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Does COVID-19 cause pre-eclampsia?

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The Coronavirus Disease 2019 (COVID-19) pandemic has had a significant impact on the provision of maternal healthcare and maternal and fetal outcomes globally[1-4]. An increase in maternal morbidity and mortality has been identified and has been attributed to a number of causes[5]. These include difficulties faced by healthcare systems in adapting to rapidly changing circumstances during the pandemic and inequity in service provision globally according to income status of countries[6].

In general, women are at increased risk of infection during pregnancy. Alterations in immune function and increased physiological demand on maternal metabolism can lead to more complicated recovery and worse outcomes[7]. In particular, pregnant women are at increased risk of severe respiratory illness, for example, influenza[8,9]. During the COVID-19 pandemic, the relationship between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and maternal health has been explored in a number of large-scale cohort studies and meta-analyses of the current literature. These studies have highlighted an apparent link between COVID-19 and preeclampsia[10-12], but it is not currently known whether or not this association is causal.

In 1965, the English statistician Sir Austin Bradford Hill proposed a set of nine criteria to assess causality in the relationship between a presumed cause and an observed effect[13]. While some argue against the exclusive use of these criteria to judge causality, arguing for example that scientific deduction is more powerful, they are still widely accepted and applied. These criteria are: the strength of the association (effect size), consistency (reproducibility), specificity, temporal sequence, biological gradient (dose-response relationship), plausibility, coherence (between epidemiological and laboratory findings), experimental evidence, and analogous evidence. Some authors include reversibility, i.e., if the cause is removed, the effect should disappear too. We assessed the relationship between SARS-CoV-2 infection in pregnancy and the development of preeclampsia against the Bradford Hill criteria.

Strength of the association

(*The larger the association, the greater the likelihood that the relationship is causal*).

A large-scale national cohort study of 342,090 women was conducted in England between 29th May 2020 and 31st July 2021 as part of the National Maternity and Perinatal Audit (NMPA)[14]. This study found that women testing positive for SARS-CoV-2 at the time of birth had higher rates of fetal death, preterm delivery, preeclampsia and delivery by emergency

cesarean section, compared with women without a positive test for SARS-CoV-2. The risk of preeclampsia or eclampsia was significantly higher for women with SARS-CoV-2 infection than those without (3.9% vs 2.5%, adjusted odds ratio [aOR], 1.55; 95% confidence interval [CI], 1.29–1.85; *P*<.001).

The INTERCOVID cohort study, a large-scale multinational study that assessed pregnancy outcomes in 43 institutions across 18 countries, compared a total of 706 pregnant women with a COVID-19 diagnosis and 1,424 pregnant women without a COVID-19 diagnosis. This study found that women with a COVID-19 diagnosis were at increased risk of preeclampsia, eclampsia and hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome (8.4% vs 4.4%; relative risk [RR], 1.76; 95% CI, 1.27-2.43). Women with both asymptomatic and symptomatic SARS-CoV-2 infection who also had risk factors for preeclampsia, such as increased body mass index (BMI), diabetes, pre-existing hypertension or other chronic co-morbidities, were found to have four times greater risk of developing preeclampsia or eclampsia compared to women who did not have SARS-CoV-2 infection. Women with a COVID-19 diagnosis were also at increased risk of preterm birth (RR 1.59; 95% CI, 1.30-1.94). The majority (83%) of preterm births in women with a COVID-19 diagnosis were medically indicated; the leading indication was preeclampsia/eclampsia/HELLP (24.7%). Moreover, when a maternal morbidity and mortality index (MMMI) was calculated, women with symptomatic SARS-CoV-2 infection were found to have a higher incidence of several pregnancy complications including pregnancy-induced hypertension, preeclampsia, eclampsia, HELLP syndrome and maternal death, compared with women with asymptomatic infection[15].

A recent systematic review of 28 studies included 790,954 pregnant women across the globe, of whom 15,524 were diagnosed with SARS-CoV-2 infection[12]. The meta-analysis of adjusted ORs found that SARS-CoV-2 infection during pregnancy was associated with a significant increase in the odds of preeclampsia (pooled OR 1.58, 95% CI 1.39-1.80; P<0.0001; I^2 = 0%; 11 studies). There was also an increased risk of severe preeclampsia (OR 1.76, 95% CI 1.18-2.63; I^2 =58%; 7 studies), eclampsia (OR 1.97, 95% CI 1.01-3.84; I^2 =0%, 3 studies), and HELLP syndrome (OR 2.10, 95% CI 1.48-2.97; 1 study) in women with the infection.

Several large cohort studies that highlighted important outcomes such as increased maternal morbidity in UK and US populations, including the PANCOVID (UK) and AAP-SONPM (US) registry study[16,17], were not designed specifically to assess the incidence of preeclampsia or other hypertensive disorders of pregnancy, so unfortunately did not add any data useful for addressing this question.

Consistency (reproducibility)

(*Consistent findings observed by different persons in different places with different samples strengthens the likelihood of an effect being causal*).

A recent systematic review and meta-analysis by Conde-Agudelo and Romero[12] included a total of 28 studies including 790,954 pregnant women. Of these 28 studies, 14 were conducted in North America, 6 in Europe, 5 in Asia, and 2 in Latin America. The remaining study was performed across 18 countries. This meta-analysis assessed heterogeneity among studies by visually inspecting forest plots and by estimating I^2. Significant heterogeneity was pre-defined as an I^2 value ≥ 30%. The pre-specified subgroups analysed to explore potential sources of heterogeneity were defined according to the severity of SARS-CoV-2 infection (asymptomatic illness vs symptomatic illness), study design (retrospective cohort vs prospective cohort vs cross-sectional), study of the association (as primary aim vs as secondary aim), control for confounding factors (yes vs no), geographic location (North America vs Europe vs Asia vs Latin America vs Multi-region), sample size (<200 vs 200-999 vs 1000-5000 vs >5000), test used for diagnosing SARS-CoV-2 infection (RT-PCR vs RT-PCR or antigens vs antibodies in serum vs mixed/unclear), and timing of the diagnosis of SARS-CoV-2 infection (at any time during pregnancy vs at admission for delivery). The impact of risk of bias on results was also examined by performing a sensitivity analysis that included only studies with a low risk of bias.

This analysis found that the direction and magnitude of the effect of SARS-CoV-2 infection during pregnancy on preeclampsia was consistent across most pre-specified subgroup and sensitivity analyses. However, smaller studies (<200 women), those with a retrospective design that did not adjust for confounding factors, and studies from Asia, reported slightly higher ORs than larger, cross-sectional studies that did adjust for confounding factors.

It should be recognised that this meta-analysis was dominated by two large cross-sectional studies, one from the UK[14], the other from the US[18], which between them contributed 748,526 (94.6%) of the 790,954 pregnant women included in this meta-analysis, which could potentially temper the conclusions drawn around reproducibility in different countries and ethnicities. However, this UK study[14], which included White (76.3%), Asian (12.2%) and Black (4.6%) pregnant women, found that the association between SARS-CoV-2 and preeclampsia persisted even after multiple regression adjusting for maternal age, ethnicity, parity, pre-existing diabetes mellitus, pre-existing hypertension, and socioeconomic deprivation measured using Index of Multiple Deprivation 2019 (IMD).

The INTERCOVID study[20] found that women who were overweight at the first antenatal visit and were subsequently diagnosed with COVID-19 had the highest risk of

preeclampsia/eclampsia (RR, 2.62; 95% CI, 1.57-4.36), suggesting that being overweight modifies the effect of COVID-19 exposure.

In summary, there is good evidence around the consistency of this association, but further evidence is needed.

Specificity

(*Causation is likely if there is a very specific population at a specific site and disease with no other likely explanation*).

Preeclampsia is a disease specific to pregnancy. The risk factors for the development of preeclampsia are well-documented and include hypertensive disease in previous pregnancy, chronic hypertension, chronic renal disease, diabetes mellitus or autoimmune disease, nulliparity, age ≥40 years, raised BMI ≥35 kg/m^2, family history of preeclampsia, interpregnancy interval >10 years, or conception by in-vitro fertilization[21,22]. Low dose aspirin, started before 15 weeks' gestation, reduces the risk of preeclampsia[23].

It is not clear whether pregnant women are at increased risk of contracting SARS-CoV-2 infection, but the risk factors for developing more severe COVID-19 in pregnancy are similar to those in non-pregnant individuals, namely Black, Asian or minority ethnicity, overweight/obesity, or chronic co-morbidity (in particular asthma and hypertension)[19]. The overlap in risk factors for preeclampsia and severe COVID-19 highlight the potential for confounding in the association between the two conditions.

The 28 studies included in the Conde-Agudelo and Romero meta-analysis[12] varied significantly in the maternal factors for which they adjusted, but most adjusted for maternal age, BMI, pre-existing comorbidities, and race/ethnicity. Fourteen studies did not adjust for any confounders or perform any matching of variables. Four studies were designed specifically to evaluate the association between SARS-CoV-2 infection during pregnancy and preeclampsia[15,24-27]. Of these, one[24] did not adjust for any confounding factors; one[25] adjusted for race and parity, one[26] adjusted for race, BMI, the use of low dose aspirin, and chronic hypertension; and one[15] adjusted for maternal age, parity, cigarette smoking, overweight/obesity, history of diabetes, cardiac disease, hypertension, or renal disease, and history of adverse pregnancy outcomes. The unadjusted odds ratios (95% CI) for the association between SARS-CoV-2 infection during pregnancy and preeclampsia for these four studies were, respectively: 1.94 (1.09-3.46), 1.33 (0.64-2.75), 1.76 (1.01-3.05), 1.93 (1.34-2.78). These compare to the pooled OR for all 28 studies included in the Conde-Agudelo and Romero meta-analysis[12] of 1.62 (1.45-1.82). It is clear that adjustment for the known risk

factors for preeclampsia has been incomplete at best, but these results suggest that the relationship between SARS-CoV-2 infection in pregnancy and subsequent preeclampsia is maintained even after adjustment for some of these potential confounding factors.

Temporal sequence

The systematic review by Conde-Agudelo and Romero[12] included studies with a diagnosis of SARS-CoV-2 infection at any point in pregnancy. Of the 28 studies included, 15 included women diagnosed with the infection at any point during pregnancy; the other 13 studies included women in whom infection was diagnosed at the time of admission for delivery. These latter 13 studies included one from the UK[14] and one from the US[18], which between them contributed 748,526 (94.6%) of the 790,954 pregnant women included in this meta-analysis. It is unlikely, therefore, that any meaningful information on the temporal relationship between SARS-CoV-2 infection and the development of preeclampsia can be drawn from these 13 studies.

Few studies have focused on women in whom preeclampsia preceded a diagnosis of SARS-CoV-2 infection. In one study that did[27], of the 51 cases of preeclampsia, 21 were diagnosed before SARS-CoV-2 infection, seven at the same gestational age, and 23 after SARS-CoV-2 infection. When the 21 women in whom preeclampsia was diagnosed before SARS-CoV-2 infection were compared with those who did not develop preeclampsia, there was a trend towards an increased risk of subsequently developing moderate or severe COVID-19 [unadjusted RR=2.28(0.92-5.61) (p=0.07), adjusted RR= 1.96 (0.8-4.84) (p=0.14)].

In this study[27], among the 23 cases of preeclampsia diagnosed after SARS-CoV-2, the median interval from diagnosis of SARS-CoV-2 infection to the diagnosis of preeclampsia was 16 days (interquartile range [IQR] 7-61 days). Only one other study[25] reported on the time from the diagnosis of SARS-CoV-2 infection and the diagnosis of preeclampsia. In this study, this median interval was 3.79 weeks (IQR 0.43-13.0 weeks). The hazard ratios for this association were 2.88 (95% CI, 1.20-6.93) for infection diagnosed before 32 weeks' and 2.74 (95% CI 0.98-7.71) for infection diagnosed at or after 32 weeks' gestation.

In the absence of prospective cohort studies of women with and without a diagnosis of SARS-CoV-2 infection evaluating the subsequent development of preeclampsia, there is likely to be significant under-reporting of women who had this infection but did not go on to develop preeclampsia. In most women included in the current studies, the diagnosis of SARS-CoV-2 infection was made in the third trimester; given that the origins of the pathophysiology of preeclampsia are thought to arise in the first and early second trimesters, it might be expected

that any causal relationship would be more readily established with SARS-CoV-2 infection at those earlier gestations.

In conclusion, the temporal relationship between pre-eclampsia has been suggested by these studies but has not been confirmed.

Biological gradient (dose-response relationship)

(Greater exposure should generally lead to greater incidence of the effect).

In the systematic review by Conde-Agudelo and Romero[12] both asymptomatic and symptomatic SARS-CoV-2 infection significantly increased the odds of preeclampsia. However, this association was stronger for patients with symptomatic illness (OR 2.11, 95% CI 1.59-2.81) than for those with asymptomatic infection (OR 1.59, 95% CI 1.21-2.10).

A meta-analysis[28] of 1,219 pregnant patients giving birth in one of 33 US hospitals used the National Institutes of Health (NIH) criteria for severity of SARS-CoV-2 infection: asymptomatic, mild, moderate and severe. In adjusted analyses, compared with asymptomatic women, severe-critical COVID-19 was associated with an increased risk of hypertensive disorders of pregnancy (40.4% vs 18.8%, aRR 1.61, 95% CI 1.18-2.20). However, mild-moderate COVID-19 was not associated with adverse perinatal outcomes compared with asymptomatic women.

The INTERCOVID study reported that longer duration of symptomatic COVID-19 was associated with increased relative risk of preeclampsia, eclampsia or HELLP syndrome[15].

A retrospective observational study[27] of 1,223 pregnant women in the UK compared the severity of SARS-CoV-2 infection in pregnancy and the likelihood of subsequent preeclampsia. Patients were classified into four groups according to disease severity based on NIH criteria: asymptomatic, mild, moderate and severe. The model included adjustment for the prior risk of preeclampsia based on maternal characteristics and medical history, using a competing risk model. Women in whom the diagnosis of preeclampsia was made before the diagnosis of SARS-CoV-2 infection were excluded from the analysis. Compared with a background (expected) risk of preeclampsia of around 1%, the observed incidence of preeclampsia in those with asymptomatic, mild, moderate and severe SARS-CoV-2 infection was 1.9%, 2.2%, 5.7%, and 11.1%, respectively. This monotonic relationship was statistically significant (chi-square test for trend; p=0.0017). After adjusting for differences in the prior risk of preeclampsia as determined by the competing risk model, severe COVID-19 disease was associated with an almost 5-fold higher risk of preeclampsia than was asymptomatic infection (aRR=4.9; 95% CI 1.56-15.38). Moderate or severe COVID-19 was also associated with a greater risk of preeclampsia compared to those with asymptomatic or mild infection (aRR=

3.3; 95% CI 1.48-7.38). The authors argued that their finding that the more severe the SARS-CoV-2 infection, the greater the risk of preeclampsia, supports the hypothesis of a causal relationship.

Plausiblity

(*A plausible mechanism between cause and effect*).

Several mechanisms have been proposed by which SARS-CoV-2 infection might cause systemic complications such as high blood pressure, liver injury and thrombocytopenia, as well as the respiratory disease typical of COVID-19[29]. One theory proposes the involvement of the angiotensin converting enzyme 2 (ACE2) receptor. Activation of the renin-angiotensin-aldosterone system (RAAS) ultimately leads to the cleavage of angiotensin I to angiotensin II by ACE. Angiotensin II, via a number of mechanisms (potent arteriolar vasoconstriction, increased renal tubular sodium reabsorption, increased aldosterone secretion, increased anti-diuretic hormone secretion) leads to an increase in blood pressure[30]. ACE2 acts as a counterbalance to ACE by cleaving and hydrolysing angiotensin II into angiotensin, a vasodilator.

It has been demonstrated that the SARS-CoV-2 virus enters cells in the lungs and other organs via the ACE2 receptor[31]. The spike S1 protein of the SARS-CoV-2 virus binds to the enzymatic domain of ACE2 receptor on the cell surface, resulting in the translocation of the virus into the cell[32]. The binding of the virus to ACE2 causes down-regulation of this enzyme, resulting in reduced conversion of angiotensin II to angiotensin, allowing angiotensin II to act relatively unopposed. The ACE2 receptor is also expressed in both the syncytiotrophoblast and the cytotrophoblast[33] in the placenta, where it plays an important role in trophoblast proliferation, angiogenesis, and arterial blood pressure regulation during pregnancy. Downregulation of ACE2 by SARS-CoV-2 there may lead to placental oxidative stress and the release of antiangiogenic factors, including soluble fms-like tyrosine kinase-1 (sFlt-1) and a reduction in pro-angiogenic factors, leading to the characteristic features of preeclampsia and HELLP syndrome[34-40] (Figure 1). One study[41] examined the potential role of SARS-CoV-2 infection in preeclampsia by assessing differentially expressed genes from clinical and experimental datasets. SARS-CoV-2 infection was found to upregulate sFlt-1 and endoglin (both antiangiogenic factors that cause vasoconstriction), nitric oxide modulators, and prothrombotic related molecules.

There are, therefore, several plausible mechanisms by which SARS-CoV-2 infection could lead to the development of preeclampsia.

Coherence (between epidemiological and laboratory findings); experimental evidence

The laboratory evidence cited above that demonstrates downregulation of ACE2, increased production of antiangiogenic factors, nitric oxide modulators and prothrombotic molecules by SARS-CoV-2 is consistent with the epidemiological data.

Some histopathological studies have also identified placental lesions in COVID-19. Many viruses are known to cause histopathological changes in placental morphology, with characteristic changes seen in some cases of antenatal Zika virus and Cytomegalovirus infection[42,43]. Some reports suggest that, when compared to controls, placentas of women with severe COVID-19 showed histopathological changes associated with poor maternal vascular perfusion[44]. This included decidual arteriopathy, peripheral and central villous infarction and villous agglutination. It is currently unknown what impact asymptomatic or mild SARS-CoV-2 infection might have on the placenta. Another study found that microvasculopathy was the most common finding in placentas of women positive for SARS-CoV-2 infection[45] suggesting that placental histopathological changes differ according to timing of delivery in relation to COVID-19 progression, i.e. whether in the acute stage or when viral clearance has already been achieved. The placenta of a patient with symptomatic COVID-19 at the time of delivery had prominent lymphohistiocytic villitis and was one of two placentas that showed maternal malperfusion changes. This may indicate that placental changes may be most likely to occur during the acute phase of the disease[45,46].

Experiment

Prospective cohort studies would potentially provide valuable evidence around the nature of the relationship between SARS-CoV-2 infection and preeclampsia. These studies should compare pregnant women with and without SARS-CoV-2 infection, including the measurement of those hematological, biochemical and immunological factors associated with COVID-19 and pre-eclampsia, as well as placental histopathological examination. Clearly, a randomised trial would be neither feasible nor ethical.

Analogous evidence

One meta-analysis identified a higher incidence of preeclampsia in pregnant women with coronavirus spectrum infections (including severe acute respiratory syndrome (SARS), Middle East Respiratory Syndrome (MERS) and COVID-19) than in the general pregnant population[11].

Reversibility

(*If the cause is deleted then the effect should disappear too*).

If SARS-CoV-2 infection can cause preeclampsia, then vaccination against COVID-19, antiviral therapies, and COVID-19 pandemic mitigation measures would be expected to reduce the risk of preeclampsia. One preprint study[47] compared pregnancy outcomes between women vaccinated or unvaccinated against COVID-19. Vaccination protected against SARS-CoV-2 infection prior to delivery (1.4% vs 11.3%; RR 0.13, 95% CI 0.03-0.50; P=0.003), and was also associated with a non-significant decrease in the incidence of preeclampsia (0.7% vs 1.2%; RR 0.58, 95% CI 0.08-4.25; P=0.59). Ongoing randomized placebo-controlled trials of COVID-19 vaccination in pregnancy will establish whether vaccination reduces the risk of SARS-CoV-2 infection and adverse pregnancy outcomes, including preeclampsia.

Association or Causation: Are the Bradford Hill's criteria still applicable in the 21st century?

Even though the currently available evidence would support the proposed hypothesis that COVID-19 could potentially cause preeclampsia, there are several limitations, and more research is needed to address the remaining questions before this assertion is made. The reported association of approximately 1.5 (compared to strength of association of a 200-fold increase in cancer in chimney sweepers used by Bradford Hill), would be considered as too small for a proven causal link and would more conceivably be attributed to other underlying contributors (i.e. bias or confounding). Moreover, the Bradford Hill's criteria have been questioned following the advancements in genetics, exposure science and statistics in the 21st century[48]. These advancements have improved our analytical capabilities for exploring potential cause-and-effect relationships and our ability to appreciate the complexity of onset and progression of diseases. These advancements in science and our understanding of disease origin had led some researchers to question the Bradford Hill's criteria when considering multifactorial causality[48].

Conclusion

There is growing evidence that the association between SARS-CoV-2 infection in pregnancy and preeclampsia is causal, particularly in relation to the biological gradient and plausibility. Clearly, however, more evidence is needed to bolster the other criteria, particularly in relation to temporal sequence, which is perhaps the only criterion which epidemiologists universally agree is essential to causal inference[48]. It is possible that a causal link is mediated through placental or cardiovascular pathology, but further studies are required to understand these potential mechanisms.

Since the Bradford Hill criteria for helping to determine whether observed epidemiological associations are causal were published in 1965, there have been seismic advances in a range of scientific fields (e.g., molecular genetics, genomics, molecular toxicology, genotoxicology) and technology (e.g., computers, software, statistics, analytical methods). These disciplines can be used to 'peer into the black box' (as it was known at the time) between exposure and disease[48]. This means that the cause-effect relationship can often be established with a degree of certainty, leading some to argue that in these instances, reliance on the Bradford Hill criteria becomes less relevant. Others, however, argue that data integration can enhance the application of the Bradford Hill Criteria in a causal analysis by integrating new techniques into each of the criteria, making conclusions about causality more robust[48]. It must also be acknowledged that in the case of SARS-CoV-2 infection and preeclampsia, we are still just beginning to shine some light into this particular 'black box' between exposure and disease.

Healthcare professionals should be aware that SARS-CoV-2 infection in pregnant women, even in those who remain asymptomatic, is a risk factor for the subsequent development of preeclampsia. They should also be cognisant of the additive effect of the combination of these two conditions on adverse pregnancy outcomes. Pregnant women who test positive for SARS-CoV-2 will benefit from close monitoring of blood pressure, liver and renal function to allow early diagnosis of preeclampsia and HELLP syndrome[49]. It may also be useful for women presenting with preeclampsia but non-classical biochemical markers to have a SARS-CoV-2 PCR swab (where testing on admission is not universal)[49].

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FIGURE LEGENDS

Figure. Mechanism of preeclampsia in COVID-19