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COVID-19 infection and its outcome in neonates

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Μόλυνση με COVID-19 σε βρέφη και οι εκβάσεις της νόσου

Περίληψη στο τέλος του άρθρου

The frequency of COVID-19 infection in neonates and the management and outcome of SARS-CoV in this age group is a field that is, as yet, poorly documented. This review summarizes the current literature regarding the clinical characteristics, management and outcome of neonates with confirmed COVID-19. Current evidence shows that COVID-19 rarely affects neonates severely, with most cases being asymptomatic, while the most commonly reported clinical symptom is respiratory distress. The clinical characteristics of pregnant women with COVID-19 infection are similar to those of non-pregnant adult patients with COVID-19. Neonates born to mothers who are categorized as either diagnosed cases, or suspected cases of COVID-19, should be treated according to the latest guidelines. It is of great importance to conduct large-scale, well-designed cohort studies, in order to better understand the impact of COVID-19 on neonatal health.

Key words

Coronavirus
COVID-19
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1. INTRODUCTION

Coronaviruses belong to a family of viruses that carry their genetic information in a single strand of RNA which is enclosed in a protein envelope. The Coronaviridae family has several subfamilies, the most important of which is the Orthocoronavirinae subfamily that includes alpha, beta, gamma and delta coronavirus. To date, seven coronaviruses have been identified that are capable of infecting human beings, all in the alpha and beta categories. The severe acute respiratory distress syndrome coronavirus (SARS-CoV) and the SARS-CoV-2 are caused by viruses that belong to the beta genus of coronavirus.[1–3] In December 2019, an outbreak of a respiratory illness of unidentified origin was initially reported in Wuhan, in the Hubei province of China, and later the virus was isolated and characterized as SARS-CoV-2 virus. Since the initial outbreak of the epidemic, SARS-CoV-2 has spread to all continents and the World Health Organization (WHO) characterized this outbreak as a pandemic – the COVID-19 pandemic.[4]

The COVID-19 pandemic continues to spread worldwide, and at the time of writing, more than 162,184,263 infections of the new coronavirus and 3,364,446 deaths attributed to its complications have been reported.[5] COVID-19 spreads mainly through respiratory droplets or by direct contact with infected subjects. Cases of infection have also been reported in pregnant women and neonates, and in some cases, intrauterine (vertical) transmission has been reported, but the data available to support this hypothesis are sporadic and insufficient.[6]

Current literature suggests that children are less severely affected by the COVID-19 infection than the adult population. Infants aged under 1 year appear to be more vulnerable to be infected by the SARS-CoV-2 and to present higher severity than children of other ages.[7] Several recently published reviews provide an overview of the information about children with SARS-CoV-2 infection, but the available data about infected neonates is extremely limited. In view of the fact that COVID-19 is the most severe pandemic in the last 100 years, and of the limited data available for this population group, we realized that there is a need for a review focusing on cases of COVID-19 infection in neonates. Thus, the aim of this review was to summarize the clinical characteristics, management and predicted outcomes of the currently reported cases of SARS-CoV-2 infection in this population, which is characterized by increased vulnerability.

2. TRANSMISSION OF THE SARS-COV-2

According to current evidence on the transmission of SARS-CoV-2, the virus enters the receptor cells through attachment to the angiotensin-converting enzyme 2 (ACE-2). A spike protein further facilitates this process. ACE-2 is a molecule expressed in type 2 alveolar cells of the lung, in the absorptive enterocytes in the ileum and colon and in upper esophageal epithelial cells. As mentioned above, SARS-CoV-2 is transmitted through the respiratory droplets and aerosols that are products of coughing and sneezing and travel a distance of usually up to about 6 feet (2 m). A further way of transmission is through direct or indirect contact with the mucous membranes of the nose, mouth and eyes. One study also reports a case of infection through the gastrointestinal (GI) tract where the invasion of ACE-2 occurred via enterocyte expression.[8–10]

The current literature suggests that there is a risk of vertical infection, but the 5–30% risk reported in the published studies is low due to the lack of an early diagnosis. The ACE-2 receptors that facilitate the infection process are highly expressed in the placenta. The expression rate peaks at term and frequently, the virus infection in the placenta leads to miscarriage. Two studies report that 4 different infants each had a positive reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at the age of two days, while samples taken from amniotic fluid and cord blood were negative.[11,12]

Antibody specific testing for IgM and IgG in newborn serum showed positive IgM in the serum of 3 in 7 newborn infants in two different studies. The same infants tested negative by RT-PCR in samples of nasopharyngeal swab and serum. It is of note that serum IgM testing can provide both false positive and false negative results, depending on the testing technique. Consequently, it is very difficult to make a distinction between vertical transmission and early postnatal colonization in the neonatal population.[13]

Cases have been reported of neonatal detection of SARS-CoV-2 in the first 24 hours of life. Specifically, in a report of an infant born to a 41-year-old woman who had severe COVID-19 symptoms, the infant also presented severe COVID-19 symptoms, tested positive at the 16th hour of its life, and required mechanical ventilation support; serological tests for IgG and IgM were negative.[14] A similar case was reported, where a male infant, born by cesarian section to a COVID-19 positive 40-year-old woman had clinical symptoms that included feeding difficulty, hypoglycemia and temperature fluctuation. The RT-PCR test from nasopharyngeal swabs was positive on days 0 (day of birth), 2 and 7.[15] This was the first reported case where the tests were virus positive in samples derived from maternal vaginal swab, placenta and breast milk. In a recent study that analyzed multiple samples of breast milk from two COVID-positive mothers, the tests were positive in one mother on days 10, 12 and 13, but negative at later dates.[16]

Another case study described a preterm infant born to a mother with COVID-19, which presented fever after birth and was treated with a therapeutic protocol with intravenous antibiotics. The neonatal throat and nasal swabs tested negative for SARS-CoV-2 at birth, and the maternal vaginal secretions and umbilical cord blood also tested negative, but amniotic fluid samples were positive. In this case study, the infant was separated from the mother and formula-fed.[17]

The above cases increase the uncertainty concerning SARS-CoV-2 transmission by placenta or human milk, but the case studies underline the importance of protective measures to prevent horizontal transmission. However, there is a report of milk samples derived from 18 mothers who tested positive for SARS-CoV-2; the results showed that the presence of virus ribonucleic acid (RNA) in human milk is not an indication of a replication-competent virus.[18]

3. CLINICAL PRESENTATION

In general, the reported mean duration of incubation for the virus is 5.2 days, and most of the infected individuals (over 90% of cases) develop commonly recognized symptoms within the first 10 days of the initial infection. Based on these findings, a monitoring period of 14 days is proposed after a contact of an individual with a confirmed case of COVID-19. The reproduction number of the virus is defined as R0, and expresses the average number of secondary infections that are caused by an initially infected person in a neutral population. The R0 for SARS-CoV-2 ranges between 1.4 and 6.49 (mean 3.28), a number substantially higher than the R0 of H1N1 (1.2–1.6) and SARS-CoV (R0: 2–5).[19–21]

The currently available research findings show that the clinical characteristics in pregnant women with COVID-19 are similar to those in non-pregnant adult patients with confirmed COVID-19.[3,19] A recent systematic review and meta-analysis of 19 studies, with a pooled sample size of 79 women who were infected by SARS-CoV-2, SARS, and the Middle East respiratory syndrome (MERS), examined the outcome of coronavirus infection during pregnancy.[22] The authors concluded that COVID-19 infection in the mother carried a risk of 39.1% of miscarriage, 24.3% of preterm birth, 20.7% of pre-labor membrane rupture, 16% of preeclampsia and 17% of fetal growth restriction.

The overall result shows that the most common negative pregnancy effect was preterm birth, with a delivery date before 34 weeks being reported in a fairly large percentage of patients (56%). The perinatal mortality was approximately 7% and included one neonatal death and a stillbirth.[22] Even though these data can provide useful information about the adverse effect of SARS-CoV-2 in pregnancy, they only reflect a small sample of pregnancies in the early stages of the pandemic era and these events may not be correlated with neonatal or maternal infections.[21]

The symptoms of COVID-19 in neonates include lethargy, fever (temperature instability), vomiting (feed intolerance), cough, respiratory distress, diarrhea and shock. Blood samples revealed leucocytosis, lymphopenia, thrombocytopenia, high levels of creatine phosphokinase (CPK) and abnormal liver function tests (LFTs). The most frequently observed symptom was respiratory distress, and respiratory support was provided in 60 neonates (14 supported by mechanical ventilation, 25 by non-invasive ventilation and 21 by nasal oxygen). Other respiratory symptoms presented in the newborn infants are possibly related to transient tachypnea, respiratory distress syndrome or prematurity, and less likely to be caused by COVID-19.[4,14,17,23]

The most frequently observed symptoms, such as tachypnea, cough, and respiratory distress in general, lethargy, temperature instability and GI symptoms, such as diarrhea, vomiting and feed intolerance are hard to associate with COVID-19 because a number of these symptoms were evident also in infants that tested negative.[4,10,12,14,17,23] Additionally, one case study described the presence of neonatal hypotension, pneumothorax, and need for mechanical ventilation support.[12] Overall, most neonates that tested positive had a mild manifestation of COVID-19 symptoms.[4,10,12,14,17,23]

4. DIAGNOSTIC CRITERIA

The current gold standard for the detection of positive cases of SARS-CoV-2 infection is detection of viral genetic material by RT-PCR. The sensitivity of the laboratory examination depends on the type of specimen obtained from the patient, the time since collection and the quality of the specimen, the duration of the illness at the time of testing and the precision of the assay.[3,7] Literature consensus recommends the use of oropharyngeal or nasopharyngeal swab for obtaining specimens to diagnose or screen for infection at an early stage. In a recent study on the sensitivity of the RT-PCR technique in different specimens, the positivity rates were: 93% for bronchoalveolar lavage, 72% for sputum, 63% for nasal swab, 46% for bronchoscopic brush biopsy, 32% for pharyngeal swabs, 29% for feces, 1% for blood and 0% for urine.[24,25]

Specimens obtained from the lower respiratory tract show higher probability of providing positivity, because of higher viral loads at that site. For the screening of neonates, the American Academy of Pediatrics (AAP) recommends the testing of specimens with molecular assay on throat or nasopharyngeal swabs.[21] Specifically, one single swab is used to collect the samples, first from the throat and then from the nasopharynx. The test is then performed at 24 and 48 hours of specimen age. In cases where neonates are supported with mechanical ventilation, the tracheal aspirate should be used for testing.[23] The same recommendations, suggest that, in neonates that initially test positive, follow-up tests should be performed at 48- and 72-hour intervals. This interval follow-up testing should be continued until two consecutive tests provide negative results. It is also recommended by the Canadian Pediatric Society that testing should be done 2 hours after meticulously cleaning the patient's face, to avoid increased colonization, and that positive tests should be repeated after 24–48 hours.[26] The sample collection and testing procedures should be performed with precautions to avoid the risk of virus exposure via aerosol.[24,25]

The value of serological tests is a subject of scientific debate; according to current evidence, they are less likely to be diagnostic in the initial phase of acute SARS-CoV-2 infection.[17] The enzyme-linked immunosorbent assay (ELISA) has a sensitivity of 87% and immunochromatographic card examination has a sensitivity of 82%. The SARS-CoV-2 genetic code shows similarities to the genetic sequences of other viruses, resulting in false positive serological tests due to cross-reactivity.[27] A recent study, however, proved that there was a significant increase in positive diagnosis when IgM ELISA assay was used in combination with PCR for each patient, compared with the use of PCR alone.[28]

A study of placental histopathology in 16 pregnant women who had tested positive for COVID-19, reported findings of arteriopathy and vascular malperfusion. This study also reported hypertensive disorders in pregnancy in these women, that may reflect placental inflammation affecting its physiology.[14] The blood count in SARS-CoV-2 infected pregnant women may be normal, but lower numbers of lymphocytes and platelets have been reported. No changes have been reported to the levels of various enzymes, such as lactate dehydrogenase, alanine aminotransferase, creatinine kinase and alanine aminotransferase, or of inflammatory markers, such as ferritin and C-reactive protein (CRP).[29] Regarding chest X-ray findings, the reports

are varied since, they can be normal in the initial phases of infection, or present a bilateral or unilateral ground glass or patchy appearance. There does not appear to be any characteristic pattern on chest computed tomography (CT) and X-ray in neonatal COVID-19, probably because the data are limited.

5. TESTING OF PREGNANT WOMEN AND NEONATES

Establishment of a general SARS-CoV-2 screening strategy for pregnant women according to their special needs and the available resources is of great importance, and has the potential to prevent a further pandemic outbreak. Overall screening of healthcare workers, parents and neonates is crucial in the prevention strategy against SARS-CoV-2, and can produce a decrease in infection transmission in neonatal intensive care units (NICUs), even in areas where SARS-CoV-2 has a high incidence.[4]

Most medical centers in the developed countries practice the recommended testing approaches for pregnant patients, and the results are followed by the appropriate use of protective equipment in neonatal care, or isolation procedures. These strategies may not be feasible in developing countries where the resources are limited, or in cases where the birth takes place in an emergency setting. All pregnant women who have symptoms or clinical features consistent with COVID-19 should be tested according to the recommended procedures. When the symptoms persist, the tests should be repeated every 2–5 days, even if the initial screening for the virus genetic material is negative. In the case of emergency birth, this should not be delayed pending screening results, but the cases should be considered as suspect.[23]

Available research evidence suggests that these neonates should be tested within 14 days of delivery. Neonates that were in close contact with a confirmed case of COVID-19 should be tested within 14 to 28 days of delivery.[30] If the neonates are symptomatic, a specimen should be collected immediately, while asymptomatic neonates born to mothers who tested COVID-19 positive should be tested within 2–12 hours, after meticulous face cleansing. Positive cases should have a repeated test after 2–3 days and negative cases should have repeated testing after 3–5 days.[30]

6. MANAGEMENT OF COVID-19 IN NEONATAL PATIENTS

The most important areas in the perinatal management of COVID-19 positive or suspected positive neonates are the prevention of spread from mother to child and adherence to the recommended testing protocols. Pregnant women should be tested, ideally, before their admission to the clinic or hospital, with relevant prior consultation through telephone or video calls.[31] Current guidelines recommend the use of magnesium sulfate or antenatal steroids for protection of the central nervous system (CNS). Pregnant women should wear masks to prevent viral transmission through droplets, and an interdisciplinary team should discuss procedures with them before the delivery takes place, to clarify important options (e.g., delayed cord clamping, separation of the neonate from mother, feeding options, isolation, etc.).[23] The decision regarding these procedures should be made jointly, ensuring patient participation. The practicalities that affect rooming-in and separation of mother and neonate may vary according to the capabilities of the specific institutions and countries. It is important for the medical personnel to share complete and open information with the families, and to provide counseling, and choices should always be adapted according to the local situation and the specific needs.[32]

7. PRECAUTIONS

The most efficient method to utilize the available resources is to treat pregnant women as members of three categories: positive, negative, or suspect for COVID-19. In the case of possible encounters with confirmed cases of positive or suspect neonates, droplet and contact precautions should be enforced. These precautions include procedural masks, gloves, gown, and eye protection in the form of goggles or eye shield. For procedures that include bag and mask ventilation or intubation, droplet, contact and airborne precautions should be taken.[31]

Neonates that are born to mothers categorized as either diagnosed or suspected cases of COVID-19 should be resuscitated according to the latest guidelines, which also show significant benefits in the application of delayed cord clamping, although there is a small risk of viral transmission through cord blood.[4] Delayed cord clamping should be applied unless the family rejects its use. In the event of resuscitation being required, it should take place in a separate room from that used for birth, and with the least possible number of medical personnel present. In the case where no separate room is available, resuscitation should take place at least 6 feet (2 m) from the delivery table. The resuscitators are recommended to wear eye, contact and droplet protection because resuscitation may include intubation or suctioning.[33] Resuscitation maneuvers implement an increased level of aerosolization and there is also the risk

of transmission from amniotic fluid, maternal blood or other body fluids.[34] Non-invasive ventilation that is provided during resuscitation may significantly increase the possibility of infection because it is correlated with mouth leaks at a rate of 40–50%. Currently evidence suggests that the risk of acquiring a viral infection is higher during endotracheal intubation than with bag-mask (manual) ventilation.[33]

8. RESPIRATORY MANAGEMENT

Although COVID-19 symptoms in neonates vary and may involve the GI system, the CNS or the respiratory tract, the most commonly reported symptom is respiratory distress. Neonates have an increased possibility of requiring respiratory support because they may have several comorbidities, such as respiratory distress syndrome, sepsis, prematurity, transient tachypnea, which are due to perinatal conditions other than pneumonia caused by the virus.[26] The respiratory management of the neonate should be provided with the goal of optimal respiratory support, in combination with adequate protection of the healthcare workers. The main hazard regarding respiratory support in this population is the aerosol particles that may spread the disease. The available data on which the recommendations for management of neonates with COVID-19 are based is very limited, the main reason being that most neonates are negative or asymptomatic.[26]

9. NON-INVASIVE VERSUS INVASIVE RESPIRATORY SUPPORT

The standard intervention for the management of neonates with respiratory distress is continuous positive airway pressure therapy (CPAPT), and this intervention is also used to manage patients with COVID-19. A recent study showed that during nasal positive pressure ventilation, droplets that are larger than 10 μm are generated. The size of these droplets increases the possibility of them being deposited on surfaces within a certain small radius. For this reason, using CPAP with closed circuit may be the safest choice because it generates less aerosol particles, of smaller size.[35]

Endotracheal intubation is an invasive procedure that generates aerosol and should be performed by skilled individuals wearing adequate personal protection. Two studies recommend the use of low cuff pressure in both cuffed and uncuffed tubes that are used for the intubation,[29,34] and a further study recommends the use of an endotracheal tube of appropriate size to minimize leak, applied by oral, rather than nasal intubation.[34]

10. MANAGEMENT OF STABLE NEONATES

Stable neonates that are born to mothers who have tested positive for COVID-19 are usually treated in a negative pressure isolation room.[31] The greatest benefit of separation of the mother and neonate is the decrease in the probability of the neonate to be infected by the positive mother. In cases where this practice is not agreed on by the family, the mother and neonate should be roomed in (possibly with the presence of an additional COVID-19 negative caregiver). Both the mother and the caregiver should wear a face mask (N-95) and practice hand hygiene.[30] The infant should be placed at a distance of at least 6 feet (2 m) from the mother. Breast milk should be provided for the neonate, considering the numerous benefits that this provides, and in view of the scientific evidence that suggests only a small possibility of virus transmission via breast milk.[12]

11. CONCLUSIONS AND RECOMMENDATIONS

This review summarizes the clinical findings, management, and prognosis of neonates that are infected with COVID-19. The initial source of COVID-19 infection may be unclear because the infected neonates had some contact with the infected mother. Many infected neonates were admitted to hospital from home. Many infected neonates were asymptomatic, and the remaining cases presented mild symptoms, similar to an acute respiratory infection, or GI symptoms. Most of the reported cases of infected neonates underwent supported respiration and the prognosis was good, with a median length of hospitalization of approximately 10 days. Nutritional support includes breast feeding, pumped breast milk and formula. Large-scale well-designed cohort studies and other epidemiological studies are required to provide better understanding of the impact of COVID-19 on neonatal health. It is crucial for future studies in this field to apply a standardized terminology of exposures and outcomes, to permit the multi-national comparison of incidence, risk factors, and outcomes, and ultimately to promote best clinical and public health practice.[36]

ΠΕΡΙΛΗΨΗ

Μόλυνση με COVID-19 σε βρέφη και οι εκβάσεις της νόσου

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Η συχνότητα των λοιμώξεων COVID-19 στα βρέφη, καθώς και η διαχείριση και οι εκβάσεις λόγω της λοίμωξης από τον SARS-CoV είναι ένα πεδίο που παραμένει σε μεγάλο βαθμό ανεξερεύνητο. Ο κύριος στόχος της παρούσας ανασκόπησης είναι η σύνοψη της τρέχουσας βιβλιογραφίας σχετικά με τα κλινικά χαρακτηριστικά, τη διαχείριση και τις προβλεπόμενες εκβάσεις των νεογνών που είναι επιβεβαιωμένα κρούσματα με λοίμωξη COVID-19. Τα στοιχεία δείχνουν ότι η λοίμωξη COVID-19 σπάνια συνιστά σοβαρό κίνδυνο για τα νεογνά, καθώς οι περισσότερες περιπτώσεις νεογνικών λοιμώξεων είναι ασυμπτωματικές, ενώ το πλέον συχνά αναφερόμενο κλινικό σύμπτωμα είναι η αναπνευστική δυσχέρεια. Τα κλινικά χαρακτηριστικά των εγκύων γυναικών με λοίμωξη COVID-19 είναι παρόμοια με τα κλινικά χαρακτηριστικά των μη εγκύων ενηλίκων ασθενών που είναι επιβεβαιωμένα κρούσματα COVID-19. Τα νεογνά τα οποία γεννώνται από μητέρες που κατηγοριοποιούνται είτε ως διαγνωσμένα κρούσματα είτε ως ύποπτα κρούσματα της λοίμωξης COVID-19 πρέπει να τύχουν διαχείρισης σύμφωνα με τις τρέχουσες κατευθυντήριες οδηγίες. Είναι μέγιστης σημασίας η διεξαγωγή μεγάλης κλίμακας, καλά σχεδιασμένων μελετών κοόρτης, έτσι ώστε να κατανοηθεί καλύτερα ο αντίκτυπος της COVID-19 στην υγεία των νεογνών.

Λέξεις ευρετηρίου: COVID-19, Κορωνοϊός, Νεογνά, Νεογνική υγεία, SARS-CoV-2

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