

# Starvation ketosis in a pregnant woman with COVID-19: a case report

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## Summary

COVID-19 is associated with severe disease in pregnancy. Complications of the disease, or simultaneous diagnoses, may be missed if clinicians do not retain a large differential diagnosis when assessing such women. Starvation ketoacidosis is one such diagnosis which may complicate the disease and should not be missed. A 37-year-old woman, 33 weeks' gestation presented with breathlessness. Clinical history, examination and investigations supported a diagnosis of starvation ketosis of pregnancy complicating COVID-19 pneumonitis. Prompt correction of the metabolic disturbance resulted in resolution, and preterm delivery was avoided at this time. Early recognition and prompt management of starvation ketosis of pregnancy in women with COVID-19 are important in reducing maternal and neonatal morbidity and mortality. Preterm delivery may be avoided with prompt resolution of the metabolic disturbance. Clinicians should keep a wide differential diagnosis when assessing women with breathlessness. A multidisciplinary team (MDT) approach is required to facilitate optimal care.

## Learning points:

- Clinicians should maintain a wide differential when assessing women who are unwell with COVID-19 in pregnancy.
- Complications such as starvation ketoacidosis are rare but life-threatening.
- An awareness of such complications facilitates early identification of the condition, and involvement of appropriate specialists who can initiate optimal and timely management.
- In the context of pregnancy, where ketoacidosis poses a threat to the mother or baby, prompt management and resolution may avoid preterm delivery.
- Conditions that may increase the risk of developing starvation ketoacidosis include pregnancy, medication use such as corticosteroids or tocolytic therapies, previous gastric surgery, intercurrent illness and pregnancy-related conditions that might contribute towards a degree of chronic starvation.
- Multidisciplinary input supports the delivery of best practice and care for the patients.

## Background

In March 2020, the World Health Organisation declared a global pandemic of COVID-19 caused by severe acute respiratory syndrome coronavirus-2. During the third wave of the pandemic, the delta variant became predominant, during which time the case volume and proportion of severely or critically ill pregnant women infected with the virus increased exponentially. By October 2021, almost one-third (32%) of women aged 16–49 years old

requiring extracorporeal membrane oxygenation (ECMO) were pregnant, compared to 6% at the beginning of the pandemic (1).

The 'Mothers and babies: Reducing Risk through Audits and Confidential Enquiries across the UK' published rapid reports throughout the pandemic which informed practice by highlighting areas of care that could be improved to ensure the best possible outcomes for women with COVID-



19 in pregnancy. One report focused on ‘fixation errors’ in which clinicians may encounter a woman with confirmed COVID-19 and not consider all differential diagnoses of her symptoms, attributing them in full to COVID-19 infection (2). This may risk complications of the disease or simultaneous diagnoses being undiagnosed, resulting in suboptimal outcomes.

Starvation ketoacidosis of pregnancy is one such diagnosis which may complicate COVID-19 infection in the pregnant population, and should be considered as a differential diagnosis of breathlessness. We report the case of a woman with severe COVID-19 pneumonitis complicated by starvation ketoacidosis of pregnancy, and discuss the importance of early recognition and management of this complication to reduce maternal and fetal morbidity and mortality.

## Case presentation

A 37-year-old pregnant woman (G3P2) presented to the emergency department at 33 weeks’ gestation with breathlessness. She had tested positive for COVID-19 nine days earlier following a 3-day history of feeling generally unwell and non-productive cough. She had subsequently taken to her bed with little oral or fluid intake over the preceding days. Three days prior to hospital admission she had noticed an increase in her work of breathing, such that she was no longer able to mobilise short distances. She denied chest pain, calf tenderness, orthopnoea or paroxysmal nocturnal dyspnoea.

Her past medical history was notable for well-controlled asthma and gastric sleeve surgery. She took regular inhalers and vitamin B12 injections but no other regular medications. She was a non-smoker, did not drink regular alcohol and took no illicit or over-the-counter medications. She had suffered from hyperemesis

gravidarum (HG) in the first trimester, but her pregnancy had been otherwise uncomplicated.

On arrival at the hospital her respiratory rate (RR) was 32 breaths/min, oxygen saturations 95% on 4 L/min inspired oxygen, heart rate (HR) 105 beats/minute, blood pressure (BP) was 100/60 mmHg and she was afebrile. Clinical examination revealed that she was breathless at rest, exhibiting Kussmaul breathing (with ketotic breath), unable to complete full sentences and auscultation of the lung fields revealed bi-basal crepitations but no wheeze. She was clinically dehydrated. Neurological, cardiovascular and abdominal examinations were normal.

## Investigation

Routine blood tests and arterial blood test results are outlined in Table 1, with pregnancy reference ranges in brackets. Of note, the patient had a normal oral glucose tolerance test and glycated haemoglobin A1c during the pregnancy (prior to admission). She went on to have an ECG revealing a sinus tachycardia. Chest X-ray and CT pulmonary angiography confirmed COVID-19 pneumonitis but no pulmonary emboli.

## Treatment

On confirmation of a metabolic acidosis blood glucose levels and lactate levels were checked. These were normal, making a diagnosis of either diabetic ketoacidosis, lactic acidosis or sepsis less likely. The patient denied ingestion of toxins, drug or alcohol abuse, and renal function was normal, ruling out other causes of metabolic acidosis. Considering the elevated ketones and high anion gap, a diagnosis of severe COVID-19 infection complicated by starvation ketosis of pregnancy was made. It was considered that her history of gastric bypass surgery and HG may have

**Table 1** Routine bloods tests, arterial blood gas results and investigations.

Full blood count, CRP and other	Urea and electrolytes and liver function tests	Arterial blood gas
WCC $8.4 \times 10^9/L$ (6–16)	Cr $57 \mu\text{mol/L}$ (55–77)	pH 7.26 (7.34 to 7.45)
Hb 104 g/L (105–140)	Ur 1.9 mmol/L (2.4–3.8)	HCO <sub>3</sub> <sup>-</sup> 6.0 mmol/L (22 to 28)
MCV 79 fL (80–100)	Na 139 mEq/L (130–140)	PCO <sub>2</sub> 1.8 kPa (4.7 to 6.6)
Lym $0.5 \times 10^9/L$ (1.5–4.5)	K 4.1 mmol/L (3.3–4.1)	O <sub>2</sub> sats 93%
CRP 149 mg/L (<3)	Bili 8 $\mu\text{mol/L}$ (3–14)	Na 139 mmol/L (130 to 140)
Blood glucose 4.0 mmol/L (4.0–6.0)	Alb 31 g/L (28–37)	BE -18.7 mmol/L (-2 to +2)
Ketones 7 mmol/L (<0.6–1.5)	ALT 60 U/L (6–32)	Lactate 0.9 mmol/L (<2.3)
Anion gap 29 mEq/L (12–16)	ALP 156 U/L (133–418)	PO <sub>2</sub> 10.4 kPa (10.7 to 13.3)
		Cl <sup>-</sup> 104 mmol/L (96 to 106)

Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; BE, base excess; Bili, bilirubin; Cr, creatinine; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HCO<sub>3</sub><sup>-</sup>, actual bicarbonate concentration; lym, lymphocyte count; MCV, mean corpuscular volume; O<sub>2</sub> sats, oxygen saturations; PO<sub>2</sub>, partial pressure of oxygen; PCO<sub>2</sub>, partial pressure of carbon dioxide; Ur, urea; WCC, white cell count.



led to a state of chronic starvation which was exacerbated by anorexia while acutely unwell.

The patient's management was discussed with the multidisciplinary team (MDT) which included an obstetric physician, obstetric consultant, intensivist, neonatal team and midwives. The MDT considered the timing of delivery given the high fetal mortality associated with severe maternal acidosis. Following discussion, it was agreed that in the first instance treatment for COVID-19 and the metabolic disturbance would be initiated to determine whether the resolution of these parameters might improve the work of breathing and avoid the necessity for early delivery. Treatment for COVID-19 included oxygen to maintain her oxygen saturations >94% and intramuscular dexamethasone for fetal lung maturity due to the risk that early delivery may be required. Following dexamethasone administration, prednisolone and tocilizumab were initiated to treat the maternal COVID-19 pneumonitis. The use of dexamethasone and prednisolone were discussed with the MDT, as corticosteroids can worsen ketoacidosis, and administered as their benefit was considered to outweigh the risks. The metabolic disturbance was treated with intravenous 20% dextrose, 0.9% sodium chloride, 1.6% bicarbonate, variable rate insulin infusion with potassium replacement and Pabrinex® in an intensive care setting. This resulted in the resolution of the metabolic ketoacidosis over a 24-h period (Table 2).

On resolution of the metabolic ketoacidosis, the patient felt symptomatically significantly better and work of breathing was improved. Observations now included a RR of 26 breaths/min, oxygen saturations 96% on 4 L/min inspired oxygen, HR 100 beats/min, BP was 110/64 mmHg and she remained afebrile. The intravenous 20% dextrose, 0.9% sodium chloride, 1.6% bicarbonate, variable rate insulin infusion with potassium replacement and

Pabrinex® were stopped 24 h after resolution. Prednisolone was continued and low molecular weight heparin was added as venous thromboembolism prophylaxis. The patient remained stable over the next 6 days and delivery, at this stage, was avoided.

Six days later the patient's oxygen saturations deteriorated to 88%, and repeat imaging confirmed worsening pneumonitis, a pneumomediastinum and right apical pneumothorax, all recognised complications of COVID-19. A further MDT discussion agreed to a decision to deliver the baby and the patient was then commenced on ECMO in preference to intubation and ventilation to avoid further barotrauma. The baby was admitted to the special care baby unit and subsequently made a good recovery. The mother also made a good recovery being decannulated from ECMO 10 days later and discharged from the hospital a week after decannulation.

## Outcome and follow-up

Both mother and the baby were well at the follow-up 3 months later. The course of events are summarised in Fig. 1.

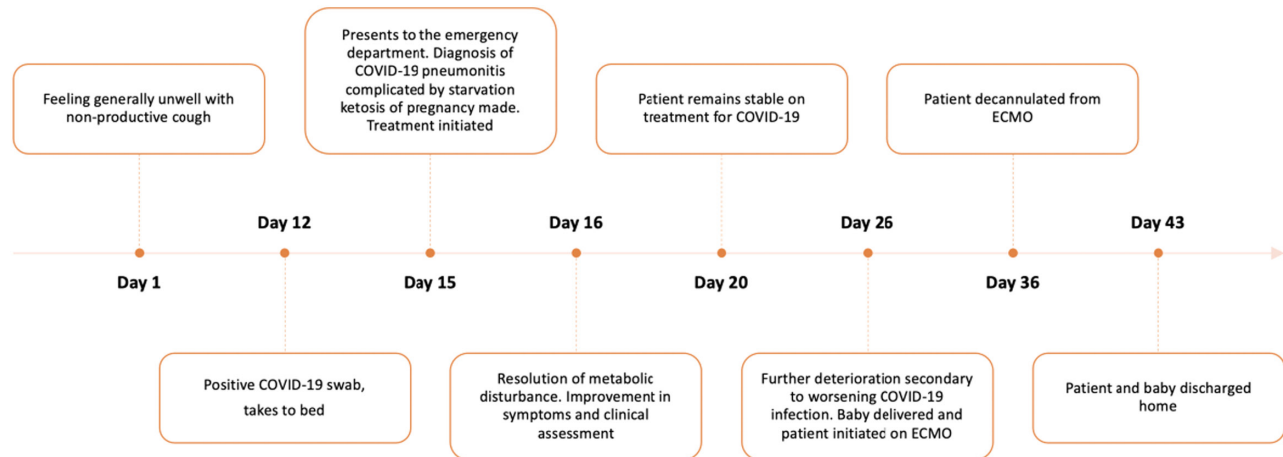
## Discussion

This case exemplifies the importance and benefits of early recognition and prompt management of complications such as starvation ketosis of pregnancy in pregnant patients with COVID-19. In this case correction of the metabolic disturbance allowed preterm delivery to be delayed which has significant implications in terms of short and long-term outcomes for the neonate. Unfortunately, the patient went on to develop further complications secondary to COVID-19 infection which required delivery of the baby and ECMO therapy which could not have been avoided.

**Table 2** Resolution of metabolic ketoacidosis over 24 h.

	Day 1		Day 2				
	22:00 h	00:00 h	03:00 h	05:00 h	08:00 h	12:00 h	22:00 h
pH	7.236	7.26	7.29	7.34	7.35	7.409	7.41
PCO <sub>2</sub> (kPa)	1.37	1.54	1.58	1.77	2.11	2.28	3.1
Act. HCO <sub>3</sub> <sup>-</sup> (mmol/L)	4.3	5.1	5.7	6.9	8.6	10.6	14.6
Stand. HCO <sub>3</sub> <sup>-</sup> (mmol/L)	7.7	8.6	9.3	10.5	12.3	14.4	14.6
BE (mmol/L)	-	-19.8	-18.7	-17.2	-15.0	-12.3	-8.4
Lactate (mmol/L)	1.3	1.2	1.4	1.4	1.5	1.6	1.2
Hb (g/L)	101	98	100	98	97	92	94
Cl <sup>-</sup> (mmol/L)	104	104	102	106	105	104	105
PO <sub>2</sub> (kPa)	9.89	10.87	10.79	10.37	12.52	11.84	11.91
Ketones (mmol/L)	-	5.5	-	2.9	-	0.9	-

Act. HCO<sub>3</sub><sup>-</sup>, actual bicarbonate concentration; BE, base excess; Hb, haemoglobin; PO<sub>2</sub>, partial pressure of oxygen; PCO<sub>2</sub><sup>-</sup>, partial pressure of carbon dioxide; Stand. HCO<sub>3</sub><sup>-</sup>, standard bicarbonate concentration.



**Figure 1**  
Timeline of events.

The mechanism of ketogenesis is described by Frise *et al.* (3). In the healthy state, starvation is reached over a period of time (usually >14 days) and rarely results in significant acidosis. Pregnant women exhibit an exaggerated response to fasting, particularly in the third trimester, as a consequence of relative lack of insulin combined with the presence of placentally derived hormones which increase insulin resistance. This ultimately reduces a woman's glycogen stores, such that during a period of starvation there is less availability of pyruvate which can enter the citric acid cycle. Alternative forms of energy production utilise adipose tissue and free fatty acids are metabolised to acetyl CoA. Once the citric acid cycle is saturated with acetyl CoA, ketones are produced which in accumulation may lead to metabolic acidosis. In the context of COVID-19 infection, counter-regulatory hormones related to stress are also likely to contribute. Additionally, carbohydrate intake is likely to be reduced in the context of vomiting or anorexia, further exacerbating this process.

There are three cases reported in the literature which demonstrate this phenomenon in women with COVID-19 without a history of diabetes mellitus, each of which presented with a short period of anorexia or vomiting in the third trimester of pregnancy and resulted in ketoacidosis (summarised in Table 3 with our case).

It is very likely that the patient described in our case had further risk factors for developing ketosis which has not been previously described in the literature in the context of COVID-19 in pregnancy. These include, firstly, the history of untreated HG in the first trimester which may have resulted in a period of starvation (7). Secondly, the history of gastric bypass surgery meant that the patient ate small meals and had a relatively low-calorie diet in

theory also contributing towards chronic starvation. This would be in keeping with previous literature which reports cases of starvation ketosis following bariatric surgery (8).

The management of starvation ketosis during pregnancy is poorly described. In 2008 a Cochrane review failed to draw any conclusions when investigating the various interventions for ketosis in labour as the six studies in the literature had few outcome measures (9). A case series described by Frise *et al.* in 2013 demonstrated that treatment with intravenous 0.9% saline and/or sodium lactate was insufficient to correct the metabolic disturbance and failure of treatment often leads to the need for early delivery (3). The authors proposed that treatment with intravenous dextrose is required to provide a source of glucose and that this should be given alongside fluids for volume replacement containing salt, thus reducing the risk of maternal and fetal hyponatraemia. In cases such as ours in which there was concern regarding a component of chronic starvation the patient was given Pabrinex® and monitored for evidence of re-feeding syndrome due to the small risk of developing Wernicke's encephalopathy. The role of intravenous bicarbonate remains controversial in the literature where it is described in the context of diabetic ketoacidosis, lactic acidosis and septic shock and has not been demonstrated to improve morbidity and mortality in humans, indicating that the focus should be on correcting the underlying cause of the acidosis (10). In our patient it was felt that as the underlying cause was being addressed, intravenous bicarbonate may improve the metabolic state that the fetus was exposed to in utero. It was given in an intensive care setting where the patient could be closely monitored for side effects such as electrolyte imbalance and QTc interval prolongation.



**Table 3** Summary of the case and previously described cases in the literature.

Demographics (age and gestation in weeks)	Presenting complaint	Reported biochemistry	Treatment of metabolic disturbance	Outcome
21-year-old (4) 37+6	2/7 Fever Headache Fatigue N&V	pH -7.34 PCO <sub>2</sub> -2.2 kPa HCO <sub>3</sub> -8.7 mmol/L BE -14.6 mmol/L PO <sub>2</sub> -20.6 kPa Lactate -2 mmol/L Urine ketones +++	10% dextrose Kcl replacement Bicarbonate supplementation	Further metabolic decompensation despite supportive measures. Respiratory decompensation followed. EmCS performed for fetal distress. Maternal condition improved after birth.
34-year-old (5) 36+3	3/7 SOB Lethargy anorexia	pH -7.25 PCO <sub>2</sub> -2.2 kPa HCO <sub>3</sub> -7.1 mmol/L BE -20.2 mmol/L PO <sub>2</sub> -30.3 kPa Lactate -0.8 mmol/L Ketones -6.8 mmol/L	10% dextrose IV insulin Fluid resuscitation Kcl replacement	Maternal metabolic acidosis resolved over 24 h, CTG failed to meet Dawes-Redman criteria therefore delivery was expedited by CS under RA.
25-year-old (6) 34+0	8/7 SOB N&V	pH 7.17 PCO <sub>2</sub> -2.3 kPa HCO <sub>3</sub> -6.4 mmol/L Ketones -5.6 mmol/L	IV dextrose IV insulin Antiemetics	Resolution of metabolic disturbance over 48 h. Discharged home after 3 days. Delivery not indicated.
37-year-old 33+0	6/7 Anorexia SOB	pH -7.26 PCO <sub>2</sub> -1.8 kPa HCO <sub>3</sub> -6 mmol/L BE -18.7 mmol/L PO <sub>2</sub> -30.3 kPa Lactate -0.9 mmol/L Ketones -7.0 mmol/L	20% dextrose Kcl replacement Bicarbonate supplementation IV insulin	Resolution of metabolic disturbance over 24 h with improvement in maternal condition. Further deterioration of respiratory function 6 days later requiring delivery and initiation on ECMO.

CS, caesarean section; CTG, cardiotocography; ECMO, extracorporeal membrane oxygenation; EmCS, emergency caesarean section; N&V, nausea and vomiting; RA, regional anaesthesia; SOB, shortness of breath.

In addition, we used intravenous insulin with potassium replacement. It should be acknowledged that there is one other report in the literature which used this approach (Table 3). In this case, further metabolic decompensation occurred despite supportive measures and respiratory decompensation was followed by an emergency caesarean section, performed for fetal distress. Maternal condition improved after birth.

This case emphasises the need to maintain a wide differential when assessing women who are unwell with COVID-19 in pregnancy. An awareness of complications such as starvation ketoacidosis will lead to early identification of the condition and appropriate management. In cases where the severity of ketoacidosis is a threat to the mother or baby, or in which attempts at respiratory compensation lead to deterioration of the mother's condition, appropriate correction of the metabolic disturbance may result in early delivery being avoided in certain cases. Clinicians should be aware of conditions that might increase the risk of developing starvation ketoacidosis including pregnancy, medication use such as corticosteroids or tocolytic therapies, previous gastric surgery, intercurrent illness and pregnancy-related conditions that might contribute towards a degree of chronic starvation.

#### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

#### Funding

This work did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

#### Patient consent

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

#### Author contribution statement

Contribution in writing the manuscript and in managing and treating the patient: MN drafted the manuscript which was reviewed by CP. The patient was managed by both MN and CP and members of the obstetric medicine team and wider multidisciplinary team at St Thomas' Hospital.

#### Acknowledgements

The authors acknowledge and thank the healthcare professionals and the wider multidisciplinary team that helped them look after this patient.



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Received in final form 6 March 2022

Accepted 3 May 2022