



Case report

Intrauterine fetal demise as a result of maternal COVID-19 infection in the third trimester of pregnancy: A case report

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ABSTRACT

Introduction: As the global pandemic continues, more information is being collected on the incidence and range of adverse maternal and fetal outcomes resulting from COVID-19 infection.

Presentation of case: We present a case of a 29-year-old unvaccinated patient at 36 weeks gestation with several days of mild symptoms after testing positive for COVID-19 who presented with a complaint of decreased fetal movement and was found to have an intrauterine fetal demise. This case was further notable for thrombocytopenia, acute postpartum hemorrhage and placental histologic findings showing morphologic changes consistent with previously reported pathology seen with maternal COVID-19 infection including marked perivillous fibrin deposition and marked acute and chronic intervillousitis.

Discussion: This case, combined with other similar reports in the literature, supports the conclusion that COVID-19 infection in pregnancy can result in severe perinatal adverse consequences regardless of initial maternal symptomatology.

Conclusion: Pregnancies affected by COVID-19 may benefit from a higher level of surveillance and proactive care and further research is warranted.

1. Introduction

As the Coronavirus presented in late 2019 and progressed into a global pandemic, more research has been conducted to investigate and better predict its outcomes. The potential health risks for research personnel are unknown, creating obstacles for the research of COVID-19 [1]. Amongst research of COVID-19 and pregnancy, attempts are being made to understand the transmission from mother to infant and its effects in entirety. Studies have indicated an increased incidence of fetal demise in pregnant women with COVID-19 versus COVID-19 negative pregnant patients [2]. Although there has been a reported rise in fetal demise with COVID-19 positive pregnancies, a study comparing pre-pandemic pregnancy outcomes and outcomes during the pandemic revealed no significant increases through December of 2020 [3], suggesting that these recent and consistent findings of COVID-19 positive mothers and fetal repercussions could be due to the manifestation of the Delta variant [3].

These COVID-19 positive pregnant patients have mild symptoms, yet thrombocytopenia has been a common finding in about one-third of the cases [4]. Studies have shown placental evidence associated with

COVID-19 positive pregnancies, including histological and molecular features of severe injury, supporting the presence of the physiologic changes that could be responsible for these outcomes [5,6]. Histological consistencies with COVID-19 positive placentas have massive fibrin deposition, trophoblast necrosis and what is now called "SARS-CoV-2 placentitis." The viral infection leads to placental hypoperfusion and poor exchange of oxygen and nutrients, resulting in intrauterine growth restriction or fetal demise [7,8]. Mechanisms are hypothesized in which the COVID-19 virus uses specific receptors to gain entry and cause architectural change to the placental tissue [9,10].

We present a case of a mildly symptomatic COVID-19 positive patient at 36 weeks gestation who was admitted due to reported decreased fetal movement and inability to detect fetal heart tones. This case was complicated by thrombocytopenia found on complete blood count at the time of admission and placental pathologic findings revealing morphologic changes consistent with COVID-19 effects. This case report has been reported in line with the SCARE Criteria [11].

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2. Patient information

A 29-year-old patient was gravida 3 para 1 who had not been vaccinated against COVID-19 was presented complaining of decreased fetal movement at 36 weeks gestation. The patient had no history of thrombocytopenia or elevated liver transaminases, with prior platelet count of 317×10^3 mL. Past medical history and labs before and during routine prenatal visits were unremarkable. Based on this presentation, COVID-19 infection was initially considered as the most likely etiology for the constellation of signs and symptoms due to lack of other evidential causes or findings.

3. Clinical findings

Vital signs on admission included a blood pressure of 122/73 mm Hg, pulse of 111 bpm, respiratory rate of 19 bpm, temperature of 36.7 °C, and oxygen saturation level of 99 %. Fetal heart tones were undetectable by doppler, and a bedside ultrasound confirmed absent fetal cardiac activity. A complete blood count collected was significant for a platelet count of 46×10^3 mL and elevated ALT and AST at 116 U/L and 84 U/L, respectively.

3.1. Timeline

She reported having had a positive COVID-19 test 5 days prior with symptoms of anosmia and low-grade fevers for the past 5 days which were treated with over-the-counter acetaminophen. Decreased fetal movement at 36 weeks was detected and ultrasound confirmed the termination.

Labor was induced with misoprostol and oxytocin.

3.2. Diagnostic assessment and interpretation

Neuraxial anesthesia is contraindicated due to thrombocytopenia and risk for epidural hematoma. The delivery of a deceased infant was completed, and lacerations are repaired with 1 % lidocaine locally and 3-0 Vicryl. The patient had ongoing bleeding after the third stage of labor of approximately 500 mL within 15 min of delivery and additional oxytocin, methergine and misoprostol was given.

3.3. Intervention

When the patient began to manifest signs of hypovolemia to include hypotension, tachycardia and presyncope symptoms, two units of packed red blood cells and 6 units of platelets were administered with resultant clinical stabilization. On postpartum day 1, repeat labs showed a platelet count of 113×10^3 mL, ALT and AST of 75 U/L and 76 U/L,

and hemoglobin and hematocrit at 7.5 g/dl and 22.8 %. The patient denied syncopal symptoms, however, was unable to void presumably secondary to vulvar ecchymosis and edema. A Foley catheter was placed and approximately 700 mL of urine output was measured. Lab values continued to improve over the next 48 h, the patient remained clinically stable and was eventually able to void spontaneously. She was discharged on postpartum day 3 and scheduled for outpatient follow-up in 2–4 weeks.

3.4. Follow-up and outcomes

Due to suspicion of possible COVID-19 influence, the placenta was obtained and sent for a pathological analysis. Gross examination of the placental tissue reveals a tan-gray maternal surface, a blue-gray fetal surface, and a placental weight of 377 g (Fig. 1). The fetal surface contains semi-prominent vasculature and mild subchorionic fibrin deposition. Upon sectioning, a focally hemorrhagic and cystic, irregular rubbery beefy red-brown parenchyma is seen. There is a moderate amount of calcification comprising approximately 40 % of the parenchyma. Accumulation of calcifications before 36 weeks is abnormal, however, at 36 weeks it is uncertain as to when the calcifications originated. Representative sections are submitted for histologic examination.

Histologic evaluation of the placenta reveals a remarkably abnormal placental plate characterized by fetal villi encased by fibrin (Fig. 2). The perivillous space has been infiltrated by chronic inflammatory cells and numerous histiocytes. The villous trophoblasts are focally necrotic. A paraffin block of the placental plate was submitted to The Massachusetts General Hospital laboratory for SARS-CoV-2 RNA in-situ hybridization testing. The final placental pathology results reveal consistencies with “SARS-CoV-2 placentitis” and a remarkably positive stain for SARS-CoV-2 RNA in-situ hybridization. The fetal membranes were negative for acute inflammation and contained a normal three-vessel umbilical cord.

4. Discussion

As the COVID-19 global pandemic continues, the incidence of adverse maternal and fetal outcomes is increasing. Evidence is being gathered in COVID-19 positive pregnant patients, including rate of fetal demise, risk of thrombocytopenia and consistency in pathologic placental morphologies. This case, along with other similar reports in the literature, supports the conclusion that COVID-19 infection in pregnancy can result in severe perinatal adverse consequences regardless of initial maternal symptomatology.

The histologic features found in this case- perivillous fibrin deposition, histiocytic intervillitis, and trophoblast necrosis - have been increasingly recognized in placentas infected with the SARS-CoV-2 virus

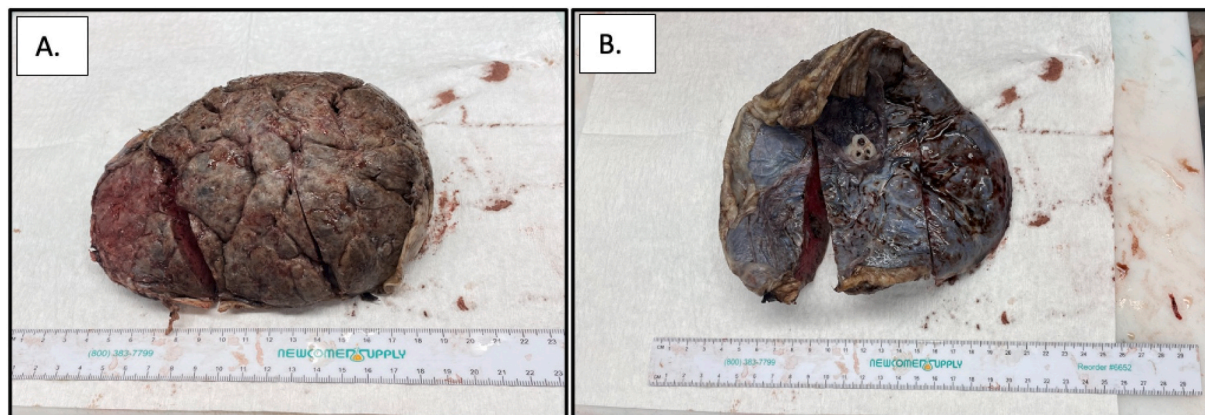


Fig. 1. Gross examination of placenta A. Maternal surface of placenta. B Fetal surface of placenta.

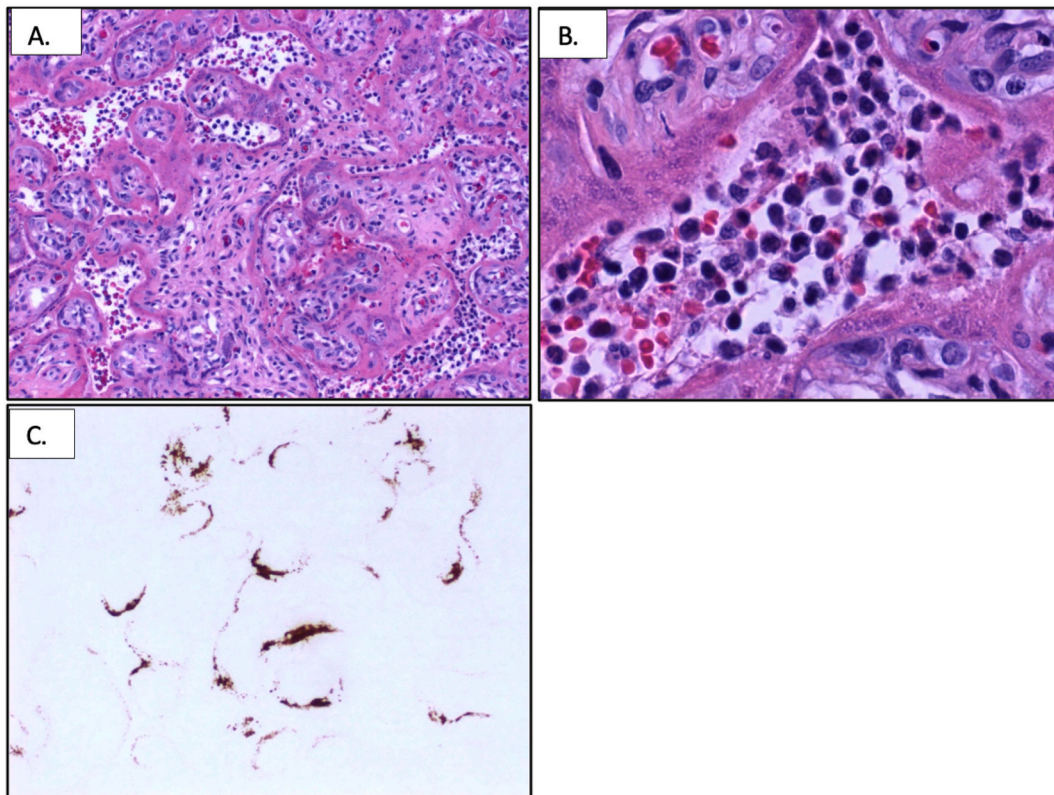


Fig. 2. Microscopic examination of placenta. A. Low power view of intervillous space with perivillous fibrin deposition, intervillitis, and trophoblast necrosis (H&E, 100 \times). B. High power view of intervillous space with abundant lymphocytes, histiocytes and neutrophils (H&E, 400 \times). C. Strongly positive SARS-CoV2 in situ hybridization (ISH) stain in villous trophoblasts (H&E, 100 \times).

and has recently been designated as “SARS-CoV-2 placentitis” (Fig. 2) [7,8]. The findings seen in SARS-CoV-2 placentitis have been previously described in the absence of infection by the virus and are strongly associated with adverse fetal outcomes [8]. Similarly, preliminary data suggests that these findings, in association with SARS-CoV-2 positivity in the placenta, are also associated with preterm birth, intrauterine growth retardation, and stillbirth [7]. The mechanism of the massive placental injury appears to be complement mediated, an exaggerated immune response to the virus in the placenta and is postulated to be similar to the effect of the virus within the lungs in severe SARS-CoV-2 infection [7]. In most cases, transplacental transmission to the fetus has not been documented; adverse fetal outcomes seem to be a result of severe placental injury, rather than SARS-CoV-2 infection in the fetus [8].

Our patient presented with mild symptoms of COVID-19, commonly found in both pregnant and non-pregnant COVID-19 patients. However, studies have shown commonality specifically in mildly symptomatic COVID-19 positive pregnant patients with adverse maternal and fetal effects, including an increased risk of thrombocytopenia. Although the exact mechanism for the thrombocytopenic effects is unknown, support for consumptive coagulopathy has been found in approximately one-third of COVID positive pregnant patients [4]. Even with mild symptoms, the virus appears to affect the morphology of the placenta in a manner that compromises its competence, therefore impacting blood supply to the fetus. Evidence has shown that viral load may play a role in the severity of the pathological morphology found in placental tissues infected with COVID-19 - the higher the viral load, the more severe pathological features have been found, and higher risk for adverse outcomes for the fetus. It is also noted that these severe adverse outcomes occur in the absence of vertical transmission [5]. This increase in consequential fetal outcomes in pregnant patients with COVID-19 became prevalent as the Delta variant began to manifest. This may

suggest that the increase in virulence of the Delta variant could be playing a role in the more recent findings of such negative fetal outcomes in these patients that were not present during the initial year of the pandemic. Further research is warranted on the effects that may be specific to the COVID-19 Delta variant and others to follow.

Placental findings in positive COVID-19 mothers reveal a viral protein, Co-V-2 spike glycoprotein, that is absent in control placental tissue in COVID-19 negative patients. This protein is present in the villi of placental tissues, despite evidence of vertical transmission. Along with Co-V-2, the viral entry protein ACE2 was found to be a target in infected pregnant patients. Both viral proteins are consistently found in the placental villi that are located near the maternal blood supply [9]. The virus uses ACE2 as its functional receptor in entering the human body. Consequences to the placenta after entry included sub-villous fibrin deposition and nonvascular fibrotic villi, which result in growth retardation and oligohydramnios in the fetus.

Due to these findings, COVID-19 positive pregnant women may benefit from pathological assessments of the placenta to determine the severity from the infection. Results of the infection on fetuses showed that organs with high ACE2 receptor expression were targeted and became hypo perfused, including the placenta. This ultimately leads to lack of blood supply and nutrients, having severe consequences ranging from growth restriction to death [10].

This case presents a severe adverse outcome to the COVID-19 infection in the third trimester of pregnancy and further supports the recognition that pregnancies affected by COVID-19 may benefit from a higher level of surveillance and preventative care including vaccination. The pathological morphologies found in this case plan to be further evaluated by placental specialists.

4.1. Patient perspective

N/A.

4.2. Informed consent

No identifying information is included in this report.

5. Conclusion

Most COVID-19 positive pregnant patients report mild symptoms that resolve in days to a week. Although mild, more severe morphologies can be occurring within placental tissue that can affect the status of the fetus. There are pathological findings that are consistent on placental tissue analysis in COVID-19 positive patients. Even without evidence of vertical transmission, the conditions of the placenta can severely impact the growth and development of the fetus – and in this case – cause fetal demise. As these findings are consistent with COVID-19 pregnancy as a likely manifestation of the Delta variant, additional precautions may be warranted with future variants which will be of undetermined virulence. Prevention and treatment strategies, including vaccination, should be further investigated as effective methods to reduce the incidence of such outcomes, and more research is warranted.

Clinical images and videos

N/A.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Consent

No identifying information in included in this report.

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Credit authorship contribution statement

Janna Summerall-Smith, MD provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; Bonnie Watkins provided analysis and interpretation of data; Tayler F. Gant, OMS IV drafted the article or revised it critically for important intellectual content; Timothy P. Villegas, MD gave final approval of the version of the article to be published; and all authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of competing interest

N/A.

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