

COVID19- and liver injury in pregnant women: a review article

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ABSTRACT

According to the World Health Organization (2022), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is liable for more than 572 million cases worldwide and more than six million deaths globally. It has been reported that pregnancy can change the disease manifestations such that gastrointestinal symptoms, which are common in pregnant women, are difficult to distinguish from COVID-19 related complications. Hence, in isolated cases of gastrointestinal or liver forms of COVID-19, diagnosis might be delayed. Previous studies have suggested that serious complications of COVID-19 in pregnancy are associated with a higher body mass index (BMI), gestational diabetes, and older age; thus, this population should be considered as high risk. In this article, we summarized previously published evidence about pregnant women with COVID-19 and liver dysfunction.

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Introduction

The coronavirus disease (COVID-19), which first appeared in 2019, was caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Its initial outbreak occurred in China, and became a major concern for public health worldwide (1).

More than three years has elapsed from the start of the COVID-19 pandemic, and most studies during this period have focused solely on non-pregnant patients COVID-19 infections. Hence, there are not enough published data about this virus infection in the pregnant population (2-4).

Based on the studies, it is clear that COVID-19 cannot

be identified as solely a pulmonary disease. In addition to respiratory symptoms, involvement of the gastrointestinal tract and liver is a principal symptom of COVID-19.

Liver dysfunction has been reported in a substantial percentage of COVID patients with or without respiratory symptoms and varying degrees of liver damage have been reported in approximately 60% of these patients as the virus can cause direct hepatocellular damage and infection. Also, activation of inflammatory components and cytokine storm may be associated

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with hepatocellular dysfunction in SARS-CoV-2 patients (5). Liver involvement in COVID-19 is a challenging issue. Papers published in 2019 and early 2020 have suggested that, although liver dysfunction is common in COVID-19 patients, it is not an obvious symptom and is not associated with poor prognosis (6).

Later published studies have revealed that liver dysfunction is connected with a higher severity of the disease although not with higher mortality (7). A multicenter study has shown that digestive symptoms are common manifestations of COVID-19, and are related to longer admission and coagulopathy (6).

Pregnancy leads to physiological, mechanical, and immunologic changes, which make pregnant women prone to many infections. Unfortunately, the effect of COVID-19 on pregnant mothers and pregnancy outcome is presently not fully understood (8, 9).

Based on the United States Centers for Disease Control and Prevention reports, the number of laboratory-confirmed cases of SARS-CoV-2 infection was double in pregnant women in comparison with non-pregnant women in the reproductive age group (10-13). Primary data have suggested that pregnant women are one of the most vulnerable groups prone to the COVID-19 disease. It is possible that physiological changes during pregnancy might make pregnant women receptive to COVID-19.

During pregnancy, women experience an increase in oxygen consumption and minute ventilation; hence, their lung capacity decreases, making them at increased risk for severe respiratory diseases. A scientific theory has suggested that immune suppression during pregnancy could possibly make women vulnerable to various infections (11).

COVID-19 clinical characteristics vary in different patients and in pregnant women, the disease manifestations can change. Gastrointestinal symptoms might occur in pregnant women, and could be difficult to distinguish from pregnancy-related complications. Hence, in isolated cases of gastrointestinal or liver forms of COVID-19, diagnosis might be delayed. In this article, we summarized previously published literature concerning pregnancy, COVID-19, and liver dysfunction.

According to our literature review regarding the epidemiology of liver damage in COVID-19 patients: COVID-19 manifests within a wide spectrum, ranging from extremely mild cases with insignificant symptoms such as sore throat or loss of smell (14) to death. Apart from pulmonary damage, other types of system involvement have been reported such as acute kidney injury, liver dysfunction, cerebrovascular events, and gastroenteritis (15, 16).

Moreover, liver involvement associated with COVID-19 has been indicated in many studies

although the exact prevalence of liver injury, degree of hepatocellular damage, and its correlation with prognosis is presently not fully understood.

A systematic review in 2020 has shown that hypoalbuminemia and abnormalities of gamma-glutamyl transferase (GGT) and aminotransferases are the most frequent forms of liver injury in COVID-19 patients, and these issues were observed more and regularly in severe cases (17).

Another study that was published in 2021 reported a 25% prevalence of liver dysfunction in COVID-19 patients that was linked with disease severity (18). Another review in 2021 suggested that, although liver damage was underestimated in COVID-19 cases, only a small portion of these cases also had clinically significant damage (19).

A recent systematic review on pathological findings done on the organs of COVID-19 patients has shown the presence of endothelial injury, thromboembolic disease, and inflammation in the liver tissue of these patients. However, vasculitis was not observed in COVID-19 patients in short-term follow-up (20).

Previous reports have documented the presence of microthrombosis in various organs such as the liver. On the other hand, liver damage might occur due to hemodynamic instability and coagulative necrosis as a consequence of hypoperfusion and hypoxia, edema or tissue congestion (20).

Viral particles have been found in hepatic cells, which is suggestive of a direct invasion of the virus (20). Mild hepatitis was reported in a third of COVID-19 cases, which was reversible due to the fact that hepatic cells have a great regenerative capacity. Main liver histological findings can be summarized as portal or lobular inflammation, Kupffer cell hyperplasia, liver congestion, vascular thrombosis, and other rare features such as necrosis or fibrosis (21).

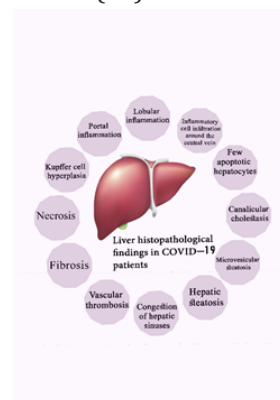


Figure 1: Liver histological findings in COVID-19 patients

Numerous researches have revealed that the critical COVID-19 patients were prone to severe

liver damage in comparison to mild patients (22). In addition, several other studies have shown a greater incidence of liver damage in male patients (23, 24). Old age is another risk factor of liver dysfunction in these patients. A study in Shenzhen indicated that higher BMI, male sex, and underlying liver problems as the main risk factors for developing liver dysfunction in COVID-19 patients (24).

A recent multicenter study in the United States has revealed that aspartate aminotransferase (AST) levels were elevated in cases with underlying liver problems, and that increases in other indicators such as GGT to high normal values, also occurred in patients with underlying liver diseases (21).

Moreover, there is evidence about the correlation between the degree of lung lesions on CT scans and severity of liver dysfunction (24). In a recent study done in Qatar on hospitalized, critically ill patients, the serum bilirubin level was shown to be an independent prognosticator of mortality (25).

Phlebo-sclerosis of the portal vein and hepatic steatosis, which is linked to liver dysfunction, might occur in COVID-19 patients (26). Zhang has shown that COVID-19 led to abnormal liver biochemistry results, like increases in aminotransferases, GGT, and alkaline phosphatase levels. Some clinical scenarios for liver involvement are cellular hypoxemia as a result of severe lung lesions or cytokine release and drug toxicity (27). Direct invasion of the coronavirus is probable reason for liver dysfunction in such patients. SARS-CoV2 detection in the stool, despite negative respiratory samples, support the theory of portal venous viremia and direct virus invasion to the hepatocytes (28,29). Interactions, shock, and multi-organ dysfunction are the underlying causes

of liver impairment in COVID-19 patients. Two main theories for the COVID-19 pathogenic mechanism for liver injury are direct damage or inflammatory response to the manifestation of SARS-CoV-2 and cytokine release.

Literature review on hepatic manifestations of COVID-19 in pregnant patients

In a recent study on non-ICU hospitalized patients, about one-third of patients had liver involvement based on serologic test results (43). The precise cause is not fully understood; however, a rise in hepatic biomarkers may indicate a direct cytotoxic effect of the virus or it may be related to an immune-mediated response (30).

In a study by Deng in 2020, the prevalence of liver dysfunction in pregnant women in China with COVID-19 was reported to be about 29%, and this incidence might increase in women with a history of gestational hypertension, diabetes, preeclampsia, and a higher BMI.

Published data showed significant differences of laboratory indexes such as procalcitonin, interleukin-6 (IL-6), AST, alanine transaminase, and lactic dehydrogenase between pregnant women with and without liver dysfunction.

A small study in 2020 revealed that the need for hospitalization, hospital stay length, radiological findings, and obstetric management was not significantly higher in pregnant patients with liver dysfunction in comparison with other pregnant women (30). In Table 1, we summarized the characteristics of pregnant women with liver dysfunction that were published as a case report.

Table1. Published case report studies about COVID19- induced liver injury in pregnant women

Title	Mothers' characteristics	Manifestation	Treatment	Results
A case report with severe liver and coagulation dysfunction promptly improved after delivery	26 years old, G2,P1	Nine-day history of shortness of breath, dry cough, myalgia, nausea, abdominal pain, fever and severe liver and coagulation impairment	Emergency cesarean section was performed at gestational week 32 + 6	No evidence of any vertical transmission of COVID-19.
Preeclampsia and acute fatty liver of pregnancy	27 years old, PG, twin pregnancy	Low-grade fever for four days associated with mild cough, preeclampsia complicated by atypical HELLP syndrome and acute kidney injury	Emergency cesarean section - ICU admission and oxygen support	No evidence of any vertical transmission of COVID-19.
Severe preeclampsia complicated by acute fatty liver disease of pregnancy, HELLP syndrome and acute kidney injury	26 years old, PG	Nausea, vomiting, abdominal pain and anorexia, leading to dramatic weight loss, severe preeclampsia complicated by acute fatty liver of pregnancy (AFLP) and 'atypical' HELLP syndrome with acute kidney injury	Emergency cesarean delivery, supportive treatment.	The infant was asymptomatic for COVID-19 and was not tested as per local protocol.

Severe preeclampsia complicated by acute fatty liver disease of pregnancy, HELLP syndrome and acute kidney injury	26 years old, PG	Nausea, vomiting, abdominal pain and anorexia, leading to dramatic weight loss, severe preeclampsia complicated by acute fatty liver of pregnancy (AFLP) and 'atypical' HELLP syndrome with acute kidney injury	Emergency cesarean delivery, supportive treatment.	The infant was asymptomatic for COVID-19 and was not tested as per local protocol.
Transaminases in the COVID-19 era	34 years old, PG, twin pregnancy	Right upper quadrant pain, vomiting for two days, acute respiratory distress, elevated inflammatory markers, mildly elevated liver enzymes, low platelets, cholelithiasis and liver failure	Emergency cesarean section, supportive treatment.	-
Transaminases	34 years old, G3	Elevated inflammatory markers, mildly elevated liver enzymes	Normal vaginal delivery	No evidence of any vertical transmission of COVID-19.
Hepatic dysfunction	35 years old, G2P1	Shortness of breath and a dry cough	Normal vaginal delivery, supportive care	No evidence of any vertical transmission of COVID-19.

Notwithstanding the etiology, liver damage in COVID-19 cases is more often transitory and does not necessitate particular care. The American Association for the Study of Liver Diseases (AASLD) suggests to take into account all possible etiologies for hepatic injuries, and advises a close follow-up strategy in cases with rapidly worsen hepatic function tests (31).

Five groups of pregnant patients have been described by the Society for Maternal and Fetal Medicine (SMFM) in the form of a severity scale for the assessment of COVID-19 pregnant patients, ranging from asymptomatic to critical (21).

Hepatomegaly and serum AST are used to classify pregnant woman infected by COVID-19 (32). SMFM asks obstetricians to focus and closely follow up cases with overlapping laboratory findings between

COVID-19 infection and obstetric conditions such as preeclampsia or hemolysis, elevated liver enzymes and low platelets, otherwise referred to as HELLP (33). Moreover, a diagnosis of COVID-19 does not exclude the possibility of co-existing obstetric conditions. Diagnostic and therapeutic strategies should proceed based on national and international guidelines for obstetric and non-obstetric causes of hepatic injuries. Table-2 shows the characteristics of patients that were previously published regarding pregnancy and liver dysfunction.

It is possible for liver involvement to occur in COVID-19 patients in about all continuums of the illness. In the non-obstetric population it was reported that the rate of hepatic injury ranges from 14.8% to 53%, as illustrated by increases in AST and ALT levels (29).

Table 2. Previously published case series studies about COVID19- induced liver injury in pregnant women

Title	Finding	Conclusion
37 pregnant patients with COVID-19 and liver injury	29.7% patients had abnormal liver function tests (LFTs). 2 patients had a history of gestational hypertension and diabetes. Those with liver injury severity was associated with procalcitonin, interleukin-6 (IL-6), AST, ALT, and lactic dehydrogenase levels.	Liver function should be monitored in pregnant patients.
60 pregnant patients with COVID-19 and liver injury	Gestational diabetes and hypertension incidences were 21.6% and 18.3% respectively. Aspartate transaminase levels were higher in pregnant COVID-19 patients with hypertension than in pregnant COVID-19 patients with no comorbidities.	Liver function should be monitored in pregnant patients.
122 pregnant patients with confirmed COVID-19 and liver injury	17 (13.9%) patients had abnormal LFTs during hospitalization. Critically ill patients were three-fold higher in the abnormal LFTs group (11.8%). The hospital length of stay was significantly longer in the group of pregnant women with abnormal LFTs.	Pregnant women with COVID-19 who received antiviral treatment should be closely monitored for evaluating LFTs.

249 pregnant women with COVID-19 complicated by hepatic dysfunction	LFTs abnormalities were reported in 42.9% of patients. Majority of patients experienced asymptomatic or mild COVID-19 disease. Severe cases also had liver dysfunction. Four fetal deaths and one neonatal mortality occurred in this population. Pregnancy complications such as postpartum hemorrhage, the need for blood transfusions and, sepsis and multiorgan failure were higher in patients with hepatic involvement	Liver function should be monitored in pregnant patients. They also should be evaluated for pregnancy-related complications.
5 pregnant females with COVID-19 infection and liver injury	One patient had preterm labor. The pattern of liver involvement was hepatocellular in all cases. All five patients were discharged in stable condition.	Liver function should be monitored in pregnant patients.

Literature review on antiviral therapy and pregnancy

The United States Food and Drug Administration (FDA) has approved remdesivir for the treatment of COVID19- pregnant patients; however, remdesivir is unavailable in many countries, particularly during the disease peak waves. Moreover, almost all drugs used in COVID19- management have some effect on liver function.

A recent systematic review has shown that remdesivir administration within 48 hours from hospital admission is linked to a high rate of recovery in COVID19- pregnant patients, but clinical recovery decreases if antiviral therapy started with delay. A recent study in 2022 showed that remdesivir administration in pregnant women can cause liver function impairment. Most cases experienced elevation less than fivefold from the normal range, which is called transaminases, which is reversible.

ALT level serial monitoring is suggested in pregnant women who receive remdesivir treatment for more than five days (35,34). Hydroxychloroquine, favipiravir and non-steroidal anti-inflammatory drugs (NSAIDs) are other therapeutic options in COVID19- patients, and these drugs also can induce liver dysfunction (36).

Discussion and conclusion

COVID19- has revolutionized healthcare worldwide. This infection has led to many changes in healthcare systems and opened new global perspectives on infection control. (4).

Based on a July 2022 WHO report, severe acute SARS-CoV-2 is liable for more than 572 million cases worldwide and more than six million fatalities globally (37). A review of 2567 pregnant cases of COVID19- has shown that %7 required admission to the intensive care unit and 3.% of those patients required mechanical ventilation. In this study, mortality rate in pregnant patients was reported as less than %1, which is favorably near the general adult population rate (38).

In a study published in 2022 on pregnancy and

COVID19-, the disease severity is higher in pregnant women with liver impairment although management of patients and pregnancy outcomes did not significantly differ when compared with those with and without liver damage (39).

Choudhary also showed that the chance of neonatal COVID is not higher in pregnant patients with liver involvement. SARS-CoV-2-induced inflammatory responses can activate macrophages, monocytes, and T cells, and they establish a pro-inflammatory feedback loop, induces cytokine storms that lead to tissue damage and organ failure (39,40).

The diagnosis and management of pregnant patients with COVID19- still remains a unique clinical and ethical challenge after three years into the pandemic (11,12). Unfortunately, pregnant women have been excluded from various studies during this period as a routine criterion in research projects. Hence, we are faced with insufficient research based evidence regarding this COVID19- and pregnant women. Almost all academic centers have focused on COVID19-; thus, we have plenty of knowledge about this rapidly advancing infection, but there is not enough published evidence about pregnant women.

Clinical features of pre-eclampsia and its related endothelial damage occur because of antiangiogenic status, oxidative stress, and placental hypoperfusion. Di Mascio has confirmed that the chance of pre-eclampsia is higher among pregnant women infected with SARS-CoV-13) 2). Therefore, the spectrum of differential diagnosis might be wide and challenging in COVID-19 pregnant mothers with liver abnormalities.

Forward-Looking

To best of our knowledge, currently confirmed data about the association between the degrees of hepatic dysfunction and rising risk of adverse clinical outcomes for the general population and pregnant population does not exist. In many studies, pregnant women have been excluded because of their unique condition. Organizing a clinical trial about drug

efficacy and side effects would be extremely challenging in this population because both the mother and child should be considered.

Conclusion

It is reasonable to monitor the liver function and involvement in pregnant patients with COVID19-infection. On the other hand, it seems pregnancy works as a shield for the more serious complications of COVID19- although this mechanism is not currently understood.

Furthermore, previously published studies have suggested that serious complications of COVID19- in pregnancy are associated with higher BMI, gestational diabetes and older age, thus, this population should be considered as high risk.

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