EDITORIAL

Understanding Risk for Newborns Born to SARS-CoV-2–Positive Mothers

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As of April 2021, yet another worldwide wave of SARS-CoV-2 infections is threatening to bring new daily highs in the mortality associated with the COVID-19 pandemic. The recent emergency approvals of several vaccines and worldwide vaccination campaigns are bringing hope of an eventual containment coupled with a long road to recovery. A critical component of this recovery will be to understand and mitigate risk for the children of this pandemic. The generation born during the 1918 influenza pandemic experienced long-term consequences, including 15% lower high school graduation rates, increased cardiovascular morbidity, higher rates of mental illness in adulthood, and lower socioeconomic status, and died younger than individuals born in preceding and succeeding generations.[1] The long-term consequences of maternal SARS-CoV-2 infection in pregnancy on future child health are yet to be understood.

Related article

In this issue of *JAMA*, Norman et al[2] report important data on the public health–level significance of the COVID-19 pandemic for children born during this time. Taking advantage of centralized health care record systems in Sweden, the study reported on 88 159 infants born to 87 005 mothers between March 11, 2020 (the date the first woman in labor was diagnosed as having SARS-CoV-2 in Sweden), and January 31, 2021, representing 92% of all births in Sweden during this period. The maternal SARS-CoV-2-positivity rate was 2.6% in this sample, comprising an unspecified mixture of symptom-based and universal testing that varied by time period, region, and hospital. To assess main outcomes of neonatal morbidity and mortality, the authors used a propensity score matching strategy to match up to 4 infants per positive case based on maternal characteristics and, appropriately, not on gestational age at delivery. Norman et al found an association of maternal SARS-CoV-2 infection in pregnancy with newborns' admission for neonatal care (11.7% vs 8.4%; odds ratio, 1.47; 95% CI, 1.26-1.70), any neonatal respiratory disorder (2.8% vs 2.0%; odds ratio, 1.42; 95% CI, 1.07-1.90), and hyperbilirubinemia (3.6% vs 2.5%; odds ratio, 1.47; 95% CI, 1.13-1.90). There were no differences in neonatal mortality, length of hospital stay, or breastfeeding rates.

In addition, there was a higher rate of preterm delivery (gestational age <37 weeks) among infected mothers: 8.8% in the SARS-CoV-2–positive group compared with 5.5% in the comparison group. Because preterm birth may be in the causal pathway, the authors performed mediation analyses and found that preterm delivery could explain an estimated 89.3% of the association between maternal SARS-CoV-2 during pregnancy and any neonatal respiratory disorder. Although the higher occurrence of neonatal morbidities initially seems concerning, when put in the context of a higher rate of preterm birth in the SARS-CoV-2–positive group, the findings appear expected.

The scientific community is in need of data on short- and long-term outcomes related to children with in utero exposure to SARS-CoV-2. The associations found in the study by Norman et al and their mediation through preterm delivery add to mounting evidence from groups around the world.[3,4] It is important to distinguish these from other etiologies for neonatal respiratory disorders, including those directly related to COVID-19. Among infants born to SARS-CoV-2–positive mothers, Norman et al reported the incidence of positive SARS-CoV-2 polymerase chain reaction (PCR) test results in infants to be low (0.9%), and none of the PCR-positive infants were reported to have congenital pneumonia.

The low risk of perinatal mother-to-infant SARS-CoV-2 transmission is particularly relevant in the context of the response to the COVID-19 pandemic in Sweden. Unlike neighboring countries and other developed countries around the world, Sweden opted for a more measured strategy that focused on protection of special groups (eg, aged >70 years) and personal freedom and responsibility,[5] including no lockdowns, no mask mandates, and no enforced quarantine for infected individuals. Physical distancing was strongly recommended, and people were encouraged to work from home if possible, avoid crowded places, and avoid travel, but schools were never closed for children aged 16 years and younger and were closed for only 3 months for those aged 17 years and older.[5] In terms of women who gave birth, mothers and infants were not separated and breastfeeding was allowed, with appropriate safeguards.

While this strategy has been criticized from both within[6] and outside of Sweden[7] in the context of overall outcomes, Sweden fared worse than some Scandinavian countries but better than some other developed countries.[7] Exact comparisons are not possible due to differences in testing, disease definitions, and death attribution, but several parallels can nevertheless be drawn. During the period covered by the study by Norman et al, 5.5% of the Swedish population was infected and 0.11% died of COVID-19 (based on cumulative counts from the Johns Hopkins Coronavirus Resource Center[8] and the official statistics of Sweden[9]). During the same period, the US had an 8.0% infection rate and 0.14% death rate[8,10] despite a significantly more conservative approach. In this context, the lack of evidence for severe neonatal outcomes in 92% of all births in Sweden is reassuring, including births among mothers who tested negative for SARS-CoV-2 or whose infection status was unknown.

Additional reassurance can be gained from the fact that the reported results from Norman et al are likely overstated

because of the lack of comprehensive testing of pregnant women. In the US, approximately half of all women testing positive for SARS-CoV-2 on universal screening at admission to labor and delivery are asymptomatic,[11,12] and the relative risk of adverse maternal and neonatal outcomes increases with COVID-19 disease severity.[4,12] The SARS-CoV-2 positivity rate reported by Norman et al was 2.6% among mothers who gave birth during a period when the reported overall positivity rate was 5.5% in the Swedish population, suggesting possible misclassification of untested women with asymptomatic COVID-19 as negative and possible biased selection of women with more severe COVID-19 into the positive group. Taken together with the lack of information on maternal illness severity and infection timing, the reported associations are likely to overestimate true neonatal morbidity.

A limitation of this work is the lack of detailed attention and analysis of race and ethnicity. Health disparities are at the forefront of the COVID-19 pandemic.[13] While at first glance Sweden's population seems homogeneous, 1 in 5 people currently living in Sweden were born in other countries, and COVID-19 health disparities have been similarly reported from Sweden as from the rest of the world.[5] Norman et al used a crude "country of birth" measure to classify mothers into Nordic, non-Nordic Europe, Middle East/Africa, and other and reported that 25.5% of mothers in the SARS-CoV-2–positive group but only 15.9% in the comparison group originated from the Middle East or Africa (Table in the article by Norman et al[2]). The propensity-matched group had a similar rate of 25.5% of mothers born in the Middle East or Africa, but the case-matching strategy is difficult to interpret given the heterogeneity of this group and the absence of self-identified racial/ethnic information. Moreover, several of the maternal characteristics on which the case-matching strategy was based, including race/ethnicity, body mass index, and smoking, are associated with both the epidemiology of COVID-19 and preterm delivery,[14] potentially contributing additive effects to infant morbidity at the population level.

The important data presented by Norman et al in this issue of *JAMA* add to the growing understanding of the effects of in utero SARS-CoV-2 exposure on children and to the developing body of evidence showing an association between SARS-CoV-2 infection during pregnancy and preterm delivery. Additionally, this study offers further reassurance of a low risk of neonatal infection, morbidity, and mortality.

ARTICLE INFORMATION

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Published Online: April 29, 2021. doi:10.1001/jama.2021.6210

Conflict of Interest Disclosures: Dr Gyamfi-Bannerman reported receipt of funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the Centers for Disease Control and Prevention and reimbursement for a talk from Medela. Dr Dumitriu reported receipt of funding from the National Institute of Mental Health and the Centers for Disease Control and Prevention and pending reimbursement for a talk from Medela.

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