

# Case series of COVID-19 infection in pregnancy complicated by ketoacidosis and symptomatic breathlessness

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## Abstract

**Background:** The differential diagnosis of acute shortness of breath in a pregnant woman with COVID-19 is broad. Pregnancy is a ketosis-prone state, which can result in metabolic acidosis and tachypnoea.

**Methods:** We describe four pregnant women with COVID-19 and breathlessness where ketoacidosis was found to contribute to symptomatic tachypnoea.

**Results:** One patient did not have associated COVID-19 pneumonitis, but presented with severe tachypnoea and metabolic acidosis; three women had pneumonitis and metabolic acidosis. Corrective treatment for the metabolic abnormalities resulted in resolution of the ketoacidosis in all cases. No women had coexistent diabetes.

**Conclusion:** This is the first series of COVID-19 in pregnancy complicated by ketoacidosis and symptomatic tachypnoea. Ketoacidosis associated with COVID-19 is an important cause of tachypnoea requiring specific treatment, which should not be overlooked. Potential mechanisms for this are discussed with a framework for interpretation of blood gas results during pregnancy.

## Keywords

Pregnancy, ketoacidosis, ketosis, starvation ketosis, COVID-19

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## Background

The assessment of a pregnant woman with SARS-CoV-2 infection ('COVID-19') presenting with breathlessness often focuses on her respiratory requirements – whether treatment for pneumonitis is indicated, what respiratory support is needed and whether iatrogenic birth will aid respiratory function. However, the differential diagnosis for women with COVID-19 presenting with breathlessness includes other COVID-19-related diagnoses such as thromboembolism, non-COVID-19 causes (including other respiratory pathology, cardiac disease, anaemia) and metabolic causes.<sup>1</sup>

Pregnant women are more prone to developing ketosis, and inter-current infection may reduce the metabolic threshold at which ketoacidosis occurs. Typical features of ketoacidosis include rising concentrations of blood acetoacetate and 3- $\beta$ -hydroxybutyrate ('ketones' or 'ketoacids') and a consequent fall in serum bicarbonate. Respiratory effort increases as a compensatory mechanism (termed 'Kussmaul breathing') with a resulting fall in the partial pressure of carbon dioxide (pCO<sub>2</sub>). However, when respiratory compensation fails to maintain acid-base balance, frank acidosis occurs. Normal respiratory physiology in pregnancy does not lead to tachypnea – this remains a significant abnormality in pregnancy.

Maternal acidosis of any aetiology may not be well tolerated by the fetus and may cause fetal acidosis, fetal electrolyte disturbances and ultimately fetal cardiac arrhythmias (which may lead to intra-uterine death). Interventions to correct metabolic abnormalities

should therefore be initiated promptly after recognition for both maternal and fetal benefit.

## Cases

We present the cases of four pregnant women with confirmed COVID-19 and non-diabetic ketoacidosis admitted through our multidisciplinary obstetric medicine service during the COVID-19 pandemic.

**Patient 1** A 41-year old was admitted from the emergency department to critical care at 31 weeks' gestation in her third pregnancy with worsening shortness of breath and COVID-19 related pneumonitis, eight days after developing symptomatic infection. She was treated with steroids for COVID-19 pneumonitis and high flow oxygen. She also received steroids for fetal lung maturation in view of possible iatrogenic delivery.

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On admission, a compensated metabolic acidosis with raised blood ketones was found (see Table 1) with associated tachypnoea (respiratory rate of 34 breaths/min, with no increase in fraction of inspired oxygen requirement). There was no history of diabetes and screening tests for impaired glucose tolerance in pregnancy had been negative. A diagnosis was made of euglycaemic ketoacidosis precipitated by pregnancy, steroid administration, reduced carbohydrate intake and acute COVID-19.

Treatment with intravenous glucose and fixed rate insulin infusion resulted in correction of the ketoacidosis and resolution of tachypnoea. Her clinical condition improved without further respiratory support. Fetal monitoring was unremarkable and preterm delivery was ultimately not required. She was discharged home after nine days in hospital. Follow-up tests to exclude concomitant diabetes were negative.

**Patient 2** A 25-year old with two previous uncomplicated pregnancies was admitted to the maternity unit at 34 weeks' gestation with worsening shortness of breath and vomiting, eight days after developing symptoms of COVID-19. Peak respiratory rate was 44 breaths/min with oxygen saturation maintained above 97% on room air. Respiratory examination was normal and chest radiograph did not show any evidence of COVID-19 related pneumonitis. Arterial blood gas on room air showed normal partial pressure of oxygen and a severe metabolic acidosis (see Table 1).

A diagnosis of euglycaemic ketoacidosis precipitated by pregnancy, reduced oral intake (of carbohydrate) and acute COVID-19 was made, and treatment with intravenous dextrose, intravenous insulin and anti-emetics resulted in correction of ketoacidosis within 48 hours. No respiratory support was required and steroids were not indicated. Close fetal monitoring was unremarkable and delivery was not required. She was discharged home after three days in hospital. Follow-up tests to exclude concomitant diabetes were negative.

**Patient 3** A 27-year old with severe COVID-19 pneumonitis was admitted to critical care at 33 weeks' gestation in her second pregnancy with increasing tachypnoea and work of breathing, six days after developing symptoms of COVID-19. She received steroids, both for fetal lung maturation and for severe COVID-19. Euglycaemic compensated ketoacidosis was associated with marked tachypnoea (peak respiratory rate of 52 breaths/min) (see Table 1). The metabolic abnormalities were corrected with intravenous dextrose and insulin. However, due to worsening pneumonitis and escalating ventilatory requirements, an emergency caesarean section was performed on the second day of critical care admission. She had a prolonged admission, complicated by pneumothorax and seizures, and she was discharged home on day 26. Capillary blood glucose monitoring remained within the normal range throughout the prolonged admission.

**Patient 4** A 35-year old was admitted with COVID-19 pneumonitis at 32 weeks' gestation in her second pregnancy, seven days after developing symptoms of infection (including vomiting). CT thorax confirmed COVID pneumonitis with no evidence of pulmonary embolus; Supplemental oxygen was not required but there was persistent tachypnoea (respiratory rate of 34 breaths/min) with oxygen saturation maintained over 96%. Blood gas showed a severe compensated metabolic acidosis with ketosis (see Table 1) which was corrected with intravenous and oral dextrose and intravenous insulin, and resulted in resolution of the tachypnoea (respiratory rate less than 24/min). No steroids were administered. A concomitant urinary tract infection was diagnosed and treated with antibiotics. Fetal monitoring was unremarkable and she was discharged from hospital on day 5, and delivery was not required.

## Discussion

This is the first case series of COVID-19 in pregnancy complicated by ketoacidosis and symptomatic breathlessness. It is well described that pregnancy renders women more susceptible to developing ketosis – but there is limited data of the incidence of ketosis in pregnancy

beyond published case reports. The aetiology of ketosis in pregnancy is thought to be multifactorial, including reduced endogenous insulin production, increased glucagon production and a relative rise in insulin resistance – metabolic mechanisms to maintain euglycemia.

In addition to facilitating the uptake of cellular glucose, insulin inhibits the activity of hormone-sensitive lipase, suppressing free fatty acid oxidation and ketogenesis, opposing the counter-regulatory hormone glucagon. Catabolic changes resulting in the preferential metabolism of free fatty acids and propensity to ketoacidosis are predominately seen in women with decompensated diabetes or following a period protracted vomiting, when it is referred to as 'starvation ketosis'.<sup>2</sup>

It has been postulated that the SARS-CoV-2 virus may directly affect pancreatic beta cell function, and further reduce endogenous insulin production.<sup>3,4</sup> Ketoacidosis has been reported in COVID-19 in those without diabetes.<sup>5</sup> Gastrointestinal symptoms (including anorexia, nausea and vomiting) occur in 20% of those with COVID-19<sup>6</sup> –reduced oral intake was felt to have contributed in all of these cases.

Intercurrent infection and the administration of steroids may further reduce the metabolic threshold at which ketoacidosis occurs in pregnancy. Iatrogenic steroid administration is known to increase insulin resistance and modulate carbohydrate metabolism by promoting de novo hepatic glucose production (gluconeogenesis) as well as acting on peripheral insulin receptors within adipose tissue and muscle, increasing lipolysis and reducing cellular glucose uptake, respectively.<sup>7</sup>

Potential mechanisms to explain our findings of ketoacidosis in these women with COVID-19 would include a disproportional increase in the ratio of endogenous insulin to glucagon release, coupled with increasing insulin resistance characteristic of advancing gestation and severe illness and iatrogenic steroid use.

Following early identification, key interventions in the management of ketoacidosis include prompt rehydration and measures to curtail lipolysis, potentiated through the inhibitory effect of insulin. Insulin may either be stimulated endogenously (following carbohydrate administration) or administered parenterally in those with beta cell dysfunction or poor oral intake.

Our case series demonstrates the broad differential diagnosis for dyspnoea in pregnancy, even in women with confirmed COVID-19. Early identification of the underlying diagnosis is important – this is achieved by keeping an open and inquiring mind when assessing women with tachypnoea, consideration of normal physiological changes when interpreting results, and collaborating across the multi-disciplinary team.

Blood gas measurements are often done in women with COVID-19 to assess oxygenation. Most analysers report additional parameters useful in the holistic assessment of these women. Normal pregnancy is a condition of mild respiratory alkalosis, thought to be due to progesterone-driven hyperventilation. This results in a slight rise in the pH, moderate fall in pCO<sub>2</sub> and bicarbonate with an unchanged (or slightly increased) pO<sub>2</sub> and unchanged base excess. It is likely that normal ranges in pregnancy will differ to the ranges provided by the analyser, and it is important that pregnancy-specific reference ranges should be used for interpretation of blood gas measurements (see Table 2<sup>8</sup>).

Where metabolic acidosis is found, there are many causes to consider – for example, elevated lactate is a frequent cause of elevated anion gap metabolic acidosis that is easily ruled out by blood gas analysis.

Analysis of serum ketones is particularly useful for assessment of metabolic acidosis. However, serum ketones is not generally included with standard blood gas measurements and currently are measured separately using point of care testing devices. Serum ketones levels are felt to be normal when less than 1.0 nmol/L.<sup>9</sup>

The 'Rule of Six' (see Table 3) offers a systematic approach for interpretation of blood gas measurements, which ensures that the full information available is used for the clinical assessment of the woman.

**Table 1.** Summary of the four cases.

Case	Age, parity, BMI (kg/m <sup>2</sup> ); GDM screen <sup>a</sup>	Gestation at presentation (weeks)	COVID-19 Confirmed on PCR testing	Associated COVID-19 pneumonitis	RR and SpO <sub>2</sub> on admission	Critical care admission	Outcome	Concomitant diabetes	Peak ketoacidosis blood gas results HCO <sub>3</sub> (mmol/L) pO <sub>2</sub> (kPa) Ketones (mmol/L), pCO <sub>2</sub> (kPa)
1	41 years Para 2 BMI 29 5.1	31	Yes	Yes	RR 34/min SpO <sub>2</sub> 97% on FiO <sub>2</sub> 32%	Intensive care unit stay	Required high flow oxygen but no further respiratory support. Discharged without pre-term delivery	No	pH 7.41 HCO <sub>3</sub> 15.8 Ketones 4.2 pCO <sub>2</sub> 2.48
2	25 years Para 2 BMI 32 5.7	34	Yes	No	RR 44/min SpO <sub>2</sub> > 97% on air	No - ward based care	Discharged without pre-term delivery or respiratory support	No	pH 7.17 HCO <sub>3</sub> 6.4 Ketones 5.6 pCO <sub>2</sub> 2.30
3	27 years Para 1 BMI 41 5.6	33	Yes	Yes	RR 34 SpO <sub>2</sub> 97% on FiO <sub>2</sub> 50%	Intensive care unit stay	Delivery at 33 weeks. Prolonged postnatal admission. Baby discharged home from SCBU.	No	pH 7.40 HCO <sub>3</sub> 16.4 Ketones 4.0 pCO <sub>2</sub> 3.59
4	35 years Para 1 BMI 33 6.3	32	Yes	Yes	RR 34 SpO <sub>2</sub> 99% on air	High dependency care unit stay	Discharged without pre-term delivery or respiratory support	No	pH 7.471 HCO <sub>3</sub> 13.3 Ketones 3.0 pCO <sub>2</sub> 2.47

<sup>a</sup>Gestational diabetes screening was performed in all women at 28 weeks' gestation using a 50 g glucose load orally and blood glucose 60 min later. Negative gestational diabetes screening test if blood glucose <7.8 mmol/L. Actual blood sugar from gestational diabetes screening results shown in column 2.

**Table 2.** Comparison of pregnancy and non-pregnancy-specific reference ranges for arterial blood gas interpretation.<sup>8</sup>

	Non-pregnancy specific reference range	Pregnancy-specific reference range
pH	7.34–7.44	7.40–7.46
pO <sub>2</sub> (kPa)	10.0–13.0	10.0–13.0
pCO <sub>2</sub> (kPa)	4.7–6.0	3.7–4.2
HCO <sub>3</sub> (mmol/L)	21–27	18–21

**Table 3.** The 'Rule of Six' for blood gas interpretation.

Oxygenation
Ventilation (pCO <sub>2</sub> )
Acid base status (pH and bicarbonate)
Electrolyte abnormalities
Haemoglobin concentration
Lactate and glucose

## Summary

Tachypnoea is an important sign of respiratory and cardiac disease as well as of metabolic acidosis. In women with severe COVID-19, care must be taken to consider a holistic approach in the clinical assessment, and not make assumptions about causality of symptoms and signs. A careful and thorough review is essential, with a multidisciplinary team approach.

Ketoacidosis is an important cause of tachypnoea in pregnant women with COVID-19, especially in the third trimester, and should be considered as part of the differential diagnosis. Point of care ketone testing is available to quantify blood ketones.

Maternal acidosis may not be tolerated well by the fetus, and it should be identified early with prompt treatment given to correct the metabolic abnormalities, alongside maternal and fetal monitoring.

## Learning points

- There is a broad differential diagnosis for dyspnoea in pregnancy, even in women with confirmed COVID-19. Multidisciplinary care is essential for these women.
- Pregnancy is a ketosis-prone period, and ketosis is not well tolerated by the fetus. We have described ketoacidosis associated with COVID-19 and the potential physiological changes underlying it.
- Holistic and accurate interpretation of blood gas results using pregnancy-specific reference ranges ensures acidosis is not overlooked. The rule of six offers a structured approach for this. Point of care ketones testing is a valuable diagnostic tool for metabolic acidosis.

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## Ethical approval

The patients have given informed consent for their clinical information to be shared in an anonymised form in the case series.

## Informed consent

Informed consent was obtained from the patients for their anonymised information to be published in this article.

## Guarantor

IT is the guarantor of this article.

## Contributorship

All authors were involved in the management of these clinical cases. IT, SS and JG conceptualised the case series. IT prepared the draft manuscript. All authors were involved in the editing and review process of the submitted manuscript.

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