Updates in neonatal coronavirus disease 2019: What can we learn from detailed case reports? (Review)

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Abstract. Although the COVID-19 epidemic has lasted for months, it has not yet been successfully controlled, and little is known about neonatal COVID-19. Therefore, literature search was conducted for references in PubMed, Science Direct, ProQuest, Web of Science and China National Knowledge Infrastructure for detailed case reports on neonatal COVID-19 published as of July 15, 2020, to facilitate the clinical treatment, epidemic prevention and control of neonatal COVID-19. Forty nonoverlapping case reports focusing mainly on the demographic characteristics, transmission modes, clinical features, treatments and prognosis of neonatal COVID-19, including 3 in Chinese and 37 in English, were available.

Contents

1. Introduction

Although the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)/coronavirus disease 2019 (COVID-19) epidemic has lasted for several months, it has not yet been successfully controlled. Compared with severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus, SARS-CoV-2/COVID-19 is characterized by a long epidemic, global transmission, a large number of deaths, and difficulties in prevention and control. According to the official report of the World Health Organization, by 10:00 (Central European Summer Time), 16 July 2020, 13,378,853 cases of COVID-19 had been diagnosed globally, and 580,045 patients had died of COVID-19. Among them, there were not only many adult deaths but also child deaths (1-3), as well as a case of neonatal death due to maternal COVID-19 during pregnancy (4). Moreover, there is no specific antiviral agent to treat SARS-CoV-2/COVID-19 (5). Therefore, this disease is extremely harmful.

Currently, although the common transmission mode, clinical features and symptomatic treatments of SARS-CoV-2/COVID-19 in children and adults are relatively clear and the number of neonatal COVID-19 cases is far less than that of pediatric and adult COVID-19 cases (6). It is unclear why the number of neonatal COVID-19 is so small, and whether there are unique modes of transmission of COVID-19 in newborns or whether the clinical manifestations of neonatal COVID-19 are more nonspecific. It is unknown whether therapies used in adults can be applied to treat newborns with COVID-19 or what the short-term and long-term prognosis of neonates with COVID-19 is. There are no large, multicenter studies to address the aforementioned questions. Thus, the understanding of COVID-19 in adults and children is increasing, but little is known about neonatal COVID-19.

For this purpose, references were searched in PubMed, Science Direct, ProQuest, Web of Science and China National Knowledge Infrastructure for neonatal COVID-19 cases that were reported in detail as of July 15, 2020, to facilitate the clinical treatment and epidemic prevention and control of neonatal COVID-19. Ultimately, there were 40 nonoverlapping case reports available (7-37), including 3 in Chinese (19,27,28) and 37 in English.

2. Demographic characteristics of neonatal COVID-19

The majority of the 40 neonatal COVID-19 cases involved full-term infants, nine of which were

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premature (7,12,14,17,18,20,21,26,32), and one case did not mention the gestational age (35). The youngest neonate with COVID-19 reported to date had a gestational age of 26 weeks and 4 days, and her birth weight was only 960 g (21). A total of 10 patients were female (9,10,16,18,20,21,23-25,36). The age at which they were diagnosed with COVID-19 was as early as the day of birth (7,11) or as late as 27 days of life (DOL 27) (36). Of the 40 patients, 11 were diagnosed by DOL 3 (7-15), while 10 were diagnosed between DOL 4 and DOL 7 (8,16-23), and 19 were diagnosed between DOL 8 and DOL 28 (24-37). Among them, 12 were from the USA (21,23,29,31-34,37), 10 were from China (13,14,16,17,19,27,28), Italy (15,25,30) and Spain (8,24,35) each had 4 cases, the United Kingdom (9,18,20) had 3 cases, while Canada (11), Peru (12), Germany (10), France (7), Turkey (22), Iran (26) and Korea (36) each reported 1 case. Regarding the aforementioned demographic characteristics of neonatal COVID-19, further research is necessary.

3. Neonatal COVID-19 transmission mode

Among these 40 cases of neonatal COVID-19, except for one case that was clinically diagnosed with chest computed tomography (CT) (17), 39 were confirmed by positive SARS-CoV-2 ribonucleic acid (SARS-CoV-2 RNA). These neonates were exposed to mothers with COVID-19 *in utero* and/or contacted confirmed or suspected patients with COVID-19 (such as their parents, relatives or caregivers) after birth, even though some of the suspected patients with COVID-19 that surrounded the neonates did not undergo further SARS-CoV-2 RNA detection (26,37).

Although horizontal transmission of SARS-CoV-2 does exist, there is currently not a convincing chain of evidence for SARS-CoV-2 transmission from maternal blood, placenta, amniotic fluid or cord blood to fetuses and newborns that perfectly supports mother-to-child (vertical) transmission, though it is still highly suspected (9,11) and has even been documented (7). In general, the mother is diagnosed with COVID-19 before delivery, and the neonate has no close contact history with confirmed or suspected patients with COVID-19 after birth before onset, including their parents, other family members, relatives and caregivers. The earlier the onset of neonatal COVID-19 (especially within DOL 7), the more support there is for intrauterine transplacental transmission, but it cannot be completely ruled out that neonatal SARS-CoV-2 infection is caused by exposure to maternal blood and/or vaginal secretions during delivery. In contrast, horizontal transmission is more likely. However, the possibility, influencing factors and specific mechanisms of mother-to-child (vertical) transmission are still unclear.

Some scholars believe that vaginal delivery may increase the risk of SARS-CoV-2 infection in neonates (38), and there are indeed studies that have detected SARS-CoV-2 RNA from maternal vaginal swabs (7). However, one pregnant woman with severe COVID-19, who was admitted to the intensive care unit (ICU), had a vaginal delivery with a favorable maternal-neonatal outcome, and the newborn was not infected with SARS-CoV-2 (39). It is thought that bedside vaginal delivery in the ICU can prevent unnecessary high-risk exposure caused by excessive contact with relevant personnel during the travel between the ICU and the operating room (39). From the data of 13 newborns, who were diagnosed with COVID-19 by DOL 7 and in whom mother-to-child (vertical) transmission was highly suspected (7,9-14,16-18), it was found that, except for one case of vaginal birth (10), the babies were delivered by cesarean section. Cesarean section is not necessarily better for preventing the vertical transmission of SARS-CoV-2 from mother to child. The selection of cesarean section should mainly depend on the condition of the mother and the fetus rather than on whether the mother has COVID-19. However, the positive detection of SARS-CoV-2 RNA in maternal vaginal swabs (7) has to be considered.

Regardless of whether SARS-CoV-2 can be transmitted through breast milk, positive SARS-CoV-2 RNA detection in breast milk should be considered (40,41). Among these 40 neonatal COVID-19 cases, eight cases involved testing for SARS-CoV-2 RNA in breast milk (13,21,22,25,29,30,36), and only one case involved a positive result (22). The child was not exposed to any known patients with COVID-19 after birth (22). The initial nasopharyngeal swab of this child, collected between 8 and 10 hours after birth, was SARS-CoV-2 RNA negative, but the results were positive for the nasopharyngeal swabs, anal swabs and blood collected after consumption of non-pasteurized, frozen expressed or fresh breast milk, which highly supports postnatal horizontal transmission via breast milk (22). However, it is unclear whether there is mother-to-child (vertical) transmission, birth canal/vaginal secretion contact during vaginal delivery or unintentional contact with unknown patients with COVID-19 after birth that results in positive SARS-CoV-2 RNA in the aforementioned three types of samples on DOL 4 (22). If there is breast milk transmission of SARS-CoV-2, the probability of it occurring is also unclear. The SARS-CoV-2 load and vitality in breast milk may be one of the important influencing factors (41). Although some studies have shown that the SARS-CoV-2 IgG/IgA detected in breast milk may have immune-protection potential for offspring (42), it is necessary to be vigilant that if mothers who are suffering from COVID-19 do not protect the child intentionally or use improper protection during breastfeeding, SARS-CoV-2 may be transmitted from mother to child through droplets, close contact or other horizontal transmission modes (43). Therefore, before breastfeeding, mothers with COVID-19 should weigh the advantages and disadvantages and make well-informed decisions (44). If breastfeeding is selected, the babies must be strictly protected (45).

In addition, during the COVID-19 illness of one newborn, the child's mother developed a fever (37). Although she did not undergo further investigation for SARS-CoV-2 RNA, and even if she had COVID-19, it is unclear whether the child infected her. Because someone other than the child himself, such as the child's sick father, may have infected her or she was infected earlier and had a longer incubation period than the child, she became ill later than the newborn. Nevertheless, the infectivity of newborns with COVID-19 should be examined. In a case series, after the first confirmed neonatal COVID-19 case, all newborns in the neonatal intensive care unit were screened, and two asymptomatic neonates with COVID-19 were detected, despite the concrete infection time and transmission route of these two being unknown (8).

4. Clinical features of neonatal COVID-19

Some of the 40 newborns with COVID-19 had underlying complications, including premature birth (7,12,14,17,18, 20,21,26,32), atrial septal defects (19,20), patent foramen ovale (26), tetralogy of Fallot (23), asphyxia (7,14,24), neonatal respiratory distress syndrome (14,18,21), hemodynamically significant patent ductus arteriosus (21), pneumothorax (21), non-COVID-19-associated endotracheal intubation and mechanical ventilation (7,12,21), severe hypoxic-ischemic encephalopathy (8), meconium aspiration syndrome (8), multi-organ failure (8) and Hirschsprung's disease (8). Five cases were coinfected with methicillin-sensitive *Staphylococcus aureus* (soft tissue infection, with wound cultures from the right hand) (29), Enterobacter agglomerates (blood culture) (14), seasonal coronavirus (respiratory viral panel PCR) (20), Escherichia coli (urine culture) (37), and human metapneumovirus (nasopharyngeal swab) (37), respectively. Although it is unclear whether the aforementioned underlying diseases increase the infection risk of COVID-19 in newborns and whether the latter coinfections aggravate the condition of newborns with COVID-19, it is beneficial to prevent weak conditions, including premature delivery, asphyxia, neonatal respiratory distress syndrome and pneumothorax, and to actively control underlying diseases and coexisting infections for SARS-CoV-2 prevention.

The clinical manifestations of these 40 neonates with COVID-19 were different, although most of them had fever of varying degrees (9,10,14,17,19,26-29,31,33-37). Respiratory system abnormalities mainly manifested as nasal congestion (32,36,37), rhinorrhea (31,35), sneezing (27), coughing (10,12,25,36), perioral cyanosis (15,19), desaturation (15,19,20,24,29,31,32,37), slow breathing (15), apnea (20), tachypnea (9,19,26,32,36,37), dyspnea (12,19,24,26,37) and respiratory distress (10,26,37). Although there is no uniform international standard for clinically grading neonatal COVID-19 and accurately assessing the severity of these 40 cases, oxygen therapy (12,19,26), humidifying high-flow nasal cannula (15,20), continuous positive airway pressure (10,20) or mechanical ventilation via endotracheal intubation (32) were needed for the aforementioned SARS-CoV-2-associated respiratory problems in some cases. Some newborns had digestive system abnormalities, such as poor sucking (15), decreased feeding (7,11,20,25,27-29,32,33,37), vomiting (14,27,28,35,36), and diarrhea (25,27,28,35). In addition, there were neonates with COVID-19 with hypoglycemia (11), hypothermia (11,20,32), dehydration (37), hypotension (32), tachycardia (19,26,31-33,36,37), myocardial injury (37), cardiac insufficiency (19), conjunctivitis (31), erythematous and papular facial rash (34), cutaneous mottling (26), and neurological abnormalities such as irritability (7,34,35), lethargy (10,14,20,26,29,37), and increased deep tendon reflexes (35).

Three patients were asymptomatic and lacked chest imaging data (22,25,30), and the other four children were asymptomatic with abnormal chest imaging, including one case of chest X-ray abnormality (21), one case of chest CT abnormality (13), and two cases of abnormal pulmonary ultrasound (8). The reported chest imaging findings from these patients were nonspecific. There were no abnormal findings in some cases (9,12,26,33,36). The other findings included thickened lung texture (13), hazy opacities (27,28,31), bilateral perihilar streaking (29), perihilar opacification (37), hypoinflated lungs (31), perihilar peribronchial thickening and bibasilar opacities (37), high-density nodular (13) or patchy shadows (19) (chest CT), ground-glass opacities (15,20,24), bilateral opacities (23,32,37), increased lung marking (chest CT) (16), diffuse multiple consolidation (19) and pneumonia (10,14).

The routine examination results of these newborns were also variable, ranging from normal (10,12,20,26,34) to mildly abnormal, including conditions such as leukocytosis (14,19), leukopenia (21,33,37), lymphopenia (13,14,21,22,31,37), neutropenia (11,29,31,37), thrombocytopenia (14,28), coagulopathy (14), positive fecal occult blood (28), an increased white blood cell count and leukocyte esterase positivity in the urine (37), elevated C-reactive protein (8,17,22,31), procalcitonin (14,37), erythrocyte sedimentation rate and lactic acid (19), aspartate aminotransferase (13,29), creatine kinase (13,22,35), creatine kinase-MB (14), lactate dehydrogenase (35), liver enzymes (9,11), cerebrospinal fluid proteins (7), high-sensitivity troponin T (37), N-terminal pro-brain natriuretic peptide (19,37), and CD4/CD8 (27), elevated interleukin 10, hypercoagulability and decreased left ventricular ejection fraction (37), transient mild acidosis (24) and borderline low IgG (37). No severe abnormality was reported in their routine examinations. In three cases, the cerebrospinal fluid was negative for SARS-CoV-2 RNA (7,9,10).

The symptoms, signs, routine laboratory abnormalities and chest imaging findings of the aforementioned newborns with COVID-19 are not specific to COVID-19. The diagnosis of COVID-19 was mainly based on the positive SARS-CoV-2 RNA detection results [from nasopharyngeal swabs (7-37), rectal swabs (7,9-11,14,22,27,28,36), blood (7,9,11,22,36), urine (36), bronchoalveolar aspirate (7,8), oropharyngeal swabs (36), and saliva specimens (36)]. Moreover, SARS-CoV-2 RNA-positive results can occur earlier than abnormal clinical manifestations (9). Only one case of neonatal COVID-19 was diagnosed with consideration of chest CT abnormalities (17). Serum SARS-CoV-2 antibody detection was performed in three cases (12,19,30), of which one involved SARS-CoV-2-IgM positivity and SARS-CoV-2-IgG negativity (19), one reported only SARS-CoV-2-IgG positivity (30), and one reported negative result for both antibodies (12). Nasopharyngeal swabs, oropharyngeal swabs, rectal swabs, blood, urine, saliva and other SARS-CoV-2 RNA-positive samples have the possibility of carrying live SARS-CoV-2, which not only provides an opportunity to improve the positive detection rate and effectively reduce the missed diagnosis rate but also provides evidence on how to effectively block the transmission route and prevent further transmission of COVID-19. The significance of serum SARS-CoV-2-IgM and SARS-CoV-2-IgG in the clinical diagnosis, curative effect monitoring and prognosis assessment of neonatal COVID-19 remains to be studied.

In general, the majority of patients with COVID-19 are adults, and the case-fatality rate is very high among elderly individuals and patients with basic chronic diseases such as cardiovascular disease and diabetes (46). In children, COVID-19 is mostly clustered, with a lower incidence, milder symptoms, and lower mortality than in adults (3). According to the present review, the incidence of COVID-19 in newborns is far less compared with that in children. The clinical manifestations of neonatal COVID-19 are even less specific, especially in SARS-CoV-2-infected premature infants (21). If we are not vigilant, a missed diagnosis or misdiagnosis is very easy and can even lead to the outbreak of neonatal COVID-19 nosocomial infection. Although there is a report of newborns dying shortly after birth from maternal COVID-19 during pregnancy (4), there are few newborns who have died directly or indirectly from COVID-19, and none of the 40 newborns included in the present review died. However, due to the limited number of cases included in the present review, the clinical manifestations and other characteristics of neonatal COVID-19 need to be further clarified by large, multicenter studies.

5. Interhospital transport in neonatal COVID-19

Two reports involved neonatal COVID-19 interhospital transfer (19,37). Yu *et al* (19) reported in detail a case of neonatal COVID-19 that involved successful long-distance interhospital transport via ambulance. The success of this case mainly depended on an administration that could organize and coordinate all aspects of the transport in a unified manner, various preparations (including protective equipment) before the transfer, effective protection, observation and treatment of the child during transportation, and strict disinfection of facilities after the transfer (19). The aforementioned reports can provide references for COVID-19 newborns who need interhospital transfer.

6. Treatment of neonatal COVID-19

Although people continue to explore feasible treatments for COVID-19 and have experience fighting major infectious diseases such as severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus, there is still no specific therapy that can be used in the clinical treatment of COVID-19. Comprehensive supportive treatment-oriented therapy has been given more attention. The 40 neonatal COVID-19 cases included in the present study also lacked specific treatment regimens; among those used, empiric antimicrobials in the early stage of the disease were more commonly applied (9,11,13,15,19,20,26,29,31-35,37). When COVID-19 newborns had hypoxia (15,19,20,29,31,32,37), apnea (20), or dyspnea (10,12,26,37), they were treated with oxygen therapy (12,19,26,29,31,37), humidifying high-low nasal cannula (15,20), continuous positive airway pressure (10,20), or even mechanical ventilation via endotracheal intubation (32). One of newborns developed pneumothorax during mechanical ventilation and then underwent tube thoracostomy (32). Those who also had hypothermia (11,20,32), hypoglycemia (11), hypercoagulability (37), dehydration (37), systemic vasodilation (31), hypotension (32), and cardiac insufficiency (19), needed extra warmth (11,20), intravenous glucose supplementation (11), enoxaparin and aspirin (37), volume expansion (31,32,37), vasopressors (32), and treatments involving fluid restriction, furosemide and improvement of cardiac function (19). A few patients were treated with antivirals, such as interferon (19,28), ribavirin (19), lopinavir/ritonavir (19), remdesivir (37), oseltamivir (26), and hydroxychloroquine (32). One infant was infused with immunoglobulin, albumin and red blood cells (19). No patient used hormones, convalescent plasma, continuous renal replacement therapy or extracorporeal membrane oxygenation. The treatment of neonatal COVID-19 continues to involve a comprehensive approach focusing on symptomatic and supportive therapy. The necessity, efficacy and safety of related therapies (such as antivirals) need to be given more attention in subsequent studies.

7. SARS-CoV-2/COVID-19 vaccine

Controlling the source of infection, cutting off the route of transmission, and protecting susceptible people are three important factors in the prevention and control of infectious diseases, including COVID-19. People around the world are working together to address the aforementioned three aspects to eliminate SARS-CoV-2/COVID-19. Among the measures being taken, the development of anti-SARS-CoV-2 vaccines to improve herd immunity and protect susceptible people from infection is highly anticipated. Currently, the development of vaccines against SARS-CoV-2 is in full swing, and some of the vaccines have entered clinical trials (47-49). The preliminary research results from China (47,49) and the United States (48) indicate that these vaccines offer certain immunogenicity and immune protection, but the strength of immune protection, duration of immune protection, and related side effects are still not very clear, and these studies focus only on adults (47-49). The specific efficacy of these vaccines in children, including newborns, has not been studied, which is also an urgent problem that needs to be addressed. If the relevant vaccines are successfully developed and can be widely used in susceptible newborns, they will be extremely useful in the prevention and control of neonatal COVID-19.

8. Prognosis of neonatal COVID-19

From the data of the 40 patients, it was found that one patient was not admitted (30), and the hospitalization time reported for the remaining patients was between 2 (33,37) and 33 (18) days. Among the hospitalized patients, one was a 32-week premature infant who was hospitalized for 33 days (18), and another premature baby with a gestational age of 26 weeks 4 days was still in the hospital when the original paper was submitted by Piersigilli *et al* (21). The long hospital stay of these two infants may be directly associated with prematurity rather than with COVID-19. The newborn with the longest hospitalization (30 days), mainly due to COVID-19, had congenital atrial septal defects, pneumonia and cardiac insufficiency, showing recurrent fever, oxygen dependence, dyspnea and increased N-terminal pro-brain natriuretic peptide levels. The patient eventually had to be transferred to another hospital for further treatment and was subsequently discharged in good condition (19). Most of these newborns with COVID-19 were in good condition when discharged, and only one case had fever again, approximately 4 hours post-discharge (37). Meanwhile, most of the patients whose follow-up statuses were briefly reported showed no abnormalities at follow-up (11,22,26,28,33). Only one patient sought multiple medical treatments due to repeated fever, 5 times within 4 weeks after discharge, and his nasopharyngeal swabs for SARS-CoV-2 RNA remained positive 20 days after the initial positive detection (37). Apart from that, no other abnormalities were reported during the follow-up (37). The condition of a newborn with COVID-19 and neurological abnormalities also gradually improved during short-term follow-up (7). Although there has been no report of neonatal COVID-19 death to date, the short- and long-term outcomes are still unclear because of the limited research data available.

9. Conclusion and prospects

SARS-CoV-2/COVID-19 is extremely harmful. Horizontal transmission is the main mode of transmission, but in special groups of mothers and newborns, vertical transmission is highly suspected and has even been confirmed. Usually, the mother is diagnosed with COVID-19 before delivery, and the child has no history of close contact with patients with COVID-19 after birth before onset. The earlier the onset of neonatal COVID-19, the more support there is for mother-to-child (vertical) transmission. Otherwise, horizontal transmission is more likely. Breast milk transmission has been nearly confirmed. Whether newborns are breastfed should be determined after weighing the pros and cons, and these infants should be protected during daily care activities, such as breastfeeding, to eliminate horizontal transmission through possible breastmilk and non-breastmilk-associated routes (such as droplets, aerosols, close contact). Regardless of the clinical manifestations, laboratory examinations, or imaging findings of neonatal COVID-19, there is no obvious specificity, which makes the clinical diagnosis and epidemic prevention and control of neonatal COVID-19 difficult. Fortunately, despite the lack of specific treatments, no deaths from neonatal COVID-19 have been reported. It seems that its short-term outcome may be relatively favorable. In addition, standardization and optimization of the treatment of COVID-19 and development of SARS-CoV-2 vaccines are urgent. The specific mechanism and prognosis of neonatal COVID-19 and the immune protection provided by the SARS-CoV-2 vaccine to neonates are still not very clear and urgently need to be studied.

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Competing interests

The authors declare that they have no competing interests.

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