



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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

to gain insight into the relationship between mental health symptoms and adverse pregnancy outcomes is warranted. ■

Emily S. Miller, MD, MPH
Division of Maternal-Fetal Medicine
Department of Obstetrics and Gynecology
Northwestern University Feinberg School of Medicine

250 E Superior St., Suite 05-2146
Chicago, IL 60657
emily-miller-1@northwestern.edu

The author reports no conflict of interest.

© 2021 Published by Elsevier Inc. <https://doi.org/10.1016/j.ajog.2021.08.044>

SARS-CoV-2 related myocardial injury might explain the predisposition to preeclampsia with maternal SARS-CoV-2 infection



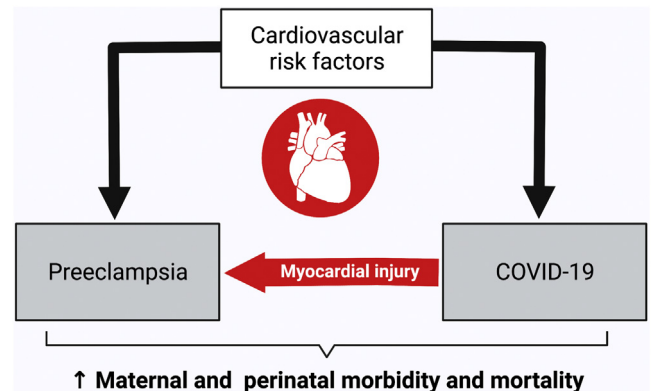
TO THE EDITORS: We read with interest the article by Conde-Agudelo and Romero.¹ Their meta-analysis showed that SARS-CoV-2 infection during pregnancy increases the risk of preeclampsia by 62%. It also showed that this association remained significant even after adjusting for the confounding risk factors such as maternal age, body mass index, preexisting comorbidities, and ethnicity. Their meta-analysis also effectively proved that the latter preexisting maternal cardiovascular risk factors cannot entirely explain the nature of the relationship between SARS-CoV-2 infection and preeclampsia. Furthermore, the authors demonstrated a bidirectional “dose-response” effect, with SARS-CoV-2-infected pregnancies having a 2-fold higher risk of severe preeclampsia; second, the association between infection and preeclampsia is stronger in symptomatic than in asymptomatic cases with COVID-19. Put together, these results suggest that maternal COVID-19 infection predisposes a patient to and triggers the development of preeclampsia. Although the mechanisms underlying COVID-19–related multiorgan manifestations are not completely understood, cardiovascular dysfunction is typical, and we believe that the possibility of an association between the latter finding and preeclampsia should be explored further.

Having maternal cardiovascular dysfunction predisposes a patient to preeclampsia. It predominates at the presentation of the disorder and persists as a cardiovascular legacy for decades following birth.² It is entirely plausible that the complex relationship between COVID-19 infection and acute, severe cardiovascular dysfunction that has been described outside pregnancy may also occur during SARS-CoV-2 infection in pregnancy.³ Indeed, cardiovascular risk factors such as hypertension, diabetes mellitus, and obesity are also predisposing factors for COVID-19 infection. Moreover, COVID-19 infection itself is known to cause acute myocardial injury, myocarditis, acute coronary syndrome, arrhythmia, and thromboembolism. SARS-CoV-2-related myocardial injury seems to be mostly related to a massive systemic inflammation and has been confirmed by elevated troponin and pro-B-type natriuretic peptide concentrations and left ventricular

dysfunction, both in and outside pregnancy. The finding of superimposed cardiovascular dysfunction in pregnant women who are critically ill because of COVID-19 is associated with an increased (13.3%) maternal mortality rate.⁴

Placental histologic studies are of limited value in understanding the pathophysiology of the COVID-19–related preeclampsia risk, because these are only available after birth and not during disease development. The authors suggested that a placentally-derived angiogenic imbalance may explain the predisposition to preeclampsia in maternal SARS-CoV-2 infection. We hypothesize that even in asymptomatic SARS-CoV-2 maternal infection, myocardial injury and subclinical cardiovascular dysfunction leading to acquired uteroplacental malperfusion and ischemia may lead to an angiogenic imbalance and the subsequent development of preeclampsia (Figure).² Further studies on the assessment of the maternal

FIGURE
Relationship among cardiovascular risk factors, SARS-CoV-2 infection, and preeclampsia



Created with [BioRender.com](https://www.biorender.com).

Giorgione. SARS-CoV-2 related myocardial injury and predisposition to preeclampsia. *Am J Obstet Gynecol* 2022.

cardiovascular system by noninvasive imaging techniques and cardiac biomarkers in pregnancies complicated by SARS-CoV-2 infection could be beneficial to improve the prenatal and postnatal care of these women, considering the worse prognosis related to the myocardial injury and also, to prove this hypothesis. ■

Veronica Giorgione, MD

Molecular and Clinical Sciences Research Institute
St. George's University of London
London, United Kingdom

Basky Thilaganathan, MD, PhD, FRCOG

Molecular and Clinical Sciences Research Institute
St. George's University of London
London, United Kingdom
Fetal Medicine Unit
Department of Obstetrics and Gynaecology
St. George's University Hospitals NHS Foundation Trust
London
United Kingdom
basky@pobox.com

The authors report no conflict of interest.

V.G.'s doctoral work is a part of the iPLACENTA project, which has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement no 765274.

REFERENCES

1. Conde-Agudelo A, Romero R. SARS-COV-2 infection during pregnancy and risk of preeclampsia: a systematic review and meta-analysis. *Am J Obstet Gynecol* 2021. [Epub ahead of print].
2. Melchiorre K, Giorgione V, Thilaganathan B. The placenta and preeclampsia: villain or victim? *Am J Obstet Gynecol* 2021. [Epub ahead of print].
3. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. *Nat Rev Cardiol* 2020;17:543–58.
4. Mercedes BR, Serwat A, Naffaa L, et al. New-onset myocardial injury in pregnant patients with coronavirus disease 2019: a case series of 15 patients. *Am J Obstet Gynecol* 2021;224. 387.e1–389.

© 2021 Elsevier Inc. All rights reserved. <https://doi.org/10.1016/j.ajog.2021.09.043>

Mechanisms that may underlie a causal association between SARS-CoV-2 infection and preeclampsia



We thank Giorgione and Thilaganathan for their interest in our study about the relationship between SARS-CoV-2 infection and preeclampsia.¹ The authors of the letter have articulated and summarized the emerging evidence that supports the role of maternal cardiovascular dysfunction in the genesis of preeclampsia.² Some of the evidence is derived from studies showing a higher risk of preeclampsia and fetal growth restriction in women with congenital heart disease than in those without the disease. Giorgione and Thilaganathan propose that SARS-CoV-2 infection may injure the myocardium and that this injury leads to uteroplacental malperfusion and predisposes patients to preeclampsia.

The myocardial injury associated with SARS-CoV-2 infection may be attributed to multiple causes, including the effects of the virus on the cardiovascular system, cytokine storm syndrome, microvascular thrombosis, and organ damage by direct virus entry facilitated by the expression of the cell membrane angiotensin-converting enzyme 2 receptor.³ Indeed, recent studies have shown that SARS-CoV-2 can infect cardiomyocytes, thus causing contractile deficits, cytokine production, sarcomere disassembly, and cell death *in vitro*.⁴ In nonpregnant patients, the prevalence of myocardial injury, which is defined as an elevated concentration of cardiac troponin >99th percentile, ranges from 12% in unselected COVID-19 cases to 41% in critically ill

patients.³ In a series of 20 pregnant women with SARS-CoV-2 infection and severe or critical illness presenting at 7 hospitals located in the state of New York, 4 of them (20%) had elevated cardiac troponin concentrations, 3 (15%) had elevated levels of the brain natriuretic peptide, whereas 13 (65%) had a normal concentration of both.⁵ The frequency of gestational hypertension or preeclampsia was 28.6% (2 of 7 patients) among patients with elevated cardiac biomarkers and 23.1% (3 of 13 patients) among those with normal cardiac biomarkers ($P=.79$). A case series study from a single tertiary care hospital in the Dominican Republic reported that among 154 symptomatic pregnant patients with SARS-CoV-2 infection, 15 (9.7%) developed myocardial injury.⁶ According to the corresponding author of this study (Dr. Lina Karout), who kindly provided us with additional information, the frequency of preeclampsia among patients with and without myocardial injury was 26.7% (4/15) and 38.8% (54/139), respectively, ($P=.39$). At the time of writing this reply, we could not identify additional basic, epidemiologic, and clinical studies that addressed the relationship between SARS-CoV-2 infection-associated myocardial injury and preeclampsia.

In summary, the hypothesis that myocardial injury related to SARS-CoV-2 infection might explain the development of preeclampsia among infected pregnant women is interesting and needs further study. ■