

Placental pathology concerning sudden foetal demise in SARS-CoV-2 positive asymptomatic pregnant female

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Aims. Coronavirus disease 2019 is responsible for a worldwide increase in morbidity and mortality. The relationship of this infection to mother-to-child vertical transmission has not been elucidated yet. However, recent reports indicate a foetal death rate of up to 3%.

Methods. We report a case of sudden pre-term foetal demise in a woman positive for SARS-CoV-2 but asymptomatic, with physiological course of pregnancy.

Results. One of the possible explanations of sudden foetal death may be acute placental insufficiency caused by a SARS-CoV-2 placental infection or the development of foetal inflammatory response syndrome (FIRS).

Conclusion. Considering the potential risk of foetal demise, questions remain regarding foetal monitoring and the timing of labour and delivery in the second and third trimesters, particularly in asymptomatic or mild maternal SARS-CoV-2 infection. A relevant multidisciplinary team must also be aware of these risks associated with possibly fatal consequences.

Key words: SARS-CoV-2, COVID-19, placenta, foetal demise

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by a novel coronavirus, now called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The vast majority of those infected are asymptomatic or have only mild to moderate cold- or flu-like symptoms. Cough, fever, and dyspnoea are other relevant symptoms. Serious complications, such as pneumonia and severe hypoxia, have been reported in patients with COVID-19, particularly in the elderly, immunosuppressed patients, and those with chronic diseases (e.g., diabetes, cancer, and chronic lung disease). In association with the occurrence of new virus mutations, a tendency for an increase in SARS-CoV-2 positivity in the younger population has occurred. However, these symptoms and complications may also occur in pregnant women. The relationship of this infection to mother-to-child vertical transmission has not been elucidated yet. However, recent reports of the Centers for Disease Control and Prevention indicate a foetal death rate of 2.2%-3% (ref.^{1,2}). It seems that one of the main causes of intrauterine foetal death may be morphological and functional changes in placental tissue³. We report a case of foetal demise in a woman positive for SARS-CoV-2 but asymptomatic.

CASE REPORT

A 21-year-old secundigravida primipara with controlled hypothyroidism in her personal history and normal course of

pregnancy, together with negative prenatal screening (including ultrasound, toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and human immunodeficiency virus), tested positive for SARS-CoV-2 at 29+2 weeks of gestation. She had no COVID-19 symptoms, and she was followed by the outpatient department. The results of cardiotocography (CTG) and ultrasound (US) at 30+4 weeks of gestation (9th day of SARS-CoV-2 positivity) were normal. CTG revealed a heart rate of 150 bpm, variability of undulatory type, spontaneous accelerations, no decelerations, and no contractions (Fig. 1). US revealed BPD 79 mm, HC 306 mm, AC 253 mm, FL 62 mm, EFW 1,659 g +/- 242 g (51.8% Williams), normal placental appearance, normal Doppler flow parameters (UA-PI 0.73, MCA-PI 1.58, and CPR 2.16 (52nd percentile)), cervical length 30 mm, and no cervical funnelling. The patient was admitted to the hospital 4 days later at 31+1 weeks of gestation with mild vaginal bleeding, no presence of foetal movements, and no signs of rupture of membranes. Maternal vital signs were normal (BP 138/84 mmHg, HR 88 bpm, BT 36.0 °C, and SpO₂ 99%). US confirmed foetal asystole. Uncomplicated induced labour and delivery were finished within 3 h. A female foetus with a weight of 1,650 g and length of 41 cm was delivered with no morphological abnormalities. Maternal laboratory parameters were as follows: predelivery – WBC 8.9 x 10⁹/L, Hb 13.7 g/L, Hct 0.42, PLT 134 x 10⁹/L, CRP 33.7 mg/L and postdelivery – WBC 9.8 x 10⁹/L, Hb 11.3 g/L, Hct 0.34, PLT 124 x 10⁹/L, and RT-PCR anti-SARS-CoV-2 positive, respectively. The patient was discharged home the same day with a normal postpartum course.

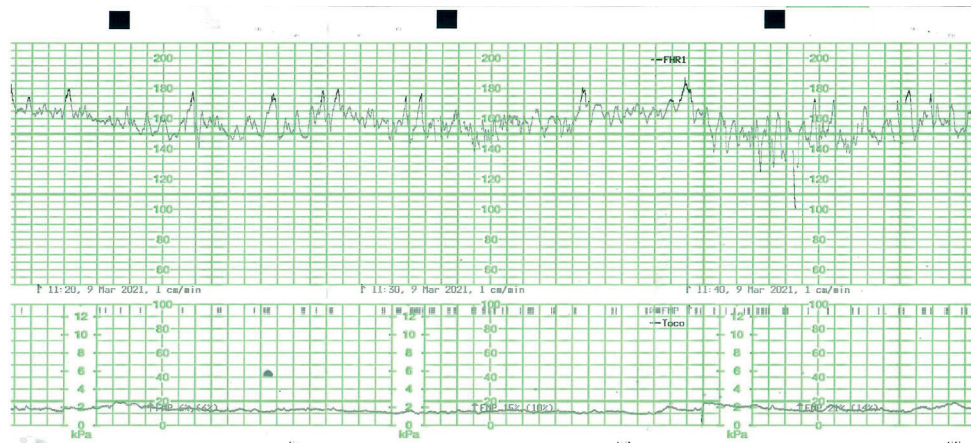


Fig. 1. Cardiotocography at 29+2 weeks of gestation.

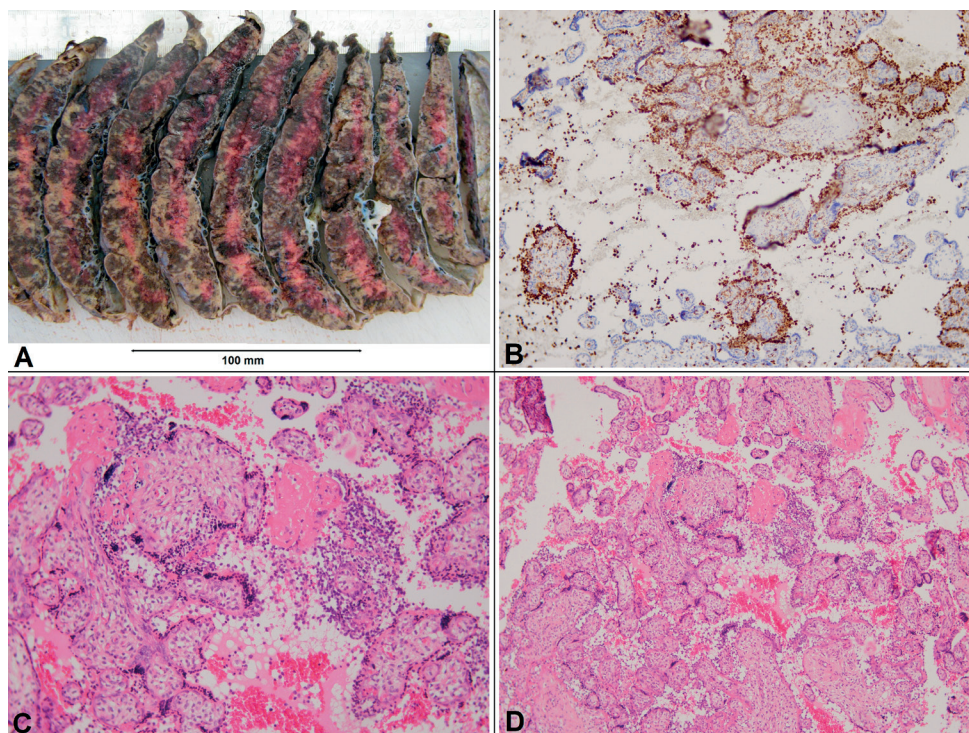


Fig. 2. Histopathological assessment of placenta.

A – macroscopic appearance of the placenta; B – immunohistochemistry for histiocytic intervillitis (CD68 antibody stain, x100); C and D – remnants of hypo- and avascularised mature chorionic villi enveloped by florid, predominantly histiocytic inflammation with neutrophils, finally destroying the trophoblast, without spread into the villous stroma (Haematoxylin and eosin, x200 and x100).

Histological results confirmed a placenta with CD68 positivity (a predominantly intervillous histiocytic inflammatory reaction with dispersed neutrophils and massive fibrin deposits), “maternal floor infarctions,” mature chorionic villi, reduced and/or missing placental vascularity, absence of the trophoblastic superficial layer, and no signs of amnionitis or funisitis. Foetal organs had an appropriate degree of maturation with no morphological abnormalities (Fig. 2).

DISCUSSION

Many epidemiological studies have linked SARS-CoV-2 infection to an increase in overall morbidity and mortality worldwide. This infection is asymptomatic or with only mild flu-like symptoms in most cases. A large proportion of those affected are completely cured, but some individuals may develop post-COVID syndrome. The main organs affected are the lungs whose injury can lead to respiratory insufficiency, failure, and even death.

The main biological manifestations of SARS-CoV-2 infection are pneumocyte damage, alveolar haemorrhage, macrophage clustering, intra-alveolar fibrin exudate, interstitial fibrosis, and inflammatory infiltrate. Major vascular findings, including thrombi in medium- and large-calibre vessels, platelet microthrombi, and fibrin microthrombi, have also been detected^{4,5}.

Unlike postpartum life, where the role of respiration is taken over by the lungs, the exchange of foetal respiratory gases takes place in the placenta. It is also a natural relative barrier between mother and foetus. Therefore, it may play a significant role in the vertical spread of SARS-CoV-2 infection from mother to foetus.

Previous testing indicated a placental infection with SARS-CoV-2. Trophoblastic cells, which are in direct contact with the maternal blood in the intervillous space, showed marked expression of angiotensin-converting enzyme 2 (ACE2) throughout pregnancy. ACE2, as a receptor, mediates the entry of SARS-CoV-2 into human cells, supporting the fact that the virus can infect the placenta via a receptor-mediated mechanism. As a result, it can cross the placental barrier towards the foetus. However, such vertical transmission needs further investigation^{6,7}.

In our case, we found a placenta with CD68 positivity (a predominantly intervillous histiocytic inflammatory reaction with dispersed neutrophils and massive fibrin deposits), "maternal floor infarctions," mature chorionic villi, reduced and/or missing placental vascularity, absence of the trophoblastic superficial layer, and no signs of amnionitis or funisitis. Foetal organs had an appropriate degree of maturation with no morphological abnormalities. Our findings are in agreement with the results published by Menter et al. They documented different time points regarding SARS-CoV-2 infection. In acute COVID-19, prominent lymphohistiocytic villitis may occur and may potentially be attributable to SARS-CoV-2 infection of the placenta. Furthermore, they found histopathological signs of maternal and foetal malperfusion, and they hypothesize this may have a relationship with an altered coagulative or microangiopathic state induced by SARS-CoV-2. (ref.⁸)

Acute or chronic placental insufficiency induced by SARS-CoV-2 infection can be responsible for subsequent miscarriage or foetal growth restriction^{7,9}. Similarly, such a condition could result in foetal loss in the higher stages of pregnancy.

In addition to the morphological and functional damage to the placenta itself, the foetus may be endangered by other mechanisms. Some authors hypothesize that systemic inflammation occurs in response to maternal viral infection in the absence of vertical transmission of the virus. It will be important to consider the virus as a nidus for foetal inflammatory response syndrome (FIRS) and resulting morbidity¹⁰. A higher rate of perinatal foetal distress and admission to the neonatal intensive care unit has been identified in neonates born to mothers infected with SARS-CoV-2. (ref.^{11,12}) Neonates affected by FIRS have multiorgan system involvement and higher morbidity after adjustment for gestational age. McCarty et al. hypothesize that FIRS is secondary to exposure to mater-

nal SARS-CoV-2 infection in utero and can occur in the absence of proven vertical transmission¹⁰. Also, a novel childhood hyperinflammatory syndrome presumed to be associated with and subsequent to SARS-CoV-2 infection. The following multisystem inflammatory disorder in children (MIS-C) most commonly affects young children and is characterized by persistent fever, systemic hyperinflammation, and multisystem organ dysfunction¹³. Therefore, we can assume, FIRS secondary to maternal SARS-CoV-2 infection could be a cause of foetal and neonatal morbidity and mortality.

On the other hand, in a large, single-institution cohort study (252 tested positive for SARS-CoV-2), infection during pregnancy was not associated with adverse pregnancy outcomes. Neonatal infection may be as high as 3%, but the paradox is that it may occur predominantly among asymptomatic or mildly symptomatic women¹⁴.

In our case, there was a sudden death of the foetus, which did not show signs of chronic placental insufficiency. Its birth weight and length were appropriate for gestational age, and diagnostic methods before determining foetal death showed no pathology of the foetus, placenta, or umbilical cord. Foetal demise occurred within 4 days after the last examination, despite an asymptomatic maternal infection. Postpartum examinations showed only placental injury. Therefore, we hypothesize that one of the possible explanations may be sudden foetal death due to acute placental insufficiency caused by SARS-CoV-2 placental infection or the development of FIRS with fulminant foetal death.

The strengths of this case report include consistent prenatal screening and diagnosis of foetal well-being, reliable methods confirming maternal SARS-CoV-2 infection, and histopathological assessment by experienced paediatric pathologists. The main limitation is the single case with no foetal and placental SARS-CoV-2 RT-PCR testing.

CONCLUSION

Considering the potential risk of foetal death, questions remain regarding the manner and frequency of foetal monitoring, the decision to terminate the pregnancy, and the timing of labour and delivery in the second and third trimesters, particularly in asymptomatic or mild maternal SARS-CoV-2 infection. These questions can only be answered by further studies, but a relevant multidisciplinary team must also be aware of these risks associated with possibly fatal consequences.

ABBREVIATIONS

COVID-19, Coronavirus disease 2019; SARS-CoV-2, Acute Respiratory Syndrome Coronavirus 2; CTG, Cardiotocography; US, Ultrasound; BPD, Biparietal diameter; HC, Head circumference; AC, Abdominal circumference; FL, Femur length; EFW, Estimated foetal weight; UA-PI, Umbilical artery-pulsatility index; MCA-PI, Middle cerebral artery-pulsatility index; CPR, Cerebroplacental

ratio; BP, Blood pressure; HR, Heart rate; BT, Body temperature; SpO₂, Oxygen saturation; WBC, White blood cells; Hb, Haemoglobin; Hct, Haematocrit; PLT, Platelets; CRP - C-reactive protein; RT-PCR, Real-time polymerase chain reaction; CD-68, Cluster of differentiation 68; ACE2, Angiotensin-converting enzyme 2; FIRS, Foetal inflammatory response syndrome; MIS-C, Multisystem inflammatory disorder in children.

Author contributions: KB: manuscript writing, figures; JS: prenatal diagnosis and manuscript revision; TP, TR, EKO: literature search; JM, LP: histopathological analysis and manuscript revision; Eku: manuscript revision and approval.

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