

# Current evaluation of amenorrhea

*The Practice Committee of the American Society for Reproductive Medicine*

Birmingham, Alabama

Amenorrhea is the absence or abnormal cessation of the menses. Primary and secondary amenorrhea describe the occurrence of amenorrhea before and after menarche, respectively. (Fertil Steril® 2008;90:S219–25. ©2008 by American Society for Reproductive Medicine.)

Amenorrhea is the absence or abnormal cessation of the menses (1). Primary and secondary amenorrhea describe the occurrence of amenorrhea before and after menarche, respectively. The majority of the causes of primary and secondary amenorrhea are similar. Timing of the evaluation of primary amenorrhea recognizes the trend to earlier age at menarche and is therefore indicated when there has been a failure to menstruate by age 15 in the presence of normal secondary sexual development (two standard deviations above the mean of 13 years), or within five years after breast development if that occurs before age 10 (2). Failure to initiate breast development by age 13 (two standard deviations above the mean of 10 years) also requires investigation (2). In women with regular menstrual cycles, a delay of menses for as little as one week may require the exclusion of pregnancy; secondary amenorrhea lasting three months and oligomenorrhea involving less than nine cycles a year require investigation.

The prevalence of amenorrhea not due to pregnancy, lactation or menopause is approximately 3% to 4% (3, 4). Although the list of potential causes of amenorrhea is long (Table 1), the majority of cases are accounted for by four conditions: polycystic ovary syndrome, hypothalamic amenorrhea, hyperprolactinemia, and ovarian failure. Other causes are seldom encountered in a typical reproductive medicine practice. In highly specialized referral centres, only 10 to 15 patients per annum were seen with primary amenorrhea, and a similar number with secondary amenorrhea (5–7). The World Health Organization (WHO) has summarized the causes: in WHO group I there is no evidence of endogenous estrogen production, normal or low FSH levels, normal prolactin levels, and no evidence of a lesion in the hypothalamic-pituitary region; WHO group II is associated with evidence of estrogen production and normal levels of prolactin and FSH; and WHO group III involves elevated serum FSH levels indicating gonadal failure (8).

Amenorrhea may occur with sexual ambiguity or virilization, but usually in these cases amenorrhea is not the primary

complaint. The sexual ambiguity or virilization should be evaluated as separate disorders, mindful that amenorrhea is an important component of their presentation (9).

## EVALUATION OF THE PATIENT

History, physical examination, and estimation of follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and prolactin will identify the most common causes of amenorrhea (Fig. 1). The presence of breast development means there has been previous estrogen action. Excessive testosterone secretion is suggested most often by hirsutism and rarely by increased muscle mass or other signs of virilization. The history and physical examination should include a thorough assessment of the external and internal genitalia.

The genital examination is abnormal in approximately 15% of women with primary amenorrhea. A blind or absent vagina with breast development usually indicates Mullerian agenesis, transverse vaginal septum, or androgen insensitivity syndrome. If a genital examination is not feasible, an abdominal ultrasound may be useful to confirm the presence or absence of the uterus.

When the physical examination is normal (the majority of cases), the initial investigations should exclude pregnancy and estimate FSH and prolactin concentrations. Estimation of TSH is useful to rule out subclinical hypothyroidism, even in the absence of thyroid-related symptoms. If there is gonadal failure, a karyotype should be done if the woman is less than 30 years of age to identify chromosomal abnormalities, including the presence of a Y chromosome as may be seen in mosaic Turner syndrome or Swyer syndrome. If the serum prolactin is persistently elevated, and there is no history of medication or drug use that may elevate prolactin, magnetic resonance imaging (MRI) is preferred to identify a pituitary tumor. When FSH values are normal or low, the problem is most often polycystic ovary syndrome or hypothalamic amenorrhea. Tables 2 and 3 show the distribution of the common causes of primary and secondary amenorrhea, respectively, in clinical practice (5–7).

## CAUSES OF AMENORRHEA

### Anatomical Defects

When all or part of the uterus and vagina are absent in the presence of otherwise normal female sexual characteristics,

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**TABLE 1****Classification of amenorrhea (not including disorders of congenital sexual ambiguity).**

- I. Anatomic defects (outflow tract)
  - A. Müllerian agenesis (Mayer-Rokitansky-Kuster-Hauser syndrome)
  - B. Complete androgen resistance (testicular feminization)
  - C. Intrauterine synechiae (Asherman syndrome)
  - D. Imperforate hymen
  - E. Transverse vaginal septum
  - F. Cervical agenesis—isolated
  - G. Cervical stenosis—iatrogenic
  - H. Vaginal agenesis—isolated
    - I. Endometrial hypoplasia or aplasia—congenital
- II. Primary hypogonadism
  - A. Gonadal dysgenesis
    - 1. Abnormal karyotype
      - a. Turner syndrome 45,X
      - b. Mosaicism
    - 2. Normal karyotype
      - a. Pure gonadal dysgenesis
        - i. 46,XX
        - ii. 46,XY (Swyer syndrome)
  - B. Gonadal agenesis
  - C. Enzymatic deficiency
    - 1. 17 $\alpha$ -Hydroxylase deficiency
    - 2. 17,20-Lyase deficiency
    - 3. Aromatase deficiency
  - D. Premature ovarian failure
    - 1. Idiopathic
    - 2. Injury
      - a. Chemotherapy
      - b. Radiation
      - c. Mumps oophoritis
    - 3. Resistant ovary
      - a. Idiopathic
- III. Hypothalamic causes
  - A. Dysfunctional
    - 1. Stress
    - 2. Exercise
    - 3. Nutrition-related
      - a. Weight loss, diet, malnutrition
      - b. Eating disorders (anorexia nervosa, bulimia)
    - 4. Pseudocyesis
  - B. Other disorders
    - 1. Isolated gonadotropin deficiency
      - a. Kallmann syndrome
      - b. Idiopathic hypogonadotropic hypogonadism
    - 2. Infection
      - a. Tuberculosis

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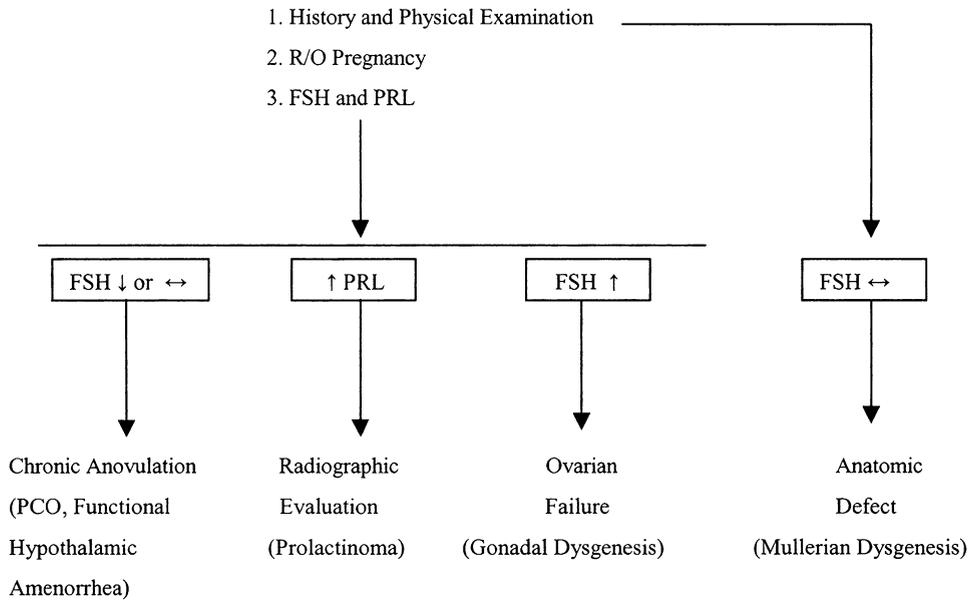
**TABLE 1****Continued.**

- b. Syphilis
    - c. Encephalitis/meningitis
    - d. Sarcoidosis
  - 3. Chronic debilitating disease
  - 4. Tumors
    - a. Craniopharyngioma
    - b. Germinoma
    - c. Hamartoma
    - d. Langerhans cell histiocytosis
    - e. Teratoma
    - f. Endodermal sinus tumor
    - g. Metastatic carcinoma
- IV. Pituitary causes
  - A. Tumors
    - 1. Prolactinomas
    - 2. Other hormone-secreting pituitary tumor (ACTH, thyrotropin-stimulating hormone, growth hormone, gonadotropin)
      - b. Mutations of FSH receptor
      - c. Mutations of LH receptor
    - d. Fragile X syndrome
  - 4. Autoimmune disease
  - 5. Galactosemia
- V. Other endocrine gland disorders
  - A. Adrenal disease
    - 1. Adult-onset adrenal hyperplasia
    - 2. Cushing syndrome
  - B. Thyroid disease
    - 1. Hypothyroidism
    - 2. Hyperthyroidism
  - C. Ovarian tumors
    - 1. Granulosa-theca cell tumors
    - 2. Brenner tumors
    - 3. Cystic teratomas
    - 4. Mucinous/serous cystadenomas
    - 5. Krukenberg tumors
    - 3. Nonfunctional tumors (craniopharyngioma)
    - 4. Metastatic carcinoma
  - B. Space-occupying lesions
    - 1. Empty sella
    - 2. Arterial aneurysm
  - C. Necrosis
    - 1. Sheehan syndrome
    - 2. Panhypopituitarism
  - D. Inflammatory/infiltrative
    - 1. Sarcoidosis
    - 2. Hemochromatosis
    - 3. Lymphocytic hypophysitis
  - E. Gonadotropin mutations (FSH)
- VI. Multifactorial causes
  - A. Polycystic ovary syndrome

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**FIGURE 1**

Suggested flow diagram aiding in the evaluation of women with amenorrhea.



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the diagnosis is usually Mullerian agenesis, which accounts for approximately 10% of cases of primary amenorrhea. Mullerian agenesis is associated with urogenital malformations such as unilateral renal agenesis, pelvic kidney, horseshoe kidney, hydronephrosis, and ureteral duplication. Mullerian agenesis must be differentiated from complete androgen insensitivity because the vagina may be absent or short in both disorders. Complete androgen insensitivity is rare, having an incidence as low as 1 in 60,000 (10), but it comprises approximately 5% of cases of primary amenorrhea (Table 2). The simplest means of distinguishing between Mullerian agenesis and complete androgen insensitivity is by measuring serum testosterone, which is in the normal male range or higher in the latter condition (11). Complete androgen insensitivity is suggested by family history, the absence of pubic hair, and the occasional presence of inguinal masses. The diagnosis can be confirmed by a 46, XY karyotype. The incidence of gonadal malignancy is 22%, but it rarely occurs before age 20 (12). A plan should be established for the timely removal of the gonads following breast development and the attainment of adult stature.

Other anatomic defects include imperforate hymen (1 in 1,000 women), transverse vaginal septum (1 in 80,000 women), and isolated absence of the vagina or cervix (13). These conditions are more likely to present with cyclic pain and an accumulation of blood behind the obstruction which can lead to endometriosis and pelvic adhesions. Amenorrhea after an episode of postpartum endometritis or an operative procedure involving the uterus, particularly curettage for postpartum hemorrhage, elective abortion, or a missed

abortion, is usually due to intrauterine synechiae. If the vaginal opening is patent and the cervix is visualized with a speculum, a sound or probe can confirm the presence or the absence of cervical stenosis or scarring (9). To evaluate intrauterine synechiae, an imaging procedure (hysterosalpingogram, sonohysterogram, or hysteroscopy) is indicated.

### Elevated FSH Levels

Lack of gonadal function is marked by high FSH levels. Gonadal failure can occur at any age, even in utero, when it is usually the result of gonadal agenesis or gonadal dysgenesis. Gonadal failure in genetically XX individuals is ovarian failure; when this occurs at any time before onset of sexual maturation, there will be primary amenorrhea and incomplete breast development. Genetically XY individuals with gonadal failure will have female genitalia because Mullerian inhibiting factor and testosterone will not be produced. Gonadal tumors occur in up to 25% of women with a Y chromosome; unlike complete androgen insensitivity, these gonads do not secrete hormones and should be removed at the time of diagnosis (14).

Gonadal dysgenesis (streak gonads) can occur with normal XX and XY karyotypes and a variety of abnormal karyotypes, most commonly 45,X (Turner syndrome), in which oocyte loss is accelerated after 18 weeks in utero (15, 16). Turner syndrome is often diagnosed in early childhood because of the well-known phenotypic characteristics (short stature, webbed neck and low hairline), and therefore many patients do not present for assessment of primary

<b>TABLE 2</b>	
<b>Common causes of primary amenorrhea (4, 6).</b>	
<b>Category</b>	<b>Approximate frequency (%)</b>
Breast development	30
Mullerian agenesis	10
Androgen insensitivity	9
Vaginal septum	2
Imperforate hymen	1
Constitutional delay	8
No breast development: high FSH	40
46 XX	15
46 XY	5
Abnormal	20
No breast development: low FSH	30
Constitutional delay	10
Prolactinomas	5
Kallman syndrome	2
Other CNS	3
Stress, weight loss, anorexia	3
PCOS	3
Congenital adrenal hyperplasia	3
Other	1

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amenorrhea. Uncommon causes of ovarian failure include FSH or LH receptor mutations (17, 18), galactosemia, 17  $\alpha$ -hydroxylase or 17,20-lyase deficiency, and aromatase deficiency (19–21).

In premature ovarian failure (POF), amenorrhea, persistent estrogen deficiency, and elevated FSH levels occur prior to the age of 40, and this condition affects 1% to 5% of women (22, 23). Iatrogenic causes of POF, such as chemotherapy and radiation therapy for malignancy, have a potential for recovery. Ovarian function may fluctuate, with increasingly irregular menstrual cycles before the final depletion of oocytes and permanent ovarian failure. The resulting fluctuation in gonadotropin levels accounts for the lack of accuracy associated with a single FSH value (24).

Ovarian failure is confirmed by documenting an FSH level persistently in the menopausal range. In women under 30 with POF, a karyotype should be obtained to rule out sex chromosome translocation, short arm deletion, or the presence of an occult Y chromosome, which is associated with an increased risk of gonadal tumors. About 16% of women who are carriers of the premutation of Fragile X syndrome experience premature menopause (19). A thorough family history should be obtained because several autosomal disorders have been associated with ovarian failure, including mutations of the phosphomannomutase 2 (PMM2) gene, the galactose-1-phosphate uridylyltransferase (GALT) gene, the FSH receptor (FSHR) gene, chromosome 3q containing the Blepharophthalmosis gene, and the autoimmune regulator (AIRE) gene, re-

sponsible for polyendocrinopathy-candidiasis-ectodermal dystrophy (25). A further indication for karyotype and genetic investigation is that some patients with POF have children for whom the genetic information may be useful.

Up to 40% of women with POF may have autoimmune abnormalities, most commonly autoimmune thyroiditis (26, 27). POF is slightly more common in women with insulin-dependent diabetes mellitus, myasthenia gravis, and parathyroid disease than in healthy women (28). Autoimmune lymphocytic oophoritis may be seen in Addison's disease, in which 10% to 60% of cases may have ovarian failure, but this condition is extremely rare (1 per million women). Ovarian biopsy is not indicated in clinical practice, but because autoimmune POF could be a component of a polyglandular syndrome, patients can be screened for other abnormalities by means of TSH, thyroid autoantibodies, fasting glucose, and electrolytes (29). Thyroid autoantibodies may increase the ability to identify individuals likely to develop subsequent primary hypothyroidism. No currently available validated serum antibody marker can confirm a clinical diagnosis of autoimmune premature ovarian failure. Also, at this time, no therapy for infertile patients with autoimmune ovarian failure has been proven effective in a prospective controlled study.

Patients with ovarian failure should be offered estrogen and progestin treatment to promote and maintain secondary sexual characteristics and reduce the risk of developing osteoporosis. In adolescents with gonadal failure, the aim is to

<b>TABLE 3</b>	
<b>Common causes of secondary amenorrhea (5).</b>	
<b>Category</b>	<b>Approximate frequency (%)</b>
Low or normal FSH	66
Weight loss/anorexia	
Non-specific hypothalamic	
Chronic anovulation including PCOS	
Hypothyroidism	
Cushing's syndrome	
Pituitary tumor, empty sella, Sheehan syndrome	
Gonadal failure: high FSH	12
46 XX	
Abnormal karyotype	
High prolactin	13
Anatomic	7
Asherman syndrome	
Hyperandrogenic states	2
Ovarian tumor	
Non-classic CAH	
Undiagnosed	

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mimic pubertal development with low-dose estrogens, increasing gradually to augment breast development, avoiding progestin until the breast mound and areola have developed. Rarely, some ovarian follicles remain in women with ovarian failure so that spontaneous ovulation and conception are possible, even in women taking exogenous estrogen with or without a progestogen (29).

### Elevated Prolactin Levels

Hyperprolactinemia is associated with decreased estradiol concentrations and amenorrhea or oligomenorrhea. Prolactin concentrations are higher in women with amenorrhea than in those with oligomenorrhea (30). With persistent hyperprolactinemia, after ruling out primary hypothyroidism, MRI of the pituitary is indicated. Mildly elevated prolactin levels may be a sign of another organic central nervous system lesion, such as congenital aqueductal stenosis, non-functioning adenomas, or any condition which causes pituitary stalk irritability. In women with hyperprolactinemia, the prevalence of a pituitary tumor is 50% to 60% (31). The likelihood of a pituitary tumor was unrelated to the level of prolactin (31), and only 16% of the variability in tumor size was associated with prolactin level ( $r=0.40$ ,  $p<.001$ ) (32).

Usually, however, patients with amenorrhea have larger tumors than patients with oligomenorrhea. The poor correlation between tumor presence and prolactin level indicates that MRI should be performed whenever prolactin levels are persistently elevated. In most amenorrheic women with hyperprolactinemia, prolactin levels do not decline without treatment, and the amenorrhea does not resolve as long as the prolactin levels remain elevated (30, 32). In the absence of another organic condition, dopamine agonists are the preferred treatment of hyperprolactinemia with or without a pituitary tumor.

### Normal or Low FSH Levels

Amenorrhea associated with normal or low FSH values and chronic anovulation is frequently unexplained. The most common diagnostic categories are hypothalamic amenorrhea and polycystic ovary syndrome, and in each case similar but less common conditions must be excluded. Hypothalamic amenorrhea is characterized by inconsistent GnRH drive, while in polycystic ovary syndrome GnRH pulses are persistently rapid or increased, leading to excessive LH synthesis, hyperandrogenism, and impaired follicular maturation (33). Differentiating hypothalamic amenorrhea from polycystic ovary syndrome depends on clinical judgment aided by the presence of obesity and androgenization, which are typical features of polycystic ovary syndrome. This judgment also is relevant to the prognosis because obesity and androgenization tend to reduce the likelihood of conception (34).

Estradiol concentration does not effectively distinguish between hypothalamic amenorrhea and polycystic ovary syndrome. Although hypothalamic amenorrhea implies that levels of estradiol should be low, while normal levels of estradiol are expected with polycystic ovary syndrome, estradiol

concentrations tend to fluctuate and each condition is associated with both normal and low estrogen production. As an indication of endogenous estrogen levels, the duration of the amenorrhea and clinical features are more important than measurement of estradiol, the progesterone challenge test, or presence of cervical mucus. Although the progesterone challenge test might seem to characterize estrogen production, withdrawal bleeding correlates poorly with estrogen status and the test imposes a delay on the diagnostic process. The false positive rate is high: up to 20% of women with oligomenorrhea or amenorrhea in whom estrogen is present have no withdrawal bleeding (35). The false negative rate is also high; withdrawal bleeding occurs in up to 40% of women with amenorrhea due to stress, weight loss, exercise, or hyperprolactinemia where estrogen production is usually reduced (36) and in up to 50% of women with ovarian failure (29).

### Hypothalamic Amenorrhea

Functional disorders of the hypothalamus or higher centers are the most common reason for chronic anovulation. Psychogenic stress, weight changes, undernutrition, and excessive exercise are frequently associated with functional hypothalamic amenorrhea, but the pathophysiologic mechanisms are unclear. More cases of amenorrhea are associated with weight loss than with anorexia, which is rare (15 cases per 100,000 women per year), but amenorrhea with anorexia nervosa is more severe (37, 38). Women involved in competitive sports activities have a three-fold higher risk of primary or secondary amenorrhea than others, and the highest prevalence is among long-distance runners (39). Infrequently, hypothalamic dysfunction occurs before menarche and presents as primary amenorrhea in approximately 3% of adolescents; usually secondary sexual characteristics will develop and menstrual cycles will evolve without therapy (40).

Chronic debilitating diseases, such as uncontrolled juvenile diabetes, end-stage kidney disease, malignancy, acquired immune deficiency syndrome, or malabsorption, which are uncommon in women of reproductive age, may lead to anovulation and amenorrhea through a central mechanism.

Other rare causes of hypothalamic amenorrhea include isolated gonadotropin deficiency. This is most often due to Kallmann syndrome, which is associated with defects in olfactory bulb development. Thus, these women may have anosmia as well as amenorrhea and low gonadotropins due to gonadotropin-releasing hormone (GnRH) deficiency (41). Mutations in gonadotropin-releasing hormone receptor genes also may be associated with hypogonadotropic hypogonadism (42). Pituitary disorders that cause anovulation include Sheehan syndrome, necrosis of the pituitary gland, and empty sella syndrome (43). When amenorrhea persists and stress, excessive exercise, or weight loss can be confidently excluded as causes, MRI may be indicated to rule out organic disease in the central nervous system, hypothalamus, or pituitary gland.

Women with hypothalamic amenorrhea are susceptible to the development of osteoporosis (44). Unless the primary cause can be easily treated, cyclic estrogen-progestin therapy

or oral contraceptive pills should be initiated to prevent excessive bone loss. If pregnancy is desired, good nutrition and optimal body weight are important objectives but may be difficult to achieve. Ovulation induction with clomiphene citrate, exogenous gonadotropins, or pulsatile GnRH therapy should be offered (45).

### Polycystic Ovary Syndrome

When amenorrhea is associated with evidence of androgen excess, the most common disorder is polycystic ovary syndrome (PCOS). Less commonly, amenorrhea with hyperandrogenism arises from adrenal diseases, such as non-classical adrenal hyperplasia and Cushing syndrome or from androgen-producing tumors (46). Other disorders that may cause chronic anovulation (Table 1) are much less common than PCOS, and in each case special characteristics are likely to direct the investigation toward a specific diagnosis.

PCOS is characterized by menstrual disturbances ranging from dysfunctional uterine bleeding to oligomenorrhea and amenorrhea, hyperandrogenism, and infertility. Seventy-five percent of North American women with PCOS are obese (47). PCOS patients are more likely to present with oligomenorrhea (76%) than amenorrhea (24%) (34, 48). The symptoms often occur first at menarche, but the signs of androgen excess may not become evident until several years later and these signs increase over time.

The 1990 National Institutes of Health/National Institute of Child Health and Human Development (NIH/NICHHD) criteria for PCOS, although not a consensus, were as follows: (1) ovulatory dysfunction, (2) clinical evidence of hyperandrogenism (hirsutism, acne, androgenic alopecia) and/or hyperandrogenemia, and (3) exclusion of other related disorders such as hyperprolactinemia, thyroid abnormalities, and non-classical adrenal hyperplasia (49). An international consensus conference held in 2003 concluded that the syndrome “encompasses a broader spectrum of signs and symptoms of ovarian dysfunction than those defined by the original diagnostic criteria” (50). Therefore, participants concluded that individuals must have two out of three of the following features to be classified as having PCOS:

- 1 Oligo- and/or anovulation.
- 2 Clinical and/or biochemical signs of hyperandrogenism.
- 3 Ultrasound evidence of polycystic ovaries.

In addition, other etiologies such as congenital adrenal hyperplasia, androgen secreting tumors, and Cushing syndrome must have been excluded. This definition is open to challenge because at least one study has noted that ultrasonographic criteria for diagnosis of PCOS are not useful because one-fifth of women with regular cycles have ovaries that appear polycystic (51). Many of the participants of the conference argued that hyperandrogenic women with PCOS may have regular menstrual cycles. No doubt the definition will continue to evolve with new research findings.

Although several endocrine abnormalities are associated with PCOS, there is no universally accepted definition based

on hormonal criteria. Serum androgen levels usually range from upper normal to two-fold higher than normal in women with PCOS. Prolactin levels are mildly elevated in 10% to 25% of women with PCOS. The LH/FSH ratio may be greater than 2, but gonadotropin values are not useful to confirm the diagnosis (47, 49–51).

Women with PCOS are frequently insulin resistant; insulin sensitivity is reduced by 30% to 40%, leading to hyperinsulinemia, but the insulin response may be inadequate because of beta-cell dysfunction. Thus, PCOS patients are pre-disposed to glucose intolerance (52). Impaired glucose tolerance occurs in 31% of PCOS patients, but fasting glucose is elevated in only 7.5%. It can be argued that women with PCOS should be screened for type 2 diabetes (52, 53). Obesity further exacerbates insulin resistance, and higher insulin concentrations are associated with higher androgen levels (34).

### CONCLUSIONS

- Amenorrhea is an uncommon presentation in reproductive medicine.
- The four most common causes are polycystic ovary syndrome, hypothalamic amenorrhea, ovarian failure, and hyperprolactinemia.
- The initial useful laboratory tests are FSH, TSH, and prolactin.
- Differentiating hypothalamic amenorrhea from polycystic ovary syndrome depends on clinical judgment, aided by the presence or absence of androgenization.

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