Case report

Successful continuation of pregnancy in a patient with COVID-19-related ARDS

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SUMMARY

A 33-year-old pregnant woman was hospitalised with fever, cough, myalgia and dyspnoea at 23.5 weeks of gestation (WG). Development of acute respiratory distress syndrome (ARDS) mandated invasive mechanical ventilation. A nasopharyngeal swab proved positive for severe acute respiratory syndrome coronavirus 2 by reverse transcription-PCR. The patient developed hypertension and biological disorders suggesting pre-eclampsia and HELLP (haemolysis, elevated liver enzyme levels and low platelet levels) syndrome. Pre-eclampsia was subsequently ruled out by a low ratio of serum soluble fms-like tyrosine kinase-1 to placental growth factor. Given the severity of ARDS, delivery by caesarean section was contemplated. Because the ratio was normal and the patient's respiratory condition stabilised, delivery was postponed. She recovered after 10 days of mechanical ventilation. She spontaneously delivered a healthy boy at 33.4 WG. Clinical and laboratory manifestations of COVID-19 infection can mimic HELLP syndrome. Fetal extraction should not be systematic in the absence of fetal distress or intractable maternal disease. Successful evolution was the result of a multidisciplinary teamwork.

BACKGROUND

The new severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first reported in China in December 2019. The infection spread quickly, reaching all continents, and was declared by the WHO as a pandemic on 11 March 2020.

Pregnancy is a challenging and vulnerable period. Generally, pregnant women are in a high-risk group for infectious diseases due to gestational immunological and physiological changes in their cardiorespiratory and immunological system.[1 2] According to previous experience with influenza and coronaviruses responsible for severe acute respiratory syndrome and Middle East respiratory syndrome, respiratory tract infections could cause severe adverse pregnancy outcomes, such as miscarriage, premature delivery, intrauterine growth restriction and maternal death.[3 4] Maternal management and fetal safety become major concerns. However, data on pregnant women with SARS-CoV-2 infection are scarce and contradictory.[5–8] The effect of SARS-CoV-2 on pregnancy is not clear. As yet, there is no evidence indicating a worse outcome in pregnant women than that of the general population during COVID-19 infection.[9] However, data collection and successive research are necessary. Whether severe respiratory involvement should mandate delivery in order to improve the mother's status, despite the risk of extreme prematurity, is debated.[10] There is no recommendation for the management of pregnant women with COVID-19 severe infection.

In this context, multidisciplinary teamwork and personalised decision, considering maternal and fetal clinical conditions, are essential.

We report the case of a pregnant woman with COVID-19-related acute respiratory distress syndrome (ARDS) at 23.5 weeks of gestation (WG) whose pregnancy was continued. She spontaneously delivered a healthy boy at 33.4 WG.

CASE PRESENTATION

A 33-year-old pregnant woman (gravida 2, para 1) presented with fever, cough, myalgia and dyspnoea for 4 days at 23.5 WG. A cervical cerclage had been performed at 22 weeks due to a short cervix and history of preterm delivery. She had no history of hypertension prior to pregnancy, and had no oedema nor any visual disturbances. No proteinuria was found during a previous follow-up.

On admission, her temperature was 39.2°C, her pulse rate was 106 per minute, and her blood pressure was 125/75 mm Hg. Her respiratory rate was 46 per minute with accessory muscles involvement and pulse oxygen saturation was 94% breathing 2 L/min nasal oxygen. Her tendon reflexes were brisk. The cervix examination was normal, excluding the risk of a spontaneous preterm delivery. She was referred to the intensive care unit (ICU) on 17 March 2020 due to rapid respiratory exhaustion despite high-flow nasal oxygen and needed tracheal intubation and mechanical ventilation. She developed severe hypertension (180/83 mm Hg) despite adequate sedation.

INVESTIGATIONS

Arterial PO_2 under invasive mechanical ventilation was 125 mm Hg with an FiO_2 of 80% (resulting in a P:F ratio of 156) and 10 cm H_2O positive end-expiratory pressure. A tracheal aspirate was positive for SARS-CoV-2 by PCR. Chest radiography showed bilateral interstitial and alveolar opacities which predominated in the lung bases (figure 1). A diagnosis of COVID-19-related ARDS was given. The investigations revealed mild anaemia with minimal haemolysis, thrombocytopaenia, lymphocytopaenia and elevated hepatic aminotransferases. Proteinuria to creatininuria ratio was 0.14 g/

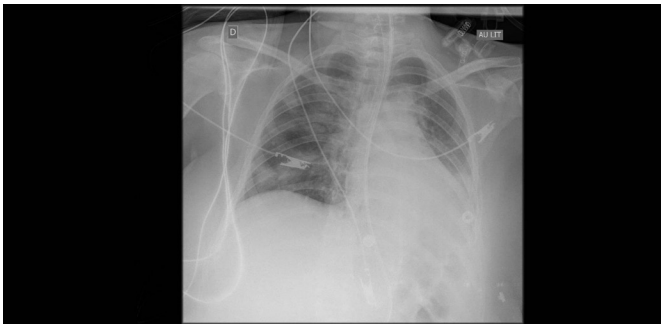

Figure 1 Chest radiography at the time of intubation. As expected in a moderate acute respiratory distress syndrome, bilateral alveolar opacities are not extensive (they are mainly present in the bases), but they were responsible for marked hypoxaemia despite high-flow nasal oxygen and this led to the patient's intubation. Opacities likely worsened during the course, as attested by severe oxygenation defect, but we decided not to take other chest roentgenogram for safety reasons.

mmol (upper limit of normal 0.03 g/mmol). Renal function was normal. The serum soluble fms-like tyrosine kinase-1 (sFlt-1) to placental growth factor (PlGF) ratio was normal (table 1).

Abdominal ultrasound ruled out a subcapsular haematoma of the liver. Fetal ultrasound examination was normal with normal Doppler flows.

DIFFERENTIAL DIAGNOSIS

Many elements of the clinical and biological picture were compatible with pre-eclampsia (high blood pressure appearing after 20 WG and significant proteinuria to creatininuria ratio) and incomplete HELLP (haemolysis, elevated liver enzyme levels and low platelet levels) syndrome. Indeed, there was presence of thrombocytopaenia and elevated liver enzymes, but haemolysis was minimal as attested by mildly decreased levels of serum haptoglobin and lactate dehydrogenase, which however eventually returned to normal values (table 1). The sFlt-1 to PlGF ratio pleaded against pre-eclampsia and the biological disorders were considered secondary to SARS-CoV-2 infection.[11]

Other aetiologies of acute hypoxaemic respiratory failure were ruled out. Indeed, there was no evidence of fluid overload states: heart failure was excluded by clinical (there was no history of orthopnoea, paroxysmal nocturnal dyspnoea, history of dyspnoea on exertion, jugular venous pressure was normal) and echocardiographic examination and renal function were normal. Bacterial pneumonia causing ARDS was ruled out by culture of tracheal aspirate and negative blood culture. A search for *Legionella* antigen in urine was negative.

Table 1 Biological characteristics on intensive care unit admission and on day 9

Variables	Baseline	Day 9	Reference
Leucocyte count (×10^9/L)	4.46	8.22	4.02-11.42
Haemoglobin (g/L)	105	90	115-150
Lymphocyte count (per mm^3)	710	1890	1200–3600
Platelet count (×10^9/L)	86	338	150-500
Schistocytes (%)	<1		<1
Haptoglobin (g/L)	0.52	1.53	0.56–2.0
Lactate dehydrogenase (U/L)	388	298	125–245
Prothrombin time (%)	76	86	70–120
Aspartate aminotransferase (U/L)	93	39	15–37
Alanine aminotransferase (U/L)	91	43	14–59
Total bilirubin (µmol/L)	12	11	<17
Serum urea (mmol/L)	3.2	6.7	2.5–7.4
Serum creatinine (mg/dL)	0.48	0.39	0.56–1.13
Proteinuria (g/L)	1.81	0.40	<0.1
Proteinuria:creatininuria (g/mmol)	0.14		<0.1

TREATMENT

The patient received mechanical ventilation with a lung protective strategy[12 13] for moderate ARDS. She developed severe hypertension (180/83 mm Hg) despite adequate sedation. Persistent severe hypertension required an intravenous infusion of nicardipine and labetalol and an intravenous infusion of magnesium sulfate.

Empiric antibiotic treatment including cefotaxime and spiramycin was started on admission and stopped at 48 hours in the absence of any argument for a bacterial infection.

Recent studies have reported a high prevalence of thrombotic events in COVID-19.[14] In pregnant women, the physiological hypercoagulability state and reduced mobility may increase this risk of thrombotic-related morbidity.[15] Thus, thromboprophylaxis using low-molecular weight heparin was administered (enoxaparin 40 mg two times per day).

Corticosteroid treatment for fetal lung maturation was discussed when a caesarean section for maternal indication was contemplated. This treatment was withheld as the diagnosis of pre-eclampsia was ruled out and maternal respiratory status stabilised.

OUTCOME AND FOLLOW-UP

Since the diagnosis of pre-eclampsia was ruled out on the above arguments, repeated discussion with the obstetrical and intensive care teams led to the decision to continue pregnancy until the fetus might be delivered without excessive risk of prematurity despite the mother's critical respiratory condition. Regression of hypertension and of abnormal tendon reflexes allowed for discontinuation of antihypertensive medications and of magnesium sulfate. Laboratory abnormalities resolved. This reinforced the decision to let the pregnancy evolve. Indeed, favourable respiratory evolution allowed weaning from mechanical ventilation after 10 days and discharge from hospital on day 19.

On 24 May 2020, she spontaneously delivered a healthy eutrophic boy at 33.4 WG. A nasopharyngeal swab for SARS-Cov-2 was negative by reverse transcription-PCR.

DISCUSSION

Some biological disorders linked to SARS-CoV-2 infection may mimic pre-eclampsia: sFlt-1 to PlGF ratio takes a major value in such context

In this case, severe hypertension and biological disorders suggested the diagnosis of pre-eclampsia. The modesty of proteinuria did not rule out this diagnosis since, according to the New York Heart Association (NYHA) consensus for hypertension during pregnancy, proteinuria is not mandatory to ascertain diagnosis.[16] A diagnosis of HELLP syndrome was evoked despite the modesty of haemolysis.

HELLP is an acronym which refers to the triad of microangiopathic haemolysis with elevated liver enzymes and a low platelet count. HELLP syndrome is a serious complication of pre-eclampsia with both high maternal mortality and morbidity and possible fetal death or induced prematurity. Delivery is the cornerstone of treatment for this complication.

Some biological disorders linked to SARS-CoV-2 infection associated with hypertension may mimic a pre-eclampsia or a HELLP syndrome.

Determination of the sFlt-1 to PlGF ratio is a major diagnostic tool for pre-eclampsia. Indeed, a ratio of 38 or lower has a strong negative predictive value.[11]

Fetal extraction is the cornerstone of treatment for this syndrome and was contemplated. Before taking this grave decision, which would result in the birth of an extremely premature infant with low or no chance of survival, we decided to take the sFlt-1 to PlGF ratio into account. This ratio, when normal, has good negative predictive value. The sFlt-1 to PlGF ratio was as low as 13 and strongly argued against a diagnosis of pre-eclampsia.[11] This reassuring result and the patient's stable condition under mechanical ventilation allowed us to defer delivery. Active surveillance of clinical and biological status of the patient continued. Normalisation of blood pressure allowing for cessation of antihypertensive treatment and a rapid increase in platelet count and normalisation of liver enzymes definitively ruled out HELLP syndrome.

A recently issued paper[17] deals with COVID-19 mimicking pre-eclampsia. However, the study reports several cases of severe COVID-19 pneumonia but does not give a definition for it (no detail on oxygenation nor chest X-rays), and contrarily to our case none of the reported patients needed mechanical ventilation. In addition, caesarean section was decided based on pneumonia severity (here also without definition) in most cases. This is in contrast to our case which shows that even in a dramatic condition, pregnancy can continue in a mechanically ventilated patient under strict surveillance and lead to natural delivery.The statement from the patient shows how she was happy with our approach.

Role of corticosteroids in this context

Such treatment might have been discussed in order to both hasten fetal lung maturity and improve the chance of survival during COVID-19. However, the evidence in favour of a beneficial effect of corticosteroids during severe COVID-19 was not available when we cared for this patient. In addition, French health authorities warned against the use of corticosteroids pending an adequate trial be available. Dexamethasone for fetal lung maturation was discussed but not administered at the time of hospitalisation in the ICU as the French recommendations are to administer only one course of corticosteroids. This treatment is thus only given when a delivery in the next 4 weeks is highly probable, which was not judged to be the case at this point.[18]

Pregnancy may be continued during COVID-19 infection despite ARDS

This case illustrates the possibility that ARDS due to COVID-19 in a pregnant patient can completely resolve while pregnancy continues, allowing for the delivery of a healthy baby 8 weeks after recovery.

A recent study did not suggest an increased risk of severe COVID-19 in pregnant women. However, a caesarean section rate as high as 93% (63 of 68) has been reported.[19] Almost half of births were preterm in women with severe disease and resulted from the decision to end pregnancy in the hope of improving maternal condition.

Our case suggests that in the absence of fetal distress, without other complications and if the respiratory condition is controlled, pregnancy should be allowed to continue under strict surveillance during COVID-19 infection complicated by

Patient's perspective

I don't really know where to start and what to write so I start from the beginning. I remember arriving at Louis Mourier's emergency room because I could hardly breathe, I never thought I would have been positive for COVID-19 as this virus and its related symptoms were unknown to the vast majority including myself at this moment. I was then told that I was positive for COVID 19 and that I had to stay in the hospital, I remember putting on the gown. It's a bit fuzzy but I can also remember 'the oxygen I had in my nose' as was the case for several other patients in the emergency room. The nurses insisted on the importance of this oxygen 'mask'. She shouted, 'it's important to keep your masks on, you need oxygen'. And then nothing, I don't remember anything, intubation, coma, nothing. I woke up in this white room, still with this oxygen 'mask', with the device that takes the blood pressure from the arm that is tightly tied up. I don't know why but I felt both fear and pain. To tell the truth I didn't understand what was happening but I was afraid of the dreams I had. Strangely I remember those dreams, where I prayed that I could raise my two-year-old son that I had after 6 years of marriage. This first child was so long awaited that even in my dream I did not want to abandon him. He was born prematurely (31 WG) and he still needs me, I could not abandon him. I had to wake up! I encouraged myself in my dream. This dream, where I was in a judgment and I had to present myself but my turn never came. People passed in front of me and I insisted on presenting myself in vain…and still full of other dreams. So I woke up with a big fear and anxiety, I ripped the catheter out of my wrist, the tapes I had and I asked to go home. I didn't understand, and then doctors arrived I think, wondering if I wanted to see my husband. I had missed him so much. My husband arrives (his presence has motivated me so much for the future) and tells me that I have been in a coma for 2 weeks… the shock! Who could sleep for 2 weeks I didn't understand… He tells me that I am still pregnant and that the baby is fine too. I didn't understand why I would not still be pregnant. I listened to what I was told but didn't understand too much. If I'm not mistaken once I woke up, I spent 3 days in that white room, or rather 3 long nights. Time didn't go by, I missed my family, but this lack also motivated me. The more I listened to the nurses, the faster I would be out (I remember not being a very wise patient). Now I can free up a room, the doctors tell me I'm fine, and I go down to the maternity ward for a week. Finally, my discharge is organised, I am followed very closely by the gynaecology team. We have the results of the ultrasounds of the MRI and blood tests and baby is very well. For my part, I cannot say that I am in great shape, but I have made a lot of effort to be well. I walk but I always need rest, my legs are very heavy, I use my arms too but they tire me very quickly. At 33.4 WG, my membranes rupture and I feel contractions. I am taken in charge very rapidly in the obstetrical emergency room and I give birth very quickly. HE is finally here, my little premature soldier and he is doing well, even very well, a long way like his brother, but all that is behind us. I still ask my husband many questions who has also been very disturbed, I ask the doctors, we do a lot of research on my case and similar cases. I also learn around me that some women in my case have had caesarean section. In this way, I would like to thank all the doctors who made the decision not to end my pregnancy while I was in a coma and who did the best they could to keep me alive. We are all doing very well.

Learning points

- The COVID-19 infection itself should not be an indication for delivery.
- In the absence of fetal distress and if the respiratory condition is controlled, pregnancy may be continued during COVID-19 infection despite acute respiratory distress syndrome.
- Signs and symptoms of pre-eclampsia may be confused with biological disorders caused by severe COVID-19 infection.
- A normal serum soluble fms-like tyrosine kinase-1 to placental growth factor ratio is an important clue against the diagnosis of pre-eclampsia and takes a major value in such context.
- Multidisciplinary teamwork and personalised management are essential to provide the best possible care for pregnant women with COVID-19 infection.

ARDS, even at the price of prolonged mechanical ventilation. Fetal extraction should be carefully discussed and should in no way be systematic.

In this context, personalised decision, considering maternal and fetal clinical conditions, is essential. Successful evolution was the result of a multidisciplinary teamwork.

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