Infant Outcomes Following Maternal Infection with SARS-CoV-2: First Report from the PRIORITY Study

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Abstract

Infant outcomes after maternal SARS-CoV-2 infection are not well-described. In a prospective U.S. registry of 263 infants born to mothers testing positive or negative for SARS-CoV-2, SARS-CoV-2 status was not associated with birth weight, difficulty breathing, apnea or upper or lower respiratory infection through 8 weeks of age.

Key words:

SARS-CoV-2

COVID-19

Pregnancy

Newborn

Introduction

Maternal viral infection in pregnancy and the peripartum and postpartum periods can adversely affect infant outcomes. While studies have reported that maternal SARS-CoV-2 infection increases the risk of preterm birth[1] and can be vertically transmitted,[2-5] overall risks for infants born to mothers with SARS-CoV-2 are not yet well-described. Currently, national and international guidelines for management of infants born to mothers with SARS-CoV-2[6-8] are based on limited data without outcomes reported past the neonatal period. A more complete understanding of infant outcomes after maternal SARS-CoV-2 infection would inform guidelines and policies to manage this important and growing segment of the population.

To address this urgent need, we report here early findings from infants born to mothers enrolled in the **PR**egnancy Coronav**I**rus **O**utcomes **R**eg**I**s**T**r**Y** (PRIORITY), an ongoing nationwide study of pregnant or recently pregnant women who have confirmed or suspected SARS-CoV-2.

Methods

PRIORITY is a prospective cohort study enrolling U.S. individuals ≥13 years old with suspected or confirmed SARS-CoV-2 during pregnancy or in the first 6 weeks after pregnancy. This manuscript reports infant outcomes for live births occurring to 179 mothers who had a positive test for SARS-CoV-2 and 84 mothers who had a negative test for SARS-CoV-2 and excludes live births of 10 mothers suspected of SARS-CoV-2 who were not tested. Maternal outcomes from PRIORITY will be reported separately.

Mothers were recruited nationally through outreach by professional organizations, traditional media, social media, and word of mouth to healthcare providers. Once recruited, informed consent was obtained by the study team from the mother, for herself and her infant; births occurred at over 100 hospitals across the U.S. PRIORITY was approved by the University of California San Francisco Institutional Review Board (IRB #20-30410).

Clinical and demographic data was collected from mothers by phone, email or text at the time of enrollment, after birth and at 6-8 weeks after delivery, with participants reporting results of SARS-CoV-2 tests performed by their own providers. Consistent with the registry design, most outcomes were obtained by maternal report. For outcomes for which confirmation was crucial including birth defects and positive infant testing for SARS-CoV-2, infant medical records were obtained from the electronic medical record of the hospital of birth to confirm the maternal report. In addition, convenience samples of 61 (34.1%) of 179 maternal reports of maternal SARS-CoV-2 and of 24 (54.5%) of 44 maternal reports of neonatal intensive care unit (NICU) admission were also adjudicated from the medical record; all (100%) of these medical records correlated with the maternal report.

PRIORITY initiated enrollment on March 22, 2020, with a sample size of 1200 women justified by feasibility and an initial focus on gathering urgently needed data on birth defects, NICU admission, abnormal newborn examination, positive infant test for SARS-CoV-2 and respiratory complications at birth. Additional infant outcome items were IRB approved and added to both the birth questionnaire and the 6-8 week questionnaire on May 13, 2020. See Supplementary Table 1 for infant questionnaire items and the dates that their collection was initiated. PRIORITY enrollment and follow up is ongoing; for this manuscript, we report data available by June 22, 2020.

We calculated the incidence and associated 95% confidence intervals for adverse outcomes using exact binomial techniques. We used chi-square analysis and Fisher's exact test to compare the proportion of outcomes between infants whose mothers tested positive for the virus and those whose mothers tested negative.

Results

Our cohort of 263 infants included 179 and 84, respectively, born to mothers testing positive or negative for SARS CoV-2. Among those testing positive, 146 (81.6%) were symptomatic, while among those testing negative, 53 (63.1%) were symptomatic (p=0.001).

See the Table for other clinical and demographic characteristics by maternal SARS CoV-2 status.

In this cohort of 263 infants, 44 infants (17%) were admitted to the NICU; fast breathing or difficulty breathing was reported for 14 (11%) of 127 infants surveyed after expansion of the birth questionnaire, and apnea was reported for 2 (1.6%). These characteristics did not differ between mothers testing positive for SARS-CoV-2 compared to those who tested negative. Among infants born to mothers who first tested positive 0-14 days prior to delivery, 20 (26.0%) of 77 were admitted to the NICU compared to 10 (12.2%) of 82 born to mothers who first tested positive more than 14 days prior to delivery (p=0.04). Infants born to mothers who first tested positive 0-14 days prior to delivery were also born earlier as compared to infants born to mothers who first tested positive more than 14 days prior to delivery (mean 37.5 versus 39 week gestation, p=0.0009). Additionally in this cohort, 16 mothers first tested positive for SARS-CoV-2 after delivery; the positive test for this subgroup occurred a median of 6 days after delivery with an interquartile range of 1-12 days after delivery. Infants born to mothers who first tested positive 0-14 days prior to delivery were less likely to room in with mothers than were those born to mothers who first tested positive more than 14 days prior to delivery or after delivery (see Supplemental Table 2).

Two infants born to mothers who tested positive for SARS-CoV-2 in the third trimester were reported to have birth defects, each with multiple congenital anomalies reported. One of these had cardiac, vertebral, renal and pulmonary anomalies while the other had facial, genital, renal, brain and cardiac anomalies. One mother who tested negative for SARS-CoV-2 also reported an infant with gastrointestinal, renal and cardiac anomalies.

Through 6-8 weeks of age, no pneumonia or lower respiratory tract infection was reported. Among 56 infants assessed at 6-8 weeks of age for upper respiratory infection (URI), URI was reported for two (5.0%) infants of SARS-CoV-2 positive mothers and 1 (6.3%) infant of a SARS-CoV-2 negative mother (p=0.85). In the first 6-8 weeks of follow up, 2 (1.1%) infants born to SARS-CoV-2 positive mothers tested positive for SARS-CoV-2, and

one had an indeterminate SARS-CoV-2 test. One was a late preterm infant with a positive nasopharyngeal swab for SARS-CoV-2 at 24 hours of life and a negative nasopharyngeal swab for SARS-CoV-2 at 48 hours of life; this infant breastfed and roomed in after birth and was discharged home at 2 days of life. The other was born at 26 weeks gestation and received expressed donor milk. This infant's initial SARS-CoV-2 test was negative at 24 hours of life, positive at 48 hours of life and negative at 6 and 8 days of life; she had a clinical course notable for mild lymphocytosis, anemia and unilateral corneal opacification of unknown etiology and otherwise typical of gestational age. The estimated incidence of a positive test for SARS-CoV-2 among infants of mothers with positive testing for SARS-CoV-2 was 1.1% (0.1%, 4.0%). No infant required re-hospitalization in the follow-up period.

Discussion

Among 263 initial infants enrolled in the PRIORITY study, adverse outcomes, including preterm birth, NICU admission, and respiratory disease did not differ between those born to mothers testing positive for SARS-CoV-2 and those born to mothers testing negative. No pneumonia or lower respiratory tract infection was reported in this cohort through 6-8 weeks of age. Among infants born to mothers who tested positive for SARS-CoV-2, the estimated incidence of a positive infant SARS-CoV-2 test was low at 1.1% (0.1%, 4.0%), and infants had minimal symptoms. Overall, these results are reassuring and suggest that infants born to mothers infected with SARS-CoV-2 generally do well in the first 6-8 weeks after birth.

Our study has several limitations. First, we are unable to estimate the incidence of infant SARS-CoV-2 infection because infant testing was incomplete and might be biased by both false-positive and false-negative results. Further research is needed to report infant incidence of SARS-CoV-2 after maternal infection. Second, since PRIORITY's control group includes both symptomatic and asymptomatic women testing negative for SARS-CoV-2, it may not be representative of all U.S. pregnancies. However, these inclusion criteria allowed sampling of control mothers who were more similar to the exposed group in all respects

except for SARS-CoV-2 test results, which may enhance causal inference for the effect of SARS-CoV-2 on infant outcomes. Third, PRIORITY's current racial and ethnic distribution underrepresents maternal Latina ethnicity and Black race compared to a concurrent CDC assessment of U.S. pregnant women infected with SARS-CoV-2 that reported race/ethnicity as 46% Hispanic, 22% Black and 23% White.[9] Barriers to registry participation are expected given the historical harm related to research participation and systemic racism experienced by Black, Indigenous, People of Color communities and the current burden of SARS-CoV-2 in these communities and may impact the generalizability of our findings.[10] In May 2020, PRIORITY launched a Reproductive Health Equity and Birth Justice Core to increase enrollment of underrepresented groups and engage with partners in highly impacted communities. Fourth, the timing of maternal testing in this cohort was determined at the clinical sites and may not have coincided with the onset of illness. Therefore, while we found that NICU admission and earlier gestational age were more common for infants born to mothers testing positive for SARS-CoV-2 0-14 days before delivery than for those testing positive at other times, these associations may reflect hospital practices for management of mothers testing positive for SARS-CoV-2 rather than infant physiology.

Overall, PRIORITY's initial findings regarding infant health are reassuring. Further investigation with longer follow up periods and larger sample sizes will be needed to make a definitive determination of the risk of vertical transmission, neonatal illness, and the incidence of congenital anomaly and are planned for the PRIORITY cohort.

NOTES

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Table: Maternal and infant characteristics, by maternal SARS-CoV-2 status

	SARS-CoV-2 positive N (%) or mean (SD) (n=179)	**SARS-CoV-2 negative** N (%) or mean (SD) (n=84)	p-value
Maternal age[a]	31.5 ±5.4*	31.7 ±5.2	0.78
Maternal race/ethnicity[a]			
American Indian/Alaskan Native	0 (0)	0 (0)	
Asian	14 (7.9)	6 (7.3)	0.87
Black or African American	20 (11.3)	6 (7.3)	0.32
Hispanic or Latina	49 (27.7)	17 (20.7)	0.23
Native Hawaiian or other Pacific Islander	1 (0.6)	1 (1.2)	0.58
White	103 (58.2)	59 (72.0)	0.033
Mother college graduate[a]	99 (56.1)	57 (69.5)	0.33
Income ≥$100,000[a]	71 (40.1)	38 (46.3)	0.87
Geographic region[a]			<0.0001
Midwest	46 (26.1)	16 (19.5)	
Northeast	58 (33.0)	11 (13.4)	
South	32 (18.2)	11 (13.4)	
West	40 (22.7)	44 (53.7)	
Mother hospitalized at time of study enrollment[a]	18 (10.2%)	7 (8.5%)	0.67
Mother in intensive care unit at time of study enrollment[a]	6 (3.4%)	0 (0.0%)	0.09
Gestational age at birth[b]	38.3 ±2.6	38.2 ±2.8	0.77
Preterm birth[b]	21 (13.9)	9 (16.1)	0.69
Birthweight (g)[c]	3211 ±738	3198±831	0.99
Delivered vaginally	106 (59.2)	50 (59.5)	0.79
Primiparous mothers	79 (44.1)	32 (38.1)	0.36
Female infant[d]	42 (52.5)	17 (39.5)	0.17
Birth defect	2 (1.1)	1 (1.2)	0.96
Breast milk after birth	148 (83.1)	77 (91.7)	0.07
NICU admission	31 (17.3)	13 (15.5)	0.71
Abnormal newborn exam	3 (1.7)	1 (1.2)	0.76
Infant positive for SARS-CoV-2	2 (1)	0 (0)	0.17
Fast or difficulty breathing[d]	11 (13.8)	3 (7.0)	0.26
Upper respiratory infection[e]	2 (5.0)	1 (6.3)	0.85
Apnea[e]	0 (0)	2 (4.7)	0.052
Rooming in with mother[d]	57 (71.3)	34 (79.1)	0.35
Breastfeeding at 6-8 weeks[e]	35 (87.5)	14 (87.5)	1.00

[a]This item assessed among 176 and 82 infants of mothers testing positive or negative, respectively, for SARS-CoV-2; [b]This item assessed among 151 and 56 infants of mothers testing positive or negative, respectively, for SARS-CoV-2; [c]This item assessed among 173 and 83 infants of mothers testing positive or negative, respectively, for SARS-CoV-2; [d]This item assessed among 80 and 43 infants of mothers testing positive or negative, respectively, for SARS-CoV-2; [e]This item assessed among 40 and 16 infants of mothers testing positive or negative, respectively, for SARS-CoV-2;