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Serum hepatic biomarkers in women with obstetric cholestasis and a concurrent SARS-CoV-2 infection

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Abstract

Aim: The aim of the study was to evaluate the association between SARS-CoV-2 infection and serum hepatic biomarker levels among women with obstetric cholestasis.

Methods: In this prospective study, we recruited all pregnant women admitted in our hospital with obstetric cholestasis. Among those with a concurrent SARS-CoV-2 infection, we evaluated the following serum hepatic biomarkers: aspartate aminotransferase (AST), alanine aminotransferase (ALT), and biliar acids (BA).

Results: Among the 88 women enrolled in the study, 20 presented with a SARS-CoV-2 infection while 68 were negative. SARS-CoV-2 infected women were younger (mean age 30.5 ± 5.7 vs. 34.3 ± 5.4; $p < 0.01$) and in a greater percentage of non-Caucasian ethnicity when compared to noninfected women (60.0% vs. 17.6%; $p < 0.01$). Regarding levels of hepatic biomarkers, they showed higher levels of AST (111.5 ± 134.1 vs. 37.3 ± 43.4 UI/L; $p = 0.02$), ALT (132.2 ± 115.7 vs. 50.5 ± 73.173.1 UI/L; $p < 0.01$), and BA (41.4 ± 46.8 vs. 18.4 ± 13.4 μmol/L; $p = 0.04$) compared to noninfected patients. No significant differences in maternal or fetal outcomes were found between infected and noninfected women.

Conclusion: SARS-CoV-2 infection was associated with higher levels of liver enzymes in patients with obstetric cholestasis. This could be the result of a possible hepatic involvement in patients with SARS-CoV-2 infection.

Key words: biliar acid, covid-19, obstetric cholestasis, pregnancy, SARS-CoV-2 infection, transaminases.

Introduction

The SARS-CoV-2 pandemic has had a deep impact on health services worldwide, including antenatal care. In Northern Italy, one of the first areas in Europe to be involved by the pandemic outbreak, the virus largely spread among the pregnant population.[1] The effect of the SARS-CoV-2 infection on this population has not been fully analyzed, especially among women whose pregnancies are complicated by obstetric cholestasis.[1–3] 3 This complication affects between 0.2% and 2% pregnancies[4] and its incidence varies widely from 0.1% to 24% according to ethnicity and geographic areas.[5] The highest incidence of obstetric cholestasis has been observed among South American women, while in Europe and in United States the incidence ranges between 0.1% and 1.5% of pregnancies.[5] Multiple pregnancies, in vitro fertilization and a

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maternal age greater than 35 years are also associated with a higher incidence of cholestasis.[4] A dysfunction of the intra-hepatic bile ducts causes bile acids (BA) to be secreted into the hepatic capillaries, leading to an abnormal serum concentration of BA and consequently to pruritus. Most patients complain of mild pruritus; however, severe itching and jaundice complicate up to 10%–15% of cases.[5] Intense itching, typically of the palms and soles, of the abdomen and of the upper limbs represents the main symptom of intrahepatic cholestasis of pregnancy.[4] Obstetric cholestasis usually occurs in the third trimester of pregnancy and up to 80% of women is diagnosed after the 30th week of gestation.[4–6]

Elevated levels of serum BA represent the most sensitive and specific marker of intrahepatic cholestasis[7,8] and are used as a diagnostic tool when other causes of itching or liver dysfunction have been excluded.[5–8] An upper limit of total serum BA comprised between 10 and 14 μmol/L is considered normal in most studies, however, in fasted women it can be reduced to 6 to 10 μmol/L.[4]

As far as liver enzymes are concerned, an elevated alanine aminotransferase (ALT) concentration is more sensitive for the diagnosis of cholestasis compared to aspartate aminotransferase (AST). In patients with intrahepatic cholestasis, ALT serum levels may raise from 2 to 30-fold compared to normal levels.[9–12] At an ultrasonographic examination, intrahepatic bile ducts usually appear normal. This finding may be useful to exclude other causes of cholestasis.[5]

The most frequently used treatment for obstetric cholestasis is ursodeoxycholic acid, which reduces both serum BA levels and itching.[13]

Adverse pregnancy outcomes associated with obstetric cholestasis include spontaneous and iatrogenic preterm delivery, meconium-stained amniotic fluid, neonatal respiratory distress syndrome, and stillbirth.[5,12]

Such complications are positively related to maternal levels of BA.[4–9] No method of fetal monitoring has been shown to reduce the risk of adverse outcomes or to predict adverse perinatal outcomes. However, regular cardiotocography and monitoring of fetal wellbeing by the means of ultrasonography may reassure both clinicians and patients, although several cases of normal cardiotocography in the hours and days preceding fetal death have been reported.[4]

SARS-CoV-2 infection occurring during pregnancy is classified as a complication of pregnancy, especially in women with comorbidities such as obstetric cholestasis.[14,15]

This study aimed to evaluate the association between SARS-Cov-2 infection and serum hepatic biomarker levels (i.e., AST, ALT, and BA) among women with obstetric cholestasis.

Methods

This prospective single-center study was carried out in our Institution Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy, one of the six maternity hubs designed by the Regional Health Authority for pregnant affected by SARS-CoV-2.

All women admitted to our Institution and diagnosed with obstetric cholestasis underwent a nasopharyngeal swab for SARS-CoV-2 at time of admission in accordance to the Italian National Guidelines.[16]

Obstetric cholestasis was diagnosed in women with signs and/or symptoms of intrahepatic cholestasis who presented with a serum BA concentration ≥10 μmol/L, ALT ≥32 UI/L, AST ≥30 UI/L, when other causes of itching or liver dysfunction had been excluded.

In accordance with national guidelines, all pregnant patients had been screened for main liver diseases during the first trimester, undergoing venous sampling for transaminases, hepatitis B and C, HIV, Toxoplasma, Rubella.[17]

In order to exclude other hepatic disorders, all patients with obstetric cholestasis underwent a hepatic ultrasonographic examination. Fasting was required before the venous sampling to avoid the effects of digestion on liver enzymes and in particular on BA.

Exclusion criteria were the following: neoplasms of the liver and of the biliary tract, HELLP syndrome, viral hepatitis, primary biliary cirrhosis, primary sclerosis cholangitis, autoimmune hepatitis, alcohol or drug abuse, a history of liver transplantation, and positive first trimester screening for main liver diseases.[17]

According to our local protocol, all women with obstetric cholestasis were prescribed 600 mg of ursodeoxycholic acid per day, which was increased according to symptoms and liver function tests. Serum AST, ALT, and BA were monitored twice a week.

Labor was induced between 34 and 37 weeks of gestation in all women with BA ≥100 μmol/L. In all

other cases, labor was induced at full term. The control group included all women with a diagnosis of obstetric cholestasis whose nasopharyngeal swab for SARS-CoV-2 was negative at time of admission in our Institute.

Obstetric and neonatal outcomes were retrieved from hospital records and included into a computer database.

The study was approved by the Institutional Review Board of Fondazione IRCCS Ca′ Granda, Ospedale Maggiore Policlinico, Milan, Italy (No.1512; date: April 2020).

Statistical analysis

Continuous variables were expressed as mean and SDs, whereas categorical ones as absolute frequencies and percentages. Student's *t* test and chi-squared test were used to compare distributions of continuous and categorical variables, respectively. The associations and the corresponding 95% confidence intervals (CIs) between each serum hepatic test (i.e., AST, ALT, and BA) and selected maternal characteristics were evaluated using univariate and multivariate linear regression models. The complete model included the following terms: maternal age (years, in continuous), pre-pregnancy body mass index (BMI) (kg/m^2, in continuous), ethnicity (other, South European), parity (primiparous, multiparous), in vitro fertilization, gestational diabetes, gestational age at time of diagnosis of cholestasis (weeks, in continuous), and SARS-CoV-2 infection. All analyses were conducted using R Statistical Software, version 4.0.5 (R Core Team 2021).

Results

Table 1 shows maternal characteristics and serum hepatic values of 88 pregnant women with obstetric cholestasis. Women with a concurrent SARS-CoV-2 infection were more likely to be younger ($p = 0.01$) and multiparous ($p = 0.05$) compared to women not affected by SARS-CoV-2. Moreover, the two groups differed for ethnicity ($p < 0.01$). Women with SARS-CoV-2 infection showed significantly higher levels of AST ($p = 0.02$), ALT ($p < 0.01$), and BA ($p = 0.04$) compared to noninfected patients.

Obstetric, maternal, and fetal outcomes are reported in Table S1.

Table 2 shows univariate and multivariate analyses for AST levels and maternal characteristics. In the

Table 1 Maternal characteristics and hepatic blood tests according to SARS-CoV-2 infection in 88 women with obstetric cholestasis

Characteristics	SARS-CoV-2 infection		*p*-Value
	Yes ($n = 20$)	No ($n = 68$)	
Maternal			
Age (years)[a]	30.5 (5.7)	34.3 (5.4)	0.01[b]
Pre-pregnancy BMI (kg/m^2)[a]	23.8 (4.5)	22.1 (3.0)	0.14[b]
Ethnicity[c]			
Other	12 (60.0)	12 (17.6)	
South European	8 (40.0)	56 (82.4)	<0.01[d]
Parity[c]			
Primiparous	10 (50.0)	52 (76.5)	
Multiparous	10 (50.0)	16 (23.5)	0.05[d]
In vitro fertilization[c]			
No	17 (85.0)	62 (91.2)	
Yes	3 (15.0)	6 (8.8)	0.70[d]
Gestational diabetes[c]			
No	13 (65.0)	58 (85.3)	
Yes	7 (35.0)	10 (14.7)	0.09[d]
Gestational age at time of diagnosis of cholestasis (weeks)[a]	30.6 (4.7)	30.4 (5.2)	0.84[b]
Hepatic blood tests			
Aspartate aminotransferase (UI/L)[a]	111.1 (134.1)	37.3 (43.4)	0.02[b]
Alanine aminotransferase (UI/L)[a]	132.2 (115.7)	50.5 (73.1)	<0.01[b]
Bile acids (μmol/L)[a]	41.4 (46.8)	18.4 (13.4)	0.04[b]

Abbreviation: BMI, body mass index.; [a]Expressed as mean and SD.; [b]Student's *t* test.; [c]Expressed as absolute frequencies (*n*) and percentages (%). and [d]Chi-squared test.

Table 2 Univariate and multivariate linear regression models for aspartate aminotransferase (AST) according to selected characteristics

Characteristics	Univariate		Multivariate[a]	
	β (95% CI)	*p*-Value	β (95% CI)	*p*-Value
Age (year)	−4.887 (−7.718, −2.057)	<0.01	−5.025 (−8.142, −1.908)	<0.01
Pre-pregnancy BMI (kg/m^2)	2.816 (−2.115, 7.747)	0.26	2.385 (−2.322, 7.092)	0.32
Ethnicity (South European)	−31.734 (−69.245, 5.776)	0.10	0.087 (−40.897, 41.071)	0.99
Parity (multiparous)	37.002 (0.645, 73.360)	0.05	42.526 (4.348, 80.703)	0.03
In vitro fertilization (yes)	−9.086 (−65.084, 46.913)	0.75	17.725 (−36.412, 71.863)	0.52
Gestational diabetes (yes)	−3.629 (−46.627, 39.369)	0.87	−39.215 (−82.064, 3.634)	0.07
Gestational age at cholestasis diagnosis (weeks)	1.224 (−2.150, 4.597)	0.47	2.057 (−1.124, 5.239)	0.20
SARS-CoV-2 infection (yes)	73.835 (36.541, 111.130)	<0.01	45.651 (2.701, 88.601)	0.04

Abbreviations: BMI, body mass index; CI, confidence interval. and [a]Mutually adjusted.

Table 3 Univariate and multivariate linear regression models for alanine aminotransferase (ALT) according to selected characteristics

Characteristics	Univariate		Multivariate[a]	
	β (95% CI)	*p*-Value	β (95% CI)	*p*-Value
Age (year)	−2.076 (−5.482, 1.330)	0.23	−2.096 (−5.778, 1.586)	0.26
Pre-pregnancy BMI (kg/m^2)	7.518 (2.098, 12.937)	<0.01	6.695 (1.135, 12.255)	0.02
Ethnicity (South European)	−33.104 (−75.909, 9.701)	0.13	−9.332 (−57.745, 35.080)	0.70
Parity (multiparous)	26.238 (−15.714, 68.217)	0.22	19.734 (−25.364, 63.831)	0.39
In vitro fertilization (yes)	18.217 (−45.438, 81.871)	0.57	24.303 (−39.648, 88.235)	0.45
Gestational diabetes (yes)	−7.549 (−56.469, 41.371)	0.76	−35.236 (−85.852, 15.380)	0.17
Gestational age at cholestasis diagnosis (weeks)	1.883 (−1.946, 5.713)	0.33	2.839 (−0.919, 6.598)	0.14
SARS-CoV-2 infection (yes)	81.606 (38.942, 124.270)	<0.01	58.348 (7.613, 109.083)	0.03

Abbreviations: BMI, body mass index; CI, confidence interval. and [a]Mutually adjusted.

Table 4 Univariate and multivariate linear regression models for bile acids according to selected characteristics

Characteristics	Univariate		Multivariate[a]	
	β (95% CI)	*p*-Value	β (95% CI)	*p*-Value
Age (year)	−0.295 (−1.304, 0.713)	0.56	0.084 (−1.034, 1.201)	0.88
Pre-pregnancy BMI (kg/m^2)	−0.623 (−2.280, 1.035)	0.46	−1.151 (−2.838, 0.537)	0.18
Ethnicity (South European)	−1.074 (−13.831, 11.682)	0.87	4.889 (−9.806, 19.584)	0.51
Parity (multiparous)	6.364 (−6.014, 18.743)	0.31	5.590 (−8.099, 19.279)	0.42
In vitro fertilization (yes)	4.565 (−14.162, 23.291)	0.63	2.058 (−17.353, 21.469)	0.83
Gestational diabetes (yes)	−0.168 (−14.560, 14.225)	0.98	−4.786 (−20.150, 10.578)	0.54
Gestational age at cholestasis diagnosis (weeks)	0.848 (−0.269, 1.966)	0.14	0.547 (−0.594, 1.688)	0.34
SARS-CoV-2 infection (yes)	22.964 (10.330, 35.597)	<0.01	26.458 (11.058, 41.858)	<0.01

Abbreviations: BMI, body mass index; CI, confidence interval. and [a]Mutually adjusted.

univariate analysis, levels of AST were significantly negatively associated with maternal age ($\beta = -4.887$; 95% CI: −7.718, −2.057; $p < 0.01$) and positively associated with parity ($\beta = 37.002$; 95% CI: 0.645, 73.360; $p = 0.05$) and SARS-CoV-2 infection ($\beta = 73.835$; 95% CI: 36.541, 111.130; $p < 0.01$). The multivariate analysis showed similar associations for maternal age ($\beta = -5.025$; 95% CI: −8.142, −1.908; $p < 0.01$) and parity ($\beta = 42.526$; 95% CI: 4.348, 80.703), whereas the association for SARS-CoV-2 infection was slightly attenuated ($\beta = 45.651$; 95% CI: 2.701, 88.601; $p = 0.04$).

Table 3 shows the analyses for ALT levels. In the univariate analysis, a significantly positive association emerged for pre-pregnancy BMI ($\beta = 7.518$; 95% CI: 2.098, 12.937; $p < 0.01$) and SARS-CoV-2 infection

(81.606; 95% CI: 38.942, 124.270; $p < 0.01$). The multivariate analysis confirmed these associations with a β of 6.695 (95% CI: 1.135, 12.255; $p = 0.02$) for pre-pregnancy BMI and of 58.348 (95% CI: 7.613, 109.083; $p = 0.03$) for SARS-CoV-2 positive group.

Lastly, SARS-CoV-2 infection significantly increased serum BA levels in both the univariate ($\beta = 22.964$; 95% 10.330, 35.597; $p < 0.01$) and in the multivariate ($\beta = 26.458$, 95% CI: 26.458, 41.858; $p < 0.01$) analyses, as shown in Table 4.

Discussion

Our results confirmed that both treatment protocols used for obstetric cholestasis and for SARS-CoV-2 infections in pregnant patients can be used concurrently and have been shown to be effective and safe when applied to women with cholestasis and a concomitant SARS-CoV-2 infection, despite the fact that patients with infection present significantly higher increases in transaminases (i.e., AST and ALT) and BA. The efficacy of the therapeutic protocols was demonstrated as no cases of childbirth occurred before 34 weeks of gestation and no cases of umbilical cord pH lower than 7.10 were observed. Furthermore, although several women developed respiratory symptoms, especially in the third trimester, as reported in previous studies,[18,19] obstetric and neonatal outcomes were not significantly different between the two groups.

In addition to respiratory symptoms, SARS-CoV-2 infection also causes hepatic dysfunction, which is described in more than half of cases[20–26] and is considered a poor prognostic factor. Liver dysfunction may be related to a primary infection of the hepatocytes or be due to secondary hypoxic injury.[20,24–26] In patients who died from SARS-CoV-2 infection, post-mortem histological examination showed hepatocyte swelling and apoptosis, inflammation and central lobular necrosis.[24] These findings, which are also present in acute viral hepatitis, may explain an increase of BA in patients with SARS-CoV-2, due to a reduced ability of the hepatocytes to reabsorb BA from the portal circulation.[20,25] Furthermore, SARS-CoV-2 appears to infect cells by binding to the ACE2 receptor. This receptor is poorly expressed in hepatocytes, but is widely expressed on the bile duct cells.[25] We can therefore hypothesize that the viral infection of the bile duct cells may cause their dysfunction and a subsequent accumulation of BA, creating a toxic damage of the hepatocytes.[25]

Data presented so far on liver function in patients with SARS-CoV-2 is mostly relative to nonpregnant patients.[20–26] In pregnant women with a SARS-CoV-2 infection, the finding of high levels of BA creates a diagnostic doubt as to whether the liver dysfunction is due to obstetric cholestasis, SARS-CoV-2 or both. However, it is reasonable to hypothesize that in pregnant women with obstetric cholestasis the two pathogenic noxae concur to worsen hepatic function.

Pathogenesis of obstetric cholestasis is multifactorial, although estrogen seems to be the main factor involved, as it disrupts hepatic absorption and the efflux of BA.[4–12]

To our knowledge, the literature lacks of evidence regarding whether increasing degrees of hepatic dysfunction determine an increased risk of adverse outcomes of pregnancy. Nor is it known whether prognostic markers used for the general population can be specifically applied to a pregnant population.[27]

Both Huang et al.[22] and Wu et al.[25] report higher serum ALT levels in nonpregnant patients with SARS-CoV-2 infection who required ICU care.

Up to date, numerous studies have evaluated the outcome of pregnancies complicated by a SARS-CoV-2 infection,[1,3,18,19] however, only one case of a pregnancy complicated by obstetric cholestasis and a concurrent SARS-CoV-2 infection has been described in detail.[27]

Anness et al.[27] presented the case of a South Asian woman in the third trimester of pregnancy with a symptomatic SARS-CoV-2 infection and severe hepatic impairment. At time of admission at 28 weeks of gestational age, the patient presented with dyspnea and significantly elevated levels of ALT (571 UI/L) and BA (57 μmol/L), without itching.[27] The increased levels of BA in this patient raised the question of whether the cause was obstetric cholestasis or SARS-CoV-2 pneumonia. Both BA and ALT levels improved with the resolution of the infection. No medical treatment for the liver dysfunction was administered and the patient delivered a healthy neonate at term.[2]

Regarding diagnosis of higher rate of gestational diabetes (GD) in group with SARS-CoV-2 infection, has been described that preexisting diabetes mellitus or GD is present in around 13% of women with confirmed SARS-CoV-2 infection in pregnancy.[28]

Finally, as recent cases of hepatitis adenovirus in children have unfortunately shown, many respiratory viruses possess high tropism for hepatocytes and

Sars-CoV-2 does not appear to be different. Therefore, in presence of these infections the evaluation of liver function should never be underestimated.[29–33]

When this study was conducted (from January 1 to December 31, 2020) in Lombardy most of the SARS-CoV-2 sequences (51.7%) belonged to the B.1 strain, while 36.4% belonged to the B.1.1 strain and 9.8% was assigned to the B.1.5 lineage.[34]

In our study, we confirmed what has already been reported in other works, that is that immigrants and ethnic minorities are more prone to contracting SARS-CoV-2 due to sociodemographic conditions.[24,35–37] Moreover, our population of pregnant women with a SARS-CoV-2 infection had a lower mean age compared to other studies which indicate an age greater than 35 years as a possible risk factor for infection.[24,28,35–37] Our findings may be explained by the fact that women belonging to ethnic minorities are usually pregnant at an earlier age compared to Italian women, as we have already described in a previous study.[38] A possible limitation of the present analysis may be represented by the fact that patients presenting with fever (body temperature greater than 38°C) were prescribed 1 g paracetamol orally or intravenously every 8 h until the fever ceased; however, our patients never exceeded the recommended dose of 3 g per day, which is to be considered safe for liver injuries.[39]

Another possible limitation of this analysis may be represented by the fact that a different number of patients came to our institution due to the pandemic. We have already shown in our previous study that between 2019 and 2020 there were no differences in the characteristics of the population that gave birth in our center.[38] Furthermore, between 2019 and 2020 there was no significant difference in the proportion of obstetric cholestasis; in fact, the proportions of diagnosed women with cholestasis admitted in our institution were 1.5% and 1.7% in 2019 and 2020, respectively ($p = 0.42$).

Furthermore, as described, alcohol abuse was among the criteria for excluding patients from the study. A limiting factor is that this detail was obtained from the interviews to our patients at each obstetric visit and was not validated by clinical data. Of our 88 patients, all reported not consuming alcohol during pregnancy and none of them showed signs and symptoms related to alcohol abuse. The main strength of this study is that it was conducted in one of the six reference centers for the treatment of pregnant women with SARS-CoV-2 infection in Lombardy, the first region to be affected by the pandemic in Europe and one of the regions with the highest diffusion rates of infection.[1] Furthermore, this is the first study to describe a population of pregnant women with obstetric cholestasis and a concurrent SARS-CoV-2 infection.

In conclusion, distinguishing between liver damage due to obstetric cholestasis and that due to SARS-CoV-2 infection is a challenge. Our analysis shows a close correlation between increased liver markers and SARS-CoV-2 infection. The virus could directly or indirectly interact with the activity of hepatocytes in pregnancy. However, the concomitant presence of obstetric cholestasis and a SARS-CoV-2 infection does not seem to cause different maternal and fetal outcomes compared to women with cholestasis only.

Author contributions

All authors were part of the guideline group within Francesco D'Ambrosi, Manuela W. Ossola, Matteo Di Maso and Enrico Ferrazzi contributed significantly to the conception, planning, carrying out, and analysis of the manuscript. Roberta Erra, Giulia E. Cetera, Chiara M. Soldavini and Anna Viscardi contributed to data curation. Francesco D'Ambrosi was the primary writer of the manuscript. All authors read, revised and consented to the publication of the final manuscript.

Conflict of interest

None declared.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author [F.D.]. The data are not publicly available due to the privacy of research participants.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1: Obstetric outcomes in 88 women with obstetric cholestasis according to SARS-CoV-2 infection