Thromboprophylaxis and Anticoagulation Strategy for COVID-19 in Pregnant Patients

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Abstract
Coagulopathy and thromboembolic events may present as serious complicationsof severe Covid-19 infection..These are associated with higher risk of mortality. As pregnancy is a hypercoagulable condition, thromboprophylaxis can reasonably be considered for pregnant women with COVID-19, particularly for those who have severe disease. The objective of this review article is to highlight appropriate thromboprophylaxis and anticoagulant therapy for them. It involves studying standard international guidelines of various professional societies, including the Royal College of Obstetricians and Gynecologists, AmericanCollege of Obstetricians and Gynecologists,The Society of Maternal Fetal Medicine and American Society of Hematology.Both printed and online journals are explored.Use of anticoagulation therapy during pregnancy and labor needs specialized care and planning.The preferred anticoagulants during pregnancy are low-molecular weight heparin and unfractionated heparin compounds.Direct-acting oral anticoagulants are not regularly used during pregnancy in consideration of safety. As thrombotic risk, coagulopathy and disseminated intravascular coagulation (DIC) are relevant in COVID-19 infection, safe and appropriate anticoagulant interventions should be prescribed to hospitalized pregnant patients with COVID-19 to mitigate the risk of thrombosis and mortality.

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Introduction

Infections are often followed by triggering of the blood coagulation system. These derangements may range from delicate activation of hemostasis evidenced by wakening of sensitive markers for coagulation factors to relatively stronger hemostatic activation depicted by slight decline in platelet count and prolongation of clotting times to fulminant disseminated intravascular coagulation [DIC] distinguished by simultaneous widespread microvascular thrombosis and profuse bleeding from different sites. There is enough evidence that activation of coagulation system together with inflammatory activation can cause microvascular thrombosis and consequently advances to multiple organ failure in patients with severe infections. Infection-associated coagulopathy has been manifested as an independent predictor of organ failure in patients with sepsis.[1]

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COVID-19-associated Coagulopathy and Thrombosis

Infection-related abnormalities of coagulation are very relevant in COVID-19. COVID-19 has often been found associated with inflammation and a prothrombotic state with rise of fibrin, fibrin degradation products, fibrinogen, and D-dimers.[2] Some studies reveal that elevations in these markers have been associated with worse clinical outcomes.[3] Furthermore, substantial proportion of patients with severe COVID-19 infection develop venous and arterial thromboembolic complications. The incidence ranges from 3 to 37% for deep venous thrombosis [DVT], 2.8 to 3.8% for arterial thrombotic events and 7 to 35% for pulmonary embolism [PE]. The resultant coagulopathy in COVID-19 infected patients is associated with higher risk of mortality.

Thromboprophylaxis During Pregnancy in the context of COVID-19

Pregnancy is considered as a hypercoagulable condition. The risk of thromboembolism is considerably higher in pregnant women in comparison to nonpregnant individuals.[4]The American College of Obstetricians and Gynecologists recommends that although there are no established data in favor or against thromboprophylaxis in the context of COVID-19 in pregnancy, thromboprophylaxis can reasonably be considered for pregnant women hospitalized with COVID-19, particularly for those who have severe disease.[5] Various professional societies, including the RCOG, ACOG and American Society of Hematology have guidelines that precisely address the management of VTE in the context of pregnancy.[6,7]

Anticoagulants during Pregnancy

Conventionally, the preferred anticoagulants during pregnancy are heparin compounds. Specifically low-molecular weight heparin and unfractionated heparin are administered for the prevention and treatment of VTE in pregnancy due to the reliability and easy administration.[8] The Society of Maternal Fetal Medicine also recommended low molecular weight heparin in critically ill or mechanically ventilated pregnant patients.[9] Direct-acting oral anticoagulants are not regularly used during pregnancy in consideration of safety.[7] Rivaroxaban is a pregnancy category C group drug, which may cause harmful effects of the fetus and neonate. Warfarin should be avoided in pregnant women as prophylaxis and therapeutic option, regardless of their COVID-19 status, specifically during the first trimester due to the concern for teratogenicity and also during the third trimester due to possibility of massive bleeding due to sudden onset of labor.

Laboratory parameters of COVID-19-associated Coagulopathy

In COVID-19, derangement of coagulation is relatively mild in uncomplicated patients and more severe in patients admitted to intensive care unit [ICU].Covid-19 pneumonia has been reported to be associated with an increase in INR, aPTT, D-dimer and fibrin degradation products.The increase in these four parameters correlates with the severity of the disease. As there is physiological rise of D-Dimer level throughout pregnancy,only its elevation is not considered as a reliable predictor of VTE. But elevated D-dimer [DD] is an important feature. Some studies reveal that increasing DD levels are associated with progression to acute respiratory distress syndrome and death.Prothrombin time [PT] is slightly prolonged. High fibrinogen and factor VIII are other distinctive features of the COVID-19 coagulopathy and their levels parallel the disease severity. Thrombocytopenia is not very common, it has been observed in 18 to 36% of hospitalized patients, antithrombin is low (or normal) and protein C is normal or increased.[10,11]

Risk factors for venous thromboembolism in pregnancy and puerperium[12]

Pre-existing:

- Previous VTE
- Thrombophilia
- Medical comorbidities e.g. type I diabetes mellitus with nephropathy, sickle cell disease, cancer, heart failure, active SLE, inflammatory polyarthropathy, nephrotic syndrome.
- Age > 35 years
- Obesity (BMI ≥ 30 kg/m^2) either prepregnancy or in early pregnancy.
- Parity ≥ 3
- Smoking

Obstetric risk factors:

- Multiple pregnancy
- Current pre-eclampsia
- Caesarean section
- Prolonged labor (> 24 hours)
- Mid-cavity or rotational operative delivery Stillbirth
- Preterm birth
- Postpartum hemorrhage

New onset/transient:

- Any surgical procedure in pregnancy or puerperium except immediate repair of the perineum, e.g. appendicectomy, postpartum sterilization, bone fracture
- Hyperemesis, dehydration
- Ovarian hyperstimulation syndrome,
- Assisted reproductive technology (ART), in vitro fertilization (IVF)
- Current systemic infection (requiring intravenous antibiotics or admission to hospital)e.g. pneumonia, pyelonephritis, postpartum wound infection.
- Long-distance travel (> 4 hours)

COVID-19 Anticoagulation Treatment[13]

Anticoagulation therapy during pregnancy and delivery needs specialized care and planning.

Prophylactic anticoagulation

VTE prophylaxis will be recommended for COVID-19 pregnant patients who are low risk.

Low risk COVID-19 pregnant patients

- Not receiving mechanical ventilation
- D-Dimer < 6 mg/L
- End Stage Renal Disease (ESRD) or IHD without clotting

Contraindications

Platelets < 25 K/uL or Fibrinogen < 50 mg/dLor active bleeding

All low risk hospitalized pregnant women with confirmed COVID-19 infection should receive prophylactic unfractionated heparin to reduce risk of venous thromboembolism.

Trimester	Dosing of Heparin
1st	5000-7500 units SUBQ Q12H
2nd	7500-10000 units SUBQ Q12H
3rd	10000 units SUBQ Q12H

Therapeutic anticoagulation

Therapeutic anticoagulation will be recommended for COVID-19 pregnant patients who are considered high risk or diagnosed with an acute VTE.

High risk COVID-19 patient (for all hospitalized patients)

- Receiving mechanical ventilation and D-dimer > 6 mg/L
- Or Acute kidney injury (S Creatinine increase 0.3 mg/dL above baseline) +/- IHD with clotting.

  For a high risk critically ill pregnant patient less than 22 weeks gestation or post-partum, enoxaparin should be considered.

Gestational Age	Kidney Function	BMI (Kg/m^2)	Dosing of Enoxaparin
Less than 22 weeks	CrCL ≥ 30 mL/min	12-49.9≥ 50	1 mg/kg SUBQ Q12H 0.8 mg/kg SUBQ Q12H
	CrCL< 30mL/min	12-49.9≥ 50	1 mg/kg SUBQ 24H 0.8mg/kg SUBQ Q24H
ESRD or AKI			0.8 mg/kg SUBQ Q24H (MAX dose 1mg/kg Q24H)

Contraindications

Platelets < 50 K/uL or fibrinogen < 100 mg/dL or active bleeding

For a high risk critically ill pregnant patient greater than 22 weeks gestation, unfractionated heparin should be considered due to its short half-life and reversibility.

Direct thrombin inhibitors should be tried as a last resort with an assessment of benefit versus risk in patients who need anticoagulation and are unable to receive heparin products (e.g., heparin-induced thrombocytopenia).

Overall specific recommendations for pregnant women with COVID-19

- If antithrombotic therapy is prescribed during pregnancy prior to diagnosis of COVID-19, this should be continued.
- For non-hospitalized patients with mildCOVID-19 infection, anticoagulants and antiplatelet therapy should not be started for prevention of VTE or arterial thrombosis unless the patient has other indications.
- For pregnant patients hospitalized for severe COVID-19, prophylactic dose anticoagulation is recommended unless contraindicated.
- Like for non-pregnant patients, VTE prophylaxis after hospital discharge is not suggested for pregnant patients. Decision about continuation of VTE prophylaxis in the pregnant or postpartum patient should be individualized considering concomitant VTE risk factors.
- Use of anticoagulation therapy during pregnancy and labor needs specialized care and planning. It should be managed in pregnant patients with COVID-19 in a parallel way as in pregnant patients with other conditions that need anticoagulation in pregnancy.
- Unfractionated heparin, low molecular weight heparin and warfarin do not accumulate in breast milk and do not induce an anticoagulant effect in the newborn. So, they can be prescribed to breastfeeding women with or without COVID-19 who require VTE prophylaxis and treatment. In contrast, use of direct-acting oral anticoagulants during pregnancy is not routinely recommended due to lack of safety data.[7]

Conclusion

As thrombotic risk, coagulopathy and disseminated intravascular coagulation (DIC) are relevant in COVID-19 infection and the resultant coagulopathy is associated with higher risk of mortality, appropriate anticoagulant interventions should be considered to hospitalized pregnant patients with COVID-19 to mitigate the risk of thrombosis and mortality .

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