

# Lactation Ketoacidosis: An Unusual Entity and a Review of the Literature

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## ABSTRACT

A 31-year-old woman presented to the hospital with symptoms of nausea, malaise, and emesis. She was breastfeeding her 10-month-old infant. She was found to have severe ketoacidosis. The patient was not in diabetic ketoacidosis or alcoholic ketoacidosis; nor had she ingested any toxins. After she was admitted to the hospital, received intravenous fluids, and stopped breastfeeding, her symptoms resolved. She was found to have lactation ketoacidosis, an uncommon condition in humans. A review of all causes of ketoacidosis is presented with special emphasis on lactation ketoacidosis.

## CASE PRESENTATION

A 31-year-old woman who was 10 months postpartum and was breastfeeding presented to the Emergency Department with nausea, fatigue, vertigo, malaise, and 1 episode of emesis. She had been well until 20 hours earlier when her symptoms began somewhat suddenly and progressed in severity such that she sought treatment in the Emergency Department. She denied having fever, chills, or diarrhea and reported having consumed nothing out of the ordinary; no one else in her household was ill. She had not ingested or used any illicit substances, alcohol, or over-the-counter or prescription medications in the days preceding her presentation. Her medical history included mild asthma, for which she took no medications on a regular basis. She had an ectopic pregnancy 6 years earlier and hyperemesis gravidum 7 years ago when pregnant with her first child. She was breastfeeding her second child, a 10-month-old daughter. She had 2 hospital admissions in the preceding 3 months, with symptoms similar to those at current presentation. In each case, she was given intravenous fluids, her symptoms quickly resolved, and she was discharged from the hospital the following day. No cause was established for her illness in either of her prior hospital admissions.

On physical examination, she appeared ill but was not in acute distress. She was alert and fully oriented. Her temperature was 35.8°C, respiratory rate was 16/min, heart rate was 92/min, blood pressure was 157/125 mmHg, and oxygen saturation was 100% breathing room air. Results of her physical examination revealed no abnormalities of her head or neck. She had clear breath sounds, normal heart tones and no murmurs, and a soft nontender abdomen. She had no abnormalities of the extremities or nervous system.

Results of the arterial blood gas analysis showed the following values: pH, 7.26; partial pressure of carbon dioxide, 31 mmHg; bicarbonate ( $\text{HCO}_3^-$ ), 13.5 mmol/L; base excess, -12.11 mmol/L; lactate, 1.0 mmol/L; chloride, 98 mmol/L; and serum ketones, ++. The remainder of her laboratory examinations revealed these values: sodium, 140 mmol/L; potassium, 3.8 mmol/L; urea, 7.9 mmol/L (normal value = 2.9-8.2 mmol/L); creatinine, 7.7 mmol/d (normal value, female = 7.0-15.8 mmol/d); glucose, 3.8 mmol/L (normal value, fasting = 3.9-6.1 mmol/L); hemoglobin  $\text{A}_{1c}$ , 30 mmol/mol (normal value = < 42 mmol/mol); salicylate, < 0.04 mmol/L; hemoglobin, 145 g/L (normal value, female = 120-160 g/L) white blood cells,  $12.1 \times 10^9/\text{L}$ ; and neutrophils,  $10.6 \times$

$10^9/\text{L}$ . Urinalysis revealed ketones at +++. Thyroid-stimulating hormone and cortisol levels were normal. An electrocardiogram demonstrated sinus rhythm. Her serum anion gap was calculated to be 32.3 mmol/L ( $[\text{Na}^+ + \text{K}^+] - [\text{Cl}^- + \text{HCO}_3^-]$ ) (reference range, 12-18 mmol/L). Her osmolar gap was normal.

A review of her two prior hospital presentations that year revealed that, on both occasions, she had an increased anion gap metabolic acidosis with positive ketones and normal blood glucose readings.

For this current illness, she was admitted to the hospital and given 2L intravenous 0.9% sodium chloride. She stopped breastfeeding for 12 hours during her admission. By the next day, she was feeling better, was tolerating a normal diet, and her pH, anion gap, and blood ketone levels had returned to normal.

A diagnosis of lactation ketoacidosis was made. The patient was discharged with advice to ensure sufficient energy intake and to avoid prolonged fasts while breastfeeding. She was seen at a follow-up visit two weeks later and again two months after her presentation. She remained well, with no further presentations of acidosis during the ensuing five months.

## DISCUSSION

Metabolic acidosis is a common finding in patients presenting to the Emergency Department. It is classically divided into two categories: those with and those without an elevated anion gap. The causes of acidosis are legion, and indeed in many teaching arenas, mnemonics are often used to facilitate recall of the most common causes of metabolic acidosis. For example,

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CUTE DIMPLES is a common mnemonic used to aid in remembering the most common causes of increased anion gap acidosis: Cyanide, Uremia, Toluene, Ethanol, Diabetic ketoacidosis, Isoniazid and iron, Methanol, Propylene glycol, Phenformin and paraldehyde, Lactic acidosis, Ethylene glycol, Salicylates.

Diabetic ketoacidosis (DKA) is the most commonly described and most commonly encountered form of ketoacidosis. There are, however, other important causes of ketoacidosis. The two most common are alcohol intoxication and starvation. Our patient did not have diabetes, nor had she consumed any alcohol preceding this or her two prior hospital admissions. A negative toxicology screen and normal osmolar gap ruled out several other possible (ingestion-related) causes of ketoacidosis. Because none of these entities appeared to be causing our patient's illness, we investigated other possibilities. To understand why our patient had ketoacidosis, a review of ketone body production is essential.

### Ketone Body Production

Ketone body production takes place in the mitochondria. There are three major ketone bodies: acetoacetate,  $\beta$ -hydroxybutyrate, and acetone. Ketone bodies are used as fuels by many body tissues, especially the brain, when there is decreased glucose availability. Ketogenesis is tightly regulated by a series of biochemical reactions and regulatory hormones. Lipoprotein lipase is activated by low insulin levels, releasing long-chain fatty acids and glycerol from triglycerides in peripheral fat stores. The fatty acids are transported to hepatocyte mitochondria, where they undergo hepatic  $\beta$ -oxidation, forming acetyl-coenzyme A (acetyl-CoA). When large quantities of acetyl-CoA are generated, the oxidative capacity of the Krebs cycle is overwhelmed, and acetyl-CoA enters into the ketogenic pathway for ketone body formation. The ketoacids acetoacetate and  $\beta$ -hydroxybutyrate alter metabolic pH, whereas acetone is responsible for the distinctive breath odor present in people with ketosis.<sup>1</sup>

### Causes of Ketoacidosis

#### Diabetic Ketoacidosis

Two predominant mechanisms lead to ketosis in DKA. First, in DKA the relative or absolute insulin deficiency with increased counterregulatory hormones (most importantly glucagon but also catecholamines, growth hormone, and cortisol) stimulate lipolysis, culminating in the production of acetyl-CoA from fatty acid. The large amount of acetyl-CoA generated exceeds the capacity of the Krebs cycle, and the excess is shunted to ketone body production.

Second, the lack of insulin results in decreased glucose utilization and a reduction in oxaloacetate production (acetyl-CoA condenses with oxaloacetate to enter the Krebs cycle). The reduced amount of oxaloacetate further reduces the abilities of the Krebs cycle to accommodate acetyl-CoA. Acetyl-CoA is then diverted from entering the Krebs cycle and instead enters the ketogenic pathway.<sup>2</sup>

#### Starvation Ketosis

Starvation ketosis is usually benign and not life threatening. Short-term (eg, overnight) fasting causes mild acidosis. Following an overnight fast, fatty acids are released from fat stores and used for ketone production. Initially, glucose levels are maintained by glycogenolysis and gluconeogenesis. As fasting becomes prolonged (days), liver glycogen stores become depleted and the body becomes more dependent on ketone bodies as a source of energy. Stimulated by low insulin levels and high counterregulatory hormones (eg, glucagon), fatty acid release increases further to fuel ketone body production. Serum levels of ketone bodies continue to increase for three to four weeks, although ketogenesis and lipolysis are maximal by three days.<sup>1,3</sup> Under these conditions, a superimposed stressor such as pregnancy, infection, or alcohol intake may precipitate life-threatening ketoacidosis. Fasting ketosis develops more quickly in women.<sup>4</sup>

#### Alcoholic Ketoacidosis

The pathogenesis of alcoholic ketoacidosis is complex. There are commonly three initiating events: 1) poor nutritional intake, 2) metabolism of ethanol, and 3) metabolic stress.<sup>1,5</sup> Long-term alcohol

use often coexists with malnutrition. The resulting depletion of protein and glycogen stores results in a functionally starving state, which promotes ketosis.<sup>1,5</sup> The metabolism of ethanol causes a rise in the ratio of nicotinamide adenine dinucleotide hydride to nicotinamide adenine dinucleotide (NADH/NAD), impairing hepatic gluconeogenesis, which leads to further ketogenesis. Superimposed metabolic stressors can be caused by dehydration secondary to vomiting from acute alcohol intake or from impaired hepatic gluconeogenesis causing hypoglycemia. This stress causes a release of counterregulatory hormones (catecholamines, glucagon), which further favors ketogenesis.<sup>1,5</sup>

#### Salicylate Poisoning

Salicylate intoxication causes metabolic acidosis via a variety of mechanisms. First, through its uncoupling of mitochondrial oxidative phosphorylation, it promotes anaerobic metabolism, thus increasing lactate production and lactic acidosis. Second, salicylates increase fatty acid breakdown and can promote hypoglycemia, both of which lead to a ketotic state. Last, the salicylic acid itself contributes to acidemia.<sup>1</sup>

#### Inborn Errors of Metabolism

In the pediatric population, a number of rare, usually recessively inherited inborn errors of metabolism predispose to ketosis and ketoacidosis. These include deficiencies in succinyl CoA:3 ketoacid CoA transferase, mitochondrial 2-methylacetoacetyl CoA thiolase deficiency and methylmalonyl-CoA mutase deficiency.<sup>1</sup> These conditions usually present in infancy or early childhood with recurrent episodes of severe ketoacidosis. An extensive discussion of these conditions is beyond the scope of this article.

#### Bovine Ketosis/Lactation Ketosis

Bovine ketosis is well described in veterinary literature.<sup>6</sup> First described in 1929, it occurs in postpartum cows and is characterized by ketonemia, ketonuria, low levels of hepatic glycogen, and hypoglycemia.<sup>6,7</sup> Bovine ketosis is thought to occur because during lactation the animal is often unable to maintain sufficient energy intake and hepatic gluconeogenesis to match the increased substrate demands of lactation.<sup>7</sup> Milk

production during lactation is an energy-intensive process, resulting in high glucose utilization.<sup>8</sup> Ruminants rely on hepatic gluconeogenesis as a glucose source for milk production.<sup>8</sup> If sufficient energy intake and hepatic gluconeogenesis cannot be maintained, a hypoglycemic, a hypoinsulinemic state results. Just as in humans, this stimulates adipose tissue breakdown, increasing substrate availability and ketone formation.<sup>8</sup> Restoration of sufficient glucose by administration of 50% dextrose solution reverses the process.

“Bovine” or lactation ketosis in humans is rare, but there have been five previously reported cases.<sup>9-13</sup> In all these cases, as in our case, a young, non-diabetic, lactating woman experienced raised anion gap acidosis with ketosis. In our patient, as in the other cases cited, rehydration and energy replacement resulted in complete resolution of the symptoms and the ketoacidosis.

## CONCLUSION

In the previously reported cases of lactation ketoacidosis, there were specific events cited as precipitating the ketoacidosis. These events included a urinary tract infection, twin lactation, a self-imposed high-protein carbohydrate-free diet, and self-imposed fasting. To our knowledge, our case is the first reported case in which no specific illness or event

was identified other than the lactation itself. Ours is also the first reported case of a woman with recurrent presentations of lactation-induced ketoacidosis.

Our case highlights the importance of lactation ketoacidosis as a cause of raised anion gap metabolic acidosis in lactating women. Awareness of the condition can help early recognition and treatment. Clinician awareness will also encourage prevention, including instructions to lactating women to ensure maintaining a balanced diet. Additionally, when lactating women are fasting for medical reasons (eg, preoperatively) or when they are admitted to the hospital for other reasons, it is important to ensure adequate and proper nutrition. ❖

## Disclosure Statement

*The author(s) have no conflicts of interest to disclose.*

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## Science and Art

Medicine is the science of uncertainty and an art of probability.

— *Interns: From Students to Physicians*, Emily Mumford, PhD, 1921-1987,  
Professor of Clinical Sociomedical Sciences