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Diagnosing and managing adrenal crisis in pregnancy: A case report

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ABSTRACT

Background: The diagnosis of adrenal insufficiency in pregnancy is relatively rare. Further, making this diagnosis can be challenging as many of the symptoms overlap with normal symptoms of pregnancy. Given the potential for severe maternal and fetal morbidity and mortality, early recognition and prompt comprehensive treatment are critical.

Case: A 24-year-old woman, G3 P2002, at 17 + 1 weeks of gestation with unremarkable prenatal course was admitted to hospital for hyperemesis gravidarum in the setting of parainfluenza with a notable blood glucose of 20 mg/dL. On hospital day two, she was transferred to intensive care after developing significant hypotension, hyponatremia, and a new finding of hypothyroidism. During her evaluation in the ICU, she was diagnosed with adrenal crisis and she showed significant improvement with glucocorticoid therapy.

Conclusions: There is a paucity of literature regarding diagnosing adrenal insufficiency in pregnancy. Adrenal crisis in pregnancy can present with symptoms similar to severe nausea and vomiting of pregnancy or hyperemesis gravidarum. Additionally, several critical laboratory tests to support the proper diagnosis require time that acute patients cannot always afford. In this patient's case, the diagnosis was made empirically with improvement after glucocorticoid administration, and was later confirmed by laboratory testing. This case highlights the importance of including adrenal insufficiency in the differential diagnosis of hyperemesis patients in order to quickly manage and treat these often acutely and severely ill patients.

1. Introduction

The adrenal cortex takes part in steroidogenesis, producing glucocorticoids, and androgen precursors. An understanding of the hypothalamic-pituitary-adrenal (HPA) axis aids in understanding the pathophysiology of adrenal disorders. In response to stressors, the hypothalamus makes and secretes corticotopin-releasing hormone (CRH), which then binds to receptors on the anterior pituitary, releasing adrenocorticotropic hormone (ACTH) into circulation. This ACTH then binds to receptors on the adrenal cortex to induce synthesis of glucocorticoids. Cortisol is the major glucocorticoid, and increases in response to stress, which activates the HPA axis. Therefore, all of its functions can be thought to allow the body to function at an increased level of physiologic stress. There are several opportunities for pathologic dysfunction through this complex system, including primary, secondary, or tertiary causes of adrenal disorders [1,2].

The fetoplacental unit plays a major role in cortisol levels in pregnancy [3]. In women with intact adrenal function, the plasma levels of free cortisol, CRH, and cortisol-binding globulin all increase in pregnancy [4]. These hormone levels increase with increasing gestational age. When comparing elevations in maternal total serum cortisol levels to those in non-pregnant controls, a mean increase of 1.3, 2.0 and 2.4 times the normal were found in the 1st, 2nd, and 3rd trimester, respectively [5]. These total and free cortisol level increases are thought to be due to increases in CRH and ACTH from the placenta. Even with these average increases in cortisol levels, the amplitude is poorly understood, and exact reference values have yet to be established [3]. With this brief review, this case highlights a rare case of adrenal crisis developing in pregnancy in a patient with no known history of adrenal dysfunction.

2. Case

A 24-year-old woman, gravida 3 para 2, at 17 = +1 weeks of gestation presented to an acute care center for persistent nausea and vomiting that had begun earlier that morning. Her prenatal course was previously complicated by mild nausea and vomiting of pregnancy. On arrival, she reported lightheadedness and there was concern for confusion and altered mental status by the provider who initially evaluated her. Her vitals were notable for blood pressures in the 100 s/60s and mild tachycardia to the low 100 beats per minute. Notably, a fingerstick blood glucose level was collected given her altered mental status and

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was found to be 20 mg/dL. She was immediately resuscitated with intravenous fluids with dextrose and antiemetics, with rapid improvement of her blood glucose levels, mental status, and overall symptomatology. She was then transferred for inpatient management and monitoring.

On arrival at the inpatient floor, the patient reported overall improvement. Her blood pressures and symptoms then remained stable overnight. Her review of systems was positive for new-onset nasal congestion, rhinitis, and cough that had begun the same morning as her presenting symptoms of nausea and vomiting. The patient revealed in interview that on several occasions in her prior pregnancies, she had low blood glucose levels associated with nausea and vomiting, requiring intravenous glucose. Her past medical history was significant for mild, intermittent asthma, anemia, and allergic rhinitis and her obstetric history included two prior term, uncomplicated, spontaneous vaginal deliveries. Her family history was notable for a diagnosis of systemic lupus erythematosus in her father.

After initial stabilization, patient developed hypotension with tachycardia despite resuscitation with 2 l of crystalloid fluids, and recurrence of her hypoglycemia without nausea or vomiting. Her rapid viral panel had also resulted by this time positive for parainfluenza virus and her thyroid stimulating hormone had also resulted significant for new hypothyroidism. A rapid response was initiated, and the patient was transferred to the intensive care unit for resuscitation.

On arrival, the critical care team was concerned for adrenal crisis after a trigger from an upper respiratory virus. She was started on intravenous hydrocortisone with immediate improvement in maternal status. She remained stable through the remainder of her hospital stay with regular fetal heart rate checks. Endocrinology assessed this patient and believed she was experiencing adrenal crisis of unknown etiology, potentially secondary to an autoimmune process as supported by several laboratory values collected during her evaluation. In particular, her cortisol level was collected immediately prior to empiric treatment and was found to be 0.5 μg/dL. Additionally, her thyroglobulin antibody level was elevated, consistent with an autoimmune disease process of the thyroid. Finally, her adrenocorticotropin hormone was undetectable on several lab assays, and her prolactin level was 17 μg/L, which is inappropriately low in pregnancy. Her diagnosis of adrenal crisis was supported with immediate improvement with glucocorticoids and a brain MRI that showed a partially empty sella with flattened pituitary gland (Fig. 1), which, although not diagnostic of secondary adrenal dysfunction, can be associated with impairment.

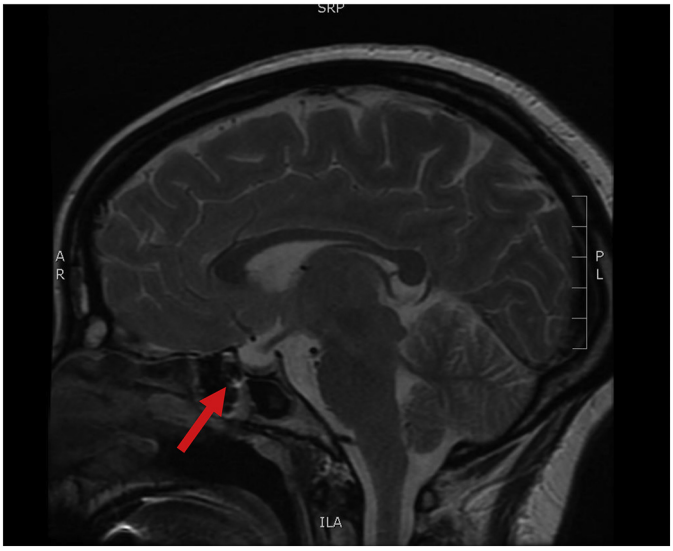

Fig. 1. Brain MRI highlighting a partially empty sella (arrow) and flattened pituitary gland.

3. Discussion

Adrenal insufficiency is defined as the inability of the adrenal cortex to produce sufficient amounts of glucocorticoids and/or mineralocorticoids. This can be potentially life-threatening, as adrenal physiology is critical in hemodynamic and electrolyte homeostasis. The diagnosis of adrenal insufficiency is based on low morning cortisol concentrations, and this diagnosis is most likely when cortisol is <5 μg/dL [6]. Standard cortisol values are poorly established in pregnancy, and while cortisol is expected to rise with increasing gestational age, reference values in pregnancy have yet to be established [5]. Additionally, an abnormal rise in cortisol levels after a stimulation test of 250 micrograms of cosyntropin can be used to diagnose adrenal insufficiency in pregnancy, for which the minimum expected peak values per trimester are 25, 29, and 32 μg/dL, respectively [5,7].

The majority of adrenal insufficiency cases during pregnancy are diagnosed prior to conception. There is typically a low clinical suspicion of new adrenal insufficiency in pregnancy, given the overlapping signs of symptoms with normal pregnancy, nausea and vomiting in pregnancy, and hyperemesis gravidarum such as fatigue, nausea, vomiting, and mild hypotension [7]. In fact, only 100 cases of adrenal insufficiency have been reported to be diagnosed during pregnancy [8].

Adrenal crisis is an acute form of adrenal insufficiency leading to hemodynamic instability, typically necessitating care in an intensive care unit and immediate intravenous glucocorticoids. When a patient progresses to adrenal crisis, timing often does not allow for cosyntropin or other testing to diagnose adrenal insufficiency, as treating empirically is far more important, as was the case with this patient. Although rare, adrenal crisis is critical to diagnose quickly, as the mortality rate without treatment ranges as high as 35%–45%. Additionally, severe maternal and fetal morbidity of untreated adrenal crisis includes poor wound healing, infection, venous thromboembolism, prolonged hospital stays, fetal intrauterine growth restriction, preterm delivery, and increased risk of Cesarean delivery [3,7]. Even in patients with a known history of adrenal insufficiency in pregnancy, the development of adrenal crisis is rare. In a prospective series of 423 patients with adrenal insufficiency, pregnancy was found to trigger adrenal crisis in 0.2%. In a study of 93 patients with known insufficiency, only 1.1% developed adrenal crisis in pregnancy. The incidence of new-onset adrenal crisis without a known pre-existing adrenal disorder is unknown [7].

As mentioned in the case, this patient's cortisol levels were low and ACTH levels were undetectable on separate laboratory draws. Typically, ACTH increases in proportion to increasing cortisol in pregnancy. While standard average values are poorly established, ACTH has been documented to range anywhere from 10 to 300 pg/mL between 10 and 40 weeks of gestation, respectively [9]. Additionally, her thyroid stimulating hormone was decreased with an increased thyroglobulin antibody, consistent with autoimmune involvement. Finally, her prolactin was within normal range for a nonpregnant woman, which is unusual, as prolactin is typically elevated in pregnancy, ranging from 35 to 600 ng/mL, with increases seen with increasing gestational age [10].

While the trigger of this patient's adrenal insufficiency is unclear, downregulation of the immune system during pregnancy coupled with her acute parainfluenza virus may have contributed to the possible autoimmune process in this case. The maternal immune system is complex in pregnancy. There is evidence that pregnancy causes generalized leukocyte activation with an increase in circulating granulocytes and a decrease in circulating lymphocytes. Therefore, it is thought that while the innate immune system is elevated in pregnancy, the adaptive immune system may be downregulated [11]. Furthermore, the molecular mimicry mechanism describes how a foreign antigen shares sequences with self-antigens, activating T-cells through T-cell receptors and leading to an autoimmune process [12]. Therefore, it is possible that the patient highlighted in this case had a viral trigger coupled with the downregulation of the adaptive immune response leading to an

autoimmune reaction and clinical manifestation of autoimmune adrenal insufficiency.

The patient in this case continued her thyroid hormone supplement and oral glucocorticoid for the remainder of her pregnancy. She went on to have a term, vaginal delivery at 38 + 2 weeks of gestation productive of a viable male newborn after presenting in spontaneous labor. She received stress-dose steroids during her labor course and remained hemodynamically stable throughout her intrapartum and postpartum stay. Her follow-up and long-term management plans are to continue titrating her thyroid hormone and glucocorticoid doses per endocrinology recommendations as well as assessing if she is still affected by her adrenal insufficiency and hypothyroidism in the nonpregnant state.

In summary, the diagnosis of adrenal insufficiency, and subsequently adrenal crisis, is difficult to diagnose given vague and overlapping signs and symptoms and the rarity at which it occurs. However, prompt diagnosis is critical in preventing significant maternal and fetal morbidity and mortality.

4. Conclusion

This patient continued her pregnancy on daily oral glucocorticoids and was discharged home with an "emergency Addison's kit" of intramuscular glucocorticoid for sick days, in order to prevent a second episode of adrenal crisis. She progressed to have an uncomplicated, term, spontaneous vaginal delivery with stress-dose steroids, which remains the recommendation in patients on glucocorticoids for adrenal dysfunction [5]. This case highlights the rarity of adrenal crisis in pregnancy, especially in patients with no known history of pre-existing adrenal dysfunction. Importantly, this case also highlights the low suspicion of adrenal insufficiency in pregnancy due to generalized and common symptoms of pregnancy. In this patient's case, it is theorized that she had a predisposition to autoimmune adrenal and thyroid dysfunction that was triggered by an upper respiratory virus, which is a common trigger for autoimmune conditions. While impossible to retrospectively diagnose, this patient may have had more mild symptoms of adrenal insufficiency in her prior pregnancies, as well. In summary, we recommend an increased level of suspicion of adrenal crisis and/or insufficiency in pregnancy in patients like the patient described in this case who have symptoms and lab findings out of proportion to their gestational age or expected severity.

Contributors

Rene MacKinnon participated in acquisition of data and drafted the article.

Allison Eubanks participated in acquisition of data and assisted in drafting the article.

Kelly Shay participated in acquisition of data and assisted in drafting the article.

Brian Belson participated in critical revision of the article for important content.

All authors saw and approved the final version.

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Conflict of Interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

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