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Commentary

The epidemiology and pathogenesis of SARS-CoV-2 infection in pregnancy: More questions than answers

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With the spread of the global COVID-19 pandemic, insights into the epidemiology and pathophysiology of SARS-CoV-2 are expanding rapidly. In the emerging body of research on this novel coronavirus, pregnant women – who are more susceptible to infections compared to non-pregnant women [1] – have received relatively little attention. The normal physiological adaptations of pregnancy, particularly of the immune and cardiopulmonary systems, can predispose women to the respiratory complications of other infections such as influenza. Limited data from previous coronavirus outbreaks suggest potentially higher mortality among pregnant women with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) compared to non-pregnant women [2]. Outcomes in pregnant women with SARS-CoV-2 infection appear less severe compared to SARS and MERS [3] though there is some suggestion that the incidence of adverse pregnancy outcomes, particularly preterm birth (PTB), may be increased in women with SARS-CoV-2 [4].

In this issue of *EClinicalMedicine*, Khalil and colleagues present a systematic review and meta-analysis of published literature on SARS-CoV-2 in pregnancy, including maternal, obstetric and perinatal outcomes [5]. This review includes >2000 women globally with data from national and regional registries. Overall they report reassuring maternal outcomes and the data indicate that perinatal and maternal mortality were rare. However similar to findings in general adult populations, pregnant women with comorbidities and obesity appear at higher risk. Of particular concern, some adverse pregnancy outcomes appeared high in women with SARS-CoV-2: for example, PTB was reported in 22% of deliveries, and was medically indicated in 18%. Overall 48% of deliveries were via caesarean section, but few studies reported indications and the contribution of iatrogenic caesarean births to preterm rates is unclear.

While this review begins to present valuable data on these important issues, ultimately it provides more questions than answers. The risk of preterm birth, its aetiology, and the contribution of iatrogenic caesarean section to preterm rates clearly require further investigation. The review also indicates substantial heterogeneity in findings, and the fundamental limitations of the studies published to date. The majority of studies included here were retrospective case series with no comparison groups; had small sample sizes; lacked standardization of case definitions (laboratory confirmation vs chest CT scans) and testing strategies (universal testing at admission for labor or other indications vs symptom-based) for SARS-CoV-2; and reported differing outcomes using differing definitions. Additionally, most women included were diagnosed with SARS-CoV-2 in their third trimester, and/or hospitalized in settings under varying admission criteria. Taken together, these issues greatly complicate interpretation of findings and in turn limit what we can say about SARS-CoV-2 in pregnancy.

In fact, despite increasing numbers of pregnant women infected with SARS-CoV-2, the current state of epidemiologic knowledge remains strikingly limited. Research on SARS-CoV-2 in pregnancy is complicated by both the methodological nuances underlying epidemiologic studies during pregnancy and the pressures of conducting research during a pandemic. The selection biases that are well known in perinatal epidemiology raise basic concerns. Criteria for testing for SARS-CoV-2 may prioritize symptomatic individuals, and the pandemic has led to alterations in health care service operations in many settings. Together, these factors may lead to selection biases as mildly symptomatic women may be less likely to access care and testing. Along with the inclusion of mainly hospitalized women in many studies here, this means that asymptomatic or mildly symptomatic women are less likely to be included in the studies reviewed compared to moderately or severely symptomatic women. This would likely impact the observed frequency of outcomes and associations involving SARS-CoV-2. Inclusion of more symptomatic women could also explain the high proportion of women in their third trimester in these studies, as infection often increase with advancing gestation [1]. Furthermore, inferences can be affected by misclassification bias when exposure or outcome status is incorrectly assigned. The current gold standard for COVID-19 case identification is reverse transcription-polymerase chain reaction testing. However in the general population, there may be a high false negative rate particularly early in the disease course and in patients with mild disease [6]. Coupled with the inclusion of women classified as cases by methods other

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than laboratory confirmation (clinical or radiologic criteria), this could lead to misclassification of COVID-19 cases. Similarly, increased PTB risk was reported in the review however PTB data can be of variable quality with gestational age (GA) assessment methods and delivery methods contributing to observed rates [7]. While measurement error in GA could lead to increased PTB incidence through misclassification, the high rate of caesarean sections is more likely to have contributed to the increased PTB incidence. Among studies reporting high rates of iatrogenic PTB, maternal compromise due to COVID-19 was the most common indication [8]. It is not clear whether this was a direct effect (biological) or indirect effect of COVID-19 and these findings should thus be interpreted with caution.

Due to the current lack of high-quality data regarding the epidemiology and pathogenesis of SARS-CoV-2 infection in pregnancy, informed public health recommendations present a challenge. As highlighted by Khalil et al., data on the effects of infections early in pregnancy, risks of preterm birth, indications for caesarean sections, the potential for vertical transmission in women with SARS-CoV-2 infection and the effect of changes in health care provision due to COVID-19 on maternal, obstetric and infant outcomes are required to inform evidence-based guidelines. To address these gaps, future research will have to consider selection of representative samples, accurate ascertainment of exposures and outcomes, standardization of definitions and robust methods to support assessment of causality. Researchers should also ensure reporting of all relevant information required to replicate the research and to make inferences regarding study outcomes. While the results by Khalil et al. add to previous reassuring data regarding SARS-CoV-2 and COVID-19 in pregnancy, more work needs to be done using rigorous and robust methods to confirm these findings.

Declaration of Competing Interest

Nothing to declare.

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