

Addison's disease presenting as shortness of breath and hypotension in early pregnancy

Avery Williams MD, Blair Buschmann MD, Afrina Rimu MD, Jennifer Phy DO

ABSTRACT

Background: Addison's disease is an adrenal cortex disorder that is considered rare, and the pathophysiology is not well understood. There are very few cases reported during pregnancy.

Case: This patient is a 30-year-old previously healthy woman who presented to the Reproductive Endocrinology and Infertility clinic at 7 weeks and 2 days pregnant with shortness of breath. After further evaluation, she was noted to have symptoms that led to the differential diagnosis of Addison's disease. The patient's 21-hydroxylase antibody was positive, which along with other tests confirmed the diagnosis. The endocrinology consultant started the patient on hydrocortisone and fludrocortisone.

Conclusion: This case adds to the literature on the relatively infrequent association of pregnancy with Addison's disease.

Keywords: Addison's disease, pregnancy, management

INTRODUCTION

Addison's disease, or primary autoimmune adrenal insufficiency, is a disorder involving the adrenal cortex that results in decreased production of glucocorticoids and mineralocorticoids. The most common cause is autoimmunity against the adrenal cortex cells or 21-hydroxylase. The disease is considered to be rare, and the pathophysiology is not well understood.¹ The current incidence is only 4–6 cases per 1 million people, making clinical suspicion for this diagnosis low on the differential diagnosis list in patient presentations. Often patients are not diagnosed until they present to the hospital in critical condition secondary to adrenal crisis. This affects the ability to treat the patient and possibly decreases the accurate reporting of the number of patients with this disease.^{2,3} Autoimmune disorders are believed to occur in people with a genetic susceptibility and then have an environmental trigger

that causes of acute dysfunction, but the triggers are unknown for this disorder.⁴ Since this disorder is so rare, there is even less research done on the presentation during pregnancy. This case report discusses a woman with no relevant past medical history, presenting during pregnancy with symptoms that were found to be due to Addison's disease.

CASE

PRESENTATION

A 30-year-old previously healthy G4P2012 at 7 weeks 2 days following frozen embryo transfer due to her husband's low sperm count presented to the Reproductive Endocrinology and Infertility (REI) clinic for ultrasound assessment and was found to be short of breath and hypotensive. She was sent to the emergency department (ED) where she complained of progressive shortness of breath with minimal exertion for about 1 week prior to presentation. She also complained of retrosternal chest pain occurring during episodes of shortness of breath that she described as a pressure sensation and rated as a 5/10 on the pain

Corresponding author: Jennifer Phy

Contact Information: Jenneifer.phy@ttuhsc.edu

DOI: 10.12746/swrccc.v10i45.1021

scale. She was found to be hypotensive (76 mmHg/54 mmHg) with decreased mean arterial pressure (62 mmHg) and tachycardic (heart rate 126 beats/minute). An electrocardiogram revealed normal sinus rhythm, no ST-T changes, no ectopy, and normal PR and QRS intervals. Computed tomography pulmonary embolus protocol was performed, and pulmonary embolism, lobar consolidation, pneumothorax, and pleural effusion were ruled out. Pulmonary vessels were within normal limits, the heart size was normal with no pericardial effusion, there were no enlarged lymph nodes, and musculoskeletal findings were within normal limits. A complete blood count revealed leukocytosis with white blood cell count elevated at 12.66 K/ μ L (normal 3.98–10.04 K/ μ L). A complete metabolic panel revealed hyponatremia of 132.0 mmol/L (normal 136–145 mmol/L). The potassium was 5.0 mmol/L (normal 3.5–5.1 mmol/L) with 1+ hemolysis on sample. Venous blood gases revealed a pH of 7.446 (normal 7.30–7.50), a low pCO₂ of 27.6 mmHg (normal 30.0–50.0 mmHg), and an elevated lactate level of 2.76 mmol/L (normal 0.50–1.60).

She was given 3L of crystalloid and ceftriaxone but remained hypotensive. She was admitted with continued intravenous fluids to the Medical Intensive Care Unit (MICU) for further evaluation of undifferentiated shock. Additional history obtained on admission to the MICU included a 2-week history of decreased intake by mouth secondary to nausea. The patient noted an associated decrease in her weight 10 weeks prior to this pregnancy but stated that her weight had been stable since becoming pregnant. She had never had any of these symptoms in prior pregnancies.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included hypovolemic shock secondary to hyperemesis gravidarum and/or peripartum cardiomyopathy, and/or distributive shock due to sepsis. A molar or tubal pregnancy with infection was also considered.

INVESTIGATIONS

After 3L of fluid, her blood pressures were stable. Respirations were not labored, and patient remained on room air. She was started on vancomycin and

piperacillin-tazobactam for possible sepsis, but 2 blood cultures were negative for growth at days 1–5. Urine culture also returned negative for growth. Methicillin-resistant *Staphylococcus aureus* (MRSA) screen by polymerase chain reaction (PCR) was negative, and *S aureus* by PCR was also negative. A repeat abdominal ultrasound was performed and showed no abnormalities. Beta-hCG level was appropriately elevated for gestational age at 62,861 MIU/mL. She received estrogen and progesterone daily for luteal support as part of her frozen embryo transfer protocol. Rheumatoid factor was <10 international units/mL (normal <14), and the anti-nuclear antibody screen was negative. A transthoracic echocardiogram was performed and revealed no functional or structural abnormalities.

Laboratory workup revealed a random cortisol level of 4.60 mcg/dL and elevated thyroid stimulating hormone of 4.54 mIU/mL (normal 0.27–4.20 mIU/mL). There are no published reference ranges for random cortisol levels but it was considered low, given her presentation with shock. On further questioning, the patient noted bilateral lower extremity muscle aches over the past few weeks and increased tanning of her skin over the past 2 months. A follow up AM cortisol was low at 3.90 mcg/dL (normal 6.0–18.4 mcg/dL). These findings suggested adrenal insufficiency and the endocrinology team was consulted. Adrenocorticotropic hormone (ACTH) stimulation test showed elevated ACTH at 1,033.0 pg/mL (normal 7.2–63.3 pg/mL). Baseline cortisol was low at 4.10 mcg/dL (normal 5.00–21.00 mcg/dL), 30-minute cortisol was low at 4.10 mcg/dL (normal 14.00–36.00 mcg/dL), and 60-minute cortisol was low at 3.80 mcg/dL (normal 14.00–41.00 mcg/dL) indicating no response to ACTH. Antibodies to 21-hydroxylase were positive indicating Addison's disease. The antithyroid peroxidase antibody was <9 IU/mL (normal high <34 IU/mL), and the thyroid stimulating immunoglobulins was <89% baseline (positive is >140% of reference control).

TREATMENT

The patient was started on hydrocortisone 40 mg in the morning and 20 mg at 3pm to be continued for 2 days followed by maintenance hydrocortisone 20 mg in the morning and 20 mg in the afternoon on

the third day. Fludrocortisone 0.1 mg BID was also started on the third day. It was discussed with the patient to double stress dose steroid dosing on days when she is ill and was counseled on possible stressors for which to use the stress dose. She was also started on levothyroxine 50 mcg daily for hypothyroidism.

OUTCOME AND FOLLOW-UP

The patient was followed up in the endocrinology clinic and REI clinic after discharge. She remained on vaginal estradiol 1 mg intra-vaginal two times per day and progesterone 200 mg intra-vaginal nightly for pregnancy support for 20 days until progesterone level was 23.95 ng/mL. The patient had a gastrointestinal illness 3 weeks after discharge and began taking stress dose steroids as advised. However, despite good PO intake and fluids, her fatigue increased significantly, and she reported tremors and trouble speaking in full sentences. Maintenance hydrocortisone was increased to 40 mg in the morning, 20 mg at 12 pm, and 10mg at 6pm, and fludrocortisone was increased to 0.1 mg twice daily. In the event of decreased PO intake, the patient was given intramuscular hydrocortisone and advised to go straight to the ED. Repeat labs showed TSH 3rd generation low at 0.01 mcIntUnit/mL (normal 0.27–4.20 mcIntUnit/mL) and free T4 within normal limits at 1.48 ng/dL (normal 0.93–1.70 ng/dL), and she was advised to stop taking levothyroxine.

The patient presented with spontaneous rupture of membranes at 37–4/7 weeks estimated gestational age. She received IV hydrocortisone 50 mg and then 20 mg orally twice daily while in labor. She subsequently delivered a liveborn male infant weighing 3690 gm by obstetrically assisted vaginal delivery with Apgar scores of 9 at one minute and 9 at 5 minutes. Hydrocortisone 20 mg was given twice daily for 2 days and then reduced to hydrocortisone 20 mg in the morning and 15 mg in the evening, which was continued until her postpartum visit with the endocrinology clinic several weeks later.

DISCUSSION

During pregnancy, the fetoplacental unit causes the HPA or hypothalamus-pituitary-adrenal axis to

increase its activity level. The placenta secretes both adrenocorticotrophic hormone (ACTH) and corticotropin-releasing hormone (CRH), and these are thought to be responsible for this increased HPA drive.^{5,6} The negative feedback response of cortisol on placental CRH is also suppressed during pregnancy, causing increased ACTH activity despite increased cortisol.⁷ In addition, the steroidogenic properties of the placenta not only cause a 2–3-fold increase in maternal plasma cortisol concentration but also an increase in cortisol binding globulin (CBG) by increasing its release from the liver. Furthermore, ongoing secretion of progesterone from the placenta displaces the cortisol from CBG, raising the free cortisol concentration similar to those found in Cushing's disease.^{8,9} These changes start to be observed during the first trimester.¹⁰ A study by Carr et al. determined that at 12 weeks, the plasma cortisol level is 14.9 ± 3.4 mcg/dL (411 ± 94 nmol/L). At 26-weeks' gestation, it increases to 35.2 ± 9.0 mcg/dL (971 ± 248 nmol/L) and then changes minimally thereafter.¹¹ In a longitudinal study conducted by Lopes et al., it was found that salivary cortisol levels were 0.13 mcg/dL (3.6 nmol/L) in nonpregnant control women; it increases as follows in pregnancy: in the first trimester the upper limit is 0.25 mcg/dL (6.9 nmol/L), during the second trimester the upper limit is 0.26 mcg/dL (7.2 nmol/L), and in the third trimester the upper limit is 0.33 mcg/dL (9.1 nmol/L).¹²

The renin-angiotensin-aldosterone system (RAAS) is also up regulated during pregnancy.¹³ The ovaries and maternal decidua cause increased secretion of renin, and the liver synthesizes an increased angiotensinogen stimulated by increased estrogen levels, leading to an increase in both angiotensin II and aldosterone.^{10,14} In this context, it is rare to diagnose any pregnant patient with Addison's disease since pregnancy causes hypercortisolism during pregnancy and may protect patients with partial deficiency.

Addison's disease in pregnancy is rare with a limited number of case reports. In 2003, a 34-year-old woman with an 8-year history of Addison's disease presented to the hospital for her first peripartum visit during her 18th week of pregnancy.¹⁵ At the time of presentation, she was found to have hypotension, hyponatremia, and cutaneous hyperpigmentation. She

was discharged with cortisone acetate 25 mg/daily and fludrocortisone 0.1 mg twice a week. When she presented to the clinic for a 24-week follow up, she continued to have hypotension and hyponatremia due to not taking her medications. The physician strongly advised her to take the prescribed medications. The patient then took her medications regularly for the rest of the pregnancy, and all checkups were normal until her 38-week appointment, when she was found to be hypertensive (140/110 mmHg). She was admitted to the hospital and laboratory tests were checked daily with no abnormal results. Induction was attempted three times with no success, and she had a c-section that resulted in a healthy baby boy. Blood tests of the newborn showed no antibodies against the adrenal gland, and he was found to have a normal functioning adrenal gland.

Another case report was published in 2011 on a patient who presented to the hospital with hyperemesis, normocytic anemia, lethargy, weight loss, and hyponatremia at 10 weeks of pregnancy.¹⁶ On physical examination, she was found to have brownish colored skin. Her morning serum cortisol was low at 26 nmol/l (reference range 150–650). She was diagnosed with Addison's disease after her ACTH was found to be high (1173 ng/l, reference range: <46 ng/l). The patient was given hydrocortisone, first intravenously (200 mg) and then orally. The patient had significant improvement in her symptoms after 2 days and was discharged on day 5. She continued taking oral hydrocortisone and fludrocortisone throughout her pregnancy. At 42 weeks of gestation, she gave birth to a healthy baby girl.

There has not been extensive research on the effect a new diagnosis of Addison's has on the course of a patient's pregnancy, the pregnant female herself, or on the baby due to the rarity of this disorder.⁵ However, this disorder needs more research to determine if there is an increased risk of morbidity or mortality during the pregnancy for mother or baby. There are some data that endocrinopathies, such as hypothyroidism and diabetes, affect fetal development, which is why it is so important to diagnose these disorders appropriately and begin the correct treatment. Another question that should be considered is whether or not the pregnancy is an environmental

trigger that induces someone with a predisposition for Addison's to fully develop the disease. This case report adds to the limited literature on the effect a primary diagnosis of Addison's disease can have on the course of a pregnancy as this patient presented with her symptoms so early in her pregnancy.

Article citation: Williams W, Buschmann B, Rimu A, Phy J. Addison's disease presenting as shortness of breath and hypotension in early pregnancy. *The Southwest Respiratory and Critical Care Chronicles* 2022;10(45): 54–58

From: Departments of Internal Medicine (AR) and Obstetrics and Gynecology (AW, BB, JP), Texas Tech University Health Sciences Center, Lubbock, Texas

Submitted: 3/3/2022

Accepted: 9/26/2022

Conflicts of interest: none

This work is licensed under a Creative Commons Attribution-ShareAlike 4.0 International License.

REFERENCES

1. Erichsen MM, Løvås K, Skinningsrud B, et al. Clinical, immunological, and genetic features of autoimmune primary adrenal insufficiency: Observations from a Norwegian registry. *J Clinical Endocrinology Metabolism* 2009;94(12). doi:10.1210/jc.2009–1368
2. Bleicken B, Hahner S, Ventz M, et al. Delayed diagnosis of adrenal insufficiency is common: A cross-sectional study in 216 patients. *Am J Med Sc* 2010;339(6). doi: 10.1097/MAJ.0b013e3181db6b7a
3. Løvås K, Husebye ES. High prevalence and increasing incidence of Addison's disease in western Norway. *Clin Endocrinology* 2002;56(6). doi:10.1046/j.1365-2265. 2002. t01-1-01552.x
4. Christen U, Herrath MG. Initiation of autoimmunity. *Current Opinion Immunology* 2004;16(6). doi: 10.1016/j.coi. 2004.09.002
5. Lekarev O, New MI. Adrenal disease in pregnancy. *Best Pract Res Clin Endocrinol Metab* 2011;25:959–73.
6. Sandman CA, Glynn L, Schetter CD, et al. Elevated maternal cortisol early in pregnancy predicts third trimester levels of placental corticotropin releasing hormone (CRH): priming the placental clock. *Peptides* 2006;27:1457–63.

7. Karaca Z, Tanriverdi F, Unluhizarci K, et al. Pregnancy and pituitary disorders. *Eur J Endocrinol* 2010;162:453–75.
8. Carr BR, Parker CR Jr, Madden JD, et al. Maternal plasma adrenocorticotropin and cortisol relationships throughout human pregnancy. *Am J Obstet Gynecol* 1981;139:416–22.
9. Demey-Ponsart E, Foidart JM, et al. Serum CBG, free and total cortisol and circadian patterns of adrenal function in normal pregnancy. *J Steroid Biochem* 1982;16:165–9.
10. Kamoun M, Mnif MF, Charfi N, et al. Adrenal diseases during pregnancy: pathophysiology, diagnosis and management strategies. *Am J Med Sci* 2014 Jan;347(1):64–73. doi: 10.1097/MAJ.0b013e31828aaeee.
11. Carr BR, Parker CR Jr, Madden JD, et al. Maternal plasma adrenocorticotropin and cortisol relationships throughout human pregnancy. *Am J Obstet Gynecol* 1981 Feb 15;139(4):416–22. doi: 10.1016/0002-9378(81)90318-5.
12. Lopes LM, Francisco RP, Galletta MA, et al. Determination of nighttime salivary cortisol during pregnancy: comparison with values in non-pregnancy and Cushing's disease. *Pituitary* 2016 Feb;19(1):30–8. doi:10.1007/s11102-015-0680-3.
13. Irani RA, Xia Y. The functional role of the renin-angiotensin system in pregnancy and preeclampsia. *Placenta* 2008;29:763–71.
14. Langer B, Grima M, Coquard C, et al. Plasma active renin, angiotensin I, and angiotensin II during pregnancy and in preeclampsia. *Obstet Gynecol* 1998;91:196–202.
15. Scrimin F, Panerari F, Guaschino S. Addison's disease and hypothyroidism untreated until twenty-four weeks of pregnancy. *Acta Obstetrica et Gynecologica Scandinavica* 2005;84(2). doi:10.1111/j.0001-6349.2005.02555b.x
16. Ebeling F, Rahkonen L, Saastamoinen KP, et al. Addison's disease presenting as hyperemesis, hyponatremia and pancytopenia in early pregnancy. *Acta Obstetrica et Gynecologica Scandinavica* 2011;90(1). doi:10.1111/j.1600-0412.2010.01003.