associated with eating disorders. Women with anorexia nervosa are also at risk for preterm labor and delivery by Cesarean section (58–60). Finally, although it is not known whether prolonged hypoestrogenism is associated with cardiovascular risk in premenopausal women, several studies using premenopausal monkeys have linked socially induced reproductive suppression to exacerbated coronary artery atherosclerosis (61, 62).

1.0 Diagnosis, differential diagnosis, and evaluation

1.1 We suggest that clinicians only make the diagnosis of FHA after excluding the anatomic or organic pathology of amenorrhea. (Ungraded Good Practice Statement)

Evidence

Clinicians can use the menstrual period in adolescent girls to recognize estrogen status and identify underlying problems (53, 63, 64). Absent or irregular menses and estrogen deficiency due to insufficient stimulation or suppression of the HPO axis in the absence of anatomic or organic pathology characterizes FHA. In this context, we use the term "organic" for those cases of amenorrhea with inappropriately low gonadotropin levels where a clear pathologic etiology exists (these might include cases where gonadotropin levels are within the laboratory reference range). We must consider a broad differential diagnosis in these cases to make certain that we have excluded underlying etiologies that may be manifesting as amenorrhea (Table 1) (65–69). Other than pregnancy, FHA and PCOS are the most common causes of secondary amenorrhea (65, 70).

Overall, we recognize three main underlying causes of FHA: weight loss, and/or vigorous exercise, and/or stress (5, 20, 21, 65, 71). These distinctions allow for the inclusion of underweight and normal-weight women and acknowledge that the etiology may vary and represent a combination of factors. Regardless of the trigger, FHA is characterized by abnormalities in GnRH secretion or dynamics (4, 33, 72). An energy deficit (which can occur independent of changes in body weight) appears to be the critical factor in both the weight loss and exercise-induced forms of FHA. In 2003, Loucks and Thuma (17) set the threshold for energy availability at 30 kcal/kg (in an acute setting), below which LH pulsatility is disrupted (73). Williams *et al.* (74) estimated that experimental reduction of energy by 470 and 810 kcal per day led to an increased frequency of menstrual disturbance. We need more studies to determine the average threshold below which women who exercise or have low dietary intake are at risk for developing menstrual disturbances. It is possible that energy thresholds vary among and

Table 1. Potential Etiologies of Amenorrhea

Congenital malformation
Septo-optic dysplasia
Holoprosencephaly
Encephalocele
Constitutional delay
Genetic conditions
Congenital deficiency of hypothalamic or pituitary transcription factors (gonadotropin deficiency)
Single-gene mutations (hypogonadotropic hypogonadism)
Hyperprolactinemia
Pituitary gland or stalk damage
Tumors and cysts [hypothalamic or pituitary tumor (hormone-secreting), craniopharyngioma, Rathke cleft cyst, other cysts, and tumors]
Infiltrative disorders (germinoma, autoimmune hypophysitis, sarcoidosis, hemochromatosis, tuberculosis, Langerhans cell histiocytosis, IgG4-related hypophysitis)
Irradiation
Infarction [apoplexy in pre-existing pituitary tumors, or following postpartum hemorrhage (Sheehan syndrome)]
Surgery
Trauma
Others
Eating disorders
Competitive athletics
Chronic disease
Mood disorders
Stress or psychiatric illness
Drugs
Thyroid
Hypothyroidism or hyperthyroidism
Adrenals
Congenital adrenal hyperplasia (select types)
Cushing syndrome
Addison disease (adrenal insufficiency)
Tumor (androgen-secreting)
Ovaries
Associated with high levels of gonadotropins
Gonadal agenesis or dysgenesis (in the setting of Turner syndrome/other)
Ovarian insufficiency
Autoimmune oophoritis
Irradiation or surgery
Not associated with high levels of gonadotropins
Polycystic ovary syndrome
Tumor (estrogen- or androgen-secreting)
Uterus (eugonadism)
Müllerian anomalies (obstructive outflow anomalies)
Asherman syndrome
Synechiae (integral to Asherman syndrome)
Pregnancy
Infectious (*e.g.,* tuberculous endometritis)
Agenesis (uterine or cervical)
Vagina (eugonadism)
Agenesis
Transverse septum
Hymen (eugonadism)
Imperforate