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Case Repor

A Case Report of An Early Neonatal Death Accompanied by Disseminated Intravascular Coagulation Caused by Severe Acute Respiratory Syndrome Coronavirus-2 Infection

Gorana P. Mitić[1], Igor G. Spasić[2], Milana D. Panjković[1,3], Biljana A. Vučković[1,3]

[1] Department of Pathophysiology and Laboratory Medicine, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia
[2] Health Care Institution for Laboratory Diagnostics Medlab, Novi Sad, Serbia
[3] Center of Laboratory Medicine, Clinical Center of Vojvodina, Novi Sad, Serbia

SUMMARY

Introduction: Women with coronavirus disease 2019 (COVID-19) during pregnancy are more likely to develop a severe form of the disease and have unfavorable pregnancy outcomes.
Case report: We report the case of a 21-year-old woman diagnosed with disseminated intravascular coagulation (DIC) caused by COVID-19, and subsequent early neonatal death. She was referred to the hospital at 29 gestational weeks due to progression of COVID-19 symptoms. Increased plasma thrombin and fibrinolytic activity were observed on admission, and low molecular weight heparin and antibiotic therapy were started immediately. After fully developing laboratory DIC was diagnosed, an emergency Cesarean section was performed. Upon delivery severe perinatal asphyxia was diagnosed in a neonate, manifested as atony and cardiac arrest. Despite cardiopulmonary resuscitation, the newborn passed away three hours after birth. The mother recovered in several days, she was discharged in good clinical condition.
Conclusion: The presented clinical case indicates the importance of an early diagnosis of DIC in SARS-CoV-2-positive pregnant women, timely therapeutic decisions, psychological support, and long-term follow-up of physical and psychological conditions.

Keywords: COVID-19, Disseminated Intravascular Coagulation, Early Neonatal Death, Pregnancy, SARS-CoV-2

INTRODUCTION

From the moment the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was identified medical experts and scientists faced numerous challenges in the detection and treatment of the various disease forms. To date, it has been proven that the majority of severe complications and deaths related to SARS-CoV-2 arise from hemostasis system disorders, affecting all three components of Virchow's triad [1,2]. Women with

Corresponding author:
Full Professor Biljana A. Vučković, MD, PhD
Specialist in Internal Medicine, Subspecialist in Clinical Genetics
Department of Pathophysiology and Laboratory Medicine, Faculty of Medicine Novi Sad, University of Novi Sad, Hajduk Veljkova 3, 21000 Novi Sad, Serbia
E-mail: biljana.vuckovic@mf.uns.ac.rs

coronavirus disease 2019 (COVID-19) during pregnancy are more likely to develop a severe form of the disease [3]. A unique complexity of maternal-fetal immune interactions is ensuring that a fetus, as a semi-allograft, can evade alloantigens and subsequent rejection. For this purpose, the maternal immune system during pregnancy is in a state of remarkable immunomodulation, i.e. relative immunosuppression, predisposing the mother to more severe infections. Concomitantly, multifactorial physiological changes of hemostasis during pregnancy are creating a pronounced hypercoagulable state [4]. A combination of these circumstances could account for a significantly higher risk for severe outcomes of SARS-CoV-2 infection in pregnant compared to non-pregnant women. Severe outcomes include thrombotic complications such as myocardial infarction and venous thromboembolism [5]. Adverse effects of COVID-19 on pregnancy outcomes are often attributed to placental insufficiency, caused by uteroplacental vascular malperfusion and thrombosis of fetal intervillous vessels [6].

Disseminated intravascular coagulation (DIC) is the most severe form of excessive activation of the hemostatic mechanism, usually triggered by endothelial damage and dysfunction, leading to consumptive coagulopathy and secondary hyperfibrinolysis. If this disorder occurs during pregnancy, both mother and fetus can be life-threatened. The incidence of DIC in SARS-CoV-2 infection during pregnancy has been reported as 0.7 to 1.3% in two large studies [7,8].

Although some systematic reviews and meta-analyses address the outcome of coronavirus infection during pregnancy, there is still a lack of data in the literature on this topic, limiting both timely prediction of potential negative outcomes and management of these patients. It is important to emphasize that while large studies provide information about the presentations and outcomes of the disease, case reports can offer more detailed insights into key clinical details.

In our report, we present the clinical course of SARS-CoV-2 viral infection in a pregnant woman complicated by the development of DIC.

CASE REPORT

The patient gave her consent for case to be published in the scientific journal Hospital Pharmacology - International Multidisciplinary Journal as an anonymous paper. A 21-year-old woman, pregnant for the first time, without comorbidities, or any thrombotic risk factors, was admitted to the COVID unit of the tertiary healthcare institution of the university rank in October 2021, at 29 weeks of gestation due to the progression of symptomatic SARS-CoV-2 viral infection, which started 10 days before admission. She complained of headache, malaise, fatigue, occasional cough and fever. She was tested PCR-positive for SARS-CoV-2 seven days before admission and treated on an outpatient basis with antipyretics, and supportive therapy. The patient voluntarily did not receive COVID-19 vaccine.

Clinical examination findings at the time of admission were as follows: body temperature 36.5° C, blood pressure 90/60 mmHg, heart rate 92/min, oxygen saturation 99%, respiration rate 15/min, without contractions or pain, without bleeding, regularly feeling the fetal movements. The ultrasound examination showed a living fetus in the cephalic position, with a physiological heart rate and estimated weight of 1090 g. Fetal Doppler flows were normal, with umbilical artery pulsation index AU PI 0.99. The placenta was anterior with ultrasound signs of diffuse point calcifications.

Laboratory tests at admission (Table 1), revealed moderate thrombocytopenia, moderate prolongation of activated partial thromboplastin time (aPTT), extremely increased thrombin activity of plasma, and slightly increased level of global activity of the fibrinolytic mechanism. A mixing study of plasma (in a 1:1 ratio) revealed coagulation factor deficiency. Based on the clinical condition and results of laboratory tests, low molecular weight heparin (LMWH) – nadroparin (Fraxiparine, Aspen Notre Dame de Bondeville, solution, 0,1 ml per 10 kg of body weight, subcutaneous injections), and antibiotics - amoxycillin + clavulanic acid (Amoksiklav, Lek farmacevtska družba DD, tablets, 625 mg three times per day, orally) and metronidazole (Orvagil, Galenika AD Beograd, tablets, 400 mg three times per day, orally) were started immediately. Cardiotocographic (CTG) monitoring was performed regularly until the worsening of the reactive curve on CTG was observed and control laboratory findings of hemostatic mechanism (Table 1), revealed in vitro fully developed DIC (with newly devel-

Laboratory Test	At the time of admission to the hospital	12 hours after admission to the hospital (before CS)	18 hours after admission to the hospital (before CS)	2 hours after CS	24 hours after CS
WBC (x10^9/L)	3.72	3.65	3.86	9.90	7.54
RBC (x10^{12}/L)	3.95	3.78	3.80	2.80	3.40
HGB (g/L)	123	117	118	88	97
HCT	0.35	0.33	0.33	0.25	0.32
PLT (x10^9/L)	98	80	79	86	94
aPTT (R)	1.52	1.55	1.56	1.40	1.27
PT (R)	1.09	1.47	1.50	1.36	1.20
TT (R)	1.30	1.36	1.88	1.89	1.53
FBG (g/L)	3.0	2.0	1.34	1.33	1.97
D-dimer (mg/L)	102.40	51.20	49.40	27.40	2.25
ECLT (min)	100	90	85	80	100
CRP (g/L)	71.12	60.9	53.94	28.97	16.45
PCT (ng/L)	0.26	0.33	0.34	0.28	0.10
LDH (IU/L)	472	513	645	545	327
AST (IU/L)	95	103	125	97	54
ALT (IU/L)	37.8	40.1	43.5	39.8	30

Table 1. Results of the patient's laboratory tests before and after Cesarean section

WBC - white blood cells
RBC - red blood cells
HGB - hemoglobin
HCT - hematocrit
PLT - platelets
aPTT - activated partial thromboplastin time
PT - prothrombin time
TT - thrombin time
FBG - fibrinogen
ECLT - euglobulin clot lysis time
CRP - C-reactive protein
PCT - procalcitonin
LDH - lactate dehydrogenase
AST - aspartate aminotransferase
ALT - alanine aminotransferase
CS - cesaeran section

oped prolongation of prothrombin time and hypofibrinogenemia), prompting the decision for an emergency cesarean section (CS). The patient's clinical condition was stable, she received two units of fresh frozen plasma before CS, and twenty-one hours after admission to the hospital she gave birth to a female newborn. The surgical procedure, performed with general anesthesia, went without any severe bleeding. There was no need for intraoperative transfusion.

Control laboratory findings of hemostatic mechanism (Table 1) showed a significant decrease in thrombin activity of plasma and normalization of activity of coagulation factors of prothrombin complex, thus 6 hours after cesarean section low molecular weight heparin in prophylactic dosages was administered (nadroparin 0,1 ml per 10 kg of body weight). The further clinical course was complicated with intraabdominal bleeding, and ultrasound examination revealed subhepatic hematoma (114x54 mm), followed by discontinuation of LMWH, abdominal drainage, and transfusion of 1 unit of fresh frozen plasma and 2 units of RBC. The patient's clinical condition, 24 hours after cesarean section was stable, and laboratory findings showed complete normalization of hemostatic parameters (Table 1). The hematoma size remained unchanged, with no other clinical signs of bleeding. Early mobilization was started, and LMWH in sub-prophylactic dose was re-administered (nadroparin 0,1 ml per 20 kg of body weight). A chest X-ray showed no signs of pneumonia or any other lung pathology. Control of hemostatic parameters during the next day showed an increase in D-dimer values and the dosage of LMWH was increased to full preventive dosages (nadroparin 0,1 ml per 10 kg of body weight) that were administered until the patient was dismissed twelve days after admission, in very good clinical condition. Professional psychological support for the patient was started during hospitalization and continued on an outpatient basis.

The newborn's Apgar score was 0 in the 1st, and 3rd minute and 1 in the 5th minute. After childbirth, the baby was in very poor condition, with perinatal asphyxia, atonic, without heart activity. Cardiopulmonary resuscitation (CPR) according to ERC guidelines was started. Response was successful after 10 minutes and mechanical ventilation was applied. Blood analyses showed severe mixed acidosis and hyperglycemia, anemia, and thrombocytopenia. RBC transfusion was applied. Unfortunately, three hours after it was born, a severe decrease in heart rate and desaturation appeared and the newborn passed away three hours after birth, despite CPR measures. Autopsy of the newborn found elements of immaturity, bleeding in the interalveolar spaces with the presence of hyaline membranes in the alveoli of the lungs (neonatal respiratory distress syndrome), which more likely led to

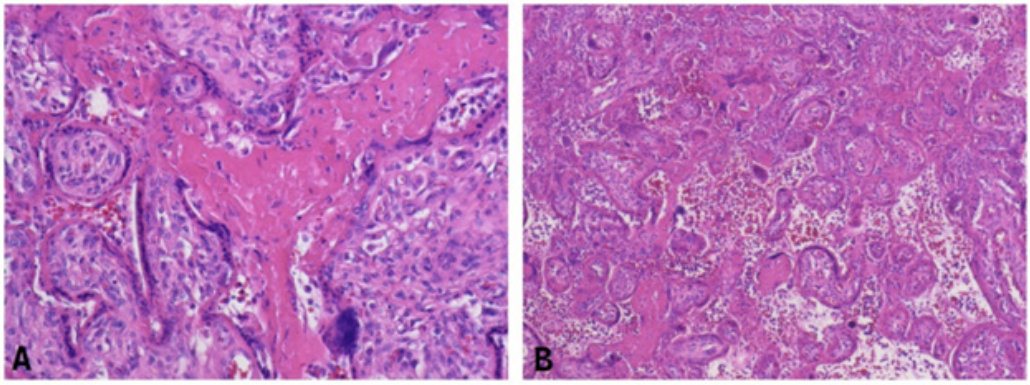

Figure 1. Fibrin deposition (A) + Villitis, HE (B) x100

Table 2. Results of the patients' hemostasis and thrombophilia laboratory tests three months after hospitalization

Laboratory Test	Result
PLT (x10^{-9}/L)	304
aPTT (R)	0.84
PT (R)	0.88
TT (R)	1.02
FBG (g/L)	2.76
D-dimer (mg/L)	0.45
ECLT (min)	120
AT (%)	98
APC (R)	4.14
fPS Ag (%)	95.1
PC Ac (%)	94
LA1 (R)	0.98
FV Leiden	no mutation
FIIG20210A	no mutation

PLT - platelets
aPTT - activated partial thromboplastin time
PT - prothrombin time
TT - thrombin time
FBG - fibrinogen
ECLT - euglobulin clot lysis time
AT - antithrombin
APC - activated protein C
fPS Ag - free protein S antigen
PC Ac - protein C activity
LA1 - lupus anticoagulant
FV Leiden - factor V Leiden

peripheral asphyxia and death.

Microscopic examination of the placenta showed slightly edematous membranes, while the umbilical cord and decidua were normal. Placental villi focally were edematous and infiltrated with a small number of lymphocytes and neutrophils with an increased number of syncytial knots. Fibrin accumulation was found in intervillous spaces as well as inflammatory cells with a predominant presence of neutrophils and lymphocytes. The diagnosis of acute intervillitis and villitis was established (Figure 1).

The patient was discharged on the 12th day of hospitalization in good clinical condition. Long-term follow-up showed that the patient was in good physical condition, and all laboratory tests were completely normal, but she was still receiving psychological assistance. As the patient was young at the moment of hospitalization and had no comorbidities or recognized risk factors for thrombotic complications, we decided to perform thrombophilia testing three months after dismission from the hospital, to have a better clinical perspective regarding the patient's thrombophilic profile, especially having in mind possible future pregnancies. According to the results (shown in Table 2), we excluded inherited or acquired thrombophilia.

DISCUSSION

The individual thrombophilic profile of women significantly changes during pregnancy to prepare organisms for severe labor bleeding. Stasis of venous blood flow and shift of the coagulation in the direction of increased thrombin activity is leading to a 4-6-fold increased risk of venous thromboembolism [2]. „Coronavirus-associated coagulopathy" is a prothrombotic condition that frequently complicates SARS-CoV-2 viral infection and can be specifically dangerous in pregnant women. Even mild or asymptomatic maternal COVID-19 cases can sometimes lead to the most severe disorder of hemostasis in the form of DIC. The majority of these cases were diagnosed in the late 2nd or early 3rd trimester with decreased fetal movement, and abnormal heart rate patterns, leading to the cesarean delivery soon after admission. High rates of perinatal morbidity require early recognition and treatment of DIC, to stop the systemic activation of the procoagulant factors in time and prevent the subsequent complications [9].

The pathophysiology of DIC in pregnancy has been described as follows: „Any condition that disrupts the integrity of the trophoblast can lead to a release of a large amount of potent Tissue Factor that will activate the coagulation cascade and propagate an inflammatory response that can easily become systemic, leading to uncontrolled thrombin generation and the subsequent development of DIC" [10].

Results of histopathology analysis of the placenta in our case report match those reported in a series of 64 fetal deaths and 4 neonatal deaths in maternal COVID-19 cases, presented with histiocytic intervillositis and increased fibrin deposition [11]. Based on this, we suspect that in the case of our patient maternal COVID-19 triggered placentitis, DIC, and early neonatal death. The first mandatory step to deal with such clinical conditions is to recognize the development of DIC as soon as possible. In our case, this disorder was recognized in an early stage, in the moment of excessive thrombin activity stimulation before secondary fibrinolysis was triggered, and before hemorrhagic syndrome appeared. This prompted our decision to initiate heparin therapy, and the significant decrease in D-dimer levels confirmed the response to treatment. The first principle of treatment for DIC is to remove or manage the underlying cause [10], presumably the placenta in this case. As signs of the critical fetal condition occurred, the decision to approach to cesarean section was timely made, significantly increasing the chances for a favorable pregnancy outcome. Early neonatal death in our case report, emphasizes the severity of COVID-19 during pregnancy. Since even mild and moderate cases of the disease, in pregnant women with no preexisting risk factors and comorbidities, can lead to dismal pregnancy outcomes, one should consider a possible application of antiviral drugs.

Though pregnant women were excluded from most of the studies dealing with antiviral therapy in COVID-19, there are, however, no known teratogenic effects of remdesivir, and it is therefore considered a treatment option in pregnancy [12, 13]. It should be emphasized that the dominant virus type in our population at that time was the Delta variant and that CDC surveillance data showed that maternal COVID-19 was associated with a relative risk of stillbirth of 1.47 (95% CI 1.27-1.71) before July 2021 (pre-Delta) compared to 4.04 (95% CI 3.28-4.97) from July to September 2021 (Delta surge) [14].

Intensive follow-up of the patient after cesarean section in this clinical situation is crucial, as triggered coagulation and fibrinolysis maintain an increased risk for both thrombotic and hemorrhagic complications in the upcoming days. That is why hemostasis parameters should be investigated daily and therapy should be adjusted according to the laboratory test results and clinical condition.

The psychological aspect of this situation, especially taking into account the absence of family and social support due to the isolation of SARS-CoV-2-positive patients, should not be neglected, and the patient should be supported by a professional from the very beginning.

In our patient's case, as she was young and without risk factors or comorbidities, we decided to conduct thrombophilia testing after the postpartum period to gain a clearer understanding of her thrombophilic profile. This information was crucial for monitoring and managing subsequent pregnancies, addressing both medical and psychological aspects for the patient amid ongoing uncertainties.

CONCLUSION

As COVID-19 is likely to continue occurring in upcoming seasons, inevitably leading to more cases of DIC in pregnant women, we aim to highlight this topic and potentially contribute our experience to improving disease outcomes. The presented clinical case underscores the importance of early diagnosis of DIC in SARS-CoV-2-positive pregnant women, timely therapeutic decisions, psychological support, and long-term follow-up of physical and psychological conditions.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

REFERENCES

1. Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. ICM. 2020;46(6):1089–1098.

2. Dobrijević D, Katanić J, Todorović M, Vučković B. Baseline laboratory parameters for preliminary diagnosis of COVID-19 among children: a cross-sectional study. Sao Paulo Med J. 2022;140(5):691-696.

3. Hammad WAB, Al Beloushi M, Ahmed B, KOnje JC. Severe acute respiratory syndrome (SARS) coronavirus-2 infection (COVID-19) in pregnancy – An overview. Eur J Obstet Gynecol Reprod Biol. 2021;263:106-116.

4. Mathad JS, Gupta A. Pulmonary infections in pregnancy. Semin Respir Crit Care Med. 2017;38(2):174-184.

5. Jering KS, Claggett BL, Cunningham JW, Rosenthal N, Vardeny O, Greene MF. Clinical characteristics and outcomes of hospitalized women giving birth with and without COVID-19. Jama Internal Medicine. 2021;181:714-717.

6. Marín Gabriel MA, Reyne Vergeli M, Caserío Carbonero S, Sole L, Carrizosa Molina T, Rivero Calle I, et al; Neo-COVID-19 Research Group. Maternal, Perinatal and Neonatal Outcomes With COVID-19: A Multicenter Study of 242 Pregnancies and Their 248 Infant Newborns During Their First Month of Life. Pediatr Infect Dis J. 2020;39(12):e393-e397.

7. Servante J, Swallow G, Thornton JG, Myers B, Munireddy S, Malinowski AK, 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.

8. Litman EA, Yin Y, Nelson SJ, Capbarat E, Kerchner D, Ahmadzia HK. Adverse perinatal outcomes in a large US birth cohort during the COVID-19 pandemic. Am J Obstet Gynecol MFM. 2022; 4:100577.

9. Carpenter J, Combs CA, Kahn B, Maurel K, Clark R; COVID-19 DIC in Pregnancy Study Group. Disseminated Intravascular Coagulation Complicating Mild or Asymptomatic Maternal COVID-19. AJOG Glob Rep. 2022 Sep 23:100110. doi: 10.1016/j.xagr.2022.100110. Epub ahead of print.

10. Erez O, Mastrolia SA, Thachil J. Disseminated intravascular coagulation in pregnancy: insights into pathophysiology, diagnosis and management. Am J Obstet Gynecol 2015; 213:452-63.

11. Schwartz DA, Avvad-Portari E, Babál P, Baldewijns M, Blomberg M, Bouachba A, et al. Placental tissue destruction and insufficiency from COVID-19 causes stillbirth and neonatal death from hypoxic-ischemic injury: a study of 68 cases with SARS- CoV-2 placentitis from 12 countries. Arch Pathol Lab Med 2022; 146:660-76.

12. Royal College of Obstetricians and Gynaecolgists, Royal College of Midwives, Royal College of Paediatrics and Child Health, Public Health England and Health Protection Scotland. Coronavirus (COVID-19) infection in pregnancy: information for Healthcare Professionals. Version 15.0: updated Monday 07 March 2022.

13. National Institute of Health (NIH). Special Considerations in Pregnancy https://www.covid19treatmentguidelines.nih.gov/special- populations/pregn... Last Updated: September 26, 2022.

14. DeSisto CL, Wallace B, Simeone RM, Polen K, Ko JY, Meaney-Delman D, et al. Risk for stillbirth among women with and without COVID-19 at delivery hospitalization – United States, March 2020-September 2021. MMWR 2021; 70:1640-1645.

Rani neonatalni smrtni ishod tokom teške infekcije SARS-Cov-2 virusom komplikovane sindromom diseminovane intravaskularne koagulacije - Prikaz slučaja

Gorana P. Mitić[1], Igor G. Spasić[2], Milana D. Panjković[1,3], Biljana A. Vučković[1,3]

[1] Katedra za patofiziologiju i laboratorijsku medicinu, Medicinski fakultet Novi Sad, Univerzitet u Novom Sadu, Novi Sad, Srbija
[2] Zavod za laboratorijsku dijagnostiku Medlab, Novi Sad, Srbija
[3] Centar za laboratorijsku medicinu, Klinički centar Vojvodine, Novi Sad, Srbija

KRATAK SADRŽAJ

Uvod: Žene zaražene koronavirusom 2019 (COVID-19) tokom trudnoće imaju povišen rizik od razvoja teže forme bolesti i nepovoljnog ishoda trudnoće.
Prikaz slučaja: U radu je prikazan slučaj 21-godišnje trudnice kojoj je dijagnostikovana diseminovana intravaskularna koagulacija (DIK) uzrokovana sa COVID-19 i posledična rana neonatalna smrt ploda. Pacijentkinja je upućena u bolnicu u 29-oj gestacijskoj nedelji zbog progresije simptoma COVID-19. Na prijemu su uočeni povišena trombinska i fibrinolizna aktivnost te je odmah započeta terapija niskomolekularnim heparinom i antibioticima. Nakon što je dijagnostikovan u potpunosti laboratorijski razvijen DIK urađen je hitan carski rez. Prilikom porođaja, kod novorođenčeta je dijagnostikovana teška perinatalna asfiksija, koja se komplikovala razvojem atonije i srčanog zastojaj. Novorođenče je, uprkos sprovedenim merama kardiopulmonalne reanimacije, preminulo tri sata nakon rođenja. Majka se oporavila u roku od nekoliko dana i otpuštena je u dobrom kliničkom stanju.
Zaključak: Prikazani klinički slučaj ukazuje na značaj rane dijagnoze DIK kod SARS-CoV-2 pozitivnih trudnica, pravovremene terapijske odluke, psihološke podrške i dugotrajnog fizikalnog i psihološkog praćenja.

Ključne reči: COVID-19, diseminovana intravaskularna koagulacija, rana neonatalna smrt, trudnoća, SARS-CoV-2

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