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Outcomes in COVID-19 Positive Neonates and Possibility of Viral Vertical Transmission: A Narrative Review

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Abstract

Objective Novel coronavirus disease 2019 (COVID-19) seems to affect adults and pediatric patients differently. While neonates are a special population, little is known about the neonatal outcomes. This study aimed to investigate the outcomes in COVID-19 positive neonates and incidence of vertical transmission of the virus by reviewing available literature.

Study Design This study is a narrative review of available literature on "COVID-19 in neonates," for which PubMed and Google Scholar were used to search the published articles.

Results We summarized the data from 39 published studies that are comprised of 326 COVID-19 positive peripartum mothers with respective neonatal outcomes. Twenty-three neonates have been reported to be COVID-19 positive. Male neonates were affected significantly more (79%) than female neonates. Approximately 3% neonates acquired infection through suspected vertical transmission. Strict infection prevention measures during the perinatal time can significantly reduce the chance of horizontal transmission of the virus. Overall, neonates were asymptomatic or mildly symptomatic regardless of gestational age at birth and required only supportive measures. There was 0% mortality in COVID-19 positive neonates.

Conclusion From available published data to date, we can conclude that the prognosis of COVID-19 positive neonates is good with no mortality. There appears to be minimal vertical transmission of the infection.

Keywords
- COVID-19
- novel coronavirus 2019
- SARS-CoV-2
- neonates
- neonatal outcomes
- vertical transmission

Key Points
- Majority of COVID-19 positive neonates showed mild clinical signs and symptoms with no mortality.
- Most COVID-19 positive neonates require only supportive measures.
- Possibility of viral vertical transmission is very low.

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It has been >6 months since the first case of novel coronavirus disease 2019 (COVID-19) was identified in Wuhan, China,[1] and >4 months since the World Health Organization (WHO) announced COVID-19 as a pandemic.[2] While medical communities over the entire world are learning about this new virus including pathogenesis, prevention, and treatment, there has been significant morbidities and mortalities all over the world. As of June 18, 2020, there are 8,242,999 confirmed cases and 445,535 deaths worldwide due to COVID-19.[3]

The overall understanding is that this disease is more dangerous in adults with increasing age along with comorbidities, compared with children.[4] There have been a few studies focused on understanding the clinical characteristics in the pediatric population.[4–7] Neonates are a special population in pediatrics who might have different level of risks and susceptibilities compared with the older pediatric population.

There have been multiple case reports, case series, and retrospective studies published regarding maternal transmission of COVID-19 to their newborns vertically and horizontally, as well as the morbidities in COVID-19 positive neonates.[8–46] This narrative review is to summarize the clinical characteristics of COVID-19 positive neonates and to investigate the possibility of vertical transmission of COVID-19 positive mothers to their newborns from published data to date (June 18, 2020).

Materials and Methods

We searched published articles in English language only through PubMed and Google Scholar with search terms such as "novel coronavirus," "COVID-19," "SARS-CoV-2," along with "neonate," "newborn," and "vertical transmission." We searched articles from November 15, 2019, through June 18, 2020. A total of 304 studies were retrieved. Articles were screened for COVID-19 reverse-transcriptase–polymerase chain reaction (RT-PCR)-positive and -negative neonates, COVID-19 positive or -negative pregnant women, sex, gestational age (GA) at birth, clinical findings, management, outcome, and possibility of vertical versus horizontal transmission. Finally, we included 39 studies,[8–46] which reported COVID-19 positive and/or negative neonates, regardless of the number of the COVID-19 positive mothers.

We only included the studies in our data table that reported outcomes of neonates (<28 days of life), regardless of GA at birth. We divided all the studies in three different sections as follows: (1) case reports, which reported only single cases of COVID-19 positive neonates; (2) case series or retrospective review, which reported ≥1 COVID-19 positive neonates; and (3) case series or retrospective review, which reported ≥1 COVID-19 positive mother with zero neonatal cases. We only included the single-center study data to avoid the risk of overlapping data with multihospital data registries.

Definitions

We defined "COVID-19 positive neonate" only if he/she had a positive severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) quantitative RT-PCR test in a nasopharyngeal sample. We considered a "COVID-19 positive mother" if she had a positive SARS-CoV-2 quantitative RT-PCR test in a nasopharyngeal sample during the peripartum period. "Infection prevention measures during the delivery" was mentioned if the baby was delivered in an isolation room and/or with personal protective equipment being worn by delivery staff and the baby was immediately isolated from the mother after delivery. Vertical transmission refers to the passage of a pathogen from mother to baby during the period before birth, while horizontal transmission refers to the passage of pathogen from an infected person to the baby after birth by either direct or indirect contact.

Results

►Table 1 illustrates the summary of 10 case reports, which reported only single cases of COVID-19 positive neonates, while ►Table 2 presents the summary of 7 case series and/or retrospective review, which reported ≥1 COVID-19 positive neonates. Both tables include the clinical presentation in the mother, mode of delivery, demographic characteristics of the neonate, age at diagnosis in the neonate, possible route of transmission, clinical/radiographical/laboratory findings, required management, and mortality. ►Table 3 includes 22 studies with ≥1 COVID-19 positive mother with no neonatal cases.

Overall, 23 neonates have been reported as COVID-19 positive till date (June 18, 2020), out of which 10 acquired infection through suspected vertical transmission. In all the studies, the total number of positive COVID-19 mothers were 326, so approximately 3% of the babies were born with some chances of vertical transmission. Six out of 20 (30%) were preterm neonates, while one study did not mention the GA at birth.[21] Eight out of 23 (35%) were diagnosed as late onset (>7 days of life) infection. Interestingly, 15 out of 19 (79%) were male neonates as two studies did not mention the sex of total four neonates who were COVID-19 positive.[19,30] The overall clinical presentation was asymptomatic to mild symptoms without any mortality. Three out of 23 (13%) required mechanical ventilation, but 2 out of those 3 neonates had additional contributing factors that could have accounted for the presence of respiratory distress.

Discussion

As the entire world is learning about COVID-19 virus, there has been sparse information available, to date, regarding neonates. We attempted to gather knowledge regarding neonatal clinical characteristics from currently published case series and case reports. To the best of our knowledge, we have reviewed one of the largest study population of 326 COVID-19 positive mothers with respective neonatal outcomes.

Though SARS-CoV-2 quantitative RT-PCR test has low sensitivity, it is still a gold-standard test at this time.[47,48] However, the availability of this test is limited as it is time consuming and requires specialized operators. Rapid antibody/serological tests have been available but are not recommended at this time to diagnose acute infection in neonates as per the

Table 1 Summary of single case reports with a COVID-19 positive neonate

Studies	Kamali Aghdam et al[8]	Alzamora et al[9]	Díaz et al[10]	Kirtsman et al[11]	Lorenz et al[12]	Coronado Munoz et al[13]	Piersigilli et al[14]	Wang et al[15]	Zamaniyan et al[16]	Zeng et al[17]
Maternal data										
COVID-19 positive mother	Symptomatic, but did not test	Yes	Yes, initial test negative, but symptomatic on postpartum day 3	Yes	Yes	Mother asymptomatic. Household woman symptomatic, but no testing	Yes (day 7 postdelivery)	Yes	Yes	Yes
Clinical presentation	Fever, cough, malaise, sweating	Severe respiratory insufficiency requiring MV	Fever, severe respiratory failure requiring MV	Fever, cough, malaise, myalgia	Fever, loss of smell and taste		Fever, cough	Fever, lower abdominal pain	Fever, cough, ARDS, required MV→ death	Fever, cough
Mode of delivery		C-section	C-section	C-section	SVD (vacuum)		C-section	C-section	C-section	
Neonatal data										
COVID-19 positive neonate	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Age at positive test	DOL 15	HOL 16	DOL 8	DOL 0	~HOL 54	3 weeks	DOL 7	HOL 36	HOL 24	DOL 17
Sex	Male	Male	Female	Male	Female	Male	Female	Male	Female	Male
GA at birth	Term	Preterm (33 weeks)	Term	Preterm ($35^{5/7}$ weeks)	Term	Preterm (36 weeks)	Preterm ($26^{4/7}$ weeks)	Term	Preterm (32 weeks)	Term
Infection prevention measures during delivery		Yes	No (no suspected COVID-19 in mother at delivery)	Yes			No (no suspected COVID-19 in mother at delivery)	Yes	Yes	
Possible route of transmission	Horizontal	Vertical	Horizontal	Vertical	Vertical	Horizontal	Horizontal	Vertical	Vertical	Horizontal
Clinical presentation	Fever (38.2°C), mottling, tachycardia (HR, 170/min), tachypnea (RR, 66/min), mild subcostal retraction	Depressed at birth due to maternal oversedation. Later, sporadic cough and mild respiratory difficulty	Intermittent hyperpnea with mild intercostal retractions	Hypothermia (35.9°C), transient feeding difficulties	Fever (38.6°C), cough, encephalitic symptoms (lethargic, high pitched cry, hyperexcitable)	Hypothermia (36.1°C), hypotension, tachycardia, respiratory failure	Pneumothorax after surfactant. Overall, clinically stable	Asymptomatic	Fever at birth, but then asymptomatic	Vomiting, diarrhea
CXR	Normal	Normal	Ground glass opacities on right side		B/L viral pneumonia	B/L linear opacities, RUL consolidation, pneumothorax	Nonspecific B/L streaky infiltrates			Slight blur: lower left and upper right lung
Chest CT								Few small areas of patchy shadows		Scattered opacities
Laboratory findings	Normal	Normal	Normal	Mild neutropenia, intermittent hypoglycemia	Normal	Leukopenia, lymphocytopenia, rhinovirus (+), ↑CRP, respiratory acidosis	Leukopenia, lymphocytopenia, ↑CRP	Lymphocytopenia, ↑CK		Normal

Table 1 (*Continued*)

Studies	Kamali Aghdam et al[8]	Alzamora et al[9]	Díaz et al[10]	Kirtsman et al[11]	Lorenz et al[12]	Coronado Munoz et al[13]	Piersigilli et al[14]	Wang et al[15]	Zamaniyan et al[16]	Zeng et al[17]
Respiratory support	None	MV (for 12 h, due to maternal oversedation)→CPAP→NC	CPAP at birth (2 h) →but none after diagnosis of COVID-19	None	CPAP (5 d, max. FiO_2: 0.26)	MV (5 d)	NIPPV→CPAP (FiO_2 0.21)	None		None
Medical management	Vancomycin, amikacin, oseltamivir + supportive	Supportive	Supportive	Ampicillin/tobramycin (48 h) + supportive	Supportive	Ampicillin/cefepime/vancomycin (48 h); HCQ/azithromycin (5 d) + supportive	Supportive	Supportive	Ampicillin/gentamicin + supportive	Supportive
Death	No	No	No	No	No	No	No	No	No	No

Abbreviations: ARDS, acute respiratory distress syndrome; B/L, bilateral; CK, creatine kinase; CK-MB, creatine kinase MB fraction; COVID-19, novel coronavirus disease 2019; CPAP, continuous positive airway pressure; CRP, c-reactive protein; C-section, cesarean section; CT, computed tomography; CXR, chest X-ray; DOL, day of life; FiO_2, fraction of inspired oxygen; GA, gestational age; HCQ, hydroxychloroquine; HOL, hours of life; HR, heart rate; max., maximum; MV, mechanical ventilation; NC, nasal cannula; NIPPV, nasal intermittent positive pressure ventilation; RR, respiratory rate; RUL, right upper lobe; SVD, spontaneous vaginal delivery.

Table 2 Summary of case series with ≥ 1 COVID-19 positive neonates

Studies	Buonsenso et al[18]	Ferrazzi et al[19]	Hu et al[20]	McLaren et al[21]			Sun et al[22]	Yu et al[23]	Zeng et al[24]		
Maternal data											
Number of COVID-19 positive mothers	2	42	7	No mother positive at time of delivery			3	7	33		
				Case 1	Case 2	Case 3			Case 1	Case 2	Case 3
Clinical presentation			Fever				Fever, cough, tachypnea	Fever	Fever, PROM	Cough	None
Mode of delivery	C-section	C-section (1), SVD (2)	C-section				C-section	C-section	C-section	C-section	C-section
Neonatal data											
Number of COVID-19 positive neonate	1	3	1	1	1	1	1	1	1	1	1
Age at positive test	DOL 15	DOL 1, 3, 3	HOL 24	DOL 11	DOL 16	DOL 16	DOL 6	HOL 36	DOL 2	DOL 2	DOL 2
Sex	Male		Male	Male	Male	Male	Male		Male	Male	Male
GA at birth	Term	Term	Term				Term	Term	Term	Term	

(*Continued*)

Table 2 (*Continued*)

Studies	Buonsenso et al[18]	Ferrazzi et al[19]	Hu et al[20]	McLaren et al[21]			Sun et al[22]	Yu et al[23]	Zeng et al[24]		
											Preterm ($31^{2/7}$ weeks)
Infection prevention measures during delivery	Yes		Yes				Yes		Yes	Yes	Yes
Possible route of transmission	Horizontal	Horizontal (2), vertical (1)	Vertical	Horizontal	Horizontal	Horizontal			Vertical	Vertical	Vertical
Clinical presentation	Asymptomatic	1 neonate had respiratory and GI symptoms, other 2 asymptomatic	Asymptomatic	Fever (38° C), cough	Fever (38.6° C)	Fever (38.9° C), abnormal activity level	Asymptomatic	Mild shortness of breath	Fever, lethargy	Fever, lethargy, vomiting	Respiratory distress syndrome, cyanosis
CXR			Normal		Normal			Mild pulmonary infection	Signs of pneumonia	Signs of pneumonia	Signs of pneumonia
Chest CT											
Laboratory findings			Normal	Normal	Normal	Urine culture positive (*Escherichia coli*)			↑procalcitonin	Leukocytosis, lymphocytopenia, ↑CK-MB	*Enterobacter agglomerans* positive blood culture, leukocytosis, thrombocytopenia, coagulopathy
Respiratory support		1 neonate required MV (1 day)	None	None	None	None	None	None	None	None	Noninvasive MV
Medical management	None	Supportive	Supportive	Supportive	Supportive	Antibiotics for UTI + supportive	None	Supportive	Supportive	Supportive	Antibiotics + supportive
Death	No	No	No	No	No	No	No	No	No	No	No

Abbreviations: COVID-19, novel coronavirus disease 2019; C-section, cesarean section; CT, computed tomography; CXR, chest X-ray; DOL, day of life; GA, gestational age; GI, gastrointestinal; HOL, hours of life; MV, mechanical ventilation; PROM, premature rupture of membranes; SVD, spontaneous vaginal delivery; UTI, urinary tract infection.

Table 3 Summary of studies with ≥1 COVID-19 positive mothers with zero neonatal cases

Studies	Number of COVID-19 positive mothers	Number of COVID-19 positive neonates
Algarroba et al[25]	1	0
Baergen et al[26]	20	0
Breslin et al[27]	43	0
Chen et al[28]	4	0
Chen et al[29]	9	0
Chen et al[30]	17	0
Dong et al[31]	1	0
Griffin et al[32]	14	0
Jain et al[33]	2	0
Khan et al[34]	3	0
Lee at al[35]	1	0
Li et al[36]	1	0
Li et al[37]	16	0
Liu et al[38]	19	0
Lowe and Bopp[39]	1	0
Penfield et al[40]	32	0
Qiancheng et al[41]	22	0
Wang et al[42]	1	0
Xiong et al[43]	1	0
Zambrano et al[44]	1	0
Zeng et al[45]	6	0
Zhu et al[46]	9	0

Abbreviation: COVID-19, novel coronavirus disease 2019.

Centers for Disease Control and Prevention (CDC) due to its limitations.[48,49] If a neonate of the COVID-19 positive mother cannot be tested, then he/she should be treated as if virus positive for the 14-day period of observation and the mother should still maintain precautions until she meets the criteria for noninfectivity as per the recommendation by the American Academy of Pediatrics (AAP).[50]

In studies by Dong et al and Zeng et al, immunoglobulin (Ig)-M levels were increased in three neonates.[31,45] They speculated that the elevated IgM antibody level may suggest that the neonate was infected in utero, as IgM does not transfer through placenta but RT-PCR was repeatedly negative on all three neonates in both studies. In response to these two studies, Kimberlin et al mentioned significant limitations of diagnosing any congenital infection on the basis of IgM levels. With limited knowledge about the COVID-19 infection, they cautioned against interpreting these results in favor of in-utero transmission.[51] Elevated IgG level in the same studies can suggest transfer of passive immunity from the mother against COVID-19.

Interestingly, male neonates were affected significantly more than female neonates, which was a similar observation in a review by Yagnik et al.[52] Seven neonates out of 23 (30%) were asymptomatic, while common clinical findings in symptomatic neonates were fever (38–39°C), lethargy, tachycardia, hypotension, respiratory symptoms (tachypnea and mild intercostal/subcostal retractions), and gastrointestinal symptoms (vomiting and/or diarrhea). Interestingly neonates were observed to be sicker if they had suspected horizontal transmission versus vertical transmission.[8,13,17] Coronado et al presented a 3-week-old neonate with severe respiratory failure requiring mechanical ventilation, who was also positive for rhinovirus, which can be a major confounding factor for the illness.[13,53] As per Alzamora et al, the newborn required intubation/mechanical ventilation possibly due to maternal oversedation and was extubated around 12 hours of life (HOL) without any issues.[9] As per Zeng et al, the newborn required intubation and mechanical ventilation possibly due to prematurity (31 weeks) and suspected sepsis due to *Enterobacter agglomerans* positive blood culture.[24] Lorenz et al observed encephalopathic symptoms in a neonate with COVID-19, which resolved with supportive measures. The sample from cerebrospinal fluid (CSF) was negative for COVID-19 RT-PCR.[12] Laboratory findings were mostly normal, while some neonates showed leukopenia/leukocytosis, lymphocytopenia, and increased inflammatory markers. Chest X-ray findings were mostly nonspecific, while some studies showed signs of pneumonia. Most of the neonates were managed with supportive care. Fortunately, no deaths were reported in COVID-19 positive neonates.

Few studies reported premature births suspected due to infection in COVID-19 positive mothers.[19,37,46] As per Zhu et al, 6 out of 10 neonates were born premature. The neonates presented with all the above mentioned symptoms along with one death, but none of the neonates had a positive RT-PCR test.[46] The possibility of false negative tests cannot be ruled out. They also speculated that COVID-19 infection in mothers may cause hypoxemia, therefore increasing the risk of perinatal adverse events such as birth asphyxia and premature birth. One more speculation might be the placental insufficiency. Li et al also observed increased preterm deliveries in COVID-19 positive or -suspected mothers, while they indicated the possible explanation being gestational complications, such as premature rupture of membranes and placental bleeding, which might not be directly related to COVID-19 pneumonia.[37]

In most studies, vertical transmission was suspected if a neonate was tested positive for COVID-19 RT-PCR within the first 48 HOL in presence of infection prevention measures in place during delivery. Out of 326 COVID-19 positive mothers, there were only 10 (3%) neonates that possibly acquired the virus through vertical transmission, which in fact were not proven. Algarroba et al showed potential viral transmission in the placenta by identifying coronavirus virions in placental villi using electron microscopy, but the newborn was COVID-19 RT-PCR negative and asymptomatic.[25] So, from these limited data we agree with Mimouni et al that vertical transmission from maternal infection to fetus probably occurs rarely.[54] Currently, AAP recommends testing the

newborns born to COVID-19 positive mothers at approximately 24 and 48 HOL.[50]

Rawat et al speculate on why neonates have been spared of COVID-19 serious symptomatology, but also caution that they can be carriers for transmission of the virus to vulnerable adults.[55] In addition to that, there is scarce information about the short- and long-term effects of infection on neonates. Therefore, it is vital to prevent infection in the neonates. Several publications have suggested steps to be taken to prevent horizontal transmission during neonatal resuscitation at delivery of COVID-19 positive mothers.[56–58] On that basis, AAP recommends to wear personal protective equipment including a gown, gloves, N95 respiratory mask, and eye protection goggles or an air-purifying respirator that provides eye protection while attending deliveries or conducting neonatal resuscitation for neonates born to COVID-19 positive mothers.[50] Delayed cord clamping has not been shown to transmit the virus as yet, and so it should be continued as per the unit policy.[32,50] The transmission through skin-to-skin contact is controversial, and hence, skin-to-skin contact can be allowed by the mother using facemasks and hand hygiene.[32,50,56]

As per current evidence, the virus is not transmitted via breast milk,[15,29] and so the benefits of breastfeeding outweigh the potential risk of infection transmission. Chandrasekharan et al recommend three different approaches to feed the baby as follows: (1) complete isolation and feeding formula/donor breast milk, (2) feed the expressed breast milk after taking strict precautions, or (3) breastfeeding with strict precautions.[56] The authors also suggest, it would be best practice to discuss with parents regarding these precautions before delivery and help them to participate in decision making. Most studies included in ►Tables 1–3 describe their infection prevention control strategies during delivery, which seem to prevent horizontal viral transmission significantly regardless of GA at birth.

In the home environment, the mother should try to maintain a distance of at least 6 feet when possible, use a face mask, and have hand hygiene along with above recommendations during feeding after discharge from the hospital. This can be accomplished by a thorough verbal education of the parents as per AAP.[50,59] As per CDC, if a neonate starts showing symptoms, other diagnoses for example, neonatal sepsis, influenza, should also be considered along with the diagnosis of COVID-19 and tested as per the availability.[60]

We included studies from different countries including China, Korea, India, Italy, Spain, Belgium, Germany, France, Australia, the United States, Canada, Iran, Peru, Honduras, and Brazil. The majority of the studies are from Wuhan, China, and so it is possible that there might be some overlap in the patient population, although we avoided including any studies from the national/local registries.

National Registry for Surveillance and Epidemiology of Perinatal COVID-19 Infection (NPC-19 Registry) in the United States has received information of 911 mother/infant dyads from 190 participating centers as of June 12, 2020, which has 30 infants positive for COVID-19. We look forward to have more insight into the outcomes of COVID-19 positive neonates and possibility of viral vertical transmission when the study is published.[61]

Conclusion

Majority of COVID-19 positive neonates showed mild clinical signs and symptoms with no mortality. Most neonates required only supportive measures. Interestingly, males were affected significantly more than females. Possibility of vertical transmission is very low and horizontal transmission appears to have been prevented with strict infection prevention measures during delivery regardless of GA age at birth. This review is based on current limited literature. As the pandemic continues, there will be more data available that could lead to significant changes in the current associations and recommendations.

Conflict of Interest

None declared.

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