Received: 21 March 2021 | Accepted: 25 March 2021

DOI: 10.1111/ppe.12773

SPECIAL ISSUE: INFECTIONS DURING PREGNANCY

Paediatric and Perinatal Epidemiology WILEY

Point: Uncertainty about estimating the risks of COVID-19 during pregnancy

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Funding information
K Palmsten was supported by a career development award from the *Eunice Kennedy Shriver* National Institute of Child Health & Human Development, National Institutes of Health [R00HD082412]

Several observational studies have described the risks of adverse perinatal outcomes following infection during pregnancy with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease (COVID-19). These studies have used retrospective data, typically recorded during health-care encounters.[1-3] Existing healthcare data are attractive for studying urgent public health questions, including risks associated with COVID-19 during pregnancy, because they can be easily accessed, and may provide rapid results in large populations. For example, using a hospital-based all-payer database of hospitalisations, Jering et al[1] recently compared in-hospital outcomes of 6380 pregnant women giving birth who had a COVID-19 diagnosis versus 400 066 who did not from April–November 2020. Among women with a COVID-19 diagnosis, increased odds of many adverse outcomes were reported including preterm birth (adjusted odds ratio [OR] 1.17, 95% confidence interval [CI] 1.06, 1.29) and preeclampsia (adjusted OR 1.21, 95% CI 1.11, 1.33).[1] Others have also reported increased risks of adverse perinatal outcomes following COVID-19 during pregnancy.[2,3] The potential risks associated with COVID-19 during pregnancy have informed clinical care and guidelines on COVID-19 vaccination during pregnancy. Therefore, it is crucial to understand the limitations of currently available data and uncertainty of results. In the flurry of recent publications on COVID-19 during pregnancy, exposure misclassification, reverse causation, selection, confounding, and inclusion of immortal time have potentially biased point estimates. Furthermore, a nuanced approach of assessing risk by maternal characteristics, timing of infection, and disease severity is needed.

Issues with exposure classification due to asymptomatic and often undiagnosed SARS-CoV-2 infection poses a unique threat to the validity of studies of COVID-19 during pregnancy. Most pregnant women with SARS-CoV-2 infections are asymptomatic for COVID-19. Flannery et al[4] reported among 83 women who were SARS-CoV-2 seropositive at delivery, 60% were asymptomatic throughout pregnancy. In a study of women universally tested for SARS-CoV-2 by polymerase chain reaction (PCR) at delivery, Reale et al reported that 86% testing positive were asymptomatic.[5] Given variability in COVID-19 screening across hospitals and over time, Jering et al[1] presumably includes patients who had and had not undergone universal screening near delivery; therefore, the study population would include undiagnosed asymptomatic cases, as well as diagnosed symptomatic and asymptomatic cases. Point estimates are likely to differ in populations with universal screening or increased identification of asymptomatic infection. A recent study[6] in a population with universal SARS-CoV-2 PCR testing at delivery reported no differences in the risks of preterm birth or preeclampsia between women with and without infection.

SARS-CoV-2 infection that resolves before delivery may not be captured by Jering et al,[1] or other data sources relying solely on identification of infection at delivery. Among women identified by Flannery et al[4] as asymptomatic and seropositive, only 54% were positive by nasopharyngeal PCR during pregnancy, even with routine screening at delivery. This suggests that the proportion of asymptomatic infections during pregnancy that clear before delivery and would be misclassified in studies using routine screening at delivery to estimate exposure *during* pregnancy may approach 50%.

Given these factors, differential exposure misclassification should be evaluated in studies relying on COVID-19 diagnosis as has been suggested for studies of maternal influenza and birth outcomes.[7] For example, it is plausible that women with preeclampsia would have more healthcare contacts and thus be more likely to be tested for COVID-19 and correctly classified, as compared to

women without preeclampsia. Sensitivity analysis[8] demonstrates that the unadjusted OR of 1.36 reported for preeclampsia in Jering et al[1] could be attenuated to 1.03 upon correction for differential exposure misclassification, assuming correct classification of those with COVID-19 is 90% in women with preeclampsia and is 70% in women without preeclampsia, and that women without COVID-19 are correctly classified.

The biologic plausibility and temporality of a positive association between COVID-19 diagnosis at delivery and preeclampsia should also be considered. Although a symptomatic SARS-CoV-2 infection would lead to a pro-inflammatory state that could increase the preeclampsia risk, it is less clear how an asymptomatic infection would contribute to the development of preeclampsia. It is possible that some women with COVID-19 diagnosed at delivery hospitalisation had subclinical disease onset, that is, placental vascular changes, or even met criteria for preeclampsia before infection. Therefore, reverse causation of preeclampsia resulting in a greater propensity for symptomatic COVID-19 or in differential detection of COVID-19 could be an explanation of an association between COVID-19 diagnosed near delivery and preeclampsia.

Selection bias is a potential concern for studies focusing on COVID-19 at delivery as only pregnancies surviving until delivery are included. Severe disease may cause maternal mortality before delivery,[2] and the impact of COVID-19 on pregnancy loss is unclear.

Another concern for observational studies of COVID-19 and adverse perinatal outcomes is confounding, or residual confounding, by factors associated with acquiring SARS-CoV-2 or having a symptomatic infection including demographic characteristics, pregnancy factors, and underlying comorbidities. Reale et al demonstrated pronounced racial and economic disparities according to SARS-CoV-2 infection, (eg, infection risk was ~12% in Hispanic, 7% in African American, and 1% in White women).[5] With experiences of racism adversely affecting heath care during pregnancy and perinatal outcomes,[9] women of colour are at increased risk for adverse perinatal outcomes independent of COVID-19. Disparities in care for COVID-19 could further exacerbate risks for COVID-19 morbidity and mortality. Lokken et al[2] reported on pregnancy complications and COVID-19-associated hospitalisations and mortality among pregnant women with SARS-CoV-2 infections in Washington State, without adjustment for confounders. COVID-19-associated hospitalisations and mortality in pregnant women were compared with the general population of 20-39 year olds, including men and women. Furthermore, testing for SARS-CoV-2 infection was not universal at the time of delivery, likely resulting in misclassification of asymptomatic cases. Risks of maternal and neonatal outcomes were presented according to trimester of SARS-CoV-2 infection and COVID-19 severity at delivery, however, data were sparse with only 11 women with severe/critical COVID-19. Immortal time bias is another concern in Loken et al and other studies classifying exposure as a binary (time-invariant) variable near the time of delivery.[10] For example, women with a COVID-19 diagnosis at delivery in pregnancies lasting 37 weeks or longer would not be at risk for preterm birth, leading to an underestimation of risk in the exposed. Despite major limitations related to confounding, exposure misclassification, and immortal time bias, the authors concluded that their data strongly supported the need to offer vaccination to pregnant women at risk for acquiring SARS-CoV-2 infection.[2]

Overall point estimates for the association between COVID-19 during pregnancy and adverse perinatal outcomes may obscure important variations in risk according to maternal characteristics, timing of infection, and severity of disease. Given the disparities in the propensity for COVID-19, effect measure modification of associations by demographic factors and underlying comorbidities should be evaluated. Furthermore, the magnitude of risk for adverse outcomes may be sensitive to the timing of SARS-CoV-2 infection during pregnancy as has been observed for maternal influenza infections.[11] Also, the etiologically relevant window for exposure depends on the perinatal outcome of interest. This is particularly relevant for studying the impact of maternal infection on fetal outcomes. For example, risk of fetal insult following maternal cytomegalovirus infection varies drastically by timing of maternal infection.[12] Jering et al estimate overall risks of adverse pregnancy and birth outcomes with COVID-19 status near the time of delivery.[1] Outcome risks are likely more nuanced, and should be studied according to gestational timing of infection. Moreover, risks should be estimated according to COVID-19 severity. Otherwise, overall risk estimates may depend on the severity case mix. Supporting this, a study comparing asymptomatic pregnant women at delivery who were SARS-CoV-2 positive with those who were SARS-CoV-2 negative reported no increased risk for preterm birth, although results were unadjusted for confounders.[13] Studies with a greater share of asymptomatic infections in their 'exposed' group may produce weaker or null associations when assessing *any* infection as compared to those with a smaller proportion of infections that are asymptomatic, assuming a greater impact of symptomatic versus asymptomatic infections on perinatal outcomes. As we are in the early phases of understanding the relationship between SARS-CoV-2 infections and pregnancy outcomes, it is even more important to stratify risk estimates by symptomatic and asymptomatic infection.

Although not without limitations, for example, volunteer bias, large prospective studies that carefully collect information on potential confounders and use serology testing throughout pregnancy to capture infection status, such as Assessing the Safety of Pregnancy in the Coronavirus pandemic (ASPIRE) study,[14] may provide different and more nuanced results than currently available retrospective database studies. Let's not be surprised if this happens. Instead, let's be prepared with a range of informed uncertainties built into our best estimates of the association between COVID-19 and adverse perinatal outcomes from the available data. Let's communicate clearly what our study questions are so that we can compare results across studies answering the same question—for example, what are the effects of SARS-CoV-2 infection at the time of delivery versus what are the effects of COVID-19 *anytime* during pregnancy? Let's acknowledge where we lack the data to conduct nuanced analyses, for example, by trimester of infection, disease severity or symptoms, or underlying comorbidities. Let's also acknowledge the pressure to yield rapid results to inform clinical and public health guidelines,

the duty to advocate for pregnant women by demonstrating their unique risk, and the concern from personal experience caring for pregnant patients with severe COVID-19, and that these factors can unconsciously impact how data are analyzed, or how results are interpreted. As Spiegelhalter and Riesch stated in their 2011 article on assessing and communicating uncertainties in the analysis of risks, "Communicate the estimates with humility, communicate the uncertainty with confidence."[15] When biases in studies of COVID-19 during pregnancy and adverse perinatal outcomes cannot be minimized through study design and data collection, sensitivity analyses to evaluate the magnitude of misclassification, confounding, and selection bias in measures of association[8,16] can help us communicate uncertainty in our results with confidence. Journal editors can facilitate this process by requiring such sensitivity analyses.

CONFLICTS OF INTEREST

No conflicts of interest to disclose.

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How to cite this article: Palmsten K, Vazquez-Benitez G, Kharbanda EO. Point: Uncertainty about estimating the risks of COVID-19 during pregnancy. *Paediatr Perinat Epidemiol*. 2022;36:450–452. https://doi.org/10.1111/ppe.12773