TO THE EDITORS:

We read with great interest Miller et al’s1 report on the association between antenatal depressive symptomatology and adverse pregnancy outcomes. In this large, multisite prospective cohort of nulliparous women across the United States, the depressive symptoms were measured using the Edinburgh Postpartum Depression Scale (EPDS)2, a 10-item self-report scale at 2 study visits—the first between 6 and 14 weeks of gestation and then again between 22 and 30 weeks—where women with depressive symptoms that worsened as the pregnancy progressed had greater odds of preterm birth.

These findings are clinically relevant, because despite advances in medical care, rates of preterm birth have increased in the last few decades, and antenatal depression has been identified as a risk factor for postpartum depression and adverse neonatal outcomes including preterm labor, low birthweight, and neonatal complications associated with increased morbidity and mortality in infants.

However, we feel it is also necessary to bring attention to some considerations emerging from the method used for this original analysis. Firstly, EPDS is a widely used instrument for the screening of depressive symptoms, but its 3-factor structure, that is, "depression" (items 7–10), "anxiety" (items 3–6), and "anhedonia" (items 1–2) might also help elucidate the spectrum of maternal gestational psychological problems and the contributing role of the anxiety and anhedonia dimensions.3 Secondly, the existence of separate anxiety and depression dimensions within the EPDS has been reported previously. Symptoms related to anxiety during gestation and immediately after delivery are frequent, and several studies have suggested that anxiety may also be associated with both negative pregnancy outcomes and the etiology of preterm birth. Theoretical models have been developed to explain the biologic effect of prenatal maternal mental health problems such as the physiological stress response of the hypothalamic-pituitary axis that is regulated by the corticotrophin-releasing hormone.4 The pathways by which the maternal mental health problems initiate a physiological sequence of events that promote early labor, however, remain largely unknown.

We strongly agree with their recommendation for future research to optimize and implement effective prevention, screening, and treatment protocols for antenatal depression as a strategy to prevent preterm birth. Along the same line of thought and considering the role of psychological distress conditions such as depression and/or anxiety during pregnancy as risk predictors for adverse birth outcomes and preterm birth, we suggest that the EPDS anhedonia, anxiety, and depression subscales be considered separately in the overall prematurity risk calculation to guide future clinical and research practices.

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REFERENCES

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Trajectories of antenatal depression research

We greatly appreciate the interest and the positive comments about our work. As Dr Zanardo and colleagues note, more detailed psychiatric phenotyping would certainly allow for a more nuanced understanding of the relationship between mental health symptoms and preterm birth. Whether this additional phenotyping includes the subcomponents of the Edinburgh Postnatal Depression Scale as they describe, or includes transdiagnostic symptom evaluations, we agree that further research
TO THE EDITORS: We read with interest the article by Conde-Agudelo and Romero. 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. 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. 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.

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). Further studies on the assessment of the maternal

![Figure](https://i.imgur.com/3j.png)

**FIGURE**

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

Hypertension, diabetes mellitus, and obesity are predisposing factors for COVID-19 infection. COVID-19 infection itself is known to cause acute myocardial injury, myocarditis, acute coronary syndrome, arrhythmia, and ischemia. SARS-CoV-2-related myocardial injury seems to be 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.

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