Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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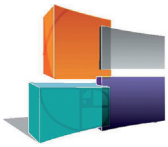

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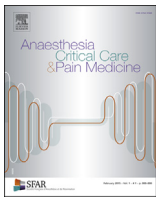

Review article

Coagulation changes and thromboembolic risk in COVID-19 obstetric patients

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As with most infections including the previous SARS-COV or MERS-COV pandemics [1], COVID-19-related disease causes a significant inflammatory state. Clinicians have observed abnormal laboratory tests results, such as increased values for D-dimers, suggesting that COVID-19 infection causes an exaggerated inflammatory response, now commonly called the cytokine storm. This inflammatory response appears to be proportional to the severity of the disease, as shown in patients presenting with severe COVID-19 [acute respiratory distress syndrome (ARDS)] and in deceased patients, suggesting that the magnitude of inflammatory response is a marker of disease severity [2–4]. Alterations in coagulation that appear as a result of the inflammatory state may also play a direct pathogenic role, mainly by causing thrombi (macro and micro) in various organs, reducing blood flow in capillaries and aggravating the local injury [5]. Blood concentrations of natural inhibitors such as antithrombin may also fall [4]. Endothelial cells are probably among the main targets of the virus. An increased incidence of embolic complications may be a marker of disease severity [6]. These phenomena probably also occur in the lungs, heart, brain and kidney, leading to multiple organ failure and even death [7,8]. At the other extreme, patients in whom the disease is paucisymptomatic generally display a much lower intensity of inflammatory response.

During previous viral outbreaks, maternal morbidity and mortality of pregnant women has been especially high [9,10]. With the current COVID-19 outbreak, outcomes in obstetric patients have not been worse than in the general population, but the inflammatory response in pregnant women with COVID-19 infection appears to be severe. In obstetric patients, interpretation of coagulation tests and possible abnormality may be even more challenging as they are confounded by pregnancy-induced coagulation changes. In normal pregnancy, fibrinogen concentration and D-dimer values increase, platelet count may decrease, both activated partial thromboplastin time (APTT) and prothrombin time are shorter due to the important rise of the plasma concentration of most coagulation factors. With COVID-19 infection, additional coagulation changes may occur, which may mirror the disease severity although robust data is still lacking. An increase in D-dimer concentrations has been observed, as well as a prolongation of both APTT and PT, the later leading to an increase in international normalised ratio (INR) values. Because these changes are confounded by pregnancy-induced increases in coagulation factors, laboratory results may not initially appear to be abnormal (i.e. falsely high as compared to non-pregnant values). Interestingly, the platelet count often remains minimally modified but in some cases, significant thrombocytopenia may occur [3].

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To date, there is scarce data to accurately report on COVID-19-associated coagulation changes in obstetric patients and identify possible mechanisms for the observed alterations. What we know has been extrapolated from studies in the non-pregnant population, from small series published to date assessing pregnant women, and from unpublished laboratory results on routine tests performed in French maternity units. In these cases, coagulation factor concentrations are often abnormally low (less than 100% and often in the range of 40–60%) and changes seem to occur in both "intrinsic" and "extrinsic" pathways. In the rare cases in which circulating anticoagulant antibodies were assessed, they were not found in the plasma of these pregnant women. In a recent report on three non-pregnant patients with severe COVID-19 infection, a major coagulopathic state was observed with thrombocytopenia, lengthened TT and highly increased D-dimer concentrations [11]. All three patients had multiple cerebral infarctions and antiphospholipid antibodies were detected.

Taken together, data obtained in pregnant and non-pregnant patients suggest that the underlying pathophysiology resulting in abnormal laboratory values is likely related to a (compensated) state of intravascular coagulation (DIC). In many patients, diagnostic criteria elaborated by the International Society on Thrombosis and Haemostasis (ISTH) are positive especially in patients with a severe illness [12]. Unfortunately, these criteria cannot be applied to pregnant women, reducing our ability to accurately characterise their coagulopathy.

Prolongation of APTT and PT will pose a significant challenge to the obstetric anaesthetist weighing risks of a general anaesthetic in a COVID-19 patient compared to those associated with a neuraxial procedure [13,14] (Appendix 1). The present consensus among French experts suggests that these above-mentioned abnormal coagulation parameters do not impede placement of a neuraxial block, since these changes more likely reflect hypercoagulability rather than an increased risk of bleeding. Indeed, a recently published Guidance suggests that abnormal coagulation results do not require correction in patients who are not bleeding [15]. Indeed, in the first small series from China, there was no apparent increase in bleeding incidence on the obstetrical side (i.e. same occurrence of postpartum haemorrhage although an increased use of oxytocic agents may be seen) [16,17] or anaesthetic complications (i.e. no report of neuraxial bleeding complications) when compared to usual practice [13,17]. In addition, due to the increased respiratory demand associated with COVID-19 pneumonia, respiratory reserve may be decreased and placement of epidural analgesia is likely to improve women's breathing efforts (and oxygenation).

Hypercoagulability increases morbidity by increasing the thromboembolic risk. Thromboembolic events may occur both during and after pregnancy. Pregnancy in itself increases the thromboembolic risk, which is even greater during the postpartum period. Due to additional coagulation changes induced by COVID-19 infection, this risk may even be greater. This is inferred from data in non-pregnant patients with severe COVID-19 infection in whom thromboembolic complications have been reported. For example, in a recent report from the Netherlands, a high incidence (i.e. 31%) of thrombotic complications has been observed in non-pregnant ICU patients infected by COVID-19 [18]. Anticoagulation (mainly low molecular weight heparin [LMWH]) has been suggested, in high non-prophylactic doses to reduce COVID-19 mortality [19]. In pregnant women however, there is no firm data and COVID-19 infection appears to be less severe than in non-obstetric patients, potentially explaining why thromboembolic complications have not yet been reported. Administration of LMWH is however suggested by several scientific bodies, mostly using prophylactic doses [15,20,21]. Specific indications remain unclear, but case by case evaluation of thromboembolic risk, including non-COVID-19 related risk factors, and multiplying the risk factor associated with infection should be considered [22]. During pregnancy (Appendix 2), French experts suggest administering LMWH to COVID-19 infected women with at least a moderate or severe thrombotic risk during the time period where clinical symptoms are present (and/or oxygen is required). Although it might be useful to maintain thromboprophylaxis for a longer period of time as recovery from COVID-19 infection may not be easily defined, the experts suggest preferring a shorter duration of treatment to reduce the risk of interaction with a complicated management of labour and/or neuraxial block placement, should delivery occur during the period of LMWH administration.

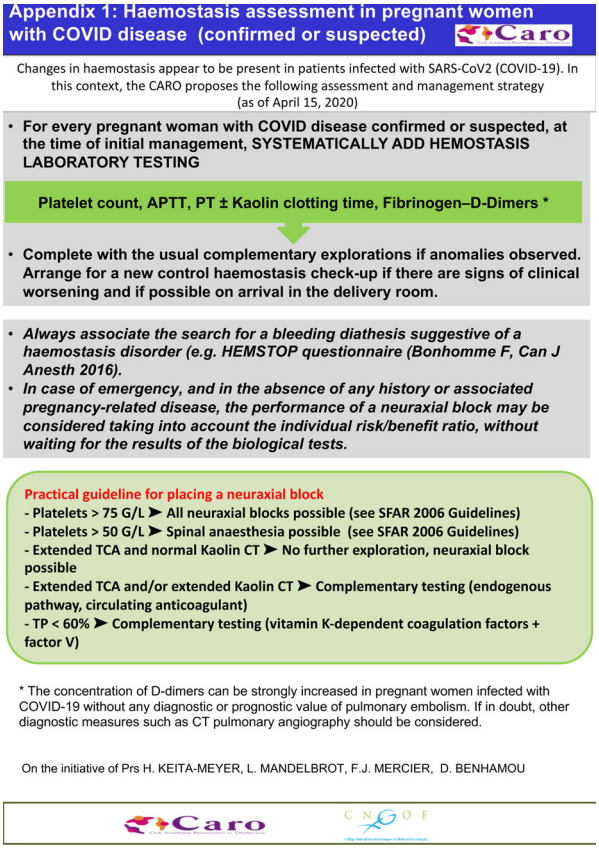
In postpartum patients with recent COVID-19 infection, benefits of thromboprophylaxis with LMWH outweigh the haemorrhagic risk, if one accepts that a strong correlation exists between the impressive biological disturbances and the risk of thromboembolic complications. Although vaginal delivery is associated 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. The optimal duration of anticoagulant treatment is unknown but should probably be adapted to the disease severity.

In women with postpartum haemorrhage, fresh frozen plasma, fibrinogen or tranexamic acid should be considered, along with antithrombin, and Tissue Plasminogen Activator with severe COVID-19 infection [23]. Tranexamic acid should be avoided in women with COVID-19-associated DIC [15].

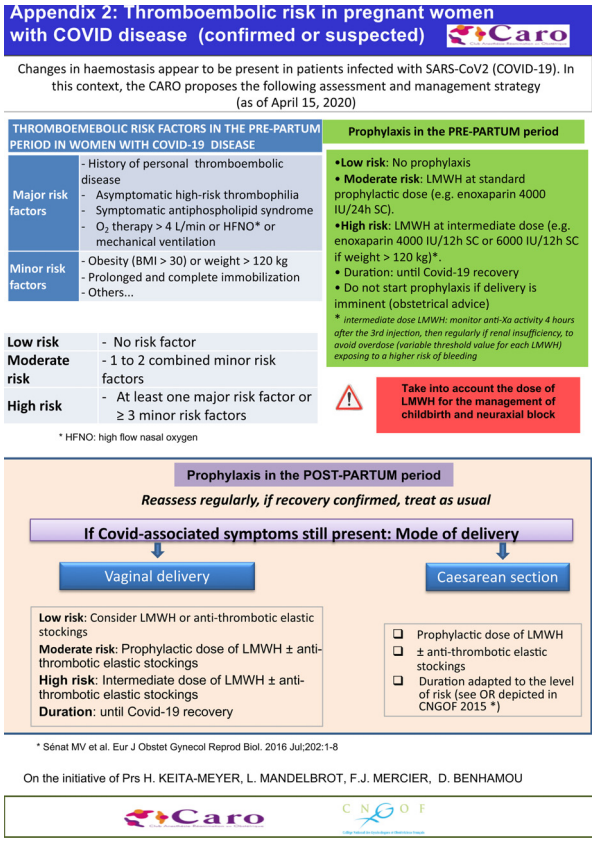
Disclosure of interest

The authors declare that they have no competing interest

Appendix 1. Appendix 1



Appendix 2



References

[1] Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol 2017;39(5):529–39. http://dx.doi.org/10.1007/s00281-017-0629-x.

[2] Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med 2020. http://dx.doi.org/10.1515/cclm-2020-0198 [pii:/j/cclm.ahead-of-print/cclm-2020-0198/cclm-2020-0198.xml.].

[3] Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. Clin Chim Acta 2020;506:145–8. http://dx.doi.org/10.1016/j.cca.2020.03.022.

[4] Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18(4):844–7. http://dx.doi.org/10.1111/jth.14768.

[5] Lillicrap D. Disseminated intravascular coagulation in patients with 2019-nCoV pneumonia. J Thromb Haemost 2020;18(4):786–7. http://dx.doi.org/10.1111/jth.14781.

[6] Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost 2020. http://dx.doi.org/10.1111/jth.14830.

[7] Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020. http://dx.doi.org/10.1001/jamacardio.2020.0950.

[8] Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int 2020. http://dx.doi.org/10.1016/j.kint.2020.03.005. pii: S0085-2538(20)30255-6..

[9] Dubar G, Azria E, Tesnière A, Dupont H, Le Ray C, Baugnon T, et al. French Registry on 2009 A/H1N1v during pregnancy. French experience of 2009 A/H1N1v influenza in pregnant women. PLoS One 2010;5(10). http://dx.doi.org/10.1371/journal.pone.0013112. pii: e13112..

[10] Louie JK, Acosta M, Jamieson DJ, Honein MA. California Pandemic (H1N1) Working group Severe 2009 H1N1 influenza in pregnant and postpartum women in California. N Engl J Med 2010;362(1):27–35. http://dx.doi.org/10.1056/NEJMoa0910444.

[11] Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med 2020. http://dx.doi.org/10.1056/NEJMc2007575.

[12] Taylor Jr FB, Toh CH, Hoots WK, Levi M. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost 2001;86(5):1327–30.

[13] Chen R, Zhang Y, Huang L, Cheng BH, Xia ZY, Meng QT. Safety and efficacy of different anesthetic regimens for parturients with COVID-19 undergoing Cesarean delivery: a case series of 17 patients. Can J Anaesth 2020. http://dx.doi.org/10.1007/s12630-020-01630-7.

[14] Bauer ME, Chiware R, Pancaro C. Neuraxial procedures in COVID-19 positive parturients: a review of current reports. Anesth Analg 2020. http://dx.doi.org/10.1213/ANE.0000000000004831.

[15] Hunt B, Retter A, McClintock C. Practical guidance for the prevention of thrombosis and management of coagulopathy and disseminated intravascular coagulation of patients infected with COVID-19. Thrombosis Haemostasis 2020. http://dx.doi.org/10.1111/jth.14853. Online ahead of print. PMID: 32302442.

[16] Liu Y, Chen H, Tang K, Guo Y. Clinical manifestations and outcome of SARS-CoV-2 infection during pregnancy. J Infect 2020. http://dx.doi.org/10.1016/j.jinf.2020.02.028 [pii: S0163-4453(20)30109-2].

[17] Zhang Y, Chen R, Wang J, Gong Y, Zhou Q, Cheng H-h. et al. Anaesthetic management and clinical outcomes of parturients with COVID-19: a multi-centre, retrospective, propensity score matched cohort study. MedRxiv 2020. http://dx.doi.org/10.1101/2020.03.24.20042176.

[18] Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020. http://dx.doi.org/10.1016/j.thromres.2020.04.013 [S0049-3848(20)30120-1].

[19] Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020. http://dx.doi.org/10.1111/jth.14817.

[20] Susen S, Tacquard CA, Godon A, Mansour A, Guarrigue D, Nguyen P, et al. Traitement anticoagulant pour la prévention du risque thrombotique chez un patient hospitalisé avec COVID-19 et surveillance de l'hémostase. Propositions du GIHP et du GFHT, SFAR 2020. https://sfar.org/traitement-anticoagulant-pour-la-prevention-du-risque-thrombotique-chez-un-patient-hospitalise-avec-covid-19-et-surveillance-de-lhemostase/last accessed April 12 2020.

[21] Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost 2020. http://dx.doi.org/10.1111/JTH. 14810.

[22] Sénat MV, Sentilhes L, Battut A, Benhamou D, Bydlowski S, Chantry A, et al. Postpartum practice: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF). Eur J Obstet Gynecol Reprod Biol 2016 Jul;202:1–8. http://dx.doi.org/10.1016/j.ejogrb.2016.04.032.

[23] Wang J, Hajizadeh N, Moore EE, McIntyre RC, Moore PK, Veress LA, et al. Tissue Plasminogen Activator (tPA) Treatment for COVID-19 associated acute respiratory distress syndrome (ards): a case series. J Thromb Haemost 2020. http://dx.doi.org/10.1111/jth.14828.