



The clinical course of SARS-CoV-2 positive neonates

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Abstract

The COVID-19 pneumonia was firstly reported in Wuhan, China, in December 2019. The disease had a rapid spread all over the world becoming an international public health emergency. Limited data were available on COVID-19 positive neonates. We reviewed relevant literature to understand the clinical course of disease and transmission routes in affected neonates. The aim of the study was evaluating the clinical course and prognosis of SARS-CoV-2 positive neonates. Based on current literature, the hypothesis of vertical transmission of SARS-CoV-2, though conceivable, remains unproven. A research conducted on PubMed database from December 2019 to April 27, 2020 revealed that were reported 25 neonates affected by SARS-CoV-2. Main symptoms were fever, cough, or shortness of breath but often these neonates did not show other symptoms during length stay in hospital. No deaths occurred.

Introduction

The COVID-19 pneumonia was firstly reported in Wuhan, China, in December 2019. The disease had a rapid spread all over the world becoming an international public health emergency [1]. It was expected that newborns were at high risk for COVID-19-related complications because of their immune characteristics and their physiological changes in cardiovascular and respiratory system at birth [2]. During previous pandemics, they were reported cases of infants suffering from respiratory infection. They were also described cases of spontaneous abortions, preterm delivery,

low birth weight, and birth defects [3, 4]. However, these studies were conducted in a small sample size. Although evidences of SARS-CoV-2 vertical transmission from mothers to foetuses have been described, many doubts remain about the confirmation of vertical transmission [5–7]. The still limited data available on COVID-19-positive infants suggest that these patients had benign infections [8], despite concerns about the possibility of being born prematurely and with low birth weight [9, 10]. Data available for SARS-CoV-2-positive preterm neonates suggest that neonates infected (even if extremely preterm) might not necessarily be susceptible to severe disease with clinically significant or major morbidity [11]. Due to concerns about the possible transmission of this new virus to immunologically naive infants and the absence of definitive studies on this risk, we have reviewed the literature to understand the potential impact of this disease. The aim of the study was evaluating the clinical course, prognosis and transmission routes of the SARS-CoV-2-positive newborns.

Methods

Pubmed database (National Library of Medicine, Washington, DC) was used to search for manuscripts on COVID-19-positive neonates from December 2019 to April 27, 2020. Articles without language limitation describing SARS-CoV-2-positive newborns ≤ 28 days of

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life, were included. The exclusion criteria were articles reporting infants >28 days of life, children and neonates with negative swabs. IgM-positive newborns were excluded if they had negative swabs because there was no conclusive evidence of infection. This result could also be caused by placental alterations allowing the passage of IgM or false-positive tests [12]. Moreover, it was reported that false-negative and false-positive rate of serum 2019-nCoV IgM were 29.8% and 3.8%, respectively, while positive- and negative-predictive value were 86.7% and 91%, respectively [13]. SARS-CoV-2-positive nucleic acid test was considered the gold standard diagnostic tool to confirm the diagnosis with a positive predictive value of 100% [13]. Research on Pubmed showed 421 papers, of which 345 excluded because they were duplicated, so only 76 articles were considered for analysis. A total of 58 articles were discarded because they met the exclusion criteria and, finally, only 18 articles were considered eligible for review (Table 1).

Data extraction

The following data were collected for newborns: gestational age, the delivery method, gender, Apgar score, epidemiological history, and comorbidity. Data on the clinical course and outcome of newborns, such as clinical manifestations, transmission route, diagnosis, treatment, length of stay, and mortality were also recorded.

Data synthesis

Primary outcomes evaluated signs and symptoms of infected newborns, transmission route, treatment, and prognosis.

Results

Twenty-five SARS-CoV-2-positive newborns were reported (Tables 2 and 3), of which 11 were Chinese (44%), 3 were Italian (12%), 2 were Iranian (8%), and the rest were Spanish or Belgian or Korean (4%) [11, 12, 14–29]. Caesarean section (CS) occurred in 16 deliveries due to clinical conditions of the mothers (64%), and only in 4 cases was chosen vaginal delivery (16%). Gestational age of the newborns and birth body weight were 37.4 ± 4 (range: 26.57–41.28) and 3041.6 ± 866 g (range: 960–4440 g), respectively. In addition, the male–female ratio hospitalized was 2.8, so male infants were more susceptible to SARS-CoV-2 infection than female. Apgar score was greater than 6 and 9 at 1 min at 5 min, respectively, except in one case of an extremely preterm neonate and another in which the newborn needed neonatal resuscitation [11, 20]. In 68% of cases, the mothers were affected by

Table 1 Literature search on Pubmed from December 2019 to April 27, 2020.

N	Query results	Results
1	Vertical transmission and Covid19	44
2	Sars-Cov-2 and newborn	52
3	Covid19 and newborn	69
4	Neonate and Novel Coronavirus	79
5	Neonate and Covid19	98
6	Neonate and Sars-Cov-2	76
Total manuscripts		421
Manuscript discarded because duplicates		345
Manuscripts screened		76
Manuscripts eligible for the analysis		18

The screening of the literature revealed 421 results but only 18 articles were eligible for the analysis.

SARS-CoV-2, in 20% they were affected both mothers and fathers and, in other cases, grandparents were infected. The possibility that third parties may have infected infants cannot be excluded.

Age at presentation and clinical features

The age disease onset was 8.2 ± 8.5 days of life (range: 1–25 days). Clinically, SARS-CoV-2 affected newborns manifested at onset fever (28%), vomit (16%), cough or shortness of breath (12%), diarrhea, lethargy or respiratory difficulty (8%) or cyanosis, feeding intolerance, hyperpnea, mild intercostal retractions, mottling, sneezing, nasal stuffiness, paroxysmal episodes (4%), while only 4/25 newborns were asymptomatic. In the 76% of cases, newborns did not showed other symptoms during clinical course while in the other cases, it was reported fever (12%), cough or vomit (8%) and finally diarrhea, hypotension, hypothermia, poor feeding, tachycardia, tachypnoea (4%). Intensive care was required for 32% of the newborns, but only a percentage of 20% was subjected to mechanical ventilation. Major complications were pneumonia (12%), respiratory distress (8%), and sepsis or pneumothorax (4%). They were not reported deaths. Length stay of the newborns was 15.8 ± 10.8 days (range: 5–40 days).

Laboratory and radiologic findings

Diagnosis of SARS-CoV-2 from admission was obtained at 3.1 ± 3.4 days (range: 1–15 days) mainly by nasopharyngeal swab. In other cases, diagnosis was obtained with samples collected from oropharynx, stool, plasma, urine, or saliva. Data on antibodies were lacking, they were reported only four studies that included immunoglobulin analysis. Buon-senso et al. [28] detected IgG slightly positive in a neonate

Table 2 Baseline characteristics of the newborns described in the studies.

Serial number	References	Age of onset of disease	Nationality	Delivery mode	Gestational age (weeks)	Age at admission	Body weight at admission (g)	Gender	Apgar score	Neonatal resuscitation	Epidemiologic history (parents infected)
1	Kamali et al. [18]	NA	Iranian	CS	NA	15 days	3460	M	NA	NO	Mother and father
2	Zhang et al. [19]	NA	Chinese	CS	40.14	5 days	NA	F	NA	NO	Mother
3	Salvatori et al. [24]	NA	Italian	NA	41.28	18 days	4440	M	NA	NA	Mother
4	Salvatori et al. [24]	NA	Italian	NA	39	10 days	3120	F	NA	NA	Mother
5	Ferrazzi et al. [27]	NA	NA	VD	NA	At birth	2450–3740*	NA	NA	NO	Mother
6	Ferrazzi et al. [27]	NA	NA	ECS	NA	At birth	2770–3430*	NA	NA	NO	Mother
7	Buonesenso et al. [28]	NA	Italian	CS	38.43	At birth	3390	M	9–10 ^v	NO	Mother
8	Piersigilli et al. [11]	NA	Belgian	CS	26.57	At birth	960	F	5 ^l -8 ^v	NO	Mother
9	Zhang et al. [19]	At birth	Chinese	CS	40	30 h	NA	M	NA	NO	Mother
10	Zeng et al. [20]	At birth	Chinese	CS	40.57	At birth	3360	M	NA	NO	Mother
11	Zeng et al. [20]	At birth	Chinese	CS	31.28	At birth	1580	M	3 ^l -4 ^v	YES	Mother
12	Zamaniyan et al. [16]	At birth	Iranian	CS	32	At birth	2350	F	8 ^l -9 ^v	NO	Mother
13	Wang et al. [4]	30 min after birth	Chinese	ECS	40.14	At birth	3205	M	8 ^l -9 ^v	NO	Mother
14	Ferrazzi et al. [27]	Few hours after birth	NA	VD	Term	At birth	2450–3740*	M	NA	NO	Mother
15	Zeng et al. [20]	2 days	Chinese	CS	40	At birth	3250	M	NA	NO	Mother and father
16	Yu et al. and Hu et al. [15, 26]	2 days	Chinese	CS	39.85	At birth	3250	M	9–10 ^v	NO	Mother
17	Zhang et al. [19]	5 days	Chinese	CS	Mature	5 days	NA	M	NA	NO	Mother
18	Alzamora et al. [12]	6 days of life	NA	CS	33	At birth	2970	M	6 ^l -8 ^v	NO	Mother and father
19	Alonso et al. [22]	9 days	Spanish	UCS	38.57	At birth	2500	F	7 ^l -9 ^v	YES	Mother
20	Zeng et al. [17]	10 days	Chinese	NA	39	17 days	4070	M	NA	NO	Mother and father
21	Zhang et al. [19]	15 days	Chinese	CS	Mature	17 days	NA	M	NA	NO	Mother
22	Wang et al. [23]	17 days	Chinese	VD	38.85	19 days	3030	M	NA	NA	Mother and father
23	Coronado et al. [25]	19 days	NA	NA	36	21 days	NA	M	NA	NA	NA
24	Han et al. [21]	23 days	Korean	VD	38.85	27 days	3730	F	NA	NO	Mother, father, grandparents
25	Chacón-Aguilar et al. [29]	25 days	NA	NA	NA	26 days	NA	M	NA	NA	Family

N number, CS caesarean section, ECS emergency caesarean section, UCS urgent caesarean section, VD vaginal delivery, NA not available

*Data of Newborns are expressed as mean ± standard deviation.

Table 3 Clinical course of the newborns described in the studies.

Serial number	References	Symptoms at onset	Other symptoms	Time between admission and diagnosis	Swabs became negative from admission	Length stay	Antibody testing	Chest X-ray or CT	Treatment			Status
									ICU	Mechanical ventilation	Severe complications	
1	Kamali AM et al. [18]	Fever, Mottling	NO	2 days	NA	6 days	NA	No lesions	YES	NO	Respiratory distress	Alive
2	Zhang et al. [19]	No symptom	NO	4 days	NA	16 days	NA	Increased lung marking	NO	NO	NO	Alive
3	Salvatori et al. [24]	Asymptomatic	NO	Same day	NA	NA	NA	NA	NO	NO	NO	Alive
4	Salvatori et al. [24]	Cough, Diarrhea	Poor feeding	Same day	NA	NA	NA	NA	NO	NO	NO	Alive
5	Ferrazzi et al. [27]	Asymptomatic	NA	1–3 days*	NO	NO	NA	NO	NO	NO	NO	Alive
6	Ferrazzi E et al. [27]	Asymptomatic	NA	1–3 days*	NO	NO	NA	NO	NO	NO	NO	Alive
7	Buonesenso et al. [28]	Asymptomatic	NA	15 days	NA	5 days	IgG+	NO	NO	NO	NO	Alive
8	Piersigilli et al. [11]	Asymptomatic	NA	7 days	14 days	NA	NA	Non-specific bilateral streaky pulmonary infiltrates	YES	YES	NO	Alive
9	Zhang et al. [19]	Shortness of Breath	NO	Same day	NA	NA	NA	Increased lung marking	NO	NO	NO	Alive
10	Zeng et al. [20]	Lethargy, Vomit, Fever	NO	2 days	6 days	NA	NA	Thickening of the lungs texture	YES	NA	Pneumonia	Alive
11	Zeng et al. [20]	Shortness of breath, Cyanosis, Feeding intolerance	NO	2 days	7 days	NA	NA	Thickening of the lungs texture	YES	YES	Respiratory distress and Pneumonia	Alive
12	Zamaniyan et al. [16]	Fever	NO	1 day	NA	NA	NA	NA	YES	NO	NO	Alive
13	Wang et al. [4]	Vomit	NO	36h	15 days	16 days	NA	Ground glass opacities in the left upper and lower lobes	NO	NO	NO	Alive
14	Ferrazzi et al. [27]	Gastrointestinal symptoms	Respiratory symptoms	3 days	NA	NA	NA	NA	YES	YES	NO	Alive
15	Zeng et al. [20]	Lethargy, Fever	NO	2 days	6 days	NA	NA	Thickening of the lungs texture	YES	NO	Pneumonia	Alive

Table 3 (continued)

Serial number	References	Symptoms at onset	Other symptoms	Time between admission and diagnosis	Swabs became negative from admission	Length stay	Antibody testing	Chest X-ray or CT	Treatment		Status	
									ICU	Mechanical ventilation		Severe complications
16	Yu et al. and Hu et al. [15, 26]	Shortness of breath	NO	36h	NA	40 days	NA	Mild pulmonary infection	NO	NO	NO	Alive
17	Zhang et al. [19]	Fever	NO	Same day	NA	30 days	NA	NA	NO	NO	NO	Alive
18	Alzamora et al. [12]	Mild respiratory difficulty, Cough	NO	16h	NA	NA	IgM -IgG -	NA	YES	YES	NO	Alive
19	Alonso et al. [22]	Hyperpnea, Mild intercostal retractions	NO	8 days	NA	NA	NA	Ground glass opacities in the right perihilar region	NO	NO	NO	Alive
20	Zeng et al. [17]	Shreezing	Vomit, fever, diarrhea	2 days	7 days	7 days	IgM -IgG -	Enhanced texture of the two lungs	NO	NO	NO	Alive
21	Zhang et al. [19]	Fever, Cough, Vomit	NO	2 days	NA	23 days	NA	Increased lung marking	NO	NO	NO	Alive
22	Wang et al. [23]	Vomit, Diarrhea	Fever, cough	4 days	10 days	14 days	IgM - IgG -	Thickening of the lungs texture	NO	NO	NO	Alive
23	Coronado et al. [25]	Respiratory difficulty	Hypotension, tachycardia, hypothermia, tachypnoea	7 days	NA	9 days	NA	Bilateral linear opacities and consolidation in the right upper lobe	YES	YES	Pneumothorax and sepsis	Alive
24	Han et al. [21]	Nasal stuffiness	Fever, vomit, cough	1 day	17 days	18 days	NA	No lesions	NO	NO	NO	Alive
25	Chacón-Agular et al. [29]	Paroxysmal episodes, fever	NO	Same day	NA	6 days	NA	NA	NO	NO	NO	Alive

N number, CT computerized tomography, ICU intensive care unit, NA not available

*These data are not specified by authors of the paper.

fed by breast milk, his mother was SARS-CoV-2 positive. In the other three case reports, IgM or IgG were negative [12, 17, 23]. The swabs became negative within 10.3 ± 4.5 days (range: 6–17 days). The radiological study of the lungs of newborns revealed thickening of the lung structure (32%), opacity of the ground lobe glass (8%), and mild lung infection, bilateral linear opacities or bilateral nonspecific striated lung infiltrates (4%). Lung lesions were not revealed in 48% of cases, in which fever, cough, diarrhea, patches, vomiting, nasal suffocation, paroxysmal episodes, and poor nutrition were reported.

Discussion

Current reviews reported clinical course data predominantly on the paediatric population with very few cases of newborns [30–36]. Based on current knowledge, treatment for SARS-CoV-2-positive newborns should be prevalently symptomatic or supportive [32, 33, 37]. After discharge, simple hygiene measures should be taken during home care as caregivers washing hands and face often, disinfecting the daily supplies of newborns with 75% medical alcohol and chlorine-containing disinfection water to wipe the floor and furniture, regular window ventilation, heat-resistant bottles and pacifiers should be disinfected at high temperature [38]. In Romania, 10 newborns resulted positive to SARS-CoV-2 because healthcare workers did not wear personal protective equipments [39]. However, all newborns were in good conditions and did not show symptoms. The Italian ministry of health reported that in Italy there were about 20–25 SARS-CoV-2-positive newborns but without severe complications [40]. Our data suggest that signs and symptoms of novel coronavirus in newborns could be less serious compared to adults. Main onset symptoms were fever, vomit, cough, or shortness of breath but often these newborns did not show other symptoms during length stay. One of the most difficult questions about COVID-19 in neonates is whether perinatal transmission of SARS-CoV-2 exists. Vertical transmission of infection usually occurs during intrauterine life by placenta, or during delivery by ingestion or aspiration of cervicovaginal secretions, and in the postpartum period by breastfeeding. Parazzini et al. [41] in a review article analysed 13 studies, including 64 women who delivered. Vaginal delivery was reported in six cases. It is recommended to practice reverse transcription polymerase chain reaction (RT-PCR) assay on tissue samples deriving from placenta, amniotic fluid, cord blood, and neonatal pharyngeal swab, to prove that there has been intrauterine viral infection. All these samples should be collected using aseptic technique to prevent contamination [42]. Xu et al. [13] reported that positive-predictive value and specificity of the 2019-nCoV nucleic acid test were

100%, but negative predictive rate and sensibility were 81% of 91%, respectively. These data suggest that if 2019-nCoV nucleic acid test give a negative result, it is necessary to repeat the swab to exclude the infection. In the case reported by Wang et al. [14], the pharyngeal swab collected at 36 h after birth was positive but umbilical cord and placental samples were negative, therefore the vertical transmission of the infection has not been confirmed. In three neonates were detected IgM antibodies in the blood by automated chemiluminescence immunoassays but respiratory swabs were negative for SARS-CoV-2 RNA by RT-PCR. The sensitivity and specificity of this immunoassays have not been extensively evaluated and could give false-positive results [42]. Wang et al. [42] observed that most of the available data concern women infected in the third trimester of pregnancy: in this case, the placental barrier could efficiently prevent the transmission of infection from mother to foetus. Chen et al. [43] collected amniotic fluid and cord blood samples from six COVID-19-positive pregnant mothers and pharyngeal swabs from offsprings: the results of all samples were negative. Lei et al. [44] conducted a similar study on four pregnant women showing similar results. In addition, vaginal secretions were negative for SARS-CoV-2. Chen et al. [45] analysed neonatal pharyngeal swab samples and placental tissues of three pregnant women with COVID-19 but all samples tested negative for SARS-CoV-2 RNA. Therefore, based on current literature the hypothesis of vertical transmission of SARS-CoV-2, though plausible, remains unproven [16, 30, 31, 46–48]. Zamaniyan et al. reported a case of a COVID-19 positive pregnant woman that delivered in severe critical conditions by CS. It was collected 5 ml of amniotic fluid during delivery that resulted positive to SARS-CoV-2, also the nasal-first throat swab of the newborn, obtained at 24 h of life, was positive to SARS-CoV-2 [16]. This case report shows that in critical conditions, vertical transmission could be possible. On the other hand, they are still unknown the effects of COVID-19 infection in the first or second trimester of pregnancy. Moreover, placental abruption or maternal-foetal haemorrhage as well as placental damage deriving from severe hypoxia in the earliest period of pregnancy in COVID-19-positive women may play an additional role in facilitating vertical transmission. Baud et al. described a case of miscarriage during the second trimester of pregnancy in a SARS-CoV-2-positive mother. The virus was finding in the placenta but not in the foetus maybe for the age of foetal development and short time of maternal infection [49]. Buonsenso et al. [28] reported 7 SARS-CoV-2-positive pregnant mothers but it was revealed the virus in the placental tissue only in one woman whose baby was instead negative. Further studies and longitudinal observation of suspect cases are still needed to solve this challenge.

Conclusions

SARS-CoV-2-positive newborns show a good prognosis, with low rate of severe complications and without deaths. Treatments are prevalently symptomatic or supportive. Vertical transmission remains unproven, and horizontal transmission is the most probably source of infection for newborns. Hygiene measures must be always taken during hospital and home care by caregivers. The gap of knowledge will be filled by seroprevalence studies in mothers and newborns. High quality studies are urgently needed about newborns to better understand clinical manifestations, clinical course, and prognosis of SARS-CoV-2-positive newborns.

Author contributions Giuseppe De Bernardo gave substantial contribution to conception and design and revising it critically for important intellectual content. Maurizio Giordano collected the data, carried out the analyses and interpretation of data and reviewed paper critically for important intellectual content. Giada Zollo, Fabrizia Chiato, Desiree Sordino, Rita De Santis, reviewed the paper critically for important intellectual content. Serafina Perrone supervised data collection, critically reviewed the paper for important intellectual content. All authors approved the final paper as submitted and agree to be accountable for all aspects of the work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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