Critical COVID-19 in a pregnant patient who presented in starvation ketoacidosis with a background history of acrorenal syndrome

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SUMMARY

A primiparous woman in her late 30s at 28+1 weeks' gestation presented with a 3-day history of abdominal pain, loss of appetite, nausea and vomiting and was diagnosed with starvation ketoacidosis. A routine admission swab returned positive for COVID-19. She had been diagnosed with acrorenal syndrome from birth. Three days post admission, she deteriorated rapidly into respiratory failure requiring intubation and ventilation. She was treated with dexamethasone, prophylactic enoxaparin, a course of piperacillin/tazobactam followed by meropenem and fluconazole and 8 cycles of proning. An emergency caesarean section was performed on day 12 of hospital admission at 29+5 weeks' gestation to improve maternal oxygenation and ventilation. The baby had deformities consistent with acrorenal syndrome but no evidence of COVID-19. She spent 23 days in the intensive care unit. Our case describes an unusual presentation of COVID-19, the challenges in managing critically ill pregnant patients along with a rare background history of acrorenal syndrome.

BACKGROUND

COVID-19 was first detected in Wuhan, China and reported to the WHO on 31 December 2019. The WHO declared a global pandemic on 11 March 2020. Our understanding of this disease has greatly developed and improved since then. The initial presentation of this patient was rare with largely gastrointestinal symptoms and starvation ketoacidosis with no medical history of diabetes.[1] Acrorenal syndrome is a rare congenital abnormality leading to renal and limb anomalies.[2] There has been no published literature of COVID-19 in patients with acrorenal syndrome. Evidence has now shown that pregnant patients are at increased risk of severe COVID-19 and death compared with non-pregnant patients.[3 4] Research has shown that pre-existing comorbidities, high maternal age and high body mass index (BMI), all categories our patient fit into, are risk factors for severe COVID-19.[3 4]

CASE PRESENTATION

Our patient was in her late 30s and at 28+1 weeks' gestation. She had a background medical history of acrorenal syndrome, which is a congenital abnormality resulting in upper limb deformities and both kidneys on one side. She also had a background of mild asthma and her BMI was 32. Additionally, her pregnancy had been complicated with intrauterine growth restriction and fetal deformities consistent with acrorenal syndrome.

She presented with symptoms of abdominal pain, loss of appetite, nausea and vomiting. Her blood gas analysis on admission showed a hyperchloraemic normal anion gap metabolic acidosis; pH 7.19, HCO_3- 7.6, base excess −20.6, glucose 5.8, lactate 1.6. Urinary ketones were 4.9. She had a negative toxicology screen for ethanol, salicylates and paracetamol. Diabetic ketoacidosis was ruled out as her blood sugar was 5.8 and was not on any oral hypoglycaemic agents. A diagnosis of starvation ketoacidosis was made. She had no respiratory signs or symptoms and did not require oxygen support at this time. On admission, she tested positive for COVID-19 following a routine PCR test.

The starvation ketoacidosis was managed with electrolyte replacement, nasogastric feeding, dextrose and sodium bicarbonate infusions. Abdominal ultrasound and MRI were performed and were normal other than confirming both kidneys on one side and an incidental finding of uncomplicated cholelithiasis. An echocardiogram was performed with no significant findings.

On day 3 of hospital admission, she developed rapidly progressive respiratory symptoms and was started on oxygen therapy and dexamethasone 8 mg intravenously. Her oxygen requirements continued to escalate, requiring high-flow nasal prongs then non-invasive ventilation (NIV). She found it particularly difficult to tolerate NIV and self-proning.

On day 4 of hospital admission, she was transferred to intensive care unit (ICU) where she was intubated and ventilated using pressure regulated volume control (PRVC) mode. Her upper limb deformities made central venous catheter(CVC) and arterial line placement difficult necessitating the use of a femoral CVC and dorsalis pedis arterial line. Fetal monitoring was done with two times per day cardiotocography (CTG) and weekly sonography. The first fetal scan was done on the day of ICU admission. The fetus was in the sixth centile for growth and estimated weight of just under 1000 g.

She was on enoxaparin 40 mg once daily subcutaneously throughout hospital admission. Magnesium levels were maintained within normal range throughout ICU admission with regular replacement.

On day 2 of ICU admission, her FiO_2 increased to 80% and positive end expiratory pressure (PEEP) to 16. The specialist centre for extracorporeal membrane oxygenation (ECMO) were contacted

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Table 1 Comparison of oxygenation/ventilation prior to proning versus 8 hours in the prone position.

	Prior to prone positioning	8 hours of prone positioning
pH	7.30	7.36
PO_2	9.06	11.2
PCO_2	5.76	5
PaO_2/FiO_2 ratio	84	241
FiO_2	80%	35%
Peak airway pressures	18	22
Mean airway pressures	15	14

Ventilatory settings remained the same in the supine and prone position other than a change in FiO_2.
FiO_2, refers to fraction inspired oxygen; PaO_2, refers to partial pressure arterial oxygen.

and said at present she wasn't a candidate for ECMO but that they should be contacted if any further deterioration occurred. A chest X-ray at this time (figure 1) showed she had developed extensive bilateral multifocal airspace consolidation.

Following a multidisciplinary discussion, the decision was made to try proning due to deteriorating respiratory function. We followed the usual local hospital protocol for proning patients with COVID-19 but a special air mattress was used with dynamic alternating cells design. There were six team members present. We used two slide sheets to allow turning. Preoxygenation with 100% O_2 for 5 min was performed. A bolus of muscle relaxant and sedation was also given. Sliding sheets were placed underneath and above patient. We rolled up the edges of the sliding sheets in what we described as a 'burrito roll'. At this point, the place on the bed where her abdomen would be placed was marked out. We then let down the air from those specific cells so there would be no pressure on her abdomen but rather on her hips and chest. We also let down an air cell where he eyes would be placed. The reduced pressure on her abdomen while prone prevented haemodynamic compromise secondary to aortocaval compression. The fetus was not monitored while she was in the prone position. We proceeded with the proning procedure in the usual method as for all other patients with COVID-19(table 1). We did not encounter any complications and she was prone responsive.

PaO_2 refers to partial pressure arterial oxygen, FiO_2 refers to fraction inspired oxygen.

Ventilatory settings remained the same in the supine and prone position other than a change in FiO_2.

She was started on a norepinephrine infusion on day 2 of ICU admission, which was at a maximum of 6 mcg/hour. She was reviewed daily by the microbiology team and the decision was made to start her empirically on piperacillin/tazobactam due to recurrent temperature spikes, raised inflammatory markers including procalcitonin and clinical deterioration. The only growth on her septic screen at that time was *Candida albicans* in her sputum.

Over the following 6 days, she made a good clinical improvement. Her FiO_2 requirement trended down to 40% and PEEP to 13. She continued to receive dexamethasone and was proned for 16 hours/day.

On day 8 of ICU admission, she began to deteriorate with increasing O_2 requirements up to 65% and recurrent temperature spikes. Her antimicrobial therapy was escalated to meropenem and fluconazole. The following day the decision was made to proceed with an emergency caesarean section. This was the recommended by the intensivist for maternal health reasons to improve oxygenation and ventilation due to decreased pressure from the gravid uterus. There was no evidence of fetal distress. Prior to the caesarean section, she was given 2 units of packed red cells as her haemoglobin was 77 g/L. She was transferred to the obstetric emergency theatre on day 9 of ICU admission. Anaesthesia was maintained with sevoflurane. Prior to incision, she was given cefuroxime 1.5 g as surgical site prophylaxis. She was given 150 mg of rocuronium in total throughout the procedure. Paracetamol 1 g and morphine 10 mg were given as pain relief. Phenylephrine infusion was used throughout and titrated to effect. A lower segmental caesarean section was performed with no complications and an estimated blood loss of 270 mL. Oxytocin 5 units were given intravenous following delivery in addition to an infusion of 40 units over 4 hours. The procedure took less than 1 hour. She remained stable throughout and was transferred back to ICU after the surgery. The baby was delivered at 29+5 weeks and weighed 1200 g. Delayed cord clamping was not performed to reduce the risk of COVID-19 transmission to the infant. The neonate was transferred to the neonatal intensive care unit (NICU) immediately for continuous positive airway pressure (CPAP) and monitoring. The upper limb deformities and ambiguous genitalia noted on the antenatal scan were confirmed. There was no evidence of COVID-19 transmission to the baby.

Day 1 postnatally, she continued to have recurrent temperature spikes and FiO_2 remained at 60% and PEEP of 14. She was on day 10 of dexamethasone and the decision was made by the respiratory team to continue at a tapering dose regime over the next 5 days. A computed tomography pulmonary angiogram (CT-PA) (figure 2) was performed which showed no pulmonary embolism but significant COVID-19 pneumonia and bibasal consolidation.

She did not receive any further cycles of proning following delivery of the baby, and thus she had a total of 8 cycles prior to delivery. Two days post caesarean section, she began to show improvement, and by day 3 post op, her FiO_2 was down to 40% with a PEEP of 14. Her sputum cultures returned positive for *Pseudomonas aeruginosa* and *Enterococcus faecium*. The obstetric team diagnosed vaginal candidiasis. On day 11 of ICU admission, her CVC and arterial lines were changed and vancomycin was added to cover for line sepsis. The tips of the lines grew staph epidermidis. She continued to improve from a

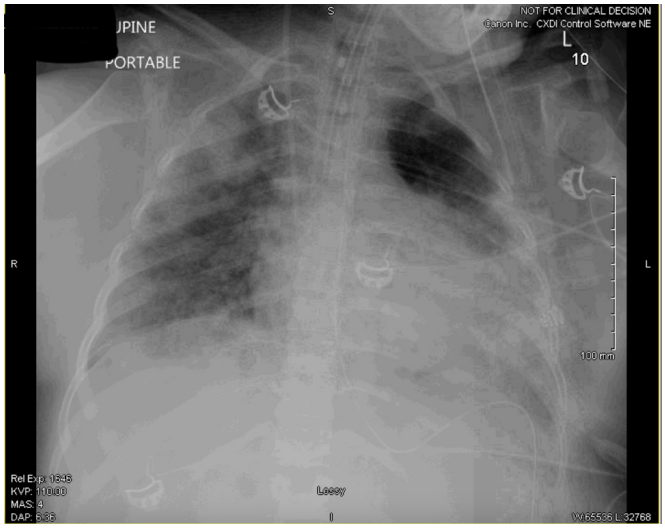

Figure 1 Anteroposterior chest x-ray showing bilateral multifocal airspace consolidation.

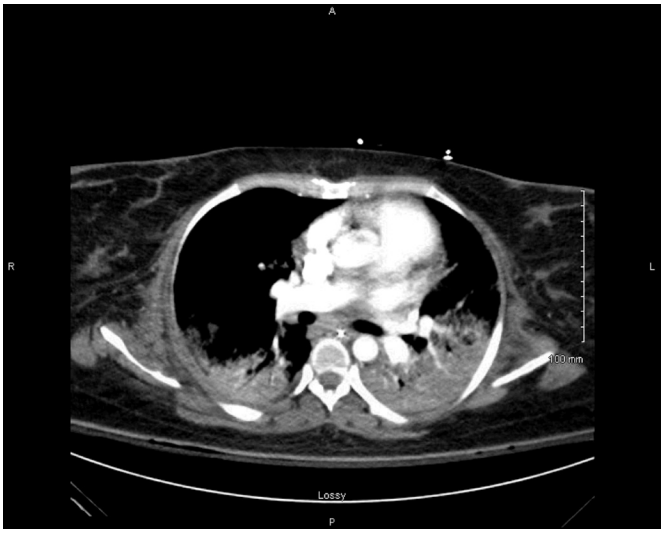

Figure 2 CT-PA showing no pulmonary embolism but extensive COVID-19 pneumonia and basal consolidation.

respiratory point of view and the recurrent temperature spikes ceased. Fluconazole was stopped following a 7-day course and meropenem was stopped following a 10-day course.

On day 17 of intubation, she was moved from PRVC to pressure support/CPAP which she tolerated well. On day 19, her sedation was weaned and she was successfully extubated and started on high-flow nasal prongs. Following extubation she became delirious requiring a dexmedetomidine infusion and regular reorientation by staff. She was updated on the progress of her baby who at that point was off CPAP and improving. A peripherally inserted central catheter (PICC) line was inserted by the radiologist due to anticipated continued difficult intravenous access.

OUTCOME AND FOLLOW-UP

She was successfully discharged to the ward following 23 days in ICU, 19 days intubated and ventilated, 8 cycles of proning and an emergency lower segmental caesarean section at 29+5 weeks' gestation. Her chest X-ray prior to discharge showed a huge improvement (figure 3). She was discharged home after a total of 42 days of hospital admission.

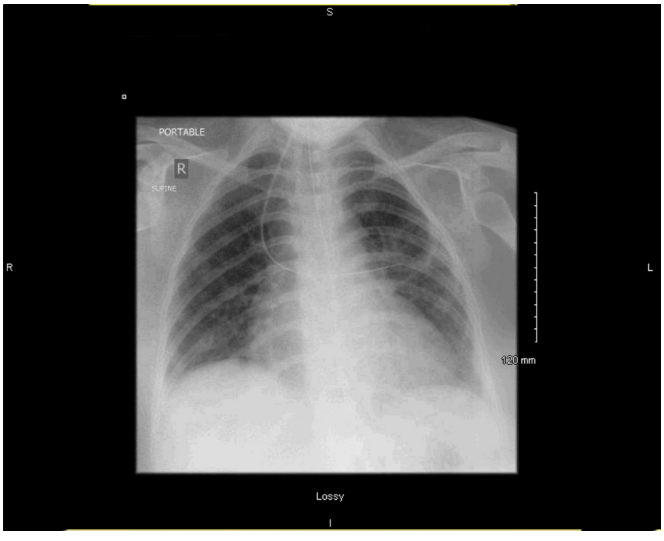

Figure 3 Anteroposterior chest x-ray prior to discharge from hospital showing improvement in bilateral consolidation

DISCUSSION

Our patient had a very unusual initial presentation of COVID-19. She was in starvation ketoacidosis at the time of admission and had no background history of diabetes mellitus. The presentation of COVID-19 varies significantly between patients but most common symptoms are fever, cough and fatigue.[5] Very little attention has been paid to the metabolic derangements in patients without diabetes caused by COVID-19. Starvation ketosis occurs when there is a switch from carbohydrate fuel in the fed state to lipid fuel in the fasting state. Ketones form from free fatty acids being broken down by the liver. If the consumption of ketones decreases, there can be a buildup of ketone bodies in the blood. Ketoacidosis is a severe metabolic disorder where the accumulation of ketone bodies causes acidosis. Ketoacidosis is rarely seen in patients without diabetes. Only one study has described the prevalence of acidosis and ketoacidosis in patients with COVID-19. This retrospective cohort study found that COVID-19 caused ketosis and ketoacidosis in patients without diabetes and lead to an increase in their length of hospital stay and mortality.[1] Their study of 658 hospitalised patients with COVID-19 found that 42 patients had ketosis on admission and 27 of these patients did not have diabetes. Five patients in total developed ketoacidosis with 2 of these patients being non-diabetic.[1] A case report of euglycemic ketoacidosis in a pregnant patient with COVID-19 was published in the *Chilean Journal of Obstetrics and Gynaecology*.[6] This patient had a similar presentation as our patient but less severe disease from a respiratory perspective. These publications suggest that COVID-19 might accelerate fat breakdown but the mechanism of COVID-19-induced ketosis and ketoacidosis needs further research. There is little published information on starvation ketoacidosis in pregnancy. Starvation ketoacidosis in pregnancy is usually precipitated by a period of severe vomiting but can be precipitated by any kind of stress (physical, emotional, infection). A case report and review of literature on this topic published in 2013 found only nine non-diabetic cases of ketoacidosis in pregnant patients from starvation alone.[7] Starvation ketosis outside of pregnancy is rare. Pregnancy has been characterised as a state of accelerated starvation (fasting hypoglycaemia) and a diabetogenic state (postprandial hyperglycaemic). During pregnancy, there is increased peripheral utilisation of glucose which leads to reduced fasting glucose and insulin levels with increased fasting ketone levels. Placental production of hormones, including glucagon and human placental lactogen, leads to insulin resistance. This increases susceptibility to ketosis particularly in the third trimester. Ketosis develops in any condition where insulin deficiency removes the brake on lipolysis and hepatic ketogenesis.[8]

Acrorenal syndrome is a rare congenital abnormality referring to congenital renal and limb anomalies. Other associated malformations include the oro-mandibular region, trachea, lungs, sweat glands, mammary glands, uterus, vas deferens, nose and eyes.[9] It was first described in 1969 by Dieker and Opitz in a case series of three patients.[2] They showed an association between major malformations of kidneys and limbs. Our patient had both kidneys on one side, absent radius and ulna bilaterally, oligodactyly and ectrodactyly. She previously had numerous operations to improve hand function including tendon release and transfer. To our knowledge, this is the first report of a critically ill patient with COVID-19 with acrorenal syndrome. Inheritance is thought to be autosomal recessive, but is poorly understood,

and has an incidence of less than one in a million.[10] The most important gene associated appears to be ZIC Family Member 3 (ZIC3).[10] Further genetic testing to characterise this syndrome will be done on this patient and her infant.

Evidence has shown that pregnant patients are at increased risk of severe COVID-19 compared with non-pregnant patients. A systematic review published in BMJ in September 2020 found that pregnant women are less likely to manifest COVID-19-related symptoms of fever and myalgia and more likely to need intensive care treatment.[4] They also found that pre-existing comorbidities, high maternal age and high BMI were risk factors for severe COVID-19 and that preterm birth rates are higher in pregnant women with COVID-19. A systematic review published in the *Journal of Pregnancy* in March 2021 found that COVID-19 in pregnant women was associated with higher rates of caesarean section and mortality.[11] Maternal mortality was found to be 1.3%. Data collection for these systematic reviews is ongoing. The Centre for Disease Control and Prevention (CDC) published a report that included more than 400 000 women with COVID-19, of whom more than 23 000 were pregnant. Pregnant patients with COVID-19 were found to have an increased risk of ICU admission, requiring invasive ventilation, ECMO and death.[3]

Our patient underwent 8 cycles of proning prior to caesarean section with 16 hours in the prone position and 8 hours supine. An article published in the *Obstetric Gynaecology Journal* highlighted that if prone positioning is performed correctly then pregnancy should not be a contraindication.[12] The authors of this article developed a clinical guideline and algorithm on how to prone pregnant patients. They recommended as with all cases of critical illness during pregnancy that maternal care and clinical decisions should be individualised with multidisciplinary input. The use of the special air mattress with dynamic alternating cells design proved extremely beneficial in preventing aortocaval compression. We deflated the cells of the air mattress that her abdomen would be lying on prior to proning her so that there would be no weight held by the abdomen. When she was prone we would monitor for any haemodynamic compromise and ensure adequate positioning with no pressure on her abdomen. Aside from this, we continued our usual protocol for proning adult intubated patients. We did not perform any fetal monitoring during prone positioning. Prone positioning has been shown to have an oxygenation and mortality benefit for patients with acute respiratory distress syndrome (ARDS) as seen in the PROSEVA study.[13] There was very little published evidence on prone positioning in pregnant patients prior to the COVID-19 pandemic. There are published case reports of successful anaesthesia in the prone position for surgical procedures in pregnant patients.[14 15] Another case report discussed the management of ARDS using prone ventilation following blunt chest trauma in a pregnant patient at 34 weeks' gestation. In this case, prone ventilation was performed for 8 hours and the patient was extubated the following day without any feto-maternal complication. During prone positioning, efforts were made to avoid pressure on the abdomen and the fetus was monitored by continuous CTG.[16] During the 2009 influenza pandemic, prone positioning was reported as being used for critically ill pregnant patients. A case report detailed the successful management of H1N1-induced ARDS in a pregnant patient at 31 weeks' gestation with use of prone ventilation. The patient was ventilated in prone position for 16 hours per day for 3 days total before being extubated. The authors used large rollers underneath the chest and iliac crest to prevent any abdominal compression. The fetus was monitored continuously with CTG and umbilical artery Doppler was also performed before and after each proning session.[17] Case reports and expert opinion have shown that prone positioning can be safely performed in pregnant patients with COVID-19 and has a good clinical outcome.[12 18]

The decision to proceed to delivery was made on the basis of maternal deterioration and the view that delivery would help improve oxygenation due to decreased demand and relieve the pressure of the gravid uterus improving ventilation. This decision was in line with the guidelines published in *American Journal of Perinatology* in April 2020 on the Management of an Obstetrical Patient on the Labour and Delivery Unit during the COVID-19 Pandemic.[19] A cohort study published in the *American Journal of Obstetrics & Gynaecology MFM* looked at pregnant patients with severe or critical COVID-19 at 12 institutions in the USA from March to April 2020. In patients with critical disease, prone positioning was used in 20% of cases. Twenty women had critical disease and 15 of these delivered preterm and 17 delivered during the course of their disease.[20] To date, the majority of pregnant patients with severe COVID-19 have had delivery by caesarean section. A case report was published detailing successful induction of labour and forceps vaginal delivery in an intubated patient with COVID-19.[21] A cohort study showed increased risk of poor outcome following caesarean section in pregnant patients with COVID-19 compared with vaginal delivery.[22] More research is required to compare the benefits of induction of labour and vaginal delivery versus caesarean section in intubated and ventilated patients with COVID-19.

Learning points

- Starvation ketoacidosis is a rare presentation of COVID-19.
- Acrorenal syndrome is a rare congenital abnormality referring to congenital renal and limb anomalies. Other associated malformations include the oro-mandibular region, trachea, lungs, sweat glands, mammary glands, uterus, vas deferens, nose and eyes.
- Pregnancy is not a contraindication to prone positioning in critically ill patients with COVID-19.

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