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COVID-19 related liver injuries in pregnancy

Sekulovski M *et al*. COVID-19 in pregnancy

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Abstract

While severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) quickly spread across the globe, our understanding of its pathogenic mechanisms evolved. Importantly, corona virus disease 2019 (COVID-19) is now considered a syndromic, multisystem, inflammatory disease involving not only the respiratory system but also the cardiovascular, excretory, nervous, musculoskeletal and gastrointestinal systems. Moreover, a membrane-bound form of angiotensin-converting enzyme 2, the entry receptor for SARS-CoV-2, is expressed on the surface of cholangiocytes and hepatocytes, suggesting COVID-19 potential to involve the liver. With the widespread distribution of SARS-CoV-2 in the population, infection during pregnancy is no longer an isolated case; however, little is still known about the course of hepatic injuries in pregnant SARS-CoV-2-positive women and their outcomes. Thus, the relatively poorly studied liver disease during pregnancy poses a great challenge for the consulting gynecologist and hepatologist. Therefore, we aimed at describing and summarizing the potential liver injuries in pregnant women with COVID-19.

Key Words: Corona virus disease 2019; Liver injury; Pregnancy; Severe acute respiratory syndrome coronavirus 2; Angiotensin-converting enzyme 2 receptors

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Core Tip: Angiotensin-converting enzyme 2 receptors are expressed in hepatocytes and cholangiocytes, suggesting corona virus disease 2019 liver involvement. Liver dysfunction is mainly observed in patients with severe or critical disease. However, little is known about the course of liver involvement in pregnant Severe acute respiratory syndrome coronavirus 2-positive women and its outcome. Reports already exist of pregnant women with severe COVID-19 infection and hepatic injury, making the liver the second most commonly affected organ following the respiratory system.

INTRODUCTION

The end of 2019 was marked by the emergence of a novel, never-before-seen disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Unprecedentedly, modern societies have faced the global threat of coronavirus disease (COVID-19), resulting in, as of 18 Dec 2022, over 649 million confirmed cases and 6.5 million deaths worldwide[1]. While COVID-19 quickly spread across the globe, our understanding of its pathogenic mechanisms began to evolve. Notably, considered a flu-like illness initially, the disease concept underwent a radical change[2]. To date, COVID-19 is perceived as a syndromic, multisystem, inflammatory disease involving the respiratory and cardiovascular systems, endocrine, nervous, gastrointestinal and hepatobiliary systems.

SARS-CoV-2 uses the angiotensin-2 converting enzyme (ACE2) receptor protein to attack the host system[3]. The cell entry receptor, ACE2, is widely expressed in the human body, including the lungs (type II alveolar cells), the gastrointestinal tract (esophageal epithelial cells and absorptive enterocytes of the ileum and colon)[4], the

hepatobiliary system (hepatocytes and cholangiocytes), the cardiovascular system (myocardial cells), the renal system (proximal tubule cells and bladder urothelial cells), and the pancreas[3].

SARS-CoV-2 can directly bind to ACE2 on the surface of cholangiocytes and hepatocytes to exert a cytopathic effect[5]. In fact, several studies reported injury to the hepatobiliary system[6], making it one of the most commonly affected besides the respiratory system[7].

With the diffuse distribution of SARS-CoV-2 in the population, infection during pregnancy is no longer an isolated case. However, liver disease during pregnancy is relatively poorly studied and poses a challenge for consulting gynecologists and hepatologists[8].

It is well-known that many physiological, mechanical, and immunologic changes occur during pregnancy that might influence susceptibility to and severity of COVID-19 in pregnant women. Evidence is accumulating that SARS-CoV-2 infection during pregnancy, especially in pregnant women with severe COVID-19, is linked to various adverse pregnancy outcomes, including pre-eclampsia (PE), preterm delivery, and stillbirth[9]. Pregnant women are also prone to many organ and system involvement during severe COVID-19 infections, including gastrointestinal tract and liver. Therefore, we aimed at describing and summarizing the potential liver injuries in pregnant women with COVID-19.

SEARCH STRATEGY

Our search methodology follows predefined rules for writing a narrative biomedical review[10]. Therefore, a comprehensive search was performed on 15 August 2022 in the LitCovid (PubMed) and Scopus databases. They were queried using the following keywords “COVID-19” or “coronavirus” or “SARS-CoV” AND “liver” OR “hepat*” OR “cholang*” and articles were extracted from inception to 15 August 2022. Bibliographies of retrieved publications were also hand-searched for important information. Relevant data were also included from preprints, papers and guidelines of relevant professional

associations to provide contextual background. Only case reports, original articles, reviews and considerations of official societies in English language were included. Relevant papers were selected as per authors' professional expertise, experience and opinions to transcribe this narrative review[10].

LIVER INJURIES IN COVID-19 PATIENTS

ACE2 receptors are expressed in hepatocytes and cholangiocytes, suggesting COVID-19 Liver involvement. Liver dysfunction is mainly observed in patients with severe or critical disease[11], and in those with altered liver biochemistry tests—elevated total bilirubin, gamma-glutamyl transferase (GGT), aspartate aminotransferase/alanine aminotransferase (AST/ALT)[12], routinely tested in patients with COVID-19. Other commonly performed laboratory tests such as alkaline phosphatase and ferritin may also suggest liver injury[13]. Pathoanatomically, microvesicular steatosis was observed, with mild lobular and portal inflammation[14]. Probably, liver injury is related to immunological aspects of COVID-19, including cytokine storm development[15]. Hepatic damage during SARS-CoV-2 infection is very diverse, ranging from mild and harmless elevation of transaminases to acute liver failure. To encompass the whole spectrum of liver disease, the clinical entity "COVID-19 associated liver injury" was recently introduced[16,17].

ACE2 expression in cholangiocyte cell clusters was significantly higher than that in the hepatocyte population (59.7% *vs* 2.6%)[5]. Cholangiocytes are involved in many aspects of liver physiology, including regeneration mechanisms, adaptive immune response, and disruption of cholangiocyte function, and can cause hepatobiliary injury. This is established by an increase in cholestatic markers, including GGT enzyme, which can be observed in patients with COVID-19, which is observed in about 54% of cases[12,18]. In addition, SARS-CoV-2 can lead to disruption of barrier and bile acid (BA) transport functions of cholangiocytes by dysregulation of genes involved in BA formation and transport[19].

Four potential causes of liver damage are discussed. The first is the direct invasion of SARS-CoV-2 on hepatocytes, leading to abnormal levels of liver enzymes. Although this hypothesis is the most accepted, hepatocytes have not been shown to express a high level of ACE2, making the liver an unlikely target for infection[20]. Other studies have shown a high level of ACE2 expression in cholangiocytes (suggesting an indirect cause of elevated liver enzymes such as cholangiocyte dysfunction)[5]. Still, alkaline phosphatase was not high in patients with COVID-19, supporting this hypothesis. Pathoanatomic data at this stage provide no evidence of SARS-CoV-2 infection of hepatocytes, suggesting this is an unlikely cause of liver damage[21]. The second possible cause of liver damage is the hepatotoxicity of drugs used to treat the disease. Abnormal liver tests may occur in women treated with multiple medications including systemic glucocorticoids, antiviral, anti-inflammatory and anticoagulant drugs during pregnancy[22]. In this number, the treatment with nonsteroidal antiinflammatory drugs and antipyretics during febrile illness, analgesics to control joint pain symptoms or headaches, which are often found in patients in the acute phase of the disease or taking antibiotics, is discussed. It is also possible that the systemic inflammatory response and multiorgan dysfunction may have contributed to the development of a cytokine storm, with subsequent liver damage, particularly observed in patients with severe COVID-19 infection. Finally, the occurrence of severe acute respiratory syndrome can lead to severe hypoxia, which subsequently results in liver dysfunction[18]. An essential role is also played by the body's overwhelming and life-threatening response to infection[23].

Cases of severe hepatitis with pronounced hepatocytolysis leading to acute liver failure have also been described[24]. The prognosis of the disease in these cases is poor. The more severe the disease, the greater the probability of liver involvement and impairment.

There are few reports and research on COVID-19 infection in children who already have chronic liver disease. It is unclear whether infections in the pediatric population are linked to cirrhosis decompensation and the onset of acute or chronic liver failure, which alone is a risk factor for a severe COVID-19 course. Furthermore, comorbidities

in adults such as diabetes, hypertension, and obesity frequently result in non-alcoholic hepatosteatosis (fatty liver disease), but this was not reported in children. Recently, liver involvement has been added in analyzing COVID-19 severity infection or multisystem inflammatory syndrome in children presentation, as well as the possibility of employing liver enzymes as a predictive indicator for the prognosis[25].

PREGNANCY AS A RISK FACTOR FOR SEVERE COVID-19

SARS-CoV-2 infection prevalence among pregnant women presenting for labor and delivery is estimated roughly from 3%-20%, depending on the age, reproductive and social-economical settings[26,27]. Even after controlling for age, race, and gender, the risk of asymptomatic infection in obstetrical patients was 15-fold greater than in surgical patients[28].

Pregnant women were three times more likely than nonpregnant women to be admitted to an intensive care unit (10.5 *vs* 3.9 per 1000), 2.9 times more likely to require invasive ventilation (2.9 *vs* 1.1 per 1000 cases), 2.4 times more likely to require extracorporeal membrane oxygenation (0.7 *vs* 0.3 per 1000 cases), and 1.7 times more likely to die (1.5 *vs* 1.2 per 1000 cases)[29].

Underlying medical conditions, such as obesity, chronic lung disease (*i.e.*, asthma), and chronic hypertension, were related to more severe COVID-19 in pregnancy. The reasons for that are chronic inflammation, altered immune system and decreased ability to tolerate infection associated with these conditions[30,31]. Furthermore, higher susceptibility to respiratory viral infections is seen in pregnant women[32], partially attributable to a phenomenon of immune modulation occurring during pregnancy[33].

The most important factors related to severe COVID-19 in pregnant women and pregnancy outcomes are presented in Figure 1.

In general, the clinical management of pregnant people with COVID-19 is comparable to that of nonpregnant people, and effective medications should not be delayed based on pregnancy status[34]. However, in addition to the direct impact of COVID-19 on pregnancy outcomes, the pandemic and its implications on healthcare systems have had

negative consequences, including higher stillbirths and maternal deaths[9,35]. Furthermore, SARS-CoV-2 infection during the first trimester of pregnancy is related to higher risk of miscarriage[36].

LIVER INJURIES IN PREGNANT COVID-19 PATIENTS

According to some theories, immunological reactions and cardiovascular changes brought on by pregnancy may accelerate the progression of the COVID-19 infection. However, little is known about the course of liver-associated diseases in pregnant SARS-CoV-2-positive women and their outcomes. Reports already exist of patients with severe COVID-19 infection and hepatic injury[6,37-39], making the liver the second most commonly affected organ following the respiratory system. Transient elevations in serum aminotransferases are common findings. Several factors, including severe hypoxemia due to acute respiratory failure, drug interactions, septic shock, and multiorgan dysfunction, have been linked to acute liver damage in severe COVID-19 infection[6].

Much of the research on COVID-19 and its effects on pregnant patients with hepatic injury is currently under investigation. One of the many studies is published by Deng *et al*[40], who compared pregnant patients without liver injury following SARS-CoV-2 infection with those who did have. They established higher levels of procalcitonin, interleukin-6, liver enzymes, and lactic dehydrogenase in pregnant patients with hepatic involvement. There were no statistical differences between the two groups with respect to the severity of COVID-19, time from onset to hospitalization, hospital stay, radiological findings, or obstetric management. Four patients with liver injury in the third trimester voluntarily chose cesarean section, two had a vaginal delivery, and the rest did not deliver. Finally, the six live births observed no fetal death, neonatal death, or asphyxia. The authors found a 29.7% prevalence of liver injury in pregnant COVID-19 patients, with worse inflammation than those who did not have a liver injury[40]. Another interesting case report was reported by Anness *et al*[41] about COVID-19 complicated by hepatic dysfunction in a 28-wk pregnant woman. However, in this case,

the authors found a correlation between the severity of SARS-CoV-2 infection and liver injury. After excluding PE and intrahepatic cholestasis (IHC) during pregnancy, because of the anamnesis of gestational diabetes and past history of IHC in the first pregnancy, they concluded that the abnormal liver tests were due to severe COVID-19 infection. The resolution of the liver function test in their patient represented her clinical improvement from the viral symptoms, which eliminated pregnancy-related liver disease as a putable diagnosis once again. Another enduring hypothesis about COVID-19 infection and hepatic injury with abnormal liver function tests is presented in a retrospective cohort study by Can *et al*[42] They considered that the aminotransferase elevation in COVID-19 pregnant women might be drug-induced as the application of lopinavir/ritonavir and hydroxychloroquine were significantly higher at the beginning of pandemics, and the course of treatment was reasonably longer in pregnant women with abnormal aminotransferases. Hence, the SARS-CoV-2 infected pregnant women who received antiviral treatment should be closely monitored for evaluating liver function tests. A similar case of drug-induced liver cytolysis in a pregnant COVID-19-infected woman was reported by Lamazou *et al*[43] as well. They described a severe course of SARS-CoV-2 infection in the first trimester in a patient treated with hydroxychloroquine because of the repeated implantation failures history, an immunological treatment, aspirin, enoxaparin and filgrastim daily for 10 mo before the embryo transfer. The patient had no pregestational comorbidities such as hypertension, diabetes, or cardiovascular disease. In the seventh gestational week (GW), the patient had abnormal liver function tests: AST, ALT and GGT 3, 5 and 2 times the upper limit of normal, respectively. Despite ruling out viral etiology (viral hepatitis cytomegalovirus, Epstein-Barr virus infection), the patient deteriorated her liver function, which improved only after stopping hydroxychloroquine. Therefore, this case raises concerns about the possible association between COVID-19 infection, prolonged usage of hydroxychloroquine and drug-induced hepatitis[43].

Managing liver injury during pregnancy is a significant challenge and requires a multispecialty approach. Thus, already established classifications help obstetric

specialists diagnose and treat pregnancy-related liver diseases efficiently. Among the most common ones are hyperemesis gravidarum, IHC during pregnancy, PE, HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome and last but not least—acute fatty liver of pregnancy (AFLP)[44].

But as mentioned before, although COVID-19 infection is gaining momentum, little is known about its influence on women with pregnancy related-liver diseases.

PE

Based on the literature data, it became clear that pregnant women who tested positive for COVID-19 have an increased risk of hypertensive disorders, and their characteristics are similar to those of hypertensive patients[45]. This statement adds to the growing body of evidence that raises concerns about the significant percentage of PE in COVID-19 pregnant patients. One of the most commonly associated comorbidities in COVID-19 pregnant patients is PE[46]. Besides the pulmonary and gastrointestinal tract, the placenta also has high expression of ACE2 receptors; thus, a SARS-CoV-2 infection could lead to its dysregulation, considering that both PE and COVID-19 infections are diseases that affect the microcirculation, resulting in prothrombotic incidents. Respectively high rates of PE are associated with severe and critical COVID-19 infection in pregnant women[47]. However, among the most promising diagnostic markers for PE are soluble endoglin, pregnancy-associated plasma protein-A, soluble fms-like tyrosine kinase 1 (sFlt-1), and placental growth factor (PlGF). Because of placental hypoxia, a common finding in PE, there will be sFlt-1 overproduction with inhibition of PlGF, respectively. This alteration could be observed in the circulation 5 wk or more before the onset of PE symptoms. The sFlt-1/PlGF ratio might also be affected by various infectious agents, among which is SARS-CoV-2 infection. Still, unregulated levels of those mediators are related to placental insufficiency[48].

This case is published by Mendoza *et al*[49], who reported in their study a distinctive percent (11.9%) of COVID-19 pregnant women that develop PE signs, underlining the fact that they only appeared in severe COVID-19 pneumonia cases. However, the

authors suspected that the signs and symptoms consistent with PE, which were present in four of five PE cases, may have resulted from the complex pharmacotherapy or renal and cardiovascular dysfunction associated with SARS-CoV-2 infection. This finding was supported by the fact that abnormal angiogenic status (sFlt-1/PlGF ratio), increased lactate dehydrogenase (LDH) and placental under perfusion typical for PE was confirmed in only one of the patients, which indicates that this case was probably an actual PE, while the other ones, Mendoza *et al*[49] classified as PE-like syndrome. Hence the cesarean section was performed on one patient as the only definitive treatment for PE. In contrast, the PE-like syndrome might not be an absolute indication for earlier delivery because of the spontaneous resolve after recovery from severe pneumonia. In conclusion, pregnant women with COVID-19 may develop a PE-like syndrome that, despite the similarities, might be appropriately differentiated by angiogenic markers, so unnecessary interventions and induced preterm labor could be avoided.

AFLP

AFLP is a rare, potentially fatal complication that occurs in the peripartum period. The Swansea criteria are widely used for the diagnosis of AFLP and include results from both clinical and instrumental findings, as well as pathological examination[50]. Choudhary *et al*[51] reported an interesting case of a PE patient with COVID-19, whose condition deteriorated in AFLP by Swansea diagnostic criteria with renal failure and severe COVID-19 pneumonia. The authors pointed out that the COVID-19 infection might mimic the symptoms of HELLP syndrome, viral hepatitis and IHC. Therefore, the best diagnostic approach would be to rule out other causes. Compared to HELLP syndrome, AFLP is associated with higher levels of liver enzyme derangement and coagulation abnormalities. In addition, it is already well-known that COVID-19 infection is frequently associated with hepatic dysfunction[52]. These findings are supported by a case report by Morton *et al*[53] about a pregnant woman with influenza hepatitis followed by AFLP. They elucidated a possible mechanism linking the two

diseases: impaired hepatic fatty acid oxidation mediated by Kupffer cell cytokine releasing, hepatic oxidative stress and hepatocyte injury resulting from viral infection. Therefore, it is possible that COVID-19 infection triggered a similar response, resulting in PE. So far, data has shown that pregnant women with severe COVID-19 infection could develop PE-like syndrome[49]. Therefore, it is of great significance for healthcare providers to be aware of its existence and monitor pregnancies with suspected AFLP with caution.

IHC of pregnancy

Due to its effect on the liver, COVID-19 infection is associated with higher aminotransferase levels, especially in pregnant patients with IHC[54]. Increased levels of serum BA are the most sensitive tool in diagnostics of IHC because of its impaired resorption as a result of estrogen. However, in the case of SARS-CoV-2 infection, there is a diagnostic doubt as to whether the hepatic dysfunction is due to IHC, SARS-CoV-2 or both[55]. Liver injury might result from a primary infection of the hepatocytes or a hypoxic injury product. Rabiei *et al*[56] reported a case of a 38-years old COVID-19 positive patient with IHC of pregnancy who was treated with ursodeoxycholic acid. Due to the worsening of her condition, she had preterm delivery in the 29th GW. The outcome was good for her and one of the three babies.

In contrast, the other two babies died due to severe pulmonary insufficiency and sepsis[56]. However, it is only reasonable to speculate that in pregnant women with IHC and COVID-19, the two pathogenic noxae (obstetric cholestasis and viral infection) concur with one another to worsen hepatic function. But, based on the published studies, we could conclude that the presence of IHC and COVID-19 infection does not affect maternal and fetal outcomes compared to women with cholestasis alone. However, despite the already existing literature data, there is still a lack of evidence regarding whether increasing degrees of hepatic dysfunction are related to an increased risk of adverse pregnancy outcomes such as spontaneous and iatrogenic preterm delivery, meconium-stained amniotic fluid, neonatal respiratory distress syndrome, and

stillbirth. Furthermore, it is unclear if the already established COVID-19 prognostic markers could be used in this cohort of patients.

HELLP, HELLP-like syndrome and hepatic rupture

Because of the seriousness of the pandemics, the research community has focused on the complex pathogenesis of COVID-19 infection. Many previously described studies reported about its multifactorial nature, including thrombocytopenia, endothelial damage, impaired aggregation, mismal bone marrow, and megakaryocyte activity[57,58].

It is also known that many of the factors mentioned above, such as endothelial damage, platelet activation and thrombosis, are also the hidden villains behind the physiopathology of HELLP syndrome and PE[59]. HELLP syndrome is a multisystemic disorder that in 0.5%-0.9% of all pregnancies, mostly in the last trimester (70%) and in multiparous women and in advanced cases that are not diagnosed or treated properly on time, could cause impaired renal function, intracranial hemorrhage, intrahepatic hemorrhage, coagulopathy, and disseminated intravascular coagulation[59]. Unfortunately, similar symptoms are presented in COVID-19 pregnant patients, which makes the diagnostic plan very difficult. Nevertheless, early recognition of the diagnosis could be life-saving, as mentioned in a study by Arslan *et al*[60] The author reported about 30-year-old prima gravida with COVID-19 and severe HELLP syndrome, whose outcome was fatal as well as her baby's. Despite the lack of conclusive evidence, given the sequence of events in the case reported, it is reasonable to speculate that COVID-19 may be an etiological factor associated with the pathophysiology of HELLP. Čivrná *et al*[61] reported another interesting case series describing the differences between the HELLP and HELLP-like syndrome caused by COVID-19. They reported that one of their patients had elevated liver enzymes, LDH and low ratio of angiogenic bio-markers without pregnancy complications. In addition, her lab data had normalized after recovering from SARS-CoV-2 infection. Hence, the authors characterized her with HELLP-like syndrome.

On the other hand, the second patient fulfilled the criteria for HELLP syndrome, and her condition deteriorated with respiratory failure and hepatic rupture. Along this line, proper recognition of the diagnosis of HELLP syndrome and the severe course of COVID-19 in pregnancy could cause a diagnostic dilemma due to its similarity with HELLP syndrome[61]. Ronnje *et al*[62] reported an interesting case report of a 26-years older woman with atypical HELLP syndrome and severe COVID-19 infection, elucidating that the symptoms between the two conditions resemble, thus the prompt diagnosis might be delayed. The authors also shared the statement that COVID-19 infection during pregnancy has been linked to an increased risk of maternal thrombotic incidents, given that pregnancy is a hypercoagulable state by itself. This conclusion that the severe COVID-19 infection caused the patient's liver injury and coagulation dysfunction was supported by the combination of high D-dimer levels and elevated liver enzymes in their case report[62].

The misdiagnosis might lead to an unnecessary intervention and iatrogenic prematurity or underestimation of symptoms severity of HELLP and delayed therapeutic intervention. Thus, further research of the topic is of paramount importance to clarify the exact mechanisms, make an adequate therapeutic strategy and avoid adverse outcomes.

As a late pregnancy-related liver disease—HELLP syndrome is a well-known culprit for various complications; among the most life-threatening ones is liver rupture/infarction[63]. Hepatic rupture has a low incidence rate (approximately 1 per 200000 pregnancies). It is primarily associated with AFLP or HELLP syndrome, rarely without associated liver disease. After excluding all non-pregnancy-related liver diseases, the clinicians should keep in mind three differential diagnoses as possible causes of liver rupture in pregnancy: HELLP syndrome, severe PE and hemangioma rupture. For the time being, reports assessing the pathogenetic mechanism of hepatic rupture in pregnant patients mainly focused on HELLP syndrome. However, with the growing impact of COVID-19 infection and millions of affected patients globally, among which are a significant percentage of pregnant women, the question arises

whether the SARS-CoV-2 could contribute to such a serious complication. One of the first to associate the COVID-19 infection and hepatic rupture in a 32-year-old pregnant patient was Ambrož *et al*[64] They published a case report about a SARS-CoV-2 infected patient in the third trimester, whose condition deteriorated in bilateral pneumonia and hemoperitoneum because of hepatic rupture. Its vascular effects (endotheliitis, procoagulation, and thrombosis) seem to be essential contributors to the worsening of hepatopathy during pregnancy, possibly by affecting the endothelium in the SIRS microenvironment, followed by liver rupture. In a paper by Ahmed *et al*[65], another hemorrhagic incident about intraabdominal hematoma was reported during severe COVID-19 infection with PE and HELLP.

In addition, there is a high percentage of infant and maternal mortality rates reported in the literature so far (42% and 39%, respectively) that the close collaboration between the obstetrician and the surgeon is mandatory[66,67]. Nevertheless, the COVID-19 complications in developing severe hepatopathy during pregnancy require further research.

PREGNANCY OUTCOMES AFTER LIVER INJURY

We reviewed the literature published so far about COVID-19-infected women with pregnancy-related hepatic injury. There were 34 pregnant COVID-19 patients with 37 babies included in our research[49,50,54,56,60-62,65,68]. We established that the most common reported liver disease was IHC during pregnancy, followed by HELLP syndrome and AFLP—61.7%, 32.3% and 2.9%, respectively. Most patients reported flu-like symptoms (n = 27), and six patients (17.65%) were diagnosed with pneumonia or ARDS. Two pregnant women complained of abdominal pain, and only one was diagnosed with intra-abdominal hemorrhage. Only one of the reported cases presented with sepsis and multiorgan failure. A significantly large percentage (88.2%) of the women underwent C-section (Table 1).

Regarding maternal mortality rate, there were 5.88% dead mothers, both of whom had HELLP syndrome (22nd and 32nd GW, respectively). Neonatal/fetal death was

found in 10.81% of the cases. Two babies were delivered in 29th GW by mothers with IHC, while the other two were delivered in 22nd and 32nd GW and their mothers were with HELLP syndrome (Table 1). Regarding the concomitant past diseases and treatment strategies, we cannot present accurate information because most authors did not report data. Another disadvantage of our research was the maternal age and the gestational age of fetuses at the time of preterm delivery due to the lack of information.

To our knowledge, this literature review is among few that have addressed COVID-19 in pregnant patients with pregnancy-related liver injury. However, despite all the collected data on the topic, there are still some missing points in etiopathogenetic mechanisms and the outcome. Therefore, the studies available are presented in Table 1.

Taken together, the results from these studies showed that liver injury should be anticipated in each pregnant individual, infected with COVID-19. Therefore, active follow-up and treatment of the condition is mandatory. However, not a single laboratory or a clinical marker could be established as biomarker for COVID-19 related liver injury. Usually, liver enzymes are elevated. However, we have to keep in mind that this elevation might be a consequence of administered therapy, such as systemic glucocorticoids, antiviral, anti-inflammatory and anticoagulant drugs. Comorbidities, such as previous liver disease, diabetes, hypertension, and obesity frequently result in non-alcoholic hepatosteatosis, may also impact on the onset and severity of liver injury caused by SARS-CoV-2 during pregnancy. Pregnancy itself is a risk factor for severe COVID-19, therefore, managing liver injury during pregnancy is a significant challenge and requires a multispecialty approach.

VACCINATION FOR PREGNANT WOMEN TO AVOID COMPLICATIONS

Pregnant women have generally been excluded from clinical trials of novel drugs and vaccinations due to worries about fetal consequences, as has been the case with COVID-19 vaccines thus far, similar to patients with autoimmune diseases[69].

Although limited data on efficacy and safety in pregnant women, the Center for Disease Control and Prevention, the American College of Obstetricians and

Gynecologists, and the Society for Maternal-Fetal Medicine have each issued guidance supporting the offer of COVID-19 vaccines to pregnant persons[70], because COVID-19 vaccines reduce mortality and complications in SARS-CoV-2 infected people, especially those at high risk for severe disease.

LIMITATIONS

Our narrative review has been conducted by using a search strategy that is adequate to retrieve related to the topic papers. Although we presented the results of these papers thoroughly, we might acknowledge few limitations. First, liver disease associated with SARS-CoV-2 infection during pregnancy is still poorly studied. This resulted in a relatively small number of case reports, original articles, reviews and considerations of official societies available. Second, despite all the collected data on the topic, there are still some missing points in etiopathogenetic mechanisms and the outcome. Most authors did not report data on the concomitant past diseases and treatment strategies, therefore, we cannot present accurate information. Another disadvantage of our research was the maternal age and the gestational age of fetuses at the time of preterm delivery due to the lack of information. And third, the nature of our narrative review did not allow us to make conclusions based on a statistical analysis of the outcomes. However, we believe that these limitations are not fatal, but they are opportunities to inform future research. Furthermore, we assume that describing and summarizing the potential liver injuries in pregnant women with COVID-19 could be of tremendous help to consulting gynecologists and hepatologists who encounter this pathology.

FUTURE DIRECTIONS

Still, many questions on how to diagnose in time COVID-19 related liver injury in pregnant women remain. An algorithm that includes diagnostic approaches to these patients, including laboratory work, clinical and imaging investigation, and most importantly—managing (treatment and follow-up). Since pregnancy, the underlying liver condition and other factors are risk factors for severe COVID-19 and adverse

outcomes, liver injury is a highly unfavorable prognostic marker. More studies that include pregnant women with COVID-19 could add valuable information to the knowledge gap and can improve the recommendations for clinical practice.

CONCLUSION

It is accepted that immunological reactions and cardiovascular changes brought on by pregnancy may accelerate the progression of the COVID-19 infection. However, little is known about the course of liver-associated diseases in pregnant SARS-CoV-2-positive women and their outcomes. Several factors, including severe hypoxemia due to acute respiratory failure, drug interactions, septic shock, and multiorgan dysfunction, have been linked to acute liver damage in severe COVID-19 infection. However, usually, transient elevations in serum aminotransferases are common findings. Much of the research on COVID-19 and its effects on pregnant patients with hepatic injury is currently under investigation. On the other hand, managing liver injury during pregnancy is a significant challenge and requires a multispecialty approach. Thus, already established classifications help obstetric specialists diagnose and treat pregnancy-related liver diseases efficiently. Among the most common ones are hyperemesis gravidarum, IHC during pregnancy, PE, HELLP syndrome and last but not least—AFLP. In addition, vaccination in pregnant women may reduce the risk of severe COVID-19 during pregnancy and adverse delivery outcomes.

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