Endocrinology, Diabetes & Metabolism CASE REPORTS

D Oliveira and others | Treatment of Addison's disease during pregnancy

ID: 17-0179; April 2018
DOI: 10.1530/EDM-17-0179

Treatment of Addison's disease during pregnancy

Diana Oliveira, Adriana Lages, Sandra Paiva and Francisco Carrilho

Endocrinology, Diabetes and Metabolism Department, Coimbra Hospital and University Center, Coimbra, Portugal

Correspondence should be addressed to D Oliveira
Email
dianapontooliveira@gmail.com

Summary

Addison's disease, or primary adrenocortical insufficiency, is a long-term, potentially severe, rare endocrine disorder. In pregnancy, it is even rarer. We report the case of a 30-year-old pregnant patient with Addison's disease, referred to Obstetrics-Endocrinology specialty consult at 14 weeks gestation. She had been to the emergency department of her local hospital various times during the first trimester presenting with a clinical scenario suggestive of glucocorticoid under-replacement (nausea, persistent vomiting and hypotension), but this was interpreted as normal pregnancy symptoms. Hydrocortisone dose was adjusted, and the patient maintained regular follow-up. No complications were reported for the remainder of gestation and delivery. Pregnant patients with Addison's disease should be monitored during gestation and in the peripartum period by multidisciplinary teams. Adjustments in glucocorticoid and mineralocorticoid replacement therapy are often necessary, and monitoring should be based mainly on clinical findings, which becomes increasingly difficult during pregnancy. Patient education and specialized monitoring are key to avoiding complications from under- or over-replacement therapy in this period.

Learning points:

- An increase in glucocorticoid replacement dose is expected to be necessary during pregnancy in a woman with Addison's disease.
- Patient education regarding steroid cover and symptoms of acute adrenal crisis are fundamental.
- Monitoring in this period is challenging and remains mainly clinical.
- The increase in hydrocortisone dose often obviates the need to increase fludrocortisone dose.

Background

Primary adrenal insufficiency or Addison's disease (AD) is a rare chronic condition (prevalence of 4–11 cases per 100 000) characterized by glucocorticoid and mineralocorticoid deficiency due to lesion of the adrenal glands through different mechanisms. In developed countries, autoimmune adrenalitis is the most common cause, accounting for more than 70% of all cases of primary hypoadrenalism (1).

The precise prevalence of AD in pregnancy is not known. Women with AD show reduced parity (2, 3), the cause of that being probably multifactorial – women with chronic diseases can be reluctant to become pregnant for concerns about associated complications, and other concomitant autoimmune diseases as type 1 diabetes and autoimmune thyroid disease can cause reduced fertility (4). The loss of adrenal androgens could play a role in the fertility of these patients, although this is not clear (2), and may affect libido and sexual activity (3). Considering this together with the rarity of the condition, a pregnant Addison patient is a very infrequent scenario in clinical practice. Gestation in these patients requires specific and attentive care. An acute adrenal crisis, with severe risk

ID: 17-0179; April 2018
DOI: 10.1530/EDM-17-0179

for mother and child, can be elicited by hyperemesis gravidarum, infections and delivery (both vaginal and cesarean) (4) or failure to adequately adjust substitution therapy doses, which can be due to poor adherence, lack of education or insufficient medical monitoring.

This case illustrates the main pitfalls in the follow-up and briefly reviews management strategies useful in this period. Although the patient presented several times with nausea, persistent vomiting and hypotension, this clinical picture was not recognized as indicative of adrenal crisis, despite the known diagnosis of AD.

Case presentation

We report the case of a 30-year-old Caucasian female, primigravida, with AD diagnosed at 13 years of age. She was usually medicated with hydrocortisone 20 mg + 10 mg. On the first trimester of pregnancy, she was admitted to the emergency department of her local hospital several times with complaints of tiredness, persistent vomiting and low arterial blood pressure (BP).

She was referred to the Obstetrics-Endocrinology specialty consult at 14 weeks gestation. She presented in the consult with BP 110/60 mmHg, heart rate 90 bpm, and marked mucocutaneous hyperpigmentation.

Investigation and treatment

Analytical evaluation at 14 weeks gestation showed ACTH > 1250 pg/mL, cortisol 0.24 µg/dL (5–25) (Figure 1). Hydrocortisone was uptitrated to 20 mg + 10 mg + 10 mg. Fludrocortisone 0.05 mg id was prescribed, however, the patient did not take it because of teratogenicity concerns.

At 20 weeks, after dose adjustment, the patient referred feeling better, with more energy and no nausea or vomiting and showed evident reduction of the mucocutaneous pigmentation. ACTH was 9.1 pg/mL (9–52), cortisol 18 µg/dL (5–25), active renin 1292 µU/mL (7–76), aldosterone 41.9 pg/mL (40–310), sodium 135 mmol/L (136–146) and potassium 4.2 mmol/L (3.5–5.1). Anti-21-hydroxylase antibodies were positive, thyroid function normal and anti-thyroid antibodies negative. Celiac disease and pernicious anemia screening was negative. Fetal ultrasound showed normal biometric measurements and morphology. At 30 weeks gestation, hydrocortisone dose was adjusted to 20 mg + 20 mg + 10 mg. The remainder of the pregnancy proceeded without complications, the patient was clinically well, with normal electrolytes, glucose and BP. Estimated fetal weight in the 50th percentile.

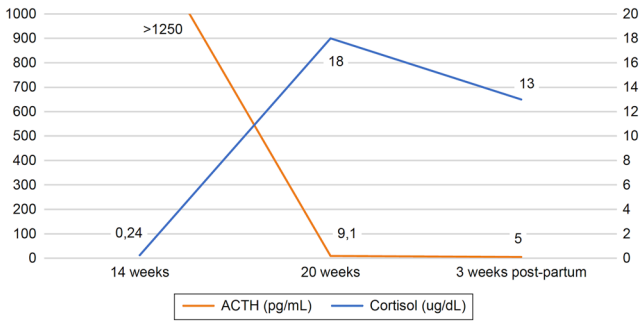

Figure 1
ACTH and cortisol values before and after hydrocortisone dose adjustment and at 3 weeks post-partum.

Outcome and follow-up

At 41 weeks gestation, she was electively committed for labor induction, and she was started on a previously defined protocol, which included intravenous administration of hydrocortisone in the active phase of labor (100 mg, 8/8 h). BP registered during labor was 119/60–139/89 mmHg. Delivery was eutocic, without incidents, and she gave birth to a feminine newborn, 4030 g, Apgar 9/10/10. After delivery, she restarted hydrocortisone p.o. in twice the dose used during pregnancy (40 mg + 40 mg + 20 mg), reduced after 48 h to the dose used in the last weeks of gestation. She maintained normal BP values, adequate energy levels and normal blood electrolytes. Hydrocortisone posology was tapered to usual maintenance doses during the following days. Two years after pregnancy, she maintains regular evaluation in the endocrinology outpatient clinic, treated with hydrocortisone 15 mg + 5 mg and fludrocortisone 0.1 mg id and aware of the necessity for specialized follow-up in a future pregnancy, if desired.

Discussion

The objective of the follow-up of a woman with AD during pregnancy is to keep the replacement therapy in doses that assure the mother and fetus health, avoiding effects of over-treatment (e.g. gestational diabetes, excessive weight gain, arterial hypertension) and of under-treatment (low birth weight (3), adrenal crisis in the mother, electrolyte imbalance).

Glucocorticoid replacement

The ideal glucocorticoid replacement dosing scheme for the pregnant patient with AD is not defined, but the need to adjust the dose throughout gestation is expected.

ID: 17-0179; April 2018
DOI: 10.1530/EDM-17-0179

A 20–40% increase is usually necessary after the 24th week, an attempt to mimic the physiologic elevation of cortisol levels that occur in that period of a normal pregnancy (5). Hydrocortisone is the glucocorticoid of choice as it does not cross the placenta (6). Monitoring, as with non-pregnant patients, is based on clinical findings but becomes more challenging during pregnancy, when rather low-specificity signs of excessive replacement (striae, weight gain) or insufficient replacement (tiredness, nausea, vomiting) are frequently present in patients with or without AD. This difficulty is illustrated by the presented case, in which complaints consistent with insufficient therapy doses were interpreted as usual symptoms of pregnancy and not as warning signs. Therapeutic education is key when it comes to hydrocortisone dosing and schedule self-adjustment or hydrocortisone self-injection in sick days or in case of vomiting. The patient must carry an identified steroid emergency card and be able to recognize clinical situations that require treatment in the hospital setting.

Mineralocorticoid replacement

Renin may not be a reliable indicator of mineralocorticoid necessity during pregnancy, as a physiologic elevation is expected in this period. Progesterone shows anti-mineralocorticoid properties, and because there is a rise in its levels during pregnancy, an adjustment in fludrocortisone dose might be needed (5). Despite that, 40 mg of hydrocortisone have a mineralocorticoid activity equivalent to approximately 0.1 mg fludrocortisone (5), and therefore, the increase in hydrocortisone dose during the third trimester may obviate the need to increase fludrocortisone dose. Monitoring is accomplished by evaluating BP in the sitting and standing position and measuring blood electrolytes. In the third trimester, an up-titration of the dose should be considered if there is hypotension or hyperkalemia despite the increase in hydrocortisone dose, and a down-titration if there is hypertension, hypokalemia or edema. After delivery, the dose used before pregnancy is resumed (7). Fludrocortisone is classified in pregnancy as category C by the Food and Drug Administration (no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks), which motivated the patient in the present case to refrain from using it. In this case, the dose of hydrocortisone after adjustment was sufficient to cover the mineralocorticoid needs.

Delivery

Delivery must be planned and monitored by a multidisciplinary team. Most deliveries occur without complications when pregnancy was carefully followed and treatment optimized. The Endocrinologist should provide the obstetric team with a written therapeutic plan regarding intravenous glucocorticoid coverage, which must be started before the active phase of labor – initial bolus of 100 mg hydrocortisone followed by continuous perfusion 200–300 mg/24 h (6).

After delivery

Twice the dose of hydrocortisone used during gestation can be resumed after delivery during 24–48 h. After that, if the mother is clinically well, it can be rapidly reduced to pre-pregnancy doses.

Conclusion

As illustrated by the present case report, pregnant women with AD must have appropriate education and be thoroughly monitored to guarantee the absence of complications through therapeutic regimen adaptation. Avoiding pitfalls is not always easy. In these cases, early referral to hospital services that allow collaboration between Endocrinology and Obstetrics is fundamental.

When the diagnosis is established and follow-up is appropriate, AD is currently compatible with pregnancy and delivery free of complications.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Patient consent
Written informed consent has been obtained from the patient for publication of the submitted article.

Author contribution statement
All the authors contributed to the critical review of the paper. Diana Oliveira is the author; Adriana Lages was involved in the drafting of the manuscript; Sandra Paiva was the patient's physician; Francisco Carrilho is

ID: 17-0179; April 2018
DOI: 10.1530/EDM-17-0179

the head of the Endocrinology, Diabetes and Metabolism Department at Coimbra Hospital and University Center.

References

1 Melmed S, Polonsky KS, Larsen PR & Kronenberg HM. *William's Endocrinology*, 13th ed., 2016 Section IV Adrenal Cortex and Endocrine Hypertension.
2 Erichsen MM, Husebye ES, Michelsen TM, Dahl AA & Løvås K. Sexuality and fertility in women with addison's disease. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 4354–4360. (https://doi.org/10.1210/jc.2010-0445)
3 Björnsdottir S, Cnattingius S, Brandt L, Nordenström A, Ekbom A, Kämpe O & Bensing S. Addison's disease in women is a risk factor for an adverse pregnancy outcome. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 5249–5257. (https://doi.org/10.1210/jc.2010-0108)
4 Anand G & Beuschlein F. Management of endocrine disease: fertility, pregnancy and lactation in women with adrenal insufficiency. *European Journal of Endocrinology* 2018 **178** R45–R53. (https://doi.org/10.1530/EJE-17-0975)
5 Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye ES, Merke DP, Murad MH, Stratakis CA & Torpy DJ. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 2016 **101** 364–389. (https://doi.org/10.1210/jc.2015-1710)
6 Lebbe M & Arlt W. What is the best diagnostic and therapeutic management strategy for an addison patient during pregnancy? *Clinical Endocrinology* 2013 **78** 497–502. (https://doi.org/10.1111/cen.12097)
7 Quinkler M, Oelkers W, Remde H & Allolio B. Mineralocorticoid substitution and monitoring in primary adrenal insufficiency. *Best Practice and Research: Clinical Endocrinology and Metabolism* 2015 **29** 17–24. (https://doi.org/10.1016/j.beem.2014.08.008)

Received in final form 6 March 2018
Accepted 23 March 2018