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Case Report

Desmopressin Stimulation Test in a Pregnant Patient with Cushing's Disease



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ABSTRACT

Objective: Hypothalamic-pituitary-adrenal axis stimulation during pregnancy complicates the investigation of Cushing's syndrome (CS). Our objective was to present the case of a pregnant patient with CS caused by a pituitary tumor in whom the desmopressin stimulation test helped in the diagnosis and led to appropriate management.

Case Report: A 27-year-old woman with 9-week gestation presented with a 2-month history of proximal myopathy. She had high blood pressure, wide purplish striae, and a 1-year history of hypertension and dysglycemia. The 8 AM cortisol level was 32.4 µg/dL (normal, 5–18 µg/dL), late-night salivary cortisol level was 0.7 µg/dL (11 PM, normal, <0.4 µg/dL), 24-hour urinary free cortisol levels were 237.6 µg/d (normal, 21.0–143.0 µg/d), and adrenocorticotropic hormone (ACTH) levels were 44.0 pg/mL (8 AM, normal, 0–46.0 pg/mL). Nongadolinium-enhanced pituitary magnetic resonance imaging revealed no obvious lesion. The desmopressin stimulation test showed a 70% increase in ACTH levels from baseline after desmopressin administration. Pituitary magnetic resonance imaging with gadolinium revealed an 8 × 8 × 7-mm³ pituitary adenoma. Transsphenoidal surgery was performed, which revealed the presence of ACTH-positive tumor cells. After tumor removal, the patient carried on pregnancy uneventfully.

Discussion: During pregnancy, ACTH levels may not be an accurate marker to help in the differential diagnosis of CS. Moreover, nongadolinium pituitary imaging might not detect small pituitary lesions.

Conclusion: In the present case, the desmopressin stimulation test suggested the diagnosis of Cushing's disease, which subsequently led to successful treatment. This suggests that the desmopressin test serves as a useful test for diagnosing Cushing's disease in pregnant individuals.

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Introduction

Pregnancy rarely occurs during the course of Cushing's syndrome (CS).^{1,2} Given the increase in maternal and fetal morbidities in women with active CS, early diagnosis and treatment of CS are essential.²

Abbreviations: ACTH, adrenocorticotropic hormone; CD, Cushing's disease; CRH, corticotrophin-releasing hormone; CS, Cushing's syndrome; GDM, gestational diabetes mellitus; MRI, magnetic resonance imaging.

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The diagnosis of CS using the usual diagnostic tests is challenging because of stimulation of the hypothalamic-pituitary-adrenal axis during pregnancy. Additionally, a physiologic rise in the adrenocorticotropic hormone (ACTH) level from the 7th week of pregnancy complicates the investigation of the etiology of CS.¹ The concern regarding gadolinium use during pregnancy is that pregnancy can affect the sensitivity of the detection of small pituitary lesions in patients with ACTH-dependent CS if nongadolinium pituitary imaging is used. Desmopressin is a vasopressin analog selective for V2 receptors. The desmopressin stimulation test has been proposed as a useful procedure for the differential diagnosis of CS.³ Desmopressin stimulates an increase in the ACTH and cortisol levels in patients with CS caused by a pituitary tumor or Cushing's disease (CD) but not in a majority of normal, obese subjects and

patients with adrenal CS or ectopic ACTH syndrome.^{3,4} However, there are limited data on the use of the desmopressin stimulation test during pregnancy.

Here, we present the case of a 27-year-old woman with CS in whom the desmopressin stimulation test helped in the diagnosis of CD and led to its successful treatment.

Case Report

A 27-year-old woman with 9 weeks of gestation was referred from the orthopedic department for the evaluation of CS. She presented with a 2-month history of proximal myopathy. Upon physical examination, she had Cushingoid appearance; wide, purplish striae; bruising; and proximal muscle weakness. Her blood pressure was 160/100 mm Hg, and her body mass index was 32.2 kg/m². Her past medical history revealed that she had hypertension, dyslipidemia, and impaired fasting glucose levels for 1 year without taking any medication. Furthermore, she had gained 20 kg in the past 2 years. The 8 AM cortisol level (chemiluminescent immunometric assay, Immulite/Siemens) was 32.4 µg/dL (normal, 5.0–18.0 µg/dL), late-night salivary cortisol level at 11 PM (electrochemiluminescence immunoassay, Roche Cobas) was 0.7 µg/dL (normal, <0.4 µg/dL), and mean 24-hour urinary free cortisol (UFC) level (radioimmunoassay, Immulite/Siemens) was 237.6 µg/d (normal, 21.0–143.0 µg/d). The ACTH concentrations at 8 AM (chemiluminescent immunometric assay, Immulite/Siemens) were 48.4 and 39.6 pg/mL (normal, 0–46.0 pg/mL) (Table 1). At 12 weeks of gestation, nongadolinium-enhanced pituitary magnetic resonance imaging (MRI) revealed a mildly bulging contour of the right side of the lateral aspect of the pituitary gland, without an obvious abnormal lesion (Fig. 1 A). The desmopressin stimulation test was then performed at 14 weeks of gestation. Serial blood samples for the determination of ACTH and cortisol levels were obtained at baseline (at 8 AM) and at 15, 30, 45, and 60 minutes after intravenous administration of 10 µg of desmopressin. The results are shown in Table 2. Compared with the level at the baseline, the ACTH levels increased from 34.7 to 58.9 pg/mL (70%) at 15 minutes after desmopressin administration (a ≥35% increase in the ACTH levels was considered an indication of CD in nonpregnant individuals) (Fig. 2).³ Pituitary MRI with gadolinium revealed an 8 × 8 × 7-mm³ circumscribed lesion with heterogeneous isointensity to hyperintensity in the right inferolateral aspect of the anterior pituitary lobe on a T2-weighted image. The lesion had delayed enhancement compared with normal pituitary tissue (Fig. 1 B). Noncontrast MRI of the adrenal glands showed bilateral normal adrenal glands without a mass or a nodule. The MRI results of other abdominal organs were unremarkable. Regarding comorbidities, she had hypertension and gestational diabetes mellitus (GDM). The hemoglobin A1C level was 5.7% (39 mmol/mol). Using a 2-step

Table 1
Laboratory Investigations of the Present Case

Variable	At 9 weeks of gestation
8 AM cortisol, µg/dL (5.0–8.0)	32.4
Salivary cortisol (11 PM, <0.4 µg/dL)	0.7
UFC (21.0–143.0 µg/d)	183.5 and 291.6
ACTH, pg/mL (8 AM, 0–46.0)	48.4 and 39.6
DHEAS (8 AM, 35.0–430.0 µg/dL)	378.0
PAC (upright position, 8 AM), ng/dL	5.2
PRA (upright position, 8 AM), ng/mL/h	2.1
Potassium, mmol/L	3.6

Abbreviations: ACTH = adrenocorticotropic hormone; DHEAS = dehydroepiandrosterone sulfate; PAC = plasma aldosterone concentration; PRA = plasma renin activity; UFC = urinary free cortisol.

strategy, GDM was diagnosed at 12 weeks of gestation. Hypertension and GDM were controlled with 750 mg of methylglucamine and 50 units of insulin per day, respectively.

A transsphenoidal surgery with tumor removal was performed at 18 weeks of gestation. Pathologic findings showed a 13 × 10 × 3-mm³ tissue with segments of the pituitary gland and tumor. There were monomorphous round nuclei, stippled chromatin, indistinct nucleoli, and pale eosinophilic cytoplasm cells. These cells were reactive with ACTH and showed loss of reticulin framework, unlike cells of the normal pituitary gland. The day after the surgery, her 8 AM cortisol level was 6.0 µg/dL. Hydrocortisone supplement was started and continued throughout the pregnancy. Antihypertensives were discontinued, and the insulin dosages were decreased to <20 units/d. At 38 weeks of gestation, she gave birth to a 2300-g male newborn (small for gestational age). Dysglycemia and hypertension resolved after the delivery. One year after the first child's delivery, the patient had a spontaneous pregnancy without GDM or hypertension. The 8 AM cortisol level was 3.9 µg/dL, and the hydrocortisone replacement was continued. The patient successfully delivered a term, 3300-g male infant, without fetal or maternal complications. Two years after the first transsphenoidal surgery, the 1-µg cosyntropin stimulation test was performed; the basal cortisol level was 11.7 µg/dL, and the peak serum cortisol level was 23.8 µg/dL. Therefore, the steroid replacement was withdrawn.

Discussion

Herein, we presented the case of a 27-year-old woman who was evaluated during her first pregnancy for clinical and laboratory features suggestive of CD. Her morning serum and late-night salivary cortisol concentrations, in addition to nonsuppressed ACTH levels, were elevated, but a definitive diagnosis was not obtained using nongadolinium pituitary MRI. However, the diagnosis of CD was suggested based on the results of the desmopressin stimulation test. Pituitary MRI with gadolinium was performed, which revealed a pituitary lesion >6 mm.

The prevalence of pregnancy is low because of reduced fertility in patients with CS. To date, there have been <300 pregnant patients with CS reported in the literature.² During pregnancy, the most frequent etiology of CS is adrenal CS (60%), followed by ACTH-producing pituitary adenomas or CD (35%) and, very rarely, ectopic ACTH (<5%).¹ In contrast, CD is the most common cause of CS in nonpregnant people (approximately 70%). The clinical diagnosis of CS during pregnancy may be missed because of overlapping features between pregnancy and CS. However, wide, purplish, cutaneous striae and proximal myopathy are signs with a high discrimination index when CS is suspected.⁵ These signs are not present in patients with a normal pregnancy.

In the present case, CS was diagnosed based on the apparent clinical features of CS, in addition to the elevated UFC and late-night salivary cortisol levels. The patient denied taking any supplements, and her 8 AM cortisol level was not suppressed, thus suggesting no etiology of exogenous steroid use. Pregnant women without CS might have elevated UFC and late-night salivary cortisol levels because of increased total and free plasma cortisol levels from the first trimester until the end of their pregnancy.⁶ This results from an elevated concentration of cortisol transport protein and an increase in placental ACTH and corticotrophin-releasing hormone (CRH) levels. According to the current guideline, UFC level determination is the recommended test when CS is suspected during a pregnancy.⁵ Because the UFC level increases during the second trimester, it might not be a reliable marker after the first trimester of pregnancy unless the level is clearly increased (up to 2 to 3 fold of the upper limit of normal values).¹ Late-night salivary cortisol level determination

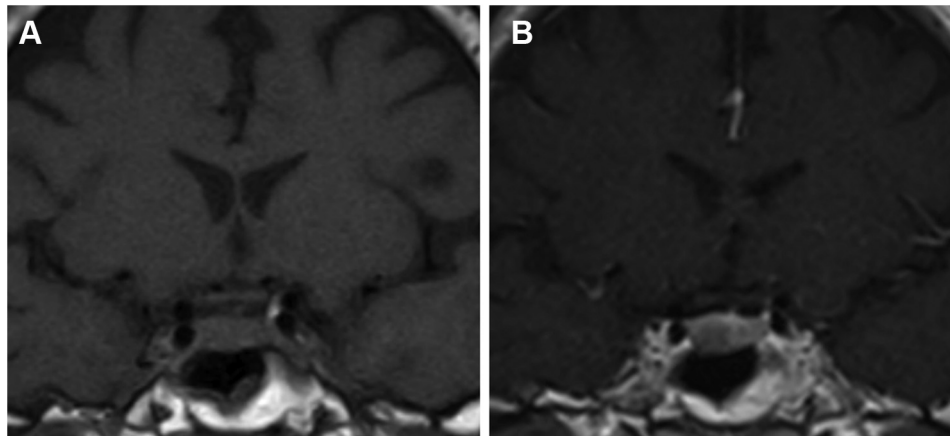


Fig. 1. Pituitary imaging of the present case. A, Nongadolinium magnetic resonance imaging of the pituitary gland at 12 weeks of gestation showing a mildly bulging contour of the right side of the lateral aspect of the pituitary gland, without an obvious abnormal lesion. B, Magnetic resonance imaging with gadolinium of the pituitary gland at 14 weeks of gestation showing an 8 × 8 × 7-mm³ circumscribed lesion with heterogeneous isointensity to hyperintensity in the right inferolateral aspect of the anterior pituitary lobe on a T2-weighted image. The lesion had delayed enhancement compared with normal pituitary tissue.

is also one of the useful tests to diagnose CS during a pregnancy because the circadian rhythm of cortisol is preserved in a normal pregnancy. Furthermore, it is not influenced by changes in binding proteins.⁷ However, a previous study has shown that the late-night salivary cortisol level increases progressively throughout a pregnancy. When compared with levels in nonpregnant women, the median value of late-night salivary cortisol in pregnant women was 1.1, 1.4, and 2.1 times higher in the first, second, and third trimesters, respectively. The cutoff values for late-night salivary cortisol during each gestational trimester were as follows: first trimester, 0.255 µg/dL; second trimester, 0.260 µg/dL; and third trimester, 0.285 µg/dL. The respective sensitivities and specificities during each trimester were as follows: first trimester, 92% and 100%, respectively; second trimester, 84% and 98%, respectively; and third trimester, 80% and 93%, respectively.⁸

Given the nonsuppressed ACTH levels after the 7th week of gestation, we were not able to summarize whether the etiology was adrenal CS or ACTH-dependent CS, which could have been either CD or ectopic ACTH syndrome. In nonpregnant individuals, ACTH suppression usually identifies adrenal CS. However, during pregnancy, the ACTH levels were nonsuppressed in half of those with adrenal CS because of continued stimulation of the maternal hypothalamic-pituitary-adrenal axis by placental CRH.¹ Therefore, the use of the ACTH thresholds in general populations can lead to a misdiagnosis while investigating the etiology of CS in pregnant individuals. The response of the hypothalamic-pituitary-adrenal axis to exogenous glucocorticoids is blunted in pregnant women. Following overnight dexamethasone administration, pregnant women without CS might have nonsuppressed plasma cortisol and UFC.⁶ In nonpregnant individuals with CS, the high-dose dexamethasone suppression test helps in the identification of CD with a sensitivity of 82% and a specificity of 50%.⁴ During pregnancy, the high-dose dexamethasone suppression test failed to identify almost half of the patients with

CD.¹ Inferior petrosal sinus sampling is usually avoided because of the risk of excessive radiation exposure. Further, because nongadolinium MRI showed no obvious pituitary lesion in the present case, in addition to the limitation of the high-dose dexamethasone suppression test and inferior petrosal sinus sampling during pregnancy, we used desmopressin stimulation to help in the investigation of CD because desmopressin can stimulate an ACTH response in a considerable proportion of patients with CD but not in most patients with adrenal CS or ectopic ACTH syndrome.^{3,4}

Desmopressin has been assigned to pregnancy category B by the U.S. Food and Drug Administration. According to the most recent update in the guideline on the diagnosis and management of CD, the desmopressin stimulation test can be used to differentiate ectopic CS and CD in patients with a normal or high ACTH level who have no adenoma or yield equivocal results of pituitary MRI. However, the guideline did not mention the use of this test in pregnant individuals.⁹ The literature regarding the use of desmopressin stimulation tests during pregnancy is limited. We were able to identify 1 study in a pregnant patient with active CS, who was surgically confirmed as having CD, in whom the desmopressin stimulation test was performed at 10 weeks of gestation and after the delivery. Compared with age-matched, healthy, nonpregnant women, there were different responses in terms of cortisol and

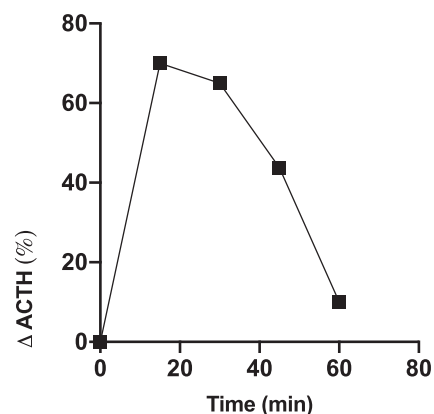


Fig. 2. Percentage of adrenocorticotropic hormone increase after desmopressin administration (time, 0 minute).

Table 2
Desmopressin Stimulation Test Results Performed at 14 Weeks of Gestation

Time	0 min	15 min	30 min	45 min	60 min
ACTH (pg/mL)	34.7	58.9	57.4	49.9	38.2
Cortisol (µg/dL)	30.6	30.2	29.7	29.6	31.0

Abbreviation: ACTH = adrenocorticotropic hormone.

ACTH levels after desmopressin administration in the pregnant patient with active CS.¹⁰ The ACTH peaks after the administration of desmopressin were higher in the pregnant patient. The CRH stimulation test was also performed in the pregnant patient with CD. The desmopressin-stimulated ACTH values during pregnancy and after the delivery were not significantly different, whereas the CRH-stimulated ACTH values were significantly higher when the test was performed after the delivery. The authors did not mention the optimal cutoff values for these diagnostic tests.¹⁰ In nonpregnant individuals, the ACTH increase of >35% at 15 minutes after desmopressin administration yielded a sensitivity of 84% and a specificity of 43% in the diagnosis of CD.³ Another recent study of ACTH-dependent CS showed that a threshold increase of 45% in the ACTH level after desmopressin stimulation helped with the identification of CD with a sensitivity of 91% and a specificity of 75%.⁴ Using the nonpregnant cutoff values for the desmopressin stimulation test, the diagnosis of CD was made in our patient, which was later surgically confirmed as CD.

Pituitary microadenomas have been shown to be the cause of CD in almost 90% of nonpregnant individuals.¹¹ Additionally, in pregnant women with CD, pituitary microadenomas have been reported to be more common than macroadenomas.^{1,12} In one study, almost 40% of pituitary microadenomas in patients with CD were invisible or poorly visible using noncontrast MRI but were detected using contrast-enhanced MRI.¹³ In a case series by Lindsay et al,¹ non-contrast MRI could not correctly identify pituitary adenomas in 38% of pregnant patients with available data. The same case series reported a pregnant patient having a normal pituitary MRI result who was later surgically confirmed as having CD based on a 3 × 3-mm² adenoma with positive staining for ACTH. In the present case, the mildly bulging contour of the pituitary gland, although without an obvious abnormal lesion, in addition to the desmopressin test results, suggested the need for contrast-enhanced pituitary MRI. Gadolinium contrast has been assigned to pregnancy category C by the Food and Drug Administration. It is water-soluble and can cross the placenta into the fetus and amniotic fluid.¹⁴ However, because nongadolinium MRI might not detect a pituitary microadenoma even in patients with normal imaging results, we suggest that physicians consider pituitary MRI with gadolinium as an initial imaging option in pregnant patients with a clinical suspicion of CD.^{1,15}

Prompt diagnosis and treatment of CS are essential because of a higher rate of fetal loss in patients with active CS who do not receive treatment than in those who receive either medical or surgical treatment. There are significantly lower rates of various fetal complications, including a low birth weight, in women with active CS than in those with cured CS.² Although medical and surgical treatments have not been compared as prognostic factors for complications, experts recommend transsphenoidal surgery in the second trimester as the treatment of choice for CD in pregnant individuals.^{1,15} Medical treatment should be the second choice when surgery cannot be performed or a late diagnosis is made.

Conclusion

In the present case, the results of the desmopressin stimulation test and pituitary MRI with gadolinium suggested the diagnosis of CD, which subsequently led to successful treatment. This suggests that the desmopressin test serves as a useful test for the diagnosis of CD even in the pregnant individuals.

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Disclosure

The authors have no multiplicity of interest to disclose.

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