

Review Article

Characteristics of Covid-19 Pneumonia in Newborns: A Systematic Review

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• Covid-19; Sars-cov-2; Neonate; Newborns; Epidemiology; Clinical

Abstract

This work aims to carry out a systematic review of the literature on the characteristics of pneumonia due to new coronaviruses on newborns, as well as to discuss the relationship of this infection with pregnancy and exposure in the neonatal period. A systematic review of the literature was carried out in the electronic databases PubMed and Scopus. Original articles that describe clinical, epidemiological and therapeutic characteristics of newborn patients with new coronavirus infection were selected. Only clinical studies that contain features of COVID-19 infection in newborns were included. Due to the scarcity of papers on COVID-19 in this approach, review cases were included in this review. A total of 53 articles were retrieved using the search strategy, of which 24 and 29 were retrieved from PubMed and Scopus, respectively. Thus, 10 articles published between January 2020 and April 2020, originating in China, South Korea and Iran, were included for qualitative classification. There are not enough evidence that support vertical transmission or clinical complications in newborns whose mothers were affected by COVID-19. However, there is a need for further clinical studies to assess these issues and to take into account contamination during childbirth.

INTRODUCTION

Since the onset of infections by the new coronavirus (COVID-19), in Hubei province, China, severe cases of pneumonia with clinical characteristics of viral infection have spread rapidly across the globe to the extent that the World Health Organization (WHO), has declared public health emergency of international interest and subsequently the occurrence of a pandemic associated with this infection [1].

Studies carried out in different places are trying to access epidemiological and clinical characteristics of this disease that has proven to be caused by SARS-CoV-2 virus, one among other viruses of the family *Coronaviridae* that cause disease in humans with variable clinical characteristics from asymptomatic cases to severe presentations, as verified in the outbreaks of SARS-COV infection (causing severe acute respiratory syndrome or SARS), and MERS-COV (causing Middle East respiratory syndrome or MERS), in previous years [2].

Since the first reports of this new disease related to SARS-COV-2 (COVID-19), an increasing number of pregnant women and children are reported, which promotes the interest of obstetricians and pediatricians in understanding the phylogenetic and pathogenic aspects of the virus as well as the natural history of the disease and clinical outcomes related to infection and its treatment [3].

The clinical characteristics of the disease in neonates are described in sparse studies that also aimed to determine the potential risk of vertical transmission of SARS-COV-2 and, although there is a need to establish better scientific study designs on this issue, the evidence collected points to the nonoccurrence of that kind of transmission [4].

The clinical behavior of COVID-19 and the supportive therapy reported so far by several studies does not seem to differ greatly between the groups of affected people who have immunological peculiarities that theoretically predisposes them to a greatest risk of morbidity and mortality from viral infections, such as the pregnant women and newborns, and the general population. This latter group accounts for the majority of the published scientific studies. The use of distinct antimicrobials has been described with clinical success among the neonatal population [5].

The assessment of the clinical course of the disease in parturient women can contribute to the development of perinatal recommendations and care. The study of the relationship between the method of delivery and the risk of transmission from the mother to the fetus are incipient and require further development. Evaluations carried out with sample collection of fetal annexes, amniotic fluid and breast milk indicate that they did not present positive testing for the virus even in the presence of maternal infection, but the highly contagious character of COVID-19 raises doubts about the care that involves breastfeeding [1].

The establishment of specific treatment for SARS-CoV-2 infection in the neonate group, as well as in the general population, depends on further studies. However, the demonstration of good neonatal outcomes among proven infected women guides to the adoption of routine individual neonatal support therapy, according to the child's allocation in the broad spectrum of severity and clinical presentation of COVID-19 and individual demands during the course of the disease [2]. In this context, this study aims to carry out a systematic review of the literature regarding the characteristics of pneumonia caused by the new coronavirus in newborns, as well as to discuss the relationship between this infection and pregnancy and exposure in the neonatal period.

MATERIALS AND METHODS

A systematic review of the literature was carried out in the electronic databases PubMed and Scopus, selecting articles published until April 24, 2020 with the keywords: ("covid-19" OR "sars-cov-2"), AND (" neonate "OR" newborns "), AND (" epidemiology "OR" clinical ") , following the items of Guidelines for Systematic Reviews and Meta-analysis (PRISMA). Original articles were selected that described the clinical, epidemiological and therapeutic characteristics of newborn patients with infection by the new coronavirus. No language restrictions were adopted. There were two independent evaluators in the analysis of the articles, with a third evaluator being consulted in cases of discrepancy.

Only clinical studies that included characteristics of COVID-19 infections in newborns were included. Due to the scarcity of works on COVID-19 in this approach, case reports were included in this review. Animal researches, literature reviews, studies with conflicting results and methodological bias were excluded from the present work. Data related to the clinical, epidemiological and therapeutic characteristics of newborn patients with infection with the new coronavirus were extracted and discussed according to the current literature.

RESULTS

A total of 53 articles were retrieved using the search strategy (24 in PubMed and 29 in Scopus). After screening by abstract and title, 28 articles were selected for evaluation in full text. Of these studies, 18 were excluded due to the lack of information regarding the objective proposed by this review. Thus, 10 articles were included for qualitative synthesis (Figure 1). The main characteristics of the included studies are shown in Table 1. This review included 10 studies published between January 2020 and April 2020, originating in China, South Korea and Iran (Table 1).

DISCUSSION

In a prospective study, Yang et al. (2020), analyzed the clinical characteristics of seven neonates born of women infected with SARS-CoV-2. All infants were born with good vitality, without choking and Apgar scores at 1 minute and 5 minutes ≥ 8 . Two premature infants presented mild dyspnea after birth, but it was relieved with Continuous positive airway pressure (CPAP), and noninvasive ventilation (NIV). Three cases presented chest radiography, one without alterations and the two cases using nCPAP support presented mild Newborn Respiratory Distress

Syndrome (NRDS). Samples of pharyngeal swab, amniotic fluid and umbilical cord blood were collected and tested by real-time polymerase chain reaction (RT-PCR); in all cases there was no positive result for SARS-CoV-2.

Chen et al. (2020), demonstrated that there is no evidence that the development of COVID-19 pneumonia during the third trimester of pregnancy is capable of leading to the occurrence of serious adverse outcomes in newborns. The study carried out tests on nine neonates for the presence of SARS-CoV-2 in amniotic fluid, umbilical cord blood and pharyngeal swabs. SARS-CoV-2 was negative in all samples, indicating that no fetal infection occurred through intrauterine vertical transmission of the virus due to maternal COVID-19 infection during a late stage of pregnancy.

Li et al. (2020), in a case-control study, compared the maternal and neonatal clinical characteristics of pregnant women with and without COVID-19 pneumonia. A higher rate of prematurity and low birth weight was observed in confirmed maternal cases, but all were related to complications such as premature rupture of membranes and bleeding of the placenta, occurrences not directly related to COVID-19 pneumonia. The infection by COVID-19 was not found in the neonates and none presented neonatal conditions with serious complications.

In the retrospective study by Yu et al. (2020), a newborn child of a mother affected by COVID-19 was considered infected with SARS-CoV-2 36 hours after birth. The test was positive in the pharyngeal swab sample; however, in samples of placenta and umbilical cord blood, the tests were negative, which indicates that intrauterine vertical transmission probably did not occur, and the infant was contaminated after birth. The newborn had mild dyspnea and a chest X-ray showed a small focus of pulmonary infection compatible with COVID-19. The newborn was discharged after two weeks of general care and ventilatory support, after two consecutive negative test results.

Even though vertical transmission of SARS-CoV-2 has not been found, perinatal infection by COVID-19 can have adverse effects on newborns. The study by Zhu et al. (2020), analyzed ten newborns born to women with confirmed COVID-19 infection and out of these, six had a Pediatric Critical Illness Score (PCIS) lower than 90, indicating absence of severity. PCIS is a scoring system widely used in Chinese hospitals that uses physiological parameters to analyze the severity of disease risk and mortality in pediatric patients. The total score is 100 points and the lower the score, the more critical the child's condition is; values ≤ 70 points correspond to a very critical state, 80 points are classified as critical and values > 80 are classified as non-critical. The score assesses 10 parameters: PaO₂, pH, urea and creatinine, hemoglobin, serum sodium and potassium, gastrointestinal system, respiratory rate, heart rate and systolic blood pressure.

Thus, in the work of Zhu et al. (2020), the main symptom in newborns was dyspnea (n = 6), but other early symptoms such as fever (n = 2), thrombocytopenia accompanied by abnormal liver function (n = 2), tachycardia (n = 1), vomiting (n = 1) and pneumothorax (n = 1) were observed. Pharyngeal swab samples were collected on the 1st and 9th day after birth for nucleic acid amplification tests for SARS-Cov-2; all with negative results. Five

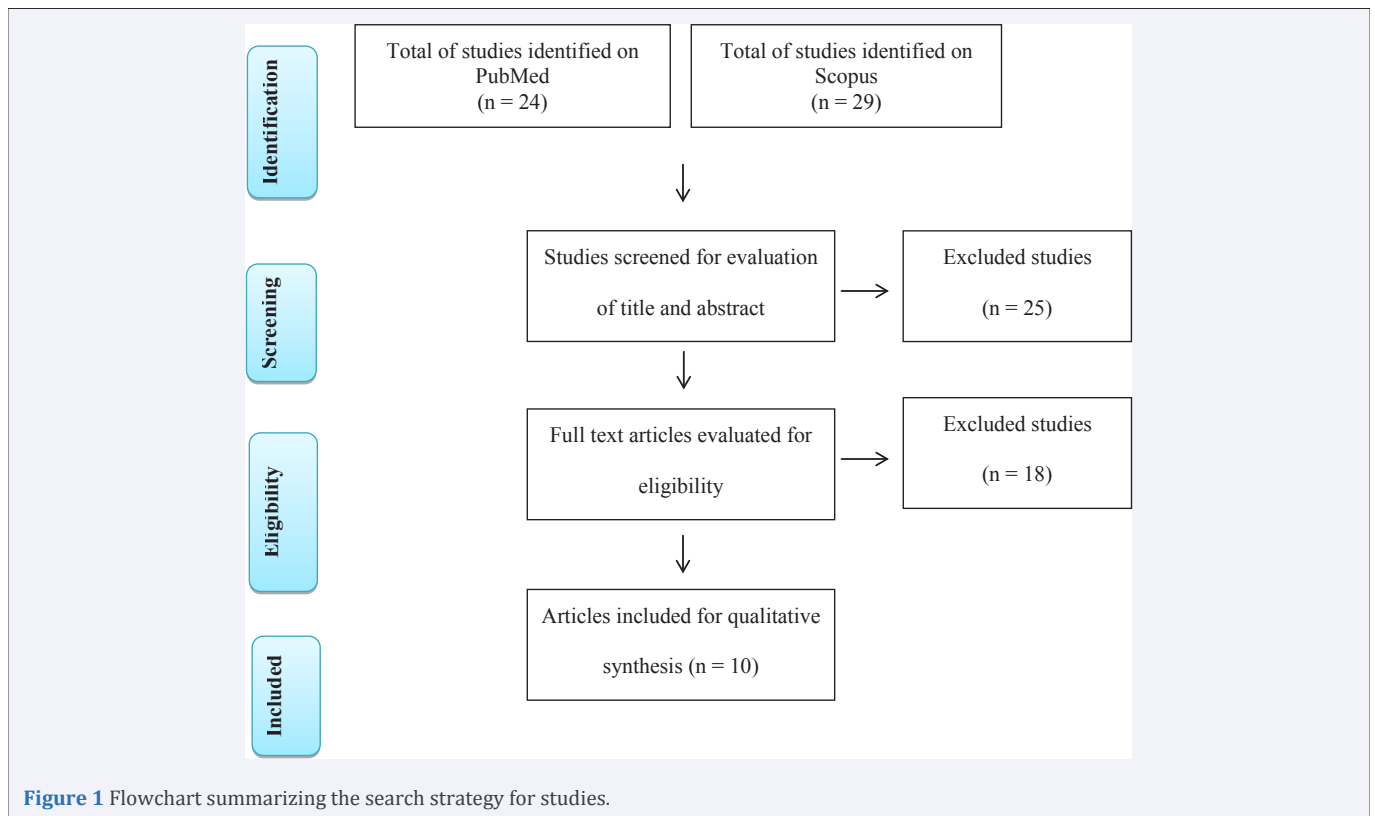


Table 1: Synthesis of the studies selected in the final sample.

Author and Year	Study Country	Objective	Methodology	Results	Conclusion
Yang et al., (2020)	China	It was reported the clinical characteristics of infants born to infected pregnant women with SARS-CoV-2	The clinical characteristics, laboratory data and results of 7 newborns delivered by pregnant women infected with SARS-CoV-2 were prospectively collected and analyzed.	Samples of pharyngeal swab in 6 cases, amniotic fluid and umbilical cord blood in 4 cases were tested by qRT-PCR, and there was no positive result for SARS-CoV-2 nucleic acid in all cases	SARS-CoV-2 infection in late pregnant women does not cause adverse results in their newborns; however, it is necessary to separate them from mothers to avoid possible threats.
Li et al., (2020)	China	Analyze data on maternal and neonatal outcomes of pregnant women with COVID-19 pneumonia	A case-control study was conducted to compare clinical characteristics, maternal and neonatal outcomes of pregnant women with and without COVID-19 pneumonia.	COVID-19 infection was not found in newborns and none developed severe neonatal complications.	Serious maternal and neonatal complications were not seen in pregnant women with COVID-19 pneumonia who had vaginal or cesarean delivery.
Liu et al., (2020)	China	Describe the clinical course of four babies of women affected by COVID-19.	Description of the compilation of clinical course reports of four live newborns of pregnant women with COVID-19 infection	Four babies were born of pregnant women who tested positive for COVID-19. Out of the three babies consented to the diagnostic test, none of them tested positive for the virus or developed severe clinical symptoms.	No COVID-19 vertical transmission was detected. Future studies for viral infection in the placenta and various fluids and physiological substances in children will be detected in the future.
Yu et al., (2020)	China	Clarify the clinical characteristics and obstetric and neonatal outcomes of pregnant women with COVID-19.	In this retrospective, single-center study, we included all pregnant women with COVID-19 who were admitted to Tongji Hospital in Wuhan, China. Clinical characteristics, treatments and maternal and fetal outcomes were assessed.	The results of pregnant women and newborns were good. Three newborns were tested for SARS-CoV-2 and one newborn was infected with SARS-CoV-2 36h after birth.	The clinical characteristics of patients with COVID-19 during pregnancy were similar to the characteristics of non-pregnant adults with COVID-19 that have been reported in the literature.

Chen et al., (2020)	China	Evaluate the clinical characteristics of COVID-19 during pregnancy and the potential intrauterine vertical transmission of COVID-19 infection.	Evidence of intrauterine vertical transmission was assessed by tests for the presence of SARS-CoV-2 in amniotic fluid, umbilical cord, neonatal blood, and neonatal pharyngeal smear samples. Breast milk samples were also collected and tested in patients after the first lactation.	Amniotic fluid, umbilical cord blood, neonatal pharyngeal smear samples and breast milk samples from six patients were tested for SARS coronavirus-2, and all samples tested negative for the virus.	The results of this small group of cases suggest that there is currently no evidence of intrauterine infection caused by vertical transmission in women who develop COVID-19 pneumonia in late pregnancy.
Han et al., (2020)	South Korea	We reported changes in viral load over time in a 27-day-old newborn with COVID-19 who had fever, cough and vomiting	RNA from clinical samples was extracted using the MagNA Pure 96 DNA kit and small volume Viral NA (Roche, Germany), according to the manufacturer's instructions.	SARS-CoV-2 RNA was detected in the newborn's clinical samples from several sources, including nasopharynx, oropharynx, plasma, urine, feces and saliva samples.	As newborns can have systemic complications, it is essential to monitor them, as well as to have good hygiene practices by caregivers.
Aghdam, Jafari and Eftekhari (2020)	Iran	Presentation of a case report of a 15-days-old newborn who was admitted with fever, lethargy, skin rash and trouble breathing without cough.	The Polymerase Chain Reaction Assay with Reverse Transcription (RT-PCR) was performed for the newborn and proved to be positive. The newborn was isolated and submitted to supportive care. Antibiotic and antiviral treatment was implemented.	The results of the patient test were: leukocytes $\frac{1}{4}$ 6700 / mL (L: 36%, N: 42%), Hb / 14.4 g / dL , PLT $\frac{1}{4}$ 351.000 / mL , BS $\frac{1}{4}$ 59 mg / dL , BUN / 16 mg / dL , Cr $\frac{1}{4}$ 0.3 mg / dL , CRP $\frac{1}{4}$ 1 mg / L, ABG: PH $\frac{1}{4}$ 7.42, PCO2 $\frac{1}{4}$ 28.5 mmHg, PO2 $\frac{1}{4}$ 74 mmHg, HCO3 $\frac{1}{4}$ 22 meq / L, BE $\frac{1}{4}$ 1 , 5 mmol / L, SaO2 $\frac{1}{4}$ 93% These results were normal for newborns.	When a newborn has nonspecific symptoms of infection with an additional history of COVID-19 in their parents, this indicates the need for PCR tests for new coronaviruses.
Khan et al., (2020)	China	It was reported adverse pregnancy outcomes in pregnant women infected with COVID-19 pneumonia and the risk of intrapartum transmission of COVID-19 vaginally.	All three pregnant women tested positive for COVID-19 using quantitative RT-PCR (qRT -PCR) in samples from the respiratory tract and blood samples. In order to assess neonatal infection with COVID-19, umbilical cord blood samples and neonatal swab were collected after delivery in the operating room and tested using quantitative RT-PCR (qRT-PCR).	None of the three newborns delivered by natural birth was infected with COVID-19. Only one newborn was delivered prematurely. No neonatal deaths and stillbirths were observed in pregnant women infected with COVID-19.	No vertical transmission of COVID-19 in the third trimester of pregnancy was found. We found no evidence of intrapartum maternal-neonatal transmission of COVID-19 through vaginal delivery.
Fan et al., (2020)	China	We present two cases of SARS-COV-2 infection associated with COVID-19 during the third trimester of pregnancy.	Three SARS-COV-2 target genes, including the open reading frame 1ab (ORF1ab), the nucleocapsid protein (N) and the Envelope protein (E) were identified with the qRT-PCR kit (Bioperfectus Technologies, China) by Quantstudio Dx Real-time PCR system.	We did not identify SARS-COV-2 in any of the products of conception and in newborns.	This report provided evidence of a low risk of intrauterine infection by vertical transmission of SARS-COV-2.
Peng et al., (2020)	China	Presentation of a case with possible vertical transmission of the COVID-19.	The amniotic fluid, vaginal secretions, placenta, umbilical cord blood, breast milk, mother's venous blood and the newborn 's throat and anal samples, sputum, venous blood and urine samples were all negative for SARS-COV-2, which is consistent with published studies.	During his stay in the hospital, a series of nucleic tests for SARS CoV -2 of the throat and anal swabs, serum, bronchoalveolar lavage fluid and urine were negative. The nucleic acid tests of the mother's amniotic fluid, vaginal secretions, umbilical cord blood, placenta, serum, anal swab and breast milk were also negative.	The most tested case to date confirmed that vertical transmission of COVID is unlikely, but more evidence is still needed.

neonates were discharged after clinical evaluation, four remained under observation and one case evolved to neonatal death.

The case report by Chen et al. (2020), followed the clinical evolution of three newborns of mothers with COVID-19 infection. The neonates had negative tests for COVID-19 72 hours after birth, which were performed using pharyngeal swab samples. None of the babies had severe symptoms, such as fever, cough, diarrhea, or evidence of radiographic or hematological abnormalities. However, two children had, after birth, skin rashes of unknown etiology and spontaneous resolution. The lesions were located throughout the body in a maculopapular pattern and in red miliary papules.

In Han et al. (2020), the clinical manifestations of the newborn who tested positive for COVID-19 were mild fever (37.6° C), blood pressure of 82/53 mmHg, heart rate of 145 beats per minute, ventilatory rate of 62 breaths per minute and oxygen saturation level of 95%. Although the SARS-COV-2 RNA was identified in samples of feces, saliva, urine, nasopharynx and oropharynx, the hospitalization of the newborn and the care received were essential for the radiological examination to show no lung damage, the laboratory tests to be normal and to maintain constant weight gain. It is worth noting that the newborn had a high viral load and the mother only mild symptoms, but both recovered without antiviral therapies. According to Fan et al. (2020), there is the possibility of producing sufficient neutralizing antibodies without developing serious conditions and these passive antibodies can have a protective effect on infants through breastfeeding. However, in the study in question, even without the detection of SARS-COV-2 in breast milk during follow-up, breastfeeding was discouraged.

However, Aghdam, Jafari and Eftekhari (2020), portrayed a newborn of 15 days with fever, lethargy and trouble breathing, heart rate of 170 / min (tachycardia), respiratory rate of 66 / min and oxygen saturation level of 93 %, testing positive for COVID-19 next. Unlike the case of Han et al., (2020), the newborn was submitted to a therapy that involved the administration of antibiotics (Vancomycin and Amikacin), antivirals (Oseltamivir), and oxygen therapy. The current treatment obtained good results and the examinations involving arterial blood gases, glucose and chest X -ray were satisfactory, reflecting the effectiveness of the therapy used.

Furthermore, the vertical transmission of COVID-19 is a very controversial and debatable topic. The study by Khan et al. (2020), addressed three pregnant women (34 weeks, 38 weeks and 39 weeks of gestation, respectively), who tested positive for COVID-19, whose childbirths were normal. The pregnant woman at 34 weeks of gestation had fever (37.3°), and cough, needing to perform a premature birth; the Apgar score of the newborn was 8 for the first minute and 9 for the fifth minute. Furthermore, the Apgar score for the other two children was 9 and 10. Even with the situation presented by the patients, there was no death and no child tested positive for COVID-19, but the study pointed out that premature birth may have been caused by psychological stress during pregnancy associated with COVID-19 pneumonia. Finally, to prevent and control viral infection, therapy for pregnant women involved the administration of antivirals (Oseltamivir), antibiotics (Azithromycin), oxygen therapy and

Chinese medicine, contributing to the improvement of patients.

Similar to the situation reported in Khan et al. (2020), in the case elucidated in Peng et al. (2020), a pregnant woman tested positive for SARS-COV-2, requiring hospital isolation, with subsequent administration of antivirals, antibiotics, oxygen to stabilize the condition and dexamethasone to stimulate the child's lung development, preparing for premature delivery. After the procedure, the premature newborn (Apgar score 9 and 10 for 1 minute and 5 minutes), had mild breathing difficulties. The patient was initially treated with gentamicin, ampicillin and pulmonary surfactant having a good responsiveness to the continuous positive pressure in the upper airways and testing negative for SARS coronavirus-2 in samples of oropharyngeal swab, anal swab and research in urine. Thus, the current case evidenced that the vertical transmission of the virus was not confirmed, highlighting the improbable and questionable characteristic of this type of contagion. In the study by Duan, Jin and Zheng (2020), it was showed that the SARS-COV-2 receptor in cells, the angiotensin-converting enzyme (ECA2), has a deficient expression in the different types of cells belonging to the placental interface, highlighting the low risk of transmission of the virus in the intrauterine environment from mother to child.

In light of this, the evidenced studies show promising perspectives about the approach of COVID-19 pictures in pregnant and newborn patients. In this sense, we observed a low risk of vertical transmission of the virus, evidenced by the negative tests for COVID-19 of many newborns and by the effectiveness of pharmacological therapies, promoting the improvement of symptoms and ensuring that no deaths occur. In addition, according to Peng et al. (2020), only a few basic studies explored the possibility of transmission through the newborn's contact with the vaginal canal and breast milk. Because of this, even without detection of COVID-19 in breast milk, some studies, such as Fan et al. (2020), do not encourage breastfeeding during treatment.

CONCLUSION

There is no consistent evidence that COVID-19 pneumonia during the first months of pregnancy is capable of promoting the occurrence of serious adverse outcomes in newborns. The reported complications, premature rupture of membranes and bleeding from the placenta, were not directly related to COVID-19. There is insufficient evidence to affirm vertical transmissibility, but there are reports of post-birth contamination. Even though the vertical transmission of SARS-CoV-2 has not been found, perinatal infection by COVID-19 can have adverse effects on newborns, such as dyspnea. Therefore, there is a need for more clinical studies to assess the consequences of the clinical manifestations of COVID-19 for newborns and the possibilities of contagion during delivery.

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