Pregnancy and the Risk of Severe COVID-19 Infection: Methodologic Challenges and Research Recommendations

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Running title: Pregnancy and the Risk of Severe COVID-19 Infection

INTRODUCTION

Optimal prevention and treatment of infectious diseases requires identifying segments of the population at elevated risk of developing severe disease that would benefit from heightened efforts to prevent exposure or utilize of personal protective equipment. If vaccines are available, these are the groups that would have high priority for access and warrant outreach efforts to encourage their use. Elevated burden of disease could, in theory, result from 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 COVID-19, have a 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 asserted for pandemic 2009-2010 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 risk of serious maternal illness, which may also result in harm to the fetus through other pathways.

Both immunologic and physiologic 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 can enhance vulnerability to severe respiratory or cardiovascular disease, particularly in later gestation when physiological demands of pregnancy are greatest.

In this commentary, we address the methodologic considerations studies assessing the risk of severe COVID-19 among pregnant women, a topic of great interest with direct policy relevance.[5]

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

Epidemiologic studies typically rely on “detected disease,” not actually on the “occurrence of disease.” Pregnancy may influence infectious disease detection due to the enhanced degree of clinical scrutiny associated with women’s greater health awareness, regular contact with health care providers through prenatal care, and increased surveillance for health problems during prenatal care. If pregnancy increases care-seeking behavior 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 inconvenience of scheduling and planning a visit to a health care 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 hospital for labor and delivery would result in significant surveillance bias,[6] with extensive testing among pregnant women resulting in a higher overall rate of detected COVID-19 disease particularly from more mild 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, thus, 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 health care 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 recognized, there are myriad behavioral 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 socializing that may affect risk of acquiring infections and/or severity of infection-related illness. While 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 to 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 intervention related to severe COVID-19 infection.[2,7] The most recently published update of the meta-analysis from Allotey et al.[8] (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 to 2.95; seven studies, 601 108 women) and need for invasive ventilation (2.59, 2.28 to 2.94; six studies, 601,044 women) and extracorporeal membrane oxygenation (2.02, 1.22 to 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 CDC, pregnant, symptomatic women had higher all-cause mortality compared to non-pregnant, symptomatic women with COVID-19[2] (1.5 versus 1.2 per 1,000 cases; RR 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 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:

1) 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 behavior or the vigilance of the clinician, and are thus less susceptible for 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, mild disease, and severe disease as distinctive outcomes.

2) 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 prior to labor and delivery would help to mitigate biases resulting from comprehensive testing and incidental detection at hospital admission.

3) 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 health care 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.

4) Focus on health indicators least likely to be affected by the pregnancy: In examining 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 hospitalization 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 modeling, 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 thus isolate the effect of pregnancy.

Acknowledgements: None.

Disclosure of interests: The authors report no competing interests.

Contribution to authorship: All authors wrote sections of the manuscript draft and edited the full draft manuscript.

Details of ethics approval: Not applicable.

Funding: None

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