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.

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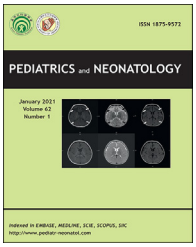

Original Article

Safety of vaginal delivery in women infected with COVID-19

Miriam Lopian [a,b,*,1], Lior Kashani-Ligumsky [a,b,1], Shelly Czeiger [a,b], Ronnie Cohen [a,b], Yehudit Schindler [d], Daniel Lubin [b,c], Ioanna Olteanu [a,b], Ran Neiger [e], Joseph B. Lessing [a,b], Eli Somekh [b,c]

[a] *Department of Obstetrics and Gynecology, Mayanei Hayeshua Medical Center, Bnei Brak, Israel*
[b] *Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel*
[c] *Department of Pediatrics, Mayanei Hayeshua Medical Center, Bnei Brak, Israel*
[d] *Laboratory of Microbiology, Mayanei Hayeshua Medical Center, Bnei Brak, Israel*
[e] *Department of Ob/Gyn, University of South Carolina Columbia, SC, USA*

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Key Words
COVID-19;
Intrapartum transmission;
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Background: There is limited data regarding the safety of vaginal delivery in women infected with COVID-19. Our goal was to assess the safety of vaginal delivery in women infected with COVID-19 and the risk of neonatal infection.
Methods: This was a single medical center cohort study. Data were collected about the outcome of twenty-one women with laboratory-confirmed COVID-19 infection who delivered between March 23, 2020, and May 8, 2020.
Results: Twenty-one gravidas were diagnosed with COVID-19 infection. None required admission to the intensive care unit (ICU) and there were no fatalities. Seventeen delivered vaginally and four by caesareans. Apgar scores of all neonates were 9 at 1 min and 10 at 5 min. One neonate was diagnosed with COVID-19 infection 24 h after birth.
Conclusions: Vaginal delivery in women infected with COVID-19 is not associated with a significant risk of neonatal infection.

* Corresponding author. Mayanei Hayeshua Medical Center, 17 Harav Povarski Street, Bnei Brak, Israel.
E-mail address: miriamlopian@gmail.com (M. Lopian).
[1] Contributed equally.

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1. Introduction

The first cases of the novel coronavirus (COVID-19) infections were diagnosed in December 2019 in Wuhan (Hubei, China).[1] By March 2020, the World Health Organization (WHO) declared COVID-19 a pandemic.[2] At the time of writing, over 15 million people around the globe have been diagnosed with COVID-19 infection and over 630,000 have died due to this infection. Women continue to give birth amidst a climate of great uncertainty regarding the potential impact of COVID-19 infection on pregnancy.

Current guidelines regarding the management of COVID-19 infection during pregnancy are largely based on data from non-pregnant patients, small case series of pregnant women with COVID-19, and outcome of pregnancies affected by other coronaviruses, namely Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS).[3,4] The purpose of this study was to evaluate maternal and neonatal outcomes of women diagnosed with COVID-19 infection around the time of delivery and to assess whether vaginal delivery was associated with an increased risk of neonatal infection.

2. Materials and methods

This was a single-center study conducted at the Mayanei Hayeshua Medical Center (MHMC) in Bnei Brak, Israel, affiliated with Tel Aviv University. Data were collected on all women diagnosed with COVID-19 infection who delivered between March 23, 2020 and May 8, 2020. Testing for maternal infection was performed in symptomatic women or those who had a history of exposure to infected individuals. Women with RT-PCR-diagnosed COVID-19 infection or suspected COVID-19 infection, pending PCR confirmation, were delivered in a separate delivery ward or operating room. Patients and attending staff wore masks and protective gear throughout delivery. Immediately after delivery, mothers were separated from their neonates and admitted to the coronavirus ward. Neonates were admitted to the neonatal unit in a separate ward to their mothers. There was no physical contact between the mother and neonate during admission. Women were encouraged to breastfeed via expressed milk with the protection standards described by the CDC guidelines.[5] Neonates born to women who tested positive for COVID-19 were tested at 24, 48 h and 5—7 days after birth. Neonates who tested positive for COVID-19 were also tested 14 days after birth. Neonatal follow-up was performed 14 days after discharge.

Nasopharyngeal samples from women and neonates were collected using FLOQS swabs (Copan Diagnostics, Murrieta, California, USA) and UTM viral transport medium (Copan Diagnostics, Murrieta, California, USA). Virus inactivation was performed prior to RNA extraction, using the LB buffer (Seegene Inc, Seoul, Republic of Korea). RNA extraction from samples was performed using the EZ1 Virus Mini Kit v2.0 by the EZ1 Advanced XL instrument or the QIAcube Connect system (Qiagen, Hilden, Germany), according to manufacturer's instructions. For the EZ1 (400 μl) and the QIAcube (700 μl) each sample was subjected to extraction with an elution volume of 60 μl. Confirmatory testing was performed using a magLEAD kit (Precision System Science Co., Ltd., Chiba, Japan), and 400 μl of each sample was subjected to extraction with an elution volume of 50 μl. An internal control was included in each extraction assay to monitor RNA extraction and real-time polymerase chain reaction RT -PCR quality. The multiplex RT- PCR assay was performed using the Allplex™ 2019-nCoV Assay (Seegene Inc, Seoul, Republic of Korea). RT -PCR was performed on a CFX96 real-time PCR system (Bio-Rad, Hercules, California, USA). The SARS CoV-2 genes detected by our assay include the RNA-dependent RNA polymerase (RdRp), envelope (E), and nucleocapsid (N) genes.This assay was conducted according to the kit manufacturer's instructions. The limit of detection for the 'E' and 'N' gene was 4167 copies/mL and for the 'RdRp' gene, 1250 copies/mL. The clinical sensitivity was 20/20 for the 'N' and 'E' genes and 19/20 for the 'RdRp' gene. A non-template (water) control was included in every RT -PCR run.

Symptomatic medical staff and those exposed to infected patients without appropriate protection as described by the CDC guidelines[5] were tested for COVID-19. No member of the medical staff tested positive for COVID-19.

The data was analyzed using the analyzer module of the software and results were interpreted in accordance with the Israeli Ministry of Health guidelines.[6]

This study was approved by the ethics committee at the Mayanei Hayeshua Medical Center.

3. Results

Twenty-one pregnant women with PCR-confirmed COVID-19 infection were delivered. The average maternal age was 30 years (range 21—44). Five women had gestational diabetes and one had Intrahepatic Cholestasis of Pregnancy. The others had no obstetric complications and no significant comorbidities. The median gestational age at delivery was 39 weeks' gestation (range 32—41). Nineteen women were at term (≥37 weeks' gestation), one was delivered by a repeat caesarean at 33 weeks due to suspected dehiscence of a uterine scar and one delivered at 32 weeks after having premature rupture of membranes and developing spontaneous labor. On admission, 10 patients were asymptomatic (Table 1). Two women received treatment with azithromycin (500 mg once a day for 5 days) and hydroxychloroquine (200 mg twice a day for 10 days) and one patient received azithromycin only, per the recommendations of infectious disease physicians, based on their clinical presentation. No woman required oxygen support, none were admitted to the intensive care unit and none required intubation. There were no fatalities.

Seventeen women delivered vaginally, two of them by vacuum extraction due to non-reassuring fetal status. Four women were delivered by caesarean section due to three previous caesareans, breech position, a non-reassuring fetal status and suspected uterine rupture in a woman with a history of two previous caesareans (Table 1). Apgar scores of all neonates were 9 at 1 min and 10 at 5 min. Average birth weight was 3353 g (range 1920—4070). All birthweights were appropriate for gestational age (Table 1). One neonate (born to patient 1) was diagnosed with COVID-19 infection by PCR analysis of nasopharyngeal swabs taken at 24 and 48 h of age and twenty neonates had

Table 1 Maternal and neonatal characteristics and outcomes among pregnant women tested positive for SARS-Cov-2 during delivery.

	Gravidity	Parity	Onset from COVID-19 diagnosis to delivery	Gestational age at delivery	Significant clinical findings	Significant laboratory findings	Mode of delivery	Time from membranes rupture to delivery	Neonatal weight at birth(g)	Neonatal SARS-CoV-2 quantitative PCR at 24 and 48 h of age
Patient 1	2	1	2 days	$37^{4/7}$	Fever, Malaise, Cough, Headache	Lymphopenia[a] Elevated CRP[b] Elevated ALT or AST[c]	VE	6hr	2770	Positive
Patient 2	1	0	2 days	$41^{1/7}$	—	Lymphopenia Elevated CRP	VE	30 m	3620	Negative
Patient 3	2	1	2 days	$41^{1/7}$	—	Lymphopenia	SVD	2 h 30min	2950	Negative
Patient 4	3	2	4 h	$39^{3/7}$	Cough	Lymphopenia	SVD	12min	3980	Negative
Patient 5	13	9	2 days	$33^{2/7}$	—	—	CS	0min	1920	Negative
Patient 6	9	6	2 days	$37^{2/7}$	—	—	SVD	3min	2800	Negative
Patient 7	5	4	1 h	$38^{2/7}$	—	Elevated CRP	SVD	7min	3750	Negative
Patient 8	4	3	5 days	$39^{6/7}$	Cough	—	SVD	6min	3540	Negative
Patient 9	11	7	5 h	$40^{5/7}$	Cough, Dyspnea, Headache, Anosmia, Evidence of pneumonia by X-RAY	Lymphopenia Elevated CRP	SVD	3min	3830	Negative
Patient 10	5	4	2 weeks[d]	$39^{6/7}$	Cough	—	SVD	4min	3610	Negative
Patient 11	1	0	25 h	$41^{2/7}$	Diarrhea, Evidence of pneumonia by X-RAY		CS	0min	3147	Negative
Patient 12	12	9	21 h	$41^{5/7}$	Cough	Lymphopenia	SVD	NA	3796	Negative
Patient 13	1	0	20.5 h	$39^{2/7}$	—	Elevated CRP	CS	0min	3520	Negative
Patient 14	2	1	2 weeks	$40^{1/7}$	Malaise, Anosmia, Sore throat	—	SVD	1 h 6min	3605	Negative
Patient 15	2	1	5 h	$39^{6/7}$	—	Leukocytosis[e] Elevated CRP	SVD	18min	3100	Negative
Patient 16	8	6	5 days	$32^{3/7}$	Cough	Lymphopenia Elevated ALT or AST	SVD	5min	2270	Negative
Patient 17	7	6	1 h 30min	$38^{4/7}$	—	—	CS	0min	3400	Negative
Patient 18	10	7	2 weeks	$41^{3/7}$	Sore throat	—	SVD	38min	3735	Negative
Patient 19	4	3	12 h	$40^{2/7}$	Myalgia, Malaise, Anosmia	—	SVD	18min	4070	Negative

Patient 20	6	3	2 h	$39^{6/7}$	—	Elevated CRP	SVD	2min	3410	Negative
Patient 21	6	3	6 days	$40^{0/7}$	Evidence of pneumonia by X-RAY	Elevated CRP	SVD	5min	3610	Negative

COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NA, not applicable; VE, vacuum extraction; SVD, spontaneous vaginal delivery; CS, cesarean section.

[a] Lymphocyte count of $<1.1 \times 10^3$ cells/μL.

[b] CRP level of >10 mg/L.

[c] ALT level of >45U/L or AST level of >35U/L.

[d] For patients who were diagnosed with COVID-19 two weeks before delivery, repeat test for SARS-CoV-2 was performed on admission to delivery and was found still positive.

[e] Leukocyte count of $>14 \times 10^3$ cells/μL.

negative PCR swabs at 24 and 48 h of age as well as 5—7 days of age. The mother of this baby (patient 1) presented at 37 weeks' gestation with a persistent cough and malaise. Her temperature on admission was 38.4°C. Her oxygen saturation was normal, she was hemodynamically stable and not dyspneic. There was no evidence of leukocytosis, rather, there was lymphopenia (0.74×10^3 cells per microliter), a C-reactive protein of 63 mg/dl and alanine aminotransferase of 78U/L. Other laboratory results were unremarkable. Other than a transient mild fetal tachycardia of 170 beats per minute, fetal status was reassuring and there was no clinical evidence of chorioamnionitis. The patient was tested for COVID -19, and once this infection was diagnosed, she was isolated in the coronavirus ward. She continued to have a fever, including on the day of delivery. On hospital day three, her membranes ruptured. She underwent an induction of labor by oxytocin and delivered 6 h later by vacuum extraction due to a non-reassuring fetal status.

A male neonate weighing 2770 g was delivered with Apgar scores of 9 and 10 at 1 and 5 min, respectively. Arterial cord blood gas analysis showed normal pH and lactate. Vital parameters were normal throughout his admission and he did not require respiratory support or an admission to the NICU. Nasopharyngeal swabs were first collected at 24 and at 48 h of life: they were tested with RT-PCR and were both positive for the SARS-CoV-2 genes. Feeding was provided using expressed milk with the protection standards described by the CDC guidelines.[5] The neonate did not receive antiviral medications or any other specific treatment and was discharged from the hospital after 7 days. He tested negative for COVID-19 at 7,14 and 17 days of life. An examination at 14 days of life was normal. None of the staff members who were in contact with the mother and the neonate were found to be positive for COVID-19.

4. Discussion

The purpose of the study was to ascertain the safety of vaginal delivery in COVID-19 positive women and the risk of neonatal infection. Of the 21 women in our cohort, 17 (81%) delivered vaginally and four (19%) by caesarean section, all due to obstetric indications. There were no cases of fetal or neonatal death, no neonatal asphyxia, and all neonates had good Apgar scores. The two neonates who were admitted to NICU for respiratory support was delivered at 32 and 33 weeks' gestation and were discharged with no complications. The outcome of the women who delivered vaginally and of their newborns suggests that COVID-19 infection during delivery is not an indication for caesarean section. These findings support the WHO guidelines that decisions regarding mode of delivery in patients with COVID-19 infection should be based on obstetric indications.[7] Despite these guidelines, according to a recent review by Zaigham et al., over 90% of deliveries described in the literature were via caesarean section.[8] The indications for these caesarean deliveries included obstetric considerations such as non-reassuring fetal status as well as non-obstetric concerns regarding maternal-neonatal transmission.[8]

Our data suggest that COVID-19 infection in the third trimester does not increase maternal morbidity compared to the infection in non-pregnant women. None of our patients required oxygen therapy, none were admitted to the intensive care unit, and there were no cases of maternal mortality. Our results are in line with other case series that were recently published. Chen et al.[9] and Liu et al.[10] described cohorts of nine and fifteen pregnant women, respectively, and reported no ICU admissions or deaths. Similarly, in the largest cohort published to date, Breslin et al.[11] describe the outcomes of forty-three pregnant women with COVID-19 infection, of whom thirty-seven had mild symptoms (86%), four had a severe infection and two were in critical condition requiring ICU admission. From our study and these publications, it appears that the outcomes of pregnant women infected with COVID-19 are different from the high rates of morbidity and mortality seen in pregnant women during the epidemics of Influenza[12] and other coronaviruses, namely SARS[13] and MERS.[14] Indeed, Wong et al.[13] reported that infection with SARS virus during pregnancy was associated with a 25% mortality rate and a 50% rate of ICU admission, 33% of women required ventilation.

The only baby in our cohort who was found to be infected with COVID-19 tested positive 24 h after birth. The risk of acquiring this infection was most likely not affected by mode of delivery; all cases of neonatal COVID-19 infection described in the literature were delivered by caesarean section[8,15–17] and a report described an early neonatal infection, detected at 36 h of life, of a neonate born via a caesarean section.[17] On the other hand, amongst the few reports of women with COVID-19 infection who delivered vaginally, there have been no neonatal infections.[8] The source of the single neonatal infection case in our cohort is not clear as placenta, amniotic fluid and maternal and newborn blood were not tested. A recent case report documented a transplacental transmission of SARS-CoV-2 during late pregnancy. Transplacental transmission may cause placental inflammation and neonatal viremia.[18] Other reports of potential perinatal transmission have been published, but some failed to detect SARS-CoV-2 in neonates or only reported the presence of specific antibodies,[19,20] whilst others found the virus in the newborn samples but the transmission route was not clear.[21]

Although an external source for infection is unlikely since strict infection control measures were implemented during and after delivery, it cannot be ruled out. Another possibility is an intrapartum respiratory spread: the mother wore a face mask during delivery, but at times she required the use of an oxygen mask due to non-reassuring fetal status. Delivery was in accordance with droplet precautions, but it was not in an airborne infection isolation room (AIIR). Since the neonate was in this room for several minutes after birth, it is possible that the neonate was infected through droplets or aerosolized particles, a risk both with caesarean and vaginal delivery. Another possibility is intrapartum infection during delivery itself: the neonate who was found to be infected was delivered 6 h after the membranes ruptured (the longest interval in our cohort). It is possible that this latency from membrane rupture to delivery increased the risk of transmission, independent of the mode of delivery. While no studies of PCR testing of vaginal secretions for COVID-19 have been published so far, it is known that with increasing duration of membrane rupture prior to delivery women colonized with other infections, such as Group B Streptococcus (GBS), Herpes Simplex Virus (HSV) and Human Immunodeficiency Virus (HIV), have a higher risk of perinatal transmission.[22–24] For this reason, the American College of Obstetrics and Gynecology (ACOG) recommends caesarean delivery of women with active genital HSV infection and ruptured membranes,[25] although there is probably no benefit of caesarean delivery when the duration of membrane rupture exceeds 4 h.[26] A recent report suggested that patients with severe COVID-19 infection had higher viral loads and a long virus-shedding period that may increase the risk of virus transmission,[27] similarly to the correlation between maternal viral load and the risk of perinatal transmission in women infected with HIV, Hepatitis C and Hepatitis B.[28–30] We do not know the viral load levels in the infected women; however, it is possible that the transmission of the infection to the neonate at the time of delivery correlated with a high viral load at the time of an acute illness. The mother of this newborn was the only patient in our series who was febrile at the time of delivery, which may indicate a higher risk of transmission: both in our study, and in cases described by Wang et al.[17] and Vivanti et al.,[18] COVID-19 positive women who gave birth to infected neonates were febrile during labor. In our cohort, none of the neonates born vaginally to women who were afebrile during delivery were infected. In a febrile pregnant woman who is not in labor, therefore, it seems reasonable to consider delaying delivery until the patient has defervesced. Similarly, in such women it seems reasonable to shorten the interval from membrane rupture to delivery (e.g. through augmentation or a cesarean delivery).

While our results are encouraging, they should be approached with caution. Case series, including the current one, report results of a small number of patients. Furthermore, our cohort and that of Breslin[11] included a high proportion of asymptomatic patients (47% and 30%, respectively), diagnosed as part of a universal screening program or due to contact history, whereas studies of previous epidemics described pregnant patients admitted with respiratory symptoms.[12–14] It is also possible that due to the short latency between disease onset and delivery, the effects of pregnancy on disease outcomes were attenuated. Reports describing the effect of viral infection on fetal growth were published after intrauterine infection with other viruses, namely, varicella zoster[31] rubella[32] and cytomegalovirus.[33] However, due to the short latency between the diagnosis of infection and delivery in our cohort, we cannot comment on the effect of COVID-19 infection on pregnancy course and fetal growth. In our study, PCR testing for SARS-CoV-2 was only performed on days 1, 2 and day 5–7 postpartum. Whilst the average incubation period for SARS CoV-2 is around 6 days, it can extend to 14 days.[34] Therefore, we cannot exclude the possibility that neonates that had initially tested negative for SARS CoV-2 did not seroconvert within the 14-day incubation period. That said, all exposed neonates were followed up by a physician at 14 days of life and were asymptomatic with normal clinical examinations.

Our results demonstrate that vaginal delivery is not associated with a high risk of neonatal infection. Acute febrile illness during delivery or increased latency from membrane rupture to delivery may increase the risk of neonatal infection. Larger cohorts and analyses of vaginal and perianal colonization by COVID-19 are required to further assess the maternal and neonatal safety of vaginal delivery in COVID-19 infected mothers, and possible risk factors and modes of transmission of fetal or neonatal infection.

Declaration of competing interest

The authors declare that they have no competing interest.

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