

Case report

COVID-19 complicated by hepatic dysfunction in a 28-week pregnant woman

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SUMMARY

The COVID-19 outbreak has spread across the globe at an alarming rate. As the pandemic escalates, experience of COVID-19 in pregnant women is accumulating. We present a case of COVID-19 pneumonia in a 28-week pregnant woman with a known low lying placenta. The patient had deranged liver function tests at presentation, along with elevated bile acids. We discuss the differential diagnosis of these findings, and the possible mechanisms of hepatic injury in COVID-19. The low lying placenta in this patient meant that we had to carefully consider the application of recommendations for thromboprophylaxis in pregnant COVID-19 patients. With supportive management, this patient improved enough to be discharged, and has gone on to deliver a healthy neonate at term.

BACKGROUND

In December 2019, an outbreak of viral pneumonia, later attributed to the novel coronavirus, SARS-CoV-2, was reported in the city of Wuhan, China.¹ By 30 January 2020, COVID-19 had been declared a public health emergency of international concern.² At the time of writing, there are currently over 18 million confirmed cases worldwide, and almost 700 000 deaths attributed to COVID-19.³

As the pandemic continues to escalate, experience of COVID-19 in pregnant women is accumulating. However, the majority of evidence amassed so far reports on the maternal and fetal outcomes of these cases, rather than any diagnostic complexities or challenges encountered specifically in pregnant patients. Here, we discuss a case of COVID-19 in a 28-week pregnant woman with placenta praevia, complicated by significant hepatic involvement.

CASE PRESENTATION

The patient was a 35-year-old para 1 of South Asian ethnicity, in her second pregnancy. Her first pregnancy had been complicated by obstetric cholestasis (OC), but alanine transaminase (ALT) and bile acids (BA) levels at 21 weeks gestation in this pregnancy were normal. The patient had had several episodes of minor antepartum haemorrhage (APH) in this pregnancy. The detailed anomaly scan revealed a low lying placenta, but all other investigations, including hepatitis serology, and a glucose tolerance test at 24 weeks gestation were unremarkable.

She presented to our tertiary level hospital at 28⁺⁵ weeks gestation with shortness of breath and a dry cough. Her symptoms had begun with rhinorrhoea

approximately 6 days previously, and been progressively worsening. At the time, one household contact was hospitalised with pneumonia presumed to be COVID-19, and another was unwell at home, with milder symptoms.

On arrival, the patient had a respiratory rate of 42/min, oxygen saturations in room air of 96%, pulse rate of 133/min and a normal temperature of 36.7°C. Examination of the chest revealed left lower lobe crackles, and scattered wheeze. Both calves were soft and non-tender, with no difference in circumference.

INVESTIGATIONS

Baseline laboratory investigations are shown in [table 1](#). Chest X-Ray (CXR) showed bilateral patchy perihilar inflammatory changes suggestive of either a viral pneumonia or pulmonary oedema. There was no cardiomegaly.

DIFFERENTIAL DIAGNOSIS

The examination of the patient and the normal cardiac size on the CXR were not suggestive of a cardiac or thromboembolic cause for her symptoms. Given her presentation and history of exposure, a diagnosis of presumed COVID-19 pneumonia was made. Swab results confirming detection of SARS-CoV-2 RNA, and excluding other respiratory viral pathogens were received on day 3.

The significantly elevated ALT on the initial blood investigations was unexpected, and prompted a second line of laboratory investigations, shown in [table 2](#), to identify the cause, and extent of the hepatic impairment. The elevated bile acid (BA) level raised the question of whether this episode of COVID-19 pneumonia could be coexistent with OC. However, the patient did not complain of any itching and both the BA and ALT levels improved with resolution of her COVID-19 symptoms, as shown in [table 3](#).

TREATMENT

Following discussion with respiratory physicians, the patient was managed supportively with oxygen therapy, salbutamol nebulisers, intravenous fluids and paracetamol, according to treatment guidelines at the time. She was also given intravenous antibiotics to cover any superimposed bacterial infection, and intramuscular steroids for fetal lung maturity in case of deterioration warranting delivery. She experienced a minor APH on the day of admission, and so was managed on the labour ward. The obstetric,



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Table 1 Baseline laboratory investigations

	Result	Normal third trimester values ²²
Hb (g/L)	128	95–150
WCC ($\times 10^9/L$)	6.6	5.6–16.9
Neutrophils ($\times 10^9/L$)	5.21	3.9–13.1
Lymphocytes ($\times 10^9/L$)	1.16	1.0–3.6
Platelets ($\times 10^9/L$)	157	146–429
Creatinine ($\mu\text{mol/L}$)	53	35–80
ALT (U/L)	571	2–25
Albumin (g/L)	38	23–42
Total bilirubin ($\mu\text{mol/L}$)	13	1.7–18.8
CRP (mg/L)	60	0.4–8.1

Abnormal results highlighted in bold.

ALT, alanine transaminase; CRP, C reactive protein; Hb, haemoglobin; WCC, white cell count.

anaesthetic, neonatal, respiratory and intensive care teams were all involved with decisions regarding her care. As she experienced no subsequent vaginal bleeding, and her clinical course was improving, she was given low molecular weight heparin (LMWH) from day 2, in line with the Royal College of Obstetricians and Gynaecologists guidance on thromboprophylaxis for pregnant COVID-19 patients.⁴

OUTCOME AND FOLLOW-UP

With supportive management, this patient's condition improved over the course of several days. Resolution of the abnormal laboratory investigations is shown in table 3.

She was discharged home on day 4 and advised to self-isolate. Given the history of recurrent episodes of APH in the context of a placenta praevia, we did not discharge her with anticoagulants. Her ongoing pregnancy was complicated by one further episode of minor APH at 31 weeks. An ultrasound for placental location at 32 weeks gestation showed the placenta was no longer low lying, but the foetus was noted to be macrosomic. Her HbA1c and fasting glucose level were both subsequently found to be raised, and she was diagnosed with gestational diabetes mellitus (GDM), which was managed with metformin therapy. She went on to deliver a healthy 3200g infant by forceps at 39⁺¹ weeks gestation following an induction of labour.

DISCUSSION

As the COVID-19 pandemic continues to unfold, evidence regarding its effect on pregnant women is continuing to

Table 2 Second line laboratory investigations

	Result	Normal third trimester values ²²
LDH (U/L)	194	82–524
GGT (U/L)	34	3–26
BA ($\mu\text{mol/L}$)	53	0–11.3
APTT (s)	36.2	24.7–35.0
PT (s)	13.5	9.6–12.9
INR	1.0	
Mitochondrial antibody	Negative	
Smooth muscle antibody	Negative	
CMV IgM	Not detected	

Abnormal results are highlighted in bold.

APTT, activated partial thromboplastin time; BA, bile acids; CMV, cytomegalovirus; GGT, gamma-glutamyl transpeptidase; INR, international normalised ratio; LDH, lactate dehydrogenase; PT, prothrombin time.

Table 3 Resolution of abnormal laboratory investigations

	Day 1	Day 1+6 hours	Day 2	Day 3	Day 4	Day 13
Plt ($\times 10^9/L$)	157	139		160	200	345
ALT (U/L)	571	481	330	232	162	24
BA ($\mu\text{mol/L}$)		53	13	11	21	7
CRP (mg/L)	60	54	40	18	12	

ALT, alanine transaminase; BA, bile acids; CRP, C reactive protein; Plt, Platelets.

accumulate. We present a case of COVID-19 in the third trimester of pregnancy, complicated by severe hepatic impairment. As with most other cases of COVID-19 reported in the literature,^{5,6} this patient presented with symptoms in the third trimester of pregnancy. Our patient was of South Asian ethnicity, a risk factor known to be associated with the need for hospitalisation.^{4,6} She presented with dyspnoea and a respiratory rate of 42/min at rest, meeting the WHO criteria for severe category disease (see table 4). Pre-existing diabetes mellitus or GDM is present in around 13% of women with confirmed SARS-CoV-2 infection in pregnancy.⁶ While our patient was not diagnosed with GDM in her first pregnancy, or at the time of presentation with COVID-19 in this gestation, she did subsequently develop GDM following her recovery.

Immune adaptation to pregnancy is highly complex and not yet completely understood. Data suggest that there is a shift away from cell-mediated immunity, towards a humoral response,⁷ but it is unclear if this renders the mother more susceptible to viral infections, since it appears to also be a dynamic modulation which differs according to the pathogen involved, and the stage of pregnancy.⁸ Maternal oxygen consumption is increased due to the raised metabolic rate, and the elevation of the diaphragm due to the gravid uterus reduces functional residual capacity.⁹ Together, these changes may exacerbate hypoxic sequelae arising from pathological processes such as respiratory infections.

Despite this apparent physiological disadvantage, current evidence suggests that pregnant women are not more likely to contract COVID-19 than the general population.⁴ A recent systematic review⁵ of 2567 cases of COVID-19 in pregnancy reported 7% of cases required admission to the intensive care unit (ICU), 3.4% required mechanical ventilation and mortality of <1%, which compares favourably with figures for a general adult population.¹⁰ In addition, compared with women infected with other coronaviruses, SARS and Middle East respiratory syndrome, pregnant women affected by COVID-19 are also less likely to require ICU admission or mechanical ventilation.¹¹ The mechanisms by which pregnant women seem to be shielded from the most serious complications of COVID-19 are currently not yet understood.

Our patient presented with an ALT level of 571. Hepatic dysfunction occurs in up to 53% of cases of COVID-19,¹² and is generally accepted as a poor prognostic factor.^{13–16} Wang *et*

Table 4 WHO diagnostic criteria for severe and critical level COVID-19 infection¹⁰

Severe disease (13.8% of population)	Critical disease (6.1% of population)
Dyspnoea	Requiring mechanical ventilation
Respiratory frequency $\geq 30/\text{min}$	Septic shock
Blood oxygen saturation $\leq 93\%$	Multiple organ dysfunction/failure
$\text{PaO}_2/\text{FiO}_2$ ratio < 300	
Lung infiltrates $> 50\%$ of the lung field within 24–48 hours	

al¹⁶ and Huang *et al*¹⁴ both reported higher levels of ALT in COVID-19 patients who required ICU care compared with those who did not, but of note is that the average ALT levels reported in these studies (35 U/L and 49 U/L, respectively) were significantly lower than the presenting ALT level in our patient. Chen *et al*¹⁷ reported one case of COVID-19 where the ALT was 7590 U/L, but the clinical outcome for this case was not specifically discussed. There is currently no data investigating whether increasing degrees of hepatic dysfunction confer increased risk of adverse clinical outcomes, or whether prognostic markers for the general population can be specifically applied to a pregnant population.

The additional finding of an elevated BA level created a diagnostic uncertainty in this patient, as it raised the possibility that the hepatic dysfunction could be related to a coexisting obstetric cause, such as OC, rather than COVID-19. The pathogenesis of OC is multifactorial, but likely to result from inhibitory effects of oestrogen and progesterone on hepatic uptake and efflux of BA, in genetically susceptible women.¹⁸ Our patient did have a history of OC in her first pregnancy; however, she was not currently experiencing any typical OC symptoms of pruritus particularly affecting the hands and feet. The resolution of the BA level, which mirrored her clinical improvement from the viral symptoms, also did not fit with a diagnosis of OC, which would typically see the BA level normalise postnatally.

Proposed mechanisms for hepatic injury in COVID-19 include secondary inflammatory or hypoxic-mediated change, or primary infection of the hepatocytes by the virus.^{12–19} Histological evidence from postmortems of COVID-19 patients has shown ballooning and apoptosis of hepatocytes, as well as inflammation and central lobular necrosis.¹⁹ BA can also be elevated in acute viral hepatitis, possibly due to an impaired ability of the hepatocytes to uptake BA from the portal circulation.²⁰

Interestingly though, SARS-CoV-2 has been shown to infect cells by binding to the ACE2 receptor, which is only expressed in low levels on hepatocytes. In contrast, bile ducts cells express high levels of the ACE2 receptor.¹⁹ It is possible therefore, that the hepatic injury seen in COVID-19 is secondary to viral infection of the biliary tree and the resulting bile duct dysfunction causes accumulation of toxic BA within the hepatocytes, and hepatic damage.

In addition to her respiratory symptoms, our patient presented with a minor volume PV bleed, as well as deranged clotting function. The clotting abnormality could have been directly due to the COVID-19 infection, which can be associated with mild elevations in prothrombin time and activated partial thromboplastin time,²¹ or secondary to the hepatic dysfunction. COVID-19 is also associated with vascular endothelial dysfunction, and the potential for thromboembolic complications.²¹ The risk of bleeding therefore had to be carefully balanced against the risk of venous thromboembolism in this patient. Anticoagulating this patient would have increased the risk of a larger volume PV bleed, and if delivery of the foetus had become necessary, it would have increased the possibility of her requiring a general anaesthetic, which is an aerosol generating procedure. We therefore chose to delay administration of thromboprophylaxis until day 2 of her admission, and omit it at discharge.

Pregnant women with COVID-19 have high rates of preterm birth, which is usually iatrogenic.⁵ In contrast, the patient presented in this report went on to deliver a healthy neonate at term.

The rate of neonatal SARS-CoV-2 positivity in large systematic reviews and population cohort studies^{5–6} is around 1%–2%, but

Learning points

- ▶ Up to 53% of COVID-19 cases will present with abnormal liver function, but there are no data on whether increasing dysfunction correlates with increased likelihood of adverse outcome.
- ▶ Hepatic injury in COVID-19 may be secondary to bile duct infection and dysfunction.
- ▶ Pregnant women with, or recovered from, COVID-19 are recommended to have LMWH thromboprophylaxis, but this should be judged on the individual clinical picture for each patient.

evidence regarding the risk of intrauterine transmission remains inadequate and requires further investigation.

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