Patient With Successful Conception During Treatment for Cushing Disease: Case Report

Chioma Iweha, MD, and Maryann Castillo, MD
Panda Medical Associates, Peoria, AZ
Dr Iweha has no financial interests to disclose and no conflicts of interest. Dr Castillo has no financial interests to disclose and no conflicts of interest.

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INTRODUCTION

Cushing's Syndrome (CS) is a rare endocrine disorder that predominantly affects women of childbearing age and is characterized by excess secretion of adrenocorticotropic hormone (ACTH) and resulting hypercortisolism. Characteristics of CS include hyperglycemia, hypertension, menstrual irregularities, and loss of healthy bone formation.[1] Conception and pregnancy are rare among women with CS due to the effects of hypercortisolism on ovulation and reproductive hormones.

We report a case of a woman with ACTH-dependent hypercortisolism treated with pasireotide who conceived while on treatment.

Clinical Case: Patient's Journey to Correct Diagnosis

A 27-year-old woman presented to the initial consult on 9/01/2011 with a 4-year history of ongoing symptoms of hirsutism, diaphoresis, oligomenorrhea, myalgia, and acne. A physical exam revealed an overweight female with mild facial acne and hirsutism. Family history included autoimmune disease in mother (lupus and multiple sclerosis). She was frustrated by the lack of a definitive diagnosis over 4 years. She was anxious and using multiple medications (prescribed by earlier provider), including anxiolytics and analgesics, without relief of symptoms. Patient did not use alcohol and never smoked.

Table 1. Presenting Symptoms and Diagnosis: 9/1/2011

Chief Complaint	Other Findings
Body and facial hair growth	Generalized fatigue
Loss of hair on scalp	Chronic symptoms, no relief over 4 years
Oily skin and acne	Denied weight gain/loss
Irregular menstruation	Denied bleeding disorders
Muscle pain	Denied ocular disturbances
Nail	Denied respiratory symptoms
Dysgeusia (X 4 years' duration)	Denied gastrointestinal symptoms
Numbness in fingers, left hand	Denied skin changes, UTIs

Table 2. Patient characteristics at initial visit

Patient Characteristics	
Age	27 years
Height/weight	61 in/139 lb
BMI	26.3 kg/m^2
BP	110/80 mm Hg
Pulse	80 bpm
Respiratory rate	16 breaths/min
Labs TSH Testosterone Free testosterone Fasting glucose eGFR	 1.51 mIU/L 19 ng/dL 1.1 pg/mL 126 mg/dL 121 mL/min/1.73^2
Social and family history Smoking Marital status Family history	 Never Divorced Father: emphysema (age 57), mother: lupus and multiple sclerosis
Previous surgery	Abdominoplasty
Current medications	Carisoprodal 350 mg TID Cyclobenzapine 10 mg TID Lorazepam 1 mg q6-8h Methylin 5 mg TID Motrin 800 mg as needed Hydroxyzine 25 mg as needed
Diagnosis 9/1/2011	Hyperglycemia, NOS

Her symptoms were suggestive of Cushing's, but initial screening was negative at first visit. Her symptoms persisted at follow-up in 10/27/2011 and re-screening on 2/20/2012. Labs taken during the 2/20/2012 visit were consistent with a diagnosis of Cushing's. Low-dose (1mg) dexamethasone suppression test reduced morning cortisol to 1.7 µg/dL without affecting ACTH level.

Table 3. Patient Characteristics on 2/12/2012

Characteristics	
Age	29 years
BMI	30.3 kg/m^2
BP	86/60 mm Hg
Pulse	64 bpm
Respiratory rate	10 breaths/min
Current medications	Lorazepam 1 mg BID Motrin 800 mg as needed Oxycodone 15 mg q6h Ritalin 10 mg weekly Tizanidine 2 mg q8h Tramadol 50 mg q6h

Table 4. Cortisol screening results (2/20/2012)

Measurement	Result	Normal Range
Morning cortisol	26.9 µg/dL	5 to 23 µg/dL
ACTH	14 pg/mL	6 to 58 pg/mL
24-hr urinary cortisol	110.6 µg/24 hr	<100 µg/24 hr

The patient was screened for adrenal adenoma using computed tomography (CT) in April 2012 and screened for pituitary tumor using magnetic resonance imaging (MRI) in August 2012. There was no evidence of adrenal adenoma on abdominal CT or pituitary adenoma on brain MRI. Based on hypercortisolism and normal ACTH levels, ACTH-dependent CD was suspected, and abnormal IPSS confirmed diagnosis.

January 2013: Starting Treatment for CS

We advised the patient to join a clinical trial for pasireotide, and she began treatment on 1/3/2013. She initiated pasireotide injections at 0.9 mg/mL twice daily, but experienced severe nausea. Her dose was reduced to 0.6 mg/mL twice daily, which was tolerable despite some residual nausea. Patient accepted nausea because she experienced significant improvement in CS symptoms, and continued at that dosage.

June 2014: Follow-up at Clinic

The patient was next seen at our clinic in June 2014, for follow-up on CS. She reported having memory and concentration issues, and dizziness episodes that had included fainting and falling. After a little more than a year on pasireotide, she reported notable improvement in most CS symptoms and had lost some weight. However, patient continued to experience chronic pain; medications included prescription analgesics, muscle relaxants, and anxiolytics.

Table 5. Patient characteristics 6/17/2014

Characteristics	
Age	30 years
BMI	27.1 kg/m^2
BP	98/60 mm Hg
Pulse	74 bpm
Respiratory rate	16 breaths/min
Current medications	**Pasireotide 0.6 mg/mL BID** Lorazepam 1 mg BID Motrin 800 mg as needed Oxycodone 15 mg q6h Ritalin 10 mg weekly Tizanidine 2 mg q8h Tramadol 50 mg q6h

June 2015: Follow-up at Clinic

A year after her previous clinic visit, the patient returned on 6/23/2015. We were surprised to learn that she was 5.5 months pregnant, and that she had become pregnant while on pasireotide in the clinical trial. With her pregnancy confirmed, she discontinued pasireotide and left the study. Although she wasn't certain exactly when, she guessed she'd discontinued in late January or early February of that year. She said she returned to our care because CS symptoms had returned after pasireotide discontinuation. At presentation, symptoms of hirsutism, acne, fatigue, muscle aches, and hyperemesis were reported.

Physical exam showed a healthy-looking young woman in no acute distress. ENT were normal on examination. Facial hair and acne were visible. All other exams were normal and healthy.

Table 6. Presenting Symptoms and Diagnosis: 9/1/2011

Characteristics	
Age	30 years
BMI	27.1 kg/m^2
BP	98/60 mm Hg
Pulse	74 bpm
Respiratory rate	16 breaths/min
Current medications	Diazepam 5 mg BID Lorazepam 1 mg QD Oxycodone 15 mg q6h Tizanidine 4 mg BID

July 2015: Follow-up at Clinic

Patient returned for 1-month follow-up with complaint of galactorrhea and ongoing fatigue. She reported some improvement in hyperemesis. Her physical was normal. Facial hair and acne were present. Blood pressure and heart rate were elevated compared with past visits but not outside of normal. Pregnancy was proceeding without incident beyond hyperemesis.

At this visit, she continued on previous drug regimen of diazepam and lorazepam, oxycodone, and tizanitide; in addition, she was taking metoclopramide for nausea/emesis 10 mg.

September 2015: Follow-up at Clinic

Patient returned for follow-up. She said that since her last visit, she had been treated successfully with magnesium sulfate 400 mg BID for uterine contractions. At this time, her pregnancy was proceeding normally. She was no longer having hyperemesis, nausea, or vomiting.

The only CS/D symptoms she reported were fatigue and muscle aches. Comprehensive metabolic panel came back within normal range, including fasting glucose (95 mg/dL), A1C (5.3%), and thyroid assessments.

December 2015: Final Follow-up at Clinic

We last saw this patient on 12/14/2015, 9 weeks after she had given birth to a healthy baby that was born on 10/8/2015. The patient was interested in re-starting treatment with pasireotide, but decided against it because of her chronic muscle aches.

At this visit, she appeared flushed but otherwise healthy. Facial hair and acne were visible. Her physical exam was normal. She continued to have fatigue and muscle aches, but no longer had numbness or gastrointestinal symptoms. Complete metabolic panel found elevated evening cortisol (21.5 µg/dL; normal range, 3-17) and slightly elevated fasting glucose (108 mg/dL).

We subsequently had a telephone call from the patient in January 2016, where she informed us that she had restarted pasireotide treatment and was experiencing extreme nausea, which subsided on promethazine prescribed by her OB/GYN.

SUMMARY OF CONCLUSIONS

Our patient's journey with CD illustrates several challenges associated with the disease. First, and most critically, is the challenge of receiving an accurate diagnosis. The diagnosis of CD often is delayed, in part due to a lack of awareness of the disease, but also nonspecific symptoms that resemble other metabolic diseases and complex testing requirements.[1,2] Complications of CD include mood disorders and muscle disease, contributing to poor quality of life, as well as hematologic, metabolic, and bone disorders.[1]

- Our patient first experienced symptoms of hypercortisolism at age 23, but was not accurately diagnosed until age 27. During those 4 years, she became frustrated with lack of relief. She developed anxiety, hyperglycemia, and chronic pain symptoms, leading to mostly ineffective polypharmacy that did not address the underlying cause.
- Another challenge is finding effective treatment that is tolerable and accessible. Our patient was fortunate to meet criteria for clinical trial enrollment and, although she had to dose-reduce due to side effects, achieved sufficient symptom relief with pasireotide 0.6 mg twice a day. Despite ongoing mild nausea, she remained on treatment for about 2 years before discovering she was pregnant. She then discontinued pasireotide because the limited pasireotide data in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage.
- While pregnant, she was challenged by return of CD symptoms, including hirsutism, facial acne, and muscle pain that persisted throughout her pregnancy.
- After delivery of a healthy baby, she faced a final challenge to restarting treatment because she lacked health insurance. Fortunately, we later learned she was able to reinitiate treatment.

Successful conception and pregnancy are unusual in women with CD due to fertility-inhibiting hormonal effects of excess cortisol. Further, some medications for CD impede pregnancy through their mechanism (eg, mifepristone). Our patient conceiving while on treatment is promising for women with CD. Although her CD symptoms returned when pasireotide was discontinued, she delivered a healthy infant. Our case underscores the potential for successful conception for women with CD when cortisol levels are normalized with treatment that avoids suppressing menstruation.

References
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Key Words
Cushing's Disease, Cushing's Syndrome, Fertility, Hypercortisolism, Pasireotide, Pregnancy