# Pregnancy and COVID-19 - liver damage

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## Abstract

This review examines information from systematic reviews and meta-analyses, research studies, and case reports to present current knowledge about liver damage in pregnant patients having Covid-19 during pregnancy. Problems with diagnosis and differential diagnosis are examined in the context of the need to rule out other causes of liver dysfunction, including pregnancy-related liver disease. In this paper we give an overview of COVID-19 liver problems during pregnancy. Mechanisms of liver involvement in COVID-19 infection are being examined. An overview of the assessment of abnormal liver biological syndromes in pregnant patients is provided. Differential diagnostic algorithms for primary liver damage established in a pregnant woman in the context of the Covid-19 pandemic are presented. Challenges in diagnosis and etiology assessment methods and customized management options are described.

The management of pregnant women with hepatic dysfunction onset on the Covid-19 background and subsequently aggravated is discussed. The importance of anticoagulant therapy as an essential measure of symptomatic management of Covid-19 in pregnant women is emphasized, as both pregnancy and COVID-19 are thrombogenic. Hypercoagulability appears to adversely affect the pregnant women liver with Covid-19 and post Covid-19 and anticoagulant therapy has benefits in the management of liver damage associated with Covid-19.

The COVID-19 liver problems in a 33-year-old woman who was not vaccinated for Covid-19, without a history of chronic liver disease, was tested positive for Covid-19 at 33 weeks of gestation is discussed. The report of the diagnostics, differential diagnosis, and management questions in the context of liver dysfunction manifested by a significant increase in alanine aminotransferase cytolysis syndrome. The positive effect of anticoagulant therapy in resolving cytolytic syndrome is emphasized. The good maternal and perinatal result is also mentioned.

**Keywords:** pregnancy, COVID-19, liver damage, anticoagulant therapy, pregnancy-related liver disease

## Introduction

Susceptibility of pregnant women to COVID-19 and the risk of complications of COVID-19 are high in pregnancy. The available data on the exact effects of COVID-19 on pregnancy remained scarce (https://cgf.cochrane.org/news/covid-19-coronavirus-disease-fertility-and-pregnancy).

Pregnancy and childbirth generally do not increase the risk for acquiring severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection but appear to worsen the clinical course of COVID-19 compared to individuals of the same sex and age; however, most (>90 percent) infected persons recover without undergoing delivery [1].

Based on existing data, pregnant and recently pregnant women with Covid-19 may show fewer symptoms than the general population, with a general pattern similar to that of the general population.

Pregnant women are in the high-risk group for coronavirus 2 infection with severe acute respiratory syndrome (SARS-CoV-2), and the potential adverse effects of the virus on maternal and perinatal outcomes are worrying [2].

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Pregnant women are at risk for more severe Covid-19 infection and should take extra precautions, especially those over 28 weeks of gestation.

A systematic review, regularly updated to reflect emerging evidence, concluded that: pregnant and recently pregnant women with Covid-19 attending or admitted to the hospitals for any reason are less likely to manifest symptoms such as fever, dyspnea, and myalgia, and are more likely to be admitted to the intensive care unit or needing invasive ventilation than non-pregnant women of reproductive age; pre-existing comorbidities, non-white ethnicity, chronic hypertension, pre-existing diabetes, high maternal age, and high body mass index are risk factors for severe Covid-19 in pregnancy; pregnant women with Covid-19 versus without Covid-19 are more likely to deliver preterm and could have an increased risk of maternal death and of being admitted to the intensive care unit; their babies are more likely to be admitted to the neonatal unit [2].

In a retrospective international cohort study evaluating obstetric and neonatal outcomes in nearly 400 SARS-CoV-2-positive patients according to their gestational age at the time of infection, after 20 weeks it increased the risk of adverse obstetric outcomes and infection, after 26 weeks there is an increased risk of neonatal adverse events [3].

The hypercoagulable state in Covid-19 is emerging as a major pathological occurrence with serious consequences in mortality and morbidity [4].

It was found that the increased risk of SARS in pregnant women infected with the new coronavirus can be explained by physiological changes in the respiratory system and by peculiarities in the immune response in this specific population [5].

Physiological changes in the anatomical structure of the respiratory system as well as in the immune system during the pregnancy-puerperal period seem to contribute to this greater risk [5].

The INTERCOVID study group demonstrated an increased risk of morbidity and mortality in pregnant patients with SARS-CoV-2 infection, which was largely due to a diagnosis of hypertensive disorders of pregnancy, premature labor or vaginal bleeding [6].

Similar results are reported in further studies showing that a composite outcome of maternal death or severe morbidity related to hypertensive pregnancy disorders, postpartum hemorrhage or infections other than SARS-CoV-2 occurred significantly more frequently in pregnant women with SARS- CoV-2 compared to those without SARS-CoV-2 infection (13.4% versus 9.2%, respectively) [7].

A recent population-based study of over 18,000 pregnant patients in Scotland provides the first evidence of more favorable pregnancy outcomes among those who have received Covid-19 vaccination [8]. In pregnant patients with Covid-19, unvaccinated individuals represented a significantly higher proportion of Covid-19-associated hospital admissions (77 percent), Covid-19-associated critical care admissions (98 percent), and perinatal deaths (100 percent of stillbirths and neonatal deaths). The perinatal death rate in the vaccinated cohort was similar to historical background rates and the rates in pregnant people without Covid-19. These findings further support universal recommendations for pregnant people to be up-to-date with Covid-19 vaccination. Women who have Covid-19 towards the end of their pregnancy are more likely to have complications than those who are taking Covid-19 in the early stages of pregnancy or who have not had Covid-19 at all, according to this study [8].

## Prevalence and clinical features of liver lesions in Covid-19

Liver injury is common in Covid-19 patients, especially for severe patients; the dynamic change pattern of liver function indicators may be helpful to judge liver injury and evaluate the effects of treatment in patients with different clinical types [9]. The presence of liver damage has been established in hospitalized patients with Covid-19, with an incidence ranging from 14% to 58% [10-14]. Covid-19-associated liver injury is defined as any liver damage in Covid-19 patients, whether they have pre-existing liver disease [15]. Patients with or without pre-existing liver disease may present with elevated aminotransferases in the setting of Covid-19 [10,16].

Coronavirus infection (Covid-19) may cause acute liver damage and elevated transaminase levels [17]. Liver involvement is common during Covid-19 and exhibits a spectrum of clinical manifestations from asymptomatic elevations of liver functional tests to hepatic decompensation [18]. The etiology of acute liver injury in Covid-19 patients remains unclear but is likely multifactorial.

Several studies are suggesting that the degree of elevation of the transaminases is a marker of disease severity and an independent predictor of mortality [11,19]. In cohorts ranging from 12 to 1,827 patients, liver tests at admission were reported to be elevated in 40%-66.9% aspartate aminotransferase (AST) and 41.6%-67.5% alanine aminotransferase (ALT) of patients, respectively [10]. The results of several meta-analysis reported that severe cases of Covid-19 are more closely associated with liver damage and the degree of liver injury was associated with the severity of Covid-19 [20,21]. Elevated transaminases correlate with disease severity [22]. Nearly two-thirds of patients with severe Covid-19 develop elevated liver transaminases [31], with reported mean AST and ALT above 400 IU/L [24]. The range of AST and ALT elevations is usually mild (i.e., <5 times the upper limit of normal); however, higher aminotransferase levels and severe acute hepatitis have also been reported [19,25,26] The pattern of liver damage is usually hepatocellular rather than cholestatic. AST levels correlate closely with ALT levels over the course of the disease, suggesting hepatocellular origin. A higher AST

pattern than ALT has been associated with disease severity [12]. SARS-COV-2 infection may increase the levels of several biochemical and haematological biomarkers such as ALT, AST, lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), and total bilirubin [27].

AST and ALT are more commonly elevated than bilirubin or alkaline phosphatase (ALP), although the angiotensin-converting enzyme 2 (ACE2) receptor is more frequently expressed on cholangiocytes than hepatocytes [13,22,28]. Low albumin has been associated with severe Covid-19 [29]. Low serum albumin and elevated bilirubin have been associated with disease severity and mortality [22,30].

## Liver problems with Covid-19 in pregnancy

Liver problems in pregnancy are a challenge for clinicians, as they determine the need to consider the safety of both mother and fetus in clinical management decisions. Establishing abnormal liver function tests in pregnant patients in the context of Covid-19 support, especially in the third trimester of pregnancy, requires a prompt approach to diagnosis and management. The causes of liver abnormalities in women pregnant with Covid-19 are various. Patients with or without pre-existing liver disease may have elevated aminotransferases in the context of Covid-19 [23].

The results of a study, which enrolled 37 pregnant patients with Covid-19 in Wuhan, China, found that pregnant patients with liver damage had more severe inflammation than those without liver damage [31] Several studies confirm that SARS-CoV-2 during pregnancy is associated with higher odds of preeclampsia [32]. Increased chances of severe preeclampsia were established (odds ratio, 1.76; 95% confidence interval, 1.18–2.63; I2 = 58%; 7 studies), eclampsia (odds ratio, 1.97 95% confidence interval, 1.01–3.84; I2 = 0%, 3 studies) and hemolysis, elevated liver enzymes, low platelet (HELLP) syndrome (odds ratio, 2.10; 95% confidence interval, 1.48–2.97; 1 study ) among pregnant women with SARS-CoV-2 infection compared to those without infection, according to the results of a meta-analysis of 28 studies comprising 790,954 pregnant women, of which 15,524 were diagnosed with SARS-CoV-2 infection [32].

In an investigation that studied nine women pregnant with Covid-19, it is found that three out of nine had an increase in the concentration of ALT and AST, and in one of them, ALT, reached 2093 U/l [33].

We note the importance of the differential diagnosis of liver lesions coinciding with pregnancy, installed de novo on the background of pregnancy in the context of Covid-19, with particular liver diseases for pregnancy, especially in the third trimester of pregnancy.

### Mechanisms of hepatic impairment in Covid-19

A coherent relationship has been established between the severity of Covid-19 and liver damage, and the mechanisms of liver damage are uncertain and of multifactorial origin [20].

Several mechanisms of liver injury have been proposed, including inflammation related to cytokine storm, hepatic ischemia, direct viral injury, and drug-induced liver injury, but the etiology remains unclear [11].

It is suggested that direct infection of hepatocytes or cholangiocytes is unlikely to be a major mechanism of liver damage. A potential cause of the hepatic injury may be the systemic effects of Covid-19. Covid-19 complicated by sepsis leads to hypoxic lesions and hepatic ischemia.

Hypoxic liver damage may be marked by an increase in serum transaminases due to impaired oxygen supply [34]. Complications of Covid-19 can lead to hypoxemia, ischemia and shock, and microthrombi can disrupt liver infusion [35] Coronavirus 2019 (Covid-19) is associated with a hypercoagulable condition associated with acute inflammatory changes and laboratory findings that are different from acute disseminated intravascular coagulation (DIC), except for those with very severe disease [4]. Fibrinogen and D-dimer are elevated, usually with a modest prolongation of prothrombin time (PT) and partially activated thromboplastin time (aPTT) and mild thrombocytosis or thrombocytopenia [36]. The hypercoagulability status of Covid-19 is described as a major pathological event with serious consequences for mortality and morbidity [4]. Accumulating data such as SARS-CoV-2 leads to hypercoagulation, thus increasing the risk of thrombosis in patients. Thrombosis is a potential cause of liver damage in Covid-19 [37]. Thrombocytopenia is reported in 36.2% and elevated dimer D levels in 46.4% of patients with Covid-19, correlated with more severe cases [38]. It was observed that microvascular thrombosis can lead to organ damage and can potentially affect liver function [39]. Patients with Covid-19 who experienced thrombotic events had dramatic levels of alkaline phosphatase [40]. It is suggested that patients with Covid-19 are more likely to develop disseminated intravascular coagulation [41]. Elevated D-dimer levels and fibrin degradation levels, and prolonged prothrombin time correlate with a poorer prognosis in patients with SARS-CoV-2 [42].

The results of the Wuhan autopsy revealed the infiltration of lymphocytes and monocytes into the portal area, with thrombosis and congestion in the sinuses. The liver has been found to have hepatocyte degeneration along with lobular necrosis and neutrophil infiltration [43]. Post mortem hepatic histology of patients infected with SARS-CoV-2 has suggested that lobular inflammation, vascular changes, and steatosis are the main histological findings. Histological findings of post-mortem liver specimens for 27 patients who died of Covid-19 in Manaus, Brazil showed that most liver specimens had evidence of sinusoidal congestion (n = 23; 85.2%) and ischemic necrosis (n = 26; 96.3%), while 17 (63%) had steatosis, of which 5 showed moderate or severe steatosis [43].

The results of several studies show that vascular congestion in the liver is observed in most cases of Covid-19 [43] and that the vascular events observed in the liver of infected patients are probably due to well-documented systemic coagulopathy of Covid-19 disease, which is characterized by thrombocytopenia and elevated levels of D-dimer, as well as varying degrees of thrombosis, affecting small to large vessels in several organs [44]. It is suggested that hepatic vascular changes are secondary to ischemia caused by cardio-respiratory dysfunction characteristic of severe Covid-19 cases [45].

Drug-induced liver damage (DILI) in the clinical care of patients with Covid-19 may be an additional cause of liver damage [46] A retrospective cohort study that included 122 pregnant women with confirmed Covid-19 found that drug use was the most important risk factor for liver damage during hospitalization [47] Several factors are known to play a potential role in the contribution and causation of DILI in pregnancy [48].

Physiological changes that occur during pregnancy affect the pharmacokinetics of the drug:

✓ Increased hepatic blood flow influences the metabolism of drugs, with high liver extraction.

✓ Decreased serum albumin levels due to hemodilution may alter the pharmacokinetics of the drug.

✓ The altered hormonal environment has a significant effect on hepatic metabolic enzymes.

Comorbidities (malnutrition, obesity, diabetes and pre-existing liver disease) are important in the contribution of DILI; drug-related factors, such as pharmacological class, dose, and polypharmacy; the presence of infections, the intestinal microbiome, alcohol consumption, smoking status, environmental pollutants and socio-economic conditions [49]. Drug-induced liver damage can be direct (hepatocellular pattern of liver injury), idiosyncratic (cholestatic pattern of liver injury), or indirect (mixed pattern of liver injury) [50]. The direct form is the commonest and has become the leading cause of acute liver failure in western countries [51]; it is related to the pharmacological properties of the drug, is dose-dependent, and can affect any individual. The idiosyncratic form is not predictable, is rare, has variable features, and affects susceptible individuals [52]. The indirect form occurs due to a drug exacerbating a pre-existing liver disease or inducing clinical manifestation of subclinical liver disease. Liver damage associated with medication during pregnancy are potentially rare complications but can adversely affect both mother and foetus. Although many drugs can directly cause hepatotoxicity, idiosyncratic liver damage is common during pregnancy [49]. Many of the medicines used to treat Covid-19 are potentially hepatotoxic, and their use as a polypharmacy added to the proinflammatory state increases the risk of DILI [53]. Patients with severe Covid-19 infection and patients with pre-existing liver disease should not be given too many drugs (more than 2) with a potential hepatotoxic effect [54]. It is important to check for clinically significant drug interactions in patients taking Covid-19-specific therapies (e.g., remdesivir, dexamethasone). This can be done with the assistance of a drug interaction program, such as Lexicomp Drug Interactions and Drugs.com A recent study in Spain found that the incidence of DILI in patients with Covid-19 was higher than in patients admitted for other reasons. Most cases were mild, with a hepatocellular mechanism and subsequent recovery. A high incidence of previous hepatitis Covid-19 was observed in DILI. The most commonly associated drugs were hydroxychloroquine, azithromycin, tocilizumab, ceftriaxone, lopinavir / ritonavir, paracetamol, remdesivir, and enoxaparin, with RUCAM causation being defined as probable in 51.2% of cases [55]. The establishment of DILI registries in different countries is an encouraging development it is recommended to report DIDI based on Roussel Uclaf Causality Assessment Method (RUCAM) and other well-known validated methods of DILI assessment [54].

## Peculiarities of clinical and paraclinical manifestations of Covid-19 in pregnancy

The proportion of asymptomatic cases of Covid-19 in pregnant women is high, however it is not clearly defined and continues to be assessed within different studies. A systematic review and meta-analysis has found that pregnant women and those recently pregnant with Covid-19 who attend a medical institution or are hospitalized for any reason are less likely to show symptoms such as fever, dyspnea and myalgia, but are more likely to be admitted to the intensive care unit or need invasive ventilation than non-pregnant women of reproductive age [56]. It has been reported that women who are pregnant and have Covid-19 compared to those pregnant, but without Covid-19 are more likely to give birth prematurely and may be at increased risk of maternal death and be admitted to the intensive care unit, their children are more likely to be admitted to the neonatal unit [56,57]. The evidence suggests that the presence of risk factors (co-morbidities and ethnicity) increased the likelihood of pregnant women being symptomatic in case of Covid-19 infection [58]. Higher odds of complications were also observed amongst symptomatic pregnant women [58]. Risk factors for severe Covid-19 in pregnancy, such as pre-existing comorbidities, non-white ethnicity, chronic hypertension, pre-existing diabetes, high maternal age and high body mass index are [56] must always be considered when assessing the symptomatic cases.

## Evaluation of patients with Covid-19 and abnormal biochemical tests of liver function during pregnancy

It is important to analyze the pattern of liver test abnormalities as a whole with the other laboratory changes typical for single liver diseases characteristic for pregnancy.

There is a need to estimate the level of D-dimer in all cases of symptomatic Covid-19 during pregnancy.

The level of transaminases in patients with Covid-19 usually has a slight increase, less than 5 times the upper limit of normal, but higher levels of aminotransferases and even severe acute hepatitis have also been reported [19,59]. With the increase in transaminases in patients with Covid-19 there may be an increase in LDH, bilirubin and alkaline phosphatase, and a decrease in albumin [19,59].

The initial assessment of pregnant patients with Covid-19 and abnormal liver biochemical and functional tests but no acute liver failure is similar to the assessment of a non-pregnant patient and will include history, physical examination, laboratory studies and liver ultrasound. It is also necessary to consider gestational age and physiological changes in pregnancy to guide further research (Figure 1).

It is necessary to exclude:

• Pregnancy-induced liver diseases, unique to pregnancy:

✓ primary (intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy);

✓ systemic diseases with hepatic manifestations: pre-eclampsia with severe characteristics, including eclampsia; HELLP syndrome; hyperemesis gravidarum.

• Liver diseases that have an increased risk of occurrence during pregnancy - they can be exacerbated by pregnancy through physiological changes related to pregnancy: gallstones and vascular diseases (Budd-Chiari syndrome).

• Liver diseases that are not related to pregnancy, but:

✓ coincide with pregnancy, newly developed during pregnancy (e.g. acute viral hepatitis, Covid-19-associated hepatopathy, etc.);

✓ are pre-existing in pregnancy (chronic liver diseases).

**Evaluation of causes acute liver failure during pregnancy in pandemic Covid-19 era**

• Pregnancy-related:

✓ Common causes: occurring at ≥20 weeks of gestation: AFLP; preeclampsia with severe features, HELLP syndrome;

✓ Exceptional: occurs at gestational age <20 weeks: hyperemesis gravidarum.

• Nonpregnancy-related:

✓ Common causes - acute viral hepatitis, DILI, ischemic hepatitis;

✓ Rarely - severe liver damage in the context of Covid-19.

*Note:*

✓ Hepatocellular pattern: a disproportionate elevation in serum aminotransferases compared with ALP. Other characteristics of liver enzymes (i.e., magnitude of aminotransferase elevations) are interpreted similarly to patterns in nonpregnant patients.

✓ Cholestatic pattern: a disproportionate elevation in the alkaline phosphatase compared with the serum aminotransferases. However, ALP will be normally elevated during pregnancy due to placental production (i.e., typically <2 times the upper limit of normal).

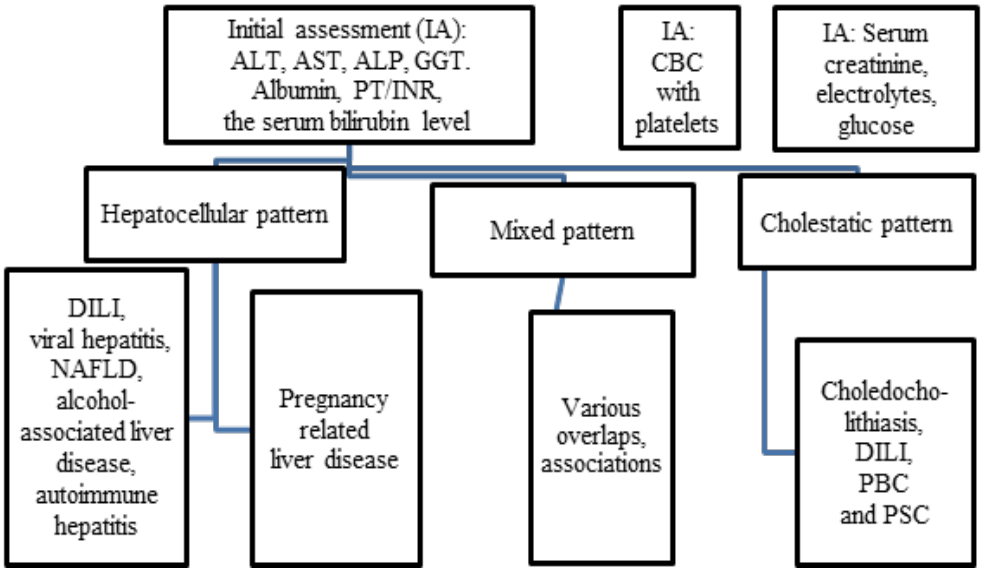


**Figure 1.** Assessment of the cause of liver damage in pregnant women with risk stratification according to clinical presentation and term of gestation.

✓ The R value (also known as the R factor) can be used to help determine the likely type of liver injury (hepatocellular versus cholestatic) in patients with elevated aminotransferases and alkaline phosphatase. In pregnant patients, the R value will not be accurate and cannot be used to determine the pattern of liver injury.

✓ R value = (ALT ÷ ULNV ALT) / (alkaline phosphatase ÷ ULNV alkaline phosphatase).

The R value is interpreted as follows:

➢ ≥ 5: Hepatocellular injury

○ 2 to <5: Mixed pattern

➢ ≤ 2: Cholestatic injury

✓ Biochemical markers of liver injury: AST; ALT; ALP; GGT; LDH, bilirubin.

✓ Markers of hepatocellular function: albumin; bilirubin; PT; INR.

*Abbreviations:* IA, initial assessment; ALT, alanine aminotransferase; AST, aspartate aminotransferase; alkaline phosphatase, ALP; CBC, complete blood count; LDH, lactate dehydrogenase; ULNV, upper limit of normal value; IU, international units; PT, prothrombin time; INR, international normalized ratio, APTT, activated partial thromboplastin time; HELLP, hemolysis, elevated liver enzymes and low platelet counts; ICP; intrahepatic cholestasis of pregnancy; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; DILI, drug induced liver injury; NAFLD, nonalcohol-associated fatty liver disease.

## Differential diagnosis of Covid-19-associated liver dysfunction with pregnancy-induced liver disease

Interpretation of liver injury marchers (including ALT, AST, ALP, GGT and bilirubin) and interpretation of hepatocellular function markers (albumin and bilirubin, prothrombin) in women with Covid-19 is often problematic. Clinical features, the time of onset of symptoms, and gestational age should be considered, as these factors provide information to distinguish diseases that are unique to pregnancy. Differential diagnosis of Covid-19-induced liver injury with pregnancy-induced liver disease, including AFLP and HELLP syndrome, should be imperative, as only early diagnosis of the cause can provide appropriate management. It should be noted that some laboratory abnormalities related to Covid-19 (elevated liver enzymes, thrombocytopenia) are similar to those that occur in severe preeclampsia and HELLP syndrome.

AFLP and HELLP syndrome may share common clinical, laboratory, histological, and genetic characteristics, and differential diagnosis is often difficult [60]. In distinguishing these two pregnancy related liver diseases it is important to note that HELLP is more likely to occur in patients with high blood pressure, but AFLP often occurs in the absence of hypertension and approximately 50% of patients with AFLP do not have thrombocytopenia [60]. For the prompt diagnosis of AFLP, it is important to consider the combination of Swansea criteria with pregnancy-induced antithrombin deficiency, thus it is suggested incorporating antitrypsin activity for less than 65% in the diagnostic criteria for AFLP [60].

Pregnant patients with severe hepatic impairment require urgent multidisciplinary consultation with specialists in various fields, including maternal-fetal medicine and hepatology, and a prompt approach.

## Current evidence-based guidelines recommend:

• All pregnant women admitted with confirmed or suspected Covid-19 should be offered anticoagulation with the prophylactic dose of LMWH, unless the birth is expected within 12 hours or there is a significant risk of bleeding. The use of anticoagulant therapy during labour and delivery requires specialized care and planning and should be managed in pregnant women with Covid-19 in a similar way as in pregnant women with other conditions that require anticoagulation during pregnancy.

• For women with severe Covid-19 complications, the appropriate dosage regimen for LMWH should be discussed with a multidisciplinary team, including a senior obstetrician or clinician experienced in the management of venous thromboembolism during pregnancy.

• All pregnant women who have been hospitalized and have had confirmed Covid-19 should be given thromboprophylaxis for 10 days after discharge from hospital. A longer duration of thromboprophylaxis should be considered for women with persistent morbidity.

## Clinical case reporting

Caucasian pregnant woman, 33 years old, G2P1, 34 weeks' gestation (WG), non-smoking, no alcohol intake and no personal or family history of liver disease, obesity and diabetes, was admitted to a tertiary hospital on 18 March 2021. She denies pregnancy-related liver disease in previous pregnancy. For current pregnancy - evidence from the first trimester, with negative serology for viral hepatitis, no ultrasound evidence of gallstones, no health problems until recent history.

Diagnosed on 05 March 2021, at 32 WG, with Covid-19, symptomatic, manifested by fever up to 38.5 degrees Celsius, weakness, dry cough. She underwent treatment in a city hospital from 05.03.21 to 14.03.21 and was discharged with an improvement in her condition, but a slight increase in transaminases and mild palmar itchy. On the outpatient basis, on 18.03.21, ALT - 1067 U/L and AST - 557 U/L, total bilirubin 31.3 μmol/L, fibrinogen - 8.15 g/L, D-dimer - 3169.41 ng/ml and Prothrombin after Quick - 144.47%. She is urgently referred to a tertiary hospital, with complaints on admission of dull pain in the lower

abdomen, palmar cutaneous pruritus, of low intensity, onset on the 7th day of treatment for Covid-19, being then of a higher intensity, large and spread in the neck area, on the chest, palms and soles, but decreased in dynamics.

She has a brief hospital discharge epicrisis from her previous hospitalization.

Upon admission to the pregnancy therapy department, she was consulted by a multidisciplinary team, including a hepatologist. Lactate dehydrogenase – 232 U/L and alkaline phosphatase – 350 U/L. A decision was made to initiate immediate treatment with LWNM anticoagulant. In the dynamics there is a clinical and laboratory improvement, thus, on 25.03.21 ALT - 453 U/L and AST - 171 U/L, total bilirubin 16.1 µmol/L, fibrinogen - 4.69 g/L, D-dimer – 1242 ng/ml and Prothrombin after Quick - 135%. During the follow up, the thrombocytes were at normal level. The patient was discharged home and the treatment is guided by telemedicine. On April 18, 2021, she gave birth to a healthy baby boy. Anticoagulant therapy was continued after birth, but the dose of enoxaparin was decreased. After birth, the cytolysis syndrome decreased (ALT: 56-49-30 U/L and AST 40-24-22 U/L), with subsequent normalization. On April 26, April 21, on the 8th day after birth, a sudden increase in D-dimer to 7395 ng/mL was established, which required the correction of anticoagulant therapy with continued monitoring of D-dimer, coagulogram and liver samples. Investigation was recommended for acquired thrombophilia and hereditary thrombophilia but was not performed.

## Discussion

The immune system is characterized by a modulated immune state during pregnancy and the immune response is unique during pregnancy [5].

There is growing evidence of possible negative maternal outcomes of Covid-19 infection during pregnancy and advocates for pregnant women to be recognized as a vulnerable group during the current pandemic [61]. Several cases of Covid-19 in the 3rd trimester of pregnancy, associated with liver damage, have been reported in the literature [61,62].

Inflammatory markers, including C-reactive protein levels, were found to be higher in pregnant women with Covid-19 with liver damage than those without liver damage, and pregnant women with liver damage were shown to have more severe inflammation than those without liver damage [23].

Covid-19 is known to be associated with a state of hypercoagulation associated with acute inflammatory changes and laboratory findings that are different from acute disseminated intravascular coagulation (DIC), except for those with very severe disease [4,63]. The hypercoagulatory state induced in Covid-19 shows clinical and laboratory features that partially overlap with bacterial sepsis-induced coagulopathy (SIC) and disseminated intravascular coagulation (DIC) but represents a unique condition that has hence been termed Covid-19-associated coagulopathy (CAC) [41].

**Table I.** Results of laboratory tests during and after symptomatic COVID-19 infection.

| 2021 | ALT (U/L) | AST (U/L) | TBIL (µmol/L) | BC (µmol/L) | Cr (µmol/L) | FER (ng/L) | Fg (g/L) | D-D (ng/ml) | aPTT (sec.) | PI (%) | INR | BA (µmol/L) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **RV** | 2 to 25 | 4 to 32 | 18.81 to 1.71 | 0 to 10 | 35.37 to 79.58 | 13 to 116 | 3.6 to 6.2 | < 500 | 24.7 to 35.0 | 78-120 | 0.8 to 1.09 | < 10 |
| **06.03** | 108 | 70 | 28.3 | 4.1 | 91.4 | | - | - | | | | - |
| **08.03** | 180 | 120 | 41.3 | | | | - | - | | | | - |
| **11.03** | 196 | 92 | | | | | - | - | | - | | - |
| **18.03** | 1067 | 557 | 31.3 | 14.88 | 49.6 | 327 | 8.15 | 3170 | | 144.5 | | |
| **19.03** | 796 | 399 | 25.70 | 24 | | | 5.30 | | | 132.3 | 0.88 | |
| **23.03** | 530 | 251 | 18.8 | 17.60 | | | 4.68 | | | 135.2 | | |
| **25.03** | 453 | 171 | 16.1 | 10.40 | | 135.8 | | 1242 | | | | 15.3 |
| **01.04** | 108 | 35 | 11.6 | 6.10 | | 82 | 7.43 | 1000 | | | | 16.3 |
| **06.04** | 63 | 29 | 11.3 | 5.30 | | 69.3 | 7.43 | | 29.80 | | | 9.20 |
| **09.04** | 80 | 41 | | | | | 7.95 | 1428 | 28.80 | | | |
| **17.04** | 66 | 30 | | | | | 8.83 | 1056 | 30.80 | | 0.87 | |
| **18.04** | The birth of a living, healthy baby | | | | | | | | | | | |
| **19.04** | 56 | 40 | 9.0 | | 50.1 | | 4.0 | | | 134.0 | 0.89 | |
| **26.04** | 49 | 24 | 5.30 | 11.3 | | | 3.94 | 7395 | | | | |
| **04.05** | | | | | | | | 2128 | | | | |
| **11.05** | 30 | 22 | | | | 63.7 | 3.08 | 481 | | | | |

*Abbreviations:* ALT, Alanine Transaminase; AST, Aspartate Aminotransferase; TBIL, Total Bilirubin; BC, Conjugated Bilirubin; CRP, C-Reactive Protein; Cr, Creatinine; FER, Ferritin; Fg, Fibrinogen; aPTT, activated partial thromboplastin time; PI, Prothrombin index; INR, International Normalized Ratio; BA, Biliary Acids; D-D, D-dimers; RV, reference values in the 3rd trimester of pregnancy

*Note:* 06.03.21-11.03.21 - the period of hospitalization in the city hospital for Covid-19; 18.03.21- 26.03.21, the period of hospitalization in the tertiary hospital for liver lesions; 17.04.21 - 27.04.21 - outpatient evaluation, through telemedicine; 18.04.21 - 20.04.21 birth and follow-up in hospital after birth; 21.04.21 - 11.05.21 - outpatient evaluation, postpartum.

CAC is characterized by widespread deregulation of coagulation parameters, such as increased D-dimer and prolonged prothrombin time, whereas platelet counts are only slightly reduced [64]. The precise mechanism of CAC is still under investigation and seems highly complex due to the specific pathophysiological environment created by SARS-CoV-2 infection, which is influenced by a plethora of mediators. Immunothrombosis represents a crucial link among systemic hypercoagulability, endothelial dysfunction, and respiratory failure, where neutrophils, immunogenic platelets, and a dysregulated coagulation cascade work as partners in injury leading to immunothrombotic tissue injury in Covid-19 [65,66]. Physiological changes during pregnancy may exacerbate the procoagulant condition caused by Covid-19 [67]. Several studies on the use of prophylactic and/or therapeutic anticoagulation in Covid-19 have found that anticoagulation has been associated with improved, dose-free survival [68], and prophylactic treatment with LMWH was rapidly included in the standard treatment of inpatients. Recent results from a retrospective cohort revealed a similarly beneficial association of survival with LMWH treatment, which may be supported by the antiviral effects of LMWH [69]. Prophylactic treatment with LMWH was included in the standard treatment of inpatients with Covid-19.

We analyzed the treatment given at the hospitalization stage for Covid-19 to the pregnant woman reported case and noted that in that period no prophylactic and/or therapeutic anticoagulation had been used, despite the standard recommendation for hospitalized Covid-19 patients, and immediately initiated anticoagulant therapy with enoxaparin. Clinical presentation of the patient in the reported case with elevated aminotransferases in the third trimester of pregnancy in combination with cutaneous pruritus required further investigation.

We considered several causes, even if the pruritus was unpronounced and had occurred (appeared) in the background of the drug treatment for Covid-19. Abdominal ultrasound was negative for gallstones and bile ducts. The detection of a high level of serum bile acids in pregnant patients with cutaneous pruritus and elevated aminotransferases required a differential diagnosis of intrahepatic pregnancy cholestasis (PCI), possibly overlapping with liver dysfunction caused by Covid-19.

The positive diagnosis of intrahepatic pregnancy cholestasis (ICP) is based on the presence of itchy skin associated with high levels of total serum bile acid, elevated aminotransferases or both, in the absence of diseases that can produce similar results and laboratory symptoms and all resolve quickly after birth. Detection of elevated bile acids required a repeated assessment of bile acid concentration in fasting conditions, knowing the risk of major fetal and neonatal complications (increased risk of intrauterine death, amniotic fluid stained with meconium, premature birth and neonatal respiratory distress syndrome), when bile acids exceed the level of 40-100 μmol / L in a woman pregnant with CPI. Among the typical laboratory findings for PCI, an increase in serum bile acid concentration is the finding of the key diagnosis [70]. Pregnant women with ICP have serum aminotransferases, usually twice the upper limit of normal, but may reach values greater than 1000 IU/L, like those reported in the reported case [70]. Alkaline phosphatase is not informative for the diagnosis of ICP due to the expression of placental isoenzyme. In the present case, the total bilirubin concentrations were increased until the onset of pruritus and reached maximum values (41 μmol/L) on the 4th day of Covid-19, but subsequently decreased in dynamics until normalization. The disappearance of pruritus and the normalization of bile acid (BA) and bilirubin levels a few weeks before birth, correlated with the decrease in transaminases does not fit well with a positive diagnosis of ICP, in which all symptoms resolve quickly only after birth. However, if ursodeoxycholic acid (UDCA) is started empirically in pregnant women with PCI, high levels of bile acid and transaminases usually decrease, and the patient presented has been treated with UDCA. We have not found in the literature the association of liver damage in Covid-19 with ICP, but it is known that a small subgroup of women with ICP may have an identifiable underlying liver disease [71], including, are established associations with viral hepatitis C [72].

Liver diseases associated with drug use during pregnancy are discussed in the literature [49]. In the reported case, the differential diagnosis of drug-induced hepatitis should be considered, as it is known that the administration of drugs in the clinical care of patients with Covid-19 may be an additional cause of liver damage, especially since physiological changes that occur during pregnancy may affect the pharmacokinetics of the drug [46]. The patient showed a hepatocellular pattern of lesion, characterized by a disproportionate increase in serum aminotransferases compared to alkaline phosphatase. However, the association with hepatotoxicity in the reported case is unlikely, given that cytolysis was present until the initiation of Covid-19 care and ALT increased surprisingly after drug withdrawal. To estimate the probability of DILI in clinical practice we frequently use https://www.rccc.eu/scores/RUCAM.html , but in the revised literature we did not find data on whether this program can be applied in a specific way to a pregnant population.

The patient had no symptoms such as polyuria and polydipsia, nausea, vomiting, abdominal pain, anorexia, nausea, which are characteristic of acute fatty liver pregnancy and the laboratory findings were not compatible with AFLP.

Coronavirus 2 (SARS-CoV-2) infection with severe acute respiratory syndrome may worsen pre-existing comorbidities and additional vigilance is required in such cases. Preeclampsia is one of the most

common comorbidities seen in pregnant women with Covid-19 infection, [73]. SARS-CoV-2 during pregnancy is associated with a higher chance of preeclampsia [32]. Women with severe Covid-19 may develop pre-eclampsia-like syndrome (PE) characterized by preeclampsia-like signs and symptoms, such as high blood pressure, proteinuria, thrombocytopenia, elevated liver enzymes, and this may be distinguished from actual PE by evaluation sFlt-1 / PlGF, LDH and UtAPI [74].

In the reported case, there were not certified diagnostic criteria for HELLP syndrome: 1) hemolysis, determined by at least two of the following: peripheral smear with schistocytes and burr cells; serum bilirubin ≥ 20.52 μmol/L; low serum haptoglobin (≤2.94 μmol/L) or lactate dehydrogenase (LDH) ≥2 x higher than normal; severe anemia, unrelated to hemorrhage - hemoglobin 80 -100 g / L); 2) increased liver enzymes: AST or ALT ≥ 2 times higher than normal; 3) low platelets: <100,000 cells / μL. The pregnant woman we reported had lactate dehydrogenase and platelets within the norm, her blood pressure was monitored, and she was constantly within the normal range.

The patient reported in this case was not vaccinated against Covid-19 until pregnancy and did not receive the vaccine during pregnancy. Currently, evidence suggests that vaccination reduces the risk of developing Covid-19 and reduces the severity of the disease if a revolutionary infection occurs.

The patient presented was diagnosed with liver disease associated with Covid-19 with pronounced cytolytic syndrome, but also with cholestasis syndrome, which raised questions of differential diagnosis. Ursodeoxycholic acid treatment soon benefited from resolving pruritus and normalizing bile acids and bilirubin. Cytolysis syndrome could probably have been less expressed if anticoagulant therapy had been initiated in time. However, subsequent anticoagulant treatment had a positive effect on the course of liver disease. Transaminases decreased but remained slightly elevated until birth. We mention that in the liver disease associated with Covid-19 in pregnancy there is an improvement of the cytolytic syndrome parallel to the decrease of D-dimers by performing anticoagulant therapy. We highlight the benefits of continuing anticoagulant therapy after birth for cases of liver damage associated with Covid-19 in the third trimester of pregnancy.

## Conclusions

• Covid-19 infection during the third trimester of pregnancy increases the risk of developing liver damage.

• In the pregnant patient hospitalized with Covid-19, liver, hematological and coagulation function parameters should be routinely measured, including, to guide management decisions.

• Liver damage in the pregnant patient with Covid-19 is multifactorial and may cause a cumulative impact.

• For the patient pregnant with Covid-19 and those recently recovered from Covid-19 it is necessary to stratify the risk and cause of liver damage depending on the clinical presentation and term of gestation, with differentiation of unique liver diseases for pregnancy.

• Life-saving evidence-based therapies, such as corticosteroids, should not be refused to people taking Covid-19 if they are indicated but require anticoagulant prophylaxis.

• Caring for pregnant women with Covid-19 requires a multidisciplinary team.

• Prophylactic anticoagulant therapy in pregnant women with Covid-19 and after recent treatment with Covid-19, has benefits not only for the prophylaxis of venous thromboembolism, but also for the prevention and management of liver damage in Covid19.

• Personalized administration of anticoagulant therapy with LMWH to women pregnant with Covid-19 or recovered from Covid-19 also has the benefits of ameliorating liver damage caused by Covid-19 with a network of liver samples.

• The time of birth of patients who have recently recovered from symptomatic Covid-19 should be individualized according to maternal-fetal status and gestational age, and decision-making should be individualized.

• Given the increased severity of Covid-19 in pregnant women, we support and encourage vaccination.

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