Table 2. Common Causes of Anovulation and Accompanying Laboratory Patterns

	LH (IU/L)	FSH (IU/L)	LH/FSH	E2 (pg/mL)	P4 (ng/mL)	AMH (ng/mL)	PRL (ng/mL)	TSH (μU/mL)	T4 (μg/dL)	DHEA-S (μg/dL)	17OHP (ng/dL)	T (ng/dL)
Functional hypothalamic anovulation	<10	<10	~1	<50	<1	>1	Low nl	Low nl	Low nl	nl	nl	Low nl
Ovarian insufficiency menopause	>15	>15	FSH > LH	<50	<1	<0.5	nl	nl or ↑	nl or ↓	nl	nl	Low nl
PCOS	<15	<10	LH > FSH	<50	<1	nl or ↑	High nl	nl	nl	High nl	nl	High nl or slight↑
Nonclassical CAH	<15	<10	LH > FSH	<50	≤1	nl	nl	nl	nl	High nl	↑	↑
Hyperprolactinemia	<10	<10	LH < FSH	<50	<1	nl	↑	nl or ↑	nl	nl or slight ↑	nl	nl

Abbreviations: 17OHP, 17-hydroxyprogesterone; nl, normal; P4, progesterone; PRL, prolactin; T, testosterone.

(137). However, defining an absolute level that is diagnostic of PCOS or other causes of hyperandrogenism is difficult; familiarity with local assays is paramount (138). Levels of adrenal androgens tend to be higher in normal-weight compared with overweight women with PCOS (139). A serum AMH concentration is an indicator of ovarian reserve (140, 141) and can be an additional helpful assessment measure in women with PCOS (142). In FHA, gonadotropins will be lower than expected for PCOS. Similarly, in a patient with primary ovarian insufficiency, the diagnosis could be delayed because hypothalamic amenorrhea attenuates gonadotropin secretion.

If the patient has signs of virilization and/or substantial elevations in DHEA-S and/or testosterone (free or total), an 8 AM 17-hydroxyprogesterone level can serve as an initial screen for nonclassic CAH, although a high-dose ACTH stimulation test may be necessary to confirm the diagnosis. Clinicians should also consider this type of morning testing in patients at risk based on ethnicity or family history (143). High DHEA-S levels in concentrations that far exceed the normal range (*e.g.,* DHEA-S >600 μg/dL) might indicate an adrenal tumor (144). Some patients with poorly differentiated adrenal tumors may have higher circulating levels of DHEA than DHEA-S (145).

If clinicians suspect Cushing syndrome, a 24-hour urinary free cortisol, late-night salivary cortisol, or a 1-mg overnight dexamethasone suppression test are reasonable screening tests. If hypercortisolism is present, clinicians should obtain one additional positive test to confirm the diagnosis (146). When the cause of FHA is stress, the increase in cortisol secretion is less than that seen with Cushing syndrome, and the circadian pattern (although amplified) is preserved (5). Thus, increases in cortisol concentrations compared with controls are greatest overnight and in the early morning hours, but are typically still within the normal range. Studies have variably reported an increase in basal (147) or pulsatile (14) cortisol secretion in patients with FHA compared with controls, depending on the method researchers used to assess cortisol secretory dynamics. Rarely, secondary adrenal insufficiency presents as fatigue and anovulation, and it may require an ACTH stimulation test for diagnosis. Acromegaly may present with amenorrhea or irregular menstrual cycles, along with an elevation in growth hormone, insulin-like growth factor (IGF)-I, and (occasionally) prolactin concentrations (148). Poorly controlled diabetes may present as oligomenorrhea or amenorrhea from reduced GnRH drive and is diagnosed with an elevated hemoglobin A1C level (149).

IGF-I, a nutrition-dependent factor that stimulates osteoblast function and bone formation, can be another useful factor to measure, especially in cases of FHA with a low bone mass (150, 151). In those patients with overlapping FHA and anorexia nervosa, there may be relative GH resistance—a pattern that is common in the setting of malnutrition, associated with metabolic bone alterations, and that shows improvement with nutritional rehabilitation (152). Similarly, studies have shown low DHEA-S levels in adolescents and young women with FHA in the setting of anorexia nervosa, despite the presence of hypercortisolemia and adequate ACTH (153–155). The actions of DHEA may be mediated through IGF-I (156). Thus, this hormonal deficiency may further mediate low concentrations of IGF-I.

2.5 After excluding pregnancy, we suggest administering a progestin challenge in patients with FHA to induce withdrawal bleeding (as an indication of chronic estrogen exposure) and ensure the integrity of the outflow tract. (2l⊕⊕⊕○)

Evidence

Absence of withdrawal bleeding after a course of progestin may indicate outflow tract obstruction or low endometrial estrogen exposure (157, 158). The response to a progestin challenge can provide additional information about a patient's estrogen status, especially in