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Commentary

Pregnancy and the risk of severe coronavirus disease 2019 infection: methodological challenges and research recommendations

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Introduction

Optimal prevention and treatment of infectious diseases requires identifying segments of the population at elevated risk of developing severe disease who would benefit from heightened efforts to prevent exposure or to use personal protective equipment. These are the groups that would have high priority for vaccine access and warrant outreach efforts to encourage vaccine use. Elevated burden of disease could, in theory, result from some combination of a greater prevalence of infection with a typical distribution of disease severity or from a typical prevalence of infection with a greater risk of severe disease. Many infectious diseases, including coronavirus disease 2019 (COVID-19), have a wide spectrum of severity; however, the primary public health concern is severe manifestations that can lead to serious morbidity or death.

Pregnant women are often considered a potential high-risk group for identifying, preventing and treating infectious diseases. An elevated risk of severe illness and mortality among pregnant women was identified for pandemic 2009/10 influenza[1] and as data accrue, the same has been reported recently with regard to COVID-19.[2] With some infectious diseases, risk is primarily to the fetus (e.g. teratogenic viruses like rubella or vertically transmitted viruses like HIV) and protecting fetuses from exposure to the infectious agent is the goal, irrespective of maternal illness. Conversely, other infectious diseases (e.g. influenza) increase the risk of serious maternal illness, which may also result in harm to the fetus through other pathways.

Both immunological and physiological adaptations occur in pregnancy that can predispose pregnant women to increased susceptibility to infection, or severity of disease if infected.[3,4] Immunological modulation in pregnancy, including a shift from cell-mediated to humoral-mediated immunity, which is required to protect the fetus from rejection, may increase susceptibility to certain infections or to more severe manifestations of disease. There are also physiological alterations in the cardiovascular and respiratory systems in pregnancy, beginning early after implantation and continuing throughout gestation. These adaptations, such as increased heart rate, blood volume and oxygen consumption, as well as decreased functional residual capacity of the lungs, are necessary to meet the increased maternal and fetal metabolic demands and ensure adequate uteroplacental circulation, but they can enhance vulnerability to severe respiratory or cardiovascular disease, particularly in later gestation when the physiological demands of pregnancy are greatest.

In this commentary, we address the methodological challenges encountered in examining the impact of pregnancy on severity of COVID-19 infection and offer strategies to more accurately assess the risk of severe COVID-19 among pregnant women. Clearer information on this issue has direct policy relevance in assigning pregnant women as a priority group for vaccination.[5] Given the increasingly clear evidence that severe COVID-19 infection has a detrimental effect on maternal and neonatal morbidity,[6] the question of whether pregnancy itself affects risk of severe COVID-19 infection has become increasingly important.

Methodological challenges

For epidemiologists, the question is whether pregnant women who develop severe infectious disease would not have done so, had they not been pregnant. As always with counterfactual contrasts, we cannot observe the same individuals in both the pregnant and non-pregnant state to directly answer the question, and there are a number of ways in which comparison of the risk in pregnant and non-pregnant women is susceptible to bias.

Increased surveillance

Epidemiological studies typically rely on 'detected disease', not actually on the 'occurrence of disease'. Pregnancy may influence infectious disease detection through enhanced clinical scrutiny associated with women's greater health awareness, regular contact with healthcare providers through prenatal care, and increased surveillance for health problems during prenatal care. If pregnancy increases care-seeking behaviour or contact with clinicians that leads to identification of disease that would not otherwise have been detected, it will appear that pregnant women are at increased risk of infectious diseases. A non-pregnant woman with mild or moderate respiratory symptoms may not seek medical care given the inconvenience of scheduling and planning a visit to a healthcare provider. In contrast, the vigilance associated with pregnancy, ease of reaching out to their prenatal care provider and access to health insurance while pregnant could alter the threshold for action, making pregnant women more likely to be screened, tested or diagnosed. In the case of COVID-19, there is a lower clinical threshold for testing pregnant women and, in many settings, universal COVID-19 screening practices upon admission to the hospital for labour and delivery would result in significant surveillance bias.[7] Extensive testing among pregnant women will result in a higher overall rate of detected COVID-19 disease, particularly milder or subclinical infections.

Enhanced clinical response to illness

The response of a clinician to a report of infectious disease symptoms may range from telephone contact with recommendations for managing symptoms to an office visit or hospital admission for close monitoring. The apparent risk of 'severe disease', as defined by indicators of enhanced clinical management or hospital admission, may be increased for pregnant women even if the underlying symptoms are the same as those among non-pregnant women.

Once engaged in clinical care, the likelihood of performing a diagnostic test may be greater for pregnant women and, so may elevate the frequency of case ascertainment. For instance, to the extent that a non-specific respiratory disease is the clinically assigned diagnosis in non-pregnant women versus laboratory-confirmed COVID-19 in pregnant women, the risk of COVID-19 would appear to be elevated among pregnant women only because the likelihood of having been tested and subsequently diagnosed with COVID-19 has been increased through clinical decisions. Even upon engaging with the healthcare system, pregnant women may be preferentially admitted to the hospital or provided with other forms of enhanced care.

Confounding

The risk factor profile for severe infectious disease among pregnant women may differ from that among non-pregnant women. Pregnancy is a marker in many cases of having a partner, being of sufficiently good health to conceive and either choosing to conceive (which may indicate economic stability) or having an unintended pregnancy (which may indicate lack of access to contraception or low relationship power). Once pregnancy is recognised, there are myriad behavioural changes commonly undertaken to enhance the health of the fetus, such as alterations in tobacco and alcohol use, changes in diet and physical activity and modifications in day-to-day activities such as work and socialising that may affect risk of acquiring infections and/or severity of infection-related illness. Although it could be argued that pregnancy is the cause of this cascade of changes that affect risk of severe infectious disease, they are not a result of the pregnancy per se.

Current evidence on COVID-19 and pregnancy

Available data suggest that, compared with non-pregnant women, pregnant women are less likely to report fever, muscle aches and myalgia symptoms associated with COVID-19, but may be more likely to receive medical interventions related to severe COVID-19 infection.[2,8] The most recently published update of the meta-analysis from Allotey et al.[9] (https://www.bmj.com/content/bmj/370/bmj.m3320.full.pdf) indicates that 'Compared with non-pregnant women of reproductive age with COVID-19, the odds of admission to the intensive care unit (odds ratio 2.13, 95% confidence interval 1.53–2.95; seven studies, 601 108 women) and need for invasive ventilation (2.59, 2.28–2.94; six studies, 601 044 women) and extracorporeal membrane oxygenation (2.02, 1.22–3.34; two studies, 461 936 women) were higher in pregnant and recently pregnant women.' In contrast, for all-cause mortality, the odds ratio was 0.96 (95% CI 0.79–1.18) based on 601 122 women. In the most recent analysis of US surveillance data from the Centers for Disease Control, symptomatic pregnant women had higher all-cause mortality compared with symptomatic non-pregnant women with COVID-19[2] (1.5 versus 1.2 per 1000

cases; relative risk 1.7; 95% CI 1.2–2.4) leaving the question of excess mortality associated with pregnancy unresolved.

Study design and analysis strategies to strengthen causal inference

Interpretation of surveillance data on pregnancy status in relation to COVID-19 severity calls for caution in drawing causal inferences, taking into account whether pregnant and non-pregnant patients were screened, tested or diagnosed comparably. We offer the following practical recommendations for evaluating the relationship between pregnancy and severe COVID-19, proceeding sequentially from study design to data collection to data analysis, as described below. The choice of a study population should consider whether the testing protocol during the study period is clear and if not universal, whether there is information on why individuals were tested and the clinical severity of infection. Selection of health outcomes should consider whether they are vulnerable to distortion as a result of being pregnant and seek to include those that are unlikely to be affected as an artefact of pregnancy-driven healthcare decisions. Finally, detailed covariate information is needed to effectively control confounding by the strong potential for shared predictors of both COVID-19 infection and becoming pregnant.

1 Account for testing protocols in the study population: Where there are time periods of both discretionary and universal testing of pregnant women, results should be stratified into those periods in which policy differed. Restricting cases to those identified before labour and delivery would help to mitigate biases resulting from comprehensive testing and incidental detection at hospital admission.
2 Account for the reason for having been tested: If there is documentation of the motivation for having been tested, e.g. contact with infected individual, symptoms suggestive of possible COVID-19, patient concerns, pre- or post-travel requirement, recommendation of healthcare provider, then there is an opportunity to create subgroups in which the comparison of pregnant and non-pregnant women is more likely to be reflective of the causal impact of the pregnancy itself.
3 Examine spectrum of disease severity: Stratify analyses by indicators of disease severity to identify and reduce surveillance bias. The most severe manifestations of infectious disease are far more certain to result in detection than mild cases, regardless of care-seeking behaviour or the vigilance of the clinician, and are therefore less susceptible to various forms of surveillance bias. On the other hand, without universal screening, asymptomatic or mild infections will never be detected, regardless of patient or clinician vigilance. That leaves a wide range of disease manifestations that are subject to selective diagnosis, treatment and discrepancies in management such as admission to the hospital or intensive care unit. By collecting information on a range of disease severity, there is an opportunity to consider the pattern of clinical care across outcomes to empirically assess potential surveillance bias. The comparison of pregnant and non-pregnant women should examine asymptomatic disease, mild disease and severe disease as distinctive outcomes.
4 Focus on health indicators least likely to be affected by the pregnancy: In examining the need for specific forms of medical care, focus on outcomes that are least susceptible to subjective decisions that may be influenced by the pregnancy itself. For example, the borderline between symptoms that do and do not call for hospitalisation can be quite subjective, such that the exact same clinical profile would lead to different actions. In contrast, admission to an intensive care unit or use of mechanical ventilation would tend to follow more rigorously defined protocols, regardless of pregnancy status.
5 Control confounding: Beyond the typical approach to addressing confounders through multivariate modelling, a more ambitious and effective approach might be considered to better isolate the effect of pregnancy from its many correlates. Propensity scores can be used to balance pregnant and non-pregnant women on dozens of variables and effectively control confounding if a sufficient array of covariates are measured and available. Limiting the evaluation to basic demographic attributes such as age, for example, is not likely to be sufficient to create truly exchangeable groups and so isolate the effect of pregnancy.

Recommendations for evidence synthesis

Because each of the methodological considerations described above has the potential to affect the results of studies of pregnancy and COVID-19 severity, efforts to synthesise the literature need to take these factors into account. For aggregating results, only studies that are similar to one another on these key characteristics should be combined using some simple categories: The basis for testing would ideally be identified as universal, symptom-based or uncertain/mixed. Severity of infection should be subdivided into asymptomatic, mild or severe. Specific health outcomes would be considered and grouped into those that are and are not likely to be affected by pregnancy-driven clinical decisions otherwise independent of health status. Finally, the extent to which covariates are fully addressed as potential confounders could be classified as minimal (routine sociodemographic factors) and extensive (including more detailed indicators such as body mass index and healthcare access). As the number of studies grows there should be more opportunity to effectively examine the

impact of these considerations on the pattern of results and by doing so, more accurately assess the causal impact of pregnancy on COVID-19 severity.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article. ■

References

1 Jamieson DJ, Honein MA, Rasmussen SA, Williams JL, Swerdlow DL, Biggerstaff MS, et al. Novel influenza A (H1N1) Pregnancy Working Group. H1N1 2009 influenza virus infection during pregnancy in the USA. *Lancet* 2009;374:451–8.
2 Zambrano LD, Ellington S, Strid P, Galang RR, Oduyebo T, Tong VT, et al. Update: characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status - United States, January 22-October 3, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1641–7.
3 Kourtis AP, Read JS, Jamieson DJ. Pregnancy and infection. *N Engl J Med* 2014;370:2211–8.
4 Omer SB. Maternal immunization. *N Engl J Med* 2017;376:2497.
5 US Centers for Disease Control and Prevention. *Precautions for People with Certain Medical Conditions*. Atlanta, GA: US Centers for Disease Control and Prevention; 2021 [https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html]. Accessed 7 February 2021.
6 Villar J, Ariff S, Gunier RB, Thiruvengadam R, Rauch S, Kholin A, et al. Maternal and neonatal morbidity and mortality among pregnant women with and without COVID-19 infection: the INTERCOVID Multinational Cohort Study. *JAMA Pediatr* 2021;175:817–26.
7 Griffith GJ, Morris TT, Tudball MJ, Herbert A, Mancano G, Pike L, et al. Collider bias undermines our understanding of COVID-19 disease risk and severity. *Nat Commun* 2020;11:5749.
8 Ellington S, Strid P, Tong VT, Woodworth K, Galang RR, Zambrano LD, et al. Characteristics of women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status - United States, January 22-June 7, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:769–75.
9 Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ* 2020;370:m3320.