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Case Report
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Vertical Transmission of COVID-19 in Mother with High Viral Load, Isolation of SARS-CoV-2 in Amniotic Fluid, Placenta, Vaginal Swab, and Breast Milk and Neonate

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Abstract

The COVID-19 pandemic is at large and evidence to suggest vertical transmission of SARS-CoV-2 is emerging. Only few authors have reported vertical transmission of COVID-19 along with isolation of SARS-CoV-2 in amniotic fluid, placenta, vaginal swab, and breast milk. We present a case of congenital transmission from an asymptomatic woman with COVID-19 infection to her neonate who developed severe symptoms and died with COVID-19. Her high viral load likely contributed to the presence of the virus in the amniotic fluid, placenta, vaginal swab and breast milk.

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Introduction

Vertical transmission of SARS-CoV-2 infection is plausible considering its resemblance with SARS-CoV but the evidence is limited so far. Only a few authors have reported vertical transmission of COVID-19 along with isolation of SARS-CoV-2 in amniotic fluid, placenta, vaginal swab, and breast milk [1-7]. We present a case of vertical transmission in an asymptomatic woman with COVID-19 and high viral load.

Case Presentation

A 35-year-old third gravida with previous 2 neonatal losses being admitted to the hospital for sugar control, at 32 weeks, was incidentally tested positive for COVID-19 on July 13th, 2020.

In her first pregnancy 4 years back, she had a preterm delivery of a 900 grams neonate who expired on day 7. In her second pregnancy 3 years back, she underwent emergency caesarean for abruption placenta at 30 weeks gestation. This baby too died at 28 days of life due to prematurity and septicemia.

In the index pregnancy, she was on regular antenatal follow-up since early gestation. She had chronic hypertension and her blood pressure was controlled on labetalol 200 mg BD. She also had gestational diabetes diagnosed at 12 weeks of gestation (HbA1C=7·6 g/dl) for which she was on metformin and insulin. Fetal growth restriction was detected at 30 weeks gestation. She also had pregnancy induced cholestasis and was receiving ursodeoxycholic acid. She was planned for admission for safe confinement and tested positive for SARS-CoV-2 infection prior to admission. Though asymptomatic, she had a high viral load and was admitted to the COVID-ward. She received antenatal steroids for fetal lung maturity and thromboprophylaxis (injection enoxaparine).

Five days after admission, she went into preterm labor (at 32+5 weeks) and underwent emergency caesarean (due to previous preterm caesarean and labor) under general anesthesia. She delivered a live-born male child weighing 1500 grams. The baby had a smooth perinatal transition and was isolated from the mother without delayed cord clamping or skin to skin contact. Sterile amniotic fluid aspirated with a syringe during caesarean before rupture of membranes, placental tissue at cord insertion and on the maternal side, and cord blood were tested for SARS-CoV-2

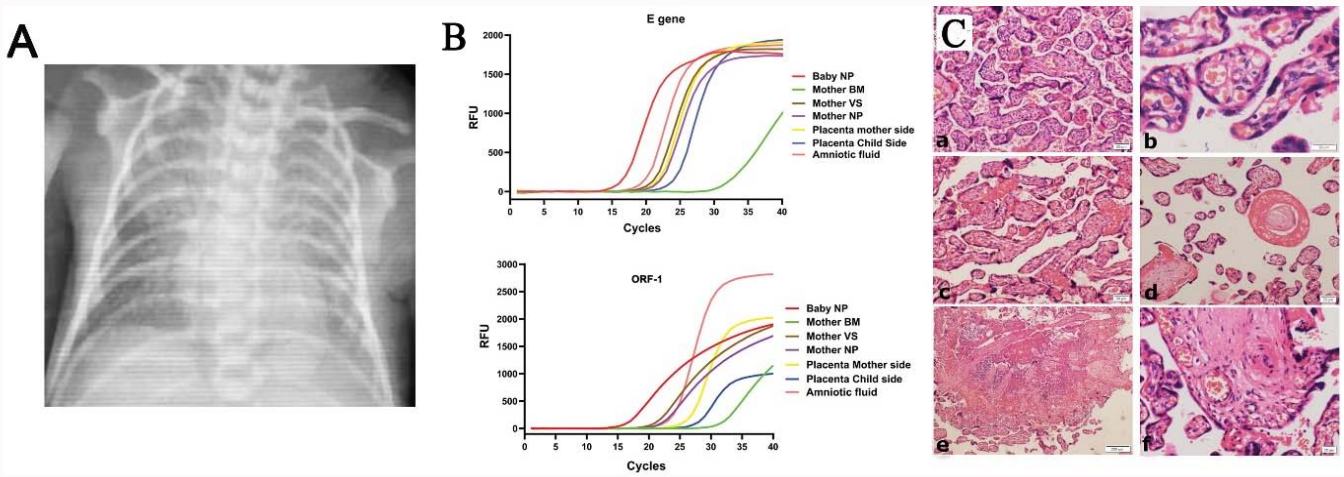

Figure 1: A) Chest-X-ray of neonate on Day 6 of life showing bilateral diffuse consolidation (Left > right) suggestive of acute respiratory distress syndrome; B) Real time Cycle threshold (Ct) values of different samples collected from mother on day of caesarean; breast milk and neonatal NPS on day 2. The graphs have been plotted by using the original Ct values on GraphPad Prism version 8 software (free trial version); C) Image panel showing placental histopathology. a and b: Normal third trimester villi; c and d: Intervillous fibrin deposition; e: necrotic focus and f: Intimal proliferation with vascular occlusion.

RT-PCR and all samples were positive. Neonatal Nasopharyngeal Swab (NPS), rectal swab, and breast milk tested on day two were also positive (Table 1 and Figure 1B). RT-PCR tests positive means samples were found positive for both SARS-CoV-2 based, E gene and ORF-1 gene. As per the kits provided by the National Institute of Virology (NIV), Pune, India, the E gene was used for screening, while ORF-1b confirmed the presence of SARS-COV-2 viral RNA in samples. Due to lack of availability of quantifiable positive control, we were not able to calculate copy number. At the time of study, the SARS-CoV-2 IgM and IgG antibody kits were not available in our hospital.

The neonate was admitted to a designated intensive care unit. Baby initially responded very well to the surfactant and in later course had only respiratory worsening. For prematurity and Hyaline membrane disease, baby received surfactant but continued to deteriorate. He had severe pneumonia (Figure 1A), leukopenia, thrombocytopenia, hypoglycemia, disseminated intravascular coagulation, and cytokine storm (hyperferritinemia, elevated C-reactive protein, and raised interleukin 6 levels) (Table 1) suggesting severe COVID-19. He received antibiotics along with methyl prednisolone (1 mg/kg/day) and intravenous immunoglobulin, but no significant improvement was seen. Sepsis was very unlikely as procalcitonin was low and blood culture was sterile. He also had prolonged bleeding at puncture sites and oro-nasal bleeding for which packed red blood cell and platelet transfusions were given. Chest X-ray done on day 6 showed bilateral white out lung. A repeat endotracheal aspirate for SARS-CoV-2 sent on day seven of life was also positive. Echocardiography on day 9 revealed evidence of pulmonary artery hypertension. The neonate had massive pulmonary hemorrhage secondary to thrombocytopenia and pulmonary artery hypertension leading to refractory hypoxia and died on day 10 of life. Unfortunately, autopsy could not be conducted due to COVID related restrictions and hospital policy. The mother remained asymptomatic, though she tested COVID positive on repeat nasopharyngeal RT-PCR even after 14 days of admission and was discharged on home quarantine on day 11 after caesarean.

The placenta weighed 570 g and measured 15 cm × 13 cm × 1.5 cm with an attached umbilical cord measuring 15 cm in length. The maternal and fetal surfaces, cord, and membranes were unremarkable macroscopically. On microscopy, the villi showed predominantly normal third-trimester morphology (Figure 1C (a,b)). There were multiple foci of intervillous fibrin deposition involving the chorionic villi focally and at times forming fibrin rings around them (Figure 1C (c,d)). There was a single microscopic necrotic focus bordered by normal appearing villi (Figure 1C (e)) and an occasional focus showing vascular endothelial proliferation and partial luminal occlusion in larger stem villi. Occasional focus of calcification was also seen. There was no evidence of any inflammation either in the chorionic villi, decidua, cord or membranes. There was no evidence of any vascular changes in the maternal vasculature.

Discussion

Evidence to suggest vertical transmission of SARS-CoV-2 is emerging. It is suggested that co-expression of ACE-2 and TMPRSS2 receptors are vital in the cytoplasmic entry of the virus. The receptors have been found expressed in major fetal organs, but are less frequently expressed in fetal kidneys [8]. These receptors are present on the placenta and it is speculated that their expression increases with gestation, thus increasing the susceptibility of transplacental infection in later gestation [9].

Vertical transmission may occur in symptomatic or asymptomatic patients but the ideal time between maternal disease acquisition and transplacental transmission is unclear [9]. Maternal morbidity/mortality, as well as perinatal mortality with COVID-19 infection, is well documented [1]. Our patient remained asymptomatic throughout her stay in hospital.

Various samples have been screened to detect possible perinatal transmission including vaginal secretions, amniotic fluid, and cord blood, placenta and breast milk [9]. As per the classification system for maternal-fetal-neonatal SARS-CoV-2 infections, our case had both maternal infection and congenital infection in the neonate (RT-PCR tested positive in both maternal NPS as well as amniotic fluid and placenta) [10]. Kotyar et al., in a meta-analysis, showed positive results, in 3.2% of 936 reported neonatal NPS, 7.7% placental tissue, 2.9% cord blood, 9.7% fecal/rectal swabs, 3.7% IgM neonatal serology but not in amniotic fluid or urine [2]. However, Vivanti et al. [3] and Zamaniyan et al. [4] have demonstrated vertical transmission along

Table 1: Results of SARS-CoV-2 test by qRT-PCR performed on mother and newborn are shown. The laboratory tests of the newborn are also summarized.

Summary of results of SARS-CoV-2 test by qRT-PCR performed on mother														
	Antenatal		Day 0*		Day 2		Day 3		Day 4		Day 7		Day 10	
Ct Value	**E**	**ORF-1b**	**E**	**ORF-1b**	**E**	**ORF-1b**	**E**	**ORF-1b**	**E**	**ORF-1b**	**E**	**ORF-1b**	**E**	**ORF-1b**
NPS	15.6	16.8	23.3	19.37	21.6	22.1	SNC	SNC	SNC	SNC	SNC	SNC	33.0	32.1
VS	SNC	SNC	25.3	23.5	20.6	21.1	SNC	SNC	24.1	24.8	24.5	24.1	26.1	27.9
BM	SNC	SNC	-ve	-ve	31.7	31.7	23.8	25.7	34.3	36.0	27.1	26.9	37.4	36.7
AF	NA	NA	19.7	18.2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Placental tissue (maternal surface)	NA	NA	21.6	20.5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Placental tissue (fetal side near cord insertion)	NA	NA	24.1	22.7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Maternal Plasma	SNC	SNC	SNC	SNC	SNC	SNC	35.4	34.6	SNC	SNC	-ve	-ve	SNC	SNC

Summary of results of SARS-CoV-2 test by qRT-PCR performed on neonate										
Postpartum	**Day 1**		**Day 2**		**Day 4**		**Day 8**		**Day 10**	
Ct Value	**E**	**ORF-1b**	**E**	**ORF-1b**	**E**	**ORF-1b**	**E**	**ORF-1b**	**E**	**ORF-1b**
NPS	-ve	-ve	16.7	16.5	20.7	19.6	SNC	SNC	Baby died	
Rectal swab	SNC	SNC	-ve	-ve	SNC	SNC	SNC	SNC		
ET aspirate	SNC	SNC	SNC	SNC	SNC	SNC	26.7	27.0		

Laboratory tests of the newborn									
	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**
Hemoglobin (g/dL)		19.1		17.9	11.1	14.4	14.7	7.9	6.4
Total leucocyte count (cells/ mm^3)		19000		3200	2700	4000	5200	8000	9900
Differential count (Polymorphs/ lymphocytes/ monocytes/ eosinophils)		P60/L19/ M8/E0.8		P67/L17/ M6/E9	P44/L37/ M9/E9	P11/L72.8/ M12.7/E2.8	P37/L44/ M12.8/E2.5	P33.5/ L51.3/ E2/ M9.4/ B3.8	P59/L25/M15
Platelet count (counts/mm^3)		42000		55000	14000	42000	45000	58000	98000
LFT(OT/PT/ ALP) (IU/L)			94/12/190	50/10/196	64/9/136	117/15/183			
CRP(mg/L)				17.7	5.46	4.5			
PCT (ng/ml)				0.355		0.8			
Acute phase reactants	Ferritin-3027ng/ml, IL-6: 26.7pg/ml (normal<7), D-dimer 2620.32 ng/ml, Fibrinogen 2.2g/L, aPTT 32.1 seconds								

Ct: Cycle threshold; NPS: Nasopharyngeal Swab; VS: Vaginal SWAB; BM: Breast Milk; AF: Amniotic Fluid; ET: Endo Tracheal, SNC: Sample Not Collected; NA: Not Applicable; LFT: Liver Function Tests; OT: Aspartate Aminotransferase; PT: Alkaline Aminotransferase; ALP: Alkaline Phosphatase; CRP: C-Reactive Protein; PCT: Procalcitonin; IL-6: Interleukin 6; *Day of cesarean section

with the presence of the virus in amniotic fluid. Viral load was higher in placental tissue than in amniotic fluid and placental histology revealed diffuse peri-villous fibrin deposition with infarction and acute and chronic Intervillositis and Immunohistochemistry (IHC) revealed intense cytoplasmic positivity of peri-villous trophoblastic cells with an antibody against SARS-CoV-2 N-protein [3]. Baergen and Heller have described fetal vascular malperfusion as a predominant histopathological finding seen in 50% of their cases and focal increase in fibrin deposits occasionally [11]. Our findings corroborate this study with an occasional focus of vascular occlusion and foci of intervillous fibrin deposition. However, maternal vascular perfusion changes described by Shanes et al. [12] were not seen in the index case. The coagulopathy associated with COVID-19 and endothelitis with disruption of the maternal-fetal interface may increase transplacental transmission of the virus [9]. Further, the demonstration of virions on electron microscopy on the fetal side of the placenta and positivity of spike proteins on IHC has also been documented [2].

Most of the cases of COVID-19 in pregnancy have been reported in the third trimester. These women have a higher risk of preterm labor. Our patient had previous preterm deliveries which may have contributed to preterm labor. Our patient also had evidence of fetal growth restriction in the few weeks before she was incidentally detected to be COVID-positive. According to various authors, prematurity, preterm ruptures of membranes, pre-eclampsia, and growth restriction have been reported in 25%, 17.6%, 6.9%

respectively [1].

Most of the cases affected in the third trimester were delivered by caesarean (86%) due to COVID-19 infection per se rather than for an obstetrical indication [1]. It is speculated that interaction with vaginal mucosa during delivery may lead to intrapartum transfer of the virus, but there is no clear evidence to suggest such a mode of transmission, or that caesarean may reduce the chances of intrapartum transmission. Though Qui et al. [13] reported negative vaginal swabs even for non-pregnant women with severe COVID-pneumonia; various authors suggest that vaginal samples be tested to see whether intrapartum transmission may occur. In our patient, though the vaginal swab was positive for SARS-CoV-2, her membranes were intact and caesarean was performed in early labor, hence intrapartum transmission is less likely. SARS-CoV-2 was demonstrated in amniotic fluid obtained during caesarean and placental tissue, which reliably suggest antepartum transmission [9].

Extrapolating from knowledge of perinatal transmission in other viral diseases like HIV, our patient's high viral load may have contributed to transmission of SARS-CoV-2 to the fetus. This case succinctly demonstrates transplacental antepartum transmission of SARS-CoV-2 to the neonate by evidence of the virus in the amniotic fluid and placenta.

Only a few reports have shown the presence of SARS-CoV-2 in breast milk, and the evidence on its infectivity and its role in vertical transmission is not clear [7,9,14]. Most academic societies recommend breastfeeding with appropriate use of masks and local hygiene and hand wash before and during breastfeeding [15]. Our patient's breast milk tested positive from day 2 onwards, which may be due to a high viral load in our patient.

We attributed the neonate's death to severe COVID-19 because the neonate had all the classical manifestations of severe COVID-19. The neonate initially responded well to the surfactant therapy but had worsening of respiratory symptoms in the later course. The chest X-ray was suggestive of severe ARDS. Though a similar clinical picture can be seen in neonatal sepsis, however, there were no risk factors for sepsis and the blood culture, procalcitonin, and CRP level were not suggestive of sepsis. Autopsy could have provided a definitive diagnosis but was not performed due to COVID restrictions in our hospital. We could not find any case in literature till the submission of this report where vertical transmission of COVID-19 led to neonatal death. However, there are many cases of neonatal death due to COVID-19, but vertical transmission has not been documented in these cases.

To conclude, this case demonstrates unequivocal evidence of vertical transmission of COVID-19 infection, possibly due to the high viral load in our patient though she was asymptomatic. Vertical transmission of COVID-19 infection is rare and larger studies with extensive sampling of placental and fetal specimens may provide more accurate evidence on its incidence.

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