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ANTI-COAGULANT THERAPY IN HOSPITALIZED PREGNANT WOMEN WITH COVID-19: A BRIEF REVIEW

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ABSTRACT

As our knowledge about COVID-19 progresses, we know that COVID-19 has a clear thrombogenic effect. Moreover, as pregnancy is a prothrombotic state, the possibility of an increased risk of venous thromboembolism (VTE) in pregnant women with COVID-19 has become an area of concern, and a number of international organizations have proposed recommendations for thromboprophylaxis in pregnant and postpartum women with COVID-19. However, these recommendations are mainly based on expert opinion. In this brief review, we explain the pathophysiology of COVID-19- associated coagulopathy with focus on pregnancy related issues, leading to make clear recommendations about anti-coagulant therapy in pregnant women with COVID-19 during hospitalization and also after discharge.

KEYWORDS: COVID-19, Pregnancy, Prothrombotic state, Venous thromboembolism (VTE), COVID-19-associated coagulopathy, Thromboprophylaxis.

INTRODUCTION

So far, there are scant studies on COVID-19-associated coagulopathy in pregnant women and whatever we know has been postulated based on studies in the non-pregnant patients. There are several reports of high rates of thrombotic complications in patients with severe COVID-19.[1,2,3]

Acute SARS-CoV-2 viremia, leads to activation of monocytes/macrophages, which produce cytokines such as interleukin-6 (IL-6) and tumor necrosis factor (TNF) that activates coagulation cascade[4,5] which leads to endothelial cell activation that involves the change from an antithrombotic phenotype to procoagulant phenotype.[6]

Immunothrombosis, a complex process consisting of inflammatory reactions, hypoxia, and the local expression of tissue factor results in pulmonary microvascular thrombosis, which is a likely contributor to the progressive respiratory dysfunction that develops in patients with SARS-CoV-2 infection.[7] That is why the majority of emboli in the pulmonary vasculature are segmental and sub-segmental thrombi as opposed to central or lobar pulmonary emboli, while, the incidence of deep vein thromboses of the extremities is low.[8] The role of thromboprophylaxis in preventing immunothrombosis remains to be elucidated.[9]

On the other hand, all three elements of Virchow's triad (endothelial injury, stasis of blood flow and hypercoagulable state) are presented in severe COVID-19 infection, so they are at high risk for VTE for up to 90 days post discharge.[10,11]

Despite primary reports from China, it is now clearer that the clinical picture is not that of DIC, as there is no increased bleeding, platelet levels usually are not low, fibrinogen levels are very elevated, so do not fit with the criteria of International Society on Thrombosis and Hemostasis (ISTH) guidelines on diagnosing DIC.[12,13] Unfortunately, these criteria cannot be applied to pregnant women, reducing our ability to accurately characterize their coagulopathy.

D-dimers which could be product of fibrin degradation or due to inflammation, are usually to be elevated in COVID-19 patients[14,15] and correlates with the COVID-19 severity.[16,17] Opposite to what happened in DIC, fibrinogen levels in COVID-19 are generally elevated[18] Platelet counts usually are not significantly decreased in COVID-19 patients.[19] There are also few reports about antiphospholipid antibodies associated with

COVID-19.[20,21] PT and aPTT may be prolonged as a preterminal event, however, their value in clinical decisions is limited.[22,23] Despite these prominent changes in hematologic elements, there is no consensus to administration of blood products in the absence of bleeding.[24-26] (Table 1)

COVID-19 in pregnant women

The USA Centers for Disease Control and Prevention (CDC) data has showed that although pregnant women with COVID-19 are not at an increased risk of death, they are more likely to be hospitalized and to require ICU admission and mechanical ventilation than are non-pregnant women.[27]

Pregnancy is a hypercoagulable condition characterized by increased prothrombotic factors (Table 1) for up to 3 months within postpartum period.[28-30] All published guidelines about thromboprophylaxis for COVID-19 in pregnancy are not evidence- based, only has relied on expert opinion.

There is a general consensus that hospitalized patients with COVID-19 should receive standard doses of thromboprophylaxis. Heparins are the anticoagulants of choice for both pregnant and non-pregnant patients with COVID-19, unless there are absolute or relative contraindications (such as active bleeding, low platelet count, or an anticipated surgical procedure or delivery within 12 hours). In addition to their anticoagulant properties, heparins have anti-inflammatory (through inhibiting thrombin and decrease the level of inflammatory biomarkers) and anti-viral effects.[7,31]

Generally, once-daily dosing with Low molecular weight heparins (LMWH) (enoxaparin 1 mg/kg = 100 units/kg, once daily) are preferred over unfractionated heparin for thromboprophylaxis in hospitalized pregnant women, if delivery is not expected within 24 hours. After delivery, unfractionated heparin is used if faster discontinuation is needed (eg, if delivery, neuraxial anesthesia, or an invasive procedure is anticipated within approximately 12 to 24 hours or at 36 to 37 weeks of gestation).[32]

High fibrinogen levels make patients more resistant to heparin, that is why prophylactic doses may be insufficient in severe and critical COVID-19.[33] The use of higher doses of LMWH (therapeutic enoxaparin: 1 mg/kg = 100 units/kg, twice daily) has been suggested for thromboprophylaxis and also treatment of VTE in hospitalized non-pregnant patients with COVID-19. Prolonged PT or aPTT is not a contraindication to administering thromboprophylaxis.[12]

Interestingly, the simultaneous anti-cytokine therapy could both ameliorate diffuse immunothrombosis and reduce the prothrombotic changes.[18,34] Anakinra (IL-1 receptor antagonist) and tocilizumab (IL-6 receptor antagonist) are both safe during pregnancy and lactation.[35]

In postpartum patients with recent COVID-19 infection, benefits of thromboprophylaxis with LMWH outweigh the hemorrhagic risk. Although vaginal delivery is associated with a lower risk of thromboembolism compared to caesarean delivery, it seems prudent to recommend LMWH in women with risk factors in addition to those infected by COVID-19. After caesarean delivery, the recommendation for thromboprophylaxis is even stronger.

There are considerable controversies about optimal duration of anticoagulants following discharge and during the postpartum period. Individuals with documented VTE require a minimum of three months of anticoagulation. Some individuals who have not had a VTE, but with moderate to severe disease, may also warrant extended thromboprophylaxis following discharge from the hospital for up to 6 weeks postpartum, depending on disease severity. The most recommended option for post-discharge prophylaxis is rivaroxaban 10 mg once-daily.[25,32]

Table 1: Changes of coagulation factors during COVID-19 and pregnancy.

Index	***Changes in COVID-19***	***Pregnancy***
activated partial thromboplastin time (aPTT)	normal or slightly prolonged	slightly shortened
Platelet count	Normal, increased or decreased	decreased
Fibrinogen	elevated	elevated
D-dimer	elevated	elevated
Factor VIII activity	elevated	elevated
VWF antigen	elevated	elevated
Protein S	Decreased	Decreased

Conflict of interest

The authors declare no conflicts of interest.

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