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RESEARCH LETTER

SARS-COV-2 and the subsequent development of preeclampsia and preterm birth: evidence of a dose response relationship supporting causality

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Condensation: The more severe COVID-19, the greater the risk of preeclampsia and preterm birth.

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BACKGROUND AND OBJECTIVE

Pregnant women affected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have a worse clinical outcome than non-pregnant women, including higher risk for admission to the intensive care unit, use of invasive mechanical ventilation, need for extra corporeal membrane oxygenation, and death than non-pregnant women with SARS-CoV-2. In addition, SARS-CoV-2 infection is a risk factor for fetal death and preterm birth. Early during the COVID-19 pandemic, a preeclampsia-like syndrome was reported in pregnant women with SARS-CoV-2.[1] This association has been confirmed by case series[2] and systematic reviews and meta-analyses.[3] An important issue is whether COVID-19 causes preeclampsia. One of the Bradford Hill criteria to assess causality is the existence of a dose response relationship between an exposure and the outcome of interest; in this case, the severity of SARS-CoV-2 infection and the likelihood of preeclampsia and this study was conducted to address this question.

STUDY DESIGN

A retrospective observational study was conducted based on data from 14 National Health Service (NHS) maternity hospitals in the UK, to assess the effects of SARS-CoV-2 infection in pregnancy. Institutions are listed in the footnote of Supplementary Table 1. This study was considered exempt of IRB review by the NHS Health Research Authority.

At each participating site, the electronic patient records were reviewed to identify patients for a diagnosis of SARS-CoV-2 in pregnant women based on a positive PCR test between 1st February 2020 and 1st May 2021. Maternal demographic characteristics and medical history, pregnancy outcomes (i.e. livebirth or pregnancy

loss, gestational age at delivery, birthweight, hypertensive disease in pregnancy and dates of onset) were obtained from the hospital databases.

Individual patient records were reviewed for relevant information about SARS-CoV-2 infection and classified into four groups according to severity based on a modified spectrum used by the NIH. First, *asymptomatic*, includes individuals who test positive for SARS-CoV-2 but who have no symptoms. Second, *mild* illness, includes individuals who have any of the various signs and symptoms of COVID-19 (such as fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging. Third, *moderate* illness, includes individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO2) ≥94% on room air. Last, *severe* illness, includes individuals who require high dependency or intensive care secondary to respiratory impairment/failure or multiorgan dysfunction.

The primary outcome was the occurrence of preeclampsia in patients exposed to SARS-CoV-2. Other outcomes examined included preterm birth and gestational age at delivery. Preeclampsia was defined as hypertension (blood pressure ≥140 mHg / ≥90 mmHg) developing after 20 weeks' gestation in a previously normotensive woman or chronic hypertension and development of new onset proteinuria (≥300 mg/24h or protein to creatinine ratio >30 mg/mmoL or >2 + on dipstick testing).

The effect of the severity of infection with SARS-CoV-2 defined as a four group factor (asymptomatic, mild, moderate, or severe) on the rate of preeclampsia and preterm preeclampsia was assessed using robust Poisson regression models using the

geepack package in the R statistical language and environment (www.r-project.org). The asymptomatic group was used as reference, and the model included adjustment for the prior risk of preeclampsia (log thereof), as defined based on maternal characteristics and medical history using a competing risk model.[4] We also compared the risk of preeclampsia in the combined group of moderate and severe COVID-19 patients against the risk in the group of asymptomatic and mild disease. The effect of the severity of infection with SARS-CoV-2 on preterm birth (<37 weeks) was evaluated while adjusting for maternal age, weight, height, race, method of conception, chronic hypertension, smoking and diabetes. The selection of these variables was performed by backward elimination. A chi-square test for trend was used to test the dose response relationship between the severity of SARS-CoV-2 infection and preeclampsia/preterm birth.

RESULTS

The characteristics of patients included in this study (n=1223) are presented in **Supplementary Table 1**. Of these, 51 (4.2%) had preeclampsia, 16 (1.3%) miscarriages, 10 (0.81%) fetal deaths, and 215 (17.6%) had preterm birth. Women with severe COVID-19 tended to be older and had higher body mass index ($p<0.05$ for both) (**Supplementary Table 1**). Of the 51 cases of preeclampsia, 21 were diagnosed before SARS-CoV-2 infection, seven were diagnosed at the same gestational age and 23 were diagnosed after SARS-CoV-2 infection. The 21 cases of preeclampsia diagnosed before SARS-CoV-2 infection were removed from further analysis. The median interval from SARS-CoV-2 infection to the diagnosis among the 23 cases of preeclampsia diagnosed after SARS-

CoV-2 was 16 days (interquartile range 7-61 days). Among the 30 cases included in the analysis, 13 had preterm preeclampsia (<37 weeks) and 17 had term preeclampsia.

The prior risk of preeclampsia in a cohort of patients with comparable risk factors as those of the study population was about 1% (**Figure 1A**). The observed rate of preeclampsia, after excluding cases diagnosed before SARS-CoV-2 infection, was higher than expected: 1.9% in asymptomatic patients, 2.2% in patients with mild COVID-19, 5.7% with moderate and 11.1% among patients with severe disease (**Figure 1A**). This monotonic relationship between the severity of COVID-19 and the risk of developing preeclampsia was statistically significant (chi-square test for trend; p=0.0017). We then compared the risk of preeclampsia between asymptomatic patients (reference group) and those with COVID-19 symptoms while adjusting for differences in the prior risk of preeclampsia as determined by the competing risk model. Severe COVID-19 disease was associated with a higher risk of preeclampsia [aRR=4.9(1.56-15.38)]. There was also higher risk for patients with moderate or severe COVID-19 diagnosis compared to those with asymptomatic or mild disease [aRR= 3.3(1.48-7.38)].

Since others have proposed that preeclampsia predisposes to COVID-19, we also assessed this hypothesis within our dataset. We included in this analysis all women who developed preeclampsia before SARS-Cov2 and those who did not develop preeclampsia. We found a trend towards an increased risk of developing moderate or severe COVID-19 after a diagnosis of preeclampsia [unadjusted RR=2.28(0.92-5.61) (p=0.07), adjusted RR= 1.96 (0.8-4.84) (p=0.14)].

We also examined the relationship between the severity of COVID-19 and the rate of preterm birth excluding from the data set those who did not have a live birth (n=1162). The rate of preterm birth was 11.7% in asymptomatic patients, 12.8% in patients with mild COVID-19, 29.9% in patients with moderate COVID-19 and 69.4% in patients with severe COVID-19 (**Figure 1B**). Similarly, the risk of preterm birth increased as function of the severity of SARS-CoV-2 (chi-square for trend, p<0.0001). Compared to asymptomatic patients, women with moderate and severe disease had a higher risk of preterm birth [moderate; aRR=2.47(1.61-3.78) and severe; aRR=5.64(4.09-7.79)]. Moreover, there was a dose response relationship between gestational age at delivery and the severity of SARS-CoV-2 infection. (**Figure 1C**). The mean gestational age at delivery was significantly earlier in women with moderate and severe SARS-CoV-2 infection than in those who were asymptomatic (asymptomatic: 38.7, moderate 37.5, severe 33 weeks, p<0.001 for both comparisons). The risk of moderate (32 - <37 weeks), very preterm (28-<32 weeks) and extreme preterm birth (<28 weeks) increased as a function of the severity of SARS-CoV-2 infection (chi-square for trend, p<0.0001 for each, Figure 1D).

CONCLUSION

The principal finding is that there is a dose response relationship between the severity of SARS-CoV-2 infection and the risk of subsequent development of preeclampsia and preterm birth. This conclusion is based on a large number of pregnant patients who tested positive for SARS-CoV-2 and a calculation of the individualized risk of preeclampsia and preterm birth for each patient based on maternal characteristics and obstetrical history. Patients with severe COVID-19 have a five-fold greater risk of preeclampsia than

asymptomatic patients. Moreover, the relative risk of developing preeclampsia in women with moderate or severe COVID-19 was 3.3 fold higher than in those with asymptomatic/mild infection. Of note, this estimate of relative risk was higher than the 1.96 estimate obtained when testing the reverse hypothesis that preeclampsia causes moderate/severe COVID-19 reported by other authors.[5] Our findings are consistent with those reported by Metz et al. in a cohort of 1,219 patients,[2] as well as those of a systematic review and meta-analysis which found that patients with symptomatic illness (OR 2.11, 95% CI 1.59-2.81) were more likely to be diagnosed with preeclampsia than those who were asymptomatic (OR 1.59, 95% CI 1.21-2.10).[3]

There was a dose response relationship between the severity of SARS-CoV-2 infection and the risk of spontaneous preterm birth ($p<0.0001$). This is consistent with other reports. We have no information about the relative contribution of medically indicated preterm birth versus spontaneous preterm birth. The fact that 43% (13/30) of the cases of preeclampsia diagnosed after SARS-Cov-2 infection were preterm preeclampsia (< 37 weeks) suggests that COVID-19 may be a cause for medically indicated preterm birth that contributes to the excess preterm birth delivery rate previously reported.[6]

This study was designed to examine whether the relationship between SARS-CoV-2 and preeclampsia/preterm birth is causal. Nonetheless, we observed the cases in which preeclampsia preceded infection with SARS-CoV-2. Whether preeclampsia can predispose COVID-19 some cases, or that the two conditions may co-occur because they share similar risk factors requires further investigation.[5]

In conclusion, we present evidence that the more severe the infection with SARS-CoV-2, the greater the risk of preeclampsia and preterm birth. SARS-CoV-2 infection can lead

206 to endothelial dysfunction, intravascular inflammation, proteinuria, activation of thrombin,
207 and hypertension, which are all features of preeclampsia. Therefore, a causal relationship
208 must be considered.

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Figure Legend

Figure 1. Association between SARS-CoV-2 infection severity and pregnancy outcomes. A) Expected and observed rates of preeclampsia in women with SARS-CoV-2 infection. B) Observed rates of preterm birth in women with SARS-CoV-2 infection who had a live neonate. C) Gestational age at delivery in women with SARS-CoV-2 infection who had a live neonate. D) Rate of moderate, very, and extreme preterm birth as a function of the severity of SARS-CoV-2 infection.