tests: β-human chorionic gonadotropin, complete blood count, electrolytes, glucose, bicarbonate, blood urea nitrogen, creatinine, liver panel, and (when appropriate) sedimentation rate and/or C-reactive protein levels. (1|⊕⊕⊕⊕)

Evidence

General laboratory testing, beginning with a β-human chorionic gonadotropin to rule out pregnancy, initiates a comprehensive workup for the adolescent or young woman with FHA. Clinicians should obtain a complete blood count, chemistry panel, liver panel, sedimentation rate, and/or C-reactive protein level in those suspected to have a chronic illness manifesting as hypogonadism. An elevated random or fasting glucose level should prompt clinicians to measure hemoglobin A1C. A high sedimentation rate and/or C-reactive protein level suggests a chronic inflammatory condition. Studies have shown that liver function tests are altered in adolescents and young women with extreme energy restrictions (131–133). However, data to support the cost-effectiveness of specific screening assessments are lacking (65).

2.4 As part of an initial endocrine evaluation for patients with FHA, we recommend obtaining the following laboratory tests: serum TSH, free T4, prolactin, LH, FSH, E2, and AMH. Clinicians should obtain total testosterone and DHEA-S levels in patients with clinical hyperandrogenism and 8 AM 17-hydroxyprogesterone levels if clinicians suspect late-onset CAH. (1|⊕⊕⊕⊕)

Evidence

If properly interpreted, a panel that includes TSH, free T4, prolactin, FSH, E2, and total testosterone detects the most important causes of amenorrhea. The pattern of hormone levels is more critical than absolute values. Patients with FHA have characteristically low or low normal LH, normal FSH concentrations (which are usually higher than LH concentrations), E2 <50 pg/mL, and progesterone <1 ng/mL; the acute gonadotropin response to GnRH stimulation is preserved (defined as a twofold to threefold rise in LH and FSH compared with baseline levels). E2 measurements are typically limited by the fact that a measurement reflects a single time point, and no single E2 value can confirm a diagnosis of FHA. However, in patients whose E2 is persistently <20 pg/mL, the response to GnRH is the only feature that may differentiate FHA from hypogonadotropic hypogonadism. With the latter diagnosis, the acute LH response would be low, but normalizes with prolonged pulsatile GnRH therapy. For E2, clinicians should follow Endocrine Society guidelines to assure assay validity and reliability (134). In FHA, thyroid function is similar to that seen with any chronic illness, that is, TSH and free T4 levels in the lower range of normal, which generally reverse to normal with weight gain and psychological recovery (5, 24, 134). Testosterone will be in the lower range of normal, and prolactin will be in the low normal range (65).

In the absence of signs of androgen excess, measuring FSH, LH, prolactin, TSH, and free T4 will generally provide sufficient information to rule out organic causes of amenorrhea or irregular menstrual cycles, including ovarian insufficiency, hyperprolactinemia, and thyroid dysfunction (primary). Elevated FSH and LH levels with low E2 (<20 pg/mL) and progesterone (<1 ng/mL) indicate low or absent ovarian reserve consistent with complete or impending ovarian insufficiency. In contrast, high FSH and LH levels with E2 >150 pg/mL and progesterone <2 ng/mL indicate the midcycle gonadotropin surge. In FHA, LH and FSH are often normal, a confusing point to clinicians, as E2 levels are low and LH/FSH ratios may be elevated when a patient has underlying PCOS. Very low and often undetectable LH and FSH levels suggest organic hypothalamic amenorrhea due to genetic mutations affecting GnRH ontogeny and function or central causes, such as pituitary, hypothalamic, or other brain tumors, and infiltrative lesions (Table 2). Evaluating basal pituitary hormones is usually sufficient to establish hypopituitarism, and pituitary stimulation tests often do not determine the causes of the pituitary hypofunction.

Assessing thyroid function and prolactin levels is important in adolescents and women with FHA (65). Food, sleep, exercise, coitus, nipple stimulation, breast examination, lactation, and many medications can elevate prolactin concentrations. If a patient has more profound hyperprolactinemia (serum prolactin >100 ng/mL), she will require additional evaluation that is beyond the scope of this guideline. If TSH is low, one should consider a diagnostic assessment for thyrotoxicosis, especially if the free T4 is high. Similarly, if TSH is high, and free T4 is low or in the lower range of normal, then clinicians must consider subclinical hypothyroidism or hypothyroidism. Conversely, a normal or minimally elevated TSH with a low free T4 may indicate central hypothyroidism.

In the workup for hyperandrogenism, familiarity with local reference ranges is important, as assays are not standardized across laboratories. Clinicians should obtain total or free testosterone levels (depending on assay reliability and noting that the former is usually more accurate) (135). Clinicians should also consider measuring serum DHEA-S to rule out adrenal etiologies (136). Some experts consider an elevated free testosterone level (measuring both total and free testosterone using a gold standard assay) the most useful indicator of PCOS

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