Severe metabolic ketoacidosis as a primary manifestation of SARS-CoV-2 infection in non-diabetic pregnancy

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SUMMARY
We present a case of a metabolic acidosis in a term-pregnant woman with SARS-CoV-2 infection. Our patient presented with dyspnoea, tachypnoea, thoracic pain and a 2-day history of vomiting, initially attributed to COVID-19 pneumonia. Differential diagnosis was expanded when arterial blood gas showed a high anion gap metabolic non-lactate acidosis without hypoxaemia. Most likely, the hypermetabolic state of pregnancy, in combination with maternal starvation and increased metabolic demand due to infection, had resulted in metabolic ketoacidosis. Despite supportive treatment and rapid induction of labour, maternal deterioration and fetal distress during labour necessitated an emergency caesarean section. The patient delivered a healthy neonate. Postpartum, after initial improvement in metabolic acidosis, viral and bacterial pneumonia with subsequent significant respiratory compromise were successfully managed with oxygen supplementation and corticosteroids. This case illustrates how the metabolic demands of pregnancy can result in an uncommon presentation of COVID-19.

BACKGROUND
The coronavirus (SARS-CoV-2) pandemic and the associated illness COVID-19 have presented a challenge to clinicians, partially due to the initial unfamiliarity with the natural course of COVID-19 and the lack of knowledge on optimal treatment strategies.1 Knowledge on SARS-CoV-2 has rapidly accumulated, most of which has focused on the unique effects of the virus on the respiratory tract. Clinical manifestation is now known to vary from asymptomatic to respiratory failure and death.2–5 Despite a rapid increase in scientific publications on COVID-19, there are still knowledge gaps regarding the course of COVID-19 in subgroups of patients. In this case report, we discuss an atypical course of COVID-19 in a woman with a term pregnancy where the primary manifestation was a severe metabolic acidosis.

CASE PRESENTATION
On 21 October 2020, a 21-year-old primigravida woman with a gestational age of 37+6 weeks was admitted to a hospital in the Netherlands with a fever of 38.0°C, complaining of headache, fatigue, nausea and vomiting. Her medical history reported childhood asthma and an iron deficiency anaemia.

She had an otherwise uncomplicated pregnancy. Gestational diabetes was routinely ruled out.

At primary presentation, the patient’s temperature of 38.0°C qualified her for routine SARS-CoV-2 PCR testing. Urinary tract infection was ruled out and fetal well-being was confirmed. Her blood pressure was 110/65 mm Hg, and she had a heart rate of 100 beats per minute. Her respiratory rate was unremarkable; she was therefore considered at low risk of sepsis and offered outpatient follow-up. The next day, the SARS-CoV-2 PCR test came back positive.

Two days later, our patient was readmitted with increasing headache, nausea, vomiting, fever, shortness of breath and thoracic pain worsening on inspiration. She was unable to tolerate any food for the past 2 days due to nausea and vomiting. Vital parameters were a blood pressure of 117/76 mm Hg, heart rate of 136 beats per minute, temperature of 38.1°C, oxygen saturation of 100% and a respiratory rate of 40 breaths per minute.

Prompted by this maternal deterioration, the patient agreed to insertion of a cervical Foley catheter, aimed at enabling induction of labour at the earliest opportunity. A broad differential diagnosis was compiled, including pulmonary (severe COVID-19, pneumonia, pulmonary embolism), cardiac (ischaemia, cardiomyopathy), gastroenterological (infection) and obstetric problems (pre-eclampsia).

INVESTIGATIONS
Pre-eclampsia was ruled out based on the absence of hypertension, haemolysis, elevated liver enzymes, low platelet count and proteinuria. An ECG did not show signs of ischaemia or arrhythmia. D-dimer was elevated (2.39 mg/L; cut-off, 0.5 mg/L), and CT angiography (CTA) was performed to rule out a pulmonary embolism. The CTA showed no signs of pulmonary embolism or pneumonia. The COVID-19 reporting and data system (CO-RADS) score and CT Severity score were both 6.6 The CO-RADS score indicates the level of suspicion for COVID-19, graded from low (1) to high (5). CO-RADS 6 refers to evidence of any pulmonary findings on CT consistent with COVID-19, in a patient with a positive SARS-CoV-2 test.6 A CT Severity score of 6 (maximum score of 25) refers to a limited proportion of the lungs being affected by COVID-19.7
Infection parameters were partially increased (C-reactive protein, 34.1 mg/L (normal, 0–5 mg/L); leucocyte count, 8.0×10⁹/L (normal value, 4.0–10.5×10⁹/L)). A white blood cell differential and procalcitonin measurement were not performed. Urine and blood cultures were negative. A sputum culture was not collected because our patient did not have a cough.

Arterial blood gas analysis revealed a high anion gap metabolic acidosis with respiratory compensation (table 1). Lactate levels, kidney function and liver function were normal (table 1).

Urinary analysis was positive for ketone bodies. Subsequently, the patient repeatedly declined further blood sampling.

The cardiotocogram trace and ultrasound did not show signs of fetal distress. Progression of the vital parameters over time and laboratory results at admission, and the blood gas are shown in figures 1 and 2, and Table 2, respectively.

**DIFFERENTIAL DIAGNOSIS**

A high anion gap metabolic acidosis can be due to the production of acids such as lactate or ketone bodies, renal failure (reduced buffer capacity) or the presence of toxins. In our patient, the lactate level and kidney function were normal. A high anion gap metabolic acidosis can also be caused by an intoxication. However, our patient denied a history of drug or alcohol abuse, and laboratory analysis showed a normal osmole gap, ruling out a metabolic acidosis caused by toxic alcohols. Paracetamol intoxication is known to be a potential cause of metabolic acidosis by 5-oxoproline excretion. However, this appeared unlikely because she had a mere 3 days of paracetamol use in a normal therapeutic dosage (1000 mg, three times a day); moreover, blood and urine samples were negative for 5-oxoproline excretion.

Finally, high levels of ketone bodies in urinary analysis indicated ketoacidosis, judged to be non-diabetic based on her medical history, which was negative for (gestational) diabetes and the fact that blood glucose levels were normal (table 1).

Ketoacidosis can be seen in non-diabetic patients during acute starvation. Pregnancy is a hypermetabolic state, to which ongoing infection is likely to have added further metabolic demand, making our patient more prone to starvation ketoacidosis. Second, there have been reports indicating an association between COVID-19 and an increased risk of (non-diabetic) ketoacidosis.

**TREATMENT**

Supportive management was started to correct the metabolic acidosis. Our aim was to prevent further formation of ketone bodies by administering carbohydrates (glucose 10%) alongside potassium and bicarbonate supplementation. To prevent deep vein thrombosis, our patient received nadroparine in a prophylactic dose (2850 IU). Paracetamol was discontinued to prevent further potential 5-oxoproline accumulation. Treatment effects were monitored with blood gas analysis.

**OUTCOME AND FOLLOW-UP**

The following 48 hours her respiratory rate was between 17 and 33 breaths per minute, oxygen saturation was 95%–100% and
heart rate was 95–118 beats per minute. Blood gas analysis supported our assessment of clinical improvement (figure 3 and table 2).

After 48 hours, the Foley catheter was expelled, and labour started with spontaneous contractions. Epidural analgesia was offered to prevent further maternal exhaustion.

During epidural catheter insertion, the patient’s condition deteriorated suddenly and rapidly. While her blood pressure remained 127/76 mm Hg, her heart rate rose to 160 beats per minute and her temperature to 39.6°C, accompanied by an increased respiratory rate of 44 breaths per minute, with a 100% oxygen saturation. Further metabolic decompensation despite supportive measures and secondary imminent respiratory decompensation was suspected. Moreover, fetal distress was suspected based on an abnormal cardiotocography (CTG) trace showing a tachycardia (180–200 beats per minute). The decision was made to perform an emergency caesarean section.

An uncomplicated caesarean section was performed, under neuraxial anaesthesia. During surgery, maternal condition was stabilised, and after birth vital parameters (figures 1 and 2) and the blood gas (figure 3) improved.

A girl was born at a gestational age of 38+3 weeks with a birth weight of 2930 g (25th birth weight centile) and an Apgar score of 7 and 8 after 1 and 5 min. Umbilical cord blood gas analysis showed an arterial pH of 7.09 with a base excess of −17 and venous pH of 7.29 with a base excess of −12.

After the caesarean section, the patient felt less sick, less dyspnoeic and had stopped vomiting.

However, 1 day after childbirth, her condition worsened again based on increasing dyspnoea and respiratory rate (23 breaths per minute), oxygen saturation (95% with 4 L O2), tachycardia (130 beats per minute) and fever (39.0°C). Oxygen administration was started because of hypoxaemia. Physical examinations, bilateral decreased breathing sounds and crackles were heard. Cold extremities on examination were interpreted as a sign of poor peripheral circulation.

A CTA showed a consolidation in the left lung suspect for a bacterial pneumonia and no signs of pulmonary embolism. The CT Severity score was 9. The COVID-19 was defined as moderate to severe based on a bacterial pneumonia and hypoxaemia. Urine, blood and vaginal cultures were negative.

Corticosteroids, antiviral drugs (remdesivir) and antibiotics (moxifloxacin) were started. In the 4 following days, her clinical condition improved. Oxygen supplementation was discontinued after 3 days. Treatment with remdesivir and corticosteroids was continued for 3 days, and antibiotic treatment with moxifloxacin was continued for 10 days.

**DISCUSSION**

In this report, we present a term-pregnant woman with a non-diabetic ketoacidosis provoked by acute starvation as a result of

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**Table 2** Blood gas analysis

| Date             | Time     | Arterial | Ventilaion | Arterial | Ventilaion | Arterial | Ventilaion | Arterial | Ventilaion | Arterial | Ventilaion | Arterial | Ventilaion | Arterial | Ventilaion | Arterial | Ventilaion | Arterial | Ventilaion |
|------------------|----------|----------|------------|----------|------------|----------|------------|----------|------------|----------|------------|----------|------------|----------|------------|----------|------------|----------|------------|----------|------------|
| 23-10-2020, 18:53| 22-10-2020, 19:29 | 22-10-2020, 20:27 | 22-10-2020, 21:35 | 22-10-2020, 22:43 | 23-10-2020, 00:51 | 23-10-2020, 02:09 | 23-10-2020, 04:17 | 23-10-2020, 06:25 | 23-10-2020, 08:33 | 23-10-2020, 10:41 | 23-10-2020, 12:50 | 23-10-2020, 14:58 | 23-10-2020, 17:06 | 23-10-2020, 19:14 | 23-10-2020, 21:22 | 24-10-2020, 00:30 | 24-10-2020, 02:38 | 24-10-2020, 04:46 | 24-10-2020, 06:54 |

- **Temperature**: 37°C
- **pH**: 7.34 to 7.39
- **PCO2**: 2.2 to 2.9 mm Hg
- **Bicarbonate**: 8.7 to 9.9 mEq/L
- **Base excess**: −14.6 to −16.6 mEq/L
- **PO2**: 20.6 to 24.8 mm Hg
- **O2 saturation**: 98.6 to 99.4%

PCO2, partial pressure of carbon dioxide; PO2, partial pressure of oxygen.

**Figure 3** Blood gas analysis over time. Adm, day of admission.
gastrointestinal complaints due to COVID-19. This is another demonstration of the ability of SARS-CoV-2 to cause illness outside the respiratory tract. Furthermore, this illustrates the increased metabolic demand in pregnancy.

Our patient presented with dyspnoea, tachypnoea, thoracic pain and vomiting since 2 days. Initially, the complaints were solely attributed to respiratory effects of COVID-19. Differential diagnosis was expanded when the blood gas analysis showed a high anion gap metabolic acidosis that was not due lactate or toxic agents. Urinalysis showed ketone bodies without indication for diabetes in her medical history, gestational diabetes this pregnancy and normal blood glucose concentrations at admission. The remaining diagnosis was starvation ketoacidosis, based on absence of oral food intake for 2 days combined with a high metabolic demand in pregnancy.

Starvation ketoacidosis is a metabolic acidosis usually caused by prolonged fasting and has been observed in non-diabetic patients. Pregnant women produce up to 2–4 times higher levels of ketone bodies in 12 hours of fasting compared with non-pregnant individuals. There is an increased risk of ketoacidosis due to the relative state of accelerated starvation as pregnancy is a hypermetabolic state.

Furthermore, ketogenesis is increased in pregnancy as it is a state of relative insulinopenia and increased insulin resistance. Insulin resistance is increased by the production of insulin antagonistic placental hormones including placental lactogen, prolactin and cortisol. In periods of stress, these hormones are increased. This leads to enhanced lipolysis and increased free fatty acids, which in turn increase production of ketone bodies.

Pregnancy also limits the body’s ability to compensate for acidosis, due to the fact that pregnant women have relative hypocapnia because of an increased minute alveolar ventilation, resulting in relative respiratory alkalosis. This is compensated by increased renal excretion of bicarbonate. The buffering capacity of bicarbonate is therefore reduced, an effect that is most prominent in term pregnancy.

Limited data suggest that COVID-19 also augments ketoacidosis. Palermo et al. speculated that COVID-19 leads to insulinopenia. Furthermore, they suggest interleukin 6 plays a role in the development of ketoacidosis in patients with COVID-19 by a maladaptive immune response to SARS-CoV-2. Although the specific role of interleukin 6 is not clear, it may act as a driver of ketosis. Non-lactate metabolic acidosis has been previously described in two non-diabetic patients with COVID-19. Another hypothesis of metabolic acidosis is that COVID-19 increases lipolysis, leading to ketogenesis and subsequent acidosis.

A clinical dilemma we faced was the timing of delivery. Because functional residual lung capacity decreases and oxygen consumption increases in a term pregnancy, desaturation can occur more rapidly. This is one of the reasons that in term-pregnant women with COVID-19 delivery should be promptly effectuated.

However, the biggest initial threat to our patient was not respiratory compromise but rather the metabolic acidosis. Maternal acidosis can cause a fetal acidosis through different pathways. In women with acidosis, uterine blood flow reduces and results in reduced placental oxygenation. Maternal acidosis also increases oxygen affinity of maternal haemoglobin, resulting in a decreased oxygen delivery to the fetus. Increasing maternal ketonaemia may lead to fetal metabolic acidosis because maternal ketoacids dissociate into organic and hydrogen ions, which pass over the placenta. Fetal CTG trace may normalise when maternal acidosis is corrected. Therefore, immediate delivery is not automatically warranted. Initially, pH improved and normalised with supportive treatment, and the CTG showed no signs of fetal acidemia, providing no red flags that could have suggested emergency caesarean delivery should be expedited.

In our case, we made the decision to start cervical priming and pursue a vaginal delivery because clinical deterioration in a few days is often seen in COVID-19. However, spontaneous onset of labour likely exacerbated metabolic demand in our patient, causing an acute metabolic decompensation. A complicating factor was that the patient had declined blood sample collection multiple times, which may have obscured our view on the condition of the patient.

Learning points

- Ketoacidosis (in pregnancy) does not always have to be related to diabetes.
- There is accumulating evidence that a COVID-19 infection may play a role in the development of ketoacidosis.
- Induction of labour can contribute to a metabolic demand in pregnant women with a SARS-CoV-2 infection, leading to a severe metabolic acidosis

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