

## A Rare Case of Addison's Disease Diagnosed During Early Pregnancy

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### Abstract

Addison's disease is a rare autoimmune condition in which the adrenal gland is attacked by the body's own immune cells, leading to a decreased production of cortisol and aldosterone. This condition can present insidiously with overlap of symptoms related to the physiologic effects of pregnancy. We report the case of a first trimester pregnant woman with a history of type 1 diabetes mellitus and Hashimoto's thyroiditis who presented with intractable vomiting and hyponatremia. The patient had presented with similar, less severe symptoms in years prior but was not diagnosed with Addison's due to confounding illnesses and other factors. Many of the patient's presenting symptoms were thought to be pregnancy related. She was eventually diagnosed with Addison's disease and oral hydrocortisone and fludrocortisone were initiated for treatment. Addison's disease is rare and is easily masked by symptoms associated with pregnancy. Timely recognition and diagnosis are necessary to prevent adverse maternal-fetal outcomes.

**Keywords:** Addison's Disease, Pregnancy, Hyponatremia, Adrenal Insufficiency

### 1. Introduction

Primary adrenal insufficiency, also known as Addison's disease (AD), is a rare condition that can be difficult to diagnose. There are an estimated 0.6 new cases of AD per 100,000 people per year, with the prevalence being 4 to 11 per 100,000 people. It is more common in women, patients with previously existing autoimmune conditions, and typically presents at 30 to 50 years of age [7]. The most common etiology of AD is bilateral T-cell-mediated destruction of the adrenal cortex, typically the zona glomerulosa and zona fasciculata, resulting in decreased serum mineralocorticoid and glucocorticoid levels [2]. In most cases of autoimmune adrenalitis, the major antibody detected targets 21-hydroxylase, a key enzyme in aldosterone and cortisol biosynthesis [1]. AD can present insidiously with a wide range of signs and symptoms, including nausea, vomiting, abdominal pain, anorexia, weakness, hyperpigmentation, hypotension, hyponatremia, and unexplained fever. Several of these symptoms can be masked by or mistaken for other conditions [12]. A number of the symptoms of AD overlap with physiologic changes associated with pregnancy. The most common symptoms in the first trimester of pregnancy include amenorrhea, mild uterine discomfort, nausea, vomiting, fatigue, dyspnea, lightheadedness, hypotension, melasma, and increased urinary frequency [13]. The most common electrolyte abnormality in pregnancy is hyponatremia, which is caused by a decrease in osmotic threshold at which antidiuretic hormone (ADH) is released [6]. At 8 weeks gestation, the renin-angiotensin-aldosterone system

is upregulated such that the normal values for aldosterone increase from 2-9 ng/dL in nonpregnant patients to 6-104 ng/dL in patients in their first trimester. Lastly, dilutional anemia occurs during pregnancy due to the total blood volume increasing more than red blood cell mass, leading to a decrease in hemoglobin, hematocrit, and RBC count [8].

Since autoimmune diseases are more common in women, there have been co-occurrences of Addison's disease and pregnancy, though it is uncommon. However, the simultaneous existence of the two conditions is becoming more common, and according to a population-based cohort study of 7.7 million live births, the prevalence of AD in pregnancy was 5.6/100,000 and rose to 9.6/100,000 over a nine-year period [9]. Pregnant patients with AD can present with severe nausea, vomiting, hypotension, weakness, and hyperpigmentation, similar to how pregnant patients present who are not suffering from AD [10].

As estrogen increases throughout pregnancy, it causes an increase in corticosteroid binding globulin (CBG) and a subsequent increase in circulating cortisol [11]. During the puerperium, cortisol declines to its levels prior to pregnancy. Due to the abrupt decline in cortisol in the early post-partum period, Addisonian crises and AD diagnoses are more common after pregnancy [4]. Patients with AD in pregnancy, especially when left untreated, are more likely to deliver preterm and via cesarian section, have impaired wound healing, infections, thromboem-

bolic events, longer post-partum admissions, and higher mortality rates. Additionally, babies born to mothers with AD have a higher risk of congenital anomalies and low birthweight [9].

## 2. Case Presentation

32-year-old 8 weeks pregnant G2P1 female with a history of type 1 diabetes mellitus and Hashimoto's thyroiditis presented with a 2-week history of severe nausea and vomiting at an outpatient prenatal visit. She reported up to 30 episodes of vomiting a day as well as lightheadedness, fatigue, confusion, and malaise. She was found to be hyponatremic with a sodium of 123mmol/L, which was a downward trend from her level of 128mmol/L two weeks prior. Additionally, she was hypotensive with a blood pressure as low as 93/59 mmHg. She was subsequently admitted to the ED at a nearby hospital where similar lab values were obtained and revealed a low serum osmolality of 259 mOsm/kg. She received isotonic saline fluid resuscitation, and her sodium rose to 130 after 48 hours. The hyponatremia was attributed to poor oral intake, physiologic effects of pregnancy, and the possibility of syndrome of inappropriate antidiuretic hormone (SIADH). She was discharged after 2 days and instructed to limit free water intake to 1.2L.

On the day after she was discharged from the hospital, the patient presented to her primary care physician to follow up on her hospital course where she reported feeling 70% better but had experienced nausea, lightheadedness, confusion, a few muscle twitches, and was not able to tolerate much food. Her blood pressure had decreased to 92/64 and her sodium was back down to 124mmol/L, so she was advised to return to the emergency room. Twenty-four hours later, she developed a fever of 100.9°F, right upper quadrant abdominal pain, and flank pain. On the same day, her AM cortisol was found to be low-normal at 6.5µg/dL. For improved control of her continued nausea and vomiting, she was given metoclopramide, but this provoked a near-anaphylactic reaction. Additionally, her sodium level stopped increasing with fluid resuscitation, so sodium chloride (NaCl) tablets were initiated.

The following day, a cosyntropin (ACTH) stimulation test was done, and the resulting stimulated cortisol level was 8.8µg/dL, suggesting adrenal insufficiency. ACTH was found to be elevated at 474pg/mL, and she tested positive for the 21-hydroxylase antibody. Her renin and aldosterone were within normal ranges. The patient was diagnosed with primary adrenal insufficiency with suspected autoimmune polyglandular syndrome type II given her history of type 1 diabetes and Hashimoto's thyroiditis, and she was started on oral hydrocortisone twice daily. Two and a half weeks after her discharge, the patient presented to her outpatient endocrinologist with residual nausea and vomiting and a sodium of 131 mmol/L. It was determined that hydrocortisone alone was insufficient in replacing her mineralocorticoid levels, so fludrocortisone 0.05mg was added to her daily treatment regimen. Several weeks later at her 18-week prenatal visit, she reported feeling better and more energized with minimal nausea and vomiting, a sodium of 135 mmol/L, and positive fetal movements with reassuring non-invasive fetal testing.

## 3. Discussion

The diagnosis of adrenal insufficiency (AI) in pregnancy is a diagnostic challenge. This is in large part due to confounding physiologic changes in pregnancy that are shared findings in those with AI, both primary AI and secondary AI, but are non-specific to any particular disease state. Because the clinical features are largely nonspecific, there is often a delay in timely diagnosis and treatment. Additionally, misdiagnoses and invasive workups are often seen, especially in those with no pre-existing history of adrenal disease [3]. To further complicate the efficiency of diagnosis during pregnancy, one of the hallmark electrolyte abnormalities associated with AI is a shared finding in pregnancy – hyponatremia. Hyponatremia is, in fact, the most common electrolyte abnormality in pregnancy.<sup>6</sup> This was seen in our patient and was initially thought to be related to hyperemesis or SIADH.

One of the elements that makes this case unique is the patient's pre-existing history of autoimmune hypothyroidism and type 1 diabetes mellitus. Once AD was confirmed, she met the diagnostic criteria for autoimmune polyglandular syndrome, type II. It is important to note that the conditions that make up this disorder can present in any order, with hypothyroidism and adrenal insufficiency symptoms sharing the largest degree of clinical overlap [5]. AI was the last condition to be diagnosed in our patient.

When formulating differential diagnoses for AI in pregnancy, such as hypothyroidism, hyperemesis gravidarum, and progesterone-mediated effects, it can be difficult to distinguish between the diagnoses because of significant clinical overlap [10]. The other complicating factor is the fact that the symptoms in AI tend to develop insidiously. A cross-sectional analysis of 216 patients retrospectively analyzed the clinical circumstances prior to and at the time of AI diagnosis. This study found that 20% of patients who had been diagnosed with AI had been dealing with symptoms for greater than 5 years prior to the time of diagnosis. Most of the patients (67%) cited they had seen at least 3 physicians and 30% of the patients had visited 5 or more physicians prior to being diagnosed with AI. Misdiagnoses were made in 68% of the patients, particularly in women and patients with primary adrenal insufficiency [3].

When looking at the patient's medical records, it became evident that she had presented to different hospital systems in the past with similar symptoms. Four and a half years prior to the time she was diagnosed with AD, she had experienced Epstein Barr virus-associated mononucleosis. Her blood pressure upon presentation at that time was 85/61. She recovered, but three months later she began to have mild persistent morning nausea, occasional vomiting, weight loss, and a low-normal sodium of 136mmol/L. After recovery, she noted persistent fatigue that was worse in the morning, and later that year, she was found to have a positive ANA with a homogenous pattern along with a positive RNP antibody. Due to her presentation of fatigue, family history of systemic lupus erythematosus (SLE), and a positive ANA and RNP, her rheumatologist performed a workup for SLE. Ultimately, her symptoms were attributed to either a post

viral chronic fatigue syndrome from mononucleosis or less than optimal sleep hygiene from her work, as she did not show other symptoms suggestive of SLE.

During the same year, the patient visited another clinic to be evaluated for Cushing's disease after having morning nausea, lightheadedness, hair thinning, and a weight gain of 10 pounds. Her morning serum cortisol and ACTH were both elevated at 28mcg/dL and 55pg/mL, respectively. She denied steroid use but reported taking ethinyl estradiol as an oral contraceptive. Her elevated serum cortisol was attributed to an increase in CBG associated with OCP use, and Cushing's disease was ruled out after obtaining a normal 24-hour urine cortisol value. Her chronic morning nausea remained persistent with unclear etiology, so a referral to gastroenterology was recommended.

Recognizing the challenges associated with timely diagnosis is critical if we are to change the paradigm and reduce the mortality risks for mother and baby for cases of AI affecting pregnancy. Prompt recognition and treatment of this disease is essential because pregnancies complicated by AI have higher rates of adverse outcomes. These outcomes include maternal mortality, preterm delivery, preterm premature rupture of membranes, thromboembolic disease, cesarean sections, wound infections, small for gestational age babies and congenital anomalies [9].

Fortunately, our patient did not experience any of these complications and delivered a healthy baby girl at 38 weeks gestation. We feel fortunate to have been able to establish the diagnosis of AD in the first trimester of pregnancy but can also attest to the difficulty in making the proper diagnosis due to significant clinical overlap of typical AD signs/symptoms and physiologic changes associated with pregnancy.

#### 4. Conclusion

Pregnancy is associated with many physiologic changes that share a clinical intersection with the signs and symptoms of AD. Timely diagnosis of AD (should we be consistent with AD/AI throughout the paper or is it acceptable to switch back and forth?) can be severely impaired by this overlap, delaying diagnoses in both pregnant and non-pregnant patients. Increased suspicion for AD should be factored into diagnostic frameworks for patients who present with symptoms and have pre-existing autoimmune disease, as the likelihood of autoimmune polyglandular disease in this population of patients is higher. Improved awareness of the diagnostic challenges associated with making a prompt and accurate diagnosis is one way to heighten the clinician's clinical suspicion for AI and guide them to initiate therapy that can improve the overall quality of life and save the patient's life.

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