Porcine ketosis: A case report and literature summary

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Summary: *Ketosis as a metabolic disease is generally not recognized under commercial swine production methods. This case report involves a sow presented for a Caesarean delivery of her piglets. During the last few weeks of gestation the sow was anorexic, had elevated liver enzymes, ketonuria, and mild ketonemia. After surgical delivery of a normal litter the urinary ketone concentrations decreased slowly. Examination of the sow's viscera following slaughter showed significant fatty degeneration of the liver. Ketosis may develop whenever there is a change from carbohydrate metabolism to fat metabolism. In the short term, ketosis is a safety measure, as ketones can be used as an energy source in glucose deficiency. In the long term, ketones accumulate in extracellular fluid and can cause nausea and inappetance. Fat accumulation can occur in hepatocytes during prolonged or repeated episodes of ketosis. In both humans and pigs, placental hormone production and increased fetal demands can have a diabetogenic effect, stimulating the production of ketones. There is no agreement as to the effects of maternal hyperketonemia on fetal development and energy stores at birth. Porcine ketosis could play a role in the overall herd health of commercial swine farms as it could be one factor influencing lactational appetite and weight loss. Prevention of porcine ketosis and related problems involves balancing energy intakes with energy demands, reducing weight and fat gain during late gestation, and avoiding any condition that can result in inappetance, especially during late gestation or lactation.*

Because it is rarely diagnosed and references to it in recent veterinary literature are sparse, the incidence of ketosis in swine is unknown. Occasionally, cases of it have been reported in association with lactation insufficiency during the nursing period.[1] In this report, we describe one case of ketosis in a pregnant sow, and discuss the possible pathophysiology based on a summary of comparative human and swine information. We suggest some potential implications for commercial swine health and production.

Clinical findings

The patient was a 2.5-year-old Landrace sow in her fourteenth week of gestation. She was presented to the Veterinary Teaching Hospital (VTH) at the Atlantic Veterinary College for a Caesarean delivery of specific-pathogen-free piglets. Approximately 3 weeks prior to being admitted, the sow had been transported 1500 km (930 miles) and maintained in a holding facility until she was delivered to the VTH.

On presentation, we noted no abnormalities. The sow was moderately obese and there was no evidence of mammary tissue enlargement. During the first 2 days of hospitalization, the sow was progressively anorexic and bruxism was noted on several occasions. After confirming pregnancy with real-time ultrasonography, we began assisted feeding. She was fed twice daily with a metal dose syringe containing a mixture of 300 mL dextrose (50% dextrose injection USP, Baxter Corporation, Toronto, Canada) and one-half to one can cat food (Prescription Diet Feline c/d, Hill's Pet Products, Mississauga, Canada) mixed with 3 L of water. The dextrose was offered as an energy source and the cat food as a highly digestible protein supplement.[2] The sow passed melena on one occasion, and a urinalysis (Multistix and Ketostix — Miles Canada, Inc. Diagnostic Division, Etobicoke, Canada) revealed moderate concentrations of ketone bodies (Figure 1).

The sow exhibited no signs of systemic illness, such as fever, and we detected viable fetuses by ultrasonography. Due to the melena and occasional episodes of bruxism, we decided to treat the patient for gastric ulceration. We treated the sow with an antidiarrheal mucous-membrane protectant (STAT Plus Electrolytes, Rogar/STB, Pointe Claire-Dorval, Canada) for 2 days at 300 mL PO BID, and with cimetidine (Apo-Cimetidine, Apotex, Weston, Canada) for 3 days at 300 mg PO BID. We continued assisted feeding twice daily to meet the sow's metabolic energy requirements. Handling was reduced to minimize stress on the sow. For the same reason, we used no injectable pharmaceuticals.

The sow remained anorexic for the remainder of hospitalization, although she was seen consuming straw. Ketone concentrations remained elevated throughout the last week of gestation. Caesarean section was performed on the predicted farrowing date and twelve normal live piglets were retrieved using aseptic technique. The piglets had normal vigor and size at birth. Serum biochemical analysis at surgery revealed elevated liver enzymes in the sow::

- SDH increased to 27 μmol/L (reference range 1–10 μmol/L);
- GGT increased to 37 U/L (reference range 0–25 U/L); and

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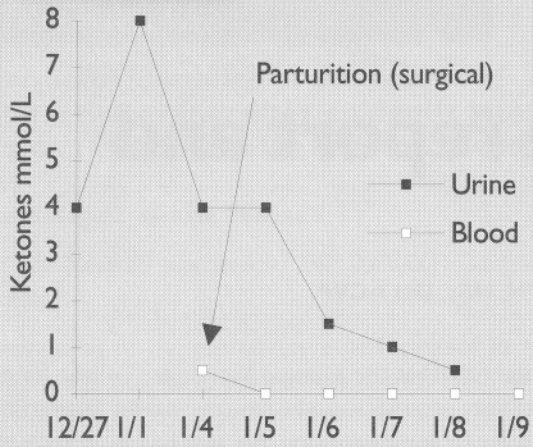
Figure 1



Consecutive urinary and blood ketone concentrations both pre- and post-Caesarean section.

- total bilirubin concentration increased to 23 μmol/L (reference range 0–0.4 μmol/L).

These values suggested hepatocyte damage and possible intrahepatic cholestasis. A slight ketonemia (<0.5 μmol/L) was also observed.

The sow recovered uneventfully from surgery. We continued assisted feeding and monitoring of urine and serum ketones until slaughter. Ketone concentrations gradually dropped to normal in the days following surgery (Figure 1), probably because the large fetal energy demand had been removed, and the sow's energy demands were being met by the feeding regimen. We never observed serum ketone values as high as those in the urine. The kidneys have a low threshold for ketone bodies; thus, ketonuria usually precedes detectable ketonemia.[3] In compliance with estimated meat withdrawal requirements for cimetidine,[4] we terminated cimetidine treatment and the sow remained in the VTH for another week before being sent for slaughter.

Following slaughter, we retrieved the organs for necropsy examination. The stomach and intestines contained small amounts of straw and we observed a shallow, healing ulcer 6 cm in diameter in the pars esophagea. The liver was uniformly pale but did not float when immersed in formalin.

Histopathological examination revealed diffuse hepatocellular vacuolation which was most severe in the midzonal and periacinar areas. These vacuoles varied from 2 mm in diameter to comprising the entire volume of the hepatocyte cytoplasm, eccentrically displacing the nucleus (Figures 2 and 3). Fat stains were not performed, as fresh frozen tissue was not available for processing. Periodic Acid Schiff's stain to detect glycogen within the vacuoles was negative.

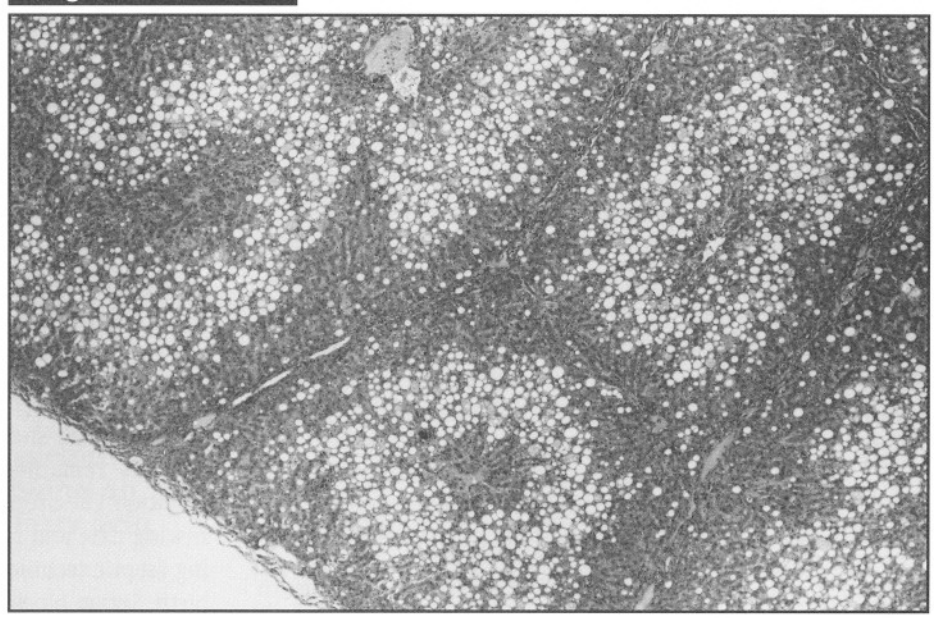
Although a physiologic deposition of fat can occur within the liver during late pregnancy and heavy lactation,[5] the fat content of this sow's liver was excessive compared to tissue sections from other periparturient sows necropsied at the Atlantic Veterinary College. Thus the histopathology results are consistent with the liver damage implied by the serum chemistry values.

Discussion

Ketosis can result from any condition where there is a change from carbohydrate metabolism to fat metabolism. When the body depends mainly on fat, instead of carbohydrates, for energy, fat is deposited in the liver. Thus, ketosis can result from a high-fat/low-carbohydrate diet, a state of absolute insulin deficiency (i.e., diabetes mellitus), or relative insulin deficiency, such as in the case of starvation.

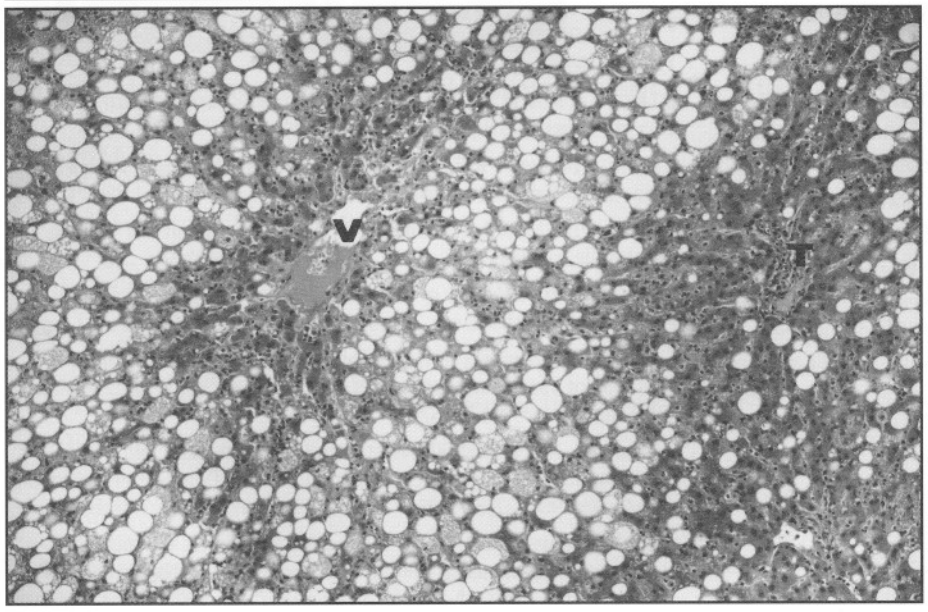
In monogastrics, glucose is the major carbohydrate the body requires to synthesize fatty acids. At normal insulin concentrations, the fatty acids are esterified into triglycerides in the liver and combined with apoproteins to form low-density lipoproteins, which are released into the blood stream as a source of energy.[6] When insulin concentrations are decreased or in cases of insulin resistance, lipolysis increases. Fatty acids are released and accumulate in the liver, overwhelming the normal mechanisms of fat metabolism. The accumulated fatty acids are converted to acetyl CoA and thence to ketone bodies — acetoacetic acid (AcAc), beta-hydroxybutyrate (BOHB), and acetone.

Figure 2



Histologic appearance of liver retreived from the abattoir. Note the extensive vacuolation of hepatocytes in central portions of hepatic lobules with relative sparing of cells around the periphery. Original magnification ×100.

Figure 3



Higher magnification photomicrograph showing marked cytoplasmic vacuolation in midzonal and periacinar hepatocytes with less severe change in the centroacinar hepatocytes. V = central vein. T = portal triad. Original magnification ×250.

to be caused by the multifactorial changes, such as hyperglycemia, hyperketonemia, and hyperosmolarity that occur during GDM.

Pigs are good models for human diabetes mellitus since their metabolism is similar to that of humans.[14] For example, they exhibit a lipoprotein metabolism analogous to that in humans and, when fed a high-fat/low-fiber diet, they become obese and may develop insulin resistance similar to that observed in human type II (non-insulin dependent) diabetes mellitus.[14] Sows can also develop GDM. Hypothesized etiologies include down-regulation of pancreatic sensitivity, an increase in placental degradation of insulin, or a decrease in target tissue sensitivity.[10] Evaluation of serum chemistry in gestating sows has revealed increased levels of free fatty acids, BOHB, and AcAc, and a decrease in triglycerides.[15] Compared to humans, there are no reports of hyperinsulinemia, but there is a longer duration of insulin release.[10]

In the short term, converting free fatty acids into ketones may be a safety measure, because ketones can be used as an energy source in cases of glucose deficiency.[6] Over the long term, however, ketones accumulate in the extracellular fluid and spill over into the blood and urine. Ketonemia induces nausea, resulting in inappetance that further increases fat mobilization, thus potentiating the ketosis. The rate of ketogenesis is proportional to the rate of lipolysis. Ketogenesis is greater in cases of uncontrolled diabetes mellitus, when there is an absolute insulin deficiency, than in starvation.[6] To halt the process, the body must be supplied with exogenous energy sources or, in the case of diabetes mellitus, with insulin therapy.

Glucose tolerance testing in sows and women has demonstrated both a diabetogenic effect and a ketogenic stimulus during pregnancy, usually without apparent diabetes mellitus resulting.[7-11] In a normal human pregnancy, sporadic ketonuria and hyperinsulinemia have been reported,[11] but decreased insulin responsiveness has been observed in late pregnancy.[12] The greatest metabolic changes occur in late gestation, as more placental hormones are produced and as fetal demands increase. When food is withheld from pregnant women at this time, there is a more rapid diversion to fat metabolism, and concentrations of free fatty acids and ketones increase.[12] In some women, gestational diabetes mellitus (GDM) may develop due to insulin resistance.[13] The infants of these women can have a higher-than-average birthweight, probably because they have heavier insulin-responsive tissues (liver, adipose) caused by increased glucose delivery across the placenta.[8] Long-term or severe GDM can cause congenital malformations, can retard fetal growth, and can increase neonatal mortality.[8] These effects are believed

Because they have a limited ability to generate glucose, porcine fetuses depend on the placental transfer of glucose. It has been hypothesized that gestational diabetogenesis may be a mechanism for maintaining adequate glucose levels and thus assuring adequate energy supply to the fetuses.[10] Several studies of gestational ketosis/GDM have been performed in sows. Investigators have used various methods to induce gestational ketogenesis, e.g., fat-feeding in late gestation,[7] maternal starving in late-gestation, and inducing diabetes mellitus, using either streptozotocin[16] or alloxan.[8] These investigators all observed fetal hyperinsulinemia, but in contrast to human infants, there was no increase in birthweights. This may be due to the lower percentage of body fat in neonatal piglets (1% compared with 16% in human neonates), and to the shorter gestation period.[16]

Gestational diabetes mellitus was found to increase milk production by sows, possibly due to some aspect of fetal metabolism or to an adaptive response of mammary tissue metabolism to the circulating ketones.[7] When mammary tissue is exposed to increased levels of BOHB prior to lactation, it may induce an increase in metabolic efficiency.[7]

Various investigators have also studied the effects of GDM on piglet mortality. The piglet's energy metabolism is particularly fragile at birth. Steele, et al. performed trials to determine whether ketosis during gestation would have any effect on neonatal energy stores. They hypothesized that maternal hyperketonemia may alter fetal development by sparing glucose as the primary energy substrate, thus making additional concentrations of glucose available for glycogen synthesis.[7] Ezekwe, et al. reported that neonatal survival increased because of the larger fetal stores of hepatic glycogen and lipids.[16] Other studies

reported no effect on energy stores.[7,17,18] Further research remains to be performed in this area to establish placental transport mechanisms.

Although mild maternal ketosis may have minimal detrimental effects on piglet viability, any prolonged inappetance and subsequent hepatic fatty change will adversely affect maternal health. Chronic hepatic lipidosis could lead to secondary health problems that can affect herd productivity because fatty livers are vulnerable to a wide range of toxic and nutritional insults.[5] The presence of periparturient ketosis may help explain why overfed and overweight gestational sows often have lower appetites after farrowing. Porcine ketosis could be a factor involved in lactational weight loss which, if excessive, can lead to herd productivity problems such as increased weaning-to-breeding intervals.[19] Similarly, loss of body condition in sows has been linked to an increased culling rate.[20] Most swine producers seek to maximize lactational feed intake.[21] Urinary or milk ketones are relatively easy to measure, and may serve as a warning indicator for suboptimal feeding or nutritional status in sows.

Treating ketosis in swine, as in other species, involves providing them with a supplementary energy source and offering them a palatable diet to balance energy intake with energy requirements. In this case, we did not observe the sow to return to a normal appetite, probably because her gestational energy demands were not being met with the assisted feeding and her liver was probably not fully functional. It is interesting to note, however, that her piglets appeared healthy and normal at birth.

Ketosis can be prevented by avoiding overconditioning of sows prior to farrowing and preventing conditions that may result in inappetance, especially during late gestation or lactation. In this specific case, the gastric ulcer may have played a role in the initial inappetance, but the appetite did not improve as the ulcer began to heal. Feeding sows with high milk production ad libitum can prevent excess loss of body fat stores and will further reduce the risk of ketone accumulation.

It is possible that the incidence of ketosis and fatty liver degeneration in sows in commercial swine herds may be more widespread than reported, as urine and serum samples are not routinely examined for the presence of ketones nor is the disease widely discussed in veterinary literature. This case and the limited human and comparative literature indicates that the condition is possible in sows. Sows with commonly encountered periparturient conditions such as metritis, urogenital infection, or mastitis could encounter some degree of ketosis secondary to the inappetance. Current treatment regimes for some of these conditions include the use of corticosteroids for the anti-inflammatory effects, but these drugs may also be effective through the stimulation of gluconeogenesis. Practitioners suggesting a treatment regime for periparturient or pregnant sows should consider the possibility and effects of ketosis in any case where there is a disruption of the sow's energy intake.

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