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Coagulopathy parameters in symptomatic and asymptomatic Pregnant Women with COVID-19

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Abstract.

Purpose: The purpose of the study was to determine if the physiological hypercoagulability during pregnancy is compounded by SARS-CoV-2 infection-induced coagulability.

Patients and methods: We retrospectively analysed (October 2020 and August 2021) modifications of the coagulation parameters recommended by the ISTH (International
Society on Thrombosis and Haemostasis) (fibrinogen, APTT, PT, INR, D-dimers complete blood count) in 96 pregnant women infected with SARS-CoV-2.

Results: Our results indicated that none patients had severe evolution of the SARS-CoV-2 infection and did not require transfer to the ICU. We also monitored the variation of such parameters, depending on subsequent SARS-CoV-2 PCR screening tests. We established that the laboratory parameters used to assess the coagulability are directly correlated with positive SARS-CoV-2 tests, and pregnancy represents a condition that islikely to increase the risk of embolisms in pregnant patients infected with SARS-CoV-2, compared with the general population. No cases of confirmed SARS-CoV-2 infection were observed in the neonates.

Conclusion: Knowledge of laboratory modifications with prognostic utility in

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relation to coagulation may be extremely valuable in the management of pregnant women with COVID-19. A better understanding of coagulopathy caused by COVID-19 would alsobe helpful to guide treatment recommendations for pregnant women. Pregnancy may also be an additional risk factor for coagulopathy in women infected with SARS-CoV-2 in both symptomatic and asymptomatic positive pregnant women.

Keywords. COVID-19; laboratory parameters; pregnant women; coagulopathy

Article I. Introduction

Data on the impact of COVID-19 in pregnancy are limited (1). The pandemic involving acute respiratory syndrome with coronavirus 2 (SARS-CoV-2) has exposed vulnerable populations and created an unprecedented global health crisis. Knowledge obtained in previous studies of coronavirus in humans suggests that pregnant women and their foetuses are highly sensitive to the coronavirus infection (2). Pregnancy increases the risk of viral infections due to physiological and immunological modifications occurring as a normal component of pregnancy, along with other modifications of the cardiovascular and respiratory system, including increased heart rate and oxygen consumption and de-creased pulmonary capacity (3). Moreover, pregnancy brings with it the physiological condition of hypercoagulability, with an increase in coagulation factors, including fibrinogen and D-dimers, which go up to 50% over the baseline in the 3rd pregnancy quarter (4). This physiological hypercoagulability is compounded by SARS-CoV-2 infection-induced coagulability. The International Society on Thrombosis and Haemostasis (ISTH) has elaborated guidelines under the guidance of health professionals with expertise in COVID-19 coagulopathy (5). The ISTH has established a scoring system to identify “sepsis-induced coagulopathy” (SIC), with a SIC score of > 4 indicating early disseminated intravascular coagulation (DIC) (6). Use of SIC scores has remained unvalidated during pregnancy as D- dimers have high values in pregnancy, and thus their prognosis value decreases. Lymphocytes play a critical role in the immune response to viral infections, and lymphopoenia is correlated with disease severity and hospitalization in COVID-19 (7). During pregnancy, measuring activated partial prothrombin time (APTT) and fibrinogen levels may also prove valuable. At present, the magnitude and frequency of COVID-19- induced coagulation anomalies during pregnancy are unknown. Increased maternal mortality and poor obstetric results in association with other coronaviruses such as SARS and MERS have already been proven (8,9). Moreover, in addition to routine measurement of D-dimers, prothrombin time and platelet counts in all patients with COVID-19, according to the guidelines of the International Society on Thrombosis and Haemostasis (ISTH), monitoring of APTT and fibrinogen levels must be considered (10,11). Sexual and other routes of SARS- CoV-2 transmission, the macrophage activation with vascular impact and SARS-CoV-2- induced cytokine storm and familial clustering of COVID-19 skin manifestations were recently described (12-14).

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Article II. Material and methods

We conducted a retrospective study on 96 pregnant women infected with SARS-CoV-2, admitted to "Buna Vestire" Obstetrics and Gynaecology Hospital of Galati between October 2020 and August 2021, for monitoring of their pregnancy and/or birth or due to respiratory symptomatology.

Data were systematized and centralized in an SPSS 18.0 database and processed using the appropriate statistical functions. A 95% confidence interval was used in data presentation. Primary indicators (minimum, maximum, frequency), mean value indicators (mean, median), and dispersion indicators (standard deviation, standard error, confidence interval for the mean) were used for descriptive statistical analysis. The Skewness test ($-2 < p < 2$) was used to validate the normality of the value series for continuous examined variables.

Qualitative significance tests, such as the chi2 test were used for comparing the distributions of frequencies. The Kruskall-Wallis test, a nonparametric test, was used for intergroup comparison of 3 or more frequency distributions; the correlations between different phenomena were identified using the Pearson correlation coefficient.

The t-Student test was used for comparing the means of any two normally distributed variables. For multiple comparisons of normal distributed series of values, a post hoc Bonferroni test was applied after one way ANOVA.

The plotting of a receiver operator characteristic (ROC) curve, which defines the aria under curve (AUC) and where the false-positive rate (specificity) is placed on the abscissa and the true-positive rate (sensitivity) on the ordinate, allowed the analysis of the sensitivity/specificity balance.

Article III. Results

3.1. General features study lot

In terms of age, the sample had the following characteristics: variations in the range 20–40 years; an average of 30.67 years ± 6.06; a median value (29 years) close to the median value. The gestation age had the following characteristics: wide variations (28.87%) in the range 6–40 weeks; an average of 32.08 weeks ± 9.26.

At the time of hospitalization only 68 out of 96 patients had specific symptomatology, 28 patients were asymptomatic.

Of the entire study batch, 45.8% of the pregnant women were admitted for delivery, i.e., they were in the last pregnancy quarter; 29.2% had a false labour or abortion imminence; and 25% were admitted for pregnancy monitoring (Table 1).

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Table 1. Admitted * Symptomatology Crosstabulation (p=0.005).

Admitted	Symptomatology					
	Specific symptomatologyn=68 (70.8%)		Asymptomaticn=28 (29.2%)		All cases n=96 (100%)	
	n	%	n	%	n	%
delivery	24	35.3	20	71.4	44	45.8
false labour orabortion imminence	24	35.3	4	14.3	28	29.2
pregnancy monitoring	20	29.4	4	14.3	24	25.0

Analysis of symptoms in the group of 68 symptomatic patients shows a frequency of 66.75% of cough, pelvic pain and low-grade fever (Figure 1).

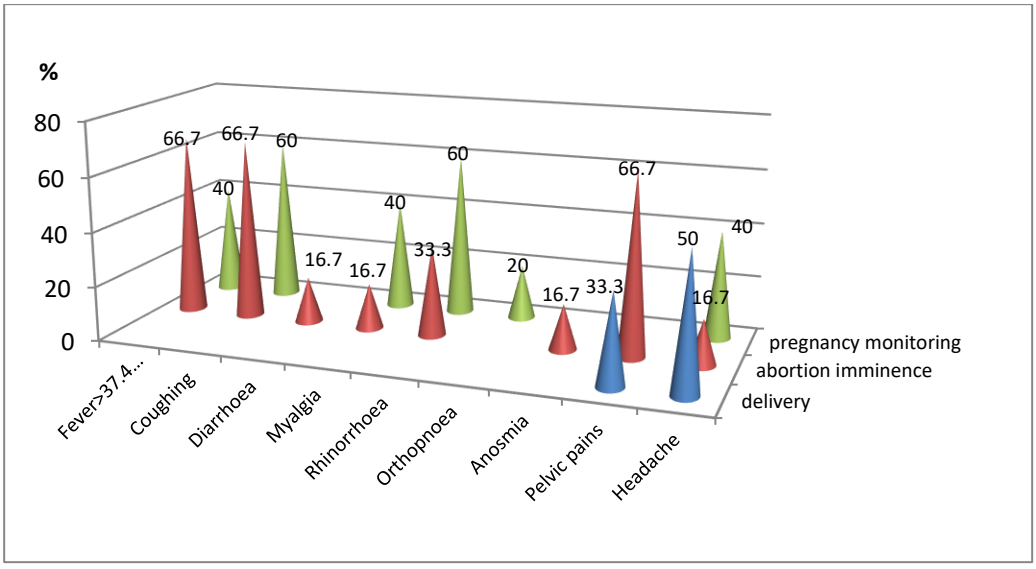

Figure 1. Frequency of signs and symptoms in symptomatic pregnant women upon admission.

3.2. Complete blood count (CBC)

Of the entire study group, 16.7% of the CBC values were normal, 83.3% had abnormal values of CBC with the highest frequency indicating anaemia, which was found in 33.3% of the pregnant

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women. Of the patients who were admitted for delivery of their baby, 45.5% had anaemia and lymphopoenia; 28.6% of the patients who were admitted due to a false labour or abortion imminence had a normal complete blood count, but 28.6% had anaemia, and 28.6% had lymphopoenia; a third of the patients who came for pregnancy monitoring had normal blood tests, while the other two third had either anaemia or lymphopoenia ($p = 0.001$). Asymptomatic patients did not have lymphopenia with thrombocytopenia or only lymphopenia regardless of the reason for hospitalization, compared to the group of symptomatic patients who had 33.3% both lymphopenia and lymphopenia with thrombocytopenia (Figure 2).

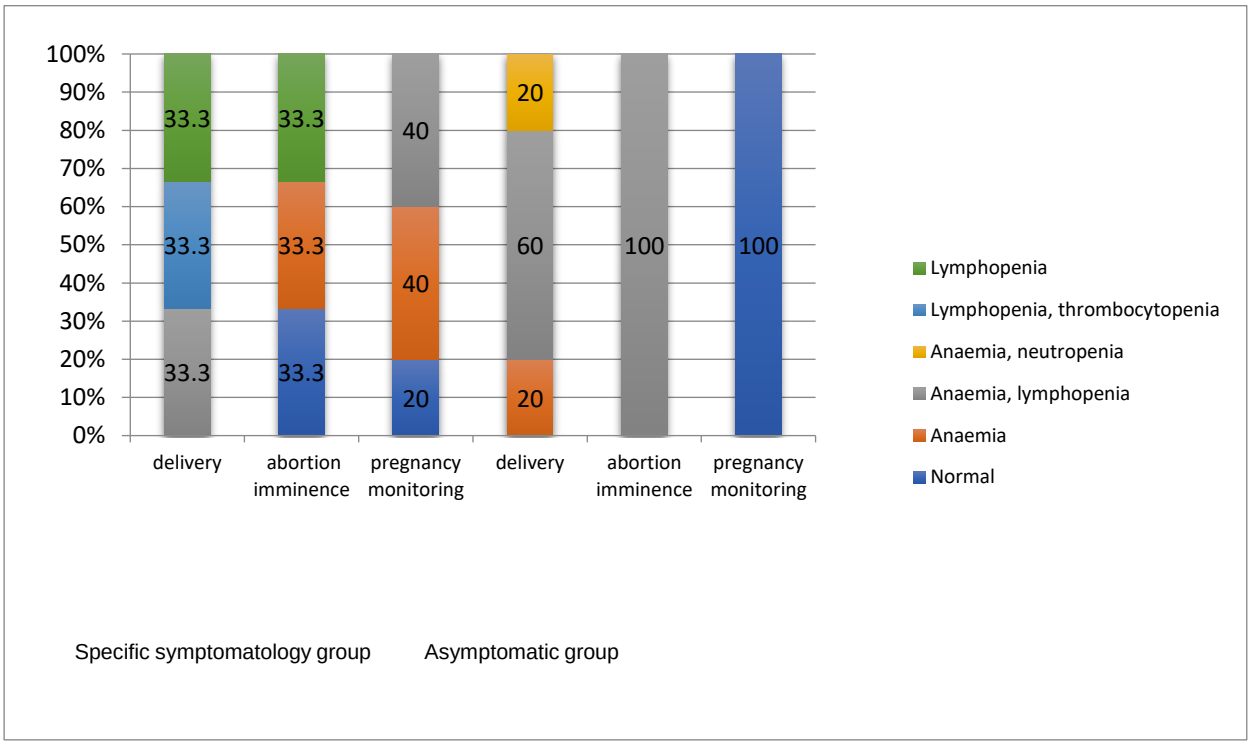

Figure 2. Correlation of admission diagnostic with CBC.

3.3. Fibrinogen

Individual fibrinogen values varied from 260 to 526.80 mg/dl, with an average level of 423.12 mg/dl ± 78.93, close to the median value (428.50 mg/dl), and the result of the homogeneity test suggested that fibrinogen was a continuous variable, so statistical significance tests could be applied. From the performed analysis, it could be seen that the fibrinogen values were normal or slightly higher values. Analysis of fibrinogen values differentiated according to symptomatic / asymptomatic patients does not show significant differences (Figure 3a, 3b).

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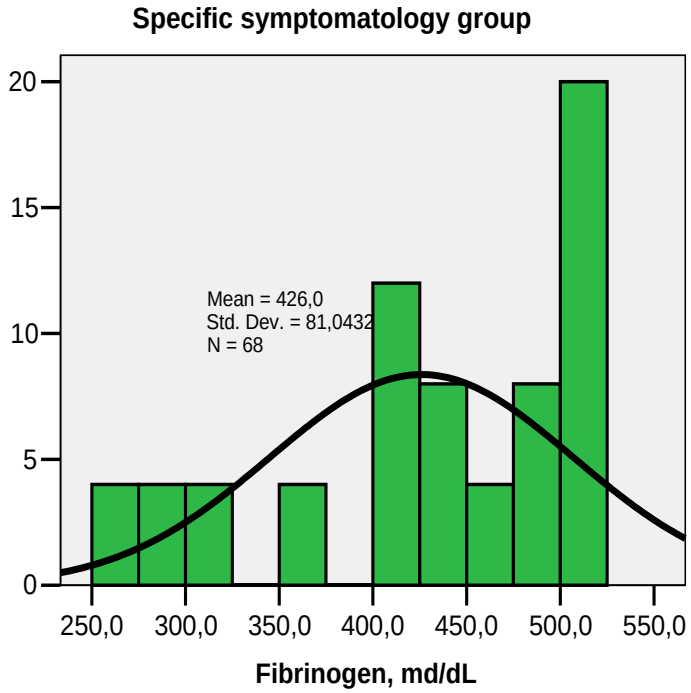

Figure 3a. Fibrinogen values histogram for symptomatic pregnant women in the sample.

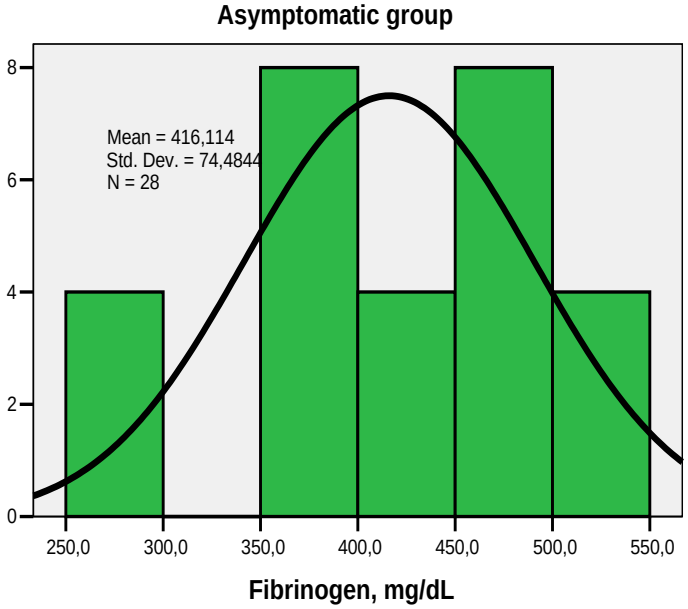

Figure 3b. Fibrinogen values histogram for asymptomatic pregnant women in the sample.

3.4. APTT (activated partial thromboplastin time)

Individual APTT values varied from 17.80 to 32.30 s, recording an average level of 21.98 s ± 2.98, close to the median value (22 s), and the result of the homogeneity test suggested that APTT was a continuous variable, so statistical significance tests could be applied. APTT values are lower in asymptomatic patients, associated with a higher risk of thrombosis (Figure 4a, 4b).

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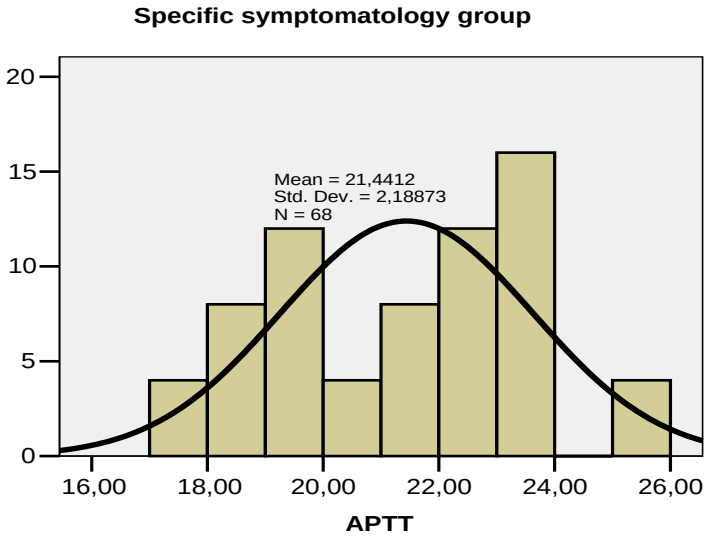

Figure 4a. APTT values histogram for the symptomatic pregnant women in the sample.

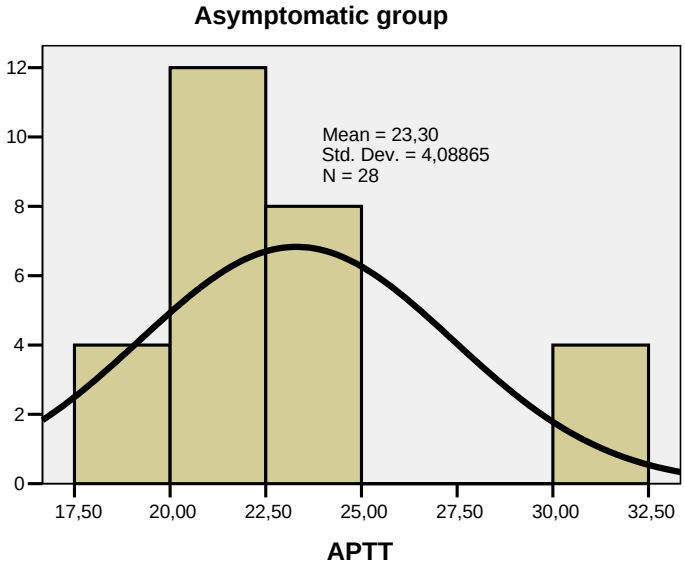

Figure 4b. APTT values histogram for the asymptomatic pregnant women in the sample.

3.5. INR (international normalized ratio)

Individual INR values varied from 0.19 to 1.90, recording an average level of 1.18 ± 0.41, close to the median value (1.20), and the result of the homogeneity test suggested that INR was a continuous variable, so statistical significance tests could be applied. The comparison between symptomatic and asymptomatic groups shows lower INR values in the asymptomatic group, values associated with risk of thrombosis (Figure 5a, 5b).

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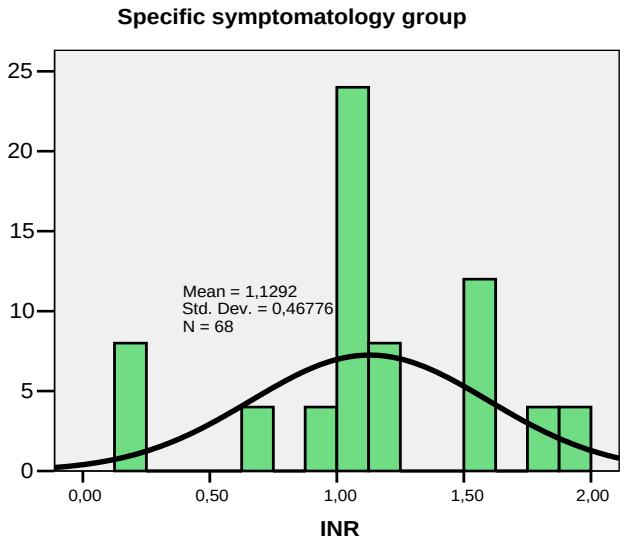

Figure 5a. INR values histogram for the symptomatic pregnant women in the sample.

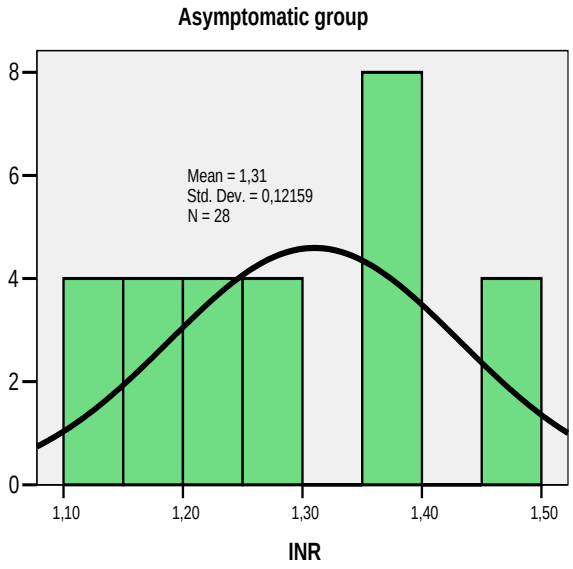

Figure 5b. INR values histogram for the asymptomatic pregnant women in the sample.

3.6. Prothrombin time (PT)

Individual PT values varied from 10.50 to 13.50 g/dl, recording an average level of 11.95 g ± 0.83, close to the median value (11.90 g/dl), and the result of the homogeneity test suggested that PT was a continuous variable, so statistical significance tests could be applied. A differentiated analysis on the studied groups does not show significant differences of PT values (Figure 6a, 6b).

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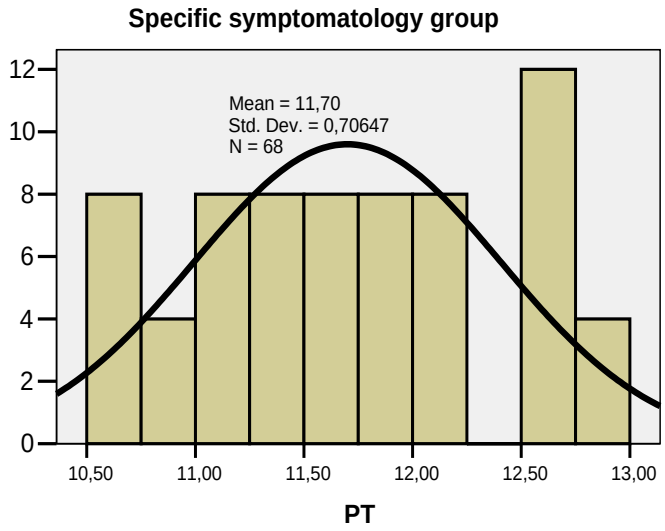

Figure 6a. PT values histogram for the symptomatic pregnant women in the sample.

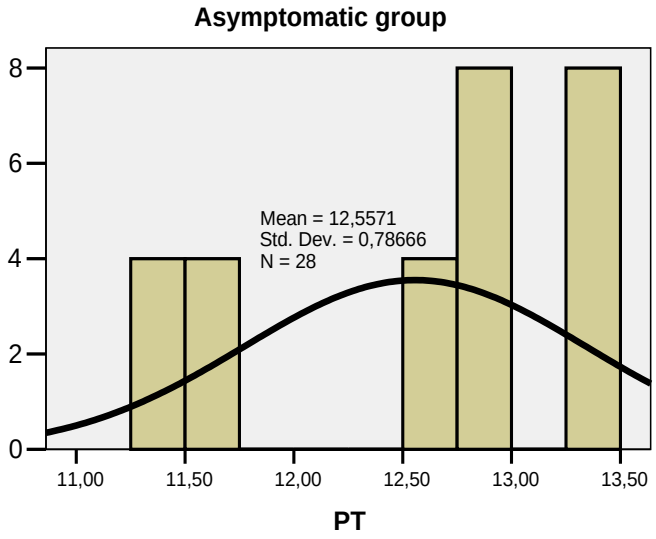

Figure 6b. PT values histogram for the asymptomatic pregnant women in the sample.

3.7. D-dimers

The analysis performed on the whole batch shows the highest average value of the D-dimers was encountered in patients with lymphopoenia (0.70 ± 0.32 µg/ml), and the lowest value of the D-dimers was seen in patients with anaemia (0.54 ± 0.19 µg/ml); nevertheless, the differences were statistically insignificant (p = 0.518). In patients with lymphopoenia and thrombocytopoenia, the D-dimer level was 0.65 ± 0.16 µg/ml. Patients with thrombocytopoenia had an average D-dimer level of 0.65 ± 0.16 µg/ml, which was slightly higher compared with the patients without this comborbidity (0.63 ± 0.18 µg/ml) (p = 0.999). In the studied cases, the D-dimers and fibrinogen were in direct, low intensity correlation (r = + 0.117; p = 0.585), and between D-dimers and total proteins, there was an indirect, low intensity correlation (r = -0.142; p = 0.509). Correlations of D-dimer values according to

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the blood count for the two groups show an association of higher values with lymphopenia in symptomatic patients and with anemia with lymphopenia in asymptomatic patients (Figure 7a, 7b).

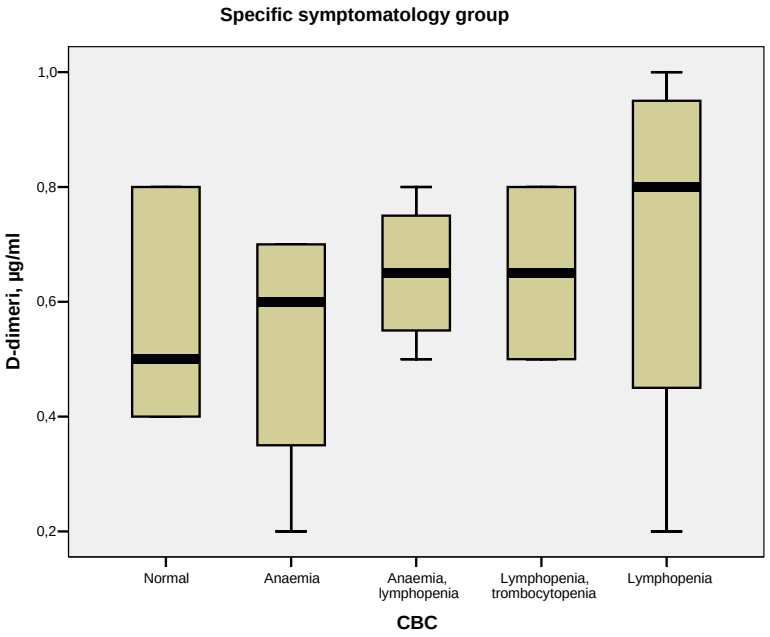

Figure 7a. Correlations of the D-dimer values with CBC- symptomatic group

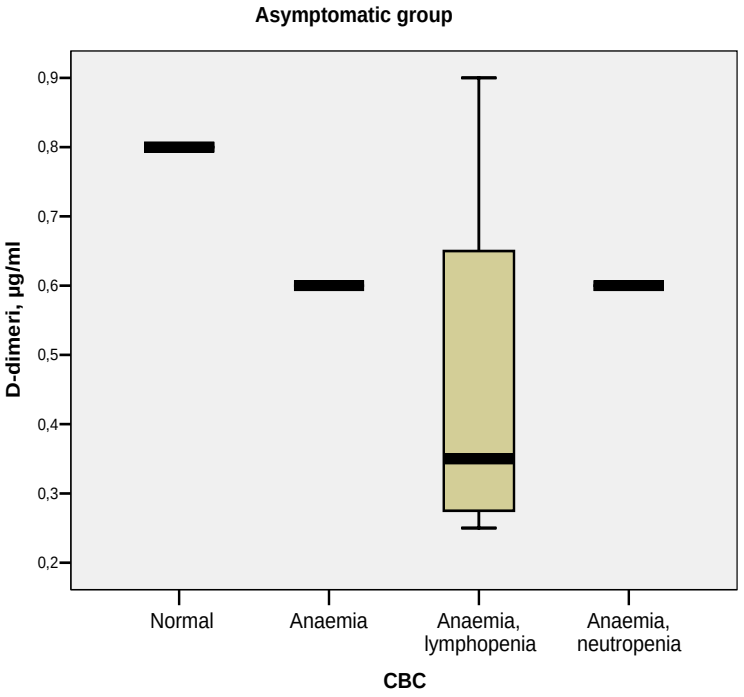

Figure 7b. Correlations of the D-dimer values with CBC- asymptomatic group

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3.8. RT-PCR SARS-CoV-2 screening

The first test upon admission was done with all 24 pregnant women, and all RT-PCR SARS-CoV-2 results were positive. In the 2nd PCR test, 20 out of 96 patients remained positive (20.8%); the number of days between the two tests varied between 5 and 15 days, with an approximate average level of 8 ± 4 days. Fever (AUC = 0.658; IC95%: 0.422–0.893; p = 0.286), a cough (AUC = 0.684; IC95%: 0.459–0.910; p = 0.214), rhinorrhoea (AUC = 0.632; IC95%: 0.386–0.877; p = 0.374) and pelvic pain (AUC = 0.658; IC95%: 0.422–0.893; p = 0.286) proved to be good predictors of the 2nd positive RT-PCR test result (Figure 8).

Of all the monitored laboratory parameters, the following proved to be good predictors of the 2nd positive RT-PCR test result: CBC (AUC = 0.626; IC95%: 0.381–0.872; p = 0.394), APTT (AUC = 0.658; IC95%: 0.314–1.002; p = 0.286), INR (AUC = 0.605; IC95%: 0.374–0.836; p = 0.374) and PT (AUC = 0.621; IC95%: 0.335–0.907; p = 0.414) (Figure 9).

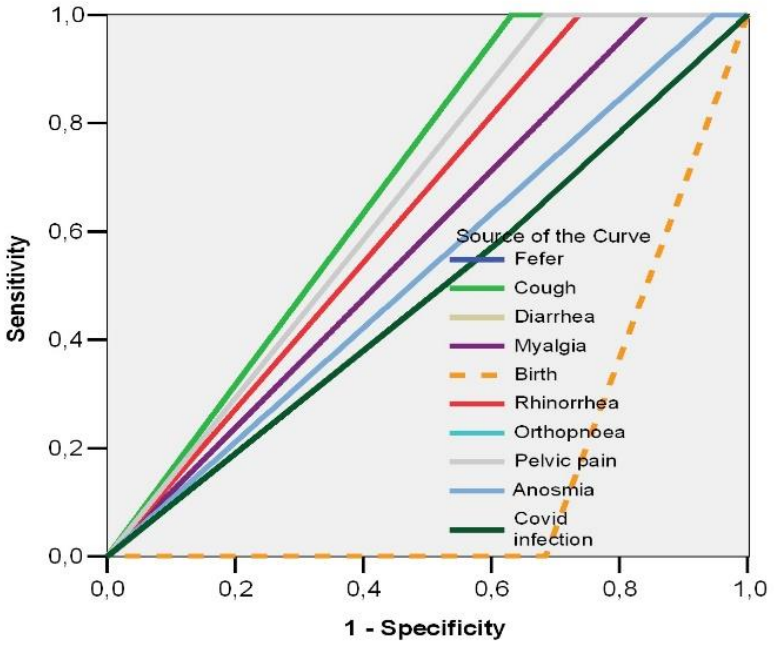

Figure 8. ROC curve: admission signs and symptoms as predictors of the 2nd positive RT-PCR test result.

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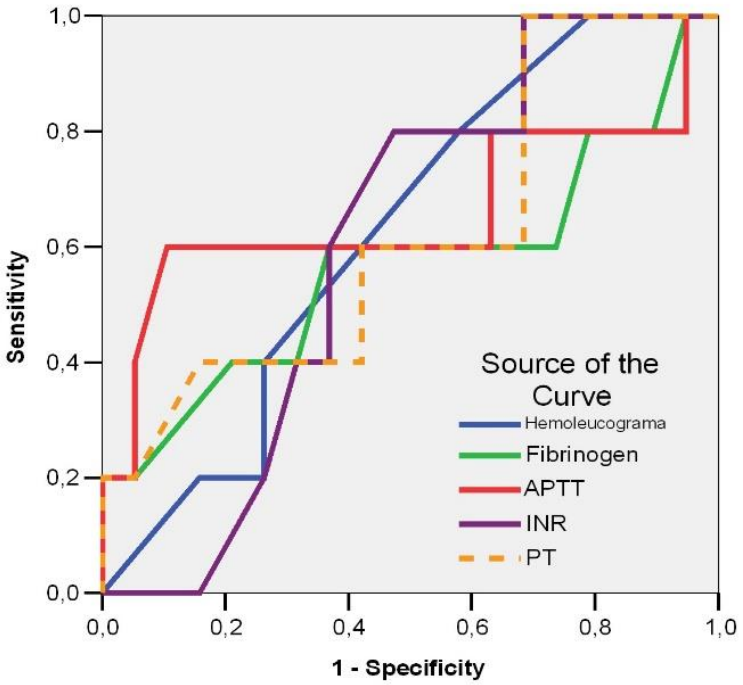

Figure 9. ROC curve: admission signs and symptoms as predictors of the 2nd positive RT-PCR test result.

3.9. Discharge tests

All 96 patients were discharged more than 14 days after the date of hospitalization (the time of the first positive PCR test), considering that they were only contagious, although 66.7% of them were still positive. By tracing the ROC curve, we emphasized the fact that the mother's age, gestational age, admission diagnostic and asymptomatic status were not good predictors of the discharge RT-PCR test. A cough (AUC = 0.625; IC 95%: 0.393–0.857; p = 0.327) and pelvic pain (AUC = 0.688; IC95%: 0.477–0.898; p = 0.142) proved to be good predictors of the discharge RT-PCR test. Of all the monitored laboratory parameters, the following proved to be good predictors of the discharge RT-PCR test: APTT (AUC = 0.609; IC 95%: 0.360–0.858; p = 0.391) and PT (AUC = 0.742; IC 95%: 0.512–0.971; p = 0.058) (Figure 10).

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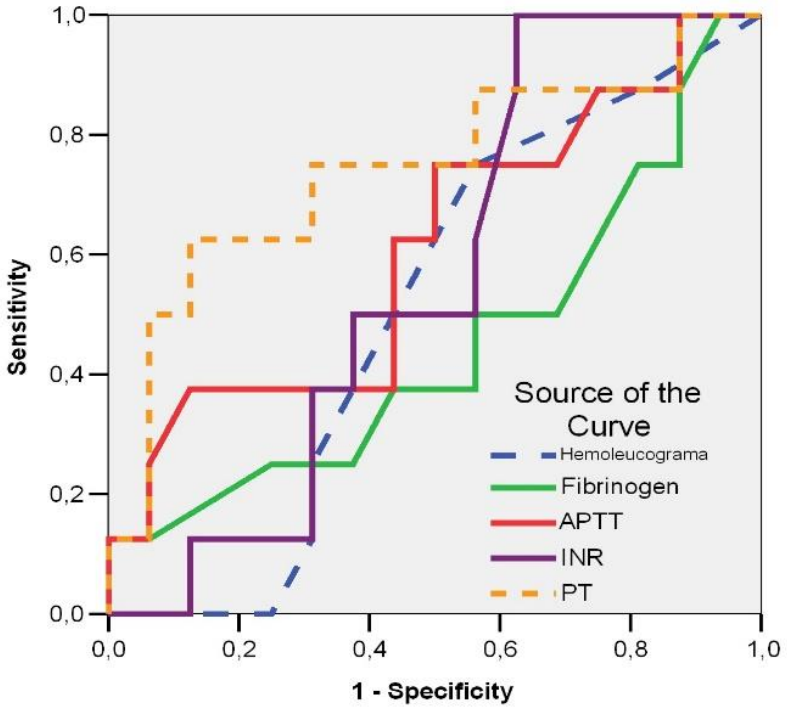

Figure 10. ROC curve: biomarkers predicting a positive RT-PCR test result upon discharge.

Discussion

Our study is retrospective and analysed 96 pregnant women infected with SARS-CoV-2, who were admitted either for pregnancy monitoring or delivery or due to mild respiratory symptomatology. All pacients were found positive upon admission. None of the patients experienced severe evolution of the SARS-CoV-2 infection, and none needed to be transferred to the ICU. While in hospital, the patients received adequate treatment for their pregnancy and also for the COVID infection. In our study we analyzed a group of 96 pregnant patients hospitalized for obstetric pathology in the hospital, but also a differentiated analysis on groups of symptomatic and asymptomatic pregnant women. Batch analysis shows that symptomatic positive SARS-CoV-2 patients have more frequent lymphopenia with thrombocytopenia and higher D-dimer values, while asymptomatic SARS-CoV-2 pregnant patients have a higher risk of thrombosis due to low APTT and INR values. As we already know that coagulation parameters suffer modifications during pregnancy, the study specifically monitored modifications of the following parameters: fibrinogen, APTT, PT, INR and CBC. Variation of these parameters was also monitored, depending on the subsequent PCR testing for SARS-CoV-2. It was established that modifications of the laboratory parameters directly correlated with positive SARS-CoV-2 tests. During a normal pregnancy, concentrations of fibrinogen and D-dimer values increase, and the number of platelets may decrease. The activated partial thromboplastin time (APTT) and the prothrombin time are both shorter due to the important increase in plasmatic concentrations of the majority of coagulation factors. In the COVID-19 infection, additional coagulation modifications may occur, which may reflect the disease severity, but solid data are still missing. An increase in D-dimer concentrations and longer APTT and PT were observed, which subsequently led to an increase in the international normalized ratio (INR). Because these modifications can be mistaken for increased pregnancy-induced coagulation factors, laboratory results may not initially seem abnormal (i.e.,

falsely higher in comparison with values in non-pregnant patients). It is interesting that platelet counts often have minimum modifications, but significant thrombocytopenia may occur in some cases. By correlation, data obtained on pregnant and non-pregnant patients suggest that the basic physiopathology is probably related to a (compensated) intravascular coagulation (DIC) condition. Unfortunately, such criteria cannot be applied to pregnant women, given the reduced capacity to exactly characterize their coagulopathy. Hypercoagulability enhances morbidity by increasing the risk of thromboembolism. Thromboembolic events may occur both during and after pregnancy. If the pregnant woman associates of several autoimmune diseases, such as thrombophilia and covid infection complete clinical examination and laboratory tests are important for the diagnosis of multiple autoimmune syndromes (15,16). Pregnancy itself increases the risk of thromboembolism, which is even higher postpartum. Due to additional coagulation modifications induced by the COVID-19 infection, this risk may be even higher. Despite all this, there are no solid data on pregnant women, and the COVID-19 infection seems less severe than in non-obstetric patients, potentially explaining why thromboembolic complications have not yet been reported. International perinatal societies and institutions have launched guidelines for the care of these patients. It is important to acknowledge that such orientations need to be updated frequently, as we continue to learn more about the evolution and impact of COVID-19 on pregnancy (17). Also, it is very important to emphasize the fact that synthetic drugs (such as anticoagulants, tetracycline, hydrochlorothiazide, statins, NSAIDS, beta blockers) have systemic and cutaneous toxic pharmacological side effects and that secondary Staphyloccocal or other types of infections can occur on the skin (with unnecessary cutaneous microbioma or incipient lesion changes) or in any other organ (18-25).

Limitations

Data regarding β-TG (β-thromboglobulin) as a platelet activation marker and TF (Tissue Fcator) as a coagulation activation marker were not available or similar.

Conclusion

Knowledge of clinical and laboratory parameters with prognosis utility can be extremely valuable in the management of COVID-19-infected pregnant women, establishing the best treatment options, balancing maternal and foetal/neonatal risks and benefits, and avoiding useless interventions. A better understanding of COVID-19-related coagulopathy in pregnant women may also be useful to guide treatment recommendations. Pregnancy may be a risk factor for coagulopathy in both symptomatic and asymptomatic positive pregnant women.

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Competing interests

The author reports no conflicts of interest in this work.

Disclosure

The authors report no conflicts of interest in this work.

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