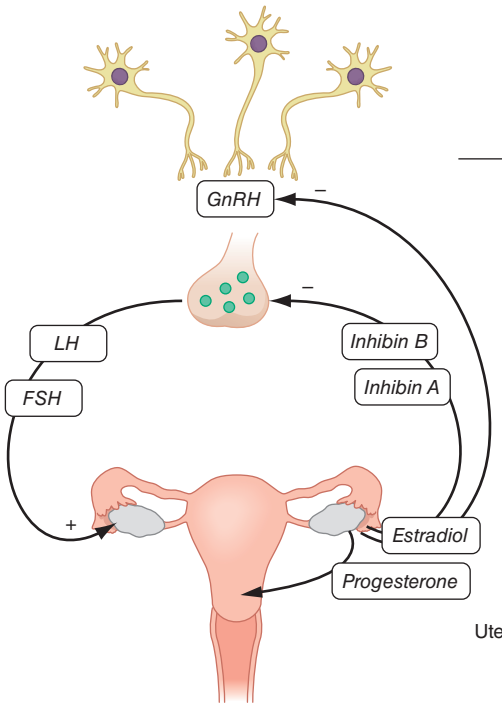

	Primary	Secondary
Hypothalamus	27%	36%
Pituitary	2%	15%
PCOS	7%	30%
Ovary	43%	12%
Uterus/outflow tract	19%	7%

FIGURE 69-1 Role of the hypothalamic-pituitary-gonadal axis in the etiology of amenorrhea. Gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus stimulates follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion from the pituitary to induce ovarian folliculogenesis and steroidogenesis. Ovarian secretion of estradiol and progesterone controls the shedding of the endometrium, resulting in menses, and, in combination with the inhibins, provides feedback regulation of the hypothalamus and pituitary to control secretion of FSH and LH. The prevalence of amenorrhea resulting from abnormalities at each level of the reproductive system (hypothalamus, pituitary, ovary, uterus, and outflow tract) varies depending on whether amenorrhea is primary or secondary. PCOS, polycystic ovarian syndrome.

TREATMENT DISORDERS OF THE UTERUS OR OUTFLOW TRACT

Obstruction of the outflow tract requires surgical correction. The risk of endometriosis is increased with this condition, perhaps because of retrograde menstrual flow. *Müllerian agenesis* also may require surgical intervention to allow sexual intercourse, although vaginal dilatation is adequate in some patients. Because ovarian function is normal, assisted reproductive techniques can be used with a surrogate carrier. *Androgen resistance syndrome* requires gonadectomy because there is risk of gonadoblastoma in the dysgenetic gonads. Whether this should be performed in early childhood or after completion of breast development is controversial. Estrogen replacement is indicated after gonadectomy, and vaginal dilatation may be required to allow sexual intercourse.

Disorders of Ovulation Once uterus and outflow tract abnormalities have been excluded, other causes of amenorrhea involve disorders of ovulation. The differential diagnosis is based on the results of initial tests, including a pregnancy test, an FSH level (to determine whether the cause is likely to be ovarian or central), and assessment of hyperandrogenism (Fig. 69-2).

HYPOGONADOTROPIC HYPOGONADISM Low estrogen levels in combination with normal or low levels of LH and FSH are seen with anatomic, genetic, or functional abnormalities that interfere with hypothalamic GnRH secretion or normal pituitary responsiveness to GnRH. Although relatively uncommon, tumors and infiltrative diseases should be considered in the differential diagnosis of hypogonadotropic hypogonadism (Chap. 403). These disorders may present with primary or secondary amenorrhea. They may occur in association with other features suggestive of hypothalamic or pituitary dysfunction, such as short stature, diabetes insipidus, galactorrhea, and headache. Hypogonadotropic hypogonadism also may be seen after cranial irradiation. In the postpartum period, it may be caused by pituitary necrosis (Sheehan's syndrome) or lymphocytic hypophysitis. Because reproductive dysfunction is commonly associated with hyperprolactinemia from neuroanatomic lesions or medications, prolactin should be measured in all patients with hypogonadotropic hypogonadism (Chap. 403).

Isolated hypogonadotropic hypogonadism (IHH) occurs in women, although it is three times more common in men. IHH generally presents with primary amenorrhea, although 50% have some degree of breast development, and one to two menses have been described in ~10%. IHH is associated with anosmia in about 50% of women (termed Kallmann's syndrome). Genetic causes of IHH have been identified in ~60% of patients (Chaps. 411 and 412).

Functional hypothalamic amenorrhea (HA) is caused by a mismatch between energy expenditure and energy intake. Recent studies suggest that variants in genes associated with IHH may increase susceptibility to these environmental inputs, accounting in part for the clinical variability in this disorder. Leptin secretion may play a key role in transducing the signals from the periphery to the hypothalamus in HA. The hypothalamic-pituitary-adrenal axis also may play a role. The diagnosis of HA generally can be made on the basis of a careful history, a physical examination, and the demonstration of low levels of gonadotropins and normal prolactin levels. Eating disorders and chronic disease must be specifically excluded. An atypical history, headache, signs of other hypothalamic dysfunction, or hyperprolactinemia, even if mild, necessitates cranial imaging with computed tomography (CT) or magnetic resonance imaging (MRI) to exclude a neuroanatomic cause.

HYPERGONADOTROPIC HYPOGONADISM Ovarian failure is considered premature when it occurs in women <40 years old and accounts for ~10% of secondary amenorrhea. *Primary ovarian insufficiency* (POI) has generally replaced the terms *premature menopause* and *premature ovarian failure* in recognition that this disorder represents a continuum of impaired ovarian function. Ovarian insufficiency is associated with the loss of negative-feedback restraint on the hypothalamus and pituitary, resulting in increased FSH and LH levels. FSH is a better marker of ovarian failure as its levels are less variable than those of LH. Antimüllerian hormone (AMH) levels will also be low in patients with POI, but are more frequently used in management of infertility. As with natural menopause, POI may wax and wane, and serial measurements may be necessary to establish the diagnosis.

Once the diagnosis of POI has been established, further evaluation is indicated because of other health problems that may be associated with POI. For example, POI occurs in association with a variety of chromosomal abnormalities, including Turner's syndrome, autoimmune polyglandular failure syndromes, radio- and chemotherapy, and galactosemia. The recognition that early ovarian failure occurs in premutation carriers of the fragile X syndrome is important because of the increased risk of severe mental retardation in male children with *FMR1* mutations. In the majority of cases, a cause for POI is not determined. Although there are increasing reports of genetic mutations in individuals and families with POI, testing for other than chromosomal abnormalities and *FMR1* mutations is not recommended.