Thromboprophylaxis in Covid–19 Positive Pregnant Women

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ABSTRACT

Objective: Serious Covid-19 disease is often complicated by coagulopathy. Most of Covid-19-related deaths have been shown to be caused by extensive intravascular coagulation disorders. Our aim in this study is to examine the importance of thromboprophylaxis in Covid-19 positive pregnant women.

Methods: Pregnant women diagnosed with Covid-19 with the polymerase chain reaction test were retrospectively analyzed and treatment processes were evaluated.

Results: A total of 18 pregnant women were followed up with the diagnosis of Covid-19. The mean age of the patients was 28.90±5.26 (18–41). Laboratory results revealed high CRP levels (11/18), lymphocytopenia (10/18) and increased neutrophil percentage (14/18). CT examinations were reported as widespread involvement findings (ground glass opacities - GGO) in 3 of 8 patients and mild fibrotic changes in 5 of the patients. Thromboprophylaxis was not applied in 4 outpatients however applied in 9/14 of the hospitalized patients. The average duration of drug use is 7.1 days (1–14). Average hospital stay is 3.3 days (2–16). The preferred dose is 40 mg 1x1/day. In a patient with suspected pulmonary embolism, 60 mg of 2x1/day enoxaparin was used. Maternal, fetal, and hemorrhagic complications were not observed.

Conclusion: Since there is a tendency to hypercoagulation in pregnancy, thromboembolic events are more common. Therefore, starting LMWH treatment before Covid-19 infection progresses could be beneficial for preventing embolic complications that may be fatal.

INTRODUCTION

Coronavirus 2019 (Covid-19) was shown to cause widespread damage to the lungs, resulting bilateral progressive pneumonia, acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC) and death. Mortality rates varies among literature and ranges from 4.3% to 14.6%.[1–3]

Although the underlying pulmonary pathophysiology is not fully understood, the knowledge and experience on this issue is increasing. Studies have shown that endothelial dysfunction, thrombin increase, fibrinolysis shutdown, coagulopathy, hypercoagulable state, blood viscosity increase, thrombosis, cellular infiltrate in lungs and consequently hypoxia develops.[4–8] In postmortem studies, reports revealed disseminated micro-thrombus, occlusion and pronounced hemorrhagic necrosis, especially in lung microvessels.[9,10] There pathologies results in deep vein thrombus (DVT), pulmonary embolism (PE), DIC and deaths, especially in severe Covid-19 infection.[11,12]

Hypercoagulability is one of the physiological changes in pregnant women. Increased factor VII, FVIII, FX, von Willebrand factor activity and fibrinogen levels are associated with hypercoagulability.[13,14] Besides, thrombin production markers such as prothrombin F1 and 2 and thrombin-antithrombin (TAT) complexes increase during pregnancy. A decrease in protein S levels and acquired active protein C resistance also causes a significant decrease in anticoagulant activity.[13] Also, plasminogen activator inhibitor type 1 (PAI-1) levels increase fivefold and plasminogen activator inhibitor type 2 (PAI-2) increases, especially in the third trimester resulting increased hypercoagulopathy.[15]

There are known risk factors for thromboembolic events in pregnancy like, obesity, prolonged immobilization and thrombophilia. Covid-19 infection is shown to cause thromboembolic complication in general population. However, it is still not known how Covid-19 infection affect pregnant woman regarding thromboembolic complication and whether it is an indication for thromboembolism prophylaxis. Here in we aim to present our approach

for preventing thromboembolic events and result of our management in Covid-19 infected pregnant woman.

MATERIALS AND METHODS

This was a retrospective cross-sectional study, conducted between 10th of March, the start of pandemics in Turkey to 1th of July, and the start of normalization process. The patients with Covid-19 infection records were scanned from the hospital database and 19 pregnant women with Covid-19 infection was included for the study. The ethical approval was obtained local ethics committee (Number:2020/514/176/10). Informed consent form was taken from all the patients.

Sociodemographic features, laboratory values of patients, lung x-ray and computed tomography (CT) findings, need for hospitalization, length of hospital stay, use of thrombophylaxis, anticoagulant dosage and duration were examined. In addition, treatment success maternal, fetal and neonatal outcome was investigated. Patients history was questioned for thrombophilia risk factors. Physical examination also was done for presence of varicose veins. Nasopharyngeal swab polymerase chain reaction (PCR) technique was used for the diagnosis of Covid-19.

RESULTS

The mean age of the patients was 28.3 (20-39) years, the mean gestational week was 31 (11–40 + 4), the mean gravida was 2.8 (1–4), and mean follow-up was time 27 days (5–45). Patients' history revealed; hypothyroidism (3), hepatitis B virus carrier (1), asthma (1), allergic asthma + Familial Mediterranean Fever (FMF) and gestational diabetes (1). None of the patients were smoking. Patients admitted hospital with cough (7), dyspnea (7), fever (4), myalgia (4), chest pain (2) and loss taste-smell sensations (1). Also, there were four asymptomatic patients. The summary of the laboratory results of the patients was summarized in Table 1. The most common abnormal laboratory results are increased CRP levels, (11/18), lymphocy-

Table 1. The laboratory results and radiologic findings of the study patients

	Mean±SD	n	%
Leukocytes (x10³/mcl)	6486.67±2861.285		
Lymphocytes (mm³)	896.00±235.184		
Neutrophils (mm³)	4293.33±1338.158		
Platelets (x10⁹/mcL)	185.40±39.089		
C-reactive protein (mg/dL)	46.107±53.3711		
D-dimer (ng/mL)	962.00±523.644		
CT findings (Early stage)		2	13.3
CT findings (Progressing stage)		4	26.6
CT findings (Severe stage)		2	13.3

CT: Computed tomography; SD: Standard deviation.

topenia (10/18), increased neutrophil percentage (14/18), and increased neutrophil/lymphocyte ratio.

In physical examination, high fever (above 37.3 °C) was found in 9 patients, blood pressure over 130/90 mmHg in 1 patient, tachycardia in 1 patient, tachypnea in 1 patient, and hypoxia in 2 patients. In the ultrasound examinations of the fetuses; one fetus had 4 weeks intrauterine growth restriction and one fetus had macrosomia 3 weeks ahead. The other fetuses have been reported as normal. All NST examinations are reactive. In lung images, x-ray was imaged in 4/18 patients; of these, extensive involvement findings were observed in 2 patients and normal findings were observed in 2 patients. Widespread involvement findings (ground glass opacities - GGO) were observed in 4 of 8 patients who underwent CT imaging and 5 of them had mild fibrotic changes (Figs. 1, 2).

Nine of the patients gave birth by cesarean section. The average birth weight is 2973 grams (1560–3460). Cesarean indications were maternal infection (4), maternal infection + asymmetric IUGR (1), maternal infection + previous cesarean history (2), labor arrest (1) and preeclampsia (1). The average of APGAR scores was 7.6 (5–8) for the 1st minute and 8.7 (7–9) for the 5th minute.
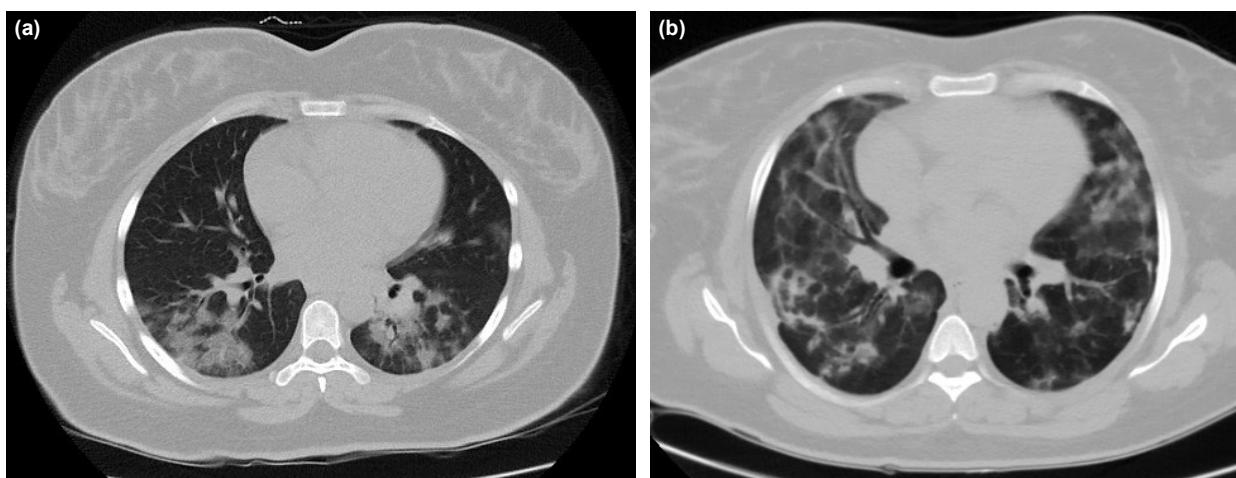

Figure 1. (a, b) Mild fibrotic changes due to Covid infection in CT imaging.

As for maternal outcomes, pneumonia (5), ARDS (1), mechanical ventilation and need for intensive care admission (1) were observed. Maternal death was not observed. When fetal and neonatal outcomes were examined, there was no complication, NICU requirement or fetal death. Premature delivery (31 weeks of gestation) was found in only one patient due to severe pre-eclampsia and previous cesarean delivery. Care and treatment of the newborn was carried out at NICU until the treatment of the mother was completed.

As medical treatment following drugs are used; hydroxychloroquine (16/18), LMWH (9/18), oseltamivir (4/18), ceftriaxone (4/18), azithromycin (2/18), vitamin C (2/18), lopinavir/ritonavir (1/18) and favipiravir (1/18). Drug-free follow-up was performed in 2 patients. The mean duration of postpartum maternal and fetal follow-up is 27 days (5–45) and there were no complications until May 30, 2020.

DISCUSSION

Hemogram, coagulometry, D-dimer and biochemical tests

In studies,[1,2,16] serious Covid-19 disease has shown to be often complicated by coagulopathy and widespread intravascular coagulation was thought to cause the deaths from Covid-19 infection.[17] It was found that there was a marked increase in inflammatory mediators and cytokines, defined as "cytokine storm" approximately 7–14 days after the initial symptoms.[18] Afterwards severe lymphopenia is observed in patients.[19] Guan et al.[20] examined 1,099 Covid-19 cases and found lymphocytopenia in 83.2% of patients, thrombocytopenia in 36.2% and leucopenia in 33.7% of the patients.

Huang et al.[2] and Wang et al.[3] showed a relationship between lymphopenia and ICU need for care. Wu et al.[21] also found a relationship between lymphopenia and ARDS. In our clinical findings, we found that CRP elevation (11/18), lymphocytopenia (10/18), increased neutrophil percentage (14/18) is higher in hospitalized patients comparing to the patients were not hospitalized.

D-dimer

Increased D-dimer values were found in 14 to 46% of the Covid-19 infected patients in general population.[19,20] According to the D-dimer results, mortality in heparin users remained basically the same, while mortality in non-users increased with D-dimer. When D-dimer increased by 6 times the upper limit, it was determined that mortality decreased by 20% with heparin treatment (32.8% vs 52.4%, p=0.017).[16,22] In a multi-center retrospective study, D-dimer increased in 260 (46.4%) of 560 patients with Covid-19 infection, and the height was more pronounced in severe cases. (59.6% in severe cases, 43.2% in non-serious cases) (20). In a study with Computed Tomography Pulmonary Angiography, D-dimer levels were compared in patients with suspected pulmonary embolism (n=25) and in patients diagnosed with pulmonary embolism (n=10). It was determined that it was significantly higher than 7000 ng/mL in those with embolism.[23]

In our clinic, 11 of 18 pregnant women diagnosed with Covid-19 had high D-dimer value. All of these patients are hospitalized. Seven of the patients were not hospitalized and their D-dimer levels were within normal limits, were not applied LMWH.

LMWH treatment was started in 8 of 11 patients with high D-dimer level. There is no cut-off value determined for D-dimer to start LMWH. D-dimer values range from 730 µg/mL to 30.000 µg/mL in patients who were on treatment. The patient with the highest value was found to be hospitalized for the longest time and combined drug therapy was needed besides higher dose of anticoagulant therapy.

Coagulometry

Covid-19 pneumonia has been reported to be associated with an increase in INR, aPTT, D-dimer and fibrin degradation products. Widespread intravascular coagulation patterns have been reported in Covid-19-related deaths, and aPTT and PT are prolonged in this group.[7] Thrombocytopenia is 5–18%, PT prolongation 2-11% and aPTT prolongation 26% was present in Covid-19 infected patients in the general population. It has been shown that the increase in these four parameters correlates with the severity of the disease.[24] There is no clear information about this issue in pregnant women in the literature, but we did not observe thrombocytopenia and abnormal coagulometry (PT, aPTT and INR values) in our study. No mortality was observed in any patient.

Deep vein thrombus, pulmonary embolism and myolard infarction

In severe Covid-19 patients, the risk of venous thromboembolism (VTE) increases due to the need for long-term bed rest. Treatment of anticoagulants for these patients has been recommended by some expert consensus in China,[25] but its effectiveness still needs to be confirmed.[16] Also, the International Society of Thrombosis and Haemostasis (ISTH) has introduced a new definition called "sepsis-induced coagulopathy" (SIC) for identifying an earlier phase sepsis-associated DIC.[26] They stated that patients who met the diagnostic criteria of SIC benefited from anticoagulant therapy.[27] Severe Covid-19 diagnosis recommended by the Chinese National Health Commission was defined as meeting any of the following items; respiratory rate ≥30 breaths/minute; arterial oxygen saturation 93% at rest; PaO_2/FiO_2 ≤300 mmHg.[28] LMWH treatments have become more prominent in patients with SIC and severe Covid-19 contemplation.[16] The only patient who meets the definition of severe infection in our clinic needed ICU and discharged without any complications. She was administered enoxaparin 60 mg is a patient who is treated twice a day.

The risk of vascular thromboembolism is up to 10% in hospitalized Covid-19 patients.[29] Prolonged immobilization, dehydration, acute inflammatory status, cardiovascular risk factors (hypertension, diabetes, and obesity), cardiovascular disease (history of coronary artery disease, ischemic stroke or peripheral artery disease), genetic thrombophilia status (Factor V Leiden mutation etc.) are potentially comorbidities[19] that increase the risk of VTE. The combination of all these factors, such as endothelial cell activation/damage, mechanical ventilation, central venous catheterization, and vascular endothelial damage, which may be caused by binding of the Corona virus to the ACE2 receptor, may lead to DVT formation and the possibility of PE. Therefore, pharmacological thromboprophylaxis is mandatory in Covid-19 patients admitted to the hospital.[19]

A recent report by EuroELSO (European Extracorporeal Life Support Organization) stated that 20% of patients under extracorporeal membrane oxygenation have pulmonary embolism. In a prospective study involving 416 consecutive patients with Covid-19 in Wuhan, China, 82 (19.7%) were found to have myocardial injuries.[19] It has also been shown that myocardial injury (MI) is associated with increased mortality in patients hospitalized with Covid-19. It is necessary to keep in mind the risk of VTE in asymptomatic or outpatients with mild Covid-19 infection as well as hospitalized patient. Early diagnosis of PE in Covid-19 patients with clinical findings of oxygenation, respiratory distress or sudden deterioration of hypotension is of great importance for improving clinical outcomes.[19]

Drug choice and dosage

Low molecular weight heparins or unfractionated heparin should be preferred to oral anticoagulants because the interactions with antiviral (especially anti-HIV protease inhibitors such as ritonavir) and antibacterial (such as azithromycin) agents. It is currently not possible to say that unfractionated heparin (UFH) is better than LMWH. However, LMWH is more preferred due to its ease of use, lack of laboratory monitoring and familiarity. The question of whether the therapeutic doses of UFH or LMWH should be taken into account for all patients is currently unknown. LMWH is the most commonly used anticoagulants to prevent DIC and VTE in patients due to its anti-inflammatory effect.[22]

Fogarty et al.[30] administered enoxaparin thromboprophylaxis to patients at doses appropriate for their weight. It was suggested as 20 mg 1×1SC in patients between 50–100 kg; 40 mg 2×1 SC in patients between 101–150 kg and 60 mg 2×1 SC for those over 150 kg. However, it is stated that despite significant, increased D-dimer levels, diffuse intravascular coagulopathy may not be evident.

Belen-Apak et al.[31] suggested the prophylactic use of minidose heparin or LMWH doses (especially dalteparin or tinzaparin) in order to reduce the viral load of the host cells and prevent the involvement of the lower respiratory tract. In our clinic, the presence of known DVT/MI/

PE history, presence of genetic mutation that may lead to thrombophilia, history of recurrent pregnancy loss, obesity, smoking, presence of varicose veins in the body, D-dimer height were taken into consideration for thromboprophylaxis therapy. The longest duration of hospitalization is 16 days, and due to the suspicion of pulmonary embolism, enoxaparin 60 mg twice daily is administered subcutaneously.

Enoxaparin was used as LMWH in 9 of the patients. The most commonly used dose is 40 mg once daily SC. High dose was preferred only for the patient with suspected pulmonary embolism. LMWH was used in all 5 patients with pneumonia. Maternal, fetal and neonatal complications were not observed. Besides complications DVT, ARDS, DIC, PE etc. were also not encountered. Hospital organization during pandemics were also changed in order to provide enough support for the patients, along with these changes patients were diagnosed with Covid-19 in a short-term period and received treatment.[32] This situation also contributed to prevent complications in our hospital.

CONCLUSION

Covid-19 infection can be fatal in severe cases with the pathologies it causes in the vascular endothelial area and coagulation system. There is a tendency to hypercoagulation in pregnancy, thromboembolic events are more common. Therefore, based on our observations, it may be beneficial to start LMWH treatment before the infection becomes critical, especially in patients considered moderate risk.

Ethics Committee Approval

Approved by the local ethics committee (Number: 2020/514/176/10).

Informed Consent

Retrospective study.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: K.K., Ö.S.; Design: Ö.S., H.A.A.; Supervision: Ö.S., A.K.; Fundings: A.D.A., Ö.S.; Materials: H.A.A., K.Ş.; Data: T.A., H.A.A.; Analysis: K.Ş., T.A.; Literature search: Ö.S., K.K.; Writing: K.K., A.S.; Critical revision: A.K., A.D.A.

Conflict of Interest

None declared.

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Covid-19 Enfekte Gebelerde Trombofilaksi

Amaç: Ciddi Covid-19 hastalığı genellikle koagülopati ile komplike olmaktadır. Covid-19 ile ilişkili ölümlerin çoğunun yaygın intravasküler pıhtılaşma bozukluklarından kaynaklandığı gösterilmiştir. Bu çalışmada amacımız, Covid-19 enfeksiyonu olan gebe kadınlarda tromboprofilaksinin önemini incelemektir.

Gereç ve Yöntem: Polimeraz zincir reaksiyonu testi ile Covid-19 tanısı alan gebe kadınlar geriye dönük olarak incelendi ve tedavi süreçleri değerlendirildi.

Bulgular: Toplam 18 gebe kadın Covid-19 tanısı ile takip edildi. Hastaların yaş ortalaması 28.90±5.26 (18–41) idi. Hastalar öksürük (7), nefes darlığı (7), ateş artışı (4), şiddetli miyalji (4), göğüs ağrısı (2) ve tat alma duyusu kaybı (1) ile hastaneye başvurdu. Laboratuvar sonuçlarında yüksek CRP düzeyleri (11/18), lenfositopeni (10/18) ve artmış nötrofil yüzdesini (14/18) görüldü. Bilgisayarlı tomografi incelemelerinde sekiz hastanın üçünde yaygın tutulum bulguları (buzlu cam opasiteleri - GGO) ve beşinde hafif fibrotik değişiklikler olarak bildirilmiştir. Dokuz hasta sezaryen ile doğurtuldu. Dört ayaktan takip edilen hastaya tromboprofilaksi uygulanmadı, ancak yatan hastaların 9/14'üne uygulandı. Ortalama ilaç kullanım süresi 7.1 gündür (1–14). Ortalama hastanede kalış süresi 3.3 gündür (2–16). Hastaların tedavisinde düşük molekül ağırlıklı heparin (LMWH) - enoksoparin tercih edildi. Tercih edilen doz 40 mg 1x1/gündür. Pulmoner emboli olduğundan şüphelenilen bir hastada 60 mg 2x1/gün enoksoparin kullanıldı. Maternal, fetal ve hemorajik komplikasyon gözlenmedi.

Sonuç: Gebelikte hiper pıhtılaşma eğilimi olduğundan, tromboembolik olaylar daha yaygındır. Bu nedenle, Covid-19 enfeksiyonu ilerlemeden önce LMWH tedavisine başlamak, ölümcül olabilen tromboembolik komplikasyonları önlemek için yararlı olabilir.

Anahtar Sözcükler: Covid-19; düşük moleküler ağırlıklı heparin; gebelik; tromboemboli profilaksisi.