



Title: Preterm delivery in pregnant woman with critical COVID-19 pneumonia and vertical transmission

Short title: Corona virus infection and vertical transmission

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Bulleled Statements:

What's already known about this topic?

Vertical transmission due to intrauterine infection has not been reported in pregnant women who develop COVID-19 pneumonia in late pregnancy.

What does this study add?

Amniotic fluid and infant PCR test was positive for COVID-19 infection. This case study raises concerns again about possible vertical transmission of COVID-19 in pregnant women infected by SARS-CoV-2 especially in critical case that undergo pregnancy termination.

Background:

Since December 2019, the novel coronavirus disease (COVID-19) infection has spread quickly from China to different parts of the world including Iran¹. Since February 18, 2020, over 12,000 confirmed cases of COVID-19 have been reported in Iran, and more than 150,000 cases in numerous other countries worldwide, with an around 3-4% mortality rate as up to March 15. One of the most important ways of viral transmission is the individuals contact in hospitals, inside families, and other crowded places, but still no finding is reported on the optimal treatment modalities or vaccines¹⁻³.

Clinical presentation:

On March 7, 2020, a 22-year-old female, who was 32-weeks pregnant, presented at emergency clinic of Imam Khomeini Hospital, Sari, Iran, with dyspnea, myalgia, anorexia, nausea, non-productive cough and fever during the fourth days before. She also had a history of controlled hypothyroidism. Her first physical examination revealed oral temperature= 37.6°C , O_2 saturation=85% with Venturi mask at 5 liters per minute of oxygen, RR=26/minute and

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respiratory distress. Lung auscultation revealed fine rales and absence of breath sounds over the left lower lung zone. She had lost her uncle a week before due to COVID-19 pneumonia. Given the patient's history and fever and cough, two nasal and throat swab samples were taken and tested to be positive for SARS-CoV-2 with SuperScript III Platinum, Quantitative Real-time PCR system Kits (Invitrogen company, USA)⁴. Chest X Ray and Chest computed tomography (CT) scan on March 8 revealed left-sided atelectasis in inferior zone and bilateral ground-glass opacities (Figure 1). Accordingly, she was isolated at Intensive Care Unit (ICU) in a negative pressure room at Imam Khomeini Hospital of Mazandaran University, the elected medical care unit for COVID-19 in Sari. Other laboratory findings included a leukocyte count of $7.80 \times 10^9/L$, neutrophils of $9.00 \times 10^9/L$, lymphocytes of $1.00 \times 10^9/L$, C-reactive protein of 32.9 mg/L. Serum levels of aminotransferase, and normal LDH. A routine pregnancy ultrasound showed a fetus with normal structure of about 30 weeks+2 days of gestational age.

On admission, treatment with Azithromycin (500mg administered intravenous every 12 hours), Ceftriaxone (1000mg every 12 hours), Kaletra (Lopinavir/ritonavir 200mg orally daily), and Tamiflu (capsule Oseltamivir oral 400mg every 12 hours) and hydroxy chloroquine (400 mg daily) were initiated, neuroprotective prophylaxis as magnesium sulphate or corticosteroid for the fetus were not administered due to unknown harmful effects on maternal condition. Since, COVID-19 is a recently recognized virus and only limited women underwent cesarean delivery till now on March 15, fear of viral shedding and vertical transmission during vaginal delivery resulted in avoidance of this fetal exposure. A multidisciplinary working team was convened,

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and based on the CT scan, low lymphocytes counts and presence of the illness, which was worsened gradually during the following three days, unfavorable cervix for induction, cesarean indication was made to terminate pregnancy instead of preterm pregnancy. Informed consent was obtained and patient underwent cesarean delivery with General analgesia due to anesthesiologist preference and patient's condition on March 11. All exposed personnel physicians wore protective equipment including gowns, N 95 mask, glasses and gloves. A preterm female infant weighing 2.35 kg was delivered uneventfully, with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. She was kept in the isolated NICU without any contact with her mother after birth. The infant was given powdered milk as a substitute of breast milk. Prior operation sample of vaginal secretion with Sterile cotton soap was obtained. During the cesarean section, 5ml of amniotic fluid was aspirated into a sterile syringe with a needle after uterine incision exactly before tearing of the membrane by gentle traction. Then the needle was removed and the amniotic fluid sample placed into sterile tubes containing 3ml of viral transport media (VTM). After delivery of the neonate, 5 ml of umbilical cord blood was aspirated and transferred to subsequent VTM. These samples immediately transferred to a specified virology center for COVID-19 with sterile, cold box (4). After delivery, nasal and first throat swabs of the newborn were obtained for COVID-19 RT-PCR tests, and all tests were negative except for amniotic fluid sample. However, the second neonate test was positive 24 hours later. After cesarean delivery, patient's dyspnea (Respiratory rate=30-35) continued and O₂ saturation was about 75-85% with nasal CPAP (continuous positive airway pressure therapy). In the fourth and six days of

operation (March 15 and 17), the patient underwent peritoneal dialysis due to ARDS. After that, she underwent single dose Remdesivir (200 mg iv single dose stat and 100 mg daily) and Prednisolone 100 mg daily. Then, her general appearance slightly improved. Nonetheless, she underwent intubation due to suddenly oxygen desaturation up to 70 % on March 21. She developed emphysema after intubation that resolved spontaneously on March 23. Her pulse rates were about 116-120 per minute and her oxygen saturation was about 85-97 % till March 24. But, she found fever on march 25 and ultrasonography found no important findings. Amikacin added to another drug administrated. Her condition dramatically worsened. Unfortunately, she died from this critical disease on March 26 at midnight.

Her neonate developed fever on birth and underwent Ampicillin and gentamicin without any antiviral drug due to pediatric team decisions. She nourished with formula and kept away from the mother. Third and fourth neonate's PCR test was positive one week later, but she was good.

Discussion:

Respiratory infection caused by novel corona virus as SARS-CoV-2 (COVID-19) recently recognized in Wuhan in China on December 31, 2019 and speared to different parts of the world including Iran¹⁻³. It is believed that Person-to-person contact and transmission of SARS-CoV-2 as droplet to be a major means of transmission, like another type of influenza.

When the infected person coughs or sneezes, these droplets can infect the environment about 6 feet⁵. Additionally, pregnant women with different kinds of viral pneumonia are at risk of

exacerbation and increasing adverse obstetric and perinatal outcomes compared with non-pregnant women, due to changes in the immune system as well as physiologic adaptation change in pregnancy like elevation of diaphragm⁶.

In this present study, we presented a pregnant woman with severe COVID-19 pneumonia who delivered a healthy preterm baby with no evidence of COVID-19 in her 32 weeks of gestation. Her RT-PCR test for COVID-19 was positive for amniotic fluid sample and second neonate nasal and throat test, but negative for vaginal secretion or umbilical cord blood or first neonate test. Also, her respiratory distress continued and exacerbated in postpartum period which required peritoneal dialysis to improve maternal health. The RT-PCR tests was positive for amniotic fluid and neonate, suggesting the infant might have been affected intrauterine by COVID-19; therefore, once more, it raised the concerns regarding possible vertical transmission of the virus in mothers with serious illness. Two prior research revealed possible vertical transmission from mothers with SARS CoV-2 in three neonates due to increased neonatal specific IgM antibodies at birth^{7, 8}. However, we couldn't measure neonate specific IgM antibody due to unavailability that may better interpret these results.

The serious maternal outcomes in this patient could be interpreted in different ways. Her relative died from COVID-19; Therefore, she was possibly exposed to a more invasive kind of viral infection that made her vulnerable to severe viral pneumonia of COVID-19. She attended the hospital four day after initiation of disease. Timely testing of SARS-CoV-2 and later gestational age are important factors for successful treatment, but our patient had delay in attending the

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hospital, that could affect treatment quality. She has no underlying disease except for controlled hypothyroidism that could not be considered as a significant risk factor for pathogenicity of virus but invasive nature of the diseases and delay in treatment had important roles in her prognosis. Also, her baby weight was about 2.35kg that was greater than the estimated normal fetus weight in 32 weeks (1800 kg), but we didn't have abnormal blood sugar test in this setting. Hence, we encounter severe features of the disease. The patient in our study was managed by a multidisciplinary team, including perinatologist, two obstetricians, pediatrics, expert in infectious diseases, Lung specialist, anesthesiologist, ICU specialists. Appropriate consultations were provided to her family. Isolation of the neonate was even more important. In this case, we tried to observe sterility in all procedures, so the risk of contamination is unlikely, but, caution should be considered in interpreting the data. In some previous studies, the authors reported 21 healthy babies delivered by infected mothers to COVID-19, but they could not detect the virus in any of the fetomaternal parts namely placenta, amniotic fluid and cord blood⁹⁻¹¹. In contrast to our study, in these studies, none of the mothers need mechanical ventilation or died; therefore, the severity of their disease is less and it could explain the possible relationship between mother's illness and amniotic fluid and neonatal infection in our study that should be confirmed in the future. We did not measure RNA viral load in the mother and specific neonatal IgM antibody in neonate prior to delivery, but future researches can examine viral load and vertical transmission in infected mothers with COVID-19 specially in severe or critical conditions. We didn't plasma convalescent as a new modality for this patient, but it has known effectiveness in SARS and

Ebola infection and etc. Another researches suggested that it has theoretically more effectiveness at the early stage of disease, but could be considered as the last option in patients with SARS whose condition continued to deteriorate despite another treatment¹².

The current case study, once again, raises concerns regarding possible vertical transmission of COVID-19 in pregnant women infected by SARS CoV-2 in contrast to the findings reported in some small studies published previously. Cumulative data of pregnant women infected by COVID-19 are necessary to better knowledge the global influence of SARS-CoV-2 on maternal and fetal health.

Disclosure of interests

The Author's had no financial, personal, political, intellectual or religious conflicts of interest.

Ethical statement

The work was approved by the ethics committee of Mazandaran University of Medical Sciences. Informed consent was obtained from the patients and her husband.

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Figure 1. High-resolution CT-Scan in 32-week pregnant woman with COVID-19 pneumonia.