Review Paper

Hepatobiliary Involvement in Neonates With COVID-19 Infection: A Narrative Review

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ABSTRACT

Background: The most common symptoms in neonates with severe COVID-19 infection have been respiratory problems. The virus may adversely affect organs such as the liver.

Methods: Studies focusing solely on liver involvement in newborns with COVID-19 infection were searched in Pubmed, Scopus, and Google Scholar databases. Eight studies were finally reviewed.

Results: Direct viral invasion (COVID-19-induced hepatitis or systemic inflammatory response) and drug-induced may contribute to liver damage in neonates. SARS-CoV-2 may be the latest spark in toxoplasmosis, other agents, rubella, cytomegalovirus, herpes infections, and fetal liver involvement may be induced by transplacental transmission.

Conclusions: Hepatic dysfunction is infrequent but important in neonates with COVID-19 infection and the mechanism of liver damage associated with COVID-19 may differ from that in adults.

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Introduction

Since the World Health Organization (WHO) declared the 2019 novel coronavirus disease (COVID-19) pandemic, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections have had a major impact on public health with high mortality rates [1-3]. The main clinical manifestations of COVID-19 involve the upper and lower respiratory system. However, it has been shown that other organs and systems, including the gastrointestinal tract and liver, may be involved [4, 5]. Previous studies in adult patients showed a significant increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activity in patients with severe critical COVID-19, but the exact mechanism of liver damage is not well understood [6, 7]. Studies show that children are less likely to be infected with SARS-CoV-2 compared to adults [8, 9]. In addition, neonates have milder clinical symptoms and non-specific laboratory or radiological abnormalities compared to older individuals [10]. Therefore, many cases of infection may remain under-recognized or subclinical early in life due to the robust neonatal immune response and proinflammatory cytokine response [11].

Similar to adults, SARS-CoV-2 may also adversely affect extrapulmonary organs such as the liver in children, and liver damage has been reported in them [4, 11-15]. In children with COVID-19, hepatitis with severe manifestations of the disease called multisystem inflammatory syndrome in children (MIS-C) has been reported [12]. Infection with SARS-CoV-2 in pregnancy is associated with adverse pregnancy outcomes and neonatal complications [16]. The exact effect of the virus on the fetus is unclear. However, most neonates born to mothers with COVID-19 have a benign and asymptomatic clinical course at birth even when the newborn is COVID-19 positive [17]. On the other hand, neonates with COVID-19 infection present a unique challenge in management [18]. To date, our knowledge about neonates and preterm infants infected with SARS-CoV-2 is limited [19, 20]. There are only a few published cases in the neonatal period that have analyzed liver involvement and the mechanism of liver injury during SARS-CoV-2 infection. We aimed to review the available literature about hepatic involvement in COVID-19 infection in neonates.

Methods

The present article conducted a narrative review of the research studies which investigated neonatal liver injury during SARS-CoV-2 infection that were indexed in PubMed, Scopus, and Google Scholar from March 2020 to July 2022. The keyword terms were COVID-19, hepatitis, liver diseases, newborn, SARS-CoV-2, and transaminases. All study types written in English were incorporated. Studies on the evaluation beyond the neonatal period and non-English articles were excluded. First, the articles were searched based on their titles. Then, the abstract sections of all articles were reviewed by the neonatologist author. Finally identified matching papers with the inclusion criteria were reviewed.

Results

In the primary search, 320 articles about liver injury in neonates with COVID-19 infection were detected. After the preliminary screening of titles and abstracts, 21 related studies were selected and in the review of the full text, 8 papers were finally identified as matching the review inclusion criteria. Different outcomes were reported in the published papers based on clinical presentation, mechanism of injury, and management. These different impacts are separately discussed below.

Discussion

Clinical manifestations

Neonates infected with SARS-CoV-2 can be asymptomatic, and involvement of the respiratory, gastrointestinal, and nervous systems is the most common manifestation in symptomatic cases [21]. Similar to other viruses, newborns with this disease will have clinical manifestations similar to neonatal bacterial sepsis, and diagnosis can be very challenging [22]. Transmission of SARS-CoV-2 from mother to newborn occurs mainly horizontally during the early postnatal period through droplets, respiratory secretions, saliva, and direct contact [23]. Vertical transmission is rare but possible, but the consequences of vertical transmission on the fetus and newborn are not yet well defined [24]. Although liver involvement is possible in neonates with SARS-CoV-2 infection, few studies have clearly described this association compared to studies in this area in children and adults [25]. Therefore, due to the lack of studies, the exact rate of liver damage in neonates with COVID-19 infection is not known. The hepatic involvement in neonates with COVID-19 infection may manifest as hepatitis (elevated transaminases) without cholestasis or as cholestatic liver disease. A mild increase in liver enzymes appears to be the most common symptom of liver damage in neonates with

COVID-19 infection. Kalamdani et al. [26] reported 12 newborns who were positive for SARS-CoV-2, and nine cases were tested for liver enzymes (AST and ALT) and the average value of AST and ALT in them was slightly increased. Sisman et al. [27] described a case report of a premature infant with the intrauterine transmission of SARS-CoV-2 infection with normal ALT and slightly elevated AST. In a case series of 33 neonates born to mothers with COVID-19 reported by Zeng et al. [28], only one premature newborn had elevated AST and ALT. Stolfi et al. [25] reported liver injury presenting with hypertransaminasemia in a term infant with vertical transmission of SARS-CoV-2. In addition to abnormal elevations of liver enzymes in neonates with COVID-19, other forms of liver involvement have been reported in several studies, which may vary depending on the mode of transmission of the infection. Kaur [29] reported a case of neonatal hepatitis as a consequence of intrauterine COVID-19 infection, which was diagnosed with conjugated hyperbilirubinemia, hepatosplenomegaly, elevated ALT, AST, and elevated COVID-19 antibody levels. Another case of neonatal cholestasis was reported by Thornton et al [30] as a case of congenital COVID-19 in a term female neonate who had severe COVID-19 infection with late-onset sepsis-like illness such as dyspnea, fever, and jaundice. Her laboratory testing showed direct hyperbilirubinemia. In further evaluation, the infant was diagnosed with biliary atresia and underwent a Kasai repair, which did not have significant postoperative complications. In a prospective study on 60 neonates born to mothers infected with COVID-19, Farhadi et al. [17] investigated the outcome of 20 newborns who had a positive RT-PCR test for SARS-CoV-2. Only one baby had jaundice, but no direct hyperbilirubinemia, increased transaminases, or liver damage were seen in these babies, even in severe cases.

Gestational alloimmune liver disease (GALD), a rare but often lethal fetal and neonatal disease has been reported in a premature male infant with suspected vertical transmission of COVID-19. The mother was infected with COVID-19 five months before delivery, and the pregnancy was complicated by intrauterine growth retardation and oligohydramnios. SARS-CoV-2 was detected in the newborn's stool after birth, and a large portosystemic intrahepatic shunt was observed in the newborn's abdominal ultrasound. The baby with the clinical picture of hemochromatosis progressed to severe liver failure with coagulopathy, direct hyperbilirubinemia, hypoalbuminemia, and high ferritin and finally died due to the complications of liver failure [19, 31]. Kaur et al. [18] reported liver damage, a significant rise of transaminases and jaundice after initiation of remdesivir in a newborn with respiratory distress and severe hypoxemia, and positive RT-PCR for COVID-19. In this case, drug-induced liver injury versus COVID-19 infection-induced hepatitis was considered for transaminitis. Very few cases of neonatal multisystem inflammatory syndrome associated with SARS-CoV-2 exposure have been reported with elevated liver enzymes and D-dimer levels [32, 33].

Although clinical and laboratory manifestations of liver involvement caused by SARS-CoV-2 have been reported scattered in newborns, it shows that liver damage in infants affected by COVID-19 infection should be thought.

Mechanism of injury

Liver injury in neonates infected with COVID-19 is less frequent. According to the reported cases, different mechanisms may play a role in the liver damage of neonates with COVID-19 infection, which include direct invasion of the virus to the baby in the form of horizontal or vertical transmission from mother to newborn (vertical transmission can manifest as congenital infection and fetopathy), liver involvement as a manifestation of multi-system inflammatory syndrome that leads to multi-organ failure, and liver damage caused by drugs (Figure 1).

Previous case series studies have shown that abnormal liver enzymes associated with COVID-19 infection are not uncommon among infected children [34], but to date data collected on abnormal liver enzymes in neonates with COVID-19 infection are rare. On the other hand, abnormal liver enzymes associated with COVID-19 infection in neonates may not have the same underlying mechanisms as in adults and children. Abnormal liver enzymes are elevated in adult patients, possibly due to the release of inflammatory cytokines as a result of SARS-CoV-2 infection [35]. Conversely, interleukins do not play a key role in abnormal liver enzymes associated with COVID-19 in pediatric patients [34]. Vertical transmission of SARS-CoV-2 from mother to infant is possible, but the consequences of this transmission on the fetus and infant are not yet well defined [17, 25]. Reports of liver involvement in vertically acquired neonatal SARS-CoV-2 cases suggest that, compared with other viruses, SARS-CoV-2 is less placentotropic but can infect and cross the placenta due to binding to angiotensin-converting enzyme-2 (ACE-2) receptors that are expressed in different fetoplacental tissues [25, 36, 37]. Therefore, one cause of neonatal liver injury is likely to

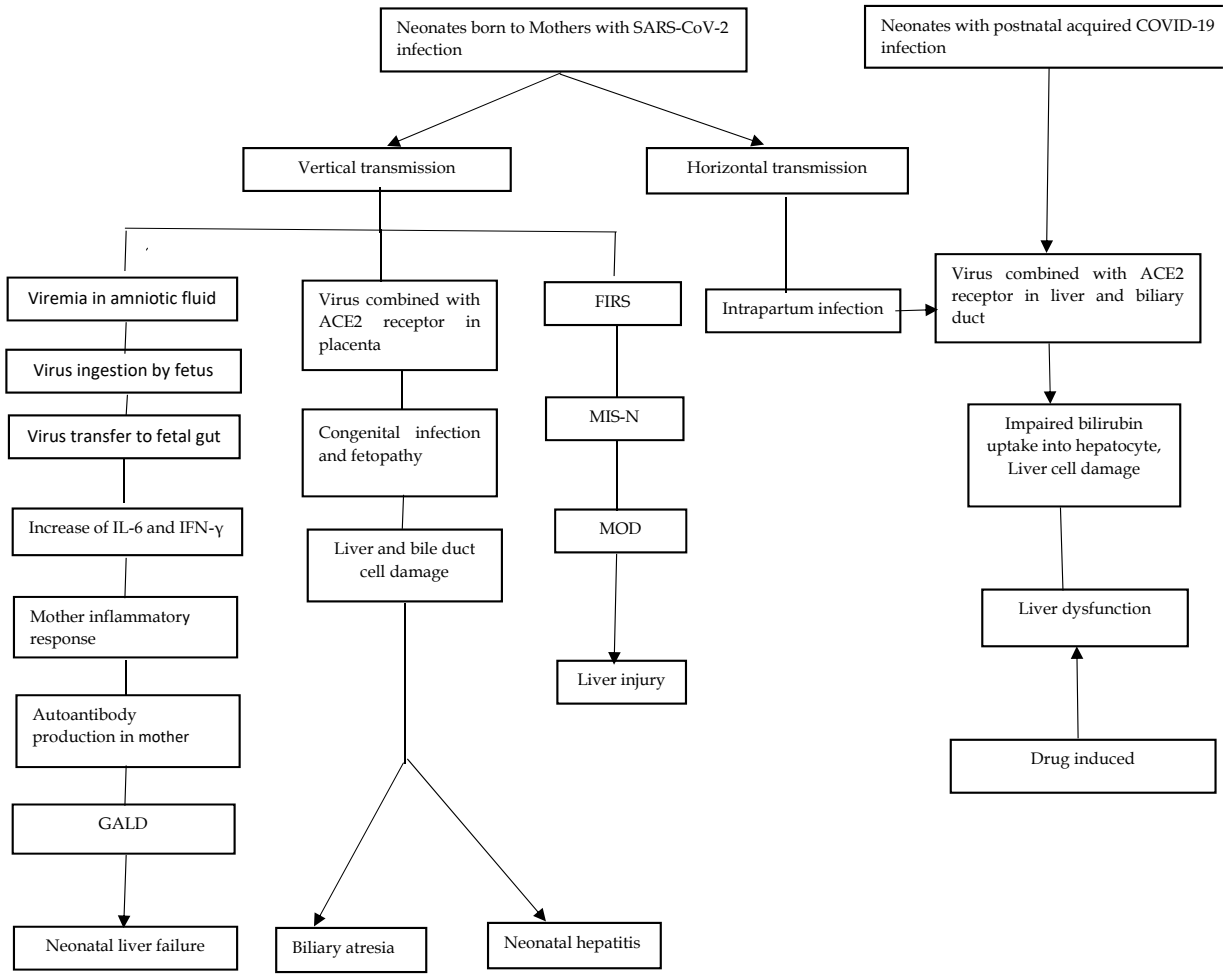

Figure 1. Mechanism of neonatal liver injury

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Abbreviations: SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: 2019 novel coronavirus disease, GALD: Gestational alloimmune liver disease; ACE2: Angiotensin-converting enzyme 2; FIRS: Fetal inflammatory response syndrome; MIS-N: Multi system inflammatory syndrome of the neonate; MOD: Multiple organ dysfunction; IL-6: Interleukin -6; IFN- Interferon- γ.

be related to a direct mechanism mediated by the coronavirus, the details of which, although related to ACE2 receptor expression in cholangiocytes and hepatocytes, are currently still unknown [25]. This mechanism can lead to neonatal hepatitis and hepatomegaly [29]. In other words, the congenital transmission of SARS-CoV-2 is possible and may be the newest spark in toxoplasmosis, other agents, rubella, cytomegalovirus, and herpes (TORCH) infection. In this case, there is a possibility of liver involvement like other TORCH infections [38]. More knowledge is needed, but this virus should be included in the work list for investigation of suspected TORCH infections in newborns. The fact that SARS-CoV-2 produces RNAemia suggests the biological plausibility of transplacental transmission via a hematogenous route from the mother to the fetus [39]. SARS-CoV-2 is also found in stool samples, suggesting that colonization of the perineum can lead to intrapartum infection of the newborn during delivery [40]. In a cohort study, Jin et al. [19] evaluated the fecal samples of 14 newborns whose mothers had COVID-19 during pregnancy. Newborns' stool was evaluated for SARS-CoV-2 RNA, spike protein, and induction of inflammatory cytokines. They found that despite a negative SARS-CoV-2 nasal RT-PCR in all newborns, viral RNA and spike protein was detected in the feces of 11 of 14 newborns as early as the first day of life. Fecal homogenates from all infants induced an inflammatory increase of interleukin-6 (IL-6) and in-

terferon-gamma (IFN-γ) from macrophages. Except for one death due to gestational autoimmune liver disease, most of the infants were clinically well. Their findings suggest intrauterine transmission of SARS-CoV-2 and possible persistent intestinal viral reservoirs in newborns. Most of the mothers in the study had COVID-19 infections that had resolved at least 10 weeks before delivery. In the baby with liver involvement, the mother was infected with COVID-19 five months before delivery. Her baby presented with severe and persistent liver failure immediately after birth and died eleven weeks later due to the same clinical picture. Autopsy findings were consistent with gestational alloimmune liver disease. Stool samples up to day 56 showed increased levels of viral RNA. Indeed, this suggests the transmission of SARS-CoV-2 in utero to the fetus, but the mechanism of transmission to the fetal gut is unclear [19]. Previous studies have reported the presence of SARS-CoV-2 viral RNAs in the amniotic fluid, and the virus may be transmitted to the fetal intestine by ingestion of this fluid by the fetus in utero [3, 19, 41]. A negative RT-PCR does not rule out the possibility of the presence of SARS-CoV-2 in other tissues of the newborn that have not been carefully studied [19]. The results of this study revealed that the risk of intrauterine transmission increases when the mother is infected with COVID-19 before the twenty seventh week of pregnancy [19]. It was not determined whether the presence of intestinal reservoirs of SARS-CoV-2 played a role in the development of gestational alloimmune liver disease in newborns. It has been known that maternal viral infections, including herpes simplex and cytomegalovirus, activate the mother's immune system. With a similar mechanism, acute liver failure caused by GALD in the mentioned baby can be due to the production of autoantibodies and excessive inflammatory response caused by the mother's COVID-19 infection during pregnancy [42, 43]. Maternal IgG antibodies attack fetal hepatocyte antigens, which leads to fetal and neonatal liver damage. Further research is needed to clarify the autoantibody response in pregnant women with COVID-19 infection and its potential risk to the fetus.

Liver injury during the postnatal period as an acquired infection with SARS-CoV-2 can occur in neonates, but there are few reports analyzing liver involvement and injury mechanisms in this form of transmission. The exact information and mechanism of liver damage in infants or children are still not fully understood [44].

The mechanism of hyperbilirubinemia and cholestasis in the Tatura study [45] has been theorized to be due to impaired active transport of bilirubin uptake into hepatocytes or liver damage caused by ACE-2 receptor expression as a target for SARS-CoV-2. Thornton et al. [30] reported direct hyperbilirubinemia and biliary atresia in a neonate with COVID-19 infection. Biliary atresia is a heterogeneous disease of unknown etiology and the role of multiple viral inflammatory factors such as cytomegalovirus has already been suggested in its development. Therefore, they theorized that infant exposure to SARS-CoV-2 may contribute to biliary damage [30, 46]. Multisystem inflammatory syndrome of

Table 1. Individual data on neonatal COVID-19-associated liver injury

Ref	Neonatal Age	Manifestation	Management	Outcome
Kaur et al. 2022 [18]	14 days (term)	Remdisivir-induced liver injury, hypertransaminasemia	Stopped Remdisivir	Improved liver injury
Jin et al. 2023 [19]	1 day (preterm)	Severe hepatic failure, hemochromatosis	IVIG	Death
Stolfi et al. 2021 [25]	1 day (term)	Hypertransaminasemia, high level of GGT	Supportive care	Improved
Kaur 2021 [29]	11 days (term)	Hypertransaminasemia,hepatomegaly, cholestasis	Phenobarbital	Improved
Thoronton et al. 2022 [30]	14 days (term)	Biliary atresia	Kasi procedure	Recovered
Shaiba et al. 2021 [32]	1 day (preterm) 1 day (preterm)	Hypertransaminasemia, MIS-N Hypertransaminasemia, MIS-N	IVIG+Hydrocortisone IVIG+Hydrocortisone	Improved Improved
Kappanayil et al. 2021 [33]	24 days (preterm)	Hypertransaminasemia,MIS-N	IVIG+Hydrocortisone	Improved
Tatura 2022 [45]	14 days (preterm)	Cholestasis	Ursodeoxycholic acid	Improved

GGT: Gamma-glutamyl transferase.

neonates (MIS- N) due to infection with SARS-CoV-2 is rare but it can lead to hepatic involvement in neonates if occurs [33]. Fetal inflammatory response syndrome (FIRS) is a multisystem inflammatory syndrome in the fetus. Newborns affected by FIRS present with varying degrees of multi-organ system involvement such as liver damage. In this case, chorionic vasculitis and recurrent infarctions are seen in the pathology of the placenta [32, 47]. FIRS caused by maternal SARS-CoV-2 infection can lead to severe neonatal complications such as liver and cardiac involvement [48]. The course of illness in neonates suggests that neonates respond differently to SARS-CoV-2 infection than children, so it may be important to re-evaluate the MIS-C criteria for generalizability to diagnose MIS-N [32].

Currently, no targeted antiviral therapy has been recommended for neonates with COVID-19 infection. Antiviral drugs may have hepatotoxic effects, and there are few reports on the use of these drugs in neonates. Abnormal liver enzymes caused by drugs are less in infected neonates than in adults and children. Fever and the use of paracetamol are less common in neonates infected with the SARS-CoV-2, but one of the significant symptoms in children is fever, and giving paracetamol to children is fully accepted [34]. Only one case of remdesivir-induced liver injury in a COVID-19-positive neonate has been reported. So, remdesivir should be used with caution and limited to cases of severe neonatal COVID-19 infection [18].

Management

The main way to treat liver damage in neonates with COVID-19 is supportive care. Liver dysfunction is usually temporary and returns to normal without specific treatment and does not require targeted hepatoprotective treatment. Most neonates were clinically well and responded to supportive care, and liver function was preserved except for one death due to GALD [19]. Immunomodulatory therapy with intravenous immunoglobulin (IVIG) with or without corticosteroids was used in neonates with MIS-N [32, 33]. In most cases of COVID-19 infection in neonates, no antiviral agent is necessary. In cases of cholestatic liver disease, ursodeoxycholic acid or phenobarbital was used and elevated levels of transaminases were resolved with conservative management such as oxygen therapy, adequate caloric intake, and fat-soluble vitamin supplements [29, 45]. One case with biliary atresia underwent a Kasai hepatoportoenterostomy procedure [30]. Table 1 shows summary of data on neonatal COVID-19-associated liver injury.

The main way to manage liver injury in neonatal COVID-19 infection seems to be supportive care and inhibition of the inflammatory response, and prevention of liver injury by careful monitoring of liver function is preferred.

Conclusion

The incidence of liver involvement in neonates with COVID-19 infection is lower than in children and adults. Little is known about in-utero infection with COVID-19 as a cause of neonatal liver injury. However, intrauterine exposure to SARS-CoV-2 can infect the fetal liver, and possible liver damage should be sought in all neonates born to mothers with COVID-19 infection. Further prospective studies and extensive follow-up are needed to determine the real effect of SARS-CoV-2 on the liver of newborns.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Conflicts of interest

The author declared no conflict of interest.

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