A case series of euglycemic starvation ketoacidosis in pregnant women with COVID-19 infection: atypical presentations

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ABSTRACT

Background: We present a case series of euglycemic starvation ketoacidosis in pregnant women with coronavirus disease 2019 (COVID-19) infection. Our patients presented with fever and typical respiratory symptoms secondary to COVID-19 infection in the third trimester. It was complicated by severe metabolic ketoacidosis, likely contributed by the hypermetabolic state of pregnancy, maternal starvation, and increased metabolic demand due to COVID-19 infection.

Case Presentation: Among most of the cases, there was a swift resolution of ketoacidosis, through timely fluid resuscitation, dextrose, and insulin. But despite those measures, most of the patients had to undergo emergency cesarean section due to maternal deterioration, preterm delivery, and fetal distress. All the mothers recovered well and were discharged home, but there was one case of neonatal death after preterm delivery.

Conclusion: These cases illustrate the importance of early diagnosis of euglycemic ketoacidosis, prompt management, and close monitoring to obviate adverse materno-fetal outcomes in pregnant women with COVID-19 infection.

Keywords: Euglycemic ketoacidosis, starvation ketoacidosis, pregnant, COVID-19, metabolic acidosis, high anion gap, case report.

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Background

Since the first case of coronavirus disease 2019 (COVID-19) was detected in Wuhan, China in December 2019, knowledge of its pathophysiology, a wide spectrum of presentation, and clinical course has surfaced rapidly. Initial presumptions based on past experiences in managing influenza and other SARS-CoV-2 diseases became evidence-based medicine, as the world transitioned from a COVID-19 pandemic to an endemic phase.

Pregnant women with COVID-19 are at an increased risk of severe disease, requiring intensive care unit (ICU) admission and ventilation compared to non-pregnant women [1] Obesity, increased maternal age, pre-eclampsia, pre-gestational diabetes, and hypertension were risk factors for severe illness and adverse perinatal outcomes [2] To date, there have only been several case reports of ketoacidosis in pregnant women with COVID-19 [3–5]. We describe the clinical course and management of four cases of pregnant women with COVID-19 infection, who had presented with severe euglycemic ketoacidosis (Table 1).

Case Presentation

Case 1

A 40-year-old woman, gravida 4 para 3, presented at 30 weeks gestation with premature uterine contractions, preceded by a 5-days history of fever, cough, runny nose, and sore throat. She had type 2 diabetes mellitus on basal bolus insulin and metformin.

On examination, she was febrile, tachycardic, tachypneic, and mildly dehydrated. Oxygen saturation was 99% on room air. She had 2:10 minutes of uterine contractions, with fetal well-being confirmed by trans-abdominal ultrasound and cardiotocography (CTG). Examination of the cardiovascular and respiratory systems was otherwise unremarkable. Capillary glucose and ketones were 9.4 and 6.3 mmol/l, respectively (Table 2).

COVID-19 polymerase chain reaction was positive. Inflammatory markers, including C-reactive protein (CRP), lactate dehydrogenase (LDH), and D-dimer were elevated. Arterial blood gas (ABG) analysis revealed high

Table 1. *Baseline demographics.*

CASE	1	2	3	4
Age (years)	40	34	34	34
Ethnicity	Malay	Malay	Malay	Malay
Parity	G4P3	G4P3	G5P4	G2P1
Period of gestation (POG) (weeks)	30	35	36	36
Co-morbidity	Type 2 diabetes mellitus $HbA1_C$ 8.5%	Gestational diabetes, Hepatitis B	Gestational diabetes	Nil
Medications	SC Actrapid 10/16/18 U TDS SC Insulatard 18 U ON Metformin 1 g BD	Nil	Metformin 1 g BD	Nil
BMI (kg/m^2)	30	30	32	25
Vaccination status	First dose: Cominarty	Nil	Nil	Nil

POG, period of gestation; BMI, body mass index.

anion gap metabolic acidosis with respiratory compensation (pH 7.33, pCO_2 20.25, HCO_3 10.5, base excess –13.3 mmol/l, anion gap 17.2 mEq/l). Serum lactate, renal and liver functions were normal (Table 2). Blood and urine cultures were negative. A diagnosis of euglycemic starvation ketoacidosis, precipitated by COVID-19 infection was made.

Fluid resuscitation with intravenous 10% dextrose infusion at 1cc/kg/hour (80cc/hour) was commenced, followed by low-dose continuous intravenous insulin infusion with potassium replacement. ABGs 4 hours later, showed improvement of metabolic acidosis (pH 7.43, pCO_2 31, HCO_3 20.6, base excess –3.2 mmol/l) with serum ketone of 1.9 mmol/l. Tocolytics and intramuscular dexamethasone for fetal lung maturation were also administered.

Unfortunately, she prematurely delivered, vaginally at 30 weeks and 5 days, resulting in neonatal death. It was followed by rapid clinical deterioration of the patient, requiring intubation and mechanical ventilation. Computed tomography pulmonary angiography (CTPA) showed moderate COVID-19 lung involvement of 50%–75%. She responded to intravenous Tocilizumab and was discharged well on day 19 of the admission.

Case 2

A 34-year-old woman, gravida 4 para 3, in the 35th week of gestation, was referred to us, following a positive SARS-CoV-2 test done for the evaluation of fever, cough, runny nose, and reduced oral intake going on for 5 days prior to her presentation. The patient had chronic hepatitis B and gestational diabetes on diet control. She became tachypneic and tachycardic on day 2 of admission. Oxygen saturation was 96% on room air. Capillary glucose and ketones were 4.9 and 5.8 mmol/l, respectively (Table 2). Fetal heart rate was 180 bpm with good fetal movements.

She had high CRP and LDH. ABG showed severe, high anion gap metabolic acidosis (pH 7.25, pCO_2 17, HCO_3 7.5, base excess –17.4 mmol/l, anion gap 19.6 mEq/l). Serum lactate, renal and liver function were normal (Table 2). A diagnosis of euglycemic starvation ketoacidosis was made.

Intravenous infusion of 10% dextrose at 1cc/kg/hour (80cc/hour), was commenced, followed by low-dose continuous intravenous insulin infusion, with potassium replacement. ABGs 12 hours later, showed improvement of metabolic acidosis (pH 7.38, pCO_2 24 kPa, HCO_3 14.2 mmol/l, base excess –9.2 mmol/l) with serum ketone of 0.7 mmol/l.

CTPA showed 26%–50% lung parenchyma involvement with segmental pulmonary embolism. Low molecular weight heparin (LMWH) and dexamethasone were initiated. The patient required a high flow nasal cannula with FiO_2 40% in the ICU. Emergency cesarean section was performed on day 16 of admission due to the cord prolapse and a 2.86 kg baby boy was delivered with a good Apgar score. They were well on discharge, 6 days after the delivery.

Case 3

A 34-year-old woman, gravida 5 para 4, presented at 36-week gestation, with a 2-week history of poor oral intake and 7-day history of fever, cough, and sore throat, and was confirmed positive for COVID-19 infection. She had gestational diabetes and was on metformin. She was tachycardic and tachypneic on day 2 of admission. Oxygen saturation was 98% on room air. Capillary glucose and ketone were 4.3 and 4.6 mmol/l, respectively. ABGs revealed high anion gap metabolic acidosis (pH 7.29, pCO_2 21 mmHg, HCO_3 9.1 mmol/l, base excess –15.5 mmol/l, anion gap 21.6 mEq/l). There was lymphopenia, high CRP, and LDH. Serum lactate and chest X-ray were normal (Table 2).

A diagnosis of euglycemic starvation ketoacidosis was made. She was managed with intravenous 10% dextrose at 1cc/kg/hour (80cc/hour), low dose continuous

Table 2. *Clinical parameters, biochemical and radiological investigations.*

CASE	1	2	3	4
COVID-19 Category	Severe	Severe	Severe	Moderate
Highest oxygen therapy	SIMV FiO_2 0.4	HFNC FiO_2 0.4	SIMV FiO_2 0.5	NPO_2 3 l/minute
Intubation	Yes	No	Yes	No
Days of intubation	2	Nil	1	Nil
Days of ICU stay	9	5	2	Nil
Duration of hospital stay (days)	19	24	9	12
Respiratory rate (breath/minute)	30	30	28	22
Oxygen saturation in room air (%)	96%	96%	96%	96%
Heart rate (bpm)	118	110	104	90
Blood pressure (mmHg)	103/44	110/77	122/78	110/74
Temperature (C)	38.7	37	36.5	37
pH (7.35–7.45 kPA)	7.33	7.25	7.29	7.26
pCO_2 (35–45 mmHg)	20.25	17	21	20
pO_2 (80–100 mmHg)	89.25	105	89	105
Base excess (mmol/l)	–13.3	–17.4	–15.5	–16
Bicarbonate (22–26 mmol/l)	10.5	7.5	9.1	9.0
Capillary ketones (<0.6 mmol/l)	6.3	5.8	4.6	3.1
Urine ketones (negative)	6+	4+	4+	4+
Capillary glucose (4.0–7.8 mmol/l)	9.4	4.9	4.3	7.6
Hemoglobin (12–17 g/dl)	11.5	12.5	13.9	12.3
Hematocrit (36%–50%)	35.4	42	42.6	36
Platelets (150–410 10^3/ul)	285	198	132	246
White cell count (4.0–10.0 10^3/ul)	12.2	9.87	9.3	6.36
Lymphocytes (1.0–3.0 10^3/ul)	2.43	1.11	0.94	Not available
Sodium (135–150 mmol/l)	134	133	135	136
Potassium (3.5–5.0 mmol/l)	3.7	3.1	3.7	3.9
Chloride (96–108 mmol/l)	110	109	108	106
Urea (1.7–8.3 mmol/l)	5.2	2.2	1.7	1.3
Creatinine (44–88 µmol/l)	69	50	45	36
Anion gap (12–16 mEq/l)	17.2	19.6	21.6	24.9
CRP (0.0–0.5 mg/dl)	13.4	3.37	8.45	8.9
Lactate (0.3–2.0 mmol/l)	1.8	0.61	1.2	0.7
Ferritin (24–336 ug/l)	231.3	72.4	74.1	77.3
LDH (140–271 U/l)	272	287	256	276
D-Dimer (≤0.5 ug/ml)	0.95	ND	2.11	1.95
Procalcitonin (≤0.5 ng/ml)	0.2	0.35	Not done	Not done
Chest X-ray	Increased peripheral pulmonary markings	Not done	Clear	Not done
CTPA (% lung involvement)	Organizing pneumonia (50%–75%)	Bilateral upper lobe segmental pulmonary embolism, organizing pneumonia (26%–50%)	Nil	Organizing pneumonia (25%–50%)

ICU, intensive care unit; LDH, lactate dehydrogenase; CTPA, computed tomography pulmonary angiography.

insulin infusion, with potassium replacement, prophylactic LMWH, and intramuscular dexamethasone for fetal lung maturation. She underwent emergency caesarean section under general anesthesia on day 3 of admission due to fetal distress, as evidenced by abnormal CTG and reduced fetal movements. A baby girl, weighing 2.9 kg was delivered with a poor Apgar score requiring intubation, ventilation, and neonatal ICU admission. Maternal metabolic acidosis resolved over 12 hours (pH 7.37, pCO_2 23 mmHg, HCO_3 13.3 mmol/l, base excess –10 mmol/l) with serum ketones 0.3 mmol/l. The mother was extubated the day after and discharged on day 9 of admission, with prophylactic LMWH after completing antibiotic and steroid therapy.

Case 4

A 34-year-old woman, gravida 2 para 1, presented at 36-week gestation, with 4-days history of cough and runny nose and 2 days of poor oral intake. COVID-19 real-time kinetic antigen swab test was positive. She had no known medical illness previously. Capillary glucose and ketones were 7.6 and 3.1 mmol/l, respectively. ABGs revealed high anion gap metabolic acidosis (pH 7.26, pCO_2 20 mmHg, HCO_3 9.0 mmol/l, base excess –16.0 mmol/l) with normal lactate (Table 2). She was diagnosed with starvation ketoacidosis.

Intravenous dextrose 10% at 1cc/kg/hour (80cc/hour) was administered, along with low dose continuous intravenous insulin infusion, potassium replacement, prophylactic LMWH, and intramuscular dexamethasone for fetal lung maturation. Metabolic acidosis resolved over 12 hours (pH 7.44, pCO_2 33 mmHg, HCO_3 23.3 mmol/l) with serum ketones of 0.6 mmol/l.

CTPA revealed 26%–50% lung parenchyma involvement. She was commenced on intravenous hydrocortisone 80 mg 12 hourly for organizing pneumonia. This was complicated by glucocorticoid-induced hyperglycemia which required regular insulin which resolved upon cessation of the steroid. The patient got improved and was discharged home on day 12. She had a successful vaginal delivery at term 1 week following the discharge.

Discussion

Starvation ketoacidosis in the non-pregnant is rare. Pregnant women are prone to severe metabolic acidosis due to an exaggerated response to circulating glucose, insulin, and ketone acids. This entity was first described by Felig and Lynch [6]. It occurs during starvation, usually by the second trimester onward. Its occurrence after 14 days of starvation in non-pregnant women, can be seen as early as 4–12 hours in pregnant women. In the absence of glucose substrate for cellular energy, enhanced lipolysis results in increased free fatty acids and b-hydroxybutyrate levels. This coupled with the production of insulin-antagonistic placental hormones, like placental lactogen, prolactin, and cortisol accelerates the ketonemic state, even with minor dietary deprivation [7].

All of our four patients presented in the third trimester and had a short preceding history of poor oral intake. Their diagnoses were made within 24–72 hours of admission They appeared relatively well clinically on presentation, despite the severity of acidosis. Three patients had pre-existing diabetes while one had glucocorticoid-induced hyperglycemia, noted during admission which may signify their underlying predisposition to ketoacidosis, on top of starvation in the third trimester of pregnancy and COVID-19 infection.

The destructive effect of SARS-CoV-2 *per se* on pancreatic beta cells along with high concentrations of pro-inflammatory cytokines like IL-6, IL-1B, and tumor necrosis factor, reduces insulin secretion and action as well as augmenting ketoacidosis [8,9]. This occurs even without a prior diagnosis of diabetes mellitus [4]. This is confounded by pregnancy's limited ability to compensate for acidosis due to relative hypocapnia. Increased minute alveolar ventilation by progesterone-induced central respiratory stimulation and lung volume changes, results in relative respiratory alkalosis with increased renal excretion of bicarbonate, especially during the third trimester [10]. The buffering capacity of bicarbonate is, therefore, reduced in the cytokine storm, causing desaturation to occur rapidly as seen in our cases with two of them requiring intubation.

Besides the occurrence of starvation ketoacidosis in non-diabetic pregnant women, one should also consider euglycemic ketoacidosis in patients with well-controlled diabetes complicating pregnancy or in gestational diabetes mellitus exhibiting normal or slightly elevated serum glucose levels, in the setting of COVID-19 infection. The manifestation of starvation ketoacidosis in both diabetic and non-diabetic patients is similar; hence, it is prudent that dextrose 10% solution and not solely saline be administered to correct the acidosis [11]. We used concomitant low-dose continuous intravenous insulin infusion for all cases, to expedite the resolution of ketosis and maintain a glucose level of 4–8 mmol/l [12,13]. All four cases experienced rapid resolution of ketoacidosis within twelve hours of dextrose and insulin infusion.

All our cases experienced clinical progression of COVID-19 infection from mild to severe category but recovered. Pregnancy is a known risk factor for severe COVID-19 illness especially in association with pre-existing comorbidities and obesity as in Case 1–3. Despite prompt recognition of starvation ketoacidosis followed by fluid resuscitation, delivery was imminent in Case 1–3 with one neonatal death and one neonatal ICU admission. Severe maternal acidosis is known to cause higher oxygen affinity to maternal hemoglobin reducing uterine blood flow and oxygen delivery resulting in poor Apgar score at birth along with increased materno-fetal morbidity and mortality [5,14].

Conclusion

The atypical presentation of euglycemic starvation ketoacidosis in pregnant women with COVID-19 infection is not well recognized. Point-of-care testing for blood ketones is prudent in the presence of reduced oral intake, even in relatively well-appearing patients. A high index of suspicion for euglycemic starvation ketoacidosis is required for a pregnant woman with or without pre-existing diabetes, to allow early diagnosis and prompt treatment to reduce the risk of adverse materno-fetal outcomes.

What is new?

Pregnant women with COVID-19 are at an increased risk of severe disease. To date, there have only been several case reports of ketoacidosis in pregnant women with COVID-19. The authors describe four cases of pregnant women with COVID-19 infection presented with severe euglycemic ketoacidosis, its management and clinical course.

List of Abbreviations

ABG	Arterial blood gas
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
CTG	Cardiotocography
CTPA	Computed tomography pulmonary angiography
ICU	Intensive care unit
LDH	Lactate dehydrogenase
LMWH	Low molecular weight heparin

Conflict of interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

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Consent for publication

Consent obtained directly from patients.

Ethical approval

Ethical approval for this case series was obtained from the Medical Research and Ethics Committee.

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Summary of the case

1	**Patient (gender, age)**	Female, age 34–40 years old
2	**Final diagnosis**	Euglycaemic starvation ketoacidosis in pregnant women with COVID-19 infection
3	**Symptoms**	Shortness of breath
4	**Treatment**	Intravenous dextrose infusion, intravenous insulin infusion
5	**Specialty**	Internal Medicine, Endocrinology
6	**Objective**	Learning from new disease: atypical presentation of COVID-19 infection in pregnant women