

# Coagulopathy State in Pregnant Women with COVID-19 Involvement: 2 Case Reports

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## ABSTRACT

Pregnant women appear to be more severely affected by COVID-19. Coagulopathy is known as one of the most challenging effects of COVID-19, and the effects of acute airway diseases resulting from the coronavirus on pregnant mothers and their fetuses can be dangerous. Two women who were pregnant suffering from coagulopathy (one of them with disseminated intravascular coagulation (DIC) and the other one with hypercoagulation) and COVID-19 infection are reported in this study. During hospitalization due to severe vaginal bleeding and placental detachment, cesarean section was performed on the first case and because of acute severe DIC, she received a massive transfusion. The second patient presented with epigastric pain and tachycardia and positive D-dimer, which was eventually treated with a diagnosis of bilateral lower extremities DVT. COVID-19 might have a variety of effects on pregnancy outcome, from vascular and placental involvement to respiratory involvement; there is an association between the coronavirus and hypercoagulopathy state and coagulopathy like DIC.

**Keywords:** Coronavirus, D-dimer, DIC-Pregnancy, DVT, hyper-coagulopathy, Placental detachment



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## Introduction

Severe Acute Respiratory Syndrome coronavirus (SARS-CoV-2) pandemic has brought susceptible communities to an erratic medical emergency all around the world (1). Lately identified virus strain of coronavirus causes an infectious disease which is called COVID-19. Individuals suffering from COVID-19 undergo mild to moderate pulmonary symptoms and get better without any specific therapy or medication.

Individuals with old age or those suffering from previous medical illnesses like cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more prone to critical symptoms of COVID-19.

A meta-analytic study done in Chicago revealed that 71% of women who were pregnant and suffering from COVID-19 had positive findings in the CT-scan of their lungs, 65% of them delivered the baby through C-section, 51% of them suffered from high temperature, 49% of them were having a low level of lymphocytes in their lab reports, 33% of them were having associated illnesses, 31% of them were having cough symptoms, 29% were having fetal distress, 23% had preterm labor, and 12% of them were in critical con-

dition or died. Moreover, women who were pregnant and suffered from COVID-19 experienced fewer cough symptoms and temperature than those individuals who are not pregnant but have COVID-19. The potential explanation for increased percentage is that women in the third trimester of pregnancy provoke early child-birth following COVID-19 illness to continue with additional therapy (2). The majority of these women prefer C-sections for delivering their baby to prevent extended labor which may spread COVID-19 infection to health professionals and may also exacerbate COVID-19 for these women. A considerable rise in intervillous thrombosis has been observed in COVID-19 patients. Research evidences revealed that due to COVID-19 infection, there are chances of a rise in thrombotic and thromboembolic disturbances which may lead to placental formation or deposition of thrombi (3). A meta-analytic study of 42 investigations done by Malas MB *et al.* comprising 8271 patients demonstrated that thromboembolic factors are high in patients suffering from SARS-CoV-2 infection. Generally, VTE, DVT, PE, and ATE rates were 21%, 20% 13%, and 2%, respectively. The VTE, DVT, PE

and ATE rates were 31%, 28%, 19%, and 5%, respectively within ICU patients. Thromboembolism considerably rises the odds of mortality by as high as 74% (or, 1.74; 95%CI, 1.012.98;  $P=0.04$ ). Morbidity and mortality due to COVID-19 continue to remain considerable in parallel with a high rate of infection (4).

## Case Presentation

### CASE 1

A 31-year-old pregnant woman with 28 weeks and 6 days of gestational age; gravida 2 para 1 with previous cesarean section due to mother request referred to the obstetric emergency department of Miandoab hospital, Iran on 27 of June 2020 with spotting and pain in lower abdomen without any other symptoms. The patient had high blood pressure 1 week before her attendance without proteinuria, which had been, treated with methyldopa 250 mg tablets twice daily and her blood pressure was controlled. At the time of her admission, her blood pressure was: 90/60 (mmHg) with a pulse rate: 98, Respiratory rate: 12 and body temperature were: 37. Fetal heart rate was recorded at 140. On pelvic examination, vaginal bleeding was contaminated with gloves and the abdomen was soft without tenderness and uterine contraction. She was admitted to a high-risk pregnancy ward and laboratory data were sent. During the patient's transfer to a high-risk ward, the patient experienced heavy vaginal bleeding (3+), and due to fetal heart rate deceleration (80), she was taken to the operation room for an emergency cesarean section. Cesarean section was done with a midline incision and general anesthesia. Fetal APGAR<sup>1</sup> score was zero and there was a diffuse detachment of placenta. After repair of incision, despite the lack of bleeding vessel, there was diffuse oozing; in the follow up of blood tests the results were as follows:

HB:9.3

HCT:28

mcv:90

WBC:11200 (Neutrophils: 87% Lymphocytes :6%)

PLT:76000

INR>6

PT>40

PTT>80

FIBRINOGEN >81

SGOT:41

SGPT:19

LDH:756

DIDIMER>0.2

CR:0.7

U/A:( PR: 3+ and RBC: 1-2)

NA:140

K: 3.5

Ca: 8

CRP: 3+

ESR: 26

After controlling of uterine atony with uterine massage and 1g rectal misoprostol with acute DIC diagnosis patient underwent infusion of 5 units packed cell, 11 units fresh frozen plasma (FFP), 5 units cryoprecipitate, and 7 unit platelet.

The patient was admitted to the ICU and in tomorrow morning visit. Then, morning at ICU; the patient suffered from shortness of breath and fever which was examined and showed tachycardia and tachypnea and fever with 39.7°C, axillary and saturation of oxygen was less than 90%. Chest x ray (CXR) was done where blunt side angles were seen, so antibiotic therapy started (Ceftriaxone 2 gram Two Times a Day and Clindamycin 900 milligram three times a day) and COVID-19 nasopharyngeal swab test for Polymerase chain reaction (PCR) was taken. Spiral chest CT scan images showed Ground glass opacity in the superior segment of the lingular lobe in the left lung and similar opacity was evident in the peripheral segment of the posterior basal segment of the lower right lung ([Figure 1](#)).

The PCR results were positive and accordingly the patient has prescribed 500 mg azithromycin and she underwent symptomatic treatment with a normal blood test. After 2 days patient's symptoms stabilized and she was discharged for home quarantine.

1. The Apgar score is a method to quickly summarizing the health of newborn children against infant mortality.



**Figure 1.** CT scan images of this patient

## Case 2

A 27-year-old pregnant woman with 33 weeks and 1 day gestational age, gravida 2, para 1 with previous NVD attended to the obstetrics emergency department of Miandoab hospital, Iran on 25 October 2020 only with epigastric pain and palpitation without any precedent of background disease. We found only tachypnea and normal lung auscultation in our physical exam. COVID-19 PCR nasal swab test followed by ECG was done which revealed the existence of sinus tachycardia. Fetal parameters in sonography were normal. In the follow-up, the D-dimer range was positive so lower extremity limb Doppler sonography and echocardiography were done which resulted in no abnormal findings. We found bi-lateral deep vein thrombosis in the popliteal and common femoral vein. Anticoagulant therapy was started and the Enoxaparin 60000 unit injection was performed twice a day. A Spiral chest CT-Scan was done and no abnormal findings were reported.

## Discussion

People who are infected with the COVID-19 experience mild to moderate respiratory illness and they don't need special treatment. Although some who have special conditions are more likely to develop serious illnesses. These special conditions can include old age or underlying diseases such as cardiovascular diseases, cancer or diabetes, etc. Disseminated intravascular coagulopathy (DIC) is associated with critical COVID-19 infection just like numerous COVID-19-related coagulopathies. Its mechanism with DIC is different from those specified with COVID-19 infection ranges from the petechial manifestations to acroischemia presentations containing in particular cyanosis of finger or toe, skin bulla and dry gangrene, and various identical frostbite illnesses (5). Today's pandemic of COVID-19 infection caused by SARS-CoV-2 novel coronavirus led to a significant amount of severely sick patients and deaths (6). Just like some

other single-stranded and encapsulated RNA viruses, coronaviruses also attain similar characteristics. Among individuals with a weak immune system, COVID-19-caused mild upper pulmonary infection may progress into more critical presentations (7).

A hypothetical link exists among peripartum duration of mothers suffering from COVID-19 infection and prompt maternal impairment with multi-organ failure and coagulation disorder. By pulmonary failure, today's SARS-CoV-2 pandemic has led to a huge amount of seriously sick individuals and deaths in the non-pregnant population. Pregnant women are more prone to viral pandemics because in pregnancy there are physiological alterations in the immune system, elevated oxygen need, and edema of the respiratory tract. Knowledge for associations of COVID-19 with other diseases is primarily important for its diagnosis and management because an abnormal lab value can indicate hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome. According to International Society on Thrombosis and Haemostasis (ISTH) guidelines besides routine lab examinations, measuring D-dimers, platelet count and prothrombin time should be done for all individuals having symptoms of COVID-19 (8). Previous studies have shown liver involvement and elevated transaminase in SARS and MERS-CoV in 60% of cases (9). In the study by Zhang *et al.*, it was shown that transaminitis are seen in 14-53% of patients with COVID-19 (10). Numerous case reports indicated that disease caused by SARS in pregnant women is linked with critical maternal infection, high chances for maternal death, and spontaneous abortion (11). Also, these studies explained clinical manifestations and findings in pregnant women suffering from COVID-19 infection in Wuhan, China, and there is no proof that pregnant women are prone to more critical illness as compare to both SARS and MERS. Despite that, negative perinatal consequences have been found including high chances of miscarriage, preeclampsia, preterm birth, and stillbirth (7). By examining the tissue pathology of the placenta considerable data concerning the condition of both mother and fetus may reveal. Pathological landmarks of the placenta during the majority of viral infections are lymphoplasmacytic villitis with the corresponding thickening of villi and inter-villous hemosiderin accumulation suchlike in Cytomegalovirus (CMV) infection (3). However, placental pathological landmarks evidence regarding COVID-19 are still unidentified. Only two case reports stated the pathological placental findings during a second-trimester miscarriage in women suffering from COVID-19 infection (7). A case-report study from China reported placental findings in three patients suffering from COVID-19 (12). A considerable rise in chances of intervillous thrombi has been seen in COVID-19 patients. of these thrombi, 85% are of fetal origin but normally, the intervillous space comprises flowing maternal blood (13).

There is a direct relationship between the coronavirus and hyper-coagulopathy state. During COVID-19

involvement, inflammation and release of the resulting cytokines cause involvement of the vascular endothelium, followed by the formation of vascular plaque. As a result of this inflammation, precoagulation factors and hemodynamic changes cause thrombosis (14).

Prothrombotic conditions caused by dysfunction of endothelial cells due to hyper-inflammatory conditions. There is a wide interaction between homeostasis and the immune system. Clotting occurs during infection due to interference with the immune system and blood cells and coagulation factors (also known as thrombo-inflammation). This process is potentially effective as it prevents the spread of pathogens and provides a supporting structure for the endothelium and the immune system: microangiopathy is caused by uncontrolled activity of this thrombosis. Progression to acute respiratory distress syndrome (ARDS) in COVID-19 disease and other conditions can be caused by uncontrolled immunothrombosis (15).

Early separation of the placenta from the wall of the uterus is called placental abruption which results in critical morbidity and mortality in mothers during pregnancy (16). In 1834, Dupuy firstly identified DIC as a state of inflammatory systemic hemostasis. This inflammatory condition turns off anti-coagulation processes which results in clotting in small and medium sized vessels. Its fundamental pathology is the injury to endothelial cells which exposes sub-endothelial collagen that leads to the creation of microthrombi. Especially among severely sick patients, abnormal hemostasis and inflammation result in organ dysfunction. Loss of coagulation factors causes a huge risk for complications like bleeding. Malignancy, infection, hypoxia, hypoxemia, trauma, burns, vascular disorders, immunologic disorders, toxins, and hepatic disease are those conditions that possibly result in DIC (17). Asymptomatic deep vein thrombosis occurrence in patients with COVID-19 is also present due to local hypercoagulable state (18).

Based on the thrombo-prophylaxis guidelines in pregnancy which is given in Table 1 (19), our second case was in low-risk group; therefore, the risk of thrombosis was very low and we did not expect thrombosis to occur with this severity. In patients at high risk of thrombosis, including increased D-dimer or sepsis-induced coagulopathy (SIC) score full dose anticoagulant therapy will be useful. A recently published study has discovered proof of heparin resistance in severely sick patients suffering from COVID-19 infections (20). It can be beneficial to measure the anti-factor Xa plasma concentration among these patients. A case-report recently identified the action of tissue plasminogen activator on patients encountering pulmonary failure and ARDS (20). White D *et al.* stated that patients admitted to ICU because of COVID-19 infection have created resistance against heparin after getting treatment with UFH and they demonstrated a declined peak in anti-Xa plasma concentrations after Low-molecular-weight heparin (LM-

WH) therapy. As mentioned earlier that heparin resistance created due to IV unfractionated heparin (UFH) is excessive, nearly 80% probably because of actions of elevated fibrinogen and factor VIII upon the aPTT and it works to reduce the APTT which is a causative factor for heparin resistance (21).

According to studies performed so far and our own experience, we recommend that pregnant patients with COVID-19 infection should be evaluated for thrombosis and also coagulopathy state and anticoagulants must be considered in high-risk patients.

**Table 1. Thrombosis risk assessment.**

Risk Assessment	Risk Factors
<b>High Risk</b>	<ul style="list-style-type: none"> <li>• Any previous VTE</li> <li>• Anyone requiring antenatal VMWH</li> <li>• High-risk thrombophilia</li> <li>• Low-risk thrombophilia + family history</li> </ul>
<b>Intermediate Risk</b>	<ul style="list-style-type: none"> <li>• Cesarean section in labor</li> <li>• BMI <math>\geq 40</math> kg/m<sup>2</sup></li> <li>• Readmission or prolonged admission (<math>\geq 3</math> days) in the puerperium</li> <li>• Any surgical procedure in the puerperium except immediate repair of perineum</li> <li>• Medical comorbidities; e.g., cancer, heart failure, active SLE, IBD or inflammatory polyarthropathy; nephrotic syndrome, type one DM with nephropathy, sickle cell disease, current MDU</li> </ul>
<b>General Risk Factors</b>	<ul style="list-style-type: none"> <li>• Obesity (BMI <math>\geq 30</math> kg/m<sup>2</sup>), either pre-pregnancy or in early pregnancy)</li> <li>• Age <math>&gt; 35</math> years</li> <li>• Parity <math>\geq 3</math></li> <li>• Elective cesarean section</li> <li>• Gross varicose veins</li> <li>• Immobility; paraplegia, PGP, long-distance travel</li> <li>• Smoker</li> <li>• Family history VTE</li> <li>• Low-risk thrombophilia</li> <li>• Current PET</li> <li>• Multiple pregnancy</li> <li>• Preterm delivery (<math>&lt; 37</math> weeks)</li> <li>• Stillbirth in this pregnancy</li> <li>• Prolonged labor (<math>&gt; 24</math> hr)</li> <li>• Mid-cavity rotational or operative delivery</li> <li>• PPH <math>&gt; 1</math> L or blood transfusion</li> </ul>

## Conclusion

COVID-19 might have a variety of effects on pregnancy outcome, from vascular and placental to respiratory involvement; there is an association between the coronavirus and hyper-coagulopathy state and coagulopathy like DIC. Systemic pro-inflammatory cytokine processes contribute to it. Deep vein thrombosis (DVT), as a subset of venous thromboembolism (VTE), is known as a major preventable cause of morbidity and mortality worldwide. Since there is a state of hyper-coagulation in pregnancy, this condition can be exacerbated with coronavirus infection. It is recommended that special attention is paid to coagulation status in the care process for those women who are pregnant and suffering from COVID-19. On another side, diffuse placental abruption and DIC are

dangerous complications of pregnancy that hurt maternal and fetal outcomes which is important in the diagnosis and management of COVID-19 in pregnant women.

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## Conflict of Interest

Authors declared no conflict of interest.

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