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Case Report

Cushing Disease Treated Successfully With Metyrapone During Pregnancy



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ABSTRACT

Background: Cushing disease (CD) during pregnancy is a rare but serious disease that adversely impacts maternal and fetal outcomes. As the sole use of metyrapone in the management of CD has been rarely reported, we describe our experience of using it to treat a pregnant patient with CD.

Case Report: A 34-year-old woman with hypertension was diagnosed with adrenocorticotropic hormone–dependent CD on the basis of a urinary free cortisol (UFC) level of 290 µg/24 h (reference range, 6–42 µg/dL) and an abnormal dexamethasone suppression test (cortisol level, 12.4 µg/dL) before becoming pregnant. She conceived naturally 12 weeks after transsphenoidal surgery and was subsequently found to have persistent disease with a UFC level of 768 µg/dL. Surgery was deemed high-risk given the proximity of the tumor to the right carotid artery and the high likelihood of residual disease. Instead, she was managed with metyrapone throughout her pregnancy and titrated to a goal UFC level of <150 µg/24 h due to the known physiologic increase in the cortisol level during gestation. The patient had diet-controlled gestational diabetes and well-controlled hypertension. She gave birth to a healthy baby boy at 37 weeks of gestation, without adrenal insufficiency in the baby or her.

Discussion: This case highlights the successful use of metyrapone throughout pregnancy to manage CD in patients in whom surgery is considered high-risk or in those with a low likelihood of cure. Although metyrapone is effective, close surveillance is required for worsening hypertension, hypokalemia, and potential adrenal insufficiency. Although no fetal adverse events have been reported, this medication crosses the placenta, and the long-term effects are unknown.

Conclusion: We describe a case of CD during pregnancy that was successfully treated with metyrapone.

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Introduction

Cushing disease (CD) is caused by endogenous overproduction of glucocorticoids due to hypersecretion of adrenocorticotropic hormone (ACTH) by a pituitary adenoma. CD during pregnancy is very rare; when it occurs, it is considered a high-risk pregnancy with many potential adverse outcomes for both the mother and fetus.¹ Infertility is common in CD due to excessive cortisol and

androgen that lead to hypogonadotropic hypogonadism.¹ Due to the rarity of CD during pregnancy, there is little guidance in terms of treatment for this patient population. Similar to that for nonpregnant patients, the first-line treatment is transsphenoidal pituitary adenoma resection, with medical therapy as the second-line treatment option. This report presents a case that highlights the use of metyrapone, a steroidogenesis inhibitor, as the sole therapy in cases in which surgery is deemed to be high-risk and unlikely curative due to the location of the tumor.

Case Report

A 34-year-old woman with a past medical history of hypertension and infertility for 6 years presented to the endocrinology department for evaluation. Aside from difficulty conceiving, her

Abbreviations: ACTH, adrenocorticotropic hormone; CD, Cushing disease; MRI, magnetic resonance imaging; UFC, urinary free cortisol.

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only complaints were nausea and easy bruising. On examination, she did not have clinical features of CD—abdominal violaceous striae, moon facies, and a dorsocervical fat pad were absent. Her laboratory results revealed an elevated prolactin level (50–60 ng/mL; reference range, 1.4–24 ng/mL), an elevated ACTH level (61 pg/mL; reference range, 0–46 pg/mL), and low follicle-stimulating hormone and luteinizing hormone levels (1.7 mIU/mL and 1.76 mIU/mL, respectively). Further testing demonstrated an elevated urinary free cortisol (UFC) level (290 $\mu\text{g}/24\text{ h}$; reference range, 6–42 $\mu\text{g}/\text{dL}$), and her cortisol level failed to suppress on a 1 mg dexamethasone suppression test (cortisol level, 12.4 $\mu\text{g}/\text{dL}$). Magnetic resonance imaging (MRI) scan of the pituitary with and without contrast showed a T2 hyperintense, hypoenhancing lesion within the right side of the sella touching the right cavernous internal carotid artery measuring 8 \times 8 \times 9 mm, consistent with a pituitary adenoma (Fig. 1).

After the presumed diagnosis of CD was made, she was referred to the neurosurgery department for transsphenoidal resection of the adenoma, which she underwent a few months later. Intraoperatively, a white friable tumor was found, and the surgery was otherwise uneventful. Three months later, however, she was found to have a persistent 8 \times 8 \times 9-mm hypoenhancing lesion extending laterally over the right cavernous carotid artery on the MRI scan. The mass approximated but did not contact the right intracranial optic nerve. The pathology from resected tissue was consistent with normal pituitary tissue with staining for growth hormone (80%), ACTH (30%), prolactin (40%), follicle-stimulating hormone (5%), luteinizing hormone (40%), and thyroid-stimulating hormone (15%), proving the surgery to have been unsuccessful.

Twelve weeks after surgery, the patient discovered that she was pregnant. At 12 weeks of gestation, her UFC level was 768 $\mu\text{g}/24\text{ h}$, and 2 midnight salivary cortisol levels were elevated at 0.175 and 0.625 $\mu\text{g}/\text{dL}$ (reference range, <0.010–0.090 $\mu\text{g}/\text{dL}$). She was experiencing easy bruising and taking labetalol 400 mg twice daily for hypertension. She had gained 4.53 kg by 12 weeks of gestation.

A second transsphenoidal surgery during pregnancy was deemed high-risk, with a high likelihood of residual disease due to the proximity of the tumor to the right carotid artery. The decision

was made to treat the patient medically with metyrapone that was started at 250 mg twice per day at 12 weeks of gestation and was eventually uptitrated based on UFC levels every 3 to 4 weeks (goal of <150 $\mu\text{g}/24\text{ h}$) to 1000 mg 3 times per day by the time of delivery with an eventual UFC level of 120 $\mu\text{g}/24\text{ h}$ (Fig. 2). Morning ACTH and serum cortisol levels were monitored for potential adrenal insufficiency.

Her hypertension was well controlled throughout pregnancy on labetalol with the addition of nifedipine XL 30 mg daily in the second trimester. She remained normokalemic, with potassium levels ranging from 3.8 to 4.1 mEq/L. She was diagnosed with gestational diabetes at 24 weeks of gestation by an abnormal 2-step oral glucose tolerance test, which was diet-controlled. The patient was induced at 37 weeks of gestation due to cervical insufficiency with cerclage in place and was given stress dose steroids along with metyrapone. She delivered a healthy baby boy vaginally without complications. His Apgar scores were 9 and 9, and he weighed 2.86 kg. At the time of delivery and 1 week later, the baby's cortisol levels were normal (6 $\mu\text{g}/\text{dL}$; normal range, 4–20 $\mu\text{g}/\text{dL}$), without evidence of adrenal insufficiency.

The patient's metyrapone dose was reduced to 500 mg 3 times a day after pregnancy, and her 2-month postpartum 24-hour UFC level was 42 $\mu\text{g}/24\text{ h}$. The patient stopped the metyrapone on her own 4 months later, and her UFC level was found to be elevated at 272 $\mu\text{g}/24\text{ h}$ (normal range, 6–42 $\mu\text{g}/24\text{ h}$). An MRI scan 1 year postpartum revealed a 10 \times 10 \times 9-mm adenoma in the right sella with some suprasellar extension without compression of the optic chiasm but with an abutment of the right carotid artery. Due to the persistently elevated cortisol level, the large size of the tumor, and potential for cure, especially if followed by radiation therapy, the second transsphenoidal surgery was recommended. However, due to the COVID-19 pandemic, the patient underwent delayed surgery 1.5 years postpartum. The pathology was consistent with a pituitary adenoma that stained strongly and diffusely for ACTH and synaptophysin. Her postoperative day 2 cortisol level was 1.1 $\mu\text{g}/\text{dL}$ (reference range, 6.7–22.6 $\mu\text{g}/\text{dL}$), and hydrocortisone 20 mg in the morning and 10 mg in the afternoon was started. She remained on hydrocortisone replacement and conceived again 1 month after her second surgery.

Discussion

We describe the case of a patient with pre-existing CD who became pregnant and was successfully managed with metyrapone throughout her pregnancy.

Although CD is rare during pregnancy, it can occur and poses risks to both the mother and fetus.^{1,2} Potential maternal complications include hypertension, preeclampsia, diabetes, fractures, and more uncommonly, cardiac failure, psychiatric disorders, infection, and maternal death.^{1,2} There is also increased fetal morbidity, including prematurity, intrauterine growth retardation, and less commonly, CD can lead to stillbirth, spontaneous abortion, intrauterine death, and hypoadrenalism.^{1,2}

It is, therefore, imperative that these patients receive prompt care to control cortisol levels. The treatment of CD during pregnancy is challenging as there are no large research trials investigating the efficacy and safety of medications in CD during pregnancy. Pituitary surgery is the first-line recommendation and should be done late in the first trimester or in the second trimester to prevent spontaneous pregnancy loss.³ In this case, however, it was believed that a second surgery would be high-risk, given the proximity of the tumor to the right carotid artery, and possibly noncurative, and thus surgery was not a feasible option. She was, therefore, successfully managed with medical therapy with metyrapone alone throughout her pregnancy.

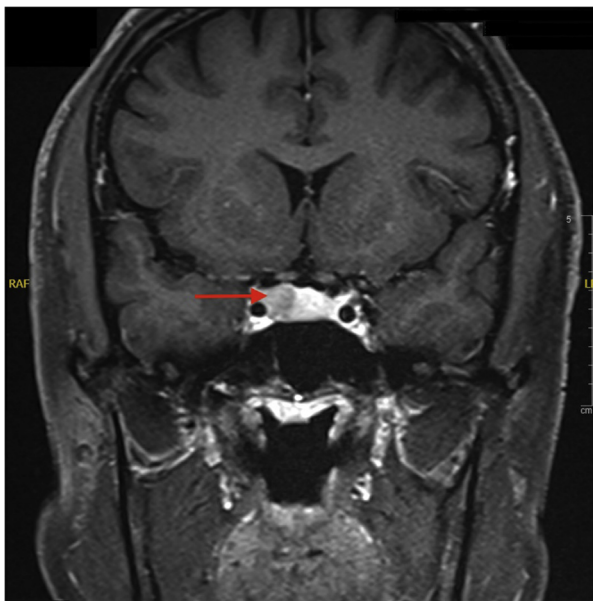


Fig. 1. T1-weighted post gadolinium coronal image of the pituitary gland with a small hypoenhancing lesion within the right side of the sella. Red arrow indicates a small hypoenhancing lesion (8 \times 8 \times 9 mm) within the right side of the pituitary extending over the right cavernous carotid artery.

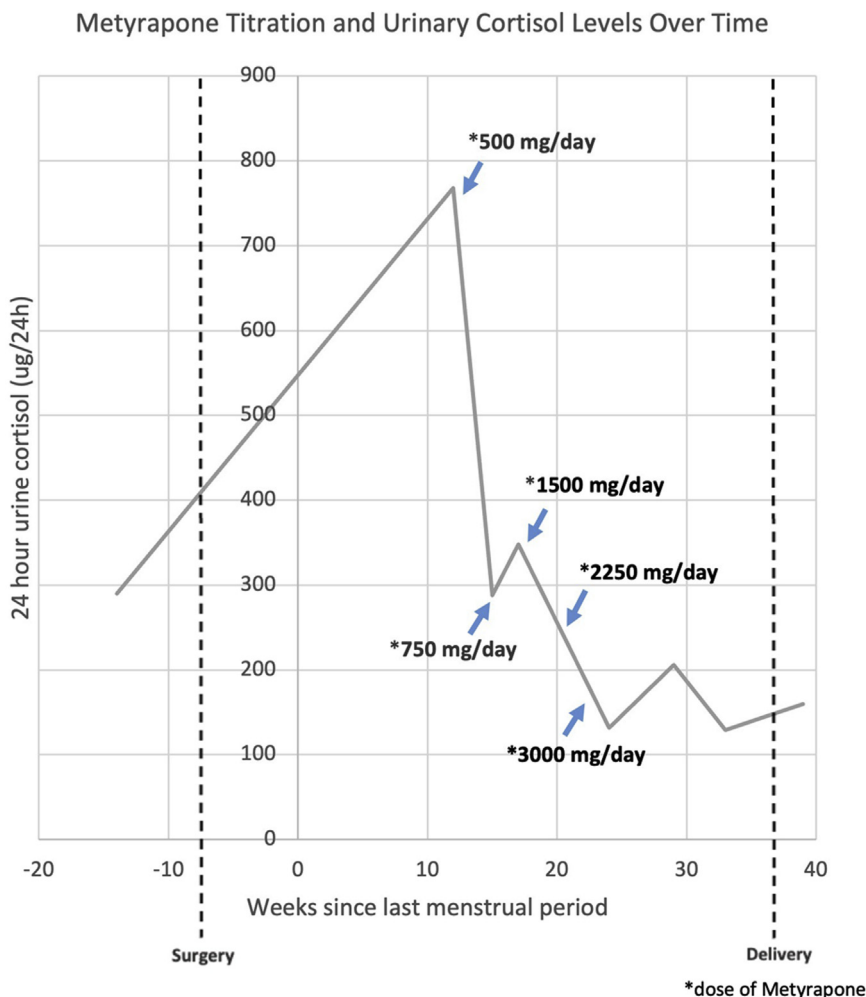


Fig. 2. This figure depicts the patient’s 24-hour urinary cortisol levels over time as well as the titration of metyrapone dosage in milligram per day.

Metyrapone use during pregnancy has been previously reported in the literature and has been shown to be effective in reducing cortisol levels.⁴⁻⁶ Although not approved for use during pregnancy, this steroidogenesis inhibitor is the most commonly used medication to treat Cushing syndrome in pregnant women.^{3,5} Due to metyrapone’s inhibition of 11-beta-hydroxylase, there is a buildup of steroidogenesis precursors such as 11-deoxycorticosterone, which can worsen hypertension, increase the frequency of pre-eclampsia, and cause hypokalemia.³ Metyrapone also leads to the elevation of adrenal androgens, which in conjunction with the accumulation of 11-deoxycorticosterone, can cause hirsutism and virilization.⁷

Although the use of cabergoline has been reported in cases with CD during pregnancy, no long-term safety data are available regarding its effects on pregnancy and the fetus. Moreover, studies assessing the effect of cabergoline in persistent or recurrent CD show a response rate of 20% to 30% only in cases with mild hypercortisolism.⁸

There is no consensus on how to medically treat patients with CD during pregnancy. We chose a goal UFC level of <150 µg/24 h because of the physiologic increase in the cortisol level to 2 to 3 times the upper limit of the normal range during pregnancy.^{3,9} During pregnancy, there is an increase in the levels of corticotropin-releasing hormone from the placenta, which is identical in structure to the hypothalamic form.⁹ This leads to

increased levels of ACTH, which stimulates the maternal adrenal glands to become slightly hypertrophic and accounts for the increase in serum cortisol levels during pregnancy.⁹ Corticosteroid-binding globulin also increases during pregnancy, along with serum free cortisol, leading to UFC increasing to 3-fold the normal range.⁹ We, therefore, aimed to keep our patient’s UFC levels approximately 3 times the upper limit of the normal range on our assay to maintain normal cortisol levels during pregnancy.

Close surveillance of patients is required for worsening hypertension, hypokalemia, and potential adrenal insufficiency.³ Although no fetal adverse events from metyrapone have been reported, the medication does cross the placenta, leading to the potential for fetal adrenal insufficiency, and its long-term effects are unknown.³

Conclusion

This case demonstrates the successful use of metyrapone alone to treat CD throughout pregnancy, resulting in the birth of a healthy baby without adrenal insufficiency. Such cases are particularly challenging given the lack of U.S. Food and Drug Administration–approved therapies and consensus on directing titration of medications and the duration of therapy.

Disclosure

The authors have no multiplicity of interest to disclose.

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