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Coagulation changes and thromboembolic risk in COVID-19 pregnant 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. Many clinicians have however observed that usual laboratory tests (D-Dimers for example) show extremely abnormal increased values, suggesting that this viral infection causes an exaggerated response, which is now commonly called the cytokine storm. This inflammatory response appears to be somewhat proportional to the severity of the disease. Indeed, patients who are affected by an acute respiratory distress syndrome and those who die have values even higher than other patients. As suggested above, the link with the inflammatory response appears essentially as a marker of disease severity [2-4]. This is however probably not the sole mechanism as the coagulation defect that appears 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 likely 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 their inflammatory response.

Pregnant women who develop COVID-19 illness may be a special population since during previous viral outbreaks, maternal morbidity and mortality has been especially high [9,10]. With the present COVID-19, such a severity is not obvious but the inflammatory response is also intense. In these patients, interpretation of the coagulation changes may even be more challenging as they are superimposed on the physiological changes induced by pregnancy. In normal pregnancy, fibrinogen concentration and D-Dimers values are increased, the platelet count often falls, both activated partial thromboplastin time (APTT) and prothrombin time shorten due to the important rise of the plasma concentration of most coagulation factors. In COVID-19 illness, additional coagulation changes may occur. Their intensity might be related to the disease severity but complete data are still lacking. An increase in D-Dimers concentration is observed, as well as a lengthening of both APTT and PT, the later leading to an increase in international normalised ratio (INR) values. Because these changes are superimposed on the physiological increase in coagulation factors, test results may not appear too abnormally low (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].

Up to now, very few direct data are available to precisely analyse these changes and their mechanism. What we know is derived from studies performed in the non-pregnant population and in the small series describing pregnant women published to date and from laboratory unpublished results of 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 these changes may occur in both the “intrinsic” and “extrinsic” pathways. In the rare cases in which circulating anticoagulant antibodies have been looked for, they were not found in the plasma of these pregnant women. In a recent report of three non-pregnant patients in whom severe COVID-19 illness had occurred, a major coagulopathic state was observed with thrombocytopenia, lengthened TT and highly increased D-Dimers concentrations [11]. The three patients had multiple cerebral infarctions and antiphospholipid antibodies were detected.

Collectively, the data obtained in pregnant and non-pregnant patients suggest that the pathophysiological mechanism leading to these 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 [4]. Unfortunately, these criteria cannot be applied to pregnant women, reducing our ability to precisely name their coagulopathy.

The lengthening of APTT and PT may pose a significant challenge to the obstetric anaesthetist since at first glance these changes may be associated with an increased risk during neuraxial puncture [12,13] (Appendix 1). The present consensus among French experts suggests that these abnormal coagulation parameters do not impede placement of a neuraxial block, given the fact that these changes more likely reflect hypercoagulability rather an increase bleeding risk. Indeed, a recently published Guidance suggest that abnormal coagulation results do not require correction in patients who are not bleeding. The validity of this strategy seems confirmed by at least two comments: first, series from China (although of small size do not report an increased risk of haemorrhage either from the obstetrical side (i.e. no more frequent post-partum haemorrhage) [14] nor from the anaesthetic side (i.e. no report of neuraxial bleeding complications) [12,15]. In addition, due to the increased respiratory frailty associated with COVID-19-induced respiratory injury, respiratory reserve may be decreased and placement of epidural analgesia is likely to decrease this effort.

Hypercoagulability may pose a threat by increasing the thromboembolic risk. This risk may occur either during or after pregnancy depending on the time at which the infection has started. Pregnancy is by itself a situation at increased thromboembolic risk and the postpartum period increases even more this risk. Due to the coagulation changes induced by the viral infection, the risk may be increased to a greater extent. This is suggested by data obtained in non-pregnant patients with a severe disease in whom thromboembolic complications have been reported. In non-pregnant contexts also, anticoagulation (mainly low molecular weight heparin [LMWH]) have been administered, sometimes in very high, non-prophylactic doses [16]. In pregnant women however, no firm data exist and in most patients the viral insult is of limited severity, possibly explaining why thromboembolic complications may not be as injurious as suggested by the major biological changes. Administration of LMWH is however suggested by several scientific bodies, mostly using prophylactic doses [17-19]. The precise indications are still unclear but it seems wise to analyse the overall thromboembolic risk of a given patient, including traditional non-viral related risk factors and multiplying by the risk factor associated with infection [20]. 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 prolong treatment as recovery may not be easily defined, the experts suggest reducing the duration of treatment due to the complicated management of labour and neuraxial block placement, should delivery occur during the period of LMWH administration.

In postpartum patients with recent COVID-19 infection, the haemorrhagic risk associated with LMWH is thought to be lower than the thromboembolic risk, if one accepts that a strong correlation exists between the impressive biological disturbances. Although the risk of thromboembolism is lower after vaginal delivery, it seems wise to administer LMWH in this situation when personal risk factors are added to the risk associated with viral infection. After caesarean section, this seems even more logical and there may be few patients in who LMWH may not be required. The optimal duration of anticoagulant treatment is unknown but should probably be adapted to the disease severity.

Other treatments should only be considered in pregnant women in cases with haemorrhage (fresh frozen plasma, fibrinogen or tranexamic acid [except in COVID-associated DIC for the latter]) [18] or alternatively in patients with a severe form of the disease ((i.e. antithrombin, Tissue Plasminogen Activator) [21].

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Appendix 1: Haemostasis assessment in pregnant women with COVID disease (confirmed or suspected)

Appendix 2: Thromboembolic risk in pregnant women with COVID disease (confirmed or suspected)