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Pregnancy and ketoacidosis: Is pancreatitis a missing link?

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Abstract

Non-diabetic ketoacidosis is increasingly recognised in pregnancy, particularly during the third trimester, and is usually associated with vomiting. In many cases, the cause of the vomiting is not identified and resolves rapidly, alongside the metabolic abnormalities, following delivery. Here, we report three cases in which pancreatitis was identified as an underlying cause of the gastrointestinal symptoms. To our knowledge, these are the first reports of pancreatitis precipitating non-diabetic ketoacidosis in pregnancy. This case series highlights the importance of searching for a precipitant for non-diabetic ketoacidosis in pregnancy, rather than focusing solely on management of the resulting metabolic abnormalities.

Keywords

High anion gap, metabolic acidosis, ketoacidosis, pancreatitis

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Introduction

Starvation ketoacidosis is a condition characterised by a metabolic acidosis with a high anion gap and ketonaemia, in the absence of hyperglycaemia. It occurs to a mild degree in non-pregnant individuals after fasting for 14 days or more,[1] but can occur more severely and rapidly in pregnant women. A number of cases have been described during pregnancy, usually in association with a short period of vomiting, but in the majority the cause for these initial symptoms is not identified.[2] Here, we describe three cases with firm evidence of underlying pancreatitis based on presenting symptoms, serum amylase concentration and identification of relevant biliary or pancreatic pathology. These cases suggest that measurement of serum amylase concentration and appropriate imaging should be considered in the initial assessment of pregnant women presenting with starvation ketoacidosis, in parallel with treating the metabolic derangement with glucose containing fluid.

Case 1

A 23-year-old woman in her second pregnancy presented at 33 weeks of gestation with a 24-h history of vomiting, on a background of five days of upper abdominal pain exacerbated by eating. Her first pregnancy had been complicated by pregnancy-induced hypertension requiring antihypertensives, and she had undergone a forceps delivery at term. She was otherwise fit and well, with a body mass index of 33 kg/m^2, and was on no regular medications. There was no family history of gallstones or pancreatitis and she drank minimal alcohol prior to pregnancy, and none during.

Initial examination revealed mild right upper quadrant tenderness. The blood pressure was 120/72 mmHg, and urinalysis showed 1 + protein, 2 + leucocytes and nitrites. Blood tests revealed abnormal liver function (bilirubin 43 µmol/L (normal range 3–17 µmol/L (Note: from hereon, reference ranges are in the non-pregnant population unless otherwise stated.)), alanine transaminase 62 IU/L (10–45 IU/L), aspartate transaminase 65 IU/L (15–42 IU/L), alkaline phosphatase 579 IU/L (75–250 IU/L), lactate dehydrogenase 219 IU/L (110–255 IU/L)) and an elevated serum amylase 831 U/L (25–125 IU/L). Inflammatory markers and renal function were normal. Abdominal ultrasound demonstrated the presence of biliary sludge with probable calculi within the gallbladder. There was no intra or extrahepatic duct dilatation.

She was commenced on antibiotics for a presumptive diagnosis of urinary tract infection. She continued to vomit intermittently, was kept nil by mouth and given intravenous fluids (normal saline and compound sodium lactate) but 48 h after admission her symptoms had not improved. On day 3 of her admission, she became tachypnoeic and tachycardic. Arterial blood gas analysis showed a mild metabolic acidosis with respiratory compensation (pH 7.35 (7.35–7.45), $PaCO_2$ 3.46 kPa (4.5–6.0 kPa), base excess (BE) −9.7 mmol/L (+2 to −2 mmol/L), bicarbonate 16.8 mmol/L (normal range in pregnancy 18–22 mmol/L), lactate 0.7 mmol/L (<1 mmol/L)). Repeat bloods showed rising inflammatory markers (C-reactive protein (CRP) 143 mg/L). Two litres of normal saline and 1 L of compound sodium lactate were administered over the next 16 h, and repeat arterial blood sampling demonstrated a worsening metabolic acidosis (pH 7.22, $PaCO_2$ 3.49 kPa, BE −15.8 mmol/L, bicarbonate 12.5 mmol/L, lactate 0.6 mmol/L, anion gap 14.6 mequiv/L (12–16 mmol/L)). Capillary ketones were 3.7 mmol/L. The acidosis and ketosis normalised with the infusion of intravenous fluids including 500 ml of 1.26% bicarbonate and 1 L of 10% dextrose over 4 h, as well as the recommencement of oral intake.

Delivery was considered but deferred owing to continued maternal improvement. Magnetic resonance cholangiopancreatography performed five days after admission showed intra- and extrahepatic duct dilatation, with abnormalities in the tissues around the pancreas, consistent with acute pancreatitis without choledocholithiasis. She had no further episodes of pain or vomiting during the remainder of her pregnancy and at 39 weeks' gestation underwent induction of labour and delivered a 3020 g male infant. Twelve weeks postpartum she underwent an uncomplicated laparoscopic cholecystectomy. Histology revealed chronic cholecystitis and cholelithiasis.

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Case 2

A 31-year-old woman in her fourth pregnancy presented at 31 weeks of gestation with a 48-h history of nausea and vomiting, poor oral intake and epigastric pain that radiated to her back. She had previously had two vaginal deliveries and one emergency caesarean section for fetal distress at 36 weeks' gestation. Medical history was unremarkable, she was on no medication and she had no family history of gallstones or pancreatitis. She did not consume alcohol.

On admission, blood pressure and clinical examination were normal and assessment of fetal wellbeing was reassuring. Urinalysis was notable for 2+ protein and 4+ ketones. Blood tests were also abnormal with thrombocytopenia (platelets 107×10^9/L) and elevated amylase (445 IU/L). Liver function tests were mildly raised with a bilirubin 25 μmol/L, ALT 23 IU/L and alkaline phosphatase 173 IU/L. Electrolytes and renal function were normal.

During the first 24 h of admission she continued to vomit despite antiemetics and was kept nil by mouth because of a likely diagnosis of acute pancreatitis. Her clinical condition continued to deteriorate and she became increasingly tachycardic and tachypnoeic. Arterial blood gas analysis showed a partially compensated metabolic acidosis that continued to worsen despite administration of intravenous compound sodium lactate. Her peak metabolic derangement was pH 7.29, $PaCO_2$ 1.89 kPa, bicarbonate 10.6 mmol/L, BE −18.9 mmol/L, lactate 0.7 mmol/L, anion gap 13 mequiv/L. Capillary ketone concentration was elevated at 5.5 mmol/L, in the presence of normal blood glucose 4.1 mmol/L. Intravenous 10% dextrose was administered alongside compound sodium lactate and the biochemical derangement gradually corrected. Her acute pancreatitis was conservatively managed and her symptoms resolved. Abdominal ultrasound showed a probable gallbladder polyp, and no intra- or extrahepatic duct dilatation.

Following discharge she continued to experience episodes of nausea, vomiting and abdominal pain, although none so severe as to warrant hospital admission. At term she had a spontaneous vaginal delivery of a male infant weighing 3280 g, complicated by a postpartum haemorrhage requiring blood transfusion.

Subsequently, magnetic resonance cholangiopancreatography showed a lesion in the pancreas, with appearances suggestive of an intraductal papillary mucinous neoplasm, a lesion known to be associated with acute pancreatitis.[3] She went on to have an elective Whipple's procedure, although histopathological appearances of the pancreas were consistent with autoimmune pancreatitis rather than malignancy.

Case 3

A 36-year-old woman in her third pregnancy presented at 36 weeks of gestation after the sudden development the preceding evening of epigastric pain, which was worsened by eating. She had vomited approximately twice a day throughout pregnancy but this became increasingly frequent after the onset of the pain. She had presented to hospital after a similar episode 48 h previously, and had been discharged when the symptoms resolved and all blood tests, including amylase, were normal. Medical history included an elective caesarean section for delivery of twins, followed by an emergency caesarean section with a singleton pregnancy two years later. She had mild asthma for which she was not medicated, and was otherwise fit and well.

On admission, she appeared unwell with epigastric tenderness and a positive Murphy's sign. The blood pressure was 145/101 mmHg and urinalysis showed 2+ ketones and a trace of protein. Blood tests revealed abnormal liver function: bilirubin 33 μmol/L, AST 99 IU/L, ALT 88 IU/L and a grossly elevated amylase 5094 IU/L. Inflammatory markers were mildly raised: WCC 14.3×10^9/L, CRP 24 mg/L. Renal function was normal. Blood gas analysis was performed: pH 7.41, PaO_2 13.3 kPa, $PaCO_2$ 3.6 kPa, lactate 0.7 mmol/L, glucose 5.4 mmol/L, BE −6.1 mmol/L. Abdominal ultrasound was consistent with acute cholecystitis, demonstrating a thickened, oedematous, distended gallbladder containing small calculi. The common bile duct was dilated and the pancreas was not visualised.

She received intravenous compound sodium lactate and required patient controlled analgesia with fentanyl. Over several hours she deteriorated, becoming drowsy with a Glasgow Coma Score of 13, tachypnoeic with a respiratory rate of 28 breaths per minute and tachycardic at 130 beats per minute. Repeat blood gas analysis breathing high-flow oxygen demonstrated the development of a significant metabolic acidosis: pH 7.27, PaO_2 29.3 kPa, $PaCO_2$ 3.5 kPa, lactate 1.7 mmol/L bicarbonate 14.3 mmol/L, BE −13 mmol/L, anion gap 17.2 mequiv/L. Cardiotocography demonstrated evidence of fetal compromise with a baseline fetal heart rate of 160 beats per minute, reduced variability and unprovoked decelerations. In view of presumed fetal compromise immediate delivery was arranged.

A 2.55 kg live male infant was delivered by emergency caesarean section under general anaesthesia. Green-brown intraperitoneal fluid was noted. Cord gases were abnormal: arterial pH 7.14, BE −8.8 mmol/L, venous pH 7.2, BE −5 mmol/L. Apgar scores were 4, 8 and 9 at 1, 5 and 10 min, respectively. Maternal blood gas analysis following delivery showed a persistent, severe metabolic acidosis with loss of respiratory compensation owing to mechanical ventilation: pH 7.15, PaO_2 22.2 kPa, $PaCO_2$ 5.7 kPa, lactate 2.0 mmol/L, bicarbonate 14.6 mmol/L, BE −13.3 mmol/L. She remained intubated and ventilated and was commenced on intravenous meropenem for treatment of presumed biliary sepsis, along with prophylactic tinzaparin. She was transferred to the Intensive Care Unit where she was extubated the following morning, 12 h after delivery, by which point the metabolic abnormalities had resolved.

Twenty-four hours after delivery she underwent magnetic resonance cholangiopancreatography, the results of which were consistent with acute cholecystitis with multiple stones in the gallbladder. No stones were seen within the common bile duct and the biliary tree was not dilated. She made a gradual recovery, but required low molecular weight heparin therapy for a small pulmonary embolus diagnosed a week after delivery. A fortnight after discharge she was readmitted with similar abdominal symptoms. Endoscopic retrograde cholangiopancreatography was performed, during which a filling defect was seen in the distal common bile duct and a single small stone removed following sphincterotomy. Having completed six months of oral anticoagulation, she subsequently underwent an uneventful laparoscopic cholecystectomy.

Discussion

Acute pancreatitis in pregnancy

Acute pancreatitis complicates approximately 1 in 1000 to 1 in 10,000 pregnancies,[4] making it a relatively rare occurrence. Pregnancy does not affect the incidence of the condition and the commonest precipitants are gallstones, causing 70% of cases in one series, and alcohol.[5] Occasionally, pancreatitis in pregnancy can be precipitated by hyperlipidaemia but this usually occurs in the context of an underlying abnormality in lipid metabolism, rather than simply as a result of the hypertriglyceridaemia that is seen in normal pregnancies.[6] Other causes of ketoacidosis and pancreatitis were excluded in the three women described here, specifically there was no history of other potential precipitants such as alcohol intake, and no prior use of any prescribed or over-the–counter medication.

The diagnosis of acute pancreatitis is usually based on the presence of typical symptoms such as abdominal pain and vomiting, with a corresponding rise in pancreatic enzyme concentration. Abdominal imaging with ultrasound is indicated, and can identify pancreatic abnormalities such as swelling, but the pancreas is only identified in 25–50% of patients with acute pancreatitis.[7] Ultrasound is of greatest use in this setting to identify contributory pathology such as choledocholithiasis. Computerised tomography (CT) scanning is not required to confirm the diagnosis, but can be performed if there is diagnostic

uncertainty, or if there is no clinical improvement in the first 48–72 h.[8] CT can be performed in pregnancy if clinical need necessitates and magnetic resonance imaging is also an alternative.

Pregnancy does not increase the serum amylase or lipase concentration, both enzymes that are useful in the diagnosis of pancreatitis.[9] Serum lipase is of particular utility in patients with a delayed presentation, as the elevation in serum lipase persists for longer than that of serum amylase.

Pancreatitis and metabolic acidosis

In common with other serious intra-abdominal pathologies, pancreatitis may cause a metabolic acidosis. Though the degree of acidosis is a marker of severity, blood lactate itself does not appear to be universally raised and is not a criterion in commonly used severity scoring systems.[10,11] The evaluation of a patient with a metabolic acidosis is dependent on the calculation of the anion gap. A high anion gap acidosis is commonly due to lactic acid accumulation and may be seen in any critically ill patient with shock. However, if the lactate is normal, as it was in these women, or is insufficiently elevated to explain the severity of the acidosis, ketoacidosis should be considered. One difficulty is that though the normal range for blood ketones in the non-pregnant population is generally agreed to be below 0.5 mmol/L, whether this differs in pregnancy has not been established.[12]

Reduced oral intake in pregnancy, either as a result of vomiting or being kept nil by mouth, may cause significant ketosis as a result of a relative lack of insulin.[2] The ketoacidosis usually resolves with exogenous carbohydrate, an effect attributed to an increase in endogenous insulin secretion, which suppresses ketogenesis.

Acute pancreatitis is a known precipitant of *diabetic* ketoacidosis and often is the result of the hyperlipidaemia associated with diabetes mellitus itself. A number of cases of acute pancreatitis associated with ketoacidosis, in the absence of hyperglycaemia or a diagnosis of diabetes mellitus, are described in the literature. One report includes three non-pregnant individuals, all of whom had pancreatitis, ketonaemia and a high anion gap metabolic acidosis together with elevated serum amylase and lipase.[13] In one of these patients, the ketosis persisted despite intravenous carbohydrate administration and only improved as the pancreatitis resolved and serum lipase normalised. The authors postulated that in this setting, the ketosis may not simply be a result of carbohydrate lack, but a direct effect of increased serum lipase, which leaks from the inflamed pancreas. Lipase hydrolyses triglycerides to glycerol and free fatty acids; the latter are metabolised to the ketones acetoacetone and β-hydroxybutyrate.

Ketoacidosis in pregnancy

At least 18 cases of pregnant women with severe ketoacidosis and normal blood glucose are reported in the literature.[2,14–27] The majority of these cases were precipitated by a short period of reduced oral intake and vomiting. Abdominal pain was also frequently reported in these patients. A number of cases reported a normal anion gap, as seen in cases 1 and 2, despite ketoacidosis characteristically causing a raised anion gap. This can also be seen in the recovery phase of diabetic ketoacidosis, when a hyperchloraemic acidosis develops. It has been suggested that this may result from significant sodium-containing fluid administration prior to arterial blood sampling. The ketoanions acetoacetate and β-hydroxybutyrate are ionised at even the lowest urinary pH and so are excreted with a cation, most commonly Na^+ or K^+, which results in an overall loss of 'potential bicarbonate' equal to the level of urinary ketone loss. This bicarbonate is replaced in the blood by chloride, most commonly from intravenous fluid administration, which therefore results in a lower anion gap than that expected for the reduction in bicarbonate and the degree of acidosis.[1,2]

In all cases the clinical condition of the mother improved with either medical treatment of the ketoacidosis or delivery of the fetus. None of these cases report the results of further investigation of the underlying cause of the presentation reported. Serum amylase concentration is reported in only one of the 18 cases and was elevated. An abdominal ultrasound was normal and no further investigation was performed. It may be the case, therefore, that some of these patients had unrecognised pancreatitis.

Management

The management of pancreatitis in pregnancy, as in the non-pregnant population, depends on the aetiology; the severity of the episode and the gestation at which it occurs are also considerations.[4] Conservative management is often undertaken successfully in pregnancy, with definitive treatment such as laparoscopic cholecystectomy performed at an appropriate interval following delivery. If a pregnant woman with pancreatitis is kept nil by mouth, then it must be recognised that ketosis is a significant risk, and glucose-containing intravenous fluids should be considered at an early stage. Indeed, this may well be the case for pregnant women with other intra-abdominal pathologies. If ketosis occurs it should be managed with glucose supplementation; the addition of insulin may be required if hyperglycaemia develops, although this is rarely required in practice.[2]

Delivery

Cases 1 and 2 demonstrate that in common with diabetic ketoacidosis the metabolic derangement of starvation ketoacidosis can be managed in pregnancy without expedited delivery provided there is no evidence of fetal compromise. Case 3 illustrates the risk of fetal compromise if the mother becomes acidotic and unwell, leading to fetal distress and necessitating emergency delivery.

Conclusions

In contrast to *diabetic* ketoacidosis in pregnancy, which is managed medically unless there is evidence of fetal compromise necessitating emergency delivery, women with starvation ketoacidosis are frequently subjected to expedited delivery. This may reflect a failure to identify the significant ketosis; consequently appropriate treatment – glucose containing fluid – is instituted late or not at all. The first two cases described here attest the efficacy of medical interventions for ketoacidosis; the metabolic abnormalities in these women resolved with appropriate treatment, avoiding unnecessary premature delivery. In contrast, the third case demonstrates the need to expedite delivery if the metabolic abnormalities in the mother progress to the point at which fetal distress is evident.

Taken together, these cases support the view that the diagnosis of acute pancreatitis should be considered in pregnant women presenting with ketoacidosis, particularly when classical symptoms such as vomiting and abdominal pain are present. Treatment of the ketoacidosis with carbohydrate containing fluid should continue in parallel with a search for an underlying diagnosis.

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CJF conceived the article and wrote the draft. AA and BASJ summarised the cases. All authors approved the final draft.

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