Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

International Journal of Infectious Diseases 125 (2022) 192–194

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Case Report

SARS-CoV-2 vertical transmission in a twin-pregnant woman: a case report

Rosa Sessa[1], Luisa Masciullo[2], Simone Filardo[1,*], Marisa Di Pietro[1], Gabriella Brandolino[2], Roberto Brunelli[2], Paola Galoppi[2], Gianluca Terrin[2], Maria Federica Viscardi[2], Emanuela Anastasi[3], Maria Grazia Porpora[2]

[1] Department of Public Health and Infectious Diseases, Microbiology Section, "Sapienza" University of Rome, Rome, Italy
[2] Department of Maternal and Child Health and Urology, "Sapienza" University of Rome, Rome, Italy
[3] Department of Experimental Medicine, "Sapienza" University of Rome, Rome, Italy

ARTICLE INFO

Article history:
Received 17 June 2022
Revised 26 September 2022
Accepted 14 October 2022

Keywords:
SARS-CoV-2 infection
Vertical transmission
Pregnancy
Placenta
Obstetric outcomes

ABSTRACT

SARS-CoV-2 has affected millions of people around the world in recent years. Among susceptible patients, pregnant women seem to be prone to serious complications. The possibility of SARS-CoV-2 vertical transmission represents one of the most debated topics in the literature, providing inconclusive results. We present a case of a confirmed vertical transmission in a monochorial diamniotic twin pregnancy complicated by a selective intrauterine growth restriction and gestational diabetes mellitus. The analysis of different biological specimens identifies the presence of the SARS-CoV-2 genome in the umbilical cord blood of both twins, and the placental histologic examination confirmed indirect signs of viral infection, supporting the hypothesis that a transplacental infection can occur. Despite the devastating impact that SARS-CoV-2 has worldwide, neonatal infections have been infrequently reported, but they can occur under certain biologic conditions. Deep knowledge of the biological mechanisms underlying the risk of SARS-CoV-2 vertical transmission might be useful to understand the pathophysiological bases and the possible long-term implication of a mother-to-child vertical transmission.

Introduction

SARS-CoV-2 represents one of the most threatening infections in the last century, affecting millions of people worldwide (World Health Organization, 2020) (covid19.who.int).

It exhibits a great variety of clinical manifestations, which can be worsened by preexisting risk factors such as hypertension, diabetes mellitus, and cardiovascular and respiratory diseases (Allotey et al., 2020; Huang et al., 2020).

Pregnant patients seem to be prone to serious complications, in fact, affected women are more likely to have adverse obstetric outcomes like preterm birth, intrauterin growth restriction, preeclampsia, and stillbirth (Allotey et al., 2020; Jamieson and Rasmussen, 2022; Porpora et al., 2021), compared to the uninfected pregnancies.

Different mechanisms are involved in the pathogenesis of SARS-CoV-2 vertical transmission (Jamieson and Rasmussen, 2022; Sessa et al., 2022). International societies have proposed several antepartum, intrapartum, and postpartum strategies to contain the infection and accurately check the risk of fetal infection (El-Goly, 2021; Narang et al., 2020). In 2021, the World Health Organization prepared a scientific brief to describe a step-by-step process to screen for the possibility of vertical transmission, according to the timing of viral infection. Immediately after birth, they strongly suggest collecting nasopharyngeal swabs and blood samples from the newborn and subsequently searching for SARS-CoV-2 RNA and immunoglobulin (Ig) G and IgM antibodies against viral antigens (World Health Organization, 2021). Furthermore, histologic examination of placental tissue and microscopic evaluation of vascular damage should be undertaken to assess indirect signs of viral infection (Sharps et al., 2020). In light of the above, despite the increasing interest in the pathogenesis of SARS-CoV-2 vertical transmission, it remains a controversial issue, and the available data on evidence and management of positive cases lead to inconclusive results (El-Goly, 2021; Narang et al., 2020; World Health Organization, 2021).

* Corresponding author.
E-mail address: simone.filardo@uniroma1.it (S. Filardo).

https://doi.org/10.1016/j.ijid.2022.10.019

Case presentation

We report the case of a 29-year-old twin-pregnant woman at 33 weeks, gravida 2, para 1, who was admitted to our Obstetric Emergency room, complaining of uterine contractions. She had a monochorial diamniotic twin pregnancy complicated by a selective intrauterine growth restriction (sIUGR) and gestational diabetes mellitus type A1, according to Priscilla White's classification system (White, 1978).

The patient did not report any respiratory symptoms and denied being previously vaccinated. According to the hospital guidelines, she underwent a real-time polymerase chain reaction (RT-PCR) nasopharyngeal swab, tested positive for SARS-CoV-2, and was admitted into the COVID-19 obstetric ward.

Investigations

At the admission, she presented a body temperature of 36.5°C, blood pressure of 110/65 mm Hg, pulse rate of 80 bpm, and blood oxygen saturation of 98% in room air.

Ultrasound evaluation (US) showed fetus A with an estimated birth weight (EBW) of 1700 gr and normal Doppler velocimetry, and fetus B with an unequal placental sharing and a condition of selective intrauterine growth restriction (estimated birth weight = 1300 gr) with abnormal middle cerebral artery pulsatility index (1.23, <5° percentile for the gestational age). Amniotic fluid and placental insertion were normal. Non-stress test (NST) was reactive with occasional uterine contractions.

Her vital signs, blood tests, arterial blood gas analyses, non-stress test, and ultrasound evaluation were performed daily. Blood exams showed normal results, except for mild anemia and elevated C-reactive protein, whose values normalized during the hospitalization.

Treatment

Because she did not suffer from any respiratory symptoms or other medical conditions, according to the indication of the infectious disease specialist, she did not undergo any antiviral treatment. The arterial blood oxygenation was normal, so she did not require any non-invasive ventilation or supplemental respiratory imaging.

She only received a daily injection of enoxaparin 4000 International Units and 12 mg of intramuscular dexamethasone for 2 days to induce the twins' lung maturation. Fetal well-being was checked by daily cardiotocography.

Ten days later, the patient exhibited painful uterine contractions, and an emergency cesarean section was performed.

Outcomes and follow-up

Two female newborns were delivered: the first weighed 1700 gr, she had an Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score of 8 and 9 at 1 and 5 mins, respectively, and her cord blood pH was 7.22 with a base excess (BE) value of -6.8. The second girl had a weight of 1500 gr and an APGAR score of 7 and 8 at 1 and 5 mins; the cord blood gas analysis showed a pH of 7.10 with a BE of -10.8.

The newborns were transferred to the neonatal intensive care unit. At the admission, they were stabilized by a neonatologist and two trained nurses. Three nasopharyngeal swabs were collected at 1 hour, 5, and 10 days after birth. All the swabs showed negative results. Conversely, the microbiological analysis of the placental tissues and the cord blood samples detected the presence of the RNA of SARS-CoV-2 in these specimens. The laboratory findings are described in Table 1.

Table 1
Determination of anti-S, anti-N antibodies, and SARS-CoV-2 RNA in maternal and umbilical cord blood samples and SARS-CoV-2 RNA in placental tissues

Samples	
Maternal blood serum	
	Antibodies concentration
Anti-S antibodies	5.5 BAU/ml
Anti-N antibodies	0.3 U/ml
	PCR results (Ct)
Gene N	Negative
Gene E[a]	Negative
RdRp	Negative
Umbilical cord blood serum (Infant 1)	
	Antibodies concentration
Anti-S antibodies	0.088 BAU/ml
Anti-N antibodies	0.4 U/ml
	PCR results (Ct)
Gene N	37,000[b]
Gene E[a]	33,871[b]
RdRp	Negative
Umbilical cord blood serum (Infant 2)	
	Antibodies concentration
Anti-S antibodies	0.087 BAU/ml
Anti-N antibodies	0.4 U/ml
	PCR results (Ct)
Gene N	35,488[b]
Gene E[a]	34,418[b]
RdRp	Negative
Placental tissues	
	PCR results (Ct)
Gene N	35,582[b]
Gene E[a]	Negative
RdRp	Negative

[a] Gene E is not specific toward SARS-CoV-2 but is present in all Coronavirus.
[b] Ct, positive if ≤ 38. BAU: binding antibodies unit; Ct: Cycle threshold; N, nucleocapsid; PCR, polymerase chain reaction; RdRp, RNA-dependent RNA polymerase; S, spike.

Histologic examination of the placenta revealed chronic intervillositis and a diffuse placental malperfusion.

Placental and cord blood samples were clotted for 60-90 mins and then centrifuged for 10 mins at 1300xg. The serum fractions were aliquoted and stored at -80°C until analysis; 10 cm of placental tissue (including maternal and fetal interface) was immediately collected after delivery and stored in formalin solution at room temperature.

Viral RNA was extracted from serum samples (200μl) using the MOLgen Universal Extraction Kit (Adaltis, Italy). RNA extraction from placental tissue (30 mg) was performed using the RecoverAll Total Nucleic Acid Isolation Kit (Invitrogen, Thermo Fisher Scientific, USA). The extracted RNA was amplified through RT-PCR using the MOLgen SARS-CoV-2 RT-PCR Kit (Adaltis, Italy) (Bohn et al., 2020; Favaro et al., 2021). Three SARS-CoV-2 targets were identified: the N and E genes, specific for SARS-CoV-2, and the RNA-dependent RNA polymerase (RdRp) gene, present in all coronaviridae. Samples were considered positive when either the N or E genes, alone or together with the RdRp gene, were detected at ≤38 cycle threshold.

Maternal and cord blood specimens were screened for the presence of viral antibodies, which showed a positive concentration of anti-spike (S) antibodies (5.5 and 0.4 binding antibody units/ml (BAU/ml) respectively) and negative results of anti-nucleocapsid (N) antibodies (0.33 and 0.08 U/ml respectively) (Table 1).

The patient's signs and symptoms were carefully checked during the following days, and the woman was discharged in good clinical conditions three days after the delivery, whereas the preterm twins underwent intensive examinations and were safely discharged in a month.

Discussion

SARS-CoV-2 infection in pregnancy has been extensively studied, while vertical maternal-fetal transmission is still under debate (Allotey et al., 2022; Sinaci et al., 2021). Allotey et al. (2022), in fact, assessed the contributing factors of SARS-CoV-2 vertical transmission through a systematic review and meta-analysis, including 472 studies with 18,237 newborns from COVID-19-positive mothers. Their analysis suggested the rare occurrence of fetal infection, which appears to be associated with the severity of maternal COVID-19 symptoms. The reported case suggests that vertical transmission can occur: the viral genome was found in both maternal and cord blood, as well as placental tissue. Furthermore, the related histopathological alterations of the placenta add more evidence to the transplacental passage of viral particles: in fact, we observed intense intervillositis and placental malperfusion. This can be explained by the subchorionic end intervillous deposition of apoptotic cells, which severely impairs the integrity of the placental interface (Baergen and Heller, 2020; Baud et al., 2020; Miranda et al., 2019; Shanes et al., 2020). The absence of viral particles in nasopharyngeal swabs from newborns suggests the hypothesis of a different viral tropism in infants and the possible viral testing to different sites (e.g., neonatal fecal and blood samples).

In addition, the high levels of maternal anti-S antibodies and low dosages of anti-N antibodies could be related to the severity of the patient's disease. Szymczak et al., (2021) also reported that the production of anti-N antibodies is strongly associated with severe symptoms, hinting at the theory that the more aggressive the disease is, the more effective the antibody response is found. Deep knowledge of the underlying biological mechanisms might be useful to understand the pathophysiological bases and the long-term implication of vertical transmission.

Authors' contributions

RS and MGP conceived and designed the study; LM, SF, MDP, GB, RB, PG, GT, MFV and EA collected, analysed and interpreted the data; LM, GB, RB, MFV and MGP drafted the manuscript; All authors read, commented, and approved the final manuscript.

Declaration of competing interest

The authors have no competing interests to declare.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

The study was approved by the Ethical Committee (CE n. 6275/2021) of the Department of Maternal and Child Health and Urological Sciences, Sapienza, University of Rome. The patient provided written informed consent for all the established procedures.

References

Allotey J, Chatterjee S, Kew T, Gaetano A, Stallings E, Fernández-García S, et al. SARS-CoV-2 positivity in offspring and timing of mother-to-child transmission: living systematic review and meta-analysis. BMJ 2022;376.

Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, Debenham L, Llavall AC, Dixit A, Zhou D, Balaji R, Lee SI, Qiu X, Yuan M, Coomar D, Sheikh J, Lawson H, Ansari K, van Wely M, van Leeuwen E, Kostova E, Kunst H, Khalil A, Tiberi S, Brizuela V, Broutet N, Kara E, Kim CR, Thorson A, Oladapo OT, Mofenson L, Zamora J. Thangaratinam S, for PregCOV-19 Living Systematic Review Consortium. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systemtic review and meta–analysis. BMJ 2020;370:m3320.

Baergen RN, Heller DS. Placental pathology in Covid-19 positive mothers: preliminary findings. Pediatr Dev Pathol 2020;23:177–80.

Baud D, Greub G, Favre G, Gengler C, Jaton K, Dubruc E, et al. Second-trimester miscarriage in a pregnant woman with SARS-CoV-2 infection. JAMA 2020;323:2198–200.

Bohn MK, Mancini N, Loh TP, Wang CB, Grimmler M, Gramegna M, et al. IFCC interim guidelines on molecular testing of SARS-CoV-2 infection. Clin Chem Lab Med 2020;58:1993–2000.

El-Goly AMM. Management of COVID-19 infection during pregnancy, labor, and puerperium. Covid-19 infections and pregnancy. Amsterdam: Elsevier; 2021. p. 63–89.

Favaro M, Mattina W, Pistoia ES, Gaziano R, di Francesco P, Middleton S, et al. A new qualitative RT-PCR assay detecting SARS-CoV-2. Sci Rep 2021;11:18955.

Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.

Jamieson DJ, Rasmussen SA. An update on COVID-19 and pregnancy. Am J Obstet Gynecol 2022;226:177–86.

Miranda J, Martín-Tapia D, Valdespino-Vázquez Y, Alarcón L, Espejel-Nuñez A, Guzmán-Huerta M, et al. Syncytiotrophoblast of placentae from women with Zika virus infection has altered tight junction protein expression and increased paracellular permeability. Cells 2019;8:1174.

Narang K, Enninga EAL, Gunaratne MDSK, Ibirogba ER, Trad ATA, Elrefaei A, et al. SARS-CoV-2 infection and COVID-19 during pregnancy: a multidisciplinary review. Mayo Clin Proc 2020;95:1750–65.

Porpora MG, Merlino L, Masciullo L, D'Alisa R, Brandolino G, Galli C, et al. Does lung ultrasound have a role in the clinical management of pregnant women with SARS COV2 infection? Int J Environ Res Public Health 2021;18:2762.

Sessa R, Anastasi E, Brandolino G, Brunelli R, di Pietro M, Filardo S, et al. What is the hidden biological mechanism underlying the possible SARS-CoV-2 vertical transmission? A mini review. Front Physiol 2022;13.

Shanes ED, Mithal LB, Otero S, Azad HA, Miller ES, Goldstein JA. Placental pathology in COVID-19. Am J Clin Pathol 2020;154:23–32.

Sharps MC, Hayes DJL, Lee S, Zou Z, Brady CA, Almoghrabi Y, et al. A structured review of placental morphology and histopathological lesions associated with SARS-CoV-2 infection. Placenta 2020;101:13–29.

Sinaci S, Ocal DF, Seven B, Anuk AT, Besimoglu B, Keven MC, et al. Vertical transmission of SARS-CoV-2: a prospective cross-sectional study from a tertiary center. J Med Virol 2021;93:5864–72.

Szymczak A, Jędruchniewicz N, Torelli A, Kaczmarzyk-Radka A, Coluccio R, Kłak M, et al. Antibodies specific to SARS-CoV-2 proteins N, S and E in COVID-19 patients in the normal population and in historical samples. J Gen Virol 2021;102.

White P. Classification of obstetric diabetes. Am J Obstet Gynecol 1978;130:228–30.

. Definition and categorization of the timing of mother-to-child transmission of SARS-CoV-2: scientific brief. Geneva: World Health Organization; 2021. p. 2021 8 February.

World Health Organization. Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus 2019–nCoV. Geneva: World Health Organization; 2020.