

## REVIEW

# A critical review of the pathophysiology of thrombotic complications and clinical practice recommendations for thromboprophylaxis in pregnant patients with COVID-19

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## Abstract

Those who are infected with *Severe Acute Respiratory Syndrome-related CoronaVirus-2* are theoretically at increased risk of venous thromboembolism during self-isolation if they have reduced mobility or are dehydrated. Should patients develop coronavirus disease (COVID-19) pneumonia requiring hospital admission for treatment of hypoxia, the risk for thromboembolic complications increases greatly. These thromboembolic events are the result of at least two distinct mechanisms – microvascular thrombosis in the pulmonary system (immunothrombosis) and hospital-associated venous thromboembolism. Since pregnancy is a prothrombotic state, there is concern regarding the potentially increased risk of thrombotic complications among pregnant women with COVID-19. To date, however, pregnant women do not appear to have a substantially increased risk of thrombotic complications related to COVID-19. Nevertheless, several organizations have vigilantly issued pregnancy-specific guidelines for thromboprophylaxis in COVID-19. Discrepancies between these guidelines reflect the altruistic wish to protect patients and lack of high-quality evidence available to inform clinical practice. Low molecular weight heparin (LMWH) is the drug of choice for thromboprophylaxis in pregnant women with COVID-19. However, its utility in non-pregnant patients is only established against venous thromboembolism, as LMWH may have little or no effect on immunothrombosis. Decisions about initiation and duration of prophylactic anticoagulation in the context of pregnancy and COVID-19 must take into consideration disease severity, outpatient vs inpatient status, temporal relation between disease occurrence and timing of childbirth, and the underlying prothrombotic risk conferred by additional comorbidities. There is currently no evidence to recommend the use of intermediate or therapeutic doses of LMWH in thromboprophylaxis, which may increase bleeding risk without reducing thrombotic risk in pregnant patients with COVID-19. Likewise, there is no evidence to comment on the role of low-dose aspirin in thromboprophylaxis or of anti-cytokine

**Abbreviations:** ACE, angiotensin converting enzyme; aPTT, activated partial thromboplastin time; COVID-19, novel coronavirus disease 2019; DIC, disseminated intravascular coagulation; ICU, intensive care unit; IL, interleukin; LMWH, low molecular weight heparin; PT, prothrombin time; SARS-CoV-2, Severe Acute Respiratory Syndrome CoronaVirus-2; VTE, venous thromboembolism.

and antiviral agents in preventing immunothrombosis. These unanswered questions are being studied within the context of clinical trials.

#### KEYWORDS

COVID-19, pregnancy, SARS-CoV-2, thromboembolic complications, thromboprophylaxis, venous thromboembolism

## 1 | INTRODUCTION

In March 2020, the World Health Organization declared the disease caused by Severe Acute Respiratory Syndrome-related CoronaVirus-2 (SARS-CoV-2) – COVID-19 – a global pandemic. While infection with SARS-CoV-2 may be asymptomatic, COVID-19 can present with a range of manifestations from a mild flu-like illness and symptoms such as rhinorrhea, anosmia and diarrhea, to severe disease. The latter could involve pneumonia with hypoxia that requires admission to hospital, and may sometimes develop into acute respiratory distress syndrome or result in multiorgan failure and death.<sup>1</sup> Hemostatic changes and high rates of thrombotic complications have been reported in patients with severe COVID-19.<sup>2</sup> As pregnancy is a prothrombotic state, the possibility of an increased risk of thrombosis 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 suspected or confirmed COVID-19. However, these recommendations are inconsistent and based on limited evidence. This paper describes the pathophysiology of thromboembolic complications in patients with COVID-19, and presents a critical appraisal of clinical practice recommendations for thromboprophylaxis in pregnant and postpartum women with COVID-19, being managed in ambulatory and inpatient settings.

## 2 | PATHOPHYSIOLOGY OF THROMBOTIC COMPLICATIONS IN PATIENTS WITH COVID-19

Patients with severe COVID-19 may be at risk for pulmonary thromboembolic complications through at least two distinct mechanisms – immunothrombosis and hospital-associated venous thromboembolism (VTE).<sup>2-6</sup> An appreciation of these different pathophysiological mechanisms is crucial to understanding the rationale behind recommendations for thromboprophylaxis.

### 2.1 | Immunothrombosis

In evolutionary terms, the blood coagulation system developed as an effector of the immune response, with the laying down of fibrin restricting the dissemination of pathogens within the body.<sup>7</sup> Acute viremia, as with SARS-CoV-2, results in the activation of monocytes/

#### Key message

We review the pathophysiology of thromboembolic complications associated with COVID-19 and critically appraise recommendations for thromboprophylaxis in pregnant women with COVID-19.

macrophages, which produce cytokines such as interleukin-6 (IL-6) and tumor necrosis factor that can potentially trigger the blood coagulation cascade.<sup>8</sup>

The entry of SARS-CoV-2 into human target cells is facilitated by the angiotensin converting enzyme-2 (ACE-2) receptor.<sup>9</sup> These receptors are found in many tissues including pneumocytes, the heart, kidney, endothelium, macrophages and intestine. The bulk of ACE-2-expressing cells are the alveolar epithelial type II cells (type-II pneumocytes) of the lung.<sup>10</sup> The abundance of ACE-2-expressing cells in the pulmonary alveoli and the lung's vast surface area, make it highly susceptible to inhaled viruses and it is the most vulnerable target organ.<sup>11</sup> Acute viremia, such as with SARS-CoV-2, could result in a severe, multifaceted inflammatory reaction mediated through proinflammatory cytokines.<sup>12</sup> A recent study of patients with severe COVID-19 demonstrated a correlation between IL-6 and fibrinogen levels,<sup>3</sup> further supporting the theory that massive activation of the acute phase response, with increased production of coagulation factors, appears to be the predominant prothrombotic mechanism in COVID-19.

The hallmark of acute lung injury is extravascular fibrin deposition. Immunothrombosis describes the process where the inflammatory reaction, together with 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.<sup>4</sup>

Activation of monocytes and the subsequent cytokine surge can also result in endothelial cell activation, which involves the change from an antithrombotic phenotype to procoagulant phenotype. Endothelial activation, which extends beyond the lungs, results in multiple changes including the exocytosis of large von Willebrand factor multimers from Weibel Palade granules, loss of heparan sulfate from the endothelial surface, platelet activation, downregulation of thrombomodulin and production of nitric oxide.<sup>13</sup> Endothelial activation thus further contributes to the prothrombotic state.

## 2.2 | Hospital-associated venous thromboembolism (VTE)

All three mechanisms of Virchow's triad are activated in severe COVID-19 infection, since patients have reduced mobility, a pro-thrombotic state and endothelial activation, putting them at high risk for hospital-associated VTE (VTE occurring in hospital or up to 90 days post discharge).<sup>14</sup> A cross-sectional study that included 81 non-pregnant patients admitted to the intensive care unit (ICU), none of whom received thromboprophylaxis, reported a 25% (20/81) prevalence of VTE.<sup>15</sup> A number of European studies have reported what they describe as high rates of VTE (20%-42.6%) in patients admitted to the ICU and medical wards with COVID-19, despite administration of prophylactic or therapeutic doses of anti-coagulation.<sup>2,5,6</sup> An alternative explanation is that the high rates of VTE, and in particular the pulmonary emboli described on computerized tomography (CT) or pulmonary angiography, may reflect localized pulmonary immunothrombosis rather than thrombi that have embolized from the deep veins of the lower limb. This is supported by the lower incidence of deep vein thromboses of the extremities and that the majority of emboli in the pulmonary vasculature are segmental and sub-segmental thrombi as opposed to central or lobar pulmonary emboli.<sup>5</sup>

Thus, patients with severe or critical COVID-19 are at risk of both immunothrombosis as well as hospital-associated VTE. Although thromboprophylaxis is well-established to prevent the risk of hospital-associated VTE, its role in preventing immunothrombosis remains uncertain.<sup>14</sup>

## 3 | HEMOSTATIC CHANGES AND THEIR CLINICAL IMPLICATIONS IN PATIENTS WITH COVID-19

Initial reports from Wuhan, China, suggested disseminated intravascular coagulation (DIC) as a possible explanation for the markedly elevated D-dimers and prolonged prothrombin time (PT) in non-survivors with COVID-19 pneumonia.<sup>16</sup> However, it is now clearer that the clinical picture is not that of DIC, as there is no increased bleeding, platelet levels are not low, fibrinogen levels (which should be low in DIC due to consumption) are very elevated, and the changes do not fulfill the International Society on Thrombosis and Hemostasis (ISTH) guidelines on diagnosing DIC.<sup>17</sup> The hemostatic changes encountered in COVID-19 are explained below.

### 3.1 | Elevated D-dimers

Although D-dimers are a breakdown product of fibrin (fibrinolysis), D-dimers are also produced in inflammatory states and in lung injury<sup>18</sup> and are known to be elevated, often significantly, with various viral infections.<sup>19</sup> Not surprisingly, in patients with COVID-19, very high levels of D-dimers have been seen, and data from Wuhan

suggest that D-dimers have value as a prognostic marker and may correlate with the severity of illness.<sup>20,21</sup> The origin of the very elevated D-dimer levels in COVID-19 patients may at least in part be the pneumocytes, which can produce urokinase.

### 3.2 | Elevated fibrinogen

Contrary to what is described in DIC, fibrinogen levels are not reduced in patients with COVID-19, despite marked increases in D-dimer.<sup>22</sup> Instead, levels are generally very elevated, consistent with an ongoing acute phase response.<sup>23</sup>

### 3.3 | Platelets

Platelet counts are not substantially reduced in patients with COVID-19.<sup>22</sup>

### 3.4 | Antiphospholipid antibodies

At least two research papers have described antiphospholipid antibodies associated with COVID-19.<sup>24,25</sup> However, the definition of persistent antiphospholipid antibodies requires the presence of two positive tests, 12 weeks apart. As both studies only tested once, they cannot confirm their presence of persistent antiphospholipid antibodies. Indeed, transient antiphospholipid antibodies are frequently seen with acute infections, and false-positive lupus anticoagulant results are encountered in those receiving heparin.<sup>26</sup>

### 3.5 | Prothrombin time (PT) and activated partial thromboplastin time (aPTT)

PT and aPTT may be prolonged as a preterminal event, as DIC is common in multiorgan failure.<sup>16</sup> However, its value in treatment decisions is limited. It should be noted that subtle PT changes may go unnoticed if PT is reported as the international normalized ratio (INR).<sup>27</sup>

### 3.6 | Factor VIII and von Willebrand factor

These acute phase reactants are markedly increased in COVID-19, as part of the acute phase response and, in isolation, should not influence management decisions.

### 3.7 | Clinical implications

Despite these profound changes in hematologic parameters, the general consensus is that it would be premature and potentially

**TABLE 1** Reference ranges of trimester-specific levels of fibrinogen, D-dimer and activated partial thromboplastin time (aPTT) in pregnancy (from Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ, Spong CY. *Williams Obstetrics*, 23rd Ed. New York (NY): McGraw-Hill Professional, 2009, with permission from the publisher) (with permission from the publisher).<sup>51</sup>

	1st trimester	2nd trimester	3rd trimester
Fibrinogen (g/L)	2.4-5.1	2.9-5.4	3.7-6.2
D-dimer (µg/mL)	0.05-0.95	0.32-1.29	0.13-1.7
Activated partial thromboplastin time [aPTT] (seconds)	24.3-38.9	24.2-38.1	24.7-35.0

dangerous to recommend the use of these biomarkers to guide clinical decision-making with regard to admission, planning diagnostic tests, identifying high-risk cases that need treatment in the ICU, or to guide the administration of blood products in the absence of bleeding.<sup>14,28-30</sup> These decisions must be taken after complete clinical assessment. It is also suggested that blood draws are minimized, as they would prove an unproductive burden on finite phlebotomy and laboratory resources, while also result in iatrogenic anemia in seriously ill patients.<sup>28,29</sup>

#### 4 | COVID-19 AND PREGNANCY

It was initially thought that pregnant women could be at high risk of severe complications from COVID-19 as was seen in previous influenza pandemics such as influenza A virus subtype H1N1 – A(H1N1) – in 2009-2010.<sup>31</sup> Pregnant women are more susceptible to develop severe forms of certain viral infections due to pregnancy-related immune changes, at higher risk of hypoxemia given pregnancy-induced changes in their lung mechanics, and more likely to develop acute respiratory distress syndrome due to physiologically increased plasma volume and capillary leak.<sup>32</sup> Recent data from the USA Centers for Disease Control and Prevention (CDC) suggests 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.<sup>33</sup> Similarly, the public health agency of Sweden has reported a fourfold increased risk of intubation in age-matched pregnant vs non-pregnant women with COVID-19.<sup>34</sup> Although mortality from COVID-19 in pregnancy may not be as high as with previous coronavirus epidemics,<sup>35</sup> women with COVID-19 can become severely unwell, and a high level of clinical vigilance is important.<sup>36</sup>

The current literature does not signal an increased likelihood of hospital-associated VTE or immunothrombosis in pregnant women with COVID-19 when compared with non-pregnant patients with COVID-19. No VTE were reported in a USA cohort,<sup>37</sup> where 58% and 16% were on prophylactic and therapeutic unfractionated heparin and low molecular weight heparin (LMWH), respectively.<sup>38</sup> Similarly, no VTE was reported in a cohort of 427 pregnant women hospitalized with COVID-19 across the UK, although no details were provided on thromboprophylaxis.<sup>39</sup> Nevertheless, clinicians must remain vigilant.

Pregnancy is a hypercoagulable state characterized by increased prothrombotic factors, such as factors VII, VIII, X, XII, von Willebrand

factor and fibrinogen, as well as decreased protein S and altered fibrinolysis, especially in the peripartum period.<sup>40</sup> Postpartum, the prothrombotic changes of coagulation and fibrinolysis take up to 12 weeks to return to the pre-pregnancy state.<sup>41</sup> Normal levels of several coagulation biomarkers differ in pregnancy. Fibrinogen levels can double, the aPTT becomes slightly shortened,<sup>40</sup> D-dimer levels increase throughout pregnancy and, in 99% of women, levels in the third trimester are above the established normal for non-pregnant patients.<sup>42</sup> Prognostic coagulation parameters for COVID-19 must be interpreted in the light of pregnancy-specific reference ranges (Table 1). Coagulation values for COVID-19 severity have not yet been established in pregnancy and it is not known whether thresholds used in the non-pregnant population can be translated to an obstetric population.

#### 5 | RECOMMENDATIONS FOR PROPHYLACTIC ANTICOAGULATION IN PREGNANT WOMEN WITH COVID-19

##### 5.1 | Review of international guidelines

We reviewed 35 guidelines from professional societies, representing 14 countries and seven international organizations. Of these, 14 made recommendations for the prevention of VTE in pregnant patients with suspected or confirmed SARS-CoV-2 infection. A summary of recommendations from 10 of these guidelines, which made distinct recommendations, is presented in Table 2. It must be noted that published guidance on thromboprophylaxis for COVID-19 in pregnancy is extremely inconsistent and is not based on evidence, only on expert opinion.

##### 5.2 | Clinical practice recommendations based on current knowledge, published recommendations and expert opinion

It is becoming increasingly evident that decisions about initiation and duration of prophylactic anticoagulation in the context of pregnancy and COVID-19 should be individualized. These decisions should take into consideration four important factors: disease severity, whether the patient is hospitalized or isolating at home, the occurrence of disease in relation to the timing of childbirth, and the underlying prothrombotic risk conferred by comorbidities, inherited or

**TABLE 2** Summary of recommendations from international societies on the prevention of thromboembolic events in pregnant patients with COVID-19

Society (country)	Antepartum, self-isolating at home	Antepartum, hospitalized	Postpartum
Royal College of Obstetricians and Gynaecologists (RCOG) (UK) <sup>43</sup>	<p>Ensure hydration and mobilization.</p> <p>Those already receiving thromboprophylaxis should continue.</p> <p>If VTE risk score at booking visit is <math>\geq 3</math>, prophylactic LMWH should be recommended (and continued until recovery from illness - 7-14 days).</p> <p>For others, assess VTE risk through a remote or in-person clinical review and prescribe thromboprophylaxis on a case-by-case basis.</p>	VTE prophylaxis should be prescribed during admission unless contraindicated or birth expected within 12 hours.	<p>Conduct VTE risk-assessment following birth.</p> <p>For those with confirmed SARS-CoV-2 infection, prescribe prophylactic LMWH, unless contraindicated <math>\times 10</math> days.</p>
Queensland Clinical Guidelines (Australia) <sup>52</sup>	Consider VTE prophylaxis even in the absence of other risk factors. Reduced mobility resulting from self-isolation at home or from admission may also increase risk.		
Institute of Obstetricians and Gynaecologists - Royal College of Physicians of Ireland (RCPI) (Ireland) <sup>53</sup>	<p>Isolation at home is likely to cause a significant reduction in daily mobility, which may increase the risk of VTE in all pregnant women. The risk of thrombosis among this group is high and consideration for VTE prophylaxis should occur following discussion with a hematologist.</p>	<p>VTE risk assessment should be carried out on all admitted with COVID-19 infection.</p> <p>VTE prophylaxis with LMWH at standard obstetric dosing is recommended unless within 12 hours of birth.</p>	<p>For those not critically ill, prophylaxis should be considered for at least 10 days postpartum as per guidelines on sepsis in the peripartum period.</p> <p>For those critically ill, prophylaxis should be continued following discharge from ICU for 6 weeks.</p>
Philippine Obstetrical and Gynecological Society (POGS); Philippine Society Of Maternal Fetal Medicine (PSMFM) (Philippines) <sup>54</sup>	Administer Prophylactic LMWH, unless delivery is expected within the next 12 hours.		NA
The International Society of Ultrasound in Obstetrics & Gynecology (ISUOG) (International) <sup>55</sup>	Prophylactic LMWH should be considered in outpatient self-isolating patients on a case-by-case basis, according to risk factors.	Thromboprophylaxis must be considered for all pregnant women managed as inpatients, especially those with severe disease, unless delivery is imminent	NA
International Society for Infectious Diseases in Obstetrics and Gynecology (ISIDOG) <sup>56</sup>	Every parturient diagnosed with COVID-19 should receive LMWH for at least 10 days, even in the absence of other risk factors. It should even be considered to increase the dose of the LMWH in severely ill patients.		LMWH for thromboprophylaxis recommended. Dose should preferably double if severe COVID-19 illness.

(Continues)

TABLE 2 (Continued)

Society (country)	Antepartum, self-isolating at home	Antepartum, hospitalized	Postpartum
Collège National Des Gynécologues et Obstétriciens Français (CNGOF) (France) <sup>57</sup>	Risk stratification according to personal risk factors, and oxygen requirements: Weak risk = no prophylaxis, Medium risk = LMWH given at standard prophylaxis, High risk = LMWH given at higher prophylaxis dosage. Duration of prophylaxis should be maintained until recovery. Do not start prophylaxis if delivery is approaching		NA
Swiss Society of Gynecology and Obstetrics (Switzerland) <sup>58</sup>	COVID-19 patients have a higher thromboembolic risk, which is further increased by the pregnancy and postpartum situation. Consequently, thromboembolic prophylaxis should be provided on an interdisciplinary basis for COVID-19 patients during the pregnancy and postpartum.		
Swedish Society of Obstetrics and Gynecology (Sweden) <sup>59</sup>	Patients with mild to moderate symptoms = normal dose prophylaxis; Patients with pronounced symptom picture, where immobilizing hospital care is necessary; regardless of hemostasis effect = High-dose prophylaxis, and correction of hemostasis if necessary. This assessment must be done individually. Doses are based on entry weight being above or below 90 kg.		
COVID Collaborative Group, Barcelona (Spain) <sup>60</sup>	<ul style="list-style-type: none"> <li>In women with infection &gt;4 weeks before delivery, thromboprophylaxis should follow standard criteria.</li> <li>Prolonged bed-rest should be discouraged given the risk of thrombosis associated both with pregnancy and COVID infection.</li> </ul>	Prophylactic LMWH is indicated during hospitalization and 2 weeks thereafter (independent of D-dimer levels), after obtaining consent for compassionate use	Postpartum prophylactic LMWH is indicated during hospitalization and 6 weeks thereafter, due to risk of deep venous thrombosis and pulmonary thromboembolism in patients with severe COVID. Doses based on entry weight being above or below 80 kg

LMWH, low molecular weight heparin; VTE, venous thromboembolism.

acquired thrombophilias, pregnancy, the postpartum period, as well as COVID-19. Based on these parameters, we present a pragmatic approach to thromboprophylaxis in pregnancy for women with SARS-CoV-2 infection and COVID-19 (Table 3). This approach draws from published guidance and limited evidence and is also based on expert opinion.

### 5.2.1 | Antepartum management of patients isolating at home

Women who are relatively inactive may be at greater risk of developing VTE. Hence, advice on mobilization and hydration is crucial. Several societies recommend considering the use of pharmacological prophylaxis, even in the absence of additional risk factors. However, such an approach seems overzealous, especially in the absence of evidence to suggest a significantly increased risk of thrombosis, and considering that many of these women are likely to be otherwise well. Risk stratification is vital to determine which patients are at increased risk for developing VTE, based on their comorbidities. Pregnant women with other indications for prophylactic or therapeutic anticoagulation should be continued on their anticoagulation regimen, independently from their COVID-19 status.

### 5.2.2 | Management of women admitted because of COVID-19

There is a general consensus that hospitalized patients with COVID-19 should receive standard doses of thromboprophylaxis. Heparins are the anticoagulants of choice in the prevention of thrombotic complications for both pregnant and non-pregnant patients with COVID-19, unless there are absolute or relative contraindications such as active bleeding, low platelet count, heparin-induced thrombocytopenia or an anticipated surgical procedure or delivery within 12 hours. Given the problems associated with unfractionated heparin – its unreliable pharmacokinetics and short half-life, the need for continuous infusions or multiple daily doses, more frequent monitoring, a longer time required to achieve target aPTT and increased health care provider exposure due to frequency of administration and blood draws – once-daily dosing with LMWH should be the preferred method for thromboprophylaxis for all pregnant inpatients.<sup>29,43</sup> Prolonged PT or aPTT is not a contraindication to administering thromboprophylaxis. In keeping with published protocols for the peripartum period, LMWH would need to be withheld for 12 hours prior to anticipated delivery, or to facilitate administration of regional analgesia. As outlined in Table 3, a clear distinction should be made between those who test positive but are admitted

**TABLE 3** Clinical recommendations on thromboprophylaxis for pregnant and postpartum women with confirmed or suspected COVID-19

	Isolating at home		Inpatient hospitalized for non-COVID-related reason but asymptomatic or minor symptoms such as anosmia		Inpatient with pneumonia requiring supplementary oxygen but not ventilation	Inpatient with pneumonia requiring mechanical ventilation
	Low risk pregnancy and low risk for VTE	Risk factors for VTE – not receiving thromboprophylaxis	Receiving thromboprophylaxis	Risk factors for VTE – not receiving thromboprophylaxis	Inpatient with pneumonia requiring supplementary oxygen but not ventilation	Inpatient with pneumonia requiring mechanical ventilation
ANTEPARTUM	Encourage hydration and mobilization	Conduct risk assessment & consider thromboprophylaxis on an individual basis	Continue thromboprophylaxis	Conduct risk assessment & consider thromboprophylaxis on an individual basis	Give thromboprophylaxis (LMWH)	Give thromboprophylaxis (LMWH) - dose according to local critical care protocol
PERIPARTUM	NA	Follow local policy for interruption of anticoagulation prior to delivery				
POSTPARTUM (while in hospital)	Usual care	Conduct risk assessment & consider thromboprophylaxis on an individual basis	Continue usual thromboprophylaxis	Conduct risk assessment & consider thromboprophylaxis on an individual basis	Give thromboprophylaxis (LMWH)	Give thromboprophylaxis (LMWH) - dose according to local critical care protocol
POSTPARTUM (upon discharge)	Usual care Encourage hydration and mobilization	Usual care & consider thromboprophylaxis on an individual basis. Encourage hydration and mobilization	Decision based on primary indication for thromboprophylaxis. Encourage hydration and mobilization	Conduct risk assessment & consider thromboprophylaxis on an individual basis. Encourage hydration and mobilization	Conduct risk assessment & consider extended thromboprophylaxis on an individual basis. Encourage hydration and mobilization	Conduct risk assessment & consider extended thromboprophylaxis on an individual basis. Encourage hydration and mobilization

LMWH, low molecular weight heparin; NA, not applicable; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; VTE, venous thromboembolism.

for obstetric and other conditions that are unrelated to COVID-19 and those who are only mildly symptomatic or asymptomatic vs those who have COVID-19 pneumonia requiring supplemental oxygen or ICU admission and mechanical ventilation.

### 5.2.3 | Postpartum period and following discharge from hospital

There is considerable uncertainty around the optimal duration of anticoagulation following discharge, in the postpartum period, once prophylactic anticoagulation is initiated for COVID-19 in pregnancy; the need for modification to thromboprophylactic regimens based on underlying comorbidities such as preeclampsia, obesity and diabetes; or whether the mode of delivery should be used to determine the duration of anticoagulation. The decision regarding the need and duration for thromboprophylaxis depends on a number of factors including the temporal relation between active disease and delivery, disease severity and whether the patient requires thromboprophylaxis for indications other than COVID-19. As summarized in Table 3, in patients with moderate to severe disease, post-discharge thromboprophylaxis may need to be considered because of the long duration of illness and prolonged period of recovery, with increased likelihood of immobility and risk of superinfection.<sup>29</sup> Moreover, thromboprophylaxis may need to be considered for 10 days to 6 weeks postpartum, depending on disease severity, especially in those at increased risk for VTE with low risk of bleeding.<sup>29,43</sup>

## 6 | PHARMACOLOGIC OPTIONS FOR REDUCING THE RISK OF THROMBOEMBOLIC COMPLICATIONS IN PREGNANT WOMEN WITH COVID-19

### 6.1 | Heparins

In addition to their anticoagulant properties, heparins may possibly be beneficial in patients with COVID-19 because of their anti-inflammatory properties, which include binding to inflammatory cytokines, inhibiting neutrophil chemotaxis and leukocyte migration, neutralizing the positively charged peptide complement factor C5a and sequestering acute phase proteins.<sup>44</sup> In addition, they dampen the inflammatory response by inhibiting thrombin and decrease the level of inflammatory biomarkers. Theoretically they have anti-viral properties on account of their polyanionic nature, which renders them effective inhibitors of viral attachment to the ACE-2 receptor, probably through structural analogies with heparan sulfate.<sup>44</sup> Early data from Wuhan where routine thromboprophylaxis was initially not given to severely ill patients with COVID-19 pneumonia showed that subsequent use of heparin was associated with decreased mortality.<sup>22</sup> Although the mechanisms are unknown, it seems likely this may relate to reduced rates of VTE.

## 6.2 | Beyond anticoagulant therapy

A crucial consideration in patients with COVID-19 is that thrombotic complications also include immunothrombosis, which may not be prevented by administration of anticoagulants.<sup>23,45</sup> Other treatments that could be considered are discussed below.

### 6.2.1 | Anti-cytokine therapy

The simultaneous administration of anti-cytokine agents such as IL-6 and IL-1 antagonists could both ameliorate diffuse immunothrombosis and reduce the prothrombotic changes resulting in an increased risk of overt VTE.<sup>23,46</sup> Anakinra (IL-1 receptor antagonist) and tocilizumab (humanized monoclonal antibody against the IL-6 receptor) have a favorable safety profile during pregnancy and lactation, and could be considered within the confines of a clinical trial.<sup>47</sup>

### 6.2.2 | Antivirals

Although anti-cytokines are effective in low-grade arterial inflammation in the absence of overt infection, severe and ongoing viral infection may render the use of anti-cytokines in isolation ineffective.<sup>23</sup> Antivirals could help prevent replication of the virus and therefore could be considered in addition to anti-cytokine agents and anticoagulation. Antiretroviral lopinavir/ritonavir and other antivirals such as remdesivir are considered relatively safe for use during pregnancy and lactation and are being studied as part of ongoing clinical trials.<sup>47</sup>

### 6.2.3 | Correction of hypoxia

Hypoxia plays a critical role in perpetuating the hemostatic abnormalities. Supplemental oxygen should be administered to those unable to maintain an oxygen saturation >95% on room air.<sup>48</sup>

## 7 | UNANSWERED QUESTIONS AND ONGOING RESEARCH

Guidance on thromboprophylaxis for pregnant women with COVID-19 is still largely based on expert opinion. In addition to uncertainties surrounding postpartum thromboprophylaxis, other unanswered questions regarding prevention of thrombosis in pregnant patients with COVID-19 include the role of other antithrombotic agents such as low-dose aspirin. There are currently no data to support or refute the role of low-dose aspirin in the prevention of thromboembolic complications in pregnant or non-pregnant patients with COVID-19. In addition, the use of higher doses (intermediate or therapeutic vs prophylactic) of heparin has been suggested in hospitalized non-pregnant patients with COVID-19.<sup>4</sup> High fibrinogen levels (as seen in the context of severe COVID-19) make patients more resistant to heparin agents,<sup>49</sup> which



supports the suggestion that prophylactic doses may be insufficient in the context of severe and critical COVID-19. There is anecdotal evidence from a study on 16 non-pregnant patients admitted to the ICU with acute respiratory distress syndrome that a procoagulant pattern, present on standard and viscoelastic tests despite routine thromboprophylaxis,<sup>3</sup> returned to values close to normal after 14 days of higher (intermediate) doses of LMWH.<sup>3</sup> However, returning a thromboelastographic trace to normal has not been correlated with reduced risk of VTE. At this time, there is no high-quality evidence to recommend the use of intermediate or high doses of LMWH in either non-pregnant or pregnant patients. Moreover, higher doses of LMWH may increase the risk of bleeding,<sup>45</sup> with no further reduction in the risk of thrombosis. Based on current evidence, therefore, we recommend that intermediate and therapeutic doses of LMWH should not be administered to pregnant patients with COVID-19 outside of clinical trials.

Although clinical trials aimed at evaluating the optimal type, dose and frequency for antithrombotic therapy among patients with COVID-19 are ongoing worldwide, pregnant women have been excluded from several of these trials. The lack of information on therapeutic agents in pregnancy resulting from restricting the access of pregnant women to clinical trials may lead to a number of untoward outcomes, including the administration of unproven therapies, the denial or delay in administration of potentially effective medications, and over- or undertreatment due to lack of information on pregnancy-specific pharmacokinetics. This potentially exposes women to harm and highlights the importance of gathering data on the safety and effectiveness of antithrombotic therapies for COVID-19 in pregnancy.<sup>50</sup> Ensuring adequate representation of pregnant women in clinical trials evaluating antithrombotic therapies for COVID-19 is of paramount importance going forward. Until high-quality evidence from ongoing trials is available, clinicians should refrain from using intermediate and therapeutic doses of anticoagulants unless clinically indicated, and a multidisciplinary team should be involved in individualizing decisions on initiation and duration of prophylactic anticoagulation for pregnant women with COVID-19 based on the temporal nature of the event to childbirth, disease severity, inpatient vs outpatient management and the individual's underlying prothrombotic risk.

## CONFLICT OF INTERESTS

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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