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Evolution of Liver Function Biomarkers and Biochemical Blood Values in Pregnant Patients at Term Having Mild Forms of COVID-19 throughout the Pandemic

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Abstract:
Background*:Pregnant women, generally experienced COVID-19, as a mild to moderate illness, although a minority became critically ill and mortality did occur. Few studies have worked to evaluate the silent alterations of blood biochemical values in asymptomatic or mild forms of the disease. The aim of this work was to study the blood biochemical values in pregnant patients at term, in asymptomatic forms of disease, in different periods during the pandemic, when different viral variants of concern were present.*
Materials and Methods*: A total of 153 pregnant patients with an asymptomatic form of COVID-19, and 306 healthy pregnant patients, admitted for delivery in our hospital between April 1, 2020 and March 1, 2022, were studied. The biochemical blood values and liver function biomarkers, harvested closest to the time of delivery, were considered.*
Results*: Outside the normal limits, we found the doubling or even tripling of the normal values of alkaline phosphatase and lactate dehydrogenase, as well as increases in cholesterol and triglycerides in all groups and in C reactive protein in autumn 2021.*
Conclusion:*Mild forms of COVID-19 in pregnant patients do not exclude the possibility of adverse maternal outcomes.*
Key Word*: MildCOVID-19; Pregnancy; ALT; AST; Uric acid; Alkaline phosphatase;Lactate dehydrogenase; Cholesterol; C reactive protein.*

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I. Introduction

Pregnant women, generally experienced COVID-19, as a mild to moderate illness, although a minority became critically ill and mortality did occur [1,2,3]. Although pregnant women are at an immunosuppressive state due to the physiological changes during pregnancy, most patients suffered from mild or moderate COVID-19 disease with no pregnancy loss, proposing a similar pattern of the clinical characteristics of COVID-19 to that of other adult populations [4]. Pregnant women do not appear to be at a higher risk of catching COVID-19 or suffering from more severe disease than adults of similar age are [5]. Physiologic adaptations during pregnancy may offer protection against severe forms of disease [6,7,8,9]. Still, there is not sufficient evidence to establish an idea that COVID-19 would not complicate pregnancy [10,11,12]. Pregnant women with COVID-19 may be at increased risk of adverse pregnancy and birth outcomes [13]. The rates of some adverse neonatal events, including premature delivery and low birthweight were relatively high in mothers infected with COVID-19 [14,15,16].
The underlying blood composition variability of these outcomes require an intense study. Moreover, the more viral variants of concern occurred, the more and different conclusions emerged as regarded maternal and fetal

outcomes. So far, few studies have evaluated the differences between the silent alterations of blood biochemical values in mild forms of the disease, generated by various variants of concern, in pregnant patients. Though the infection was mild, the silent blood biochemical alterations may be mild or not.
The aim of this work was to study the blood biochemical values in pregnant patients at term, in asymptomatic forms of disease, in different periods during the pandemic, when different viral variants of concern were present.

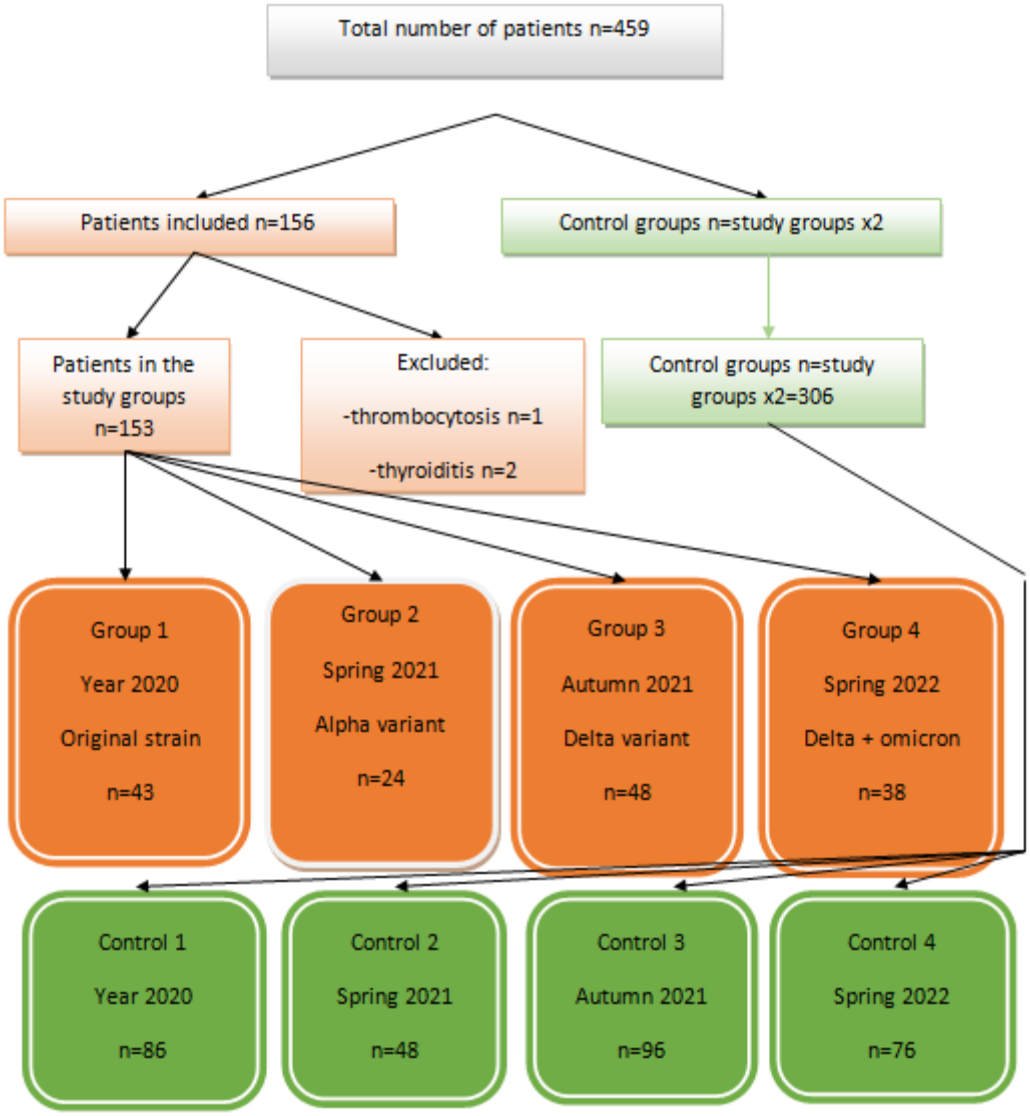
II. Material And Methods

This case-control study was carried out on patients of Elena Doamna Obstetrics and Gynecology University Hospital in Iasi, Romania, from April 2020 to March 2022. A total of 153 COVID-19 pregnant patients and 306 healthy pregnant patients were included in this study.
Study Design: Case-control study
Study Location: Elena Doamna Obstetrics and Gynecology University Hospital in Iasi, Romania.
Study Duration: April 2020 to March 2022.
Sample size: 459 patients.
Sample size calculation: All consecutive patients admitted for at term (37-41 weeks of pregnancy) delivery in this university hospital, and tested positive for RT-PCR for SARS-CoV-2 virus, with little or no symptoms, between April 2020 and March 2022, were included as the study lot. The control lot included a double number of healthy patients, age and parity-matched with the study group, admitted in the same period with the study group patients. There were four groups of patients, according to the period of time they were admitted and the type of virus circulating: group 1 (all 2020, original SARS-CoV-2 virus), group 2 (spring 2021, alpha variant), group 3 (autumn 2021, delta variant) and group 4 (spring 2022, delta and omicron variants)[17]. There were time intervals (months) between these groups when there were no SARS-CoV-2 positive patients requiring admission to the hospital. Though we labeled group 2 as spring 2021 and group 3 as autumn 2021, this was done to simplify understanding and description. The real time intervals were as follows: group 1 spanned from April 2020 to December 2020, group 2 from January 2021 to June 2021, group 3 from August 2021 to November 2021 and group 4 from December 2021 to March 2022 (the last is ongoing, but we stopped gathering data on March 1st 2022). There were 43 patients in group 1, 24 in group 2, 48 in group 3 and 38 in group 4, or 153 patients altogether. For each group of patients, we chose control group, having double the number of the study group: starting with the day of admittance of the first patient in each study group, we calculated the consecutive patients until number was fulfilled.

Subjects & selection method: All consecutive patients admitted for at term (37-41 weeks of gestation) delivery in this university hospital, and tested positive for RT-PCR for SARS-CoV-2 virus, between April 2020 and March 2022, were included as the study lot. The control lot included a double number of patients, age and parity-matched with the study group, admitted in the same period with the study group patients. (Figure 1)

There were the study group patients:
Group 1 (N=43 pregnant patients), corresponding to all 2020
Group 2 (N= 24 pregnant patients), corresponding to spring 2021
Group 3 (N=48 pregnant patients), corresponding to autumn 2021
Group 4 (N=38 pregnant patients), corresponding to spring 2022.
There were the control group patients, double the number of the study group:
Control group 1 (N=86 pregnant patients), corresponding to all 2020
Control group 2 (N= 48 pregnant patients), corresponding to spring 2021
Control group 3 (N=96 pregnant patients), corresponding to autumn 2021
Control group 4 (N=76 pregnant patients), corresponding to spring 2022.

Figure 1. Flow diagram



Inclusion criteria:

1. Pregnant patients at term (37-41 weeks of gestation)
2. Patients who tested positive for SARS-CoV-2 RT-PCR
3. Patients who presented a mild form of infection (little or no symptoms)

Exclusion criteria:

1. Patients with blood diseases (leukemia, thrombocytopenia)
2. Patients with systemic diseases (kidney failure)
3. Patients with autoimmune diseases (thyroiditis, lupus)

Procedure methodology

Patients were considered to have a mild form of disease if they had no symptoms (e.g., cough, fever, sore throat, headache or diarrhea). Written informed consent was obtained from all patients involved. The study was approved by the Ethical Committee of the Elena Doamna Obstetrics and Gynecology University Hospital in Iasi (Approval number 4/ April 2nd, 2020).

Patients' blood was harvested for analysis and RT-PCR testing upon admittance. When required, blood analysis was repeated or other blood components were determined. In this study, the blood values harvested closest to the time of delivery were considered. We performed a comparison of biochemical values between the COVID-19 pregnant patients and healthy pregnant patients, then between the four groups of COVID-19 patients.

Statistical analysis

The SPSS version 18 was used, from PASW Statistics for Windows, SPSS Inc., Chicago, IL, USA. To describe the data, we calculated the mean values and standard deviations, as well as the median and quartile values. The nonparametric Kruskal–Wallis test was used for comparisons and Shapiro–Wilk was used for normality examination. For statistical decision, a 0.05 p value was considered the cutoff for significance.

III. Result

Pregnant patients at term

The two groups are similar as regards age, gestation number and parity number (P>0.05) (Table 1):

Table no 1: Shows description of patients in the study group and in the control group (10)

Values	COVID n=153	Control n=306	P
Age (years)	28	28	0.797
Gestation (number)	2	2	0.498
Parity (number)	2	2	0.936
Gestational age (weeks)	38.83	38.67	0.838

The patients in the four study and four control groups showed no difference as regarded age, gestation, gestational age or parity number (P>0.05).

Since gestational age is an important variable affecting the markers here evaluated, we calculated it for every single group, and we found no difference:

Table no 2: Shows description of the gestational age, and number of patients, in the four groups of patients in the study group compared with the four groups in the control group. Mean values.

Groups / Gestational age (weeks)	COVID-19	n=	Control	n=	P
1	38.93	43	38.68	86	0.814
2	38.75	24	38.43	48	0.982
3	38.87	48	38.59	96	0.613
4	38.71	38	38.90	76	0.755

Blood biochemical values(10)

The blood biochemical values show some significant differences in the two groups, as regards AST and uric acid. (Table 3):

Table no 3: Shows blood biochemical values in the study group and in the control group. Mean values.

Values	COVID n=153	Control n=306	P
Uric acid	4.89	4.36	0.000
ALT	22	18	0.091
AST	29	23	0.002
Urea	19.5	20.1	0.798
Creatinine	.79	.77	0.135
Glycemia	89.2	86.1	0.093

ALT=alanine aminotransferase; AST= aspartate aminotransferase.

We further studied these values in the four groups of COVID-19 pregnant patients. There was a significant difference between the values of uric acid, ALT (alanine aminotransferase) and AST (aspartate aminotransferase), between the four groups of COVID-19 pregnant patients (Table 4).

Table no 4: Shows biochemical values in the four groups of patients. Mean values.

Values /Groups	1	2	3	4	P
Uric acid	4.97	4.13	5.40	4.58	0.01
ALT	20.98	18.85	29.91	14.86	0.04
AST	19.50	20.25	37.11	27.44	0.01
Urea	19.65	17.81	20.08	19.50	0.60
Creatinine	.81	.81	.75	.80	0.66
Glycemia	91.65	90.76	89.72	82.67	0.06

ALT=alanine aminotransferase; AST= aspartate aminotransferase.

Therefore, these values were further investigated, as shown in Table 5.

Table no 5: Shows the P values of significant differences between the four groups of patients, taken two by two, for uric acid, ALT and AST values.

Groups compared	URIC ACID	ALT	AST
1-2	.13	1.00	1.00
1-3	1.00	.46	.03
1-4	1.00	1.00	1.00
2-3	.01	1.00	.09
2-4	.80	.90	1.00
3-4	.42	.02	.09

Group 1= year 2020, group 2=spring 2021, group 3=autumn 2021, group 4=spring 2022. Significance values adjusted by the Bonferroni correction for multiple tests. ALT=alanine aminotransferase; AST= aspartate aminotransferase.

In uric acid, the only observed difference was between spring 2021 and autumn 2021, i.e., the alpha versus delta variants. In ALT (alanine aminotransferase) the only observed difference was between autumn 2021 and spring 2022, when the omicron variant occurred. It apparently affected the liver less than other variants. In AST(aspartate aminotransferase), the only observed difference was between 2020 and autumn 2021, when the delta variant occurred. Later, when the omicron variant occurred, values returned to levels similar to 2022.

Other blood biochemical values in fewer patients

We also compared other biochemical values, albeit not in all patients. Statistical significance could not be determined, and real comparisons could not be made between groups (Table 6).

Table no 6: Shows blood biochemical values in the study group and in the control group, in fewer patients. Mean values and number of patients who had that specific biochemical value determined, in each group.

Values	COVID-19	n=	Control	n=	P
Alkaline phosphatase	358.7	4	305.6	2	NA
LDH	428	26	431	13	NA
Cholesterol	231.3	9	282.1	11	NA
Triglycerides	221.3	9	219.1	9	NA
CRP	12.4	19	7.4	30	NA
Calcium	9.67	24	10.26	37	NA
Magnesium	1.77	24	2.97	39	NA
Iron	53.5	24	75.5	35	NA
Total bilirubin	.55	7	.37	2	NA
Direct bilirubin	.35	6	.13	2	NA
GGT	23.1	4	5.6	1	NA
Chloride	110.7	3	-	0	NA
K	4.22	3	-	0	NA
Na	143.8	3	-	0	NA
Alkaline reserve	22.3	3	-	0	NA
Total proteins	6.04	1	7.52	3	NA

LDH=lactate dehydrogenase, CRP=C reactive protein, GGT=gamma glutamyl transpeptidase, K= serum potassium, Na=serum natrium., NA= not applicable.

Though all the patients had no symptoms, these highly increased values of alkaline phosphatase, lactate dehydrogenase, cholesterol and triglycerides showed that there were alterations in some asymptomatic patients. Essentially, mild COVID was not as mild as previously assumed.

IV. Discussion

There was a mild nature of COVID-19 among pregnant females as the majority of patients were asymptomatic and few presented with mild symptoms[18]. Maternal and neonatal clinical course the infection is typically mild, presenting low mortality rates[19].

Uric acid levels showed a sudden increase, albeit still within normal limits, between spring and autumn 2021, when the alpha variant was replaced with the delta variant[8]. These normal values may have been the result of a balance between the influence of SARS-CoV-2 virus and that of pregnancy upon the uric acid values. Increased uric acid during the third trimester of pregnancy has been associated with adverse fetal outcomes and preeclampsia[20,21,22,23]. Decreased uric acid values during COVID-19 hospitalization has been associated with severe disease and negative outcomes[24,25,26], while increased uric acid values were associated by other authors

with severe COVID-19 disease [27,28]. Chen[29]demonstrated that abnormal uric acid levels, both increased and decreased, were associated with negative outcomes in COVID-19 patients.

There was a significant decrease in ALT values between autumn 2021 and spring 2022, when the seemingly less aggressive omega variant occurred [17]. However, the AST values increased in autumn 2021, due to the delta variant [17]. Both ALT and AST increase during pregnancy (AST more so), but their increases in these mild forms of COVID-19 were not simultaneous, and not beyond normal limits. This was in accordance with Goel[30], who found mild increases in all liver enzymes in most cases of COVID-19. This was also in accordance with Wijanpreeja[31], who demonstrated increased ALT and AST (AST more evidently) in COVID-19 patients, together with alkaline phosphatase values and GGT (more visible in severe cases). We noted increased alkaline phosphatase, up to three times higher than normal, in our mild form patients. Pregnancy may generate an increase in alkaline phosphatase levels, but only up to double the normal value [32], and that close to the time of labor. The SARS-CoV-2 virus generated an additional increase in alkaline phosphatase, in accordance with the results of Wei[33]. The increased alkaline phosphatase may appear in preeclampsia [34]or gestational diabetes mellitus [35], but none of these situations were found in the study groups, since none of these patients had high blood pressure or hyperglycemia. Wilkof-Segev[36]described extremely elevated alkaline phosphatase levels associated with negative perinatal outcomes, but with nonspecific symptoms. Elevated alkaline phosphatase was associated with cardiovascular risk [37] and intrauterine growth restriction[38]. Stanley[39] reported one normal delivery in an extremely elevated alkaline phosphatase mother without any symptoms. We reported tripling the values of alkaline phosphatase in a few patients, also without any symptoms.

The GGT values were normal in the few patients in which they were determined. Our findings were in discordance with Hwaiz[40], who found elevated ALT and AST in most COVID-19 patients. Leal [41] demonstrated increased ALT and AST, but they were not correlated with the severity of COVID-19 disease. This was not true for our patients, since ALT and AST were still within normal limits and the disease was mild.

We agreed with the authors of [42,43,44]who observed that ALT and AST increased more as the condition of the patient grew more critical. Our patients were not critical, so the ALT and AST were within normal limits, albeit slightly modified to different virus variants. Aloisio[45] showed that multiple factors, not only the SARS-CoV-2 virus, could generate liver enzyme alterations. We agreed with those results, as well.

According to Cai[46], patients with disorders of the lipid metabolism are at risk for negative perinatal outcomes. We found a few patients with highly elevated cholesterol and triglyceride levels. They were asymptomatic for COVID-19, but were at risk for negative perinatal outcomes.

We found increased levels of lactate dehydrogenase in a few patients. This was in accordance with Khalid [47], who found increased liver enzymes in COVID-19 patients; however, she also found increased APTT values, which were not found in our group of mild COVID-19 patients. Fisher [48] reported 53% sensibility of elevated lactate dehydrogenase to predict severe cases of COVID-19 in pregnant patients. We had few patients with elevated lactate dehydrogenase and they had no symptoms.

Jevtic[49]reported increased C-reactive protein in pregnant COVID-19 patients. We found that CRP was elevated only in the autumn 2021 group, when the delta variant emerged[17], but our patients were still asymptomatic.

V. Conclusion

We showed that, in mild forms of COVID-19, significant variability in values of fibrinogen, prothrombin time, uric acid, ALT and AST can occur—though still within normal limits. Outside the normal limits, we found the doubling or even tripling of the normal values of alkaline phosphatase and lactate dehydrogenase, increases in cholesterol and triglycerides in all groups, and increases in CRP in autumn 2021.

Pregnant patients with mild forms of COVID-19 displayed some blood alterations, showing that, while they may be asymptomatic for COVID-19, they and their babies are still at risk of adverse perinatal outcomes.

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