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Case Report

Euglycemic Diabetic Ketoacidosis in a Pregnant Patient on Insulin Pump Therapy

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ABSTRACT

Background/Objective: Diabetic ketoacidosis is a common endocrine emergency. A subset of patients present with euglycemic diabetic ketoacidosis, which may be diagnosed late due to its rarity and relatively lower blood glucose levels. Pregnancy is associated with euglycemic diabetic ketoacidosis, which can lead to maternal and fetal demise without prompt treatment. The objective of this case report is to describe a patient with type 1 diabetes mellitus who developed euglycemic diabetic ketoacidosis on insulin pump therapy during pregnancy.

Case Report: A 30-year-old pregnant patient at 33 weeks of gestation with type 1 diabetes mellitus on continuous subcutaneous insulin infusion presented to the emergency department with vomiting. Her serum bicarbonate of 9 mmol/L was accompanied by serum glucose of 130 mg/dL, moderate blood ketones, and urine ketones 80 mg/dL (large). She was treated with intravenous insulin infusion without complications to herself or the fetus.

Discussion: Pregnancy is a common background for euglycemic diabetic ketoacidosis and can lead to maternal and fetal demise if not addressed early. Despite insulin resistance in pregnancy, a relatively low blood glucose is maintained by increased glycogen storage and increased fetoplacental uptake. Altered acid-base physiology in pregnancy may also increase the propensity for euglycemic diabetic ketoacidosis.

Conclusion: Diabetic ketoacidosis can present in pregnancy with euglycemia, and a high index of suspicion is needed by both patients and health care teams. There are a few reports on this phenomenon in a pregnant patient using an insulin pump. Early identification and treatment are important to prevent maternal and fetal complications.

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Introduction

Diabetic ketoacidosis (DKA) is a common endocrine emergency. It is characterized by a triad of hyperglycemia (serum glucose > 250 mg/dL), metabolic acidosis (arterial pH < 7.3 and serum bicarbonate < 18 mEq/L), and ketonemia with a high anion gap.[1] In rare situations, patients may demonstrate all the other elements of DKA but with a relatively lower serum glucose (less than 200 mg/dL), referred to as euglycemic DKA (EDKA).[2] EDKA is associated with maternal and fetal morbidity and mortality.[3] The diagnosis is challenging because of its rarity. It is less familiar to clinicians, which can lead to a missed diagnosis and inappropriate management.[3] Studies have shown that even with treatment of DKA, the prolonged fetal exposure to acidosis has been associated with poor neurologic outcomes.[4] We describe the case of a 30-year-old pregnant patient at 33 weeks of gestation with type 1 diabetes mellitus (T1D) being treated with continuous subcutaneous insulin infusion (CSII); she presented to the emergency department for vomiting and was found to have EDKA that resolved with an intravenous insulin infusion.

Abbreviations: CSII, continuous subcutaneous insulin infusion; DKA, diabetic ketoacidosis; EDKA, euglycemic diabetic ketoacidosis; MDI, multiple daily injection; SGLT2, sodium-glucose cotransporter 2; T1D, type 1 diabetes mellitus.

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Case Report

A 30-year-old female, gravida 2 para 1 at 33 weeks of gestation, with a history of T1D diagnosed in early adulthood but no other medical conditions, presented to the emergency department with 2 days of nausea, vomiting, headaches, and nonspecific abdominal pain. She denied any chest pain, shortness of breath, constipation, diarrhea, or urinary symptoms. She took multivitamins and denied drinking alcohol, smoking cigarettes, or taking illicit drugs. The patient was managing her T1D with CSII via an insulin pump during pregnancy. The pump was running in manual mode at the time of consultation (see Table 1 for settings). Because the patient was referred from an outside facility, records on insulin pump settings via an online clinic account are unavailable. Her insulin-carb ratio was strengthened during pregnancy, reflecting the insulin resistance that can accompany pregnancy. The patient was not taking sodium-glucose cotransporter 2 (SGLT2) inhibitors and reported her insulin pump had been running smoothly without any issues or interruptions in insulin delivery. Her most recent hemoglobin A1c was 7.0% (53 mmol/mol) a month prior. The patient had an uncomplicated pregnancy 3 years earlier and delivered a healthy infant through cesarean delivery.

Vital signs on presentation were remarkable for tachycardia with a heart rate of 125 bpm (normal range, 60-100 bpm), a temperature of 37.1 °C, a respiratory rate of 18 breaths per minute (normal range, 12-20), a blood pressure of 131/66 mm Hg (goal < 120/80 mm Hg), and an oxygen saturation of 96% on room air (normal 92% to 100%). Physical examination was remarkable for mild distress, distended abdomen correlated with 33 weeks of gestation, and trace pedal edema. Fetal evaluation revealed an average heart rate of 165 bpm, interpreted by the obstetrics team as tachycardic with moderate baseline variability; fetal heart rate accelerations were present without any decelerations. Pertinent laboratory results are highlighted in Table 2. Chest X-ray did not show any abnormalities. Transabdominal ultrasound showed a live fetus with an estimated weight of 2900 grams, and fetal measurements correlated to 35 weeks of gestation.

The patient received 3 liters of intravenous normal saline. A DKA protocol with intravenous insulin infusion was initiated, and the patient was admitted to the intensive care unit under the obstetrics service. She received normal saline with 5% dextrose for fluid maintenance. After 24 hours of intravenous insulin infusion, the anion gap value decreased to 8 mEq/L, the bicarbonate value increased to 16 mEq/L, and the serum glucose level was 102 mg/dL. Two episodes of hypoglycemia occurred while the patient was on both intravenous insulin and CSII with her pump in manual mode, and this was addressed during the initial endocrinology consultation. The patient was discharged in stable condition and resumed insulin therapy via her insulin pump using her initial settings.

Discussion

Pregnancy is considered a diabetogenic state, marked by relative insulin resistance.[5] Several hormones produced in pregnancy, including human placental lactogen, progesterone, and cortisol, inhibit the action of maternal insulin and contribute to insulin resistance.[6,7] A reduction in buffering capacity during pregnancy increases susceptibility to metabolic acidosis and thus DKA.[8] Insulin resistance promotes enhanced lipolysis, elevated free fatty acids, and ketogenesis. The increased caloric requirement in pregnancy predisposes the mother to accelerated starvation, which can also promote ketogenesis and lower the threshold for DKA and EDKA.[5] Despite insulin resistance, pregnant women tend to maintain relatively low blood glucose levels due to increased glucose uptake by the fetoplacental unit. In addition, increased glucose excretion by the kidneys and a hemodilution effect of pregnancy are observed. Therefore, many pregnant women present with ketoacidosis despite normal or mildly elevated blood glucose levels.[9-11] According to many reports, DKA occurs in approximately 0.5% to 3% pregnant women with diabetes, and up to 30% of DKA cases are EDKA.[12] DKA and EDKA are more common during the second and third trimesters as insulin resistance increases with

Highlights

- DKA is a life-threatening emergency that can lead to poor fetal outcome in pregnancy
- Euglycemic DKA is a subtype that can be missed due to rarity and relative euglycemia
- Pregnant patients with diabetes are prone to EDKA due to multiple factors
- Ketone monitoring and pump management during illness may be different in pregnancy

Clinical Relevance

Diabetic ketoacidosis (DKA) in pregnancy often presents with relatively normal blood sugar, so it is particularly important to monitor ketones during illness. A high index of suspicion is needed by patients and health care providers, because early identification and treatment of euglycemic DKA are important to prevent maternal and fetal complications.

Table 1
Insulin Pump Settings

Setting	Time of the day	Parameter
Basal rate	12 AM-12 AM	0.85 units/h
Sensitivity factor	12 AM-12 AM	16
Carbohydrate ratio	12 AM-12 AM	4 (8 before pregnancy)
Target glucose	…	70-100 mg/dL
Insulin duration of action	…	2 h (3 h before pregnancy)

Table 2
Laboratory Workup Results at the Time of Admission

Test	Result	Reference value
White cell count ($\times 10^3/\mu L$)	15.2	4.0-11.0
Hemoglobin (g/dL)	10.6	11.7-15.5
Hematocrit (%)	32.3	35.1-46.5
Glucose (mg/dL)	130	70-99
Blood urea nitrogen (mg/dL)	14	6-22
Creatinine (mg/dL)	0.6	0.5-1.2
Sodium (mmol/L)	131	133-145
Chloride (mmol/L)	103	69-106
Potassium (mmol/L)	4.5	3.5-5.5
Bicarbonate (mmol/L)	9	20-32
Anion gap (mmol/L)	19	3-15
Blood ketones	Moderate	Negative
Urine pH	5.0	6.0-7.5
Urine glucose	150	Negative
Urine ketones	+3	Negative
Urine blood	Negative	Negative
UA leukocyte esterase	Negative	Negative
UA nitrite	Negative	Negative

Abbreviation: UA = urinanalysis.

gestational age and may be exacerbated when coupled with prolonged fasting.[13]

Common triggers for DKA and EDKA are stress, continuous vomiting, decreased oral intake, infections, poor compliance with treatment, insufficient self-management of diabetes therapy, glucocorticoid therapy, and ß-agonists which are used as tocolytic agents, and labor.[12] Use of SGLT2 inhibitor drugs has been reported to be associated with EDKA.[14] However, a previous report showed that hyperglycemic DKA also occurs in the setting of SGLT2 inhibitors.[15] No specific trigger, including pump malfunction, was identified for EDKA in this patient, although it is unclear if she was checking urinary ketone levels or following sick day rules at home.

Fetal demise during DKA may occur due to maternal hypovolemia with decreased uteroplacental blood flow; increased concentrations of catecholamines in DKA can lead to fetal hypoxemia. Additionally, acidosis with electrolyte imbalance and hyperlactatemia can disrupt the acid-base balance in the fetal circulation and worsen any existing hypoxemia. Lastly, lethal cardiac arrhythmias can occur, particularly in the setting of hypokalemia.[12] Although studies addressing long-term consequences of viable infants born to pregnant mothers with DKA are lacking, changes in neurodevelopment have been observed, including impairment of brain development (lower intelligence quotient) and an association with autism spectrum disorder.[3]

Treatment of EDKA is similar to treatment for DKA, utilizing insulin infusion and fluid resuscitation to clear ketones from the blood, resolve acidosis, normalize fluid volume status, and correct electrolyte abnormalities. In EDKA, intravenous fluids with a higher dextrose concentration may be needed to allow for safe administration of insulin.[12] Serial chemistry profiles are important to monitor the response and confirm the biochemical end point of anion gap closure. Any underlying cause should also be identified and treated. The fetal heart should be monitored closely during the management of EDKA.[16] It should be noted that DKA/EDKA rarely warrants immediate emergency delivery, because this would harm the mother and be unlikely to save the newborn; prematurity adds additional risk. If delivery is inevitable, as in cases where the maternal condition worsens despite aggressive therapy, it is associated with high maternal morbidity and mortality.

While the symptoms of DKA are nonspecific, pregnant women with T1D should be advised to seek immediate medical care for profound fatigue or unexplained nausea or vomiting. These patients should check for urinary or blood ketones at home, even if hyperglycemia is not present.[3] Health care providers and emergency room physicians should consider DKA in pregnant women with diabetes reporting the abovementioned symptoms. It is also important to consider patient and provider education on sick day rules and ketone monitoring during pregnancy. Hypoglycemia during illness complicates the administration of adequate insulin doses during ketosis.

Although there are several cases of EDKA reported in the literature, our case is unique as it occurred while the patient received CSII. To our knowledge, our case is the first one to report EDKA in a patient receiving CSII. The CSII has revolutionized the management of diabetes mellitus over the last several decades. There are many advantages to using an insulin pump compared to an insulin regimen with multiple daily injections (MDIs), including more precise and flexible insulin dosing with fewer injections.[17] Many studies and systematic reviews have demonstrated improved glycemic control and a reduction in hypoglycemia in patients with T1D who use insulin pumps compared to multiple daily insulin injections.[18] Studies show mixed results for risks for DKA in patients using an insulin pump compared to MDI, although the risk may be lower in newer generations of insulin pumps.[19] In a meta-analysis comparing CSII to conventional and MDI insulin therapy, 42 out of 854 patients on CSII (4.9%) developed DKA, versus 22 out of 858 patients (2.6%) in the combined MDI and conventional therapy group.[20] Newer models of insulin pumps with closed-loop capability may confer a different risk, however. Many factors contribute to the occurrence of DKA in patients on CSII, such as improper insulin regimen, malfunctioned pump or clogged catheters, and improper use by patients.[19]

Conclusion

DKA can present in pregnancy with normal blood glucose levels, and a high level of suspicion is needed by both patients and health care teams. Early identification and treatment are important to prevent maternal and fetal complications.

Statement of Patient Consent

The patient consented to publish the case report.

Disclosure

The authors have no conflicts of interest to disclose.

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