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Andes pediatr. 2025;96(2):253-260
DOI: 10.32641/andespediatr.v96i2.5488

CLINICAL SERIES

COVID-19 infection in neonates and post-pandemic reflections

Infección por COVID-19 en neonatos y reflexiones post-pandemia

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Received: October 14, 2024; Approved: January 2, 2025

What do we know about the subject matter of this study?

Most neonates infected with COVID-19 have a favorable clinical outcome; however, they remain at risk of severe complications, including multisystem syndrome. Vertical transmission is still under debate but is considered a possible scenario. The long-term impact has yet to be defined.

What does this study contribute to what is already known?

This work confirms the perception that the course of COVID-19 infection in the neonatal period may be more favorable. It also suggests that the neonate may be the index case in community-acquired infections, with an additional risk of severe bacterial infection. Based on post-pandemic evidence, case management should be individualized, and perinatal risk behaviors related to COVID-19 should be avoided.

Abstract

COVID-19 had a significant impact on morbidity and mortality, especially in adults. However, in children and neonates, the clinical presentation was generally less severe. Due to the severity of the disease in adults, some of the measures implemented for neonates during the pandemic proved to be misguided. **Objective:** To present a series of neonatal COVID-19 cases, with post-pandemic reflections. **Patients and Method:** A retrospective and descriptive study conducted in Colombia, involving 16 neonates infected with COVID-19, diagnosed by nasopharyngeal PCR testing. Of these, 12 (75%) were patients admitted from home, while 4 were referred from lower-complexity institutions. Sociodemographic and clinical variables and outcomes were analyzed. **Results:** In the group of patients who came from home, the most common symptoms were jaundice in 10 (83.3%) and respiratory distress in 7 (58.3%). None of the patients required mechanical ventilation. Bacterial infections were identified in 4 cases admitted through the emergency department. Among the neonates referred from other institutions, all 4 presented with respiratory distress secondary to conditions typical of the neonatal period. The source of infection was not documented in any of the cases. **Conclusions:** This

Keywords:
Neonate;
Covid-19;
SARS CoV-2;
Sepsis;
Pandemic

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Edited by:
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How to cite this article: Andes pediatr. 2025;96(2):253-260. DOI: 10.32641/andespediatr.v96i2.5488

study reported that these neonates with COVID-19 had a favorable clinical outcome. Bacterial infections were present in community-acquired cases. Additionally, in these cases, the neonate could serve as the index case, alerting to other possible community-acquired cases. Management should be individualized and long-term follow-up should be mandatory.

Introduction

In late 2019, a cluster of adults with pneumonia of unknown cause was identified in Wuhan, Hubei Province, China. Subsequently, a new coronavirus was identified as the causative agent, named "Severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2), which causes the disease today known as COVID-19. The virus has a high transmissibility, with a rapid global spread, and caused a pandemic in 2020[1]. Although adults were the most affected population, data from the American Academy of Pediatrics (AAP) report that about 9% of the cases corresponded to children. As the pandemic progressed, knowledge in this population expanded, including neonates[2]. Only one month after the pandemic was declared worldwide, the first report was published in China on maternal-neonatal care during the infection, which identified risks such as severe disease during gestation, premature delivery, possible vertical transmission, and an increase in cesarean sections without obstetric indication, among others[3]. Due to the scarce information about neonatal disease, there was variability in the management guidelines for neonates at risk of infection or with proven infection. Some of the most controversial and impactful measures at the beginning of the pandemic and perinatal care were the separation of neonates from their mothers and the halt of breastfeeding[4].

The clinical course of COVID-19 in pediatrics and neonates was characterized by less severe disease compared to adults. However, worse clinical outcomes are likely to occur in developing countries. In the neonatal period, it is possible that gestational age (< 37 weeks) and other associated conditions, such as pulmonary or cardiac pathologies, cause a worse outcome[5].

This tendency to mild disease in infancy may be related to clinical features of the neonatal immune system, such as the ability to avoid uncontrolled inflammation, a lower cytokine response, angiotensin-converting enzyme (ACE) receptor expression, less endothelial damage, and the absence of comorbidities[6]. However, the risk of severe disease persists, including neonatal systemic inflammatory response syndrome (SIRS) with a possibly fatal outcome[7].

Two forms of transmission have been described in the neonatal period: vertical transmission, considered rare but possible, and horizontal transmission, which has been demonstrated and better studied[8]. Although the prognosis in neonates is more favorable than in adults, a better characterization of the clinical picture is required, as is the long-term impact of neonatal disease, which is still under investigation.

The objective of this report is to describe the most relevant clinical and paraclinical features of neonates with COVID-19, as well as to provide post-pandemic reflections on the current management of cases.

Patients and Method

Retrospective descriptive study, identified neonates with COVID-19 infection admitted to *Clínica Magdalena*, a medium-complexity institution in Barrancabermeja, Santander, Colombia. All neonates were admitted to the Neonatal Care unit during the pandemic, between March 2020 and May 2020. A total of 75 neonates were evaluated for SARS-CoV-2 by RT-PCR with oropharyngeal swab, according to established protocol on the date described. Of these 75 cases evaluated, 24 were admitted through the Emergency Department, and 51 came from care in the early neonatal period born in the institution or referred to it.

Of these, 16 cases were positive, recording data on gestational age, weight/length, reason for consultation, route of delivery, presence of neonatal sepsis, need for oxygen, days of stay, and condition at discharge. We actively searched for possible contacts of COVID-19 cases in the family nucleus. The cases were classified into 2 groups, those admitted through the maternity service (immediate postnatal), or those admitted through the emergency department (home).

On admission, a complete blood count, C-reactive protein (CRP), bilirubin, lactate dehydrogenase (LDH), and chest X-ray were obtained in cases with signs of respiratory distress or need for oxygen. Ferritin and D-dimer analyses were not routinely performed. Other studies, such as blood cultures, urine or cerebrospinal fluid samples, were requested according to the patient's clinical condition. At the time of the study, there was no established protocol for management. A database was created with the documented variables and a descriptive analysis was performed by calculating measures of central tendency and dispersion; the Chi2 or Fisher exact tests were used for qualitative variables

and for quantitative variables the T-Student test if it presented normal distribution or Mann-Whitney test if the distribution was non-normal. The STATA®17BE software was used for the analyses. The ethics committee of the *Fundación Cardiovascular de Colombia* approved this study, with the prior consent of *Clínica Magdalena*.

Results

Sixteen cases of neonatal COVID-19 infection were confirmed, 12 (75%) were admitted via the emergency department and 4 (25%) were referred from centers of lower complexity. Of the 12 admitted via the emergency department, 4 (33%) had family contact with suspected COVID-19 infection, although none of them was confirmed.

Of the 4 referred in their first hours of life, none had a symptomatic mother or a history of contact with close relatives with suspected COVID-19. Three of the cases corresponded to preterm newborns, one of them a twin pair born at home at 34 weeks of gestation, and the third case, a preterm infant with no clearly defined cause. The mean chronological age at the time of consultation was 11.9 days, ranging from 1 to 27 days for both clinical scenarios.

The main reason for consultation was respiratory distress and jaundice. Other signs observed in the group admitted to the emergency department included fever, cyanosis, rhinorrhea, and diarrhea. In the 4 patients referred, respiratory distress associated with prematurity was the main reason for admission. The mean hospital stay was 8.5 days (Table 1). Vital signs and glycemia at admission showed no alterations.

Of the referred group, 75% (3/4) presented mild respiratory distress, which was managed with low-flow nasal cannula oxygen. In neonates admitted through the emergency department with a similar clinical presentation, the treatment was also similar. Oxygen saturation was between 87-89%, adequate values for the altitude above sea level. At the time of diagnosis, the

Table 1. Clinical and sociodemographic characteristics of newborn with COVID-19

Characteristics		Frecuencies n (%) n = 16	Origien		*p-value*
			Home n = 12 (%)	Referred n = 4 (%)	
Masculine		8 (50%)	6 (50.0)	2 (50.0)	1.000
Age (days)*		13.5 (2-19)	17.5 (11-20)	1 (1-1)	**0.004**
Weight (grams)*		3065 (2760-3485)	3140 (2951-3935)	2090 (1890-2560)	**0.008**
Gestacional Age	Preterm (<37weeks)	3 (18.7)	---	3 (75.0)	**0.007**
	Term (>37weeks)	13 (81.3)	12 (100.0)	1 (25.0)	
Delivery	Vaginal	6 (37.5)	3 (25.0)	3 (75.0)	0.118
	Caesarean	10 (62.5)	9 (75.0)	1 (25.0)	
Sepsis classification	Early onset	4 (25.0)	---	4 (100.0)	**0.001**
	Late onset	12 (75.0)	12 (100.0)	---	
Initial reason for consultation†	Jaundice	13 (81.3)	10 (83.3)	3 (75.0)	1.000
	Respiratory distress	11 (68.7)	7 (58.3)	4 (100.0)	0.245
	Cyanosis	3 (18.7)	3 (25.0)	---	0.529
	Fever	2 (12.5)	2 (16.7)	---	1.000
	Diarrhea	2 (12.5)	2 (16.7)	---	1.000
	Abdominal distention	1 (6.2)	1 (8.3)	---	1.000
	Nasal Congestion	1 (6.2)	1 (8.3)	---	1.000
LDH elevation		2 (12.5)	1 (8.3)	1 (25.0)	0.450
Hyperbilirubinemia		11 (68.7)	10 (83.3)	1 (25.0)	0.063
Respiratory support		14 (87.5)	10 (83.3)	4 (100.0)	1.000
Oxygen therapy Duration (days)*		5 (4-5)	3.5 (2-5)	5 (4.5-5.5)	0.355
Length of stay (days)*		8.5 (6-12.5)	6 (6-11.5)	14.5 (10-20.5)	**0.045**

*Median (p25-p75). p=percentil. †A patient can presente more tan one. LDH: lactate dehydrogenase.

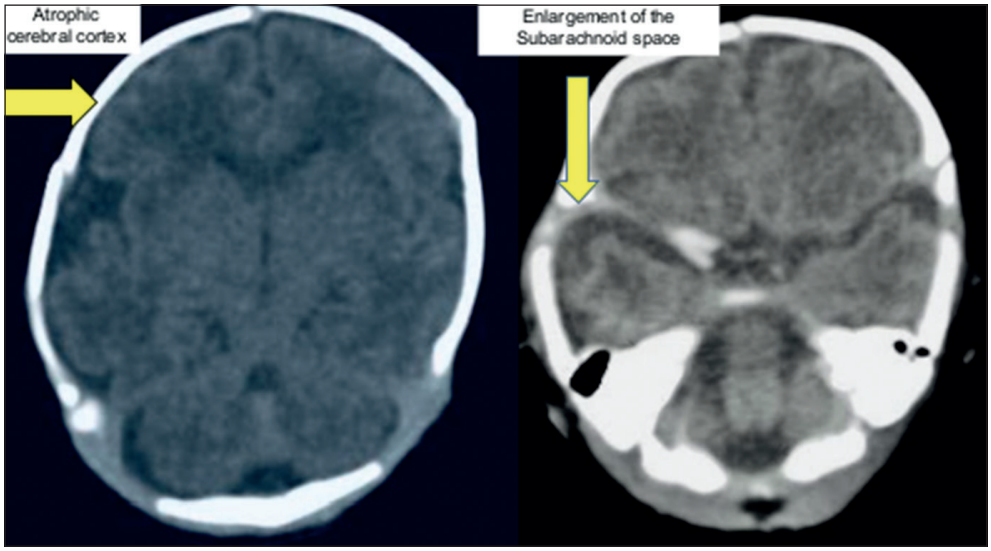

Figure 1. Simple CT scan of the skull with coronal section showing abnormalities described with yellow arrows.

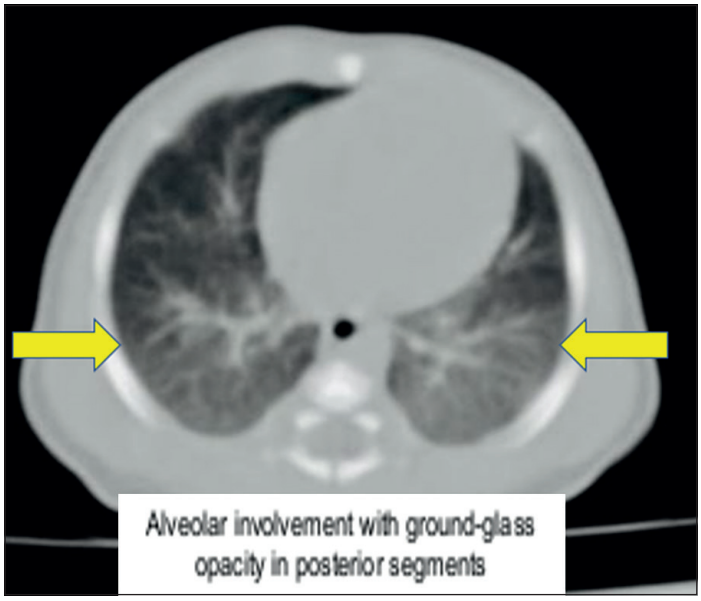

Figure 2. Axial chest CT scan showing alveolar involvement in the posterior segments (between yellow arrows).

most frequent finding was indirect hyperbilirubinemia, while blood counts were normal, including leukocytes and their differential.

CRP was elevated in 3 patients (18.7%) and LDH in 2 patients (12.5%). Bacterial infection was detected in 4 cases of those admitted through the emergency department, three urinary tract infections by *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Escherichia coli*, and one case of CNS infection by *Staphylococcus epidermidis*. In patients requiring oxygen, a chest X-ray was performed and reviewed by radiology, which reported a ground-glass pattern in 50% of cases.

The case of a neonate born at 34 weeks of gestation, weighing 2260 g, is analyzed in detail. The infant had no prenatal care or administration of prenatal steroids and exhibited early signs of moderate to severe respiratory distress, requiring orotracheal intubation and the administration of pulmonary surfactants using the InSuRe technique (Intubation-Surfactant-Extubation). Subsequently, the neonate developed abnormal hypotonia for gestational age, a pointed fontanelle, and weak sucking. Because of this, a cranial CT scan was performed on day 22 (at 37 weeks of postmenstrual age), which showed cortical atrophy (Figure 1). Complementary studies for TORCH infection and ophthalmologic assessment were normal. No signs of asphyxia were reported at the time of admission. The neonate had a hospital stay of 26 days, due to inadequate secretion management and suction rehabilitation plan. No other pathogens were isolated during their stay. Additionally, a chest CT scan was performed on another patient of those admitted through the ED due to signs of respiratory distress that showed opacity in the posterior segment (Figure 2). This patient had previously undergone a chest X-ray with similar findings and had a favorable clinical course, requiring only nasal cannula oxygen.

Discussion

Neonatal COVID-19 has been a clinical and diagnostic challenge since the beginning of the pandemic. The clinical manifestations, the route of transmission, and the impact of the infection on the pregnant woman, as well as the damage caused by the transmission to the neonate have been fundamental aspects in the

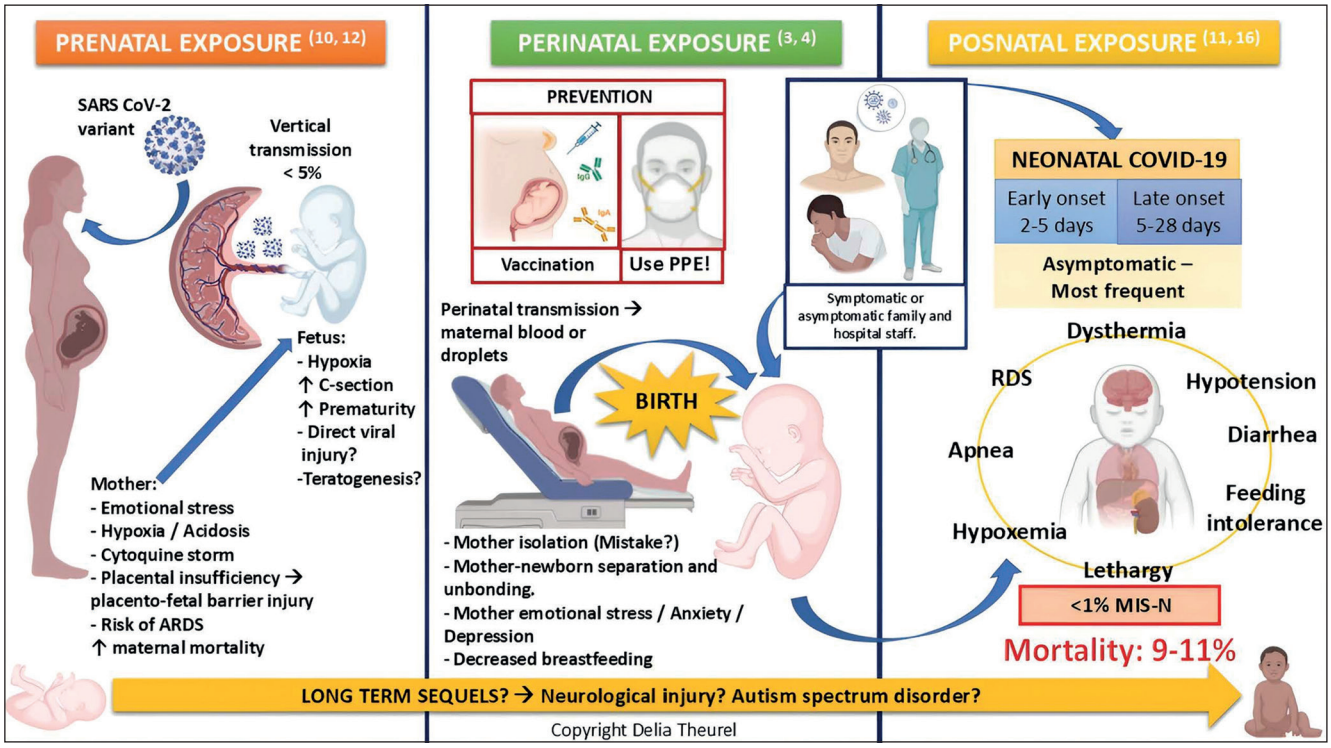

Figure 3. Diagram of the different clinical scenarios of perinatal and neonatal COVID-19. Key points post-pandemic.

management of the cases. Currently, it is considered that there were some errors in the management of cases at the beginning of the pandemic, especially during delivery, such as mother-child separation, an increase in cesarean sections, and a decrease in breastfeeding, with early and possibly long-term consequences. Figure 3 shows the different scenarios of pre-, peri- and postnatal COVID-19, which are discussed.

A relevant point of discussion is the route of transmission. None of the mothers of the reported cases underwent COVID-19 testing, and the deliveries were performed without adequate protective measures, which makes vertical transmission very improbable and horizontal transmission very probable[8,9]. Besides, according to the World Health Organization (WHO), 80% of infections in pregnant women are asymptomatic, which complicates the determination of the exact form of transmission to the neonate[9]. The debate on the risk of vertical transmission was a central issue at the beginning of the pandemic. Theoretically, the virus could reach placental tissues, and data suggest that this occurs in less than 5% of cases. It is important to note that there are established criteria for vertical infection, with early and placental testing being a mainstay in determining the mode of transmission[10]. In addition, *in utero* exposure is associated with prematurity, and this, together with the presence of congenital malformations, are factors that increase the risk of mortality[11].

Another relevant point is the clinical impact of the different variants of COVID-19. The current case series was conducted during the initial wave of the pandemic, also known as pre-Delta, which included the Alpha variant of the virus. It has been described during this phase that infection in pregnant women was predominantly asymptomatic, however, there was a higher risk of progression to intensive care in the pediatric and neonatal population. Subsequently, with the effect of maternal vaccination during the pandemic, the incidence and severity of the disease changed[11].

Different viruses are known to pose risks to the fetus during gestation, even without direct transmission, such as influenza and human immunodeficiency virus (HIV), with possible consequences on neurodevelopment. Therefore, this type of effect is not ruled out in the case of COVID-19, although these outcomes are still under investigation[12].

In our study, all neonates survived which coincides with that reported in other studies, with a favorable outcome, especially in those diagnosed on an outpatient basis and with gestational age greater than 37 weeks[5,13]. In addition, most of the cases found were community-acquired (75%). Zimmerman et al.[14] reported that 64.9% of the cases were acquired at home

and also found that fever was the most frequent symptom, which was not observed in our results. However, fever may be present in more than half of the affected cases. This sign should be considered as a neonatal SIRS criterion, which should be suspected in the presence of at least 2 system involvement, preferably with the diagnosis of COVID-19 during gestation[11].

Furthermore, an additional risk of bacterial co-infection has been described, similar to our findings. Although studies do not always confirm this association, complementary studies for severe bacterial infection, mainly urinary tract infection, in febrile infants younger than 90 days with a diagnosis of COVID-19[15] seem relevant. According to the current literature, fever associated with other symptoms, which are not necessarily respiratory, should alert to possible neonatal infection by COVID-19[14,16].

The clinical expression of the infection is variable, being asymptomatic in up to 40% of cases. Symptoms allow for classifying the severity of the picture, which determines 4 clinical spectrums: mild, moderate, severe, and critical[8]. Our cases were mild to moderate, and the symptoms were predominantly respiratory. However, in COVID-19-positive cases, respiratory symptoms are not always related to viral infection and may be mainly associated with perinatal conditions, such as prematurity[14,17].

In Turkey, a report of 11 patients indicated respiratory involvement as the main symptom, with 18% of cases requiring non-invasive mechanical ventilation, and one patient invasive mechanical ventilation, the latter conditioned by congenital heart disease rather than the viral infection itself[18]. Similar to what was observed in this study, in which patients with early infection presented mostly with mild symptoms, except for one patient who required intubation due to neonatal respiratory distress syndrome. Based on these findings, the approach to the neonate should be individualized, avoiding unnecessary interventions such as radiation and repeat laboratory studies[7,19].

However, there is a risk of developing neonatal SIRS, with systemic involvement secondary to a cytokine storm, mainly affecting the cardiopulmonary system, including tachyarrhythmias. Nevertheless, other systems, such as the gastrointestinal and nervous systems, may also be affected[11,20]. Recent reports highlight the need to monitor other clinical manifestations, particularly hepatitis and myocarditis, as they tend to appear later[21].

One of our early-diagnosed cases presented neurological clinical alterations and abnormal neuroimaging findings, a previously reported scenario, which raises the question about the neurotropic potential of the virus[22]. There are reports of viral particles at the cerebral level due to infection occurring in the third trimester, where the brain injury may simulate a hypoxic-ischemic lesion, with sequelae that may persist beyond the neonatal period[23].

Another factor to be evaluated is the patients admitted from home, whose epidemiological contact may be their mother or another family member, which makes it difficult to identify the index case in this scenario. Previous studies report that in 71% of cases, parents are the source of infection, but up to 18% of cases do not have a clearly identified source of infection[14]. However, we consider it likely that the neonate is the index case of other asymptomatic cases at home, which could help prevent the spread of this infection, both at the community level and even within intensive care units[24,25].

This study has limitations related to the small number of cases and the fact that it is a retrospective study, which limits the identification of close cases and possible intrauterine infection. In addition, the lack of follow-up of the patients prevents an evaluation of the medium and long-term impact of fetal and perinatal exposure to SARS-CoV-2.

Conclusions

Neonatal COVID-19 infection is usually asymptomatic and appears to have a generally favorable course. Symptoms in neonates may be related to underlying diseases and not necessarily to the virus. It is suggested that the viral infection may predispose to over-aggregated bacterial infections, especially in cases diagnosed in the community. Given the possible placental, fetal, and neonatal effects of COVID-19, it is crucial to study the long-term effects and consequences, especially in relation to neurodevelopment.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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