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Case Report

Diabetic Ketoacidosis Complicating Gestational Diabetes Mellitus

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ABSTRACT

Background/Objective: The prevalence of diabetic ketoacidosis (DKA) in gestational diabetes mellitus (GDM) is very low. We describe a patient with GDM in whom severe DKA with intrauterine fetal demise developed in the setting of nonadherence to therapy.
Case Report: A 33-year-old woman, G2P0010, with no preexisting diabetes mellitus (DM) presented at 30 weeks of gestation with acute-onset altered sensorium, nausea, and emesis. GDM was diagnosed at 15 weeks of gestation with a serum glucose level of 266 mg/dL (70-134 mg/dL) after 1-hour 50-gram glucose challenge test. Glycated hemoglobin (HbA1C) was 5.9% (41 mmol/mol) at the time of GMD diagnosis. Insulin was initiated at week 20 of gestation. On presentation, serum glucose level of 920 mg/dL (70-110 mg/dL), pH of 7.02 (7.32-7.43), anion gap level of 38 mmol (5-17 mmol), bicarbonate level of 5.0 mEq/L (22-29 mEq/L), and large serum ketones were found. Ultrasound showed intrauterine fetal demise. She received intravenous fluids and continuous insulin. Following the spontaneous delivery of a nonviable fetus, DKA was resolved. Negative antiglutamic acid decarboxylase, islet cell, and zinc transporter 8 antibodies, C-peptide level of 2.4 ng/dL (1.1-4.4 ng/dL), and HbA1C level of 9% (75 mmol/mol) were found. Inpatient management included basal-bolus and sliding scale insulin therapies. Metformin was added upon discharge 7 days after admission. The HbA1C levels were 5.3% (34 mmol/mol) and 5% (31 mmol/mol) at the 3- and 6-month follow-ups, respectively. Insulin was discontinued. Currently, the patient is on metformin and glucagon-like peptide 1 receptor agonist.
Discussion: The development of insulin resistance during pregnancy is driven by multiple factors. Approximately 1% to 2% of pregnant women with impaired glucose tolerance develop DKA; most cases occur in women with type 1 DM. The approximate incidence of DKA in GDM is 0.02%.
Conclusion: DKA complicating GDM is extremely infrequent, but it cannot be dismissed. Early recognition along with prompt and appropriate medical and obstetrical management is critical.
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Introduction

Diabetic ketoacidosis (DKA), a complication of diabetes mellitus (DM), is a life-threatening disorder that typically presents with hyperglycemia, high anion gap metabolic acidosis, and increased serum ketone body concentration.[1-3] Most patients with DKA in pregnancy have preexisting type 1 DM, although it can also be seen in type 2 DM (T2DM) and rarely as a complication of gestational diabetes (GDM).[1,3-7] Here, we present a case of severe DKA and intrauterine fetal demise (IUFD) in a 30-week gravida woman with GDM who reported nonadherence to a home insulin regimen throughout the pregnancy.

Case Report

A 33-year-old African American woman, G2P0010 was brought by her family to the emergency department at 30 weeks of gestation with a 3-day history of general malaise, altered sensorium, nausea, and emesis. The patient had a history of class III obesity with no diagnosis of preexisting DM, although preconception glycosylated hemoglobin (HbA1C) level was unavailable. GDM was

Abbreviations: DKA, diabetic ketoacidosis; DM, diabetes mellitus; GDM, gestational diabetes mellitus; HbA1C, glycosylated hemoglobin; IUFD, intrauterine fetal demise; PGH, pituitary growth hormone; T2DM, type 2 diabetes mellitus.

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diagnosed at 15 weeks of gestation with a serum glucose level of 266 mg/dL after 1-hour 50-gram glucose challenge test. Her HbA1C level was 5.9% (41 mmol/mol) by the time of GDM diagnosis, and insulin therapy with 10 units of neutral protamine Hagedorn insulin once daily, in addition to 5 units of regular insulin 3 times daily with breakfast, lunch, and dinner was initiated at week 20 of gestation. Nonadherence to her insulin regimen throughout the pregnancy was reported.

Her blood pressure was 70/40 mm Hg, heart rate was 150 beats/min, and respiratory rate was 26 breaths/min. The mucus membranes were dry, and the skin turgor was decreased. The serum glucose level was 920 mg/dL (70-110 mg/dL), pH was 7.02 (7.32-7.43), anion gap level was 38 mmol, bicarbonate level was 5.0 mEq/L (22-29 mEq/L), and serum potassium level was 3.4 mEq/L (3.5-5.1 mEq/L); large serum ketones were present. The white blood cell count was 24.13 $\times$ 10^3/μL (4.3$\times$ 10^3/μL to 11 $\times$ 10^3/μL), with a predominance of leukocytes. SARS-CoV-2 polymerase chain reaction was negative. IUFD was diagnosed by ultrasound. The patient was treated with intravenous fluids and continuous insulin. She also received potassium, bicarbonate, and piperacillin-tazobactam. A new HbA1C level of 9% (75 mmol/mol) was obtained. At one point, when hypokalemia worsened to 2.5 mEq/L, continuous insulin was withheld until the serum potassium level reached above 3.3 mEq/L. Approximately 20 hours after admission, she spontaneously delivered a nonviable fetus. Following this, DKA was resolved, and the patient was managed with basal-bolus and sliding scale insulin therapies. About 2 days after DKA resolution, the patient's decreased mental status returned to baseline, and further history taken from her was negative for DM before she became pregnant. The patient was subsequently transferred to the regular medicine ward, and basal-bolus insulin dose was increased given hyperglycemia between 250 and 300 mg/dL was present. After dose adjustment, the glycemia reduced to 180 to 200 mg/dL. Five days after admission, additional studies revealed negative antiglutamic acid decarboxylase, islet cell, and zinc transporter 8 antibodies, in addition to a C-peptide level of 2.4 ng/dL (1.1-4.4 ng/dL). Seven days after admission, the patient was discharged with basal insulin (25 units) twice daily, preprandial insulin (10 units) 3 times daily, and metformin (500 mg) twice daily. An outpatient follow-up visit was scheduled a week after hospital discharge; the patient returned 2 months later to our diabetes clinic. At the first outpatient visit, there was no evidence of DM as a point of care HbA1C level of 5.5% (37 mmol/mol) was obtained. The patient's body mass index was 48 kg/m^2. Preprandial insulin was discontinued, basal insulin was decreased to 25 units daily, metformin dose was increased to 1 gram twice daily, and glucagon-like peptide 1 receptor agonist was initiated. At the 3- and 6-month follow-ups, HbA1C levels of 5.3% (34 mmol/mol) and 5% (31 mmol/mol) were obtained. Currently, the patient is maintained on metformin (500 mg) twice daily and dulaglutide (1.5 mg) once a week.

Ten days after hospital discharge, an autopsy of the nonviable fetus revealed a female with macrosomia (bodyweight 1640 g [expected, 1372 $\pm$ 244 g]; heart weight 12.7 g [expected, 8.7 $\pm$ 2.3 g]), pancreatic islet cell hyperplasia, and mild adrenal granulosa layer hyperplasia. There were no congenital anomalies. Placental findings showed no evidence of inflammation or thrombosis of a 3-vessel umbilical cord, multiple focal hyperacute ischemic infarction, small intervillous thrombi associated with peripheral parenchymal infarction, and mildly increased fibrin deposition on her basal plate.

Highlights

- Understanding that diabetic ketoacidosis (DKA) as a complication of gestational diabetes mellitus (GDM) is extremely infrequent but it is a serious endocrine emergency.
- Understanding the physiologic changes that predispose pregnant women with impaired glucose tolerance to DKA
- Understanding proper outpatient management of GDM with insulin therapy and frequent follow ups as may have a signficant impact in prevention of DKA in GDM.

Clinical Relevance

Diabetic ketoacidosis in gestational diabetes mellitus (GDM) is a potentially preventable serious medical emergency by optimizing the outpatient adherence to GDM treatment and emphasizing the importance of regular blood glucose monitoring, especially in a high-risk population. Early recognition and initiation of optimal medical treatment along with adequate obstetrical care may reduce its associated fetal mortality.

Discussion

We have presented a case of severe DKA and IUFD in a pregnant woman during her last trimester of gestation as a complication of GDM diagnosed in the current pregnancy and who reported nonadherence to a home insulin regimen throughout pregnancy. DKA develops in approximately, 1% to 2% of pregnant women with impaired glucose tolerance.[7] A recent study of pregnant women in the United Kingdom by Diguisto et al[2] reported local prevalence of DKA between 0.1% and 1.6%. The same study documented an incidence of 1 in 900 of DKA in women with T2DM.[2] Because GDM is approximately 5-fold more prevalent than T2DM during pregnancy, the incidence of DKA in pregnant women with GDM is approximately 1 in 4500, underscoring that DKA in GDM is extremely infrequent. A glucose challenge test result of 266 mg/dL at 15 weeks of gestation was diagnostic for GDM in our patient. Although no preconception HbA1C level was available, the patient denied having had a preexisting diagnosis of DM. Moreover, a new HbA1C level of 9% (75 mmol/mol) obtained during the medical intensive care unit course compared with a HbA1C level of 5.5% (37 mmol/mol) at 6 weeks of gestation made the diagnosis of T2DM before conception unlikely. DKA was initially suspected in our patient because of the significantly elevated serum glucose level on presentation. However, DKA at near-normal serum glucose levels, known as euglycemic DKA, may occur more frequently in pregnancy compared with DKA in nongravid women with DM.[2,4,8] The likely mechanism of euglycemic DKA in pregnancy may be attributed to physiologic changes in pregnancy such as hemodilution, the accelerated usage of glucose for the fetoplacental component through the increased expression of placental glucose transporters, and increased glycosuria because of enhanced glomerular filtration without an analogous increase in tubular glucose reabsorption.[2,8] As seen in our patient, the vast majority of cases with DKA in pregnancy emerge mainly during the last trimester of gestation.[1,2,4,8] This observation is directly correlated with physiologic changes characteristic at this late stage which predispose pregnant women to develop DKA.[1-4,8,9] Pregnancy is a relative state of insulin resistance.[1-4,8,9] The production of insulin-antagonistic hormones such as human placental lactogen, prolactin, cortisol, pituitary growth hormone (PGH), and progesterone contribute to this state.[1-4,7,8,10] Insulin resistance may be further enhanced by inflammatory changes in adipose tissue late in pregnancy.[7] Sensitivity to insulin

decreases by 56% through 36 weeks of pregnancy and returns to the pregestation levels after delivery.[3,4,7] PGH is a significant regulator of maternal insulin resistance by enhancing gluconeogenesis and lipolysis ensuring an adequate nutrient supply for the fetoplacental unit.[10] PGH gradually increases in concentration throughout the pregnancy, with levels that rise greatly between 20 and 30 weeks of gestation.[10] It has been documented that women with GDM are found to have higher maternal serum levels of PGH.[10] An additional potential mediator that contributes to the higher incidence of DKA in the late stages of pregnancy is progesterone, which aggravates hyperglycemia by decreasing gastrointestinal motility and promoting the absorption of carbohydrates.[1,3,4] Pregnancy is considered an accelerated state of starvation, with maternal glucose serving as a major source of fetal energy leading to a decreased maternal fasting glucose level.[1,3,4,8] This, combined with relative insulin resistance, results in accelerated gluconeogenesis, glycogenolysis, and lipolysis, with an increase in free fatty acids and ketone body formation.[1,3,4,8] It has been reported that maternal ketone body levels increase by 33% during the third trimester of pregnancy compared with the postpartum period.[3] Furthermore, in a gravid state, the physiologic increase in minute alveolar ventilation leads to respiratory alkalosis that is compensated by an increase in renal bicarbonate excretion; the net result is a reduction in the buffering capacity when exposed to ketonemia.[1,3,4,8] Under these circumstances, pregnant women with DM are at risk of developing DKA more rapidly and at lower serum concentrations of glucose compared with nonpregnant women with DM.[3,4,8]

It is presumed that maternal acidosis, hyperglycemia, severe volume depletion, and significant electrolyte derangements seen in severe DKA lead to reduced uteroplacental perfusion and ensuing fetal loss from the resulting fetal hypokalemia, cardiac arrhythmia, and myocardial suppression.[1,2] Fetal demise is common, especially in severe cases of ketoacidosis that are associated with maternal coma.[5]

The most common precipitating factors for DKA in pregnancy are infection, including COVID-19,[9] insulin therapy failure or nonadherence, steroid use for fetal lung maturity in the context of premature onset of labor, dehydration, and unrecognized new-onset DM, which accounts for up to 30% of cases with DKA.[1,2,4,5,9] In our patient, we hypothesize that nonadherence to insulin therapy and dehydration perhaps complicated by an underlying infection were the contributing factors to the development of DKA.

The possibility of identifying genetic polymorphisms as predictors of DKA in routine genetic screening in women with GDM has been proposed. A study by Zhang et al[11] demonstrated an association between the presence of a genetic polymorphism rs184187143 in the *SLC26A6* gene and increased susceptibility to develop DKA in women with GDM.[11] The investigators suggest that this genetic polymorphism causes an anion exchanging dysfunction, impairing normal lactate and ketone release and transportation. Zhang et al[11] proposed that the detection of this genetic polymorphism in routine genetic screening may be a potential predictive factor for DKA in high-risk pregnant women with GDM.

Adequate volume resuscitation, insulin infusion initiation, and close monitoring of electrolytes, in addition to concomitant management of possible underlying precipitating factors for DKA in pregnancy should be established promptly.[1,4] A limiting factor experienced in our case was the worsening of hypokalemia, which may potentially delay DKA resolution. Studies do not support urgent delivery based on evidence of some degree of fetal compromise given that it may result in further maternal deterioration without significant benefit to the fetus.[1,4] In our case, it was evident that DKA resolved faster after the spontaneous delivery of a nonviable fetus.

DKA, as a complication of GDM, is extremely infrequent but it is an endocrine emergency that cannot be completely dismissed. Early recognition and prompt initiation of appropriate medical therapy combined with proper obstetrical care are key in the management. Furthermore, optimizing adherence to GDM treatment can potentially decrease the risk of DKA during pregnancy.

Author Contributions

C.A.V. conceptualized and designed the case report, collected and analyzed the data, and drafted the initial and final manuscripts. C.A.V., A.F-A., and R.B. reviewed and revised the final manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Disclosure

The authors have no multiplicity of interest to disclose.

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