















Vertical transmission of SARS-CoV-2: A prospective cross-sectional study from a tertiary center

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Abstract

The aim was to investigate the association of the delivery mode and vertical transmission of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) through the samples of vaginal secretions, placenta, cord blood, or amniotic fluid as well as the neonatal outcomes. This cross-sectional study presents an analysis of prospectively gathered data collected at a single tertiary hospital. Sixty-three pregnant women with confirmed coronavirus disease 2019 (COVID-19) participated in the study. Vertical transmission of SARS-CoV-2 was analyzed with reverse transcriptase-polymerase chain reaction (RT-PCR) tests and blood tests for immunoglobulin G (IgG)-immunoglobulin M (IgM) antibodies. All patients were in the mild or moderate category for COVID-19. Only one placental sample and two of the vaginal secretion samples were positive for SARS-CoV-2. Except for one, all positive samples were obtained from patients who gave birth by cesarean. All cord blood and amniotic fluid samples were negative for SARS-CoV-2. Two newborns were screened positive for COVID-19 IgG-IgM within 24 h after delivery, but the RT-PCR tests were negative. A positive RT-PCR result was detected in a neonate whose placenta, cord blood, amniotic fluid, and vaginal secretions samples were negative. He died due to pulmonary hemorrhage on the 11th day of life. In conclusion, we demonstrated that SARS-CoV-2 can be detectable in the placenta or vaginal secretions of pregnant women. Detection of the virus in the placenta or vaginal secretions may not be associated with neonatal infection. Vaginal delivery may not increase the incidence of neonatal infection, and cesarean may not prevent vertical transmission. The decision regarding the mode of delivery should be based on obstetric indications and COVID-19 severity.

KEYWORDS

COVID-19, delivery mode, neonatal outcome, pregnancy, SARS-CoV-2, vertical transmission

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has spread rapidly, creating an important public health problem worldwide.¹ The risk of severe coronavirus disease 2019 (COVID-19) may be higher during pregnancy than in the general population.² Available data on infection risks for pregnant women include fetal distress, abortus, preterm birth, low birth weight, and stillbirth.³⁻⁶ The transmission of SARS-CoV-2 from mother to fetus, a process termed vertical transmission, is still unclear. Existing studies in the literature have reported that vertical transmission is possible,⁷⁻¹⁰ and these studies mostly focus on placental transfer. There is limited information on the existence of SARS-CoV-2 in the female genital tract and this information may be important for evaluating both vertical and sexual transmission. There is no consensus on the delivery mode and optimal time of delivery in COVID-19 infected women. Moreover, the safety of vaginal delivery, or whether cesarean delivery prevents vertical transmission is unclear.

The issue of vertical transmission and the possibility of neonatal infection is a major concern in COVID-19 infected women. In the current study, we aimed to investigate the association of the delivery mode and vertical transmission of SARS-CoV-2 through vaginal secretions, placenta, cord blood, or amniotic fluid, as well as neonatal outcomes.

2 | MATERIALS AND METHODS

2.1 | Participants characteristics

This prospective study was performed in Ankara City Hospital, Department of Perinatology, Ankara, Turkey, between September 10 and November 23, 2020. Our hospital is one of the leading national pandemic centers which handles approximately 15,000 deliveries yearly, and our department has extensive experience dealing with COVID-19 infected pregnant women.¹¹

A total of 63 patients participated in the study (Figure 1). All pregnant women included in the study had positive reverse transcriptase-polymerase chain reaction (RT-PCR) results for SARS-CoV-2 RNA. Maternal age, gravidity, parity, number of living children, previous history of miscarriages, comorbid maternal systemic diseases, gestational age at diagnosis, symptoms, and severity of COVID-19, medications for COVID-19, maternal oxygen support requirement, laboratory test results, a gestational week at the time of delivery, route of delivery, neonatal APGAR scores, birth weight, and whether admission to neonatal intensive care unit was recorded. Clinical classifications according to the COVID-19 severity and treatments for COVID-19 were administered according to the latest national guidelines at the time of admission.¹² During the study period, none of the medical staff had symptoms or tested positive for COVID-19.

2.2 | Sample collection

2.2.1 | Maternal samples

Nasopharyngeal and oropharyngeal swabs were used to identify COVID-19 infection. When the pregnant women were in a sitting position with head and neck support, first the oropharyngeal and then the nasopharyngeal samples were taken by the swab. To ensure adequate sampling, the nasal swab was rotated for a few seconds after reaching the posterior wall of the nasopharynx. Patients with positive RT-PCR test results were followed up for delivery. Chest imaging was performed with radiography in patients with symptoms such as cough or fever.

2.2.2 | Placental, umbilical cord, vaginal secretion, and amniotic fluid samples

Placental samples were taken immediately after the delivery of the placenta. Maximum care was taken to avoid contamination of tissues. Approximately 5 cm of tissue was taken, including the umbilical cord, amniochorionic membrane, and placenta. Both vaginal secretion and amnion fluid sampling was performed before the rupture of the membranes. Vaginal samples were taken while the patients were lying on the hospital bed in the delivery room, the swab was inserted through the vagina until reaching posterior fornix and rotated for 3-5 s. To perform amniotic fluid sampling, in patients who had a vaginal delivery, a sterile needle was inserted through the vagina, and 10 cc amnion fluid was carefully taken into the injector in sterile conditions just before the rupture of the membranes, hence before the leaking of the amniotic fluid through the vagina. Similarly, in patients who gave birth with cesarean section, a needle was inserted during the C-section, and 10 cc amnion fluid was obtained in sterile conditions just before the rupture of the membranes. The sterile cover samples were transferred to the molecular virology laboratory in phosphate-buffered saline (PBS) solution within 30 min.

2.2.3 | Neonatal samples

Newborns of COVID-19 positive women were tested for RT-PCR. Similar to their mothers, nasopharyngeal and oropharyngeal swabs were used to screen the COVID-19 infection in the newborns. The newborns were stabilized by two nurses to perform nasopharyngeal and oropharyngeal swabs correctly, and then the swabs were taken in the same way as in the mothers. Samples were taken immediately after delivery and repeated 24 h later. The newborns also received a blood test for immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies within 24 h after birth. COVID IgG and IgM antibodies were reported with a single result, not separately, so we evaluated the results of IgG-IgM both together. Neonatal follow-up was made for 14 days with telemedicine.

2.2.4 | Sample transport

All samples were sent to the molecular microbiology laboratory within 2 h at room temperature; placenta tissues in sterile containers containing PBS, amniotic fluid samples in sterile tubes, vaginal swab samples in tubes containing Viral Transport Medium (various manufacturers), and cord blood samples in tubes containing EDTA.

2.2.5 | Tissue lysis

A tissue lysis process was applied to the placenta tissues before nucleic acid isolation. Approximately 2–3 mm³ of placenta tissue was sectioned and digested on a 65°C heat block with 1000 µl of Buffer ATL (Qiagen) and 50 µl of proteinase K (Qiagen) for a minimum of 3 h.

2.2.6 | Nucleic acid isolation

The same procedure was applied to all samples for nucleic acid isolation after tissue lysis. Nucleic acid isolation was performed using the EZ1 Virus Mini Kit v2.0 (Qiagen) with the EZ1 extraction device (Qiagen) according to the manufacturer's instructions.

2.2.7 | Real-time RT-PCR

SARS-CoV-2 in all samples was detected by the real-time RT-PCR method targeting Orf1ab and N genes. Real-time RT-PCR was performed by using a Coronex COVID-19 RT-qPCR Detection Kit (DS Bio and Nano Technology) with 20 µl reaction containing 5 µl of RNA, 12.5 µl of CORONEX-Covid 19 DS Mix E (RT-qPCR Master mix), and 2.5 µl of CORONEX-Covid 19 DS PP1 (Orf1ab, N and RNP gene, and primer-probe mix). Positive controls for amplification control and no-template control to assess contamination were used in each run. Thermal cycling was performed in a Rotor-Gene Q device (Qiagen) at 48°C for 20 min for reverse transcription, followed by 95°C for 2 min and then 35 cycles of 95°C for 5 s, 60°C for 10 s. Cycle threshold (C_t) values of less than 35 were defined as positive.

2.3 | Statistical analyses

IBM SPSS Statistics version 25.0 (IBM Corp.) was used to perform the statistical analysis. We used descriptive statistical methods. The mean and standard deviation were calculated for continuous and normally distributed variables. Categorical variables were presented as frequencies and percentages.

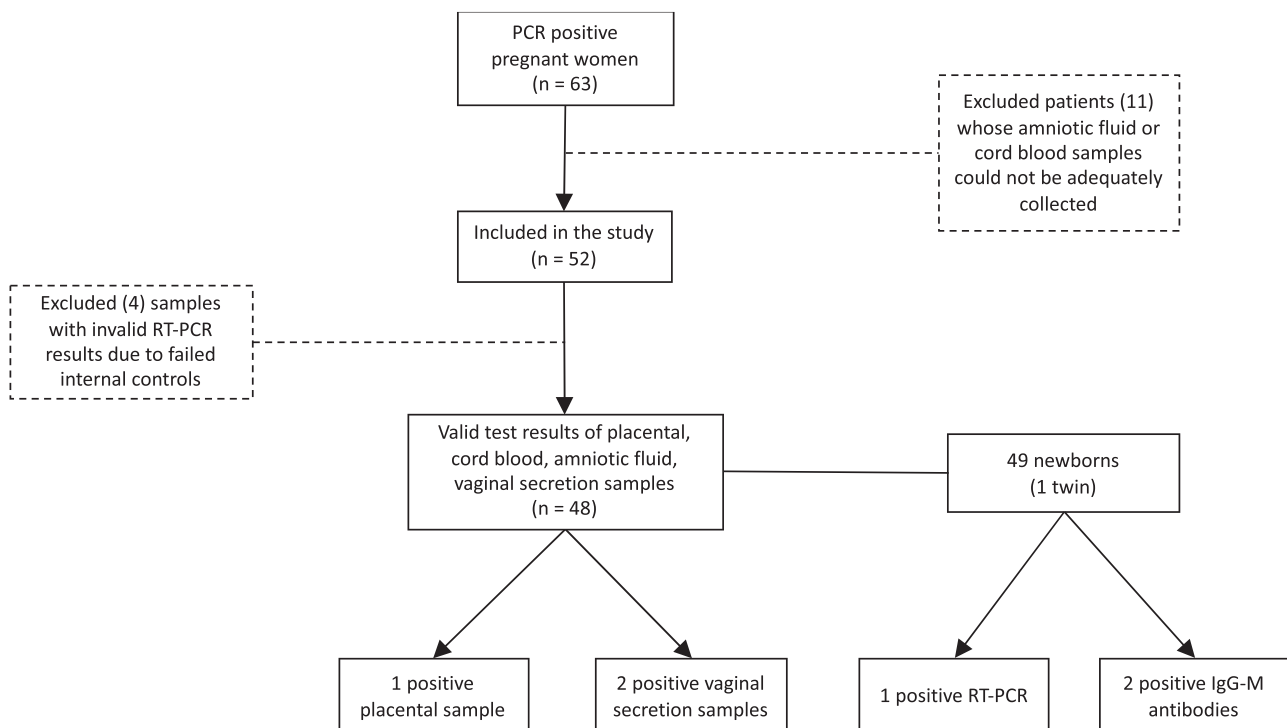


FIGURE 1 Flow chart of the study participants. IgG, immunoglobulin G; IgM, immunoglobulin M; RT-PCR, reverse transcriptase-polymerase chain reaction

2.4 | Compliance with ethical standards

Before initiating the study, the Ministry of Health of Turkey's approval and ethical board approval (E1-20-602) from Ankara City Hospital Ethical Committee was obtained. The study protocol was performed according to the Declaration of Helsinki principles, and the written informed consent containing the details of the study was obtained from all participants.

3 | RESULTS

The demographic characteristics and pregnancy features were presented in Tables 1 and 2. According to COVID-19 severity, all patients were in the mild or moderate category. None of the patients were treated in the intensive care unit. Among 48 PCR-positive women, 25 (52.0%) had no symptoms of COVID-19. Twenty-three (47.9%) patients had nonspecific symptoms such as myalgia, dry cough, sore throat, fatigue, diarrhea, and fever. A total of eight (16.67%) cases had obstetric complications. Eleven (22.9%) patients developed lymphopenia, and thirteen (27.0%) patients had leukocytosis. Platelet count was decreased in five (10.2%) pregnant women. Concentrations of transaminase, C-reactive protein, and D-dimer were elevated in 14 (29.1%), 36 (75%), and 44 (91.6%) patients, respectively. Concentrations of procalcitonin and interleukin-6 were elevated in 18 (37.5%), and 35 (72.9%) pregnant women, respectively. Radiological imaging findings suspicious for COVID-19 were observed on chest radiographs of eight (16.6%) patients. Preterm birth (<37 weeks of gestation) was observed in 17 cases (35.4%). Low birth weight (<2500 g) was observed in nine (18.7%) newborns. In 41 cases (85.4%), 5-min APGAR was greater than seven. Neonatal respiratory distress syndrome occurred in four neonates. Three had tachypnea, two had a low-grade fever but none of them had pneumonia, one died due to pulmonary hemorrhage.

Placental, umbilical cord, amniotic fluid, and vaginal secretion materials of 52 pregnant women infected with COVID-19 were analyzed for SARS-CoV-2 RNA by RT-PCR test. In four cases, the RT-PCR results were invalid due to failed internal controls as seen in Figure 1. All valid amniotic fluid and umbilical cord samples were negative for SARS-CoV-2. Only one placental sample and two of the vaginal secretion samples were positive for SARS-CoV-2. One of the three positive RT-PCR samples was obtained from a patient who delivered vaginally, and other positive samples were obtained from patients who gave birth by cesarean section. Clinical and laboratory findings of the patients with PCR-positive samples were presented in Table 3. A positive PCR result was encountered in a newborn of a mother whose placental, cord blood, amniotic fluid, and vaginal secretion samples were all negative. Moreover, two newborns were screened positive for COVID-19 IgG-IgM (Table 3).

4 | DISCUSSION

The aim of this study was to investigate the vertical transmission of SARS-CoV-2 by evaluating the vaginal secretion, placenta, umbilical cord blood, and amniotic fluid samples with the RT-PCR method and neonatal outcomes. Also, we aimed to detect whether the mode of delivery influences vertical transmission. Our findings suggest that in utero transmission is possible. Among pregnant women who tested positive for SARS-CoV-2, one positive result of placental sample and two positive results of vaginal secretion samples were detected. Among the newborns, only one had a positive RT-PCR result for SARS-CoV-2, but the transmission route was unclear. Also, two newborns were screened positive for COVID-19 IgG-IgM. Similar to the previous reports in the literature, SARS-CoV-2 was not found in amniotic fluid or cord blood.^{13,14}

Potential mechanisms for vertical transmission (viral passage from mother to fetus or newborn) are (i) via the placenta and umbilical cord during intrauterine life, (ii) via cervicovaginal secretions during delivery, (iii) via breastfeeding in the postpartum period.¹⁵ Maternal-fetal transmission through the placenta begins with the passage of viruses in the maternal circulation, from the uterine arteries to the placenta. Then, the viruses pass into the intervillous space from where they enter into the fetal circulation through the chorionic villi.¹⁶ Angiotensin-converting enzyme 2 (ACE2) is the accepted receptor of SARS-CoV-2, which is widely placed on the maternal-fetal interface and plays an essential role in the transmission of the virus.¹⁷ Data on the vertical transmission of SARS-CoV-2 is conflicting. In many reports, no evidence of vertical transmission was found regarding various samples such as amniotic fluid, cord blood, neonatal throat glands, placental swabs, genital fluid, and breast milk samples in mothers infected with the virus.^{13,14,18-20}

However, several studies exist in the literature reporting vertical transmission of SARS-CoV-2 through the placenta.⁷⁻¹⁰ Although some show electronic microscopic changes, some have reported the presence of the SARS-CoV-2 genome in the placentas, especially in the term period.^{21,22} It is revealed that the risk and rate of viral transmission increases as the gestational week progresses.¹⁵ Consistent with the previous reports, we found evidence that SARS-CoV-2 RNA can be found in placentas. Our data showed a term placenta with positive SARS-CoV-2 RNA result in which the pregnancy resulted in a cesarean delivery due to the development of fetal distress. The neonate's RT-PCR test was negative for SARS-CoV-2. Based on this result, we can say that the detection of SARS-CoV-2 in the placenta does not mean RT-PCR positivity in the newborn.

TABLE 1 The demographic characteristics of the participants

	Mean ± SD	Median	Min-max
Maternal age	28.1 ± 5.5	28	17-40
Gestational week	37.2 ± 2.6	38	27-40
Birth weight	3007.8 ± 657.5	3190	1370-4180

TABLE 2 Pregnancy features

Variable	n (%)
Gravidity	
1	14 (29.1)
2	20 (41.6)
3	7 (14.5)
4 and above	7 (14.5)
Parity	
0	18 (37.5)
1	18 (37.5)
2	10 (20.8)
3 and above	2 (4.1)
Living child	
0	19 (39.5)
1	18 (37.5)
2	9 (18.7)
3 and above	2 (4.1)
Mode of delivery	
Vaginal	10 (20.8)
Cesarean	38 (79.1)

Evidence supporting intrauterine transmission lies in the detection of elevated levels of IgM and IgG against SARS-CoV-2 in newborns.^{23,24} Recently, a positive RT-PCR result and IgM virus-specific antibodies for SARS-CoV-2 were reported in a newborn of a COVID-19 infected mother.²³ It is known that detection of IgM antibodies indicates recent exposure to SARS-CoV-2, while detection of IgG antibodies indicates exposure to the virus some time ago. In our study, two newborns had positive IgG-IgM antibodies, but RT-PCR tests were both negative for SARS-CoV-2 within 24 h after delivery. As the laboratory reported IgG and IgM together as a single result, we could not clearly reveal whether IgG, IgM, or both were positive, but as RT-PCR tests were negative in these two cases, we think that the essentially positive one was IgG. Therefore, we can claim that the newborns encountered SARS-CoV-2 in the womb during perinatal life. However, placental, umbilical cord blood, amniotic fluid, and vaginal secretion samples of these were all negative. The mothers of the IgG-IgM positive neonates had mild-moderate COVID-19, and one of them delivered vaginally. The newborns did not develop COVID-19 symptoms during the 14-day follow-up. On the other hand, the infant with positive RT-PCR for SARS-CoV-2 was followed up in the NICU for 11 days and died due to pulmonary hemorrhage. However, his mother had mild COVID-19 and discharged healthily. As pulmonary hemorrhage is a considerable complication of preterm labor, the underlying cause of neonatal death, in this case, maybe due to premature birth rather than the direct effect of COVID-19.²⁵

In a retrospective cohort, 3 of 33 infants (9%) were reported with early-onset SARS-CoV-2 infection. However, it was not possible to distinguish postpartum transmission from the intrauterine transmission as nasopharyngeal and anal swabs of PCR-positive newborns were taken on their second and fourth days in life.²⁶ An advantage of our study is that COVID-19 infection analyses in newborns were performed within the first 24 h to avoid postpartum contamination.

As the duration of contact with vaginal and perineal infected tissues containing cervicovaginal secretions is higher in vaginal delivery, it can be thought that the risk of SARS-CoV-2 transmission will increase with vaginal delivery. In contrast, in our study, SARS-CoV-2 RT-PCR tests were found negative in infants delivered vaginally. Moreover, the newborn with positive RT-PCR and one of the newborns with increased IgG-IgM for SARS-CoV-2 were born by cesarean section. On the other hand, RT-PCR positive vaginal samples were extracted from women who delivered by cesarean section, and the infants' test results were both negative for SARS-CoV-2 RT-PCR and IgG-IgM. Despite the rate of SARS-CoV-2 being higher in infants delivered by cesarean, it is not possible to attribute this result to the delivery mode as vaginal delivery numbers were low. In our study, 10 (20.8%) patients gave birth vaginally. In line with the literature, we can also argue that the delivery mode may not affect the course of COVID-19 in the mothers.²⁷

Although the studies on the impact of the COVID-19 pandemic on pregnant women and their newborns are rapidly increasing, even in the largest series, due to the relatively small number of patients who have had a vaginal delivery, the neonatal risk of COVID-19 has not been revealed yet.⁴ The existing data have shown no increase in SARS-CoV-2 infection in neonates who were delivered vaginally.^{4,28,29} This result supports the fact that vaginal delivery does not increase the risk of vertical transmission. Therefore, COVID-19 infection in the mother and so vertical transmission risk should not be a reason for cesarean section. In line with the guidelines,^{30,31} our findings suggest that decision on the mode of delivery in COVID-19 infected women should be based on obstetric indications, COVID-19 itself should not be an indication for cesarean delivery. On the other hand, we preferred cesarean delivery in women with severe symptoms and worsening COVID-19 disease, as some suggested.³²

In a recent study involving 10 pregnant women with severe disease, all vaginal sample tested negative for SARS-CoV-2.³³ In a large series on the subject, all cervical exfoliated cells, vaginal fluid, and anal swab samples of the included 35 patients were negative for SARS-CoV-2.³⁴ This might be explained by the negative expression of ACE2 in the vagina and cervix, which is the SARS-CoV-2 receptor.³⁵ The strength of our study is the relatively high number (48) of participants and the meticulous prospective analysis of various samples of pregnant women as well as their newborns.

In a retrospective analysis comparing 10 positive pregnant women for SARS-CoV-2 with 53 healthy pregnant women, there were no significant differences in neonatal outcomes between the groups, and all neonates were tested negative for SARS-CoV-2.³⁶ However, confusing reports keep coming. In a recent case, it was reported that a newborn who was positive for SARS-CoV-2 was delivered vaginally

TABLE 3 Clinical features and laboratory results of the participants with PCR-positive samples or newborns with positive IgG-IgM antibodies

	Case 1 (positive placental sample)	Case 2 (positive vaginal secretions sample)	Case 3 (positive vaginal secretions sample)	Case 4 (newborn with positive PCR)	Case 5 (newborn with positive IgG-IgM antibodies)	Case 6 (newborn with positive IgG-IgM antibodies)
Placental sample PCR	+	-	-	-	-	-
Cord blood sample PCR	-	-	-	-	-	-
Amniotic fluid sample PCR	-	-	-	-	-	-
Vaginal secretions sample PCR	-	+	+	-	-	-
Single/twin pregnancy	Single	Twin	Single	Single	Single	Single
Maternal COVID-19 severity	Mild	Mild	Moderate	Mild	Moderate	Mild
Chest imaging	-	-	Bilateral pneumonia	-	Bilateral pneumonia	Bilateral pneumonia
Maternal symptom	Myalgia, lassitude	Myalgia, lassitude	Fever, tachycardia, myalgia, lassitude, dysuria, diarrhea, dry cough	Myalgia, lassitude, fatigue	Sore throat, fatigue	Fever, fatigue
Prepregnancy BMI	30	32	30	32	31	29
Lymphocyte ($10^3/\text{mm}^3$)	1000	237	1000	1550	1140	570
Procalcitonin ($\mu\text{g/L}$)	0.07	0.02	0.33	0.02	0.11	0.12
CRP (mg/L)	70	71	23	36	32	64
IL-6 (pg/ml)	52.1	12.3	16.3	7.30	38.4	66.4
D-dimer	4	3.03	1.8	1.6	2.6	5.58
Obstetric complication	-	-	-	PPROM	-	-
Comorbid maternal disease	FMF, papillary thyroid CA	-	-	Factor V Leiden mutation	-	-
Medication use	Colchicine, levothyroxine	-	-	LMWH	-	-
COVID-19 treatment	LMWH	LMWH	LMWH, ceftriaxone, lopinavir/ritonavir, dexamethasone, piperacillin-tazobactam, nasal oxygen, immunoplasma, hydroxychloroquine, postpartum favipiravir	LMWH, azithromycin	LMWH, favipiravir, ceftriaxone, nasal oxygen	LMWH, favipiravir, ceftriaxone, nasal oxygen
Gestational age at birth (week)	39	34	39	27	39	37
Route of delivery	C/S	C/S	C/S	C/S	C/S	Spontaneous vaginal

TABLE 3 (Continued)

	Case 1 (positive placental sample)	Case 2 (positive vaginal secretions sample)	Case 3 (positive vaginal secretions sample)	Case 4 (newborn with positive PCR)	Case 5 (newborn with positive IgG-IgM antibodies)	Case 6 (newborn with positive IgG-IgM antibodies)
C/S indication	Fetal distress	Twin pregnancy	Worsening COVID-19	Fetal distress	Worsening COVID-19	-
Fetal gender	Female	Male-male	Male	Male	Female	Female
Birth weight (g)	3240	185-2150	3320	1370	2800	3410
APGAR 1st/5th min	8/9	5/7-7/9	7/9	6/8	8/9	8/10
Nasopharyngeal PCR of the newborn	-	-	-	+	-	-
IgG-IgM antibodies of the newborn	-	-	-	-	+	+
Neonatal complication	-	RDS	-	RDSLW	-	-
NICU	-	+	-	+	-	-
Neonatal outcome	Discharged healthily	Discharged healthily on the 7th day	Discharged healthily	Died on 11th day due to pulmonary hemorrhage	Discharged healthily	Discharged healthily

Abbreviations: C/S, cesarean section; CA, cancer; CRP, C-reactive protein; FMF, familial Mediterranean fever; IgG, immunoglobulin G; IgM, immunoglobulin M; IL-6, interleukin-6; LBW, low birth weight; LMWH, low molecular weight heparin; NICU, neonatal intensive care unit admission; PCR, polymerase chain reaction; PPRM, preterm premature rupture of membranes; RDS, respiratory distress syndrome.

from a woman whose rectal and fecal swabs were positive for SARS-CoV-2.³⁷ And they inferred that using prelabor anorectal swabs in pregnant women who tested positive for COVID-19 may reduce the risk of perinatal transmission during vaginal delivery. They also emphasized that even if the swab results were positive, a vaginal delivery could be performed after safety measures were taken.³² This can be thought of as a limitation of our study in that we did not perform prelabor anorectal sampling in patients who gave birth vaginally. Safety measures include the use of an enema in the second stage of labor which may potentially prevent stool leakage and reduce the amount of viral load at birth. Similarly, perineal cleaning with standard disinfection methods before the second stage of labor and after the engagement of the fetal head may be useful.³²

To the best of our knowledge, this is the first study examining comprehensive test results of vaginal secretions, placenta, cord blood, or amniotic fluid samples at the same time on pregnant women positive for SARS-CoV-2 and as well as the neonatal outcomes.

5 | CONCLUSION

Vertical transmission of SARS-CoV-2 seems possible. However, evidence supporting vertical transmission is still insufficient. We demonstrated that SARS-CoV-2 could be detected in the placenta and vaginal secretions of pregnant women. Contrary to fear, vaginal delivery may not increase the incidence of neonatal infection, and cesarean may not prevent vertical transmission. The decision regarding the mode of delivery should be based on obstetric indications and COVID-19 severity. Although the main spread of the virus is by respiratory droplets, sexual transmission of the virus is another issue that needs to be addressed in further studies. Comprehensive analyses on larger series from multiple specimens are required to evaluate further the neonatal safety of vaginal delivery and possible risk factors of vertical transmission in mothers infected with SARS-CoV-2.

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CONFLICTS OF INTEREST

The authors declare that there are no conflict of interest.

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REFERENCES

1. WHO/Europe. Coronavirus disease (COVID-19) outbreak—WHO announces COVID-19 outbreak a pandemic. <https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news/news/2020/3/who-announces-covid-19-outbreak-a-pandemic>. Accessed June 7, 2021.
2. Ellington S, Strid P, Tong VT, et al. Characteristics of women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status—United States, January 22–June 7, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:769–775. <https://doi.org/10.15585/mmwr.mm6925a1>
3. Turan O, Hakim A, Dashraath P, Jeslyn WJL, Wright A, Abdul-Kadir R. Clinical characteristics, prognostic factors, and maternal and neonatal outcomes of SARS-CoV-2 infection among hospitalized pregnant women: a systematic review. *Int J Gynaecol Obstet*. 2020; 151(1):7–16. <https://doi.org/10.1002/ijgo.13329>
4. Dubey P, Reddy SY, Manuel S, Dwivedi AK. Maternal and neonatal characteristics and outcomes among COVID-19 infected women: an updated systematic review and meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. 2020;252:490–501. <https://doi.org/10.1016/j.ejogrb.2020.07.034>
5. Halici-Ozturk F, Ocal FD, Aydin S, et al. Investigating the risk of maternal-fetal transmission of SARS-CoV-2 in early pregnancy. *Placenta*. 2021;106:25–29. <https://doi.org/10.1016/j.placenta.2021.02.006>
6. Abdelazim IA, AbuFaza M, Al-Munaifi S. COVID-19 positive woman presented with preterm labor: case report. *Gynecol Obstet Reprod Med*. 2021; 1–3.
7. Mahyuddin AP, Kanneganti A, Wong JLL, et al. Mechanisms and evidence of vertical transmission of infections in pregnancy including SARS-CoV-2. *Prenat Diagn*. 2020;40(13):1655–1670. <https://doi.org/10.1002/pd.5765>
8. Patanè L, Morotti D, Giunta MR, et al. Vertical transmission of coronavirus disease 2019: severe acute respiratory syndrome coronavirus 2 RNA on the fetal side of the placenta in pregnancies with

- coronavirus disease 2019-positive mothers and neonates at birth. *Am J Obstet Gynecol MFM*. 2020;2(3):100145. <https://doi.org/10.1016/j.ajogmf.2020.100145>
9. Vivanti AJ, Vauloup-Fellous C, Prevot S, et al. Transplacental transmission of SARS-CoV-2 infection. *Nat Commun*. 2020;11(1):3572. <https://doi.org/10.1038/s41467-020-17436-6>
 10. Hosier H, Farhadian SF, Morotti RA, et al. SARS-CoV-2 infection of the placenta. *J Clin Invest*. 2021;130(9):4947-4953. <https://doi.org/10.1172/JCI139569>
 11. Sahin D, Tanacan A, Erol SA, et al. Updated experience of a tertiary pandemic center on 533 pregnant women with COVID-19 infection: a prospective cohort study from Turkey. *Int J Gynaecol Obstet*. 2021;152(3):328-334. <https://doi.org/10.1002/ijgo.13460>
 12. Turkish Ministry of Health. General Directorate of Public Health, COVID-19 (SARS-CoV-2 infection) Guideline, Scientific Committee Report: https://covid19bilgi.saglik.gov.tr/depo/rehberler/COVID-19_Rehberi.pdf?type=file. Accessed August 21, 2020.
 13. Zhu H, Wang L, Fang C, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. *Transl Pediatr*. 2020;9(1):51-60. <https://doi.org/10.21037/tp.2020.02.06>
 14. Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet*. 2020;395(10226):809-815. [https://doi.org/10.1016/S0140-6736\(20\)30360-3](https://doi.org/10.1016/S0140-6736(20)30360-3)
 15. Silasi M, Cardenas I, Racicot K, Kwon J-Y, Aldo P, Mor G. Viral infections during pregnancy. *Am J Reprod Immunol*. 2015;73(3):199-213. <https://doi.org/10.1111/aji.12355>
 16. Schwartz DA, Dhaliwal A. Infections in pregnancy with Covid-19 and other respiratory rna virus diseases are rarely, if ever, transmitted to the fetus: experiences with coronaviruses, HPIV, hMPV RSV, and influenza. *Arch Pathol Lab Med*. 2020;144(8):920-928. <https://doi.org/10.5858/arpa.2020-0211-SA>
 17. Li M, Chen L, Zhang J, Xiong C, Li X. The SARS-CoV-2 receptor ACE2 expression of maternal-fetal interface and fetal organs by single-cell transcriptome study. *PLoS One*. 2020;15(4):e0230295. <https://doi.org/10.1371/journal.pone.0230295>
 18. Wang L, Shi Y, Xiao T, et al. Chinese expert consensus on the perinatal and neonatal management for the prevention and control of the 2019 novel coronavirus infection (First edition). *Ann Transl Med*. 2020;8(3):47. <https://doi.org/10.21037/atm.2020.02.20>
 19. Fan C, Lei D, Fang C, et al. Perinatal transmission of 2019 coronavirus disease-associated severe acute respiratory syndrome coronavirus 2: should we worry? *Clin Infect Dis*. 2021;72(5):862-864. <https://doi.org/10.1093/cid/ciaa226>
 20. Chen S, Huang B, Luo DJ, et al. [Pregnancy with new coronavirus infection: clinical characteristics and placental pathological analysis of three cases]. *Zhonghua Bing Li Xue Za Zhi*. 2020;49(5):418-423. <https://doi.org/10.3760/cma.j.cn112151-20200225-00138>
 21. Sisman J, Jaleel MA, Moreno W, et al. Intrauterine transmission of SARS-COV-2 infection in a preterm infant. *Pediatr Infect Dis J*. 2020;39(9):e265-e267. <https://doi.org/10.1097/INF.0000000000002815>
 22. Algarroba GN, Rekawek P, Vahanian SA, et al. Visualization of severe acute respiratory syndrome coronavirus 2 invading the human placenta using electron microscopy. *Am J Obstet Gynecol*. 2020;223(2):275-278. <https://doi.org/10.1016/j.ajog.2020.05.023>
 23. Dong L, Tian J, He S, et al. Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn. *JAMA*. 2020;323(18):1846-1848. <https://doi.org/10.1001/jama.2020.4621>
 24. Zeng H, Xu C, Fan J, et al. Antibodies in infants born to mothers with COVID-19 pneumonia. *JAMA*. 2020;323(18):1848-1849. <https://doi.org/10.1001/jama.2020.4861>
 25. Su BH, Lin HY, Huang FK, Tsai ML, Huang YT. Circulatory management focusing on preventing intraventricular hemorrhage and pulmonary hemorrhage in preterm infants. *Pediatr Neonatol*. 2016;57(6):453-462. <https://doi.org/10.1016/j.pedneo.2016.01.001>
 26. Zeng L, Xia S, Yuan W, et al. Neonatal early-onset infection with SARS-CoV-2 in 33 neonates born to mothers with COVID-19 in Wuhan, China. *JAMA Pediatr*. 2020;174(7):722-725. <https://doi.org/10.1001/jamapediatrics.2020.0878>
 27. Cai J, Tang M, Gao Y, et al. Cesarean section or vaginal delivery to prevent possible vertical transmission from a pregnant mother confirmed with COVID-19 to a neonate: a systematic review. *Front Med (Lausanne)*. 2021;8:634949. <https://doi.org/10.3389/fmed.2021.634949>
 28. Xiong X, Wei H, Zhang Z, et al. Vaginal delivery report of a healthy neonate born to a convalescent mother with COVID-19. *J Med Virol*. 2020;92(9):1657-1659. <https://doi.org/10.1002/jmv.25857>
 29. Cao D, Chen M, Peng M, Yin H, Sun G. Vaginal delivery in women with COVID-19: report of two cases. *BMC Pregnancy Childbirth*. 2020;20(1):580. <https://doi.org/10.1186/s12884-020-03281-4>
 30. World Health Organization. Clinical management of severe acute respiratory infection when COVID-19 is suspected. <https://www.who.int/publications/i/item/10665-332299>. Accessed June 7, 2021.
 31. Royal College of Obstetricians & Gynaecologists. Coronavirus (COVID-19) infection and pregnancy; 2020. <https://www.rcog.org.uk/en/guidelinesresearch.services/guidelines/coronavirus-pregnancy>. Accessed April 23, 2021.
 32. Carosso A, Cosma S, Serafini P, Benedetto C, Mahmood T. How to reduce the potential risk of vertical transmission of SARS-CoV-2 during vaginal delivery? *Eur J Obstet Gynecol Reprod Biol*. 2020;250:246-249. <https://doi.org/10.1016/j.ejogrb.2020.04.065>
 33. Qiu L, Liu X, Xiao M, et al. SARS-CoV-2 is not detectable in the vaginal fluid of women with severe COVID-19 infection. *Clin Infect Dis*. 2020;71(15):813-817. <https://doi.org/10.1093/cid/ciaa375>
 34. Cui P, Chen Z, Wang T, et al. Severe acute respiratory syndrome coronavirus 2 detection in the female lower genital tract. *Am J Obstet Gynecol*. 2020;223(1):131-134. <https://doi.org/10.1016/j.ajog.2020.04.038>
 35. Uhlén M, Fagerberg L, Hallström BM, et al. Proteomics. Tissue-based map of the human proteome. *Science*. 2015;347(6220):1260419. <https://doi.org/10.1126/science.1260419>
 36. Liao J, He X, Gong Q, Yang L, Zhou C, Li J. Analysis of vaginal delivery outcomes among pregnant women in Wuhan, China during the COVID-19 pandemic. *Int J Gynaecol Obstet*. 2020;150(1):53-57. <https://doi.org/10.1002/ijgo.13188>
 37. Carosso A, Cosma S, Borella F, et al. Pre-labor anorectal swab for SARS-CoV-2 in COVID-19 pregnant patients: is it time to think about it? *Eur J Obstet Gynecol Reprod Biol*. 2020;249:98-99. <https://doi.org/10.1016/j.ejogrb.2020.04.023>

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