Diabetic Ketoacidosis And Pregnancy

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***Abstract*: This paper describes the clinical course of a young diabetic primigravida who presented to her physician with vomiting and abdominal pain. Despite the conventional doses of intravenous fluid and insulin that were used to treat her suspected diabetic ketoacidosis, she remained severely acidotic and developed increasing abdominal pain. Two hundred twenty units of regular insulin over a 5-hour period were required to reverse the lipolysis, acidemia, and abdominal pain, which characterized her severe episode of diabetic ketoacidosis. This discussion emphasizes the importance of insulin in the reversal of the hyperglycemia and acidosis that accompany a diabetic crisis. The roles of bicarbonate, phosphorous, magnesium, insulin, potassium, and fluids are discussed along with conditions such as pregnancy, infection, pancreatitis, and abdominal pain, which can complicate the management of diabetic ketoacidosis. (J Am Board Fam Pract 1990; 3:207-15.)**

Diabetic ketoacidosis sometimes can be managed in a standard fashion (insulin and intravenous fluids), but when it is complicated by pregnancy or infection, the management becomes more troublesome. This case report describes the presentation, problems, and clinical decisions surrounding a patient with severe ketoacidosis. When hyperglycemia does not respond to traditional therapy, the physician must consider causes of insulin resistance, as well as the use of high-dose insulin regimens to halt lipolysis and reverse the ketosis and acidosis.

Case Presentation

An 18-year-old woman came to the office after 4 days of nausea, vomiting, intermittent abdominal cramping, and loose stools. She gave no history of fever, recent travel, or unusual food or water consumption. She had juvenile onset diabetes for 8 years but had not complied with prescribed dietary and insulin regimens for the last 4 years. Usually, she took 36 units of NPH human insulin in the morning and 20 units in the evening, but she had taken no insulin in 24 hours. Her last menses occurred 7 weeks ago; she was sexually active with one partner and used no contraception. She had poor social supports and was living with her boyfriend.

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When first examined, she appeared acutely ill and prostrate but was not unconscious or in shock (temperature, 37.2°C [98.96°F]; blood pressure, 120/60 mmHg; pulse rate, 100 beats/minute; respiratory rate, 28 breaths/minute; height, 164 cm [5 ft, 4 in]; weight, 64 kg [141 lbs]). Her heart and lungs were normal, but she had diffuse abdominal tenderness without distention or enlargement of her liver or spleen. There was no sign of rectal abnormalities, but a test for occult blood in her feces was slightly positive. She had a yellow vaginal exudate, showing many white cells microscopically, but the cervix was not tender or inflamed. Her slightly enlarged uterus was nontender, and the adenexae were normal.

A presumptive diagnosis of diabetic ketoacidosis was made, probably precipitated by acute gastroenteritis and possibly complicated by early pregnancy.

The patient was admitted to the hospital (about 20 miles from the office); a normal saline infusion was started, and cultures of blood, urine, throat, stool, vagina, and cervix were obtained. Table 1 presents her chronology of management. The laboratory data obtained immediately upon admission to the hospital are shown in Table 2, Column 1. The serum B-HCG (beta subunit of human chorionic gonadotrophin) was positive. The urinalysis showed 5 to 10 white cells per high power field and trace bacteria. Serum calcium was normal. An arterial blood gas determination showed a pH of 6.99 and a pCO_2 of 12.2 mmHg (1.6 kPa).

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Table 1. Chronology of Initial Management.

0 Hours	Office visit. Presumptive diagnosis of DKA precipitated by acute gastroenteritis. Pregnancy suspected.
3 Hours	Admitted to hospital where laboratory confirmation of DKA and pregnancy established. White cell count, 31,900; 72 percent neutrophils; 5 percent bands. Abdominal pain increasing; stomach lavaged with clear return and no occult blood. Normal saline infusion of 2000 mL completed shortly after admission. Regular insulin 6 units IV bolus plus infusion at rate of 2 units per hour. Half normal saline infusion begun at 500 mL per hour.
5 Hours	White cell count 41,000 with 23 percent bands. Hyperglycemia and acidosis unchanged. Regular insulin 20 units IV bolus plus infusion at rate of 6 units per hour. Sodium bicarbonate (89.2 mEq) added to each liter of half normal saline.
8 Hours	Hyperglycemia diminishing but abdominal pain worse and localizing to the right lower quadrant. Insulin infusion reduced to 3 units per hour. Potassium chloride 40 mEq added to each liter of half normal saline; infusion rate 250 mL per hour. Clindamycin and gentamycin given.
15 Hours	Ketoacidosis and hyperglycemia persist. Serum amylase 641 units. 50 units regular insulin given by IV bolus, and rate of insulin infusion increased to 10 units per hour. Sodium bicarbonate 44.6 mEq given via bolus, and half normal saline with sodium bicarbonate infusion continued at 200 mL per hour. Potassium chloride discontinued.
17 Hours	No improvement on metabolic measurements. 50 units regular insulin given by IV bolus, and continuous infusion of 10 units per hour continued. Half normal saline discontinued. Dextrose 5 percent and water with 50 mEq potassium chloride and 89.2 mEq sodium bicarbonate per liter infused at 200 mL per hour. Additional 44.6 mEq sodium bicarbonate given in bolus form.
19 Hours	Some improvement in metabolic measurements noted. 50 units regular insulin bolus given IV and 10 unit per hour infusion maintained. Dextrose 5 percent and water mixture reduced to 150 mL per hour. Additional 40 mEq of potassium chloride given.
20 Hours	Arterial pH normal; pCO_2 beginning to rise. Patient clinically improved. Bolus of 20 units insulin given IV, and infusion continued at 10 units per hour. Hydrating solution changed to 5 percent dextrose and water with 60 mEq potassium chloride per liter. Abdominal ultrasound confirmed intrauterine pregnancy, 8.7 weeks' gestation.

Summary of therapeutic agents used during initial management:

Intravenous fluids	
Normal saline	2700 mL
Half normal saline	2800 mL
5 percent dextrose and water	1800 mL
Insulin	
Via bolus (in increments of 6, 20, 50, 50, 50, and 20 units)	196 u
Via constant infusion (at rates from 2 to 10 units per hour)	86 u
Sodium bicarbonate	300 mEq
Potassium chloride	190 mEq

Her abdominal pain increased. A nasogastric tube was inserted and her stomach was lavaged; the clear contents tested negative for blood. Chest and abdominal roentgenograms and electrocardiogram were normal. A 6-unit intravenous bolus of regular insulin was given, and a 2-unit per hour infusion was begun. One hour after the insulin therapy was instituted, the white cell count had risen to 41,000/μL (41.0 $\times$ 10^9/L) with 23 percent band neutrophil forms, but the hyperglycemia and acidosis were unchanged.

At this time, a 20-unit bolus of regular insulin was given intravenously. During the next two hours, the patient received a liter of half normal saline, 89.2 mEq (89.2 mmol) of sodium bicarbonate and an additional 12 units of regular insulin by continuous infusion. The laboratory data shown in Column 2 of Table 2 were obtained. The patient continued to be quite alert and complained of more abdominal discomfort, now localizing her pain to the right lower quadrant. Blood pressure, pulse rate, respiratory rate, and temperature were unchanged from admission. Clindamycin and gentamycin were administered because of the leukocytosis, pain, and acidosis that were suggestive of an intra-abdominal infection. Potassium chloride was added to the intravenous infusion; the insulin rate was decreased to 3 units per hour; and the sodium bicarbonate was stopped.

Seven hours later, hyperglycemia, severe ketoacidosis, and leukocytosis persisted. The pH was 7.06, and the pCO_2 was 10 mmHg (1.4 kPa). The serum amylase was 641 Somogyi units/dL (1190 u/L). Fifty units of regular insulin were administered in bolus form, and the insulin infusion rate was increased to 10 units per hour. A sodium bicarbonate infusion was begun. The laboratory data obtained 90 minutes after institution of these measures are shown in Table 2 Column 3. The pH was 7.068, and the pCO_2 was 8.8 mmHg (1.2 kPa).

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An additional 50-unit bolus of regular insulin was given, and 40 mEq (40 mmol) of potassium chloride were infused over the subsequent 90 minutes. The acidosis began to show signs of resolution, and another 50-unit bolus of insulin was administered. The laboratory data 1 hour after this third 50-unit bolus are shown in Table 2, Column 4. The pH was normal, and the pCO_2 was beginning to rise.

The patient now reported less abdominal pain and, for the first time, was requesting oral fluids. Her temperature was 37.8°C [100.04°F]. The intravenous solution was changed to 5 percent dextrose and water with 60 mEq (60 mmol) of potassium chloride added to each liter. A final insulin bolus of 20 units was given, and the infusion rate was later reduced to 5 units per hour. Abdominal sonography showed an intrauterine pregnancy with an estimated age of 8.7 weeks; the gall bladder, liver, and kidneys were normal. Her subsequent hospital course was uneventful, and the amylase level and white cell count returned to normal. The patient later underwent elective termination of the pregnancy.

Diabetic Ketoacidosis in Pregnancy

Diabetic women who become pregnant are at an increased risk for a variety of adverse events including diabetic ketoacidosis (DKA). The reported frequency of DKA in pregnancy varies widely, ranging from 2 percent to 24 percent of all pregnant diabetics.[1] There are no figures available for maternal mortality during pregnancy from DKA, but the mortality for nonpregnant adults in the United States approaches 10 percent from a single episode of DKA.[2]

Infection

Physiologic stress such as infection or dehydration is the most common precipitator of DKA.[3] One clue to an unsuspected infection may be the lack of expected serum glucose response to insulin. Infection can reduce the rate of glucose decline by 50 percent.[2,3] In this patient, the early nausea, vomiting, and diarrhea most likely represented a gastroenteritis that triggered the ketoacidosis. However, multiple sites were cultured to detect occult infection that could account for the severity of her illness. Bacterial sinusitis, carbuncles, and abscesses (which may be particularly hard to detect in the rectal, vaginal, and interdigital areas), and urinary tract infections can be occult foci of infection.

Diabetic ketoacidosis, even in the absence of infection, is commonly accompanied by a leukocytosis. A white cell count ranging from

Table 2. Laboratory Data.

Column	1	2	3	4
Time	1600	2320	0830	1158
Date	06/19	06/19	06/20	06/20
Glucose	473 mg/dL (26.3 mmol/L)	301 mg/dL (16.7 mmol/L)	239 mg/dL (13.3 mmol/L)	180 mg/dL (10.0 mmol/L)
Serum acetone	1:16	1:16	1:16	1:16
Sodium	133 mEq/L (133 mmol/L)	134 mEq/L (134 mmol/L)	136 mEq/L (136 mmol/L)	135 mEq/L (135 mmol/L)
Potassium	5.8 mEq/L (5.8 mmol/L)	3.9 mEq/L (3.9 mmol/L)	2.9 mEq/L (2.9 mmol/L)	4.7 mEq/L (4.7 mmol/L)
Carbon dioxide	5 mEq/L (5 mmol/L)	6 mEq/L (6 mmol/L)	5 mEq/L (5 mmol/L)	9 mEq/L (9 mmol/L)
Calculated anion gap	23 (23)	16 (16)	17 (17)	11 (11)
Creatinine	2.2 mg/dL (190 μmol/L)	2.3 mg/dL (200 μmol/L)	2.3 mg/dL (200 μmol/L)	1.3 mg/dL (110 μmol/L)
Urea nitrogen	23 mg/dL (8.2 mmol/L of urea)	18 mg/dL (6.4 mmol/L of urea)	16 mg/dL (5.7 mmol/L of urea)	15 mg/dL (5.4 mmol/L of urea)
Osmolality calculated	291 mOsm/kg (291 nmol/kg)	281 mOsm/kg (281 nmol/kg)	281 mOsm/kg (281 nmol/kg)	275 mOsm/kg (275 nmol/kg)
Amylase		299 Somogyi units/dL (550 u/L)	748 Somogyi units/dL (1380 u/L)	661 Somogyi units/dL (1220 u/L)
White cell count	31,900/mL (31.9×10^9/L)	32,400/mL (32.4×10^9/L)	37,800/mL (37.8×10^9/L)	
Segmented neutrophils	72% (0.72)	75% (0.75)	74% (0.74)	
Bands	5% (0.05)	15% (0.15)	14% (0.14)	
Hemoglobin	16.9 g/dL (169 g/L)	14.3 g/dL (143 g/L)	15.3 g/dL (153 g/L)	

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15,000/μL to 20,000/μL (15.0×10^9/L to 20.0×10^9/L) is frequently seen in DKA.[4] This elevation is thought to be related to dehydration and hemoconcentration, elevated cortisol, or catecholamines.[2,4,5] The total leukocyte count, however, on admission has been shown to have little or no value in predicting infection in the diabetic who is out of control.[6]

The only predictor of infection in the ketoacidotic patient is the degree of band neutrophil elevation.[6] In a retrospective chart review of patients with DKA who were investigated for occult infection, all the patients who had major infections necessitating antibiotics had greater than 10 percent band neutrophil forms. Using this as an indicator of infection, 83 percent of the patients in that study could be correctly categorized as having major infection.[6] The observed sensitivity of a band neutrophil count of 10 or greater for major infection was 100 percent, and the specificity was 80 percent.

For the patient described here, the combination of rising leukocytosis with increasing band forms and localizing abdominal pain increased suspicion of intra-abdominal infection. Cholecystitis, pancreatitis, and mesenteric vascular insufficiency occur with greater frequency in diabetics,[5] can trigger DKA, and, along with appendicitis and ruptured ectopic pregnancy,[7] were considered as possible sources of the patient's problem. Serious consideration was given to an exploratory laparotomy. It was not clear whether the DKA was the cause or result of the abdominal pain, acidosis, hyperamylasemia, and leukocytosis. The decision was made to continue medical management, realizing that the acidosis could take twice as long to correct as the hyperglycemia.[3]

Abdominal Pain

Abdominal pain was one of the most challenging management problems in this case. The pain can be severe enough in DKA to mimic significant abdominal disease in up to 22 percent of patients.[7] The diagnosis of abdominal pathology can be further confused by the nausea and vomiting that occur in most diabetics with ketoacidosis.[8] The source of gastrointestinal symptoms, including pain, is unclear. Hepatic capsule enlargement, increased hormone and glucose levels inhibiting gastric motility, and insulin deficiency itself are proposed etiologies.[9] The typical pain of DKA is generalized when unaccompanied by intraperitoneal pathology and can be characterized by marked tenderness and guarding.[5,9] In most cases, the pain, nausea, and vomiting associated with DKA resolve with appropriate treatment of the metabolic disturbance.[5] Resolution of the acidosis (not the hyperglycemia) usually is associated with the resolution of abdominal pain. No relation exists between the blood glucose and abdominal pain or the presence of abdominal pathology that could account for the abdominal pain.[10]

In patients who have abdominal pain with DKA, serious consideration should be given to conditions other than ketoacidosis. Primary abdominal or retroperitoneal pathology (e.g., acute pyelonephritis) can precipitate DKA and, thus, must be diagnosed and appropriately managed if the resulting ketoacidosis is to be corrected.

Pancreatitis

Pancreatitis was suggested in this patient because the initial location of the pain, elevated amylase, nausea, vomiting, and history of diabetes all favored the diagnosis. Even the localization of pain to the right lower quadrant, although more consistent with appendicitis or fallopian tube pathology, could have reflected evolving pancreatitis.[11] However, the rapid resolution (within hours) of this patient's abdominal findings with the correction of her severe acidosis argues against a diagnosis of pancreatitis as the cause of her DKA. The incidence of pancreatitis in pregnancy has been reported to range from 0.87/10,000 to 2.35/10,000 deliveries.[11] The disease can develop in any trimester or the postpartum period but appears to be most common in the third trimester.[9,12,13] There is a propensity for occurrence in the primipara,[12,14] as well as the diabetic.[15] When pancreatitis occurs in pregnancy, the cause is usually unknown. However, when an etiology can be identified, it is most commonly primary disease of the gall bladder.[9]

Serum amylase can be elevated when acidemia from any cause is present.[16] Thus, in diabetic ketoacidosis the test loses some of its specificity and positive predictive value for acute pancreatitis. A rise in the serum amylase commonly occurs in DKA.[4,17] A study of nongravid patients with DKA showed the occurrence of hyperamylase-

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Table 3. Etiology of Hyperamylasemia.

Pancreatitis	Ovarian disease
Acidemia	Neoplasm
Diabetic ketoacidosis	Advance renal cell insufficiency
Cholecystitis	Mesenteric thrombosis
Hepatitis	Parotitis
Intestinal obstruction	Perforated duodenal ulcer
Ruptured aortic aneurysm	Fallopian tube disease
Shock	

mia to be 79 percent,[18] with no correlation between the degree of hyperamylasemia and clinical or laboratory indices of DKA.[5,18]

There are many causes for hyperamylasemia,[9,18,19] and these are listed in Table 3. There are conflicting reports whether normal pregnancy alone elevates the serum amylase.[20,21]

Had hyperamylasemia and abdominal pain not diminished so dramatically with the resolution of the acidosis, further investigation of the pancreas might have been indicated. A markedly elevated amylase-creatinine clearance ratio (greater than 10 percent) has been shown to be consistent with a pancreatic source of elevated amylase in one study.[18] However, diseases other than acute pancreatitis (including diabetic ketoacidosis) can be associated with elevated amylase-creatinine ratios, giving the test a low specificity for the diagnosis of pancreatitis and limiting its clinical usefulness.[18,22] Isoenzyme assays could have been used to help determine the origin of the high amylase. A salivary pattern, while not necessarily implying a salivary origin, does exclude the pancreas from consideration.[19] An elevated serum lipase level may also be helpful in making the diagnosis of acute pancreatitis.

Acidosis, Pregnancy, and Insulin Resistance

The development of ketoacidosis at relatively low glucose levels in pregnancy is due to hormonal changes. DKA may develop when the glucose is in the range of 150 mg/dL (8.36 mmol/L) to 300 mg/dL (16.65 mmol/L).[3] Placental estrogen and progesterone enhance peripheral glucose use, which results in lower fasting glucose levels.[2] Less insulin is subsequently required, and lower insulin levels lead to triglyceride hydrolization and free fatty acid release. This release is responsible for the two-to-fourfold elevation in ketone bodies that is observed in early normal pregnancy.[2]

The serum bicarbonate often is low in pregnancy (18 to 21 mEq/L [18 to 21 mmol/L]), which is due to a progesterone-induced increase in alveolar ventilation and an accompanying increase in renal bicarbonate excretion to maintain maternal pH.[2] The combination of increased ketone body production and diminished bicarbonate buffering capacity causes the gravida to be more prone to metabolic acidosis even in the absence of underlying diabetes.[23]

Free fatty acids, in addition to generating ketone bodies and predisposing to acidosis, are implicated in insulin resistance. During pregnancy, their elevation has been found to cause insulin resistance in hepatic and peripheral tissues.[24,25] In addition, acidosis caused by elevated ketone bodies reduces insulin binding, particularly in fat cells.[25] Insulin binding and action are strongly dependent on pH. This patient was at risk for insulin resistance because of her pregnancy-induced ketosis and diminished buffering capacity and because of the degree of acidosis she had attained (pH 6.99 units on admission).

Other etiologies have been proposed for insulin resistance[23-27]; these are listed in Table 4.

The effect of insulin resistance in this patient was persistent hyperglycemia and acidosis. It could be argued that sufficient insulin was not given initially. However, the rather large requirement (220 units of regular insulin over 5 hours) is much more than the current literature suggests as "standard" therapy for DKA.[2-4,17,24,28,29] Even at the point where 32 units of insulin were given during a 2-hour period earlier in the course, there

Table 4. Proposed Causes of Insulin Resistance.

Elevated in pregnancy
Human placental lactogen
Prolactin
Cortisol
Chromium
Placental insulinase
Dyridoxine-xanthurenic acid
Glycogen
Elevated counter-pregnancy hormones in DKA
Growth hormone
Catecholamines
Glucagon
Cortisol
Miscellaneous
Hypophosphatemia
Hypomagnesemia
Hyperglycemic-induced hyperosmolarity

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was marginal improvement in the acidosis. The argument could be made that had high normal doses of intravenous insulin (10 units per hour) been given over a long enough period of time, hyperglycemia and acidosis might have resolved without the use of much higher doses of insulin.

Insulin

The use of low-dose insulin regimens in the treatment of DKA now seems generally accepted.[2-4,17,24,28,29] Relatively small amounts of insulin are usually enough to inhibit lipolysis, ketogenesis, and gluconeogenesis. This inhibition improves extrahepatic use of glucose and ketone bodies.[30] There continues to be debate on the relative frequency of hypokalemia and hypoglycemia with low- versus high-dose insulin therapy.[17] Recommended initial doses of regular insulin intravenously in the treatment of DKA are 0.2 to 0.4 units/kg[2,3,31] with a continuous infusion of 0.1 units/kg/hour[31] or 2 to 10 units per hour.[2,3,24,32] The average rate of glucose decline with appropriate therapy should be about 10 percent per hour[31] or 75 to 100 mg/dL/hour (4.2 to 5.6 mmol/L/hour).[2,3,28,32]

Doses of 50 to 200 units of regular insulin have been used in the past to treat DKA, with a proportion given intramuscularly or subcutaneously and the rest given intravenously.[32,33] When the initial dose does not yield an appropriate glucose decline within the first hour, repetition of the loading dose can be considered.[3] If there is no decrease in ketones or rise in pH after 3 to 4 hours of insulin therapy, up to 50 units of insulin per hour can be given.[3]

The initial insulin doses (2 to 6 units per hour) were enough to decrease the blood glucose but were not sufficient to inhibit lipolysis and ketogenesis. An important function of insulin therapy in DKA is to reverse the acidosis. Despite a declining blood glucose, persistent acidosis can be an indication for additional insulin. This may be the most important point in the management of the patient. It was only after a sufficient amount of insulin reversed the lipolysis and, subsequently, the acidosis that the patient began to improve. Had her abdominal findings and leukocytosis persisted despite the resolution of the acidosis, surgical intervention would have been likely. This patient almost underwent laparotomy because it was not obvious that the ketoacidosis was responsible for her abdominal pain. Definitive management included the increase of insulin while continuing to search for other causes of acidosis, such as infection and ischemia.

Large insulin doses can be problematic, because they can cause a rapid decline in serum glucose and subsequent hypokalemia. Rapid normalization of blood glucose is thought to reduce serum osmolality and cause cellular edema, which can predispose to seizures and possible central nervous system damage.[34] However, there is some evidence that the development of cerebral edema can precede changes in blood chemistry, so the precise mechanism and nature of the intracellular solute responsible for cerebral edema are still unclear.[35]

Fluids and Sodium

Central nervous system edema has also been linked to hyponatremia and inappropriate fluid replacement.[36] However, when the increased plasma concentration of an osmotically active solute, such as glucose, is associated with increased plasma osmolality, the clinical signs of hypotonicity are absent despite laboratory evidence of hyponatremia. Thus, it is difficult to use serum sodium depression as a predictor of cellular edema.

Serum sodium levels are typically normal or reduced[28] in DKA so that in a situation like this patient's where fluid replacement is desired but laboratory data are not immediately available, normal saline is usually a safe initial choice for hydration. The use of normal saline prevents rapid reversal of osmotic gradients, overexpansion of the intracellular compartment, and the development of cerebral edema.[37]

Total fluid deficits can range from 3 to 10 liters.[2,3,31,35,38] A patient's fluid loss is usually estimated to be approximately 75 to 100 mL/kg body weight.[38] Initially, 2 liters of normal saline can be infused during the first hour in adults, thereafter reducing the rate to 150 to 200 mL per hour.[2]

Hypernatremic or hyperosmolar states can be indications for fluid other than normal saline. A sodium concentration greater than 155 mEq/L (155 mmol/L) or an osmolality greater than 320 mOsm (320 nmol/kg) prompts consideration of half normal saline.[2,3,37] When the glucose falls to 250 mg/dL (13.9 mmol/L), the hydrating solution should be changed to 5 percent dextrose and wa-

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ter to prevent excessive intracellular fluid accumulation as rehydration takes place.[38] Persistent vomiting or severe volume depletion can be indications for half normal saline in 5 percent glucose.[35]

Potassium

Most patients with DKA have normal to high potassium levels despite a total body potassium deficit of 3 to 12 mEq/kg (3 to 12 mmol/kg) of body weight.[17,28,38] Opinion varies about when potassium replacement should be instituted in DKA. Starting with the first liter of hydrating solution,[38] starting when the serum potassium values are known,[29,37] and starting when the urine output is established[39] have all been suggested.

In most patients, hypokalemia will be a greater threat to survival than hyperkalemia, so early yet cautious replacement of potassium adjusted by serum potassium levels, electrocardiographic monitoring, and urine output seems warranted.[17] Monitoring potassium replacement is especially important when large and rapid insulin doses are anticipated. This offers the best protection against hypokalemia-induced arrhythmia. This patient was not receiving potassium prior to her high insulin therapy, and the potassium rapidly fell from 6 mEq (6 mmol/L) to 2.9 mEq (2.9 mmol/L) with the 50-unit bolus of insulin. Potassium can be replaced at rates of 10 to 30 mEq/hour (10 to 30 mmol/hour), and as much as 60 mEq/hour (60 mmol/hour) may be required for persistent hypokalemia.[29]

Phosphate

Serum phosphate, like potassium, is typically normal or elevated upon admission[17,28] despite total body phosphate deficiency.[28] In addition, the serum phosphate level usually falls with insulin therapy.[29] Hypophosphatemia has been related to diminished oxygen carrying capacity,[28] altered levels of consciousness, hemolysis, rhabdomyolysis, cardiomyopathy,[40] compromised ventricular performance, decreased ventilation, delayed recovery from infection,[39] and diminished production of high-energy phosphate bonds.[37] However, despite a number of clinical trials, there is no evidence that phosphate therapy provides a beneficial effect in the routine management of DKA.[40-43]

Magnesium

Serum magnesium levels in DKA, like potassium and phosphate, do not give a true indication of total body magnesium stores.[44] Insulin resistance[26] and asystole[45] have been attributed to hypomagnesemia in DKA. Clinical manifestations of low serum magnesium levels (less than 1 mEq/L [0.5 mmol/L]) include hyperexcitability, psychotic behavior, tetany, tonic-clonic focal and generalized seizures, ataxia, vertigo, muscular weakness, tremor, depression, and irritability.[46] Controversy exists over the necessity of routine magnesium therapy in DKA.[17,47]

Bicarbonate

Another controversy in the therapy of DKA is the use of bicarbonate. Advantages claimed for bicarbonate use include improved myocardial function, elevation of the ventricular fibrillation threshold, increased tissue sensitivity to insulin, and reduction in coma recovery time.[48] However, central nervous system edema,[49] paradoxical exacerbation of central nervous system acidosis,[3,50] and hypokalemia-induced arrhythmia[48] are conditions caused by bicarbonate administration in DKA. There is no clear, agreed-upon indication for the use of intravenous bicarbonate in the treatment of DKA.[48-50]

Some sources recommend empiric treatment of acidosis in DKA when the pH is less than 7.0[3,38] or 7.1.[2,37] Sodium bicarbonate in the amount of 200 mEq (200 mmol) infused slowly over 2 to 4 hours has been suggested.[38]

The recommendation has been made to use the $PaCO_2$ as an indicator of the need for bicarbonate supplementation.[31] Patients too weak to hyperventilate sufficiently to reduce the $PaCO_2$ under 20 mmHg (2.7 kPa) with a bicarbonate less than 10 mEq/L (10 mmol/L) are said to require alkali.[31] In this situation cardiovascular collapse is imminent.

A summary of the therapeutic agents sometimes considered in the management of DKA is presented in Table 5.

Creatinine

In diabetic ketoacidosis, there is an interference of acetoacetate with the measurement of creatinine by the alkaline picrate method.[17] Creatinine measured by this method may be falsely elevated in DKA because of the effect of acetoacetate, pos-

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Table 5. Summary of Therapeutic Agents Considered in DKA.

Fluid: Normal saline
2 liters over the first hour, then
150 to 200 mL per hour until glucose is less than 250 mg/dL, then
5 percent dextrose and water.
Insulin: Regular insulin IV
Bolus 0.2 to 0.4 units/kg, then
Drip 0.1 units/kg/hour.
If glucose does not decrease 10 percent per hour or acidosis persists, repeat initial bolus. If no response to re-bolus, consider giving up to 50 units of IV insulin per hour while searching for causes of insulin resistance.
Potassium: 10 to 30 mEq/hour (up to 60 mEq/hour if necessary)
No indication for routine use of:
Phosphate
Magnesium
Bicarbonate

sibly generating unnecessary concern over renal function. This might have been responsible for the persistent creatinine elevation in this case report. Once the acidosis was reversed, the creatinine returned to normal.

Summary

Diabetic and nondiabetic gravidas have a tendency toward acidosis, which is due to the hormonal changes of pregnancy. Diabetic ketoacidosis can occur at much lower glucose levels in the pregnant state.

The abdominal signs and symptoms in DKA can mimic an acute abdomen. This clinical picture usually resolves with the correction of the ketoacidosis.

Hyperamylasemia is a common finding in DKA and is not necessarily indicative of pancreatitis. When pancreatitis is suspected, serum amylase isoenzyme and serum lipase elevations can incriminate the pancreas as the source of elevated amylase.

Ketoacidosis and pregnancy can contribute to insulin resistance. Failure of treatment with standard low-dose insulin regimens should prompt the use of greater insulin doses. A persistent acidosis, despite a declining glucose, can be an indication for more aggressive insulin therapy while searching for other causes of acidosis.

In general, normal saline is the preferred fluid therapy in DKA, and in the adult, 2 liters can be given over the first hour. Potassium supplementation will most always be necessary, although there is controversy about when to begin. There does not appear to be strong evidence for the routine use of phosphate, magnesium, or bicarbonate.

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