Pregnancies associated with primary adrenal insufficiency

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Objective: To provide a framework for the clinical presentation, evolution, treatment, and outcome of the unusual association between primary adrenal insufficiency (AI) during pregnancy and life-threatening complications for the mother and fetus.

Design: Case reports.

Setting: Pregnant women with AI treated in the Endocrine and Diabetes Department, Hospital Universitario de Maternidad y Neonatología, Córdoba, Argentina.

Patient(s): Three pregnant women with AI.

Intervention(s): Review of hospital records.

Main Outcome Measure(s): Clinical, laboratory features, treatment, and outcome.

Result(s): Two women with AI were diagnosed before conception, and one was diagnosed during gestation. Two of the cases were associated with other autoimmune diseases. Two newborns were born with signs of fetal distress, and one passed away hours later. Poor outcome was related to low compliance with treatment.

Conclusion(s): AI is often overlooked during pregnancy because of its rarity and pregnancy-like symptoms. Nevertheless, other autoimmune diseases, hyponatremia, metabolic acidosis, nausea and vomiting, and orthostatic hypotension that does not improve with usual treatment or persists after first trimester should evoke a diagnosis of AI. If diagnosis and treatment are properly managed, pregnancy, labor, and delivery may occur without complications. If not, AI is associated with high maternal and fetal morbidity and mortality. (Fertil Steril 2008;90:1199.e17–e20. ©2008 by American Society for Reproductive Medicine.)

Key Words: Primary adrenal insufficiency, pregnancy

The hypothalamic-pituitary-adrenal axis plays an important role during pregnancy, controlling fertility, arterial blood pressure, hydroelectrolite balance, and delivery. Untreated adrenocortical hypofunction increases maternal and fetal morbidity and mortality. Primary adrenal insufficiency (AI) affects mostly women (90%), but its exact prevalence in pregnancy is unknown. One of the leading reports was done in Norway during a 12-year span. It describes five women with six neonates, with an estimated incidence of AI in pregnancy of 1 per 3000 births (1). We studied three patients between 1992 and 2004, which represents a prevalence of 1:10,000 births.

CASE 1

A 22-year-old woman was admitted to the hospital with headaches, nausea, and vomiting in her eighth week of gestation. She began experiencing progressive fatigue, weight loss (5 kg), and muscular weakness 7 months earlier. Four days before admission, the patient experienced orthostatic dizziness, headaches, nausea, and severe vomiting.

She developed hypothyroidism after subtotal thyroidectomy due to Graves’ disease. Her mother and sister suffered from primary hypothyroidism, and her 5-year-old son had type 1 diabetes. On examination, the patient appeared severely weak. Physical examination was notable for generalized pigmentation: darkened skin creases, palm lines, knuckles, nail beds, thyroid surgery scar, mammary areolas, tongue, and buccal mucosa. While supine, her blood pressure was 80/40 mmHg, with a pulse of 100 bpm. After standing, her blood pressure dropped to 60/30 mmHg and her pulse rose to 110 bpm. Her weight was 56.8 kg, and her height was 1.67 meters.

Saline solution and 300 mg hydrocortisone IV (100 mg as a bolus dose, followed by an infusion of 200 mg given over period of 24 hours) were administered for presumed AI. Hydrocortisone was progressively tapered during 3 days to 30 mg daily by mouth, two-thirds in the morning and the rest...
in the afternoon. Laboratory samples drawn on admission revealed a serum potassium of 4 mEq/L (reference values, 3.5–5 mEq/L), sodium of 112 mEq/L (reference values, 135–45 mEq/L), and glycemia of 93 mg/dL (reference values, 70–100 mg/dL). Her pretreatment plasma ACTH level was 82 pg/mL (reference values, 5–60 pg/mL), and morning cortisol was 2 μg/dL (reference values, 5–25 μg/dL). Her TSH level was 14.9 μU/mL (reference values, 0.25–4 μU/mL). The patient was discharged after 3 days. Levothyroxine was increased from 50 to 75 μg daily, and she remained euthyroid throughout pregnancy. Hydrocortisone was unchanged. The patient’s condition improved, and she remained asymptomatic and gained 18 kg until delivery. She was instructed to monitor her blood pressure and electrolyte values.

In the twenty-eighth week, an oral glucose tolerance test showed a normal result and a TSH receptor antibodies test showed a result of 5% (normal, <14%). At thirty-eight weeks of gestation, she went into labor. She was given 50 mg of hydrocortisone IV during the second stage of labor. She gave birth to a healthy male neonate of 4100 g weight, and 47 cm length. After delivery, she went on with her previous dosage of hydrocortisone. She was discharged on the fourth day together with her neonate. Thirty-five days after delivery, she remained normal. She breast-fed for 8 months. One year and 3 months after delivery, she was diagnosed with type 1 diabetes, developing a fully autoimmune polyglandular syndrome type 2. Three years later her child remained healthy.

CASE 2
A 36-year-old woman in her eighth week of pregnancy was referred to the endocrinology department. She revealed past medical history for AI and hypothyroidism after thyroidectomy for Graves’ disease. She had two miscarriages 10 and 13 years earlier. In both cases, she had no obstetric or endocrinological surgeries. She had smoked 20 cigarettes a day for 18 years and had discontinued smoking a month before referral.

At pregnancy, she was receiving hydrocortisone 30 mg and levothyroxine 75 μg daily; she admitted to often missing doses of her treatment. Her physical examination showed a pulse of 80 bpm, blood pressure of 110/70 mmHg, weight of 59 kg, and height of 1.60 meters. She showed vitiligo around her nose, mouth, ears, eyes, and hands. Her baseline laboratory values were as follows: plasma ACTH level, 110 pg/mL; morning plasma cortisol level, 0.02 μg/dL; glycemia, 66 mg/dL; serum potassium, 4.5 mEq/L; sodium, 139 mEq/L; and TSH, 15 μU/mL. Steroid replacement treatment was not altered after the diagnosis of pregnancy, but she was encouraged to comply with treatment; levothyroxine was also increased to 112 μg daily.

She remained asymptomatic by her twenty-third week of gestation, maintaining the same hydrocortisone dose. She missed many of her scheduled office visits. At thirty-three weeks, preterm labor started spontaneously. She claimed to have fulfilled her treatment. She was given a stress dose of 100 mg of hydrocortisone IV before cesarean section (because the fetus was presenting in the transverse position) and continued with 100 mg every 6 hours for 24 hours and then tapered to her previous oral dose after 48 hours.

A female neonate was delivered (1900 g) with fetal distress and respiratory distress syndrome. Nevertheless, she survived after intensive care support. Patient and daughter were discharged and follow-up was lost.

CASE 3
A 25-year-old primigravid woman presented with signs of dehydration to the emergency room in her twenty-third week of gestation. She had had AI since she was 18, but she had abandoned treatment. A few months before admission, the patient was tired and anorectic. Those symptoms worsened with pregnancy. On physical examination, she was thin, with generalized pigmentation and dehydration. Thyroid palpation was normal. Blood pressure obtained with patient supine and standing was 110/70 and 85/55 mmHg, respectively. Admission laboratory tests showed serum potassium of 4.5 mEq/L, sodium of 112 mEq/L, glycemia of 77 mg/dL, ACTH of 70 pg/mL, cortisol of 1 μg/dL, and TSH of 0.50 μU/mL. An ultrasound showed a fetus that was small for its gestational age.

After hydration with IV normal saline, glucocorticoid replacement with hydrocortisone (100 mg given as IV bolus and then 100 mg every 6 hours) was performed. The patient felt well, her appetite increased, postural hypotension disappeared, and she was tapered to routine oral therapy, 30 mg daily. Patient was warned about the risks of abandoning treatment and follow-up. She was discharged 72 hours after admission. At 40 weeks of pregnancy she had a caesarean delivery in a downtown facility. A male neonate (2040 g) with acute cardiorespiratory failure was delivered and died 20 hours later. The mother was not taking hydrocortisone as requested during the previous weeks.

DISCUSSION
During normal pregnancy, 90%–95% of fetal cortisol derives from maternal adrenal secretions up to the thirty-third week of gestation, when fetal adrenal cortisol production increases and maternal contribution decreases. In cases of unrecognized maternal AI, transplacental passage of cortisol from the fetus to the mother might have a partial protective effect. Failure may become apparent during the stress of labor, delivery, or immediate postpartum period (2, 3).

Diagnosis of AI is often missed during the first trimester because of the similarity of its symptoms with those of normal pregnancy. AI should be considered in cases of excessive fatigue, malaise, weight loss, vomiting, postural hypotension, hyperpigmentation, abdominal pain, biochemical disturbances, and personal or family history of an autoimmune disease (4). Nausea and vomiting can be mistaken for hyperemesis gravidarum, but if they are extremely severe, persist
with usual treatment, or remain after first trimester, AI should be suspected, as in case 1. Hyperpigmentation of skin and mucosa can be present in normal pregnancy, but bluish black spots on the lips, gums, and mucosal membranes of mouth, rectum, and vagina are more evident in AI, as is darkening of the skin in nonexposed regions of the body. The darkening of the lines on the palms is typically present (2).

Diagnosis of AI should also be considered in cases of orthostasis or hypotension, even in the postpartum period. Severe cases of syncope can occur in association with addisonian crisis (5). Laboratory findings can show hyponatremia and hyperkalemia, but during normal pregnancy a small reduction in serum sodium (5 mEq/L or less) can be seen. Severe hyponatremia and/or acidosis also raise the suspicion of AI (4, 6). Fasting hypoglycemia, lymphocytosis, and eosinophilia are helpful in making a diagnosis; nevertheless, hyperkalemia is not always present.

A definite diagnosis is confirmed with plasma cortisol and ACTH levels. Blood samples must be drawn before initial treatment, but if diagnostic tests are unavailable, or if the patient is unstable with a high clinical suspicion for adrenal crisis, empirical glucocorticoid therapy is indicated. A low early morning plasma cortisol level (<3.0 µg/dL) in association with typical clinical findings confirms AI. In the early stages of pregnancy (first or early second trimester), in a clinically stable patient, AI can be excluded if basal cortisol is higher than 19 µg/dL. But during the late second and third trimester, the physiological changes of pregnancy increase plasma cortisol levels and cortisol binding protein, making the previous value unreliable.

Plasma ACTH concentration differentiates primary (elevated level) from secondary (normal or low) AI. Because ACTH levels fluctuate widely day-to-day and because of the possibility of a false low result if the sample is not managed properly (collected in prechilled EDTA tubes, transported in an ice bath with prompt refrigerated centrifugation and plasma separation), it should be tested on several occasions. In cases of high clinical suspicion for AI, Lindsay and Nieman recommend a stimulation test with Cosyntropin, suggesting a cortisol value under 30 µg/dL, before or after the test, as a diagnostic value for AI in the last part of pregnancy (late second and third trimester) (7, 8). However, these results were based on the findings of a single trial done in 18 women and six controls who received at least two doses of betamethasone for reasons other than AI (9). Thus, there is still insufficient information to determine appropriate pregnancy specific cutoff points.

Two patients had other organ-specific autoimmune disease (Graves’ disease, type 1 diabetes, and vitiligo). One of them had family members with autoimmune endocrine disease. Those findings led us to suspect AI due to autoimmune adrenalitis. As it can be a part of autoimmune polyglandular syndrome, thyroid function testing is recommended for its relevancy during pregnancy. Our patients needed to have their levothyroxine dose increased to compensate for pregnancy demands. It is essential to be aware that treatment of hypothyroidism in case of unrecognized adrenal insufficiency may trigger adrenal crisis (10, 11).

Hydrocortisone is preferred for replacement in pregnancy in daily doses of 12–15 mg/m² of body surface area. Two-thirds of the daily dose is given when the patient awakens, with the remainder given in the afternoon as in the normal circadian rhythm of cortisol. Our patients did not need an increase in their doses of hydrocortisone as described previously in other case reports (1). Hydrocortisone is also the method of choice during the acute treatment of adrenal crisis.

Mineralocorticoid requirement is a concern. Ambrosi et al., in their review, suggest its use (fludrocortisone 0.1 mg/day) with close monitoring of blood pressure, electrolytes, and plasma renin activity. Fludrocortisone must be reduced in cases of hypertension and hypokalemia and withdrawn in cases of toxemia (2). In contrast, in case 1, with close monitoring and normal values of blood pressure and electrolytes, the patient did not need fludrocortisone and had a successful outcome.

The fetus is relatively protected from excessive hydrocortisone by placental 11-β hydroxysteroid dehydrogenase 2 (11β-HSD 2), which converts active glucocorticoids, cortisol, and corticosterone to their inactive 11-keto metabolites. Dexamethasone is not recommended because it is not degraded by 11β-HSD2. Glucocorticoid and mineralocorticoid treatment is not associated with fetal loss or teratogenicity (7).

Vaginal delivery is a reasonable option when there are no symptoms of undertreatment. The hydrocortisone dose must be doubled, or a single dose of 50 mg IV during the second stage of labor must be given. If cesarean section is indicated, the patient should receive 100 mg of hydrocortisone IV or IM before surgery begins, which should be maintained every 6–8 hours and then tapered to previous oral dose in 48 hours. Two newborns presented fetal distress and respiratory distress, and one of them died after delivery. Although there are multiple reasons for those outcomes, we cannot omit the association with low treatment compliance. AI should remain high on the list of differential diagnoses in a pregnant woman with classic symptoms, significantly unbalanced biochemical profile, and personal or familial history of autoimmune disease.

REFERENCES