless they receive hormone replacement therapy. The loss of estrogen during menopause is associated with alterations in mineral, glucose, and fat metabolism and results in osteoporosis, altered body composition and fat distribution, and increased risk of cardiovascular disease.[1] In younger women, amenorrhea is also associated with considerable morbidity, both physical and psychologic. Of importance, however, amenorrhea is a symptom, not a diagnosis. Finding the underlying cause presents diagnostic challenges to physicians in many specialties, including family practice, internal medicine, gynecology, endocrinology, and pediatrics. Establishing an accurate diagnosis is essential for safe and effective management and to avoid potential complications. The goals of this review are to summarize the differential diagnosis of premature amenorrhea, to outline the complications that may arise, to suggest an approach to the assessment of women with this symptom, and to discuss a rational approach to therapeutic intervention.

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DEFINITION OF AMENORRHEA

Secondary amenorrhea, the most common type, is defined clinically as the absence of menstruation for at least 6 months in a woman with previously normal and regular menses.[2] For women with prior oligomenorrhea, the diagnosis of amenorrhea necessitates up to 12 months without menstrual blood flow or at least six cycle times. Amenorrhea during pregnancy, lactation, and after menopause is, of course, physiologic, but unexpected pregnancy is the leading cause of secondary amenorrhea in young women.

Primary amenorrhea is defined as the absence of spontaneous vaginal bleeding by the age of 14 years in girls without other signs of secondary sexual development. In the presence of otherwise normal development of breasts and pubic hair, primary amenorrhea is diagnosed only at the age of 16 years. Although these definitions are arbitrary, they acknowledge the biologic variability in normal rates of sexual maturation. The mean age of menarche has decreased steadily in the Western world during the past 100 years, probably a result of improved nutrition, and the definitions of primary amenorrhea may require modification in the future.

NORMAL MENSTRUAL CYCLE

The normal menstrual cycle depends on the complex interaction of hormones from the hypothalamus, pituitary, and ovary and on the endometrial response to these hormones.[3] Briefly, the pulsatile production of gonadotropin-releasing

hormone (GnRH) from the hypothalamus causes secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary. Under the influence of FSH, several ovarian follicles begin to grow and develop. The theca cells surrounding these follicles produce androgens that are converted to estrogens by the ovarian granulosa cells, whose growth and function are also under the influence of FSH. As the circulating concentration of estrogen increases, pituitary FSH secretion is inhibited, and most follicles undergo involution. One (or sometimes more) dominant follicle persists, however, by having sufficient numbers of granulosa cells that are maintained by up-regulation of their FSH receptors while FSH concentrations are decreasing. During this phase of the cycle, LH concentrations increase under the influence of estradiol on the pituitary (positive feedback). The granulosa cells express LH receptors that stimulate their production of progesterone. This hormone alters the sensitivity of the pituitary to LH, FSH, and estradiol, an outcome that results in a surge of LH 34 to 36 hours before follicle rupture and ovulation. The granulosa cells continue to produce progesterone for about 14 days but involute thereafter unless pregnancy is established, and embryonic production of chorionic gonadotropin maintains the corpus luteum.

The endometrium responds to the increase in estrogen during the early part of the cycle by increased thickness and vascularity and to progesterone late in the cycle by increased glandular secretion and tortuosity. Withdrawal of sex steroids, by involution of the corpus luteum, results in sloughing of the endometrium and menstrual bleeding.

CAUSES AND TYPES OF AMENORRHEA

Maintenance of a normal menstrual cycle depends on the integrated function of several hormonal systems. Disturbance at any of the several levels can disrupt the normal function and alter the pattern of menstruation or prevent it entirely. As a consequence, the differential diagnosis of amenorrhea is extensive (Table 1).

Pregnancy.—Pregnancy is one of the most common causes of secondary amenorrhea but may also cause primary amenorrhea. Although the first few menstrual cycles after menarche are often anovulatory, this is not always the case. Because it is no longer uncommon for girls to be sexually active in their early to mid teens, a sensitive discussion of this subject and a pregnancy test are necessary in the initial investigation of amenorrhea in women of almost any age.

Primary Amenorrhea.—Primary amenorrhea (Table 1) in patients with normal external genitalia is best categorized according to the presence or absence of breast development and the results of a pelvic examination—that is, presence or absence of a uterus.[4] Ambiguous external genitalia, a suggestion of in utero exposure to androgens, is normally diagnosed at birth or during infancy, but this topic is beyond the scope of this review.

Table 1.—**Causes of Amenorrhea**

- **Primary**
  - Physiologic
    - Constitutional delay of puberty
    - Pregnancy
  - Pathologic
    - *With absent or delayed breast development*
      - Hypothalamic dysfunction
        - Chronic illness
        - Anorexia, weight loss, exercise, "stress"
      - Gonadotropin deficiency
        - Kallmann's syndrome
        - Isolated gonadotropin-releasing hormone deficiency
        - Hypothalamic disease
        - Pituitary disease
      - Gonadal failure
        - Ovarian dysgenesis
      - Chromosomal abnormalities
        - Turner's syndrome (46,XO)
    - *With normal breast development*
      - Other endocrine disease
        - Hypothyroidism
        - Hyperprolactinemia
      - Testicular feminization
      - Genitourinary malformation
- **Secondary**
  - Physiologic
    - Pregnancy
    - Lactation
    - Menopause
  - Pathologic
    - *With features of androgen excess*
      - Polycystic ovarian syndrome
      - Autonomous hyperandrogenism
        - Adrenal or ovarian steroid-producing tumor
        - Ovarian hyperthecosis
      - Late-onset (nonclassic) congenital adrenal hyperplasia
    - *Without hyperandrogenism*
      - Hypergonadotropic hypogonadism
        - Ovarian failure
      - Hyperprolactinemia
      - Hypothyroidism
      - Other endocrine disease
      - Organic hypogonadotropic hypogonadism
        - Hypothalamic disease
        - Pituitary disease
      - Functional hypogonadotropic hypogonadism
        - Hypothalamic amenorrhea
      - Anatomic abnormalities

Absent Breast Development but Normal Pelvic Examination Findings. *Hypothalamic Failure.*—Constitutionally delayed puberty, a normal variant, is the most common cause of primary amenorrhea with delayed puberty. A thorough history often reveals that older siblings and the mother were also "late bloomers." Physical examination shows delayed but otherwise normal development of breasts

and pubic hair and normal findings on a pelvic examination. Psychosocial deprivation may delay pubarche, and amenorrhea rarely may be the manifesting feature of child neglect or abuse. Delayed puberty and primary amenorrhea are also seen commonly in girls with anorexia nervosa, those who exercise excessively, or those who have low reserves of body fat. Investigators have postulated that leptin has a role in these phenomena.[5] Similarly, type I diabetes, inflammatory bowel disease, juvenile rheumatoid arthritis, chronic infections, and malignant lesions all may result in delayed puberty and amenorrhea. The final common pathway through which these processes affect sexual maturation is suppression of pulsatile hypothalamic GnRH secretion by means of central mechanisms that remain poorly understood.

Pituitary Failure.—Isolated GnRH deficiency and Kallmann's syndrome are both extremely rare; they cause pubertal failure because of reduced or absent pituitary FSH secretion. In Kallmann's syndrome, the deficiency of GnRH is associated with anosmia and other subtle neurologic features. It results from failure of migration of GnRH-secreting neurons into the hypothalamus. Gonadotropin (LH and FSH) deficiency may also result from trauma (especially head injury), pituitary adenoma, craniopharyngioma, or infiltrative and inflammatory diseases of the hypothalamus or pituitary (especially sarcoidosis and lymphocytic hypophysitis). Such deficiency is usually seen in association with hypopituitarism that affects several or all of the other pituitary hormones.

Gonadal Failure.—Gonadal dysgenesis is probably the most common cause of complete failure of pubertal development. The cause remains under investigation, and current treatment is limited to hormone replacement therapy and then fertility support.

Turner's Syndrome.—The association of primary amenorrhea, delayed puberty, and short stature may suggest Turner's syndrome. Resulting from the inheritance of only one X chromosome, this syndrome is characterized by short stature, wide-spaced nipples, neck webbing, increased carrying angle of the elbows, and possible mild mental developmental delay. The ovaries are vestigial; thus, little or no estradiol is produced. The rest of the anatomy of the genitourinary tract is normal, however, and hormone substitution results in onset of puberty and menstruation but not fertility.[6] Some patients with Turner's syndrome exhibit a more subtle phenotype, and rarely sexual maturation, menarche, and even fertility occur spontaneously. These cases represent chromosomal mosaicism, in which a variable proportion of cells have a normal karyotype.

Normal Breast Development and Normal Pelvic Examination Findings. *Hypothyroidism and Hyperprolactinemia.*—Both hypothyroidism and hyperprolactinemia can affect children and adolescents. These conditions suppress secretion of GnRH, FSH, and LH and thus inhibit the menstrual cycle. Unless pituitary destruction has reached an advanced stage, pubarche and thelarche are normal. Profound hypothyroidism is a rare cause of precocious puberty; it is usually caused by the FSH-like effect of high levels of thyroid-stimulating hormone (TSH).

Other Causes.—Many of the causes of secondary amenorrhea—most notably, polycystic ovarian syndrome (PCOS) and hypothalamic dysfunction—can also cause primary amenorrhea in a patient with normal findings on physical examination.

Normal Breast Development but Absent Uterus. *Testicular Feminization.*—Profound androgen resistance, caused by a mutation in the androgen receptor,[7] prevents the influence of testicular androgens on the development of a chromosomally male fetus (46,XY karyotype). As a consequence, the newborn is a phenotypically normal female. Internal genitalia, however, are affected by testicular secretion of mullerian-duct inhibitory hormone; thus, development of the upper part of the vagina and uterus is inhibited. Because the testicular tissue is ectopic (intra-abdominal or within the inguinal canal), later malignant transformation is a risk, and surgical removal of the testes is recommended, followed by hormone substitution therapy.

Anatomic Abnormalities.—Failure of development of the uterus, often associated with renal tract anomalies (Rokitansky-Küster-Hauser syndrome), failure of uterovaginal communication (uterovaginal septum), and imperforate hymen are all rare but recognized causes of primary amenorrhea. In the two last-mentioned cases, cyclic pelvic pain is common because of normal hormonal influences on the intact uterine endometrium.

Secondary Amenorrhea.—Secondary amenorrhea can also result from structural causes, although by definition these must be acquired during postpuberty. Obliteration of the uterine cavity can occur during an intrauterine operation, with subsequent fibrous adhesions (Asherman's syndrome), and overzealous curettage or radiotherapy may almost completely destroy the endometrium. Infection, particularly tuberculous, is a rare cause of anatomic secondary amenorrhea. More commonly, however, secondary amenorrhea results from altered endocrine function that affects the hypothalamus, pituitary, or ovary. Broadly, the causes of secondary amenorrhea can be categorized into those with and those without evidence of hyperandrogenism (Table 1).

With Hyperandrogenism. *Polycystic Ovarian Syndrome.*—PCOS is by far the most common hyperandrogenic cause of amenorrhea. Although the term implies an ovarian cause and in the past this diagnosis was made on the basis of pelvic ultrasonography alone, polycystic ovaries merely signify chronic anovulation with continued production of FSH

without ovarian failure. On the basis of previous ultrasound criteria, polycystic ovaries could be diagnosed in up to 20% of normal women; however, because of modern equipment and newer diagnostic criteria, diagnosis with this modality may now be more accurate.[8] Patients with PCOS have an endocrine syndrome of mild to moderate androgen excess (of ovarian origin) in association with chronic ovulatory failure. This results in irregular or absent menses, acne, greasy or oily skin, hirsutism, and, in severe cases, mild virilization. Although patients are anovulatory, estrogen levels remain normal, and these women do not experience the consequences of hypoestrogenism. The chronic endometrial stimulation by estrogen, unopposed by progesterone, may result in dysfunctional uterine bleeding (often misinterpreted as menstrual bleeding) with chronic endometrial hyperplasia and an increased risk of endometrial carcinoma. FSH and LH levels are commonly normal, although the LH:FSH ratio may be increased because of higher than normal LH peaks. Such women are commonly (although not always) overweight and exhibit some degree of insulin resistance and hyperinsulinism, with features of the metabolic syndrome X (abdominal obesity, insulin resistance, predisposition to diabetes or impaired glucose homeostasis, hypertriglyceridemia, hypertension, and premature vascular disease).[9]

Autonomous Hyperandrogenism.—Adrenal or ovarian tumors and ovarian stromal hypertrophy (hyperthecosis) may secrete androgens autonomously beyond the normal feedback control mechanisms. Pronounced virilization may occur, which is commonly more severe than that with PCOS. Amenorrhea in association with frontal balding, severe hirsutism, increased muscle bulk, deepened voice, or clitorimegaly, particularly when the findings are recent or progressive, necessitates a search for an ovarian or adrenal androgen-secreting tumor.

Late-Onset or Mild Congenital Adrenal Hyperplasia.—Although late-onset or mild congenital adrenal hyperplasia is rare in most patient groups, it may also result in secondary amenorrhea and hyperandrogenism. Various partial deficiencies of enzymes within the cortisol biosynthetic pathway have been described, although their cause remains obscure. The most common defect is of the 21-hydroxylase enzyme, which results in an increase of 17-hydroxyprogesterone, a useful diagnostic marker for congenital adrenal hyperplasia.

Without Hyperandrogenism. *Hypergonadotropic Hypogonadism.*—Hypergonadotropic hypogonadism (premature ovarian failure) may be idiopathic, autoimmune, or due to radiotherapy or cytotoxic drugs (particularly cyclophosphamide) administered for malignant disease. Autoimmune ovarian failure may be seen in conjunction with other organ-specific autoimmune diseases, including Addison's disease, type I diabetes, and autoimmune thyroid disease, and autoantibodies against several antigens are commonly detected in the serum. The diagnosis of ovarian failure is usually straightforward because FSH will be in the postmenopausal range (greater than 20 IU/L), whereas estradiol is low (less than 30 pg/mL).

Hyperprolactinemia.—Hyperprolactinemia is most commonly the result of a small pituitary adenoma, which, in and of itself, should not affect pituitary function. It is a common cause of hypogonadotropic amenorrhea and is seen in up to 20% of women with secondary amenorrhea. Prolactin acts directly on the hypothalamus to reduce the amplitude and frequency of pulses of GnRH. Other causes of hyperprolactinemia include drugs (especially the dopamine receptor blocking agents), pituitary and hypothalamic masses (through their effect on the pituitary stalk), and hypothyroidism.

Thyroid Disease and Other Endocrinopathies.—Pronounced thyroid failure is associated with hyperprolactinemia, inasmuch as hypothalamically released thyrotropin-releasing hormone also stimulates secretion of prolactin. There may also be a direct effect of both hypothyroidism and hyperthyroidism on the feedback control of LH, FSH, and estradiol on the hypothalamus and pituitary. Altered menstrual function is a common feature of many endocrine diseases, most likely through a mechanism affecting hypothalamic control of GnRH secretion.

Hypogonadotropic Hypogonadism.—FSH secretion may be impaired directly by destructive processes affecting the pituitary, as well as indirectly by the hyperprolactinemia these processes induce. Pituitary compression or destruction may be caused by a tumor (most commonly an adenoma or craniopharyngioma), inflammation (for example, lymphocytic hypophysitis), infiltration (for example, by sarcoidosis), trauma (head injury or operation), or infarction (Sheehan's syndrome). These conditions rarely cause isolated gonadotropin deficiency, and evidence should be sought for failure of pituitary-adrenal and pituitary-thyroid axes.

Functional Hypothalamic Amenorrhea.—Functional derangement is the most common cause of hypothalamic amenorrhea. Possibly mediated by endorphins, hypothalamic amenorrhea results in abnormal GnRH pulsatility, with consequent reductions in FSH secretion. It is commonly associated with stress, which may be emotional, physical, dietary, or social.

INVESTIGATION OF AMENORRHEA

Investigation of amenorrhea does not often require extensive hormonal or imaging studies and should be guided by a thorough history and detailed physical examination. A pregnancy test should be performed in patients of almost any age.

Primary.—In patients with an absent uterus, the serum testosterone level should be measured to detect functional testicular tissue and a karyotype analyzed to determine chromosomal sex. In the presence of a Y chromosome, the gonadal tissue should be excised because of the risk of later neoplastic change. A normal female level of serum testosterone and 46,XX karyotype suggest congenital absence of the uterus and necessitate a thorough search for other (especially renal tract) anomalies.

If the uterus is intact but breast development is absent, an increased serum FSH value will distinguish peripheral (gonadal failure) from central causes. A high FSH value suggests gonadal dysgenesis or Turner's syndrome; the latter may also be clinically evident and is confirmed by a 46,XO karyotype. A low or normal FSH value in this setting suggests hypothalamic failure or gonadotropin deficiency, a much rarer cause; the latter can be excluded (if necessary) by remeasuring FSH after administration of gonadotropins for a period of several days. Failure of the FSH value to respond suggests a structural cause, and both pituitary and hypothalamic imaging are indicated.

In the presence of both an intact uterus and normal breast development, measurement of serum prolactin and TSH will exclude pronounced hyperprolactinemia and hypothyroidism, respectively. Thereafter, investigation can proceed according to that of secondary amenorrhea.

Secondary.—A thorough history and physical examination are the cornerstones in making the diagnosis of secondary amenorrhea.[10] In particular, previous menstrual and pregnancy history and symptoms of endocrine system disease should be sought. A history of weight changes and a drug, nutrition, and exercise history may also be useful. The physical examination should assess pubertal development and secondary sexual characteristics. Examination of the external genitalia and a pelvic examination are essential in the assessment of possible hyperandrogenism, in which clitorimegaly (defined as a length times width product of greater than 40 mm^2) can be a useful sign.

A suggested plan for the subsequent work-up of patients with secondary amenorrhea is delineated in Figure 1. The initial investigation should include a pregnancy test and determination of fasting glucose, TSH, and prolactin levels. Subsequently, estrogen status should be assessed. The most reliable assessment of estrogen status is the progestin challenge test. A more convenient alternative is measurement of plasma estradiol, FSH, and LH. Oral administration of medroxyprogesterone, 5 to 10 mg daily for 5 to 7 days, will induce withdrawal bleeding in most women with adequate circulating estrogen. In those who do not experience bleeding, some will respond to intramuscular administration of progesterone.[10] In women who do not experience withdrawal bleeding within 2 weeks of these stimuli, the FSH level should be measured; high values indicate ovarian failure, whereas low or inappropriately "normal" values suggest either hypothalamic-pituitary failure (hypogonadotropic hypogonadism) or an acquired uterine abnormality. Confirmation, if necessary, can be obtained with use of a cyclic estrogen and progesterone challenge; no bleeding in response to this hormonal stimulation confirms a uterine abnormality, and gynecologic assessment is necessary. Further testing of pituitary function and possibly imaging of the pituitary and hypothalamus may be necessary in cases of hypogonadotropic hypogonadism.

Women who respond to the progesterone challenge by withdrawal bleeding have adequate estrogen production. A high serum LH concentration in such women strongly supports a diagnosis of PCOS, which can be confirmed by measurement of serum testosterone and dehydroepiandrosterone sulfate (DHEA-S). Although not entirely diagnostic, an increased testosterone level relative to that of DHEA-S suggests an ovarian source for the androgen excess, whereas an increased DHEA-S level relative to that of testosterone supports an adrenal source. In the latter case, the serum 17-hydroxyprogesterone value should be determined; it is increased in the most common variant of late-onset congenital adrenal hyperplasia. Cushing's syndrome also causes increased adrenal steroid secretion and can be excluded with 24-hour urinary free cortisol measurement and dexamethasone suppression testing if indicated.

In women with clinical features of virilization and a substantially increased testosterone (greater than 200 ng/dL) or DHEA-S (greater than 7 μg/mL) level, imaging should be performed to rule out a neoplastic source of androgen production.[11] Computed tomographic scanning of the adrenal glands and ultrasonography of the ovary are the most sensitive imaging modalities. Of note, however, normal findings on ovarian ultrasonography do not completely rule out an ovarian neoplasm, and ovarian exploration may be necessary.

CONSEQUENCES OF AMENORRHEA

A delay or absence in the development of puberty and menstruation may result in considerable anxiety for children and parents, with emotional and behavioral consequences. The trauma associated with a diagnosis of Turner's syndrome, gonadal dysgenesis, testicular feminization, or developmental anomaly can be profound, and specialized psychologic support is essential. In adults, amenorrhea may cause substantial psychologic morbidity, including anxiety, altered self-image, and loss of self-esteem. This is especially true in young women, especially if fertility is desired but impaired. A sympathetic, understanding, and caring approach is needed in dealing with these issues.

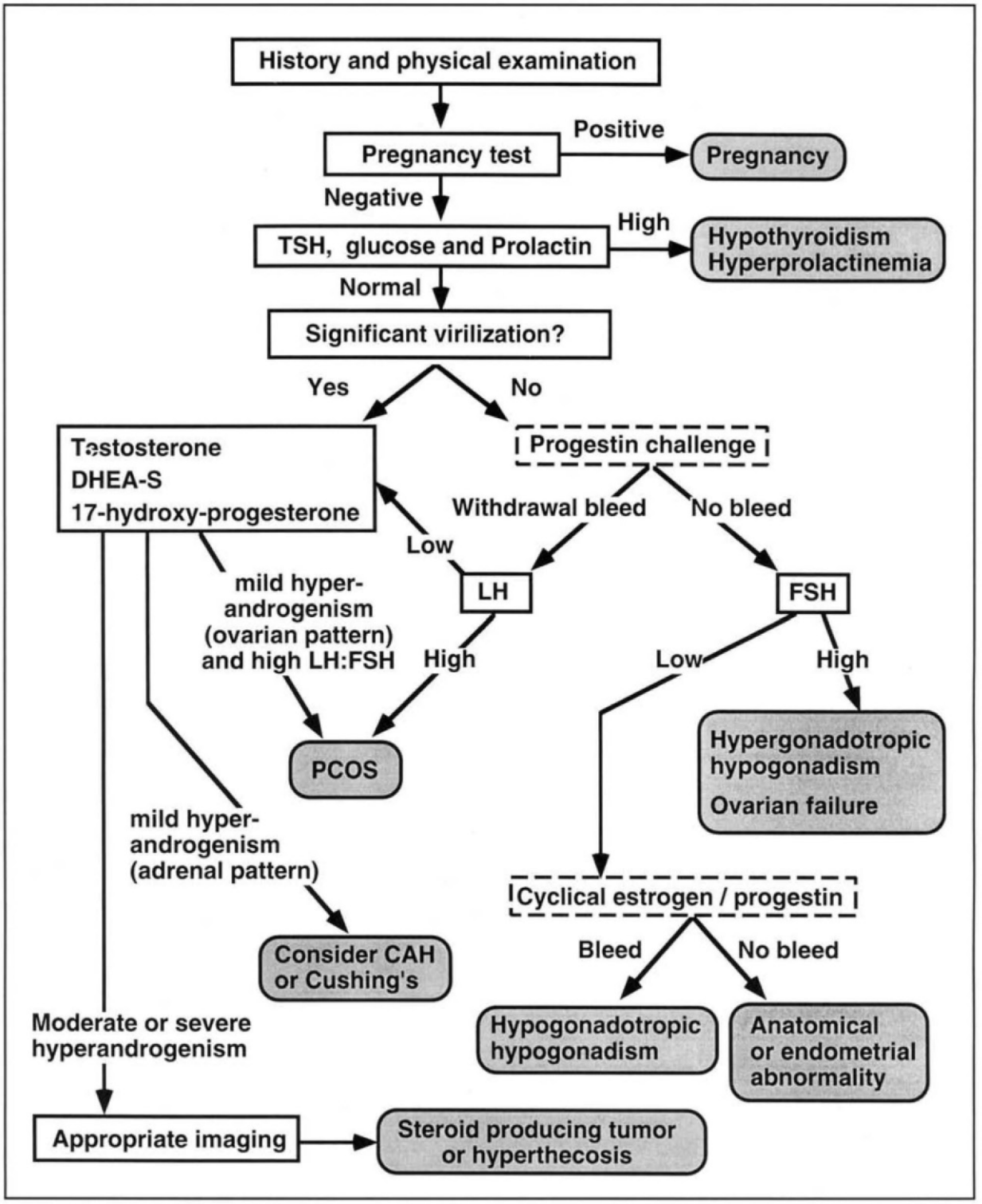

Fig. 1. Suggested algorithm for investigation of secondary amenorrhea. The progestin challenge and cyclic estrogen/progestin challenge may be unnecessary in certain clinical circumstances, and measurement of estradiol, LH, and FSH is often substituted. Patients in the diagnostic groups represented in this algorithm may need further appropriate assessment and management of underlying problem. *CAH* = congenital adrenal hyperplasia; *FSH* = follicle-stimulating hormone; *LH* = luteinizing hormone; *LH:FSH* = LH to FSH ratio; *PCOS* = polycystic ovarian syndrome.

A lack of estrogen, particularly if the circulating levels decrease rapidly, is associated with vasomotor symptoms (hot flushes and night sweats), vaginal dryness, dyspareunia, diminished libido, and anergy.

Low levels of circulating estrogen are also associated with changes in mineral metabolism, allowing increased bone resorption, renal calcium wasting, and relative hyperparathyroidism. Osteoporosis is well recognized in the postmenopausal setting, but young women with pronounced oligomenorrhea or chronic amenorrhea also lose skeletal calcium and in fact may have a greater risk of bone loss than do older women.[12] In young women, amenorrhea may prevent attainment of a desirable peak bone mass (generally achieved at age 35 years), or they may have severe premature bone loss. Both outcomes predispose such women to future osteoporosis, with considerable consequences for their future health.

No studies have addressed the risk of cardiovascular disease in young women with hypoestrogenic amenorrhea. Nevertheless, estrogen decreases low-density lipoprotein, increases high-density lipoprotein, and likely directly affects vascular endothelial and smooth muscle function. In postmenopausal women, hormone replacement therapy has convincingly been shown to decrease the risk of myocardial infarction and death. Chronic hypoestrogenemia in young women may increase their lifetime risk of cardiovascular disease.

The effect of chronic mild hyperandrogenism on the risk of cardiovascular disease in women is unknown, but a clear association has been noted between PCOS and multiple risk factors for vascular disease. In addition, the long-term estrogen stimulation of the endometrium, unopposed by progesterone, results in endometrial hyperplasia and substantially increases the risk of the development of endometrial adenocarcinoma.

MANAGEMENT OF AMENORRHEA

The goals in the treatment of amenorrhea should include the following six steps.

Establish a Firm Diagnosis.—Establishing a firm diagnosis facilitates accurate prediction of prognosis for menstrual function and fertility, if appropriate.

Treat Any Underlying Endocrine or Other Causes of Amenorrhea.—The treatment of hypothyroidism is straightforward. Hyperprolactinemia often responds well to bromocriptine; cabergoline can be administered if bromocriptine is not tolerated or proves to be ineffective. In experienced neurosurgical hands, transsphenoidal excision of a pituitary microprolactinoma is associated with a low rate of complications and a high success rate. Late recurrence rates of up to 20% have been reported, however, even after initial apparent cure; in such cases, further medical or surgical therapy may be necessary. Prolactinomas, even large ones, may shrink substantially with medical treatment, but surgical treatment is necessary for most patients with large tumors that affect vision or create pronounced mass effect and for those in whom medical treatment fails. Assessment of the pituitary-adrenal and pituitary-thyroid axes is essential in patients with macroadenomas.

For adrenal or ovarian androgen-secreting tumors, appropriate surgical intervention is needed, as for mass lesions in the pituitary or hypothalamus.

PCOS may respond to weight loss, which should be encouraged with the help of a registered dietitian and exercise physiologist, if appropriate. Weight loss is also important in modifying the cardiovascular risk in these high-risk patients. Newer drugs that have recently been approved for the treatment of type II diabetes mellitus and that alter insulin sensitivity (metformin and troglitazone) are being investigated as treatment of the underlying metabolic defects in patients with PCOS.

Patients who have hypothalamic amenorrhea may also need assistance from a registered dietitian to achieve weight gain, an exercise physiologist to assist with a modified exercise program, and occasionally a psychologist or psychiatrist to assess and treat the psychologic components of the condition.

Restore Ovulatory Cycles and Treat Infertility. **Primary Amenorrhea.**—For appropriate treatment of primary amenorrhea, an accurate diagnosis is necessary. In cases of gonadal failure, restoration of fertility is not possible, and treatment should be limited to the induction of puberty, maintenance of estrogen status, and induction of menstruation (if the uterus is intact) with use of cyclic estrogen and progesterone therapy.

For constitutional delay, induction of puberty should be undertaken cautiously and certainly at a specialist center. Estrogen is responsible both for the growth spurt and for epiphyseal closure, and thus the timing of menarche and its speed of onset may affect final achieved height in these girls; close monitoring is essential. Short stature is a common feature of Turner's syndrome; growth hormone and estrogen supplementation may increase final height, although precise dosage schedules are unknown.

Secondary Amenorrhea.—Treatment of the underlying cause of secondary amenorrhea is often sufficient to facilitate restoration of a normal ovulatory menstrual cycle in women with reversible causes of amenorrhea, although resumption of normal menstrual patterns may take several months. The physician should emphasize to patients that resumption of menstrual function, when achievable, is likely to be accompanied with resumption of fertility.

Pulsatile GnRH or gonadotropin therapy will induce ovulatory cycles in women with hypothalamic or pituitary

causes of amenorrhea. In most women with PCOS, the FSH level will respond to the antiestrogen clomiphene; this increase in FSH is sufficient to allow maturation of follicles. For patients whose FSH level fails to respond, administration of gonadotropins is effective; however, this approach in patients with PCOS is associated with a high risk of multiple pregnancies.

Some patients require more sophisticated assisted conception, depending on the underlying problem.

Treat Hypoestrogenemia and Hyperandrogenism.—If fertility is not the goal, the most effective treatment of many causes of amenorrhea is estrogen, usually oral contraceptives. In women with an intact uterus, estrogen replacement must be accompanied by progesterone, with the goal of inducing monthly withdrawal bleeding. Although menses will be restored with this approach, fertility will not. Women with PCOS may gain additional benefits from cyclic estrogen and progesterone therapy, which helps to reverse the symptoms of androgen excess. Progesterone withdrawal also results in withdrawal bleeding and negates the risk of endometrial hyperplasia. Although inducing monthly withdrawal bleeding is traditional, bleeding four to six times per year is probably sufficient to avoid the risks of endometrial hyperplasia.

Assess Bone Density and Minimize Further Losses.—Obtaining measurements of bone mineral density is simple, noninvasive, and relatively inexpensive, and such measurements provide an accurate means of assessing the risk of osteoporotic fracture. In patients with low bone mineral density, a repeated measurement after 1 to 3 years facilitates evaluation of the rate of bone loss (or gain) and is useful for assessing response to therapy. All women should be advised to maintain adequate intake of calcium (1,500 mg/day) and vitamin D (400 IU per day), which can minimize bone loss. Restoration of circulating estrogen levels is, however, the most effective method of maintaining bone health. Regardless of the cause, no woman should be hypoestrogenic for prolonged periods, and estrogen replacement is recommended if amenorrhea persists for more than 6 to 12 months.

Assess Global Cardiovascular Risk and Advise Risk Factor Reduction.—In women with PCOS, weight loss may be therapeutic for both the amenorrhea and the cardiovascular risk. Assessment and treatment of hypertension, glucose intolerance, and dyslipidemia should adhere to standard practice.

SUMMARY

Amenorrhea is a common and often distressing symptom that can be caused by a multitude of physiologic and pathologic processes. Establishing an accurate diagnosis can be challenging for both the generalist and the specialist. Nevertheless, the pronounced morbidity associated with amenorrhea and its causes and our increasing ability to intervene to correct the problem make an accurate diagnosis essential and possible. Appropriate treatment of the underlying cause is often possible. If a pathologic cause cannot be corrected, treatment should be directed at preventing the consequences of estrogen deficiency, as well as failure of progesterone withdrawal. In the future, increased understanding of the feedback control of menstruation will probably facilitate further advances in treatment strategies, particularly for women with PCOS, the most common pathologic cause of menstrual dysfunction.

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Questions About Amenorrhea

(See article, pages 1161 to 1168)

1. Which *one* of the following is the *most likely* cause of primary amenorrhea in an otherwise normal 17-year-old adolescent?
   a. Turner's syndrome
   b. Concealed pregnancy
   c. Hyperprolactinemia
   d. Testicular feminization
   e. Anorexia nervosa

2. Which *one* of the following is the *most likely* diagnosis in a 24-year-old woman with secondary amenorrhea who complains of weight gain, acne, hair loss, and depression?
   a. Cushing's syndrome
   b. Late-onset congenital adrenal hyperplasia
   c. Polycystic ovarian syndrome
   d. Hypothalamic amenorrhea
   e. Ovarian hyperthecosis

3. Which *one* of the following is the *least likely* cause of expressible galactorrhea and secondary amenorrhea in a 36-year-old woman who has a serum prolactin concentration of 60 ng/mL?
   a. Antipsychotic medication
   b. Pituitary microadenoma
   c. Pregnancy
   d. Primary thyroid failure
   e. Stress

4. Which *one* of the following is the *most likely* diagnosis in a 32-year-old woman with a 10-year history of Hashimoto's thyroiditis who has development of secondary amenorrhea associated with hot flushes and dyspareunia?
   a. Profound hypothyroidism
   b. Hypothalamic amenorrhea
   c. Hyperprolactinemia
   d. Premature ovarian failure
   e. Polycystic ovarian syndrome

5. Which *one* of the following complications *will not* be prevented by estrogen replacement therapy in a woman with secondary amenorrhea?
   a. Osteoporosis
   b. Premature vascular disease
   c. Endometrial hyperplasia
   d. Dyspareunia
   e. Hot flushes

Correct answers:
1. *b*, 2. *c*, 3. *e*, 4. *d*, 5. *c*