Bulletin of the *Transilvania* University of Braşov
Series VI: Medical Sciences • Vol. 16 (65) No. 2 – 2023
https://doi.org/10.31926/but.ms.2023.65.16.2.8

THE IMPACT OF SARS-CoV-2 ON THE COAGULATION PROFILE OF PREGNANT WOMEN

S. CASAP [1] N. CIOBANU[1] M.A. MOGA[1]
C. MARTINESCU[1] A. HUDA[2] D. FESTILA[3]

Abstract: *A prospective study was conducted in the Clinic Hospital of Obstetrics and Gynecology "Dr. I.A. Sbârcea" Braşov, which included the hospitalized pregnant women diagnosed with COVID-19 from January 1, 2020, to March 8, 2022. The aim of the study was to evaluate the influence of SARS-CoV-2 on the coagulation status, the blood levels of coagulation parameters and the presence of disseminated intravascular coagulation in pregnant women with COVID-19.*
In order to analyze the coagulation status of the pregnant women we used the following parameters: Fibrinogen level, INR, D-dimer test and the presence of disseminated intravascular coagulation.
Following the study, we concluded that the occurrence of coagulation disorders in pregnant women is related to the severity of the SARS-CoV 2. LMWH administration generally improved the prognosis of pregnancy associated COVID-19 and mostly prevented the occurrence of severe thromboembolic complications such as disseminated intravascular coagulation or deep venous thrombosis.

Key words: *COVID-19, thromboembolic risk, Disseminated intravascular coagulation*

1. Introduction

In December 2019, Wuhan, Hubei Province, China, reported the first case of coronavirus disease 2019 (Covid-19), an acute viral illness. It belongs to the beta coronavirus genus and is a single-stranded RNA virus that enters cells by binding to ACE-2 (ACE2) receptors.

Asymptomatic sickness, multi-organ failure, and acute respiratory distress syndrome are at opposite extremities of the disease's spectrum. Hospitalization is necessary to treat hypoxia due to the onset of COVID-19 pneumonia. Patients

[1] Faculty of Medicine, *Transilvania* University of Braşov
[2] School of Medicine, Maldives National University of Malé, Republic of Maldives
[3] Faculty of Dental Medicine, Iuliu Hatieganu University of Medicine and Pharmacy of Cluj-Napoca, Romania
*Corresponding author: ciobanu.natalia89@gmail.com

are categorized as severe or critical if they require mechanical ventilation, CPAP, or high flow nasal oxygen and as moderate if they require oxygen supplementation. A limited fraction of infected people still requires critical care assistance despite modern dexamethasone treatment, with less than 5% of infected people being hospitalized. The range of symptoms with mild COVID-19 is wide, but typical symptoms include dyspnea, fever, altered taste or odor, and cough. [1]

Contrary to non-pregnant women of the same age, pregnant women show similarly, however they are more likely to be asymptomatic (more than two-thirds). Their symptoms typically match the physiological markers of pregnancy.

Similar to the majority of illnesses, including the earlier SARS-COV or MERS-COV pandemics, this infection is characterized by a high inflammatory state. Doctors have seen modified laboratory test findings, such as increased D-dimers, which indicate that COVID-19 causes an excessive inflammatory response known as the "cytokine storm." As shown in patients who presented with acute respiratory distress syndrome and in died patients, this inflammatory response seems to be related to illness severity, indicating that the intensity of the inflammatory response is a measure of disease severity. [2]

The inflammatory state's effects on coagulation have a direct pathogenic role, mostly by causing macro- and microthrombi (clots) in many organs, decreasing capillary blood flow, and escalating local lesions. Natural inhibitors in the blood, including antithrombin, may also drop in blood levels. One of the virus's primary targets is likely endothelial cells. Increased embolic consequences may be a sign of a more serious illness. The lungs, heart, brain, and kidneys are also likely affected by these events, which can cause multiple organ failure and even death. The inflammatory response is often far less intense in people with paucisymptomatic illness, on the opposite extreme. [3]

Maternal morbidity and death were notably high among pregnant women during earlier viral epidemics. When it comes to the present COVID-19 epidemic, pregnant patients' outcomes were no worse than those of the general public, but the inflammatory reaction in pregnant women with COVID-19 seems to be significant. Because they are often mistaken with pregnancy-related coagulation alterations, interpreting coagulation tests and potential abnormalities in pregnant patients can be even more challenging. Because the plasma concentrations of the majority of coagulation components significantly increase during pregnancy, the D-dimer values and fibrinogen concentration rise, the platelet count may drop, and the activated partial thromboplastin time (APTT) and prothrombin time can be both shortened. [4]

Additional coagulation alterations may happen after COVID-19, and these changes may indicate how serious the illness is. D-dimer concentrations increased, APTT and PT were both prolonged, and this resulted in a rise in the international normalized ratio (INR) values. Laboratory findings initially do not look abnormal (i.e., erroneously raised relative to non-pregnant levels) because these alterations are misinterpreted for pregnancy-induced elevations in clotting factors. It's interesting to note that although there may occasionally be

substantial thrombocytopenia, the platelet count frequently just shows minor changes. [5]

In order to fully describe the coagulation alterations brought on by COVID-19 in pregnant women and to pinpoint potential causes, there are currently insufficient data available. Coagulation factor concentrations are frequently abnormally low (less than 100% and frequently in the range of 40% to 60%), and changes occur in both the "intrinsic" and "extrinsic" pathways. They were not detected in the plasma of these pregnant women in the few instances when circulating anticoagulant antibodies were examined. A substantial coagulopathic condition with thrombocytopenia, delayed PT, and very increased D-dimer concentrations was seen in a recent report of three non-pregnant individuals with severe COVID-19. [6]

When analyzed collectively, evidence from both pregnant and nonpregnant individuals point to an intravascular coagulation (ICD) condition as the most plausible explanation for the pathophysiology behind aberrant laboratory findings. The International Society of Thrombosis and Hemostasis (ISTH) diagnostic criteria are often found to be positive in patients, especially in those with a severe form of the illness. We are less able to adequately define the coagulopathy of pregnant women since these criteria cannot be used on them. [7]

Given the dangers of general anesthesia in a patient with COVID-19 compared to those related to neuraxial anesthesia, extending APTT and PT offers a considerable problem for the anesthesiologist. Currently, it is believed that these aberrant coagulation parameters, which were previously discussed, do not prevent the administration of a neuraxial block since they are more likely due to hypercoagulability than an elevated risk of bleeding. In fact, a recently released guideline contends that in patients who are not bleeding, incorrect coagulation findings don't need to be corrected. According to research conducted in China, anesthetic problems and postpartum hemorrhage did not seem to be on the rise (although there may have been an increase in the usage of oxytocin agents). [8]

Morbidity is increased by hypercoagulability by raising the thromboembolic risk. Both during and after pregnancy, thromboembolic events can happen. The chance of developing thromboembolism during pregnancy and after delivery is increased. This risk could potentially be higher due to the extra coagulation alterations brought on by the COVID-19. This is based on information from non-pregnant individuals who have a significant COVID-19 infection and have experienced thromboembolic consequences. For instance, a recent study from the Netherlands found that COVID-19-infected non-pregnant ICU patients had a significant incidence (i.e., 31%) of thrombotic problems. [9]

High non-prophylactic dosages of anticoagulant medication, especially low molecular weight heparin (LMWH), have been proposed to lower COVID-19 mortality. A case-by-case review of thromboembolic risk, including non-COVID-19 risk factors and multiplicative risk factors linked with infection, should be taken into account even though specific indications are still unknown. When clinical symptoms are evident (and/or oxygen is necessary) during pregnancy in women who have COVID-19

who have at least moderate or severe thrombotic risk, the treatment of LMWH is advised. Because recovery from COVID-19 infection is difficult to define, it may be beneficial to keep thromboprophylaxis for a longer amount of time. However, experts advocate a shorter term of therapy to lower the chances of a neuraxial block or cesarean delivery. [10]

If it is acknowledged that there is a clear association between noteworthy biological abnormalities and the risk of thromboembolic consequences, then the advantages of thromboprophylaxis with LMWH exceed the bleeding risk in postpartum women with recent infection with COVID-19. Although vaginal birth carries a lower risk of thrombosis than cesarean delivery, it would be appropriate to advise LMWH in women who also have risk factors in addition to COVID-19. The recommendation for thromboprophylaxis following cesarean birth is much more obvious. Although the ideal time frame for anticoagulant therapy is uncertain, it should be tailored to the disease's severity.

Along with tissue plasminogen activator and antithrombin, fresh frozen plasma, tranexamic acid or fibrinogen should be taken into consideration in women who have postpartum hemorrhage with severe COVID-19. [11]

2. The objective of the study

The aim of the study is to evaluate the blood levels of coagulation parameters and the presence of disseminated intravascular coagulation in pregnant women with COVID-19 in order to appreciate the influence of COVID- 19 on the coagulation status.

3. Material and methods

The study was conducted at the Dr. I.A. Sbârcea Clinical Hospital for Obstetrics and Gynecology in Brașov. This was based on prospective research that was conducted from January 1, 2020, to March 8,2022.

The study's methodology comprised cohort, longitudinal, prospective research, and it covered pregnant women hospitalized throughout the aforementioned time period and diagnosed with COVID-19. The following inclusion criteria were used to form the study group:

- Pregnant women who have been diagnosed with SARS-CoV-2 in trimester I, II, or III;
- Patients admitted from other hospital departments who have been infected with SARS-CoV-2;
- Patients who are at least 16 years old.

The following patients were excluded from the study:

- Patients who were under the age of 16 at the time of admission;
- Patients who were known to have mental conditions.

After passing the patients through these filters, the cohort consisted of 555 patients diagnosed with SARS-CoV-2 infection.

Patients with COVID 19 were identified using virus detection methods. The initial method used a quick test to quickly find IgG and IgM antibodies to SARS-CoV-2 in samples of human whole blood, serum, and plasma. The second method used involved detecting SARS-CoV-2 viral RNA using a Real Time - PCR instrument. This method amplifies viral genetic material and is a particular test for identifying the infection.

To obtain the paraclinical results, devices from the Maternity laboratory were used, these being:

• Sysmex XN 550 – hematological analyzer used to analyze hemogram parameters;

•Cobas integra 400 plus – has a wide menu that includes complete biochemistry, specific proteins, therapeutic monitoring of therapeutic drugs and many others;

• ACL Top 350 - Automatic coagulation analyzer.

In order to analyze the coagulation of the pregnant women we used parameters such: fibrinogen level, international normalized ratio (INR), D-dimer test and the appearance of disseminated intravascular coagulation (DIC). In the research we made a comparison study of three clinical forms of SARS-CoV-2 infection.

4. Results

During the study period, 555 pregnant women prospectively studied, and their characteristics are summarized in Table 1.

Characteristics of the study population Table 1

Age (mean)	**27, 95 years**
Hospitalization days (mean)	3,99 days
Gestational age (mean)	33, 35
Mode of delivery, n, C-section	241
Birth weight (grams) (mean)	3025,26

The study group was divided in three subgroups according to the severity of the infection, as it can be seen in the table 2.

Subgroups according severity of the infection Table 2

Severity	**Number of patients**
Mild	453
Moderate	86
Severe/ Critical	16

Fibrinogel levels were studied in three clinical forms of the infection, and a comparison can be seen in the bellow chart. The results has shown that in mild and moderate form of COVID-19, no significant changes of fibrinogen levels were registered. In sever forms we observed low levels of fibrinogen, such as 70 mg/dL (figure 1).

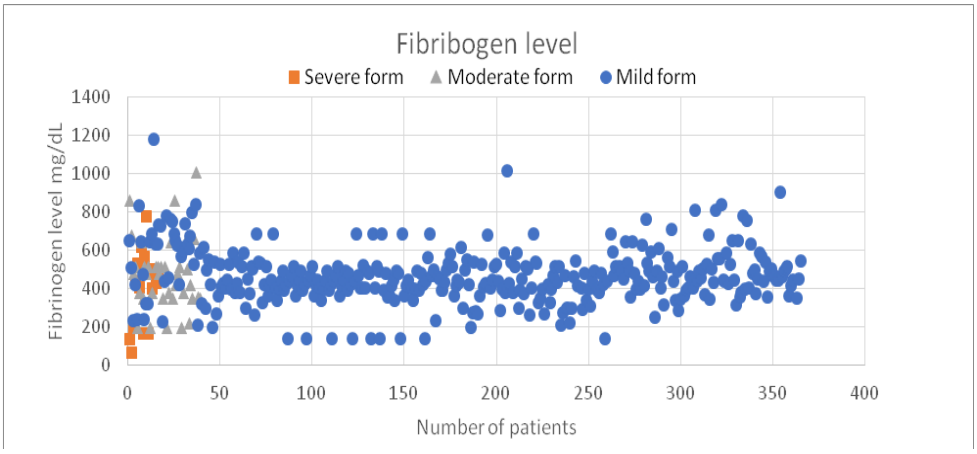

Fig. 1. *Comparison of fibrinogen levels in three clinical forms of COVID-19*

From the graph below it can be seen that the INR value did not fluctuate in the three forms of severity of the disease, having an average value of 0,99.

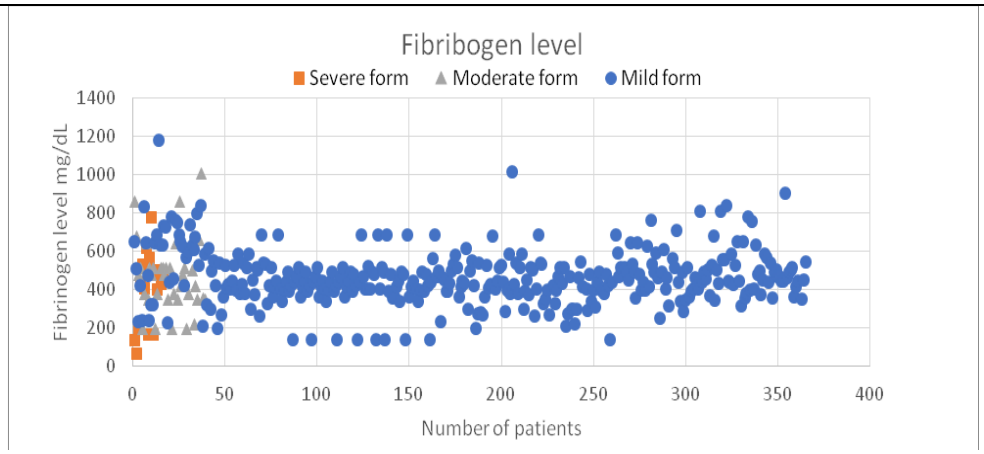

Fig. 2. *Comparison of INR levels in three clinical forms of COVID-19*

Regarding the value of D-dimers in the pregnant women included in the research, it can be observed that the highest values were recorded in severe forms of the disease, with a maximum value of 21,479 mg/ml.

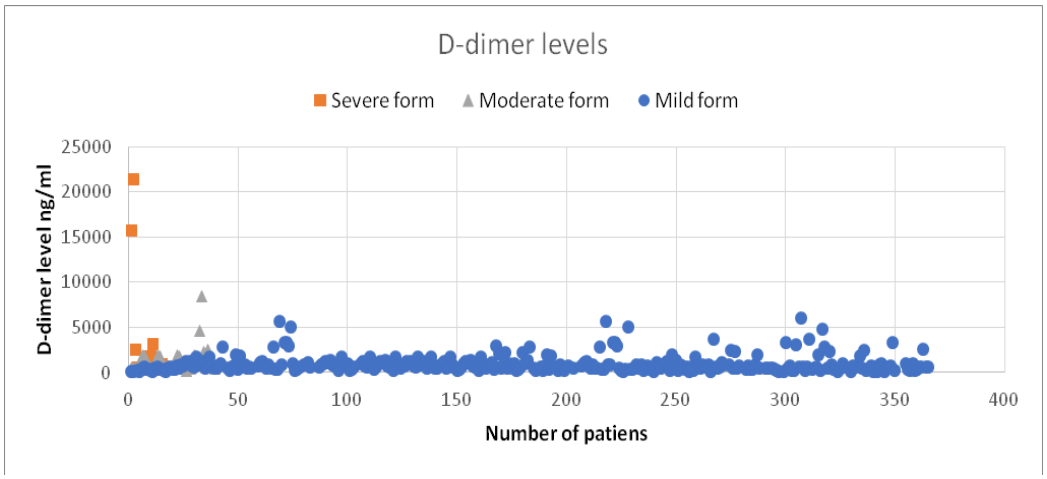

Fig. 3. *Comparison of D-dimer level in clinical forms of COVID-19*

The presence of disseminated intravascular coagulation is characteristic for severe forms of infection with the covid 19 virus, as a result we studied the

occurrence of CID in severe forms and found the presence of these complication in 31% of cases.

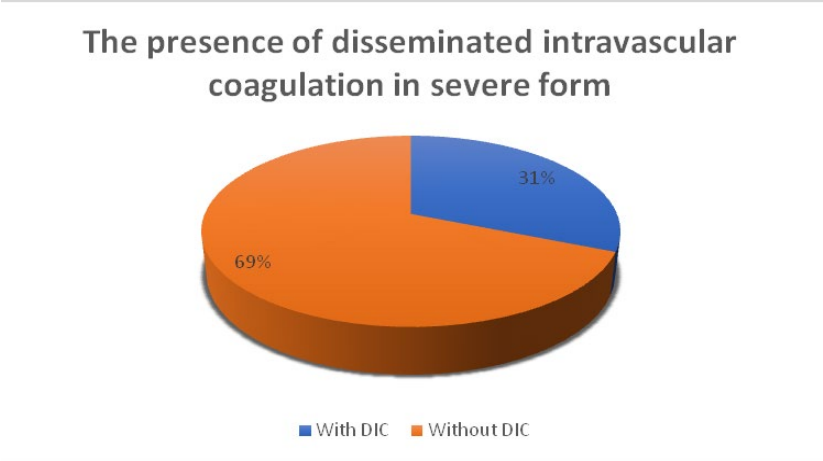

Fig. 4. *The presence of DIC in sever form of COVID-19*

Regarding the administration of low molecular weight heparin, during the study period it was administered in proportion to 100% of all patients with severe form of infection, 93% in medium forms and 89% in mild forms, as it can be seen in figure 5.

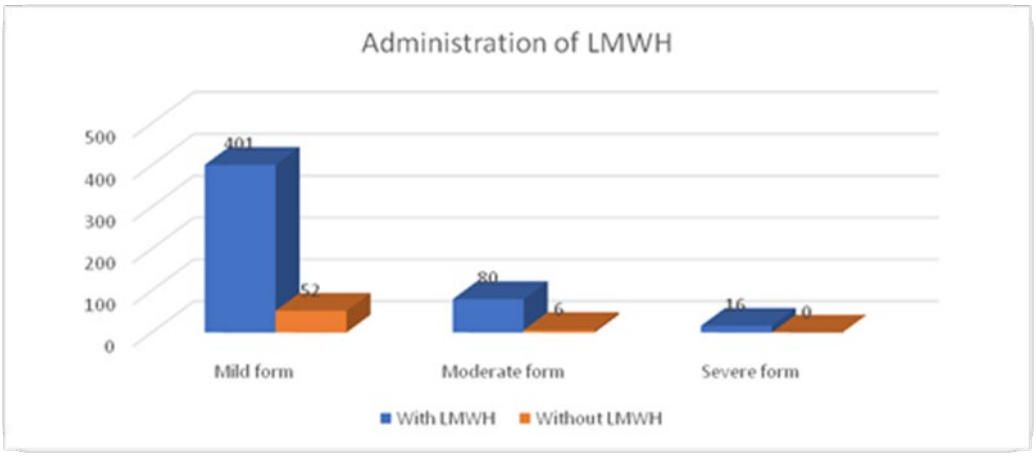

Fig. 5. *The administration of LMWH in patients with mild, moderate and severe forms of COVID-19*

5. Discussions

Pregnant women are a category of patients at higher risk of COVID-19 than the general population because to the increased risk of severe respiratory injury and other problems. Comorbidities and chronic illnesses considerably enhance the risk of problems in pregnant women. In order to avoid and treat COVID-19 thrombosis and coagulopathy, healthcare institutions must adopt clear recommendations that are centered on the pregnant mother and fetus. Since there aren't many research on pregnant women, this is challenging. [12, 13]

The cytokine storm caused by the SARS-CoV-2 is followed by a strong inflammatory response, as seen by the aberrant rise of D-dimers. Patients with COVID-19 have a higher mortality rate when their prothrombin time activity (PT-act) is less than 75%, as well as increased D-dimers and fibrin degradation products. The degree of the inflammatory response is closely correlated with the severity of the illness, with secondary coagulopathy serving as the primary mechanism, initially with micro thrombosis and afterwards with widespread thrombosis in numerous organs. Increased plasma levels of the inflammation markers or pro-inflammatory cytokines implicated can result from genetic differences that modulate this process. [14]

When a pregnant woman tests positive for COVID-19, it is sometimes necessary to monitor her for both respiratory impairment and possible problems with an acute onset (DIC). To do this, researchers look into the coagulation tests and fibrinogen levels. From a group of 1063 pregnant women with COVID-19, Servante et al. reported that 132 were hospitalized to critical care and 17 of them passed away, including two with DIC and two with PE. The findings support the current recommendation from the RCOG that all pregnant women admitted with confirmed or suspected COVID-19 receive prophylactic low molecular weight heparin (LMWH), unless delivery is anticipated within 12 hours, and continue this for 10 days after discharge. Haematological complications are more frequently observed in pregnant women with COVID-19 infection (1.26%) than in pregnant women without (0.45%). [15]

According to reports, COVID-19 pneumonia is linked to a rise of INR, aPTT, D-dimer, and fibrin degradation products. In fatalities linked to Covid-19, widespread intravascular coagulation patterns have been seen, and these deaths are characterized by prolonged aPTT and PT. Patients with Covid-19 infection in the general population had thrombocytopenia of 5–18%, PT prolongation of 2–11%, and aPTT prolongation of 26%. It has been demonstrated that the progression of these four characteristics is correlated with the disease's severity. [16]

The particular impact mediated by the virus and the severe inflammation followed by hemostatic problems are taken into consideration when determining the etiopathogenic mechanisms of coagulopathy produced by acute SARS-CoV-2. With the increased risk of thrombosis coming from the activity of cytokines and inflammatory mediators, the degree of participation of the two processes is not entirely understood. By lowering inflammation, one potential treatment approach would be connected to thrombosis prevention.

6. Conclusions

Following the study, it was concluded that the occurrence of coagulation disorders in pregnant women is related to the severity of the SARS-CoV-2. At the same time, the severity of the infection is given by the change in the coagulation status, which creates a vicious circle.

Another important aspect observed during the study is that the administration of LMWH improved and prevented the occurrence of complications such as disseminated intravascular coagulation or deep venous thrombosis.

Acknowledgements
No Acknowledgements

References

1. Rad HS, Röhl J, Stylianou N, et al. The Effects of COVID-19 on the Placenta During Pregnancy. *Front Immunol*; 12. Epub ahead of print 15 September 2021. DOI: 10.3389/fimmu.2021.743022.
2. Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. *Journal of Clinical Virology* 2020; 127: 104362.
3. Lillicrap D. Disseminated intravascular coagulation in patients with 2019-nCoV pneumonia. *Journal of Thrombosis and Haemostasis* 2020; 18: 786–787.
4. Louie JK, Acosta M, Jamieson DJ, et al. Severe 2009 H1N1 Influenza in Pregnant and Postpartum Women in California. *New England Journal of Medicine* 2010; 362: 27–35.
5. Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. *Clinical Chemistry and Laboratory Medicine (CCLM)* 2020; 58: 1131–1134.
6. Zhang L, Dong L, Ming L, et al. Severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) infection during late pregnancy: a report of 18 patients from Wuhan, China. *BMC Pregnancy Childbirth* 2020; 20: 394.
7. Heslet L. Clinical implications of a validated scoring system for disseminated intravascular coagulation*. *Crit Care Med* 2004; 32: 2548–2549.
8. Vincent J-L, Levi M, Hunt BJ. Prevention and management of thrombosis in hospitalised patients with COVID-19 pneumonia. *Lancet Respir Med* 2022; 10: 214–220.
9. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 2020; 191: 145–147.
10. Sénat M-V, Sentilhes L, Battut A, et al. Postpartum practice: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF). *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2016; 202: 1–8.
11. Wang J, Hajizadeh N, Moore EE, et al. Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): A case series. *Journal of Thrombosis and Haemostasis* 2020; 18: 1752–1755.
12. Varlas VN, Borș RG, Plotogea M, et al. Thromboprophylaxis in Pregnant Women with COVID-19: An Unsolved

Issue. *Int J Environ Res Public Health* 2023; 20: 1949.
13. Villar J, Ariff S, Gunier RB, et al. Maternal and Neonatal Morbidity and Mortality Among Pregnant Women With and Without COVID-19 Infection. *JAMA Pediatr* 2021; 175: 817.
14. Luo H, You C, Lu S, et al. Characteristics of coagulation alteration in patients with COVID-19. *Ann Hematol* 2021; 100: 45–52.
15. Servante J, Swallow G, Thornton JG, et al. Haemostatic and thrombo-embolic complications in pregnant women with COVID-19: a systematic review and critical analysis. *BMC Pregnancy Childbirth* 2021; 21: 108.
16. Tang N, Bai H, Chen X, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *Journal of Thrombosis and Haemostasis* 2020; 18: 1094–1099.