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## Re: Pre-eclampsia-like syndrome induced by severe COVID-19: a prospective observational study

### Common pathophysiology of pre-eclampsia and severe COVID-19?

Sir,

Mendoza et al.[1] recently published a prospective cohort study examining clinical features of pre-eclampsia among pregnant women with confirmed SARS-CoV-2 infection. Five of eight women (62.5%) with severe COVID-19 had pre-eclampsia or a pre-eclampsia-like syndrome, and the one subject who did not undergo delivery during the study had resolution of the pre-eclampsia-like syndrome after recovery from COVID-19. Since all five of these subjects did not have evidence of pre-eclampsia before the diagnosis of severe COVID-19 pneumonia, we agree with Mendoza and colleagues' assessment of a similar underlying pathophysiology of pre-eclampsia and severe COVID-19.[1]

One common denominator in the pathophysiology of pre-eclampsia and COVID-19 is endothelial injury. A hallmark of pre-eclampsia is disrupted placentation, which leads to endothelial dysfunction and end-organ damage. SARS-CoV-2 infects endothelial cells and COVID-19 lungs demonstrate endothelial cell injury, microthrombi and angiogenesis.[2] It is thought that the endothelial damage in both pre-eclampsia and COVID-19 can lead to multi-organ dysfunction. Furthermore, both disorders have an increased risk of non-cardiogenic pulmonary oedema and venous thromboembolism.

In the context of endothelial injury, we propose three additional shared elements of pre-eclampsia and COVID-19. There is increasing evidence that neutrophil extracellular traps (NETs), which are extruded DNA and histones released by neutrophils to destroy extracellular bacteria, play an important role in COVID-19-related immunothrombosis and endothelial damage.[3] Interestingly, NETs have also been implicated in non-COVID-19-associated pre-eclampsia and intrauterine growth restriction.[3] Another potential link between pre-eclampsia and COVID-19 is the presence of anti-phospholipid antibodies (aPLA). aPLA is a well-known major risk factor for pre-eclampsia and one study found that 52% of COVID-19 patients had elevated aPLA levels.[4] Alpha-1-antitrypsin (AAT) has been shown to prevent apoptosis as well as reduce oxidative stress and inflammation in endothelial cells. AAT has been shown to be a protective factor in pre-eclampsia through activating Smad2 and inhibiting DNA binding 4 in both an animal model and human placenta tissue.[5] AAT also inhibits TMPRSS-2,[6] the host serine protease that is required for processing of the spike protein of SARS-CoV-2 before the virus binds to its receptor to gain entry into the cells. The shared pathophysiology between COVID-19 and pre-eclampsia should be further studied and may lead to novel therapeutics which may include AAT. ■

## References

1 Mendoza M, Garcia-Ruiz I, Maiz N, Rodo C, Garcia-Manau P, Serrano B, et al. Pre-eclampsia-like syndrome induced by severe COVID-19: a prospective observational study. *BJOG* 2020;127:1374–80.
2 Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med* 2020;383:120–8.
3 Makatsariya A, Slukhanchuk E, Bitsadze V, Khizroeva J, Tretyakova M, Tsibizova V, et al. COVID-19, neutrophil extracellular traps and vascular complications in obstetric practice. *Journal of Perinatal Medicine* 2020; https://doi.org/10.1515/jpm-2020-0280
4 Zuo Y, Estes SK, Gandhi AA, Yalavarthi S, Ali RA, Shi H, et al. Prothrombotic antiphospholipid antibodies in COVID-19. *medRxiv* 2020; pre-print.
5 Feng YL, Wang N, Xu J, Zou J, Liang X, Liu H, et al. Alpha-1-antitrypsin functions as a protective factor in preeclampsia through activating Smad2 and inhibitor of DNA binding 4. *Oncotarget* 2017;8:113002–12.
6 de Loyola MB, Dos Reis TTA, de Oliveira GXLM, da Fonseca PJ, Argañaraz GA, Argañaraz ER. Alpha-1-antitrypsin: a possible host protective factor against Covid-19. *Rev Med Virol* 2020;26:e2157.

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