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ORIGINAL ARTICLE

Spectrum of neonatal COVID-19 in Iran: 19 infants with SARS-CoV-2 perinatal infections with varying test results, clinical findings and outcomes

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ABSTRACT

Background: There have been few cohorts of neonates with coronavirus disease-2019 (COVID-19) reported. As a result, there remains much to be learned about mechanisms of neonatal infection including potential vertical transmission, best methods of testing, and the spectrum of clinical findings. This communication describes the epidemiology, diagnostic test results and clinical findings of neonatal COVID-19 during the pandemic in Iran.

Materials and methods: This is a retrospective cohort study of 19 neonates infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from 10 hospitals throughout Iran. We analyzed obstetrical information, familial COVID-19 status, neonatal medical findings, perinatal complications, hospital readmissions, patterns of repeated testing, and clinical outcomes.

Results: Eleven neonates had family members infected. Five mothers were negative for COVID-19 and four neonates had no identifiable family source of infection. The neonatal mortality rate from COVID-19 was 10%. Seven newborns (37%) were discharged from the hospital as healthy but required readmission for symptoms of COVID-19. There were 2 multifetal gestations – one set each of twins and triplets, each with disparate testing and clinical outcomes. Premature delivery was common, occurring in 12 of 19 infants (63%). Initial testing for COVID-19 was negative in 4 of the 19 neonates (21%) who subsequently became positive. In 2 cases, neonates tested positive at 1 and 2 h after birth which was suspicious for vertical transmission of SARS-CoV-2.

Conclusions: These cases have notable variation in the epidemiology, clinical features, results of testing and clinical outcomes among the infected newborns. Neonates initially testing negative for COVID-19 may require readmission due to infection. Two neonates were highly suspicious for intrauterine vertical transmission. Repeat testing of neonates who initially test negative for COVID-19 is recommended, without which 21% of neonatal infections would have been undiagnosed.

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Introduction

The recognition of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the life-threatening disease that it causes, coronavirus disease 2019 (COVID-19), has led to widespread concern for its effects on pregnant women and their infants. Experiences from two previous coronavirus diseases – Middle Eastern respiratory syndrome (MERS) caused by MERS-CoV and severe acute respiratory syndrome (SARS) caused by SARS-CoV – demonstrated that these highly pathogenic coronaviruses could result in severe maternal illness and death, as well as pregnancy loss [1]. Fortunately, there were no confirmed cases of vertical transmission of either the SARS or MERS coronaviruses, either *via* the intrauterine, intrapartum, or postpartum routes of infection [2]. Because of this, however, it was not possible to characterize the potential effects of highly pathogenic coronaviruses on neonates, the efficacy of neonatal testing, or options for treatment.

As the SARS-CoV-2 has spread globally there has been increasing recognition that it can produce a spectrum of maternal disease that includes upper and lower

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respiratory infections, severe pneumonia requiring intensive care and ventilatory assistance, cardiomyopathy, thrombosis, obstetrical near-miss events, and multiorgan manifestations including multiorgan system dysfunction syndrome (MODS) and maternal death [3–10]. There was initially less information available on the epidemiological aspects and clinical effects of COVID-19 on pediatric patients, and especially neonates and young infants. As a result, there remains much to learn regarding the mechanisms for neonatal transmission, spectrum of neonatal disease, best methods of neonatal testing for COVID-19 and the long-term consequences, if any, of neonatal infection. The possibility of vertical transmission of the virus between an infected mother and her infant also remains unanswered, and to date there have been no confirmed cases of intrauterine transmission of SARS-CoV-2.

There have been just a few cohort studies of neonates with COVID-19 reported to assist in answering some of these questions [11–14]. The intent of this present retrospective case series is to describe the epidemiological and clinical findings of 19 neonates having positive reverse transcription-polymerase chain reaction (RT-PCR) testing for SARS-CoV-2 in 10 hospitals throughout Iran. It provides an analysis of the clinical features of the family members as well as infants, the results of neonatal testing for the coronavirus performed at varying times following delivery, occurrence of COVID-19 in multifetal pregnancies, and addresses the possible intrauterine vertical transmission of SARS-CoV-2.

Methods

This communication includes brief reports of the clinical histories of neonates testing positive for SARS-CoV-2 from 10 hospitals in different cities throughout Iran. These infants were identified by the local treating physicians according to National Iranian guidelines. These 19 cases were submitted to the authors in Iran for analysis and inclusion in this cohort study. Informed consents for the routine treatment, specimen collection and diagnosis were signed by the parents or guardians of newborns and relatives of the pregnant women at each of the 10 hospitals. The methods followed in this communication conform to the guidelines and ethical principles of the Declaration of Helsinki developed by the World Medical Association.

Obstetrical and delivery history, neonatal birth status including Apgar score, clinical features, radiographical findings, blood tests, as well as SARS-CoV-2 nucleic acid detection in family members were reported when that information was available. Whenever possible detailed clinical data was requested, but due to the ongoing pandemic, communications and location and distance of some of the hospitals, not all information could be obtained for every case. Neonatal nasopharyngeal (NP), endotracheal or oropharyngeal (OP) swabs were taken from the infants at the referral hospital at the times stated in the clinical histories. Neonates were evaluated for COVID-19 from specimens tested for SARS-CoV-2 nucleic acid using RT-PCR methods. Because these 19 cases were collected at geographically dispersed hospitals throughout Iran, molecular testing was performed by different laboratories using reagents from varying sources which were both imported and produced locally. In addition, there were varying amounts of epidemiological, clinical and laboratory data available between the 10 hospitals in this study. As a result of this, the origin and specifications of the RT-PCR tests that were used together with controls cannot be definitively stated beyond the fact that they were performed in accordance with accepted national standards in accredited laboratories and hospitals in Iran. The collection of neonatal and adult specimens was conducted in accordance with recommendations for collection and testing for Class II pathogens.

The case subjects were designated as Case 1 through Case 19 solely for the purposes of publication and communication of non-identifying information. These case designations are not reflective of the order of their care nor presentation of first symptoms. These cases were not selected by any form of systematic surveillance, but rather arose through a voluntary reporting by referring physicians of maternal and neonatal patients with known positive testing by RT-PCR for SARS-CoV-2. Succinct clinical histories of the 19 neonates and their pertinent family members is discussed below and summarized in Table 1.

Mothers and neonates

Case 1

An 1800-g male newborn was delivered by cesarean section at 34 weeks gestation at the Imam Khomeini Hospital, Orumiyeh, West Azerbaijan Province. The mother had high blood pressure and symptoms of COVID-19 occurring 1 week prior to delivery and had a positive pulmonary CT scan and positive SARS-CoV-2 testing at the time of her admission, necessitating delivery. The neonate's Apgar scores were 4 and 5 at 1 and 5 min after birth, and the infant required resuscitation in the delivery room. A NP swab taken from the infant 2 h following delivery was positive by RT-PCR for SARS-CoV-2. The infant was intubated, surfactant was administered by endotracheal tube, and antibiotics

Table 1. Clinical and SARS-CoV-2 testing data for 19 neonates with COVID-19.

Case No.	GA (mo)	BW (gm)	Apgar scores	COVID-19 testing in family	Infant RT-PCR testing	Neonatal clinical symptoms	Neonatal chest radiological findings
1	34	1800	4–5	(+) Mother	(+) 2 h after delivery	Respiratory distress, resuscitation, intubation	Unknown
2	31	1660	7–8	(+) Mother	(−) 3 h after delivery (+) DOL 7	Respiratory distress, fever for 2 weeks, lymphopenia, elevated LDH, hyponatremia	Diffuse consolidation
3	39	3250	9–10	No testing	(+) DOL 3	Respiratory distress, icterus, cyanosis, sepsis	White lung Bilateral lung infiltration
4	28	900	Low	(+) Mother	(+) DOL 4	Respiratory distress, intubation	RDS
5	29	1300/1600/1200	Low	(+) Mother	All triplets (−) 4 h after delivery; Triplet 2 (+) Triplet 3 (−) on DOL 3	Respiratory distress	White lung RDS
6	34	2000	9–10	(+) Mother	(+) 1 h after delivery	Admitted for check up	Normal
7	32	2300	5	(+) Mother	(−) 1 h after delivery (+) DOL 4	Respiratory distress	Pneumomediastinum Pneumothorax CT consistent with COVID-19
8	Full term	3300	Not stated	No testing	(+) DOL 25	Respiratory distress, cough, diarrhea, congenital heart disease	Diffuse lung involvement
9	39	3460	9–10	(+) Mother (+) Father	(+) DOL 24	Fever, mottling, lethargy, cough, respiratory distress	Diffuse lung involvement
10	36	2200/2000	9–10	(+) Grand- mother	(+) Twin #1 DOL 19 (−) Twin #2	Twin #1 – Cough and fever Twin #2 – Asymptomatic	CT and CXR consistent with COVID-19
11	Prob-able full term	3100	Good	No testing	(+) DOL 35	Respiratory distress, pneumonia-like syndrome	Not stated
12	28	900	Low	(+) Mother	(+) DOL 6	Extremely low birthweight, respiratory distress, intubation at birth, thrombocytopenia	Not stated
13	37	3500	9–10	No testing	(+) DOL 2 (−) DOL 10	Fever on DOL 10	Normal CXR
14	36	2000	9–10	(−) Mother	(−) DOL 1? (−) DOL 8 (+) DOL 10 (−) DOL 11,28,29	Lethargy, hypotonia/ hyporeflexia, sepsis, bradycardia	Normal CXR
15	39	3500	9–10	(+) Father (−) Mother	(+) DOL 10 (+) DOL 17	Fever, poor feeding, hypotonia, abdominal distension	CXR with mild infiltrates
16	33	1900	7	(+) Mother	(+) DOL 2 (−) DOL 14	Respiratory distress	CXR with air bronchogram
17	36	3450	9–10	(−) Mother	(+) DOL (−) DOL 20	Respiratory distress, i ntubation	CXR with white lungs and bilateral infiltrates
18	34	2100	2–3	(−) Mother	(+) DOL 1 (−) DOL 4	Resuscitation, respiratory distress, intubation, pneumonia	CXR with pneumonia
19	39	2800	9–10	(−) Mother	(+) DOL 6 (+) DOL 10 (−) DOL 12	No signs or symptoms	Normal CXR

GA: gestational age; BW: birth weight; gm: grams; mo: months; hr: hours; DOL: day of life; RT-PCR: reverse transcription polymerase chain reaction; LDH: lactate dehydrogenase; CT: computed tomography; CXR: chest radiograph; RDS: respiratory distress syndrome.

were given for 7 days. The infant was discharged home after 1 week in good general condition and isolated at home for an additional week.

Case 2

A 31-week male newborn weighing 1660 g was delivered by spontaneous vaginal delivery to a mother with fever and proven COVID-19 infection at Shariati Hospital, Tehran University of Medical Sciences (TUMS) in Tehran. Apgar scores were 7 and 8 at 1 and 5 min, and skin-to-skin contact was not permitted. The infant was transported within a closed incubator and isolated in a separate room. Shortly after delivery, he developed respiratory distress and was intubated. An endotracheal/OP swab performed 3 h after delivery was

negative for SARS-CoV-2. He became febrile on day of life (DOL) #2 which continued for 2 weeks and did not respond to antibiotics. The infant had lymphopenia and elevated lactase dehydrogenase (LDH) on admission and showed hyponatremia with inappropriate antidiuretic hormone secretion which resolved after 2 weeks. On DOL #7 a repeat OP swab was taken which tested positive for SARS-CoV-2. He was treated with hydroxychloroquine according to adult guidelines in use at that time which did not change his fever or respiratory course. He was discharged home after 3 weeks in good general condition. The infant's mother died 3 days after delivery.

Case 3

A 39-week healthy male newborn with birthweight of 3250 g was born by spontaneous vaginal delivery with no complications at the Torbat-e Jām Hospital in Torbat-e Jām, Razavi Khorasan Province. Both his mother and father were afebrile and asymptomatic and were not tested for COVID-19. The infant was discharged home on DOL #2. He required readmission on DOL #3 for severe respiratory distress and icterus and was diagnosed with sepsis. The neonate had bilateral lung infiltrations, was intubated and required high mean airway pressure to be mechanically ventilated. A NP swab was taken on the DOL #3 was positive for SARS-CoV-2 by RT-PCR. The infant is still intubated and has received different antibiotic therapies without having significant effect on his respiratory distress and chest radiographic findings.

Case 4

A premature female infant weighing 900 g was delivered at 28 weeks' gestation by cesarean section because of premature rupture of membranes for 6 h from a mother with COVID-19 positive test at the Taleghani Hospital in Tehran. Her mother had lymphopenia and high bilirubin level with signs of cholestasis – her chest CT scan showed bilateral lung involvement. The neonate required intubation after delivery due to severe respiratory distress. A NP swab performed on 4th DOL was positive for SARS-CoV-2 by RT-PCR. The infant died on 7th DOL with respiratory insufficiency and bleeding. The mother was discharged home after 2 weeks.

Case 5

Triplets were delivered by cesarean section to a mother with confirmed COVID-19 at 29 weeks' gestation at Arash Women's Hospital in Tehran. Their mother had a history of cough and fever that had begun 1 month before admission. Birthweights of the triplets were 1200, 1300, and 1600 g. NP swabs were taken 4 h following delivery from all three infants and were negative. The 1st triplet died from respiratory distress before a repeat swab could be performed, thus the follow-up status for COVID-19 was unknown. Repeat NP swabs were taken on DOL #3 from the surviving 2 triplets – the specimen from the 2nd triplet was positive for SARS-CoV-2 by RT-PCR, and the specimen from 3rd triplet was negative. Following this testing the 3rd triplet died from respiratory distress. The 2nd triplet, despite having COVID-19, survived and was discharged home with a good general condition.

Case 6

A 34-week gestational age female infant weighing 2000 g was delivered by cesarean section because her mother had symptoms of COVID-19 including cough, fever and a positive NP swab for SARS-CoV-2 at the Boo-Ali Sina Hospital in Sari, Mazandaran Province. One hour following delivery, a NP swab taken from the newborn was positive for SARS-CoV-2. The infant was treated for 7 days with ampicillin and amikacin and discharged home with her mother in good condition and isolated for more 1 week.

Case 7

A 32-week gestational age female infant weighing 2300 g was delivered by cesarean section because her mother was severely ill with COVID-19 at the Boo-Ali Sina Hospital in Sari, Mazandaran Province. The mother had presented with fever and severe respiratory distress along with signs of renal failure that required hemodialysis. There was a positive test for SARS-CoV-2 from amniotic fluid and vaginal discharge. The neonate's Apgar scores were low, and she required resuscitation. A NP swab taken at first hour of life was negative for SARS-CoV-2. Skin-to-skin contact was not permitted. The newborn's RDS score was 5, and she was treated with nasal continuous positive airway pressure (CPAP). She required supplemental oxygen for 2 more days. A repeat NP swab performed on DOL #4 was positive for SARS-CoV-2 by RT-PCR. The infant was discharged on DOL #12 in good condition.

Case 8

A 3300-g full-term male infant was delivered by normal spontaneous vaginal delivery at the Qods Hospital in Qazvin in Qazvin Province. Hydrocephaly had been identified prior to birth. No testing for COVID-19 was performed on the parents. Following delivery, the neonate was diagnosed with congenital heart disease (ventricular septal defect, atrial septal defect and pulmonary stenosis) but needed no immediate treatment and was discharged home shortly after delivery. He was readmitted on DOL #10 with cough, diarrhea, respiratory distress, and low blood oxygen saturation, and was intubated on the 3rd day of his readmission and extubated on the 5th day. A NP swab was performed in the hospital on DOL #25 was positive for SARS-CoV-2 using RT-PCR. He recovered fully and was discharged home.

Case 9

A 39-week gestational age female infant was born by cesarean section at the Ayatollah Mousavi Hospital in Zanjan, Zanjan Province. She was discharged home with her mother. The infant was readmitted at DOL #13 with cough, respiratory distress, and low blood oxygen saturation. Both of her parents were then tested and found to have COVID-19. A NP swab was performed on the infant on DOL #24 which was positive for SARS-CoV-2 by RT-PCR. After 10 days of routine medical treatment, she became stable and was discharged home, where she was isolated for an additional 4 days.

Case 10

Twin infants were delivered at 36-week gestational age at the Mustafa Khomeini Hospital in Ilam, Ilam Province. They had birth weights of 2000 and 2200 g and were discharged home on the day after delivery. The first twin was readmitted on DOL #19 with cough and low-grade fever, and a NP swab performed at the time of admission was positive for SARS-CoV-2 by RT-PCR. The baby's grandmother was identified as having COVID-19. The infant was discharged in good condition after 9 days of medical treatment. The other twin did not show any symptoms, and his NP swab was negative for the virus.

Case 11

A 35-day old baby boy was admitted because of respiratory distress to the Allameh Bohluli Hospital in Gonabad, Razavi Khorasan Province. Both parents showed no signs of infection and had not been tested for COVID-19. He was probably delivered at term, weighed 3100 g, and did not have any medical complications following his birth. At the time of admission on DOL #35 his weight was 4000 g. He required supplemental oxygen and received routine antibiotic treatment. A NP swab performed after admission was positive for SARS-CoV-2, but his parents still did not show any signs of infection. After 1-week of medical treatment, he was discharged home.

Case 12

A 28-week male infant was born at the Imam Reza Hospital in Mashhad, Khorasan-e Razavi Province. He had a birth weight of 900 g and required immediate intubation and endotracheal surfactant administration for respiratory distress. The infant's mother had been diagnosed with COVID-19 by NP swab and a positive RT-PCR. The extremely low birthweight neonate recovered gradually and was extubated after 5 days. Because his platelet count was very low, he received 2 transfusions of platelets. On DOL #6 a NP swab was performed which was positive for SARS-CoV-2 by RT-PCR.

Case 13

A 37-week female infant was delivered by cesarean section in Tehran with a birth weight of 3500 g. Her mother was addicted to opium and was symptomatic with fever and cough, but testing for COVID-19 was not performed for her. The neonatès OP swab was positive on DOL #2 for SARS-CoV-2 by RT-PCR. Beginning on DOL #10 the infant developed fever which persisted for 3 days. She was treated and recovered and was discharged home following a repeat OP swab which was negative for the virus.

Case 14

A male infant was vaginally delivered at 36 weeks gestation at the Imam Sajad Hospital in Shahriar, Tehran Province. His mother was addicted to heroin and had symptoms of fatigue and cough with a positive pulmonary CT scan, but her NP swab for COVID-19 was negative by RT-PCR. The newborn was transferred to the Neonatal Intensive Care Unit (NICU) where he was observed for neonatal abstinence syndrome, and a NP swab was negative for SARS-CoV-2 by RT-PCR. At the insistence of the parents, the infant was subsequently

discharged from the hospital. He was readmitted to NICU again on the 8th DOL with hypotonia, hyporeflexia and lethargy – a NP swab on that day was negative for SARS-CoV-2. He was diagnosed with sepsis and a second RT-PCR test from a NP swab was ordered which was positive for SARS-CoV-2 on DOL #10. His chest radiograph was normal. He developed bradycardia and dobutamin infusion with cardiac monitoring was started. Repeat tests for COVID-19 on DOL #11, 28 and 29 were all negative. He was discharged after 14 days of medical treatment in good condition.

Case 15

A 39-week gestational age male infant was delivered by cesarean section at the Day General Hospital in Tehran. He had a birth weight of 3500 g, appeared healthy and was discharged home. On DOL #10 he was readmitted to the NICU with fever, poor feeding, abdominal distension and hypotonia. His mother had a negative test for COVID-19, but his father's NP swab was positive for SARS-CoV-2 by RT-PCR. The infant's NP swab also tested positive for SARS-CoV-2 on the day of admission (DOL #10), and a repeat test 1 week after admission (DOL #17) remained positive as well. He recovered with routine care and was discharged home in good condition.

Case 16

A 33-week gestational age female infant was delivered by cesarean section because of maternal illness at the Day General Hospital in Tehran. She had a birth weight of 1900 g and required resuscitation after birth. Her mother had symptoms of COVID −19 infection accompanied by low grade fever for 16 days prior to delivery. Immediately following the infant's birth, she was admitted to the NICU where she received CPAP for 2 days. Her initial NP swab was performed on DOL #2 which was positive for SARS-CoV-2 by RT-PCR. A repeat NP swab performed on DOL #14 was negative for the virus, and she was discharged with good condition.

Case 17

A 36-week gestational age male infant was delivered by cesarean section from a diabetic mother at the at Taleghani Hospital in Gorgan, Golestan Province. He had a birth weight of 3450 g and good Apgar scores. His mother had a cough, sore throat and respiratory distress, and her NP swab was negative for SARS-CoV-2 by RT-PCR. The infant was admitted to NICU from the first hour of life. He required intubation because of respiratory distress and was treated with surfactant. A chest radiograph revealed bilateral pulmonary infiltrates. An endotracheal swab was performed on DOL #4, which was positive for SARS-CoV-2 by RT-PCR. A repeat examination on DOL #20 using a NP swab was negative for the virus by RT-PCR. He recovered well and was discharged in good condition.

Case 18

A 34-week gestational age male infant was delivered by cesarean section at the Hakim Jorjani Hospital in Gorgan, Golestan Province. His mother had been admitted to hospital with fever and cough, but her NP swab was negative for SARS-CoV-2 by RT-PCR. The infant had a birth weight of 2100 g, had low Apgar scores (2 at the first minute), and required resuscitation. He was intubated and admitted to the NICU with severe respiratory distress and a chest radiograph demonstrating pneumonia. An endotracheal swab was performed on DOL #1 following intubation which was positive for SARS-CoV-2 by RT-PCR. A repeat swab taken from the nasopharynx on DOL #4 was negative for the virus by RT-PCR. The infant remained in the NICU with respiratory distress and died on DOL #14 following pulmonary hemorrhage.

Case 19

A female 39-week gestational age infant was delivered vaginally having a birth weight of 2800 g at the Hamedan Besat Hospital in Hamedan, Hamadan Province. The infant's mother developed postpartum respiratory symptoms, fever and cough on the 6th day following delivery, but her NP swab was negative for SARS-CoV-2 by RT- PCR. The neonate did not have any signs or symptoms of COVID-19, but NP swabs performed on the 6th and 10th DOL were all positive for SARS-CoV-2. A 3rd NP swab was negative on DOL #12. She remained in good condition, did not required any treatment, and was discharged home where she was isolated.

Discussion

Following the initial development of SARS-CoV-2 infections in Wuhan, China, early studies of newborn infants showed only rare instances of neonatal infection, and although there were perinatal complications

that occurred, severe illness or mortality was uncommon among them [4,5,7,10,12,14,15]. In a recent review of 67 neonates delivered to pregnant women with COVID-19, neonatal complications included respiratory distress or pneumonia in 18%, disseminated intravascular coagulation in 3%, asphyxia in 2%, and 2 cases of perinatal death [16].

COVID-19 has resulted in widespread morbidity and mortality throughout Iran [17]. In particular, it has taken a heavy toll among pregnant women and their infants, causing both maternal as well as perinatal deaths [18,19]. However, much remains to be learned about the effects of SAR-CoV-2 on infected neonates in Iran and elsewhere in the world.

This multi-institutional retrospective adjudicated case series from Iran describes 19 neonates with COVID-19 infection following delivery and neonatal admission to any one of 10 hospitals in different regions of the country. These cases are remarkable for the notable variation present in the epidemiology, clinical features, results of testing and clinical outcomes among the infected newborns (Table 1). Our report has the expected limitations of a retrospective, multicenter case series including variation in the available information on clinical features of mother and infant, extent of testing and family members, and clinical follow-up of some cases. Because multiple hospitals and laboratories throughout Iran were involved in this study, it is not possible to standardize the molecular testing methods used at the various institutions. However, all testing was performed in laboratories with local and national approval for testing and with appropriate use of positive and negative controls.

An examination of the potential sources of neonatal infection revealed that among the 19 neonates testing positive for SARS-CoV-19, there were 11 neonates with at least one family member testing positive for COVID-19. This included 8 infants (Cases #1, 2, 4, 5, 6, 7, 12, 16) whose mothers who were the sole parent with confirmed COVID-19. One mother/father pair had confirmed COVID-19 (Case #9), and in Case #10 the grandmother had the infection. In Case #15 both parents were tested, but only the father had confirmed COVID-19 and the mother was negative. In five cases (Cases #14, 15, 17, 18, 19) the mothers were tested for COVID-19 but had negative test results. There were four cases (Cases # 3, 8, 11, 13) in which no testing of family members was performed. Among the 15 infected neonates for whom testing of family members for SARS-CoV-2 was performed, 11 infants (73%) had one or more family members also infected. Among these 11 infants, 9 (82%) had an infected mother. Five of 19 infants (26%) had mothers who were tested for SARS-CoV-2 but were negative (Cases #14, 15, 17, 18, 19). Among the 15 neonates who had at least one family member tested, there were four infected neonates (27%) for whom there was no identifiable family source of infection.

Premature delivery was common among these infants – 12 of 19 infants (63%) with COVID-19 were delivered prior to 37 weeks gestation. This included 2 very preterm deliveries at 28 weeks (Cases #4 and 12) and a set of triplets at 29 weeks (Case #5) gestation. Among the 19 neonates testing positive for SARS-CoV-2 in this cohort, respiratory distress was the most frequent presenting medical problem, occurring in 12 of the 19 (63%) infants. Three of these 12 (25%) infants had been already been discharged home and were subsequently readmitted with the initial onset of respiratory disease. Bradycardia, icterus, lung hemorrhage, thrombocytopenia and abdominal distension with poor feeding were also reported. A small number (3 of 19; 16%) of neonates having SARS-CoV-2 infection never developed symptoms or findings that were referable to their positive viral status.

It was not uncommon for newborns to be discharged from the hospital as healthy, and subsequently require readmission for onset of signs and symptoms of COVID-19 (7 of 19 infants; 37%). The time intervals between discharge and readmission varied greatly – 1 day for Case #3, 18 days for Case #10, and approximately 8–9 days for Case #8, 10–11 days for Case #9, 33 to 34 days for Case #11, 5–6 days for Case #14, and 8–9 days for Case #15. The average approximate time interval for these infants between discharge and readmission for signs of COVID-19 was 12 days. Those cases where neonates where the infant was healthy following delivery and discharged, and the initial onset of signs and symptoms of COVID-19 infection were prolonged – 8–9 days or greater – are suggestive that transplacental or intrapartum transmission was not occurring. These infants likely became developed COVID-19 postpartum from exposure to an infected family member, other infected person or an environmental source. Because the incubation period of COVID-19 in neonates remains unknown, this opinion is based upon experience with other neonatal infections.

There were two sets of multifetal gestations in this cohort – one set each of triplets and twins. In Case #5, a set of preterm triplets were delivered to a mother with confirmed COVID-19 – all three triplets were tested for SARS-CoV-2 at 4 h following operative delivery and were negative. The first-delivered triplet died

of respiratory distress before a follow-up test for SARS-CoV-2 could be performed. On DOL #3 repeat NP swabs on the two surviving triplets revealed that the 2nd triplet was positive for the virus, but that the 3rd triplet was negative. The 3rd triple died from respiratory distress following the testing. The 2nd triplet survived, despite having a positive test for the virus, and was ultimately discharged. Case #5 demonstrates the importance of repeated testing of neonates at risk for COVID-19 but leaves several observations unexplained. The reason(s) that all three triplets initially tested negative for the virus but one subsequently tested positive 3 days after delivery but another triplet tested negative; and why two triplets died shortly after birth from respiratory disease with one testing negative for COVID-19 but the triplet having the positive test surviving, are all problematic. This case encompasses some of the dilemmas and inconsistencies in trying to understand perinatal COVID-19 infection. In Case #10 preterm twins were discharged home in good condition the day after delivery, but one twin became ill 19 days after delivery and was diagnosed with COVID-19, while the other twin remained well and was uninfected. This was most likely a situation in which postpartum infection of one twin had occurred.

The neonatal mortality rate from COVID-19 was 10.5% in this cohort – two infants (Cases #4 and 18) died as a result of SARS-CoV-2 infection. Although the deaths of two of three triplets (Case #5) could not be confirmed as being due to COVID-19, the positive infection status of both the mother and the surviving triplet raises suspicion that these neonatal deaths were related to, if not caused by, COVID-19. The maternal mortality rate was 5.3%.

An interesting and potentially significant observation from this cohort was the frequency of disparities between initial testing of neonates for COVID-19 and the results of subsequent tests. The initial testing for SARS-CoV-2 was negative in 4 of the 19 neonates (21%). Case #2 was a low birth weight preterm infant whose endotracheal/oropharyngeal specimen was negative for SARS-CoV-2 at 3 h after vaginal delivery, but who tested positive on the 7th DOL. The triplets from Case #5 were all negative for the virus 4 h after delivery, but one triplet had a positive result 3 days later, and the other 2 twins died. For Case #7, despite a severely ill mother with COVID-19 and poor Apgar scores following delivery and the need for resuscitative measures, a nasopharyngeal swab performed 1 h following delivery of the infant was negative for SARS-CoV-2. On DOL #4, this infant's testing for the coronavirus was positive. In Case #14 the neonate was initially believed to be uninfected with SARS-CoV-2 following negative nasopharyngeal swabs on both the symptomatic mother as well as the infant – he remained in the hospital only to exclude the possibility of neonatal abstinence syndrome. However, on DOL #8, he was readmitted with a multiple symptoms and sepsis, and a nasopharyngeal swab was positive for SARS-CoV-2. These cases provide evidence for performing repeat testing of neonates who initially test negative for COVID-19, and who may be at risk for infection because of mothers or immediate family members having the infection or its symptoms. Had repeat testing for COVID-19 not been performed among infants in this cohort, 21% of neonatal infections would have been undiagnosed. It is also recommended that throughout this pandemic, any symptomatic neonate who has not responded to standard medical treatment should be considered for testing for COVID-19. In the present cohort of 19 neonates with COVID-19 there were no significant differences in gender, type of delivery or birth weight of infants who died or recovered after having positive RT-PCR testing for the coronavirus. With one exception, these infants had not been treated specifically for COVID-19 and had only received standard neonatal medical care as based upon standard guidelines.

The variability in test results described among these neonates raises important questions regarding issues related to diagnostic testing for COVID-19 among newborn infants Whether the infection is acquired through vertical transmission from the mother, another person or the environment, the sensitivity and specificity of using nasopharyngeal swabs to test for SARS-CoV-2 in neonates is unknown. In particular, if transplacental transmission of the virus occurs following hematogenous transfer across the maternal-fetal interface, it also is problematic whether testing for the virus using a nasopharyngeal swab (as is performed in children and adults who acquire the infection *via* the respiratory route) is a sensitive and specific method for diagnosis.

One of the most important areas of concern regarding COVID-19 among pregnant women and their infants is whether vertical transmission of the virus is occurring, and if so, when and under what circumstances it develops [20,21]. In addition to reports of neonates having late-onset positive neonatal testing for SARS-CoV-2 infection in our cohort and in others [22], there have been reports of early postpartum positivity of RT-PCR testing for SARS-CoV-2 among some neonates [14,23–25]. Two preterm infants in our series, Case #6 and Case #1, were positive for SARS-CoV-2

infection just 1 and 2 h, respectively, following cesarean section delivery. These represent some of the earliest reported neonates to have positive testing for COVID-19 in the literature and is highly suggestive that there was vertical transmission that occurred around, or shortly before, the time of operative delivery. These and other cases of early test positivity for COVID-19 in neonates emphasize the importance of delineating diagnostic criteria for intrauterine vertical transmission including transplacental and intrapartum infections [26].

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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