part for the clinical variability in this disorder. Metabolic and stress signaling is transduced to the reproductive axis, at least in part, through leptin signaling from the periphery and via hypothalamic kisspeptin control of GnRH. 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, excessive exercise, and chronic disease must be specifically excluded. An atypical history, headache, signs of other hypothalamic dysfunction, or hyperprolactinemia, even if mild, necessitates cranial magnetic resonance imaging (MRI) to exclude a neuroanatomic cause. Up to 10% of women with HA may have some features of PCOS (irregular menses, increased ovarian volume with polycystic appearing ovaries, higher anti-müllerian hormone [AMH] levels, and slightly elevated androgen levels).

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 replaced the terms *premature menopause* and *premature ovarian failure* in recognition of the continuum of impaired ovarian function encompassed by this disorder. 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 because of loss of negative feedback effects of both estradiol and the inhibins and because its levels are less variable than those of LH. 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. The presentation may include irregular menses or complete cessation of menses, hot flashes, and vaginal dryness.

Once the diagnosis of POI has been established, further evaluation is indicated because of other health problems that may be associated with POI. Although POI is most commonly of unknown cause, it also occurs in association with a variety of chromosomal abnormalities (most often Turner's syndrome), autoimmune polyglandular failure syndromes, and other rare disorders.