

Review article

The 2019 Novel Coronavirus Disease (COVID-19) and Neonates

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SUMMARY

In late December 2019, Wuhan, China, became the center of an unknown outbreak of pneumonia that spread rapidly throughout China and around the world, including Iran, and the World Health Organization (WHO) declared the novel disease a public health emergency with global concern. Since the COVID-19 outbreak, many studies have been performed on epidemiological data and clinical signs in adults. However, coherent studies in this field are very rare in infants, and support and attention to infants in the pandemic situation should be doubled due to the weakness and underdevelopment of the neonatal immune system. Therefore, the present study aimed to review COVID-19 infection in infants in which there are discussions on topics such as diagnostic tests, clinical manifestations, recommendations on breastfeeding, the criteria for discharge, and family education in pandemic conditions. The literature review shows no existing evidence of COVID-19 placental transmission from mother to infant, and that all samples prepared from amniotic fluid, umbilical cord blood and breast milk in mothers with COVID -19 was negative for COVID-19 infection, and the clinical manifestations of COVID-19 were non-specific in infants, especially premature infants. Given that there is a limited number of births from a mother with COVID-19, and because the epidemiological and clinical pattern of COVID-19 in infants is unclear, this review study describes diagnostic tests, clinical manifestations, breastfeeding considerations, discharge criteria, and family education in the current understanding of COVID- 19 infection in newborns and provides information for better management of SARS-CoV-2 infection in newborns.

Key words: SARS-CoV-2, COVID-19, coronavirus disease-2019, newborn

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BACKGROUND

Coronaviruses are a large family of viruses developing respiratory diseases with varying degrees from common colds to more serious diseases such as the Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS). The coronavirus has a large single-stranded RNA genome, with a crown-like appearance under an electron microscope (1). In late December 2019, Wuhan, the capital city of Hubei Province in China, became the center of an outbreak of pneumonia with an unknown cause that quickly spread throughout China and around the world (2). Following the global outbreak of the virus on January 30, 2020, the World Health Organization (WHO) issued a statement announcing the outbreak of an emerging disease as a public health emergency with global concern (3) and selected the official name of COVID-19 for the novel coronavirus on February 11, 2020 (4). Then, on the same day, The International Committee on Taxonomy of Viruses (ICTV) changed the name of the virus that caused the disease from COVID-19 to SARS-CoV-2 due to its pathophysiological similarity to SARS and severe symptoms of an acute respiratory syndrome (5). Recent studies and analyzes suggest that angiotensin-converting enzyme 2 (ACE2) may be the host receptor for COVID-19 (6). The enzyme is located on the surface of type II pneumocytes of the lungs, intestines, heart, oral cavity, testicles, kidneys, and placenta, and regulates the renin-angiotensin system (RAS) by adjusting ACE2 activity (7, 8). The virus after penetrating the body releases its RNA into the cytoplasm, and viral replication along with angiotensin II through AT1 receptors causes severe lung damage (9). Due to the very low presence of ACE2 receptors in the maternal-fetal interface, the COVID-19 is unlikely to be vertically transmitted to the fetus from the mother (10, 11). However, it will probably be difficult for the mother to wear the mask during vaginal delivery due to the labor process. Therefore, the infant may become infected at birth from respiratory droplets or maternal feces. Finally, if a baby is in close contact with an infected mother, the infant is likely to be infected with the virus (12). Given that there is a limited number of births from a mother with COVID-19 (13) and because of the uncertainty of the epidemiological and clinical pattern of COVID-19 in the babies born from the mothers with confirmed or suspected COVID-19, they are at risk and should be isolated and mon-

itored for pulmonary heart disease regardless of the presence or absence of clinical symptoms (14). Since the COVID-19 pandemic, many studies have been conducted on epidemiological data and clinical signs in adults, but coherent studies in infants are very rare (13). Information regarding neonatal outcomes is scarce, and optimal management of the mother and neonate is unknown (12). Due to the weakness and lack of development of the immune system of infants, especially premature infants, support and attention to infants in the pandemic situation should be doubled. Therefore, the present study was conducted to review COVID-19 in infants. This review study describes diagnostic tests, clinical manifestations, breastfeeding considerations, discharge criteria and, family education, in the current understanding of COVID-19 infection in newborns and provides information for better management of SARS-CoV-2 infection in newborns.

COVID-19 IN NEWBORNS

There is currently no evidence that SARS-CoV-2 can be transmitted transplacentally from mother to the newborn. There have been several studies concerning the intrauterine vertical transmission potential of COVID-19 and its effects on newborns, and results have shown that all the newborns of COVID-19 infected mothers in these cases were negative for the nucleic acid test (10 - 15). Salvatore et al. reported that all neonates born to 116 mothers with confirmed COVID-19 were tested at 24 hours of life and none was positive for SARS-CoV-2. Eighty-three percent of them roomed in with the mothers. All mothers were allowed to breastfeed. The neonates had a PCR test repeated at 5 - 7 days of life, which was negative in all of them. Eighty-eight percent of neonates were also tested at 14 days of life and none was positive. None of the neonates had symptoms of COVID-19 (16). To date, there are several case reports of neonates who have tested positive for SARS-CoV-2 within 48 hours. The first report was about the birth of a 40-week-old full-term baby weighing 3205 grams from an asymptomatic mother. The mother lived near the seafood market in Wuhan, but did not go to the market at all during her pregnancy, and may have acquired the infection from others. An emergency cesarean section was performed for the mother and she used the N95 mask during the cesarean section. The healthy baby was born, with the 1- and 5- minute APGAR score of

8 and 9, respectively, and without any contact with the mother. Thirty minutes after birth, the infant vomited and was isolated. The subsequent blood tests showed lymphopenia, impaired liver enzymes, and increased creatine kinase levels. The throat swab sample of the infant, collected 36 hours after birth, was positive. Breast milk was negative for COVID-19. Despite normal vital signs, a high-density nodular shadow was found in the chest CT scan of the infant under the pleura of the posterior part of the right upper lobe of the lung. Finally, the infant was discharged in good health at 16 days of age (13). Another case involved a 17-day-old infant tested positive for COVID-19 who had symptoms of fever, cough, and vomiting. In his family, the first case of infection was diagnosed in the family maid and then in his mother. The third infant was born to a mother with COVID-19 who developed a fever at 5 days of age. In the fourth case, the infant was born to a mother with COVID-19 who was diagnosed with maternal illness 30 days after birth. Shortness of breath, vomiting, cough, and fever was mild in all infants. All infants had normal vital signs (15 - 17). The results of a study of 33 infants born to mothers with COVID-19 showed that all samples, including amniotic fluid, umbilical cord blood, and breast milk were negative for COVID-19 (18). No serious cases of COVID-19 have been reported in infants. Experts believe that the infected infants may be asymptomatic or have mild symptoms, and their hospital stay in the incubator can be 3 - 7 days or even a day (19).

Neonatal clinical manifestations

SARS-CoV-2 infection can range from asymptomatic infection to severe respiratory distress in neonates (19). The incubation period of this disease is from 1 to 14 days and on average 4 - 6 days (20). The clinical manifestations of COVID-19 in the infants, especially in premature infants, are non-specific and include instability of fever or hypothermia, tachypnea, grunting, retraction due to the use of accessory muscles of breathing, nasal congestion, apnea, cough, tachycardia, unwillingness to breast-feed, drowsiness, diarrhea and vomiting, and abdominal distension (14, 19). Therefore, vital signs, respiratory symptoms, and gastrointestinal symptoms of the infant should be carefully monitored in suspected patients (19, 21).

Newborn diagnosis

The Prenatal and Newborn Management Committee of China stated that all infants born to mothers with a history of COVID-19 infection (14 days before infant birth to 28 days after delivery) and the infants who are in direct contact with people with COVID-19 are suspected of having COVID-19 infection, and stated that all of these infants should be hospitalized in the quarantine ward and monitored for vital and clinical symptoms, regardless of whether or not they show symptoms (21).

Diagnosis is based on finding the components consistent with the viral sequence genetics in the secretions of the upper respiratory tract (oropharynx and nasopharynx) or feces; it is best to send at least two samples (22). The blood samples are sent for CBC testing to detect COVID-19 and umbilical cord blood samples were taken from infants of suspected or infected mothers in the operating room or delivery room for PCR testing for the COVID-19 virus (10). Also, other infectious causes with similar symptoms, such as the flu, should be considered (21 - 24).

The laboratory tests may show the number of leukocytes as normal or lower. Lymphopenia, mild thrombocytopenia, increased creatine kinase, alkaline phosphatase, alanine aminotransferase, and lactate dehydrogenase are evident in laboratory results. The novel coronavirus may be found in upper respiratory tract secretions (oropharynx and nasopharynx) or lower respiratory tract (sputum, tracheal secretions, bronchoalveolar lavage), blood, and stool. Radiological findings in the form of pneumonia and pulmonary infiltration appear on chest x-ray, and lung ultrasound or CT scan, and ileus on abdominal x-ray (21, 25 - 26).

Personal protective equipment

Personal protective equipment includes helmets, gloves, scrubs, masks and eye protectors. Personal protective equipment should be worn before entering the patient's room and should be disposed of following standard and safety principles when leaving the patient's room. For all aerosol-generating operations, such as air suction, tracheal intubation, non-invasive ventilation, cardiopulmonary resuscitation, mask ventilation and bronchoscopy, air isolation measures and respiratory preventive measures, the use of masks (like the N95

mask) approved by the National Institute for Occupational Safety and Health (NIOSH) should be performed while completely covering the face and nose and controlling its fixation on the face (27 - 29).

Newborn treatment

The suspected infants should be placed in an incubator in an isolated room separate from the isolated room of infected infants for 14 days, and all examination devices such as cell phones and thermometers should be separate for each infant (29). There is currently no effective drug against the novel coronavirus, and the treatment of the disease is only supportive and treats the complications of the disease. Indiscriminate and irrational use of antibiotics, especially broad-spectrum antibiotics, should be avoided. High-dose surfactant injections, appropriate antibiotics at the time of hospitalization to prepare for blood culture, management of acid and base status, correction of electrolyte disturbances, respiratory support (preferably non-invasive modes or invasive mode in special cases) and the use of inhaled nitric oxide may be effective for infants with the acute respiratory syndrome. High-frequency oscillatory ventilation or extracorporeal membrane oxygenation may be necessary for infants with more severe symptoms who do not respond to conventional mechanical ventilation. Newborns with a critical condition may need a skilled medical team consisting of gynecologists, neonates, intensive care, lung, radiologist, infectious disease specialist, and neonatal intensive care unit (14, 21, 24 - 29).

Breastfeeding

Breast milk is the best nutrient for infants because it contains antibodies that boost the infant's immune system (30). The priority is to facilitate mother-infant interaction and start breastfeeding, depending on the health status of the mother and infant. The benefits of breastfeeding outweigh the risk of unknown transmission in breast milk (31). In all cases of confirmed or suspected COVID-19, breastfeeding is not prohibited. In all cases, the principles of hygiene and respiratory precaution must be observed (32). Before and after contact with the infant, hands should be thoroughly washed with soap or disinfectant, and a medical mask should be used. Touched surfaces should be cleaned and dis-

infected regularly (33). A mother with severe symptoms of the COVID-19 (respiratory distress, high fever and, cough) who is unable to care for her baby should be separated from the baby, and a healthy caregiver should take care of the infant, and the infant should be fed breast milk during this time. The mother should be informed that she should pump milk her breast milk at intervals of 2 - 3 hours, following the principles of hygiene, and store it so that the flow of milk is not interrupted. If the mother is reluctant to breastfeed or milk, the donated milk from the milk bank should be used to feed the infant. If there is a need for milk, the mother should milk by hand or with a manual or electric milking machine (34). The mother should wash her hands before touching any part of the pump or milk storage container, and before and after each milking, all the components of the milking that have been in contact with the mother's breast and hand should be washed and disinfected (34, 35).

In mothers with suspected or mild COVID-19, if the infant condition is stable, skin-to-skin contact between the newborn and the mother should be performed after washing the hands, washing the mother's abdomen and breast with soap and water, and wearing the mask (avoid washing with disinfectants, especially alcohol-based ones). If the clinical condition of mothers with suspected or mild COVID-19 is in such a way that she is unable to care for her baby, the baby should be temporarily separated from her and kept in another room by a healthy companion. If the mothers with suspected or mild COVID-19 can care for their baby, the mother and baby can be in the same room, and it is recommended that the baby be two meters away from the mother, and all breast care and breastfeeding should be followed with hygienic tips (washing hands and applying a 3-ply surgical mask) (35, 36). If it is not possible to isolate and place the infant in another room for some reason, the infant should be at least two meters away from the mother and a curtain should be placed between the mother and the infant from the ceiling to the floor (35, 37). The mother should have a well-trained healthy caregiver to take care of the infant. The caregiver of the mother should follow the principles of personal and preventive hygiene (such as frequent hand washing with water and liquid soap, and in the absence of soap, disinfectants with a base of at least 75% alcohol, masking, etc.) (24).

Discharge criteria

The criteria for discharge in asymptomatic infants are negative results of the sample prepared (two consecutive samples at an interval of 24 hours) from the secretions of the upper respiratory tract (swabs prepared from nasopharynx or oropharynx). In the infants with mild symptoms, in addition to the negative results of the samples, the fever should be stopped for at least three days, and the infants with severe symptoms can be discharged if the upper or lower respiratory tract secretions (swabs prepared from the nasopharynx or oropharynx and the sample prepared from the trachea by bronchoalveolar lavage method) or lower respiratory secretions (sputum) for up to two days (twice) are negative for COVID-19. It should be noted that in all infants, in addition to the above, the clinical symptoms of the infant should be improved and other discharge criteria should be met (21, 24 - 29).

To prevent the risk of COVID-19 infection in healthy families, the mother or caregiver of the infant at home should follow the principles of personal and preventive hygiene before and after any care and contact with the infant. Wash your face and hands with water and liquid soap for at least 20 seconds, and if there is no liquid soap, rinse with at least 75% alcohol-based disinfectant and use chlorine-containing disinfectant to clean the floor (36, 38). The baby's bottle and the pacifier should be heat-resistant and should be disinfected daily at high temperatures (35). If the mother's general condition is good and she is not hospitalized, the baby should be quarantined for two weeks at home and the baby should be breastfed following hygienic principles. A person who takes care of a baby other than the mother should be healthy and should not be at risk (36). Avoid lying on the baby's bed and touching and kissing the baby, and avoid attending ceremonies and gatherings and taking the baby with you to crowded places. If there is a family member with confirmed or suspected COVID-19 in the family, in addition to the above recommendations, if possible, a separate room with adequate ventilation for the baby should be allocated and the movement of people should be minimized (24, 35).

If a separate room is unavailable, the baby should be at least two meters away from the potential or suspected COVID-19 member (37). The baby's mother or caregiver at home, before and after

any care and contact with the baby (baby feeding, diaper changing, contact with the baby's body fluids and secretions, etc.) should wash their hands with water and liquid soap for at least 20 seconds and should use disposable masks and gloves, and throw away masks and gloves aftercare by following the principles of hygiene. Family support is needed to prevent anxiety or depression in the mother, especially in cases of separation from the baby (29, 35 - 36). In the event of symptoms in the infant (low or high body temperature, respiratory problems, and poor breastfeeding), the infant should be taken to the hospital immediately (24, 35, 36).

CONCLUSION

There is currently no evidence of COVID-19 placental transmission from mother to infant, and all samples taken from amniotic fluid, umbilical cord blood, and breast milk of mothers with COVID-19 are negative for COVID-19. Perinatal transmission of COVID-19 is unlikely to occur if correct hygiene precautions are undertaken, and that allowing neonates to room in with their mothers and direct breastfeeding are safe procedures when paired with effective parental education of infant protective strategies. Clinical manifestations of COVID-19 were non-specific in neonates, especially in premature infants. Due to the weakness and underdevelopment of the baby's immune system, all newborns born to mothers with confirmed or suspected COVID-19 are at risk and should be isolated and undergo cardiopulmonary monitoring regardless of the presence or absence of clinical symptoms. The baby's mother or caregiver should wash their hands with water and liquid soap for at least 20 seconds and should use the mask and gloves before and after any care and contact with the baby. According to previous studies, the virus has not been found in breast milk. Then, the decision should be made based on the clinical conditions of the mother and the baby by observing the hygienic principles for breastfeeding. Given that there is a limited number of births from the mother with COVID-19 and due to the uncertainty of the epidemiological and clinical pattern of COVID-19 in infants, this study describes the current conditions of the disease in the infants and suggests further epidemiological and clinical data for treatment and management of the disease in infants.

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Novi korona virus (COVID-19) u 2019. godini i novorođenčad

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SAŽETAK

Krajem decembra 2019. godine Vuhan, u Kini, postao je centar širenja nepoznate pneumonije, koja se brzo proširila Kinom i čitavim svetom, uključujući i Iran. Svetska zdravstvena organizacija je novu bolest proglasila opasnošću po javno zdravlje na globalnom nivou. Od izbijanja kovida-19, urađeno je dosta studija o epidemiološkim podacima i kliničkim znacima kod odraslih. Međutim, koherentne studije iz ove oblasti nedovoljno su rađene na novorođenčadi i podršku i brigu o novorođenčadi u uslovima pandemije, trebalo bi udvostručiti, zbog slabosti i nedovoljne razvijenosti imunog sistema dece. Stoga je cilj ove studije bio prikaz infekcije kovidom-19 kod novorođenčadi, u kojoj se razmatraju teme poput dijagnostičkih testova, kliničkih manifestacija, preporuka o dojenju, kriterijuma za otpust, kao i porodična edukacija u uslovima pandemije. Prikaz literature ne pruža podatke o prenosu kovida sa majke na dete putem posteljice i svi uzorci dobijeni iz amnionske tečnosti, krvi pupčane vrpce i mleka majki sa kovidom-19 bili su negativni na infekciju izazvanu kovidom-19. Kliničke manifestacije kovida-19 bile su nespecifične kod novorođenčadi, naročito kod prevremeno rođene dece. Uzimajući u obzir to da je broj dece rođene od majki sa kovidom-19 ograničen i da je epidemiološki i klinički obrazac kovida-19 kod novorođenčadi nejasan, ova pregledna studija opisuje dijagnostičke testove, kliničke manifestacije, razmatra dojenje, kriterijume za otpust i na kraju, edukaciju porodice u trenutnom razumevanju kovida-19 kod novorođenčadi, a takođe pruža i informacije o boljem lečenju infekcije SARS-CoV-2 bolesti kod novorođenčadi.

Ključne reči: SARS-CoV-2, kovid-19, bolest izazvana virusom korone u 2019. godini, novorođenče