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Case Report

Euglycemic Ketoacidosis in Pregnancy Complicated by COVID-19

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Summary

Euglycemic ketoacidosis (EKA) is an uncommon yet serious complication during pregnancy, which is precipitated by illness or other stressors. EKA in particular, requires a high index of suspicion. There have been reports of COVID-19 infection precipitating EKA in pregnancy as described in the literature. Our patient is a gravida 1 para 0 female at 28 weeks, 0 days who presented with gastrointestinal symptoms and concurrent acute COVID-19 illness. At time of admission, she did not have her glucose screening yet. She was diagnosed with EKA and managed with intravenous fluids and insulin administration. This resolved and she was discharged home. Our case and literature review suggest an association between COVID-19 infection in pregnancy and the propensity to develop EKA. Timely management is important to reduce adverse outcomes.

Background

Periods of increased stress from intercurrent illness, such as COVID-19, can lower metabolic threshold and precipitate ketoacidosis. During pregnancy, the presence of placental derived hormones directly impairs insulin sensitivity and can increase the risk of ketoacidosis, even in the setting of euglycemia [1]. Euglycemic ketoacidosis is defined by a biochemical triad: blood glucose levels below 200 mg/dL, increased anion gap metabolic acidosis, and ketonemia [2]. This may present a diagnostic challenge and prompt recognition and treatment are critical in pregnancy [3].

Hyperglycemia is the hallmark for diagnosis of ketoacidosis and normoglycemia may masquerade the diagnosis of ketoacidemia [4]. More often it is called diabetic ketoacidosis (DKA) in the setting of known diagnosis of diabetes. Furthermore, only 2.6 to 3.2% of ketoacidosis admissions are euglycemic, therefore, it is a rare diagnosis [5]. Interestingly, there have been reports of COVID-19 infection precipitating EKA in pregnancy. Even rarer, are cases in which patients presented with COVID-19 and EKA in pregnancy without a prior history or diagnosis of diabetes [1, 6-8]. We present one such case and a review of the literature.

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Case Presentation

A gravida 1 para 0 woman in her 20's at 28 weeks, 0 days gestation presented with nausea, vomiting and decreased appetite in the setting of COVID-19 infection. She was diagnosed with COVID-19 a week prior to current presentation and at that time, had mild upper respiratory symptoms and myalgias. She was vaccinated with two doses of Moderna, but had not received the booster. She was offered Remdesivir, but declined. She had increased sensation of heartburn and also stated she had no appetite. The patient had not yet completed a glucose screen during this pregnancy, but had no prior history of diabetes.

Her pregnancy was complicated by being rubella non-immune, fetal pyelectasis noted on ultrasound, and the patient was a carrier of spinal muscular atrophy. Her past medical, past surgical, and family history were non-contributory. She had no allergies to medications and was currently not taking any medications in the setting of ongoing nausea. Prior to this she was taking Odansetron and Famotidine for nausea and gastrointestinal reflux disease. She denied any history of tobacco use and had not recently used any alcohol during this pregnancy.

She appeared in no respiratory or acute distress and was alert and oriented x 3. Her heart, lung and abdominal exam were within normal limits and, overall, she had a normal physical exam. Fetal heart tracing was reactive. In the setting of limited PO intake, a work-up with electrolytes, urinalysis, complete blood count with differential was performed initially. The patient was managed on labor and delivery for the initial 1-2 days and then transferred to the antepartum floor during her admission.

Investigation

Her initial admission laboratory results showed a glucose of 113 mg/dL, elevated anion gap of 19 mmol/L, bicarbonate of 18 mmol/L, +4 urine ketones, lactic acid of 2.4 mmol/L, K 3.6 mmol/L and WBC of 8.04 x 103/uL. As urine ketones and anion gap were both elevated, a beta-hydroxybutyrate (β-HA) was drawn and found to be elevated to 3.57 mmol/L. Glucose levels ranged from 110-130 mg/dL during this admission. After 12 hours, her anion gap closed to 11 mmol/L and her β-HA normalized to 0.06 mmol/L.

Differential Diagnosis

Starvation ketosis in the setting of gastrointestinal symptoms with minimal PO intake and high anion gap metabolic acidosis is another diagnosis to consider. Alcoholic ketoacidosis is seen in patients with chronic alcoholism and is a common cause of high anion gap metabolic acidosis, however, our patient has no recent use of alcohol in

Author	Patient age (years)	Gestational age (weeks)	History of diabetes	Symptoms and signs	Serum glucose (mg/dL)	HCO3(mmol/L)	Anion gap	pH	Serum ketones (mmol/L)
Smati et al. [11]	36	32	Yes- Diet-controlled gestational diabetes (A1GDM)	Abdominal pain, nausea, vomiting, dyspnea	111.6	5.8	NA	7.2	15.4
Pikovsky et al. [1]	34	35	Yes-type 2	Shortness of breath (SOB), nausea, decreased oral intake.	79.2	6.2	21	6.9	5.2
	34	36	No	SOB, pleuritic chest pain, lethargy, decreased oral intake.	75.6	7.1	17.9	7.3	5.2
Velasco et al.[2]	29	34	Yes- A1GDM	Decreased oral intake	169.2	NA	NA	NA	NA
Mause et al.[12]	30	29	Yes- Gestational diabetes controlled with insulin (A2GDM)	SOB, vomiting, decreased oral intake	NA	NA	NA	NA	NA
Thorne et al.[8]	41	31	No	SOB, tachypnea	NA	15.8	NA	7.4	4.2
	25	34	No	SOB, vomiting	NA	6.4	NA	7.2	5.6
	27	33	No	SOB, tachypnea	NA	16.4	NA	7.4	4
	35	32	No	SOB, vomiting		13.3		7.5	3
Karuppas-amy et al.[13]	30	29	Yes- A2GDM	Vomiting, diarrhea, abdominal pain.	NA	NA	NA	NA	NA
Amesfoort et al.[6]	31	37	No	Headache, nausea, vomiting, fever, SOB, pleuritic chest pain.	84.6	8.7	23	7.3	NA
Espinoza et al.[7]	36	35	No	Fever, cough, vomiting, diarrhea, dyspnea, decreased oral intake.	66	8.2	25.4	7.3	NA

Table 1: Patient characteristics and clinical presentation of published cases with EDKA and COVID-19 in pregnancy.

Author	Insulin infusion Yes (Y)/No (N)	Steroids Y/N	Additional medications	Maternal Outcomes	Gestational age at delivery (weeks)	Mode of delivery
Smati et al.[11]	Y	NA	Bicarbonate repletion (HCO3)	Suspected preeclampsia requiring delivery	32	Cesarean section
Pikovsky et al.[1]	Y	Y	Remdesivir	Discharged on postpartum day 12 with baby	35	Cesarean section
	Y	Y	Low Molecular Weight Heparin (LMWH)	Discharged on day 5 with baby	37	Cesarean section
Velasco et al.[2]	Y	NA	Remdesivir, HCO3, LMWH, oxygen supplementation (O2)	Patient with normal glucose and Hemoglobin A1c (HgbA1c) 2 months after delivery	36	Cesarean section
Mause et al.[12]	Y	Y	Remdesivir, Tocilizumab, antibiotics, O2	Recurrent EDKA Intubated over 7 days after delivery	29	Cesarean section

Thorne et al.[8]	Y	N	NA	Discharged after 9 days	NA	NA
	Y	N	Antiemetics	Discharged after 3 days	NA	NA
	Y	Y	NA	Prolonged intensive care unit (ICU) stay, discharged on day 26	33	Cesarean section
	Y	N	Antibiotics for concomitant urinary tract infection.	Discharged to home	NA	NA
Karuppasamy et al.[13]	Y	N	Convalescent plasma, antibiotics	Discharged to home	37	Cesarean section
Amesfoort et al.[6]	NA	Y	Remdesivir, antibiotics, O2	Respiratory deterioration 1 day after delivery	38	Cesarean section
Espinosa et al.[7]	Y	Y	O2, HCO3, antibiotics.	Discharged on day 5	38	Vaginal Delivery

Table 2: Management and outcomes of published cases with EDKA and COVID-19 in pregnancy.

the setting of pregnancy [9]. Euglycemic ketoacidosis is a diagnosis of exclusion and an uncommon diagnosis. Furthermore, it is more commonly seen in patients who use sodium/glucose cotransporter-2 inhibitors (SGLT-2) for diabetes management [9, 10].

Treatment

The patient was admitted and given intravenous fluids (IVF) with two liters of lactated ringers. Her IVF transitioned to D10NS at a rate of 150 mL/hour and an insulin infusion was started, initially at 1 unit/hour then increased according to protocol. Her gastrointestinal symptoms improved, the insulin infusion was discontinued, and she tolerated a regular diet.

Outcome and Follow-Up

After her gastrointestinal symptoms improved and insulin infusion was discontinued she was discharged the next day. A 50 g oral glucose tolerance test was performed one week after discharge and was 98 mg/dL. The patient returned for routine prenatal care two weeks after discharge and continued routine prenatal care until she was delivered at 41 weeks of gestational age three months after this admission.

She had a spontaneous vaginal delivery with a 2nd degree perineal and labial laceration, repaired with suture without any issues. After delivery she had uterine atony which was resolved with increased pitocin rate, bimanual uterine massage, methergine 0.2 mg, hemabate 0.25 mg, and cytotec 1000 mcg dose. She had a total blood loss of 955 cc. She had no post-partum complications at her six week post-partum visit.

Discussion

We used the terms "*euglycemic ketoacidosis*", "*pregnancy*" and "*COVID-19*" for our PubMed literature review. As of January 2022, EKA in pregnancy complicated by COVID-19 infection was identified in 13 cases including ours (Table 1). The majority of cases presented with gastrointestinal symptoms and decreased oral intake. Eight cases had no history of diabetes, but were all managed with standard treatment for DKA including intravenous fluid resuscitation, intravenous insulin infusion and electrolyte replacement. The majority had resolution of EKA except one case with recurrent ketoacidosis. Maternal and neonatal outcomes were overall reassuring, however varied depending on severity of other clinical aspects of COVID infection [i.e. worsening respiratory status] (Table 2).

Pregnancy is a diabetogenic state with increased insulin resistance, enhanced lipolysis, elevated free fatty acids and increased ketogenesis. Blood glucose levels tend to be lower in ketoacidosis in pregnancy than in the non-pregnant state due to the increased glucose uptake by the fetoplacental unit and a reduction in glycogenolysis and hepatic gluconeogenesis. Hence, increased stress secondary to intercurrent illness or prolonged starvation may predispose the pregnant woman to severe metabolic acidosis with a normal blood glucose [11-13]. Our case and literature review suggest an association between COVID-19 infection in pregnancy (especially with gastrointestinal symptoms) and the propensity to develop EKA, regardless of diabetes history. Pikovsky et al. suggest a possible mechanism is the direct pancreatic islet cell injury and downregulation of angiotensin converting enzyme 2 expression resulting in glycemic dysregulation [1].

Most pregnant women with COVID-19 are asymptomatic or have mild symptoms. However, in addition to management of respiratory illness with supplemental oxygen, steroids and antivirals, we must have a high index of suspicion for EKA, especially in those with gastrointestinal symptoms and decreased oral intake. Unrecognized metabolic acidosis can worsen respiratory status and this may be misinterpreted as a primary respiratory insult rather a contributory effect requiring a completely different treatment. Timely management is key to reducing the risk of adverse maternal and fetal outcomes.

Learning Points

- Euglycemic ketoacidosis (EKA) requires a high index of suspicion and may be missed as euglycemia masks the diagnosis.
- Pregnant individuals with COVID-19, especially those with gastrointestinal symptoms and decreased PO intake, may be susceptible to the development of EKA, regardless of their diabetes history.
- EKA requires prompt and early intervention with aggressive treatment utilizing intravenous fluids, insulin, and electrolyte repletion to reduce adverse fetal and maternal outcomes.

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