Research Articles

Neonatal COVID-19 exposures and infections: a systematic review of modes of transmission, manifestations and management

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Keywords: neonate, sars-cov-2, covid-19

<https://doi.org/10.29392/001c.16684>

Journal of Global Health Reports

Vol. 4, 2020

Background

Since the emergence of the novel coronavirus disease (COVID-19) in December 2019, several publications have emerged describing the manifestations of the disease in different age groups. Reports from the newborn group have however been sparse. This review summarizes the mode of transmission, clinical presentations as well as treatment and outcomes of COVID-19 in neonates.

Methods

A systematic search for literature was conducted in April and in August 2020. The databases searched include PUBMED, Ovid MEDLINE, EMBASE, CINAHL, Web of Science, and Google Scholar. The search terms used included COVID-19, SARS-CoV-2, Corona virus, Newborn, Neonate, exposure, vertical transmission, breastfeeding, droplet infection. We included primary studies that were carried out globally either in hospitals or in the communities such as case reports, case series, cross-sectional studies and other qualitative or quantitative studies and published in English language, between January and August 2020.

Results

Fifty six studies were included in this review. Studies were conducted in China, Iran, South Korea, Peru, USA, Spain, Belgium, France, and Australia. A total of 416 neonates were examined between few hours old and 28 days of age. A total of 38 neonates had PCR-confirmed COVID-19 disease following testing. Fourteen (36.8%) out of the 38 neonates that tested positive had no symptoms. Clinical features reported were mild and include systemic features such as fever (4.1%), respiratory features such as tachypnoea (5.1%), cardiovascular, gastrointestinal, and dermatological features. Radiological features reported include pneumonia (1%), ground glass opacity (2.9%), consolidation (0.7%), increased lung markings (0.3%). Person to person transmission was more common. Treatment was generally supportive.

Conclusions

There is little evidence of vertical transmission in neonates. Neonatal survival following COVID-19 infection is very high perhaps due to mild nature of the disease in this age group. More research using higher quality study designs and methodologies is recommended.

A novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in December 2019 in Wuhan, Hubei Province, China.¹ Since then the disease has spread to many countries and was declared a public health emergency of international concern (PHEIC) by the World health organization on 30 January 2020.² Prior to this time, 6 coronavirus species were known to cause human disease, four

of which is known to cause common cold-like infections in immunocompetent humans (229E, OC43, HKU1, NL63), the other two namely, severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV), are zoonotic in origin and are known to cause severe respiratory disease in humans. A lot is known about the disease whose common symptoms are fever, cough and shortness of breath. Globally, as at 8th

September 2020, there have been 27,236,916 confirmed cases of COVID-19, including 891,031 deaths, reported to WHO with increasing numbers everyday.³

In spite of all efforts to contain the pandemic, the number of infections and deaths from COVID-19 keeps increasing. Elderly persons and adults with other background medical conditions have been the worst affected.⁴ Many documented studies on COVID-19 are mostly on adults and some on older children with few on neonates.

In Italy, Japan, and Thailand, there were community based infections with cases of SARS-CoV-2 associated pneumonia reported in children.^{4–6} Reported paediatric cases were mainly family cluster cases with epidemiological links to adults.^{4–6} Paediatric cases appear to have a milder clinical course than those in adults and rarely deaths have been reported in children.⁶ These may imply that pediatric cases may play a role in community spread of SARS-CoV-2 since the viral shedding may continue from nasal secretions as well as through fecal matter for several weeks after diagnosis.⁷ Infections of SARS-CoV-2 in neonates have been said to be mild also.⁷ The reason behind the less susceptibility and mild infections of SARS-CoV-2 in neonates is largely unclear especially as neonates are not generally protected from respiratory viral infections. Although vertical transmission of COVID-19 is still being debated, maternal COVID-19 infections especially when associated with severe hypoxia and fever may result in fetal distress, premature delivery and other risks.

Limited evidence exists however on mode of transmission, prevalence and clinical features of COVID-19 in neonates. It has been shown that mothers may transmit the infections by droplets during breastfeeding or by vertical transmission.⁸ Common presentations of fever and respiratory signs have been found to occur in neonates with COVID-19 however other existing co-morbidities such as prematurity and chromosomal disorder makes it unclear as to the actual cause of these signs.^{1,9} Other times, neonates may present with non-specific symptoms such as lethargy and dehydration making diagnosis difficult. Treatment of COVID-19 have been largely symptomatic with no definitive therapy.^{3,7} Drug trials have been largely done in adult population. A clear understanding of the symptomatology of COVID-19 among neonates, its mode of transmission and diagnosis is needed to improve public health and clinical response. There is some knowledge gap with regards to COVID-19 in neonates despite its epidemiological importance, and therefore, it is our objective to describe the documented modes of transmission, clinical features, treatment, complications and outcome of infections of SARS-CoV-2 in neonates by a systematic review of existing literature.

METHODS

The Preferred Reporting Items for systematic Reviews and Meta-Analysis (PRISMA) checklist for reporting a systematic review or meta-analysis protocol was used for this review (Online Supplementary Document, Appendix 1).¹⁰

SEARCH STRATEGY AND SELECTION CRITERIA

A systematic search for literature was conducted on 5th April 2020 and on 4th August 2020. The databases searched include PubMed, Ovid MEDLINE, EMBASE, CINAHL, Web of Science, and Google Scholar. Other COVID-19 data provided freely by various institutions on their websites were also retrieved. The search terms used included keywords, text words and medical subject headings (MeSH) terms and sub-headings of the following: COVID-19, SARS-CoV-2, Corona virus, Newborn, Neonate, exposure, vertical transmission, breastfeeding, droplet infection.

Box 1. Selection criteria

Inclusion criteria

- Primary Studies (Original studies) that used any study design
- Studies published in English language
- Studies that reported COVID-19 exposure, transmission, infection, and disease in the newborn

Exclusion criteria

- Review articles
- Studies published in other languages

INCLUSION AND EXCLUSION CRITERIA

We included primary studies that were carried out globally either in hospitals or in the communities such as case reports, case series, cross-sectional studies and other qualitative or quantitative studies and published in English language, between January and August 2020 which reported COVID-19 exposure, transmission, infection, and disease in the newborn.. Review articles and studies in other languages apart from English were excluded.

STUDY SELECTION

A total 1250 studies were identified from the initial search of databases and institutional sources 1830 from other sources including institutionally provided data. After duplicates were removed, the number of remaining publications was 530 articles, and these were reviewed for inclusion based on information contained in titles and abstracts.

Studies not addressing exposure of transmission to or infection in newborns were excluded to give a total of 109 full text articles. These were assessed further, and 56 full text articles were included for the review ([Figure 1](#)).

DATA EXTRACTION

A data extraction form was developed and reviewed by all authors. Data was extracted for each paper using the standardised form with the following domains: the name of first

Figure 1. PRISMA FLOW DIAGRAM

author and year of publication, study location, study design, clinical features, laboratory and radiological findings, diagnosis of Covid-19, treatment and outcome. Two of the reviewers extracted the data independently and discrepancies were resolved by discussion and consensus. The references were tracked using EndNote reference manager where duplicates were also removed.

QUALITY ASSESSMENT OF STUDIES

Quality assessment of studies was done using the Newcastle Ottawa Scale for Case Control Studies,¹¹ Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies,¹² and the Tool for Evaluating the Methodological Quality of Case Reports and Case Series¹³ (Online Supplementary Document, Appendix 2). All the case reports and case series included in this review fulfilled the quality criteria (Online Supplementary Document, Appendix 3). For the cross sectional studies, most of the studies had “not applicable” or “cannot determine” as responses to the questions on sample size calculation, measurement of exposure and outcome variables and on statistical analysis, but fulfilled the criteria with regards to questions on study objec-

tives, study population and sampling (Online Supplementary Document, Appendix 4).

ETHICS CONSIDERATIONS

Ethical approval was not required for this study because it is a systematic review with no direct involvement of human or animal study participants.

RESULTS

STUDY CHARACTERISTICS

Fifty-six studies were included in this review. Thirty one of the studies were conducted in China while the remaining studies were carried out in Iran (five)^{1,14–17}, South Korea (two)^{2,18}, USA (seven)^{3,19–24}, Italy (four)^{25–28}, Spain (three)^{29–31}, Peru (one)⁴, France (one)³², Australia (one)³³, Belgium (one)³⁴ (Table 1). All the studies were published between January and August 2020 (Table 1). The study designs included in this review were 33 case reports, 13 case series, one expanded case series, one case control study,

and eight cross-sectional studies([Table 1](#)). From the included studies, a total of 416 neonates were examined between few hours old and 28 days of age. A total of 38 neonates had PCR-confirmed COVID-19 disease following testing ([Table 2](#)). Fourteen (36.8%) out of the 38 neonates that tested positive had no symptoms.^{14–16,23,25,29,34–39}

Table 1: General characteristics of studies included in the review

First Author	Year	Month	Country	Region or State	Type of Study	No of neonates
Alzamora ⁴	2020	April	Peru	NS	Case report	1
Dehan Liu ⁴⁰	2020	March	China	Wuhan	Case series	11
Mi Seon Han ²	2020	April	South Korea	Seoul	Case report	1
Peng Z ⁵	2020	April	China	Chongqing	Case report	1
Na Li ⁴¹	2020	March	China	Wuhan	case control	17
Pu Yang ⁴²	2020	April	China	Wuhan	Case Series	7
Siyu Chen ⁹	2020	March	China	Hubei	Case series	5
Wei Liu ⁴³	2020	April	China	Wuhan	Cross sectional	19
Xiali Xiong ⁶	2020	April	China	Beijing	Case report	1
Lingkong Zeng ⁴⁴	2020	March	China	Wuhan	Cross sectional	33
Kamali Aghdam ¹	2020	April	Iran	Tehran	Case report	1
Lingkong Zeng ⁷	2020	April	China	Wuhan	Case report	1
Wang Shaoshuai ⁸	2020	March	China	Wuhan	Case report	1
Chen Yan ⁴⁵	2020	March	China	Wuhan	Case report	4
Munoz ³	2020	May	USA	Houston	Case report	1
Zhu ⁴⁶	2020	Feb`	China	Wuhan	Cross sectional	10
Nan Yu ⁴⁷	2020	March	China	Wuhan	Cross sectional	7
Cuifang Fan ⁴⁸	2020	March	China	Wuhan	Case series	2
Li Yao ⁴⁹	2020	March	China	Hefei	Case report	1
Zhuang Siying ⁵⁰	2020	February	China	Wuhan	Case report	1
Bai Bailiang ⁵¹	2020	March	China	Shaanxi	Case report	1
Patek Paul ²¹	2020	April	USA	Royal oak	Case report	1
Sinelli MT ²⁷	2020	May	Italy	Monza	Case report	1
Hantoushzadeh Sedigheh ¹⁴	2020	April	Iran	Tehran	Case series	7
Vikramaditya Dumpa ²²	2020	May	USA	New York	Case Report	1
Xiaolin Hu ³⁷	2020	April	China	Wuhan	Case series	7
Alonso Diaz ³¹	2020	April	Spain	Madrid	Case report	1
Iqbal S ²⁴	2020	April	USA	Washington	Case report	1
Khan S ⁵²	2020	April	China	Wuhan	Case series	17
Belinda Lowe ³³	2020	April	Australia	Queensland	Case report	1
Ferrazzi E ²⁸	2020	April	Italy	Lombardia	Cross sectional	42
Zamaniyan M ¹⁵	2020	April	Iran	Sari	Case report	1
Lu D ⁵³	2020	April	China	Hefei	Case report	1
Wang J ⁵⁴	2020	March	China	Wuhan	Case report	1
Sun M ³⁸	2020	May	China	Zhengzhou	Case series	3
Wu Y ⁵⁵	2020	May	China	Wuhan	Case Series	5
Piersigilli ³⁴	2020	May	Belgium	Brussels	Case report	1
Chen Huijun ³⁹	2020	February	China	Wuhan	Cross sectional	9
Xiaotong Wang ⁵⁶	2020	February	China	Suzhou	Case report	1
Zhi-Jiang Zhang ³⁶	/2020	March	China		Case series	4
Zeng H ⁵⁷	2020	March	China	Wuhan	Case series	6
Dong Lan ⁵⁸	2020	March	China	Wuhan	Case report	1
Buonsenso ²⁵	2020	April	Italy	?	Case series	2
Noelle ²³	2020	May	USA	New York	Cross sectional	18
Jie Yan ⁵⁹	2020	July	China	Wuhan	Expanded case	116

First Author	Year	Month	Country	Region or State	Type of Study	No of neonates
					series	
Yan Ting wu ³⁵	2020	July	China	Wuhan	Cross sectional	30
Eun-Kyung Lee ¹⁸	2020	July	South Korea	Daegu	Case report	1
Fatemeh Eghbalian ¹⁶	2020	July	Iran	Hamadan	Case report	1
Gregorio-Hernández ²⁹	2020	June	Spain	?	Case series	2
Serafina Perrone ²⁶	2020	May	Italy	Parma	Case report	1
Mahdavi ¹⁷	2020	June	Iran	Shahroud	Case Report	1
Rishi Lumba ¹⁹	2020	July	USA	New York	Case report	1
Rocio ³⁰	2020	June	Spain	Barcelona	Case report	1
Salik ²⁰	2020	May	USA	New York	Case report	1
Ying Xiong ⁶⁰	2020	July	China	Wuhan	Case report	1
Soumeth Abasse ³²	2020	August	France	Mayotte	Case report	1

Table 2: Clinical, laboratory presentations, and management outcomes of COVID-19 exposed and infected neonates

First Author	Clinical features	Laboratory findings	Radiological findings	Diagnosis of COVID-19	Treatment	Outcome
Li Yao	None	Normal	ND	Negative nasopharyngeal, anal, peripheral blood samples	None	Alive
Zhuang Siying.	Reduced milk intake	Elevated Myoglobin and CK-MB	Normal	Negative urine, pharyngeal, breast milk, peripheral blood sample	Supportive	Alive
Bai Bailiang.	None	ND	ND	Negative amniotic, placental, breast milk and cord blood sample	Supportive	Alive
Patek Paul	Fever, cyanosis, reduced milk intake, fussiness	Decreased neutrophil, deranged liver function test	bilateral perihilar streaking without focal	Positive nasopharyngeal sample	Supportive, oxygen, antibiotic, antiviral	Alive
Sinelli MT	Cyanosis, poor suck, bradypnoea	Normal white blood cell parameters, Arterial blood gas analysis demonstrated moderate hypoxia	mild bilateral ground-glass opacities	Positive nasopharyngeal sample	Supportive, oxygen, antibiotic	Alive
Hantoushzadeh Sedigheh	None (5) Not applicable (5)	ND (4) Lymphopenia (1) Not applicable (5)	ND (5) Not applicable (3)	Negative (2) Positive on day 7 (1) ND (3) Not applicable (5)	Supportive (2) None (3) Not applicable (5)	Fetal demise (3) Alive (5)
Vikramaditya Dumpa	Fever, feed intolerance, tachycardia	Normal white blood cell parameters	ND	Positive nasopharyngeal sample	Supportive, antibiotic	Alive
Xiaolin Hu	None (7)	Normal white blood cell parameters (7), normal liver function test (7), normal creatinine kinase (7), normal C-reactive protein (7), normal procalcitonin (7)	Normal (7)	Positive nasopharyngeal, oropharngeal, amniotic fluid, peripheral blood sample (1) Others (6) negative samples	Supportive (1), antibiotic (1), None (6)	Alive (7)
Alonso Díaz	Fast breathing, dyspnea, cyanosis,	Mild acidosis	Ground glass opacities mainly in the perihilar area	Positive nasopharyngeal sample	Supportive, oxygen, antibiotic	Alive
Chen S	None (5)	ND (5)	ND (5)	Negative nasopharyngeal sample	Supportive (5) Antibiotic (5) Antiviral (5)	All alive
Iqbal S	None	Normal white blood cell parameter	ND	Negative nasopharyngeal, oropharyngeal, rectal sample	Supportive	Alive
Chen Y	None (2) Fast breathing (1) Dyspnea (1) Edema (2) Rash (20	Normal white blood cell parameters (3) Normal LFT (3) ND (1)	Normal (3) ND (1)	Negative throat sample (4)	Supportive (4) Oxygen (1)	Alive
Xiong X	None	Normal immunogloblin	ND	Negative nasopharyngeal, throat, rectal, amniotic fluid, placental, breast milk	Supportive	Alive
Khan S	Not available	ND	Normal USS finding	Positive throat samples in 2 babies, Negative amniotic, placental, cord blood in 17 babies	Supportive	Alive
Belinda Lowe	None	ND	ND	Negative throat sample	Supportive	Alive
Ferrazzi E	Abdominal distension, fast	ND	ND	Positive nasopharyngeal samples (3)	Supportive	All alive

First Author	Clinical features	Laboratory findings	Radiological findings	Diagnosis of COVID-19	Treatment	Outcome
	breathing, dyspnea, cyanosis, feed intolerance, reduced milk intake (1)				(42) Oxygen (1) Antibiotic (1)	
Zamaniyan M	None	ND	ND	Positive nasopharyngel and amniotic fluid samples. Negative throat sample	Supportive	Alive
Lu D	None	ND	Normal findings	Negative nasopharyngeal, oropharyngeal, peripheral blood	Supportive	Alive
Munoz AC	Nasal congestion, fast breathing, dyspnea, reduced milk intake, tachycardia, hypothermia, hypotension	Lymphocytosis, increased cytokine levels, acidosis	bilateral linear opacities and consolidation in right upper lobe	Positive nasopharyngeal sample	Supportive, oxygen, antibiotic	Alive
Wang J	Fever, vomiting, reduced milk intake, diarrhea	Thrombocytopenia, positive for occult blood, Normal LFT, CK, immunoglobulin, cytokines	Patchy fuzzy shadows	Positive anal, throat sample	Supportive, interferon	Alive
Sun M	None (1) Fast breathing (2) Dyspnea (2)	Neutrophilia (1)	Normal finding (1), ND (2)	Positive (1) Negative (2)	Supportive (3) Oxygen (2) Antibiotic (2)	All alive
Wu Y	None (5)	Leucopenia (1) Lymphopenia (1) Positive immunoglobulin (1)	ND (1)	Negative throat sample (1) Positive breast milk sample (1)	Supportive (5)	All alive
Wei Liu	None	Normal white blood cell, CK, LFT, immunoglobulin, cytokine	Normal	Negative stool, throat, amniotic fluid, breast milk samples	Supportive	Alive
Kamali Aghdam	Fever, fast breathing, dyspnea, lethargy, tachycardia, mottling	Normal white blood cell parameters, LFT, CK	Normal	Positive nasopharyngeal sample	Supportive, oxygen, antibiotic, antiviral	Alive
Piersigilli	None	Lymphopenia	Bilateral streaky infiltrates	Positive nasopharyngeal sample, Negative breast milk sample	Supportive, oxygen	Alive
Zhu Huaping	Fever (), abdominal distension (), fast breathing (6), cyanosis, feeding intolerance, vomiting, reduced milk intake, tachycardia	Thrombocytopenia (2), deranged LFT (2),	Evidence of Infections, RDS, Pneumothorax, granular and scattered patchy shadows	Negative nasopharyngeal sample	Supportive, oxygen,	Alive (9) Neonatal death (1)
Peng Z	Fast breathing, moaning	Leucopenia, reduced procalcitonin	Reduced lung volume	Negative saliva, plasma, urine, anal, throat sample	Supportive, oxygen, antibiotics	Alive
Wang Shaoshuai	Ruddy skin appearance, vomiting	Lymphopenia, deranged LFT, increased cytokine	Thickened lung texture, High density nodular shadow	Positive nasopharyngeal, anal samples. Negative placental, breast milk and cord blood samples	Supportive, antibiotic	Alive
Cuifang Fan	Fever (1), abdominal distension (1)	Lymphopenia (2)	Diffuse haziness (1) ND (1)	Negative nasopharyngeal, amniotic fluid, placental, breast milk, cord blood samples	Supportive, antibiotics	Alive
Yu Nan	None (6) Fast breathing (1)	ND (7)	Evidence of mild pulmonary infection (1)	Positive nasopharyngeal sample (1) Negative nasopharyngeal sample (2) ND (4)	Supportive (1) Antibiotic (1)	All alive
Zeng Lingkong	Fever (2), fast breathing (3),	Leucocytosis (1), normal LFT (3),	Evidence of pneumonia (3)	Positive nasopharyngeal and anal	Supportive	All alive

First Author	Clinical features	Laboratory findings	Radiological findings	Diagnosis of COVID-19	Treatment	Outcome
	lethargy (1), vomiting (1)	increased CK (1)		samples (3) Negative amniotic fluid, breast milk and cord blood samples (3)	(3), Oxygen (1) antibiotic (1)	
Huijun Chen	ND (9)	Increased CK (1)	ND (9)	Positive nasopharyngeal (1), negative nasopharyngeal samples (5), ND (3) Negative amniotic, breast milk and cord blood samples (9)	Supportive (9)	All alive
Xiaotong Wang	None	ND	ND	Negative stool, throat, amniotic fluid, placental and cord blood samples	Supportive	Alive
Zhi-Jiang Zhang	None (1) Fever (2), dyspnea (1), vomiting (1), cough (1)	ND (4)	ND (1) Increased lung markings	Positive nasopharyngeal samples (2) Positive anal samples (2)	Supportive (4)	All alive
Zeng H	None	Elevated immunoglobulin (2)	ND	Negative throat and peripheral blood samples	Not available	All alive
Dong Lan	None	Leukocytosis, elevated immunoglobulin and cytokines,	Normal	Negative nasopharyngeal samples	Not available	Alive
Zeng Lingkong	Ruddy skin appearance, fast breathing, vomiting, sneezing, reduced milk intake	Normal white blood cell parameters, LFT, CK, immunoglobulin	Opacities	Positive anal, pharyngeal samples	Supportive	Alive
Buonsenso	None (2)	ND (2)	ND (2)	Positive nasopharyngeal samples	Supportive (1)	All alive
Pu Yang.	None (6), vomiting (1)	Elevated cytokines (5)	Evidence of RDS (5)	Negative throat, amniotic fluid, cord blood samples	Supportive (7)	All alive
Alzamora.	Dyspnea, cough	Normal white blood cell parameters, immunoglobulin	Normal	Positive nasopharyngeal sample	Supportive, oxygen	
Noelle	None	ND	ND	Negative nasopharyngeal	Supportive, oxygen	Alive
Jie Yan	None	ND	ND	Negative	Oxygen (1)	Alive (115) Fetal death (1)
Yan Ting wu	None (29) Fever (1)	Leukocytosis (5) Neutrophil (5) ND (25)	Opacities (5)	Positive nasopharyngeal samples (2)	Supportive (5) Interferon (3) None (25)	All alive
Mi Seon	Fever, vomiting, cough, jaundice, tachycardia	Normal white blood cell parameters, LFT, CK, immunoglobulin	Normal	Positive nasopharyngeal, oropharyngeal, saliva, stool, plasma, urine	Supportive	Alive
Na Li	ND	ND	ND	Negative throat samples	Supportive	All alive
Dehan Liu	ND	ND	ND	Negative nasopharyngeal samples	None	All alive
Eun-Kyung Lee	None	Normal white cell parameters	Normal	Negative nasopharyngeal, oropharyngeal, stool, urine, amiotic fluid, placenta, peripheral blood and cord blood samples	None	Alive
Fatemeh Eghbalian	None	Normal white cell parameters, LFT	Normal	Positive oropharyngeal, stool, saliva, plasma, urine, anal, throat, rectal, pharyngeal, amniotic fluid, breast milk,	None	Alive

First Author	Clinical features	Laboratory findings	Radiological findings	Diagnosis of COVID-19	Treatment	Outcome
				peripheral blood, cord blood		
Gregorio-Hernández	None	ND	thin pleural line with conserved lung sliding (1), B-lines, consolidation (1), A pattern, B lines, superficial consolidation (1)	Positive nasopharyngeal samples (2) Positive bronchoalveolar aspirate (1)	None (2) Supportive (1) Oxygen (1)	All alive
Serafina Perrone	None	ND	ND	Negative nasopharyngeal and breast milk samples	Supportive (1) Oxygen (1)	Alive
Mahdavi	Fever, dyspnea, lethargy, cyanosis, cough, reduced milk intake, nasal congestion	Normal white cell parameters	Consolidation with air bronchograms	Positive nasopharyngeal sampl	Supportive, oxygen, antibiotic, antiviral	Alive
Rishi Lumba.	None	Neutrophilia, normal cytokine, LFT, CK, immunoglobulin	Normal	Negative nasopharyngeal, oropharyngeal, stool, saliva, plasma, urine, anal, throat, rectal, pharyngeal, amniotic fluid, breast milk, peripheral blood, cord blood	Antibiotic	Alive
Rocio	Fever, nasal discharge, hypertonia	Normal white cell parameters and LFT, increased CK	Normal	Positive nasopharyngeal sample	Antibiotic	Alive
Salik	Fast breathing, cyanosis, lethargy, feed intolerance	ND	Bilateral pulmonary granular opacities and reduced lung volumes	Positive nasopharyngeal sample	None	Alive
Soumeth Abasse	None	Normal white cell parameters and LFT, increased CK	Ground glass opacities and consolidation	Positive nasopharyngeal sample	None	Alive
Ying Xion.	Not available	Neutrophilia, lymphopenia, increased cytokines	Bronchovascular shadows and ground-glass opacity	Positive oropharyngeal sample	None	Alive

ND: Not documented; LFT: Liver function test; Creatine kinase;

CLINICAL AND LABORATORY FEATURES

The following are clinical and/or laboratory examinations and results that were described by the studies.

CLINICAL FEATURES

1. Systemic features: Thirteen studies reported neonatal fever after birth to a COVID-19 positive mother with a total of 17 neonates.^{1,2,17,21,22,30,35,36,38,44,46,48,54} Four studies showed that four neonates had lethargy.^{1,17,20,44} Swollen superficial lymph nodes was identified in a COVID-19 positive male neonate,⁷ and hypothermia was reported in one neonate (Table 3).³
2. Respiratory features reported include cough (four neonates),^{2,4,17,36} nasal discharge, congestion and stuffiness (6 neonates),^{1-3,17,30} tachypnoea (21 neonates),^{1,3,5,7,28,31,38,44-47} respiratory distress syndrome (5 neonates),^{42,44} mild respiratory distress (3 neonates),^{1,4,32} moaning (3 neonates),^{5,45} asphyxia (4 neonates),^{38,44,59} and sneezing (1 neonate) (Table 3).⁷
3. Cardiovascular features include tachycardia in 5 neonates, cyanosis in 12 neonates, dyspnoea in 9 neonates,^{1,4,17,28,31,36,38,45} and hypotension in one neonate (Table 3).³
4. Skin/dermatological features reported include cutaneous mottling (one neonate),¹ whole body jaundice (one neonate),² rash (3 neonates),^{45,46} ruddy skin colour (2 neonates),^{7,8} and skin ulceration (one neonate) (Table 3).⁴⁵
5. Gastrointestinal features: Abdominal distension was reported in 3 neonates,^{28,46,48} reduced feeding and feeding intolerance in 8 neonates,^{3,7,22,28,44,46} and reduced milk intake in 8 neonates.^{3,7,17,21,28,46,50,54} Milk refusal, bloating and gastric bleeding was reported among COVID-19 negative neonates born to positive mothers in one study.⁴⁶ Nine studies reported vomiting in nine neonate^{2,7,8,30,36,42,44,46,54} (Table 3) while diarrhoea was reported in two neonates in two studies.^{7,54}

RADIOLOGICAL AND LABORATORY RESULTS

1. SARS-CoV-2 testing following childbirth: 38 (9.0%) neonates had PCR confirmed COVID-19 infection. For majority of the babies, nasopharyngeal swab was used for testing.
2. Radiological features reported include bilateral perihilar streaking (one neonate),²¹ ground glass opacities (12 neonates),^{3,7,20,27,31,32,35,60} consolidation (3 neonates),^{3,17,32} patchy fuzzy shadows (one neonate),⁵⁴ bilateral streaky infiltrates (one neonate),³⁴ pneumothorax (one neonate),⁴⁶ reduced lung volume (two neonates),^{5,20} thickened lung texture (one neonate),⁸ diffuse haziness (one neonate),⁴⁸ mild pulmonary infection (two neonates),^{46,47} pneumonia (4 neonates),^{44,48} Respiratory distress syndrome (RDS) (4 neonates),^{38,42,46} Bronchovascular shadows (2 neonates),^{46,60} increased lung markings

(3 neonates) (Table 4).³⁶

3. Other laboratory findings identified include: Elevated white blood cell (WBC) count (10 neonates),^{35,44,45,58} Abnormal Liver Function Test (LFT) (four neonates),^{8,21,46} Elevated cytokines (two neonates),^{3,42,58} elevated creatine kinase (nine),^{8,30,39,42,44} Lymphopenia (6 neonates) (Table 4).^{8,14,34,48,55}

TRANSMISSION

Among the 38 neonates that tested positive, vertical transmission was reported in 11 neonates, while horizontal transmission was reported in 17 babies. The route of transmission was not clear in the remaining babies (Table 5).

TREATMENT RECEIVED

Treatment was supportive for majority of the babies. Few received antiviral (9 neonates),^{1,9,17,21,47} antibiotics 23 neonates),^{1,3,5,8,9,17,19,21,22,27,28,30,31,35,37,38,44,48} and oxygen therapy/ventilation (22 neonates) (Table 4).^{4,5,17,21,23,26-29,31,34,38,42,44,45,59}

OUTCOMES AND COMPLICATIONS

The complications reported include pneumonia, pneumothorax, refractory shock, and hypoxic respiratory failure. Neonates who tested positive were discharged after they tested negative to the virus. All the COVID-19 positive babies survived (Table 2). Three of the studies reported neonatal death in 5 neonates but these babies were not tested before death.^{14,46,59}

DISCUSSION

The review examined studies that looked at the exposure to, transmission and infection of neonates as well as clinical manifestation, laboratory findings and outcomes of neonates whose mothers had COVID-19 infection. Few neonates of mothers with COVID-19 infection in this review tested positive to the virus. This finding does not support vertical transmission as a major mode of infection of the newborn. It should be noted however that quite a number of the neonates were delivered through caesarean section and the health care workers may have observed adequate infection prevention and control measures. Some of the neonates who had positive results had close contacts with other family members diagnosed with coronavirus and possibly got the infection from person-to-person transmission.¹⁻³ Wang et al⁸ reported a positive test of COVID-19 in a 36 hour-old neonate in Wuhan, China. A possibility of nosocomial infection was entertained by the authors because the initial cord blood and placenta test results were negative for severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). However, the finding of positive nasopharyngeal and anal swabs among 3 out of 33 neonates whose mothers had COVID-19 pneumonia by day 2 of life by Zeng et al⁴⁴ raises the possibility of vertical transmission. Duran et al⁶¹ in a systematic review of neonatal cases also did not

Table 3: Summary of neonatal clinical presentations by number of studies

Clinical Features		Number of studies	Number of babies (Proportion of exposed and positive babies with symptoms)
Systemic Features	Fever ^{1,2,17,21,22,30,35,36,38,44,46,48,54}	13	17(4.1%)
	Lethargy ^{1,17,20,44}	4	4(1.0%)
	Lymphadenopathy ⁷	1	1 (0.2%)
	Hypothermia ³	1	1 (0.2%)
	Edema ⁴⁵	1	2(0.5%)
Respiratory Features	Cough ^{2,4,17,36}	4	4(1.0%)
	nasal discharge, nasal congestion and stuffiness ^{1-3,17,30}	6	6(1.4%)
	Tachypnoea ^{1,3,5,7,20,28,31,38,44-47}	12	21(5.1%)
	RDS ^{42,44}	2	5(1.2%)
	Mild respiratory distress ^{1,4,32}	3	3(0.7%)
	Moaning/Mild grunting ^{5,42}	2	3(0.7%)
	Asphyxia ^{38,44,59}	3	4 (1.0%)
	Sneezing ⁷	1	1(0.2%)
Cardiovascular Features	Tachycardia ^{1-3,22,46}	5	5(1.2%)
	Dyspnoea ^{1,4,17,28,31,36,38,45}	8	9(2.2%)
	Cyanosis ^{3,17,20,21,27,28,31,38,44,46}	10	12(2.9%)
	Hypotension ³	1	1(0.2%)
Skin/ Dermatological features	Cutaneous mottling ¹	1	1(0.2%)
	Whole body Jaundice ²	1	1(0.2%)
	Rash ^{45,46}	2	3(0.7%)
	Ruddy Skin colour ^{7,8}	2	2 (0.5%)
	Skin Ulceration ⁴⁵	1	1(0.2%)
Gastrointestinal Features	Abdominal Distension ^{28,46,48}	3	3(0.7%)
	Reduced feeding and feeding intolerance ^{3,7,22,28,44,46}	6	8 (1.9%)
	Reduced milk intake ^{3,7,17,21,28,46,50,54}	8	8(1.9%)
	Bloating and gastric bleeding ⁴⁶	1	1(0.2%)
	Vomiting ^{2,7,8,30,36,42,44,46,54}	9	9(2.2%)
	Diarrhoea ^{7,54}	2	2(0.5%)

find any evidence of vertical transmission of corona virus.

Most of the neonates who were positive for SARS-CoV-2 had mild clinical symptoms. Mild symptoms according to World Health Organisation (WHO) interim guideline is when the patient has uncomplicated upper respiratory tract viral infection with non-specific symptoms such as fever, fatigue, cough, malaise and rarely may present with diarrhea,

nausea, and vomiting.⁶² This finding is similar to reports in older children who also presented with mild or moderate clinical symptoms.^{63,64} The findings of cough, tachypnea, nasal discharge in neonates who tested positive for COVID-19 observed in this review is in keeping with findings in some studies carried out among older children and adults.⁶⁵⁻⁶⁷

Table 4: Laboratory features, Radiological features, and Treatment

Features	Number of Studies	Number of Neonates (Proportion of exposed and positive babies with symptoms)
Radiological Features		
Bilateral perihilar streaking ²¹	1	1(0.2%)
Ground glass opacities ^{3,7,20,27,31,32,35,60}	8	12(2.9%)
Consolidation ^{3,17,32}	3	3(0.7%)
Patchy fuzzy shadows ⁵⁴	1	1(0.2%)
Bilateral streaky infiltrates ³⁴	1	1(0.2%)
Pneumothorax ⁴⁶	1	1(0.2%)
Reduced lung volume ^{5,20}	2	2(0.5%)
Thickened lung texture ⁸	1	1(0.2%)
Diffuse haziness ⁴⁸	1	1(0.2%)
Mild pulmonary infection ^{46,47}	2	2(0.5%)
Pneumonia ^{44,48}	2	4(1.0%)
RDS ^{38,42,46}	3	4(1.0%)
Bronchovascular shadows ^{46,60}	2	2(0.5%)
Increased Lung markings ³⁶	1	3(0.7%)
Laboratory Features		
Elevated WBC count ^{35,44,45,58}	4	10(2.4%)
Abnormal LFT ^{8,21,46}	3	4(1.0%)
Elevated Cytokines ^{3,42,58}	3	3(0.7%)
Elevated Creatine Kinase ^{8,30,39,42,44}	5	9 (2.2%)
Lymphopenia ^{8,14,34,48,55}	5	6(1.4%)
Treatment		
Antiviral ^{1,9,17,21,47}	5	9(2.2%)
Interferon ^{35,54}	2	4(1.0%)
Antibiotics ^{1,3,5,8,9,17,19,21,22,27,28,30,31,35,37,38,44,48}	18	23(5.5%)
Oxygen/ventilation ^{3-5,17,21,23,26-29,31,34,38,42,44,45,59}	17	22 (5.3%)

WBC: White blood cell; RDS: Respiratory distress syndrome

Table 5: Modes of neonatal COVID-19 exposures and transmissions in included studies

Mode of transmission	Number of Studies	Number of babies
Horizontal (Person to Person) ^{1-3,7,14,21,22,25,27,28,31,34,36,38,39,54}	16	17
Vertical transmission ^{4,35-37,59}	5	11
Uncertain about mode of transmission ^{8,15,29,44,47}	3	10

Lymphopenia observed among these neonates has also been reported in older paediatric age groups.⁶⁸ In adults with COVID -19 infection, lymphopenia is associated with poor prognosis and is an indicator of severe disease.⁶⁸⁻⁷⁰ Possible explanations for lymphopenia include direct infection of the lymphocytes, damage to lymphoid organs, disruption of activities of cytokines resulting in apoptosis of lymphocytes.⁷⁰ Fever was a significant finding in newborns delivered to COVID-19 positive mothers, despite the fact that quite a number of these babies were negative. This

could be as a result of maternal cytokines transferred passively to the fetus and evoking immune response in the neonatal period. The implication of this finding is the fact that the presence of fever in a newborn during this period of COVID-19 pandemic may be a good reason to screen mothers for SARS-CoV-2 infection. In adult populations, fever was also a frequent finding alongside fatigue and cough during presentation in the hospital.^{65,66}

Gastrointestinal symptoms appear to be a common finding in neonates who were positive for COVID-19. These

have also been reported among other paediatric age groups.⁷¹ Symptoms such as reduced feeding, vomiting and diarrhea may be due to the body's response to acute viral replication in the gastrointestinal tract. Therefore, the presence of gastrointestinal features in a neonate born to a COVID-19 positive mother or who may have been exposed to a COVID-19 positive individual, may raise a suspicion of COVID-19 infection in the neonate. SARS-CoV-2 RNA has been demonstrated in stool samples of hospitalized patients with COVID-19 with some still having positive stool test even after respiratory samples have tested negative, thereby posing a risk of feco-oral transmission.⁷²

There is currently no definitive drug treatment for COVID-19 infection. In this review, supportive therapy which includes administration of intravenous fluids, intranasal oxygen were the mainstay of treatment for COVID-19 positive neonates because many of them had mild clinical symptoms. Some of the neonates received intravenous antibiotics as a way of preventing secondary bacterial infection. A few studies documented the use of antiviral drugs like oseltamivir and acyclovir.^{1,9,14,18} The effect of these drugs in the clinical course of COVID-19 infection is still being evaluated. In this review most of the neonates did not receive antiviral drugs and still had good outcome. The use of oseltamivir has been reported among adults with COVID-19 infection without significant outcome or change in disease progression.⁶⁵ Chloroquine and hydroxychloroquine have been demonstrated to have in vitro activity against SARS-CoV-2.⁷³ The combination of hydroxychloroquine and azithromycin has been reported to improve clinical outcomes among adult population in France,⁷⁴ though this was a retrospective study and therefore has its limitations. In a randomized control trial in Spain among adult population with mild COVID-19 infection, no benefit was observed with use of hydroxychloroquine.⁷⁵ Recently the U.S Food and Drug Administration (FDA) issued emergency use authorization of remdesivir for the treatment of suspected or laboratory confirmed severe cases of COVID-19 in adult and children.⁷⁶ Therefore, more clinical trials are needed to determine the effective drug treatment for COVID-19 in both adults and children.

Most of the neonates born to COVID-19 mothers had good outcomes. This finding gives credence to the fact that the infection is mild in neonates. Since there is currently no evidence of transmission of the virus in breast milk and because of the mild illness in this age group, WHO interim guideline recommends that infants born to mothers with suspected, probable or confirmed COVID-19 should be fed according to standard infant feeding guidelines, while ap-

plying necessary precautions for infection prevention and control.⁶²

STRENGTHS AND LIMITATIONS

One of the strengths of this study is that it's a comprehensive global review. Secondly, it included both babies that tested negative though exposed to COVID-19 positive mothers and babies that tested positive. One limitation of this review is that it included mainly case reports and case series, which do not provide high quality evidence; however, these are the major kinds of research available considering the fact that neonatal COVID-19 is a new and evolving disease.

CONCLUSIONS

The clinical manifestations of COVID-19 in neonates are mild and outcomes are better than in adult population. There is currently little evidence of vertical transmission in neonates. Given immunological susceptibility of neonates and the fact that COVID-19 is a newly emerged and evolving disease, it is important to continue in-depth research using higher quality study designs and methodologies.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

AUTHORSHIP CONTRIBUTIONS

OBE, CDO: study conceptualization and design. OBE, ICA, INO, CDO, OUA, OWD, EE: data extraction, analysis and interpretation of results, manuscript drafting and approval of the final manuscript for publication.

COMPETING INTERESTS

The authors completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available upon request from the corresponding author), and declare no conflicts of interest.

Submitted: September 11, 2020 GMT, Accepted: September 14, 2020 GMT

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SUPPLEMENTARY MATERIALS

Online Supplementary Document

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