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REVIEW ARTICLE

Clinical manifestations and radiologic abnormalities in neonates with COVID-19: a rapid systematic review

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Coronavirus Infections, Infant, Newborn, Signs and Symptoms.

Abstract

Objective: A rapid systematic review of clinical manifestations and radiologic abnormalities in neonates with diagnosis of COVID-19 (with a RT-PCR positive swab). **Methods:** Search at PubMed, SciELO and LILACS databases with the keywords COVID-19 OR Coronavirus AND ("neonat*" OR "newborn" OR "recém-nascido"), up to June 5th, 2020. **Results:** 344 articles were captured at the databases. A secondary caption occurred for one article. After all exclusions, 21 articles remained at the final analysis, representing 30 neonates. Thirty-three percent were asymptomatic and 66.7% were symptomatic. No death was reported. The most frequent clinical manifestations were fever (60%), tachypnea or dyspnea (60%), nasal discharge (30%), and hemodynamic abnormality (30%). Radiologic infiltrates occurred in 70% of patients, and from these, five neonates had no tachypnea or dyspnea. **Conclusions:** Few studies were published regarding neonatal infection confirmed by positive RT-PCR in the neonate and this reinforces the importance of summarizing all obtained information up today. In this study, most of the neonates were symptomatic and death was not observed. The high frequency of radiologic abnormalities suggests that pulmonary compromise may occur, even when the neonate has no respiratory symptoms.

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INTRODUCTION

The devastating impacts of the novel coronavirus pandemic on global public health has warranted the development of intense scientific investigation on the subject. Coronaviruses are enveloped positive-stranded RNA viruses broadly disseminated in humans, mammals, and birds that cause severe respiratory, enteral, liver, and neurological diseases. Severe acute respiratory syndrome (SARS) caused by the coronavirus was initially reported in 2002 and 2003 in outbreaks in China. In late 2019, various health clinics in China reported groups of patients with pneumonia of unknown cause epidemiologically connected to a seafood and meat market in Wuhan. Infection by the novel coronavirus was identified and the disease (Covid-19) emerged rapidly as a global cause of severe respiratory involvement in adults[1].

According to the Brazilian Ministry of Health's 17th Epidemiological Newsletter issued on Week 21, Brazil had 347,398 confirmed cases of COVID-19 by May 23, 2020. A total of 22,013 (6.3%) individuals had died, 182,798 (52.6%) were being followed, and 142,587 (41.0%) had recovered from the disease. In the pediatric population, 916 cases of SARS by COVID-19 had been recorded involving children and adolescents aged 0-18 years, most of which affecting children aged 12 years and younger. Of the 548 (59.8%) cases of SARS by COVID-19 with signs of advancing disease, 449 (69.9%) recovered and 99 (15.3%) died. Infections and deaths were not stratified to consider newborns[2].

It has been suggested, since the first reports of COVID-19, that children suffer from milder, different forms of the disease when compared to adults[3]. However, few neonatal cases of COVID-19 have been published, with insufficient evidence of vertical transmission and horizontal transmission considered more likely. In addition, no specific clinical sign has been attributed to the disease in newborns[4].

Some peculiarities may explain why COVID-19 manifests differently in children. One of the possibilities explored is that the entry of the virus in cells requires the presence of angiotensin-converting-enzyme-2, which is immature in children. More effective T-cells and decreased response capability via cytokine storm have also been indicated as protective factors against severe disease. Higher levels of hemoglobin in newborns have also been listed as a potential protective factor. The virus is known to attack the 1-β chain of hemoglobin, present only in adult-type hemoglobin, to dissociate the iron of heme to form porphyrin, thereby decreasing hemoglobin levels and producing hypoxia[5].

Pregnant women tested positive have been followed during and after delivery. A recent systematic review that looked into pregnant women with COVID-19 for neonatal outcomes found only one newborn with the disease, free of clinical signs of interest[6]. On the other hand, a compilation of 13 cases of neonatal COVID-19 described fever, lethargy, tachypnea, and respiratory failure in newborns. The authors indicated that a literature review summarizing the traits of neonatal disease was in order[7].

This study aimed to describe the frequency of clinical manifestations and imaging alterations in cases of newborns with COVID-19 reported in the literature.

METHODS

This rapid systematic review included papers reporting on newborns diagnosed with COVID-19. The population of interest comprised newborns (age < 28 days) diagnosed with COVID-19 based on positive swab reverse transcription-polymerase chain reaction (RT-PCR) tests. The endpoints were: fever (axillary temperature > 37.8°C), lethargy, irritability, coughing, exanthema, hemodynamic alteration (poor perfusion, mottled skin, or decreased pulse amplitude), infiltrate in imaging scans, tachypnea or dyspnea, vomiting, refusal to eat, coryza, seizures, conjunctival hyperemia, diarrhea, and death.

One of the authors performed searches on databases Pubmed, Scielo, Lilacs and a secondary search based on the references of the included papers. The following search keywords were used: Covid-19 OR Coronavirus AND (neonat* OR newborn OR recém-nascido), without period restrictions. Searches for papers concluded on June 5, 2020. Studies written in Portuguese, Spanish, and English were included. Case reports, case series, cohort, prospective and retrospective, and case-control studies were included. Editorial papers were excluded. A secondary search for papers was carried out based on review articles available. The two authors extracted data in an independent manner, using a specific electronic form based on Microsoft Excel, in which data on the authors, study design, number of participants, institution, study period, objectives, and abstracts containing the main clinical findings were collected. The extracted data was compared and differences were resolved via consensus between the authors. The appraisal tool developed by Briggs was used in the analysis of the methodological quality of the papers. Only studies meeting 70% or more of the criteria assessed in the tool were included[8]. Summary measurements comprising review findings were treated with Stata version 13.0 (Stata Corp, LP). Frequencies and medians, minimum and maximum values, and interquartile ranges (IQR) were calculated.

RESULTS

A total of 344 articles were compiled from the three databases. One hundred and fifty were excluded for duplicity or publication type. Another 163 were excluded for discussing topics other than the ones connected with the subject of this review. Four were excluded for language (three published in Chinese and one in French). The preliminarily selected articles were read and one additional paper taken from the references of one of the articles was included; seven were excluded for

not reporting evidence of positive swab RT-PCR tests (Figure 1). Twenty-one articles were ultimately included in the final review stage, comprising the data from 30 newborns (Table 1).

None of the 30 newborns included in this review died. Sex was reported in 25 studies, and 76% of the subjects were males. Gestational age was reported in 24 studies, yielding a median gestational age of 273 days (39 weeks) and an IQR of 259-280 days. Five newborns were preterm. Median weight at birth was 3,205g (IQR 2,500-3,360g). The lowest weight reported was 960g. Three newborns had other comorbidities; one was diagnosed with tetralogy of Fallot.

The earliest test was performed in a newborn one hour after birth and the latest 27 days after birth. Median time after birth in newborns tested positive for the disease was 168 hours (seven days), IQR 48-360 hours. The shortest time between birth and start of symptoms was one hour and the longest was 25 days; median time between birth and start of symptoms was 199 hours (8.3 days), IQR 33-432 hours. In asymptomatic newborns, the median time between birth and having a positive test was 96 hours (four days), with swabs taken between one hour and 360 hours (15 days) after birth, IQR 36-168 hours. In symptomatic newborns, the median time between birth and having a positive test was 204 hours (8.5 days), ranging from 16 to 648 hours (27 days), IQR 48-480 hours (Graph 1).

Ten (33.3%) newborns were asymptomatic and 20 (66.7%) had symptoms. The most frequent clinical manifestations are shown in Table 2.

None of the 14 newborns with imaging alterations had tachypnea or dyspnea, and five did not have respiratory symptoms. Two of the five preterm newborns had imaging alterations and three presented with tachypnea or dyspnea. Most of the imaging alterations were observed in full-term newborns (12 subjects).

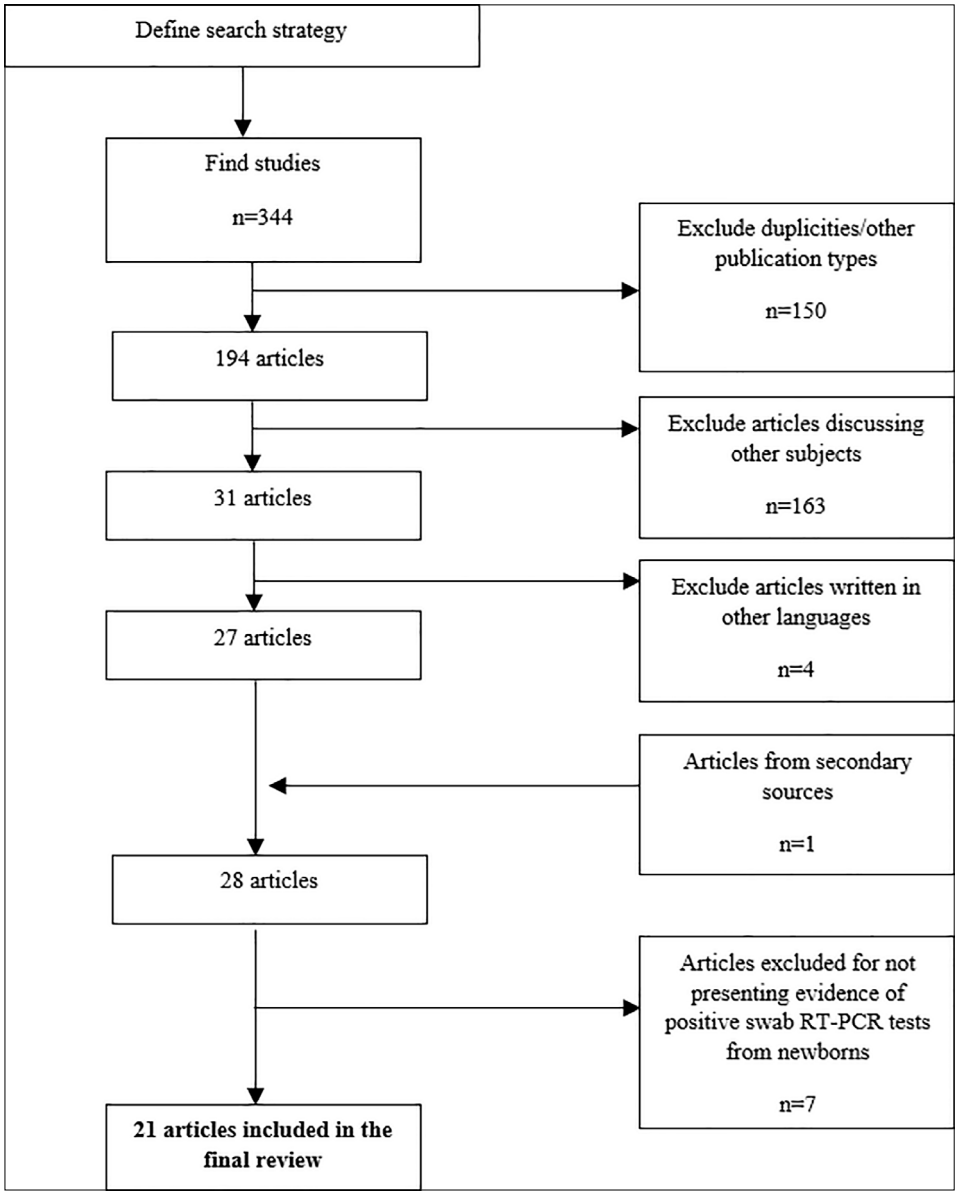


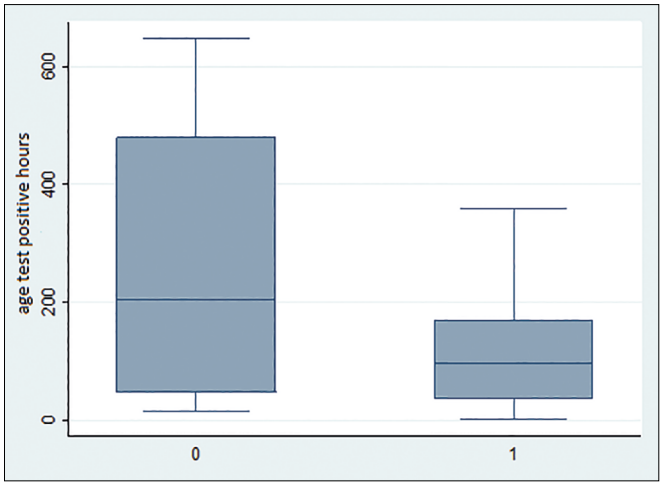
Figure 1. Study selection - Review on clinical manifestations and imaging alterations in newborns with COVID-19.

Table 1. Clinical manifestations and imaging alterations in newborns with COVID-19.

Authors, reference	Study design	Included newborns (n)	Country	Clinical findings	Lung imaging findings
Wang et al., 2020[9]	Case report	1	China	Asymptomatic	Chest X-ray images of 3-day old patient showing diffuse lung infiltrate. Chest CT scans on 5-day-old patient showing high density areas under the pleura of the posterior segment of the upper lobe of the right lung.
Zhang et al., 2020[10]	Case series	4	China	Two newborns with fever, 1 with shortness of breath, 1 with coughing, and 1 with no symptoms. Onset of disease recorded in hospital for 2 newborns and at home for 1 newborn.	3 newborns with chest CT scans showing high density areas in the lungs.
Yu et al., 2020[11]	Case series	1	China	Mild shortness of breath.	Chest X-ray images showing mild lung infection.
Zeng et al., 2020[12]	Case series	3	China	Two full-term newborns, one with lethargy and fever and the other with lethargy, vomiting, and fever. The third patient was a preterm newborn with a gestational age of 312/7 weeks, Apgar score 3/4/5, hospitalized for RDS.	Chest X-ray images of the three patients consistent with pneumonia.
Ferrazi et al., 2020[13]	Case series	3	Italy	Two asymptomatic newborns; one newborn with dyspnea and vomiting.	Not described.
Alzamora et al., 2020[14]	Case report	1	Peru	A preterm newborn with a gestational age of 33 weeks, intubated in the delivery room for respiratory depression from sedatives administered to the mother. On day 6 after birth the newborn had mild difficulty breathing and sporadic coughing	Normal chest X-ray images.
Aghdam et al., 2020[15]	Case report	1	Iran	Fever, lethargy, dyspnea, and mottled skin.	Normal chest X-ray images.
Munoz et al., 2020[16]	Case report	1	United States	Nasal congestion, tachypnea, hemodynamic alterations (hypotension, tachycardia), refusal to feed, hypoxemia, and hypothermia. The patient had a pneumothorax after tracheal intubation.	Chest X-ray images showing bilateral linear opacity and consolidation in the upper right lobe
Han et al., 2020[17]	Case report	1	Republic of Korea	Fever, nasal congestion, coughing, and vomiting.	Normal chest X-ray images.
Sun et al., 2020[18]	Case report	1	China	Asymptomatic.	Imaging procedures not performed.
Hu et al., 2020[19]	Case series	1	China	Asymptomatic.	Normal chest X-ray images.
Buonsenso et al., 2020[20]	Case series	1	Italy	Asymptomatic.	Imaging procedures not performed.
Piersigilli et al., 2020[21]	Case report	1	Belgium	Extreme preterm newborn with a gestational age of 26 4/7 weeks, weighing 960g, for HELLP syndrome. Patient presented with RDS, pneumothorax, and significant PDA. The patient was hospitalized on account of prematurity.	Chest X-ray images did not show signs of parenchymatous infiltrate during the first week after birth; 17 days after birth there were signs of non-specific bilateral infiltrate.
Dumpa et al., 2020[22]	Case report	1	United States	Fever with tachycardia and refusal to eat.	Imaging procedures not performed.
Patanè et al., 2020[23]	Case report	2	Italy	Asymptomatic. One of the subjects was a late preterm newborn (35 1/7 weeks of gestational age).	Imaging procedures not performed.
Chacón-Aguilar et al., 2020[24]	Case report	1	Spain	Fever, episodic paroxysms (seizure?) associated with feeding and sleeping, irritability, coryza, vomiting, and diarrhea	Imaging procedures not performed.
Diaz et al., 2020[25]	Case series	1	Spain	Mild tachypnea with retractions and drops in saturation during sleep and feeding.	Chest X-ray images showed mild ground-glass opacity predominantly in the right pre-hilar area.
White et al., 2020[26]	Case series	2	United States	Fever, coryza, and hypoxemia in ambient air. One newborn presented with bilateral conjunctivitis, tachycardia, and systemic vasodilation.	Chest X-rays showed low lung volume with opacity without focal consolidation in any of the patients.

Salik e Metha, 2020[27]	Case report	1	United States	Newborn with tetralogy of Fallot presented desaturation and tachypnea seven days after birth, deterioration of cyanosis, feeding intolerance, and increased lethargy. The subject was intubated for apnea and had a pulmonary-to-systemic shunt placed.	Chest X-ray images showed bilateral lung granular opacity and decreased lung volume.
Precit et al., 2020[28]	Case report	1	United States	Lethargy, coryza, dyspnea, refusal to eat.	Chest X-ray images showing bilateral ground-glass opacity, without focal consolidation, suggesting viral etiology.
Paret et al., 2020[29]	Case report	1	United States	Fever, irritability, facial maculopapular rash.	Imaging procedures not performed.

CT=computed tomography, RDS= respiratory distress syndrome, PDA= patent ductus arteriosus.



Graph 1. Hours between birth and having a positive test for asymptomatic (1) and symptomatic (0) newborns.

Table 2. Summary of clinical manifestations and imaging alterations of newborns with COVID-19 reported in 21 studies (n=20).

Clinical/imaging alterations	Frequency (%)
Infiltrate	14 (70.0)
Fever	12 (60.0)
Tachypnea or dyspnea	12 (60.0)
Coryza	6 (30.0)
Hemodynamic alterations	6 (30.0)
Vomiting	5 (25.0)
Lethargy	4 (20.0)
Coughing	3 (15.0)
Refusal to eat	3 (15.0)
Irritability	2 (10.0)
Seizures	1 (5.0)
Exanthema	1 (5.0)
Diarrhea	1 (5.0)
Conjunctival hyperemia	1 (5.0)

DISCUSSION

This review included case reports and case series describing newborns diagnosed with COVID-19 via RT-PCR testing. The small number of subjects featured in each of the included studies impedes the establishment of the actual clinical magnitude of this condition in neonatal life, and thus calls for the compilation of data published in larger numbers of studies. With the exception of one article from Peru, the studies included in this review were performed in continents other than South America[14].

The earliest diagnosis of COVID-19 was performed one hour after birth and 50% were positive for the disease by seven days after birth[23]. Asymptomatic newborns were diagnosed earlier than symptomatic newborns, probably as a consequence of exposure to a mother with the disease. Newborns without epidemiological signs of exposure to the virus at birth developed symptoms after discharge and were diagnosed at a later moment. Wang et al, 2020, reported the case of a full-term newborn tested positive based on an RT-PCR test run on an oropharyngeal swab 36 hours after birth. Although the newborn and his mother had not been with each other until then, the source of infection was not established. The newborn remained asymptomatic[9]. There is no evidence of vertical transmission of the virus, with horizontal transmission remaining as the most probable path of dissemination of COVID-19 between newborns. Preventive strategies must be developed to preclude exposure of newborns to individuals with suspected disease.

Although most newborns had symptomatic disease, no deaths were reported in the included studies. Earlier clinical manifestations occurred within one hour of birth and 50% had symptoms 8.3 days after birth. It is important to understand that many of the signs and symptoms of neonatal COVID-19 are seen in other conditions frequently observed in newborns. The pandemic requires that infection by the novel coronavirus be included in the differential diagnosis for late and early-onset neonatal sepsis, pneumonia, and respiratory distress syndrome, among others. Piersigilli et al. followed an extreme preterm newborn with a gestational age of 26 4/7 weeks born through a C-section as the mother was diagnosed with HELLP syndrome. The mother presented with fever and coughing two days after delivery, and both were diagnosed with COVID-19. The newborn was on non-invasive ventilation, was administered a surfactant via a minimally invasive method within the first hours after birth, and developed a posterior pneumothorax after surfactant administration. These clinical alterations were considered to stem from prematurity. The newborn was diagnosed with COVID-19 seven days after birth

and progressed well[21]. Zeng et al. also reported the case of a newborn with a gestational age of 31 2/7 weeks who remained asymptomatic throughout their hospital stay[12]. Similarly, Alzamora et al. described the case of a newborn with a gestational age of 33 0/7 weeks diagnosed 16 hours after birth who also progressed well. The respiratory symptoms presented early on were also attributed to neonatal respiratory distress syndrome and chest X-ray images were normal; however, this newborn presented with coughing at a later moment[14]. These cases suggest that even in preterm newborns symptomatic disease may be mild.

The most commonly described clinical manifestations were fever, tachypnea or dyspnea, coryza, and hemodynamic alterations. Infiltrate in imaging scans was also a frequent finding. Nearly all newborns with infiltrate were full-term subjects, i.e., they did not present with alterations stemming from lung immaturity. Five newborns with infiltrate did not have tachypnea or dyspnea, which indicated the relevance of imaging methods in patients with suspected disease. The medium and long-term progression of pediatric COVID-19 is unknown, and future respiratory sequelae cannot be ruled out. Good care practice dictates that laboratory and imaging tests should not be ordered for children not presenting signs of severe disease. However, a consensus statement published by the Brazilian Ministry of Health established that since newborns are deemed a risk group and signs and symptoms of severe disease are broad – ranging from persistent fever, refusal to eat, skin pallor, hemodynamic alterations, sensory alterations, to respiratory symptoms – testing is warranted[30]. Vomiting and refusal to eat, both digestive symptoms, have been reported in the literature, thus indicating that any clinical alteration be investigated in newborns exposed to COVID-19. Procianoy et al. suggested that no specific set of clinical manifestations may be consistently tied to neonatal COVID-19, since published cases described asymptomatic subjects or individuals with mild to moderate symptoms[4]. The compilation of cases published in this review sheds light on such interpretation, as it contradicts the notion that most individuals are asymptomatic. Most newborns had symptoms and respiratory manifestations were the most frequent finding.

This review has its limitations. The small number of included individuals impedes broader comparisons; the fast-growing number of publications on the topic require constant analysis of the subject. Publication bias is a possibility, since symptomatic cases are more likely to be published than asymptomatic ones, although any literature on COVID-19 is welcome and needed right now. In a scenario in which little information is available on neonatal COVID-19, this observational study shed light on the clinical manifestations seen in newborns tested positive with COVID-19, and not only on subjects exposed to the disease.

Most of the published cases of neonatal COVID-19 featured symptomatic newborns, with no deaths reported. Half of the newborns were tested until seven days after birth and half of the symptomatic cases had manifestations until 8.3 days after birth. The most frequent clinical manifestations were fever, tachypnea or dyspnea, coryza, and hemodynamic alterations. Imaging alterations were also frequent, even in newborns without respiratory symptoms.

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