CLINICAL VIGNETTE

Overcoming the Challenge of Diagnosing Adrenal Insufficiency in a Patient Taking Combined Oral Contraceptives

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Case

A 38-year-old woman, without significant past medical history, presented to endocrinology with fatigue, lightheadedness, poor appetite, and weight loss over a period of two years.

On exam, the patient was afebrile, with sitting blood pressure of 120/84, and HR 105, but with orthostatic hypotension standing. Weight was 110 lbs (BMI 16.73 kg/m^2), decreased over two years from her reported usual weight of 140 lbs. Exam revealed normal cardiac rate and rhythm, clear lungs and normal thyroid exam. There was no hyperpigmentation of oral mucosa or palmar creases.

She had taken combined oral contraceptives (COC) for years for the prevention of pregnancy. A year ago, she stopped COC for 2 months and her periods were regular at that time. She did not take any other medications or supplements.

The initial laboratory evaluation included normal thyroid testing, as well as AM cortisol, ACTH and DHEA-S to rule out adrenal insufficiency. ACTH was very elevated at 828 pg/mL (ref: 4-48 pg/mL). Serum cortisol measured at 8 a.m. was normal at 18 mcg/dL. DHEA-S was low at 345 ng/mL. Despite the normal appearing 8 a.m. serum cortisol, adrenal insufficiency was still considered given the patient's presenting symptoms and the highly elevated ACTH, low DHEA-S and recognized effect of COC increasing total serum cortisol level by increasing cortisol binding globulin (CBG).

A cosyntropin stimulation test was scheduled with serum and salivary cortisol and DHEA-S obtained at baseline and at 30 and 60 minutes following 0.25 mg cosyntropin (Table 1).

Table 1: Cosyntropin Stimulation Testing

	Baseline	30 min after cosyntropin	60 min after cosyntropin
Serum cortisol	15 mcg/dL	17 mcg/dL	17 mcg/dL
Salivary cortisol	0.064 ug/dL	0.076 ug/dL	0.101 ug/dL
DHEA-S (ref. Adult Female: 400-3600 ng/mL)	286 ng/mL	280 ng/mL	304 ng/mL

The patient was diagnosed with Addison's disease based on these results. 21-hydroxylase antibody level was measured to confirm diagnosis and returned positive, and aldosterone level was 5.8 ng/dL. She was initially started on hydrocortisone and fludrocortisone was added later. Her symptoms of dizziness and fatigue improved. Twelve months later, her weight increased to 137 lbs (BMI 20 kg/m^2).

Discussion

Oral estrogen increases total serum cortisol levels by elevating circulating CBG concentration. This effect is particularly relevant when evaluating for adrenal insufficiency as elevated CBG leads to falsely elevated total serum cortisol levels, which can potentially mask the diagnosis. To circumvent this issue, additional diagnostic tests can be considered.

Total cortisol has been shown to increase by 67% in those receiving oral estrogen when compared to controls. However, the same study showed no difference in salivary cortisol levels between the group on oral estrogen versus the control group. Salivary cortisol testing measures free cortisol and is not affected by CBG.[1] For this reason, measuring salivary cortisol during cosyntropin stimulation testing is considered when there

is interference from COC. Salivary cortisol levels were studied during cosyntropin stimulation testing in women on combined oral contraceptives vs controls and were found to be slightly lower, rather than more elevated as seen with serum cortisol. More importantly, COC use did not appear to alter the lower limit of normal of salivary cortisol levels. Therefore, the lower limit of normal for salivary cortisol can be used to rule in or rule out adrenal insufficiency in women on COC.[2] A salivary cortisol level greater than 12.6 nmol/L (0.46 ug/dL) 60 minutes after cosyntropin administration is considered a normal response.[3]

DHEA-S secretion is low in both primary and secondary adrenal insufficiency due to destruction of adrenal tissue and inadequate ACTH production. Therefore, baseline measurement of DHEA-S is helpful to support the diagnosis of adrenal insufficiency and prompt confirmatory testing, like ACTH stimulation testing. Since DHEA-S level is not affected by cortisol binding globulin, levels are not affected by COC use and can be used as a reliable marker in that population. Patients with central adrenal insufficiency appear to have low serum DHEA and DHEA-S at baseline and after ACTH stimulation. Decreased DHEA appears to precede that of cortisol in that patient population.[4] Therefore, measurement of DHEA-S as part of ACTH stimulation testing has a role in diagnosis of adrenal insufficiency, especially in those taking COC as its levels are not affected by oral estrogen.

Finally, 21-hydroxylase antibody measurement can be helpful in diagnosing autoimmune primary adrenal insufficiency. It is found in 90% of patients with primary adrenal insufficiency when known non-autoimmune causes have been excluded. These patients retain antibody positivity up to 30 years after diagnosis.[5]

In conclusion, normal AM serum cortisol does not exclude the diagnosis of adrenal insufficiency in patients taking COC as serum cortisol is affected by COC. Other diagnostic tests should be used to diagnose or rule out adrenal insufficiency. Salivary cortisol measurements during cosyntropin stimulation test can be useful as they are not affected by CBG, and dynamic measurement can be easily obtained. Baseline DHEA-S as well as DHEA-S measurement during ACTH stimulation testing also provides additional diagnostic value. Finally, in patients with autoimmune primary adrenal insufficiency, the presence of 21-hydroxylase antibodies further confirms the diagnosis.

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