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.

Preeclampsiada risk factor to get infected with COVID-19 or a selection bias?

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TO THE EDITORS: In the recent report of the INTERCOVID study—a prospective international study—the authors observed an association between COVID-19 and preeclampsia.[1] The hypothesis formulated for the observed association was that preeclampsia is a vascular condition that precedes infection by SARS-CoV-2, and it increases the risk of COVID-19. This underlying pathway is unclear and could reflect selection bias. Considering this issue, the selection of women might overestimate the association. Firstly, the controls should be identified as cases if they have developed the disease, and the probability of developing the disease should be consistent in both the groups. However, 50% of nondiagnosed COVID-19 cases had not been tested, and serology to exclude previous COVID-19 infection was performed only in 32 (2.2%) women. Secondly, the reason for testing women, especially those who were asymptomatic, could vary depending on whether preeclampsia is present or not (ie, independence on the outcome of preeclampsia is not consistent across exposure to COVID-19). This point raises the possibility of Berkson bias. Thirdly, the authors did not discuss that a vaccine campaign could have affected the number of cases. Fourthly, because of the progressive implementation of adequate polymerase chain reaction (PCR) testing and the prolonged shedding of RNA in respiratory samples, the result of the PCR test across 18 countries could have resulted in a bias in the diagnosis of cases. Adjustment on the site or bivariate analysis according to the cycle threshold value of quantitative reverse transcriptase PCR could be interesting.

It has been observed in adults that hypertension could be a sequela in patients with SARS-COV-2 infection.[2] In contrast, no association was found between the delay of COVID-19 infection and birth if >7 days. Women with vascular conditions or severe COVID-19 are at a greater risk of getting seriously ill rather than being positive on an PCR test.[3] The delay between a positive COVID-19 test and the occurrence of preeclampsia could help to overcome these assumptions.[4] ■

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INTERCOVID prospective longitudinal study: preeclampsia and COVID-19

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TO THE EDITORS: Based on the hypothesis of a pathologic relationship of SARS-CoV-2 and multifaceted endothelial damage,[1] Papageorghiou et al[2] reported a strong association between COVID-19 and preeclampsia from the INTERCOVID study. Although we appreciate the meticulous work that the authors did, to present adequate statistics to identify this association, we are concerned that there is a risk of misclassification in the control group that could lead to an overestimation of the effect.

In their study, pregnant women diagnosed with COVID-19 had a positive SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) reaction in 92.7% of the cases, whereas only 50% of the 1459 pregnant "control" population ("noninfected") underwent testing via an RT-PCR or antibody test. Because there is a high prevalence of SARS-CoV-2 infected patients that are asymptomatic, the risk of misclassification and misinterpretation is high. These asymptomatic cases (both for COVID-19 and possibly, for preeclampsia) may dilute the association reported. Indeed, symptomatic patients were all tested for SARS-CoV-2 and included in the positive group; whereas, asymptomatic patients without testing, may represent infected patients without the severity criteria, particularly when considering endothelial damage, thus, reducing the absolute risk of vascular complications in the "not-diagnosed group."

This study would be more convincing if the authors provided a complete sensitivity analysis, including only the patients tested for SARS-CoV-2 in both the groups to the readership.

With the present results, the association between SARS-CoV-2 and preeclampsia could be overestimated owing to the asymptomatic pregnant population in the control group. ■

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The link between COVID-19 and preeclampsia

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We thank the authors for their interest in our work.[1,2] Boujenaha[3] suggests that the association between COVID-19 and preeclampsia[1] may be because of selection bias, as the nondiagnosed group included women without a negative test (Desseauve et al[4] make the same point); we acknowledge that this group may have included a small number of unidentified, asymptomatic, and infected women. However, this is not a strong source of bias, because including infected women in the reference group would dilute, rather than strengthen, the observed association. Secondly, although it is possible that preeclamptic women admitted to the hospital were more likely to be diagnosed with COVID-19, the study design[2] avoided such systematic bias by selecting 2 women immediately after a diagnosed woman *at the same level of care*, as the reference group. Thirdly, the study ended in February 2021 when vaccine use in pregnancy was still uncommon; the case numbers here would be largely unaffected. Finally, adjustment by study site as a covariate and using mixed-effects models with random slopes by site were conducted in the study, and the results were very similar (Table 2 in the original report).

We have now undertaken further analyses that are restricted to undiagnosed women who had a negative polymerase chain reaction or antibody test result, reducing the total sample size to 1359 women. The association between COVID-19 diagnosis and preeclampsia (compared with Table 2 in the original report) had a similar but slightly reduced risk ratio (RR) of 1.71 (95% confidence interval [CI], 1.14−2.56) in the unadjusted and 1.52 (95% CI, 1.01−2.31) in the full model (adjusted for maternal age, previous parity, tobacco use during pregnancy, overweight status, and the history of diabetes, cardiac disease, hypertension, kidney disease, or adverse pregnancy outcomes). The associations with hypertensive disease in pregnancy and gestational hypertension (GH) (previously reported in Table 4) were similar, with a slightly increased RR for GH. The RRs for hypertensive disease in pregnancy and GH were 1.61 (95% CI, 1.21−2.13) and 1.80 (1.21−2.68), respectively, in the unadjusted model; and 1.47 (95% CI, 1.10−1.95) and 1.66 (95% CI, 1.11−2.47), respectively, in the adjusted model.

We initiated a pragmatic, observational study within routine clinical care just a few days after the World Health Organization declared COVID-19 a global pandemic[5] and long before universal testing became available. By carefully selecting women diagnosed with COVID-19 and a reference group, we obtained vitally important data, quickly. Strict quality control measures were implemented to ensure that the enrolment of women who were not diagnosed was unbiased; the data have been explored for possible selection bias using several strategies. The results remain largely unchanged, suggesting that the association between COVID-19 and preeclampsia is not because of confounding by common risk factors. ■

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