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Longitudinal Evaluation of Antibody Persistence in Mother-Infant Dyads Following SARS-CoV-2 Infection in Pregnancy

RUNNING TITLE: Antibody Responses in SARS-CoV-2 in Pregnancy

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ABSTRACT

Background: There are limited data on how COVID-19 severity, timing of infection, and subsequent vaccination impact transplacental transfer and persistence of maternal and infant antibodies.

Methods: In a longitudinal cohort of pregnant women with PCR-confirmed SARS-CoV-2 infection, maternal/infant sera were collected at enrollment, delivery/birth, and 6 months. Anti-SARS-CoV-2 spike IgG, IgM and IgA were measured by ELISA.

Results: 256 pregnant women and 135 infants were enrolled; 148 maternal and 122 neonatal specimens were collected at delivery/birth; 45 maternal and 48 infant specimens were collected at 6 months. Sixty-eight percent of women produced all anti-SARS-CoV-2 isotypes at delivery (IgG, IgM, IgA); 96% had at least one isotype. Symptomatic disease, and vaccination prior to delivery, were associated with higher maternal IgG at L&D. Detectable IgG in infants dropped from 78% at birth to 52% at 6 months. In the multivariate analysis evaluating factors associated with detectable IgG in infants at delivery, significant predictors were 3rd trimester infection (OR 4.0), mild/moderate disease (OR 4.8), severe/critical disease (OR 6.3), and maternal vaccination prior to delivery (OR 18.8). No factors were significant in the multivariate analysis at 6 months postpartum.

Conclusions: Vaccination in pregnancy post-COVID-19 recovery is a strategy for boosting antibodies in mother-infant dyads.

Word Count: 200

Keywords: COVID-19 in pregnancy; SARS-CoV-2 in pregnancy; transplacental transfer

BACKGROUND

In the absence of an approved COVID-19 vaccine for neonates, transplacental transfer of functional SARS-CoV-2 antibodies to the neonate at birth may confer protection against disease [1-6]. Passive immunity via transplacental transfer and breastfeeding is most crucial during the first 6 months of life, when the infant is particularly vulnerable [7]. There are limited data on how COVID-19 severity, timing of infection, and subsequent vaccination impact the efficiency of transplacental transfer as well as persistence of maternal and infant antibodies after birth [8-14].

It is well-established that pregnancy confers an increased risk of COVID-19 complications, including the need for invasive ventilation, extracorporeal membrane oxygenation, and death [15-17]. While mother-to-child transmission of SARS-CoV-2 is rare [18], COVID-19 in pregnancy is associated with an increased risk of prematurity [19] and stillbirth [20]. Furthermore, the long-term effects of perinatal SARS-CoV-2 infection to the infant are unknown. Our previous research suggests that neonates born to mothers with severe and critical COVID-19 during pregnancy may undergo immune re-wiring at birth [21], underscoring the need to further understand perinatal SARS-CoV-2 infections and maternal immune activation. Recent seroprevalence studies based on detection of anti-nucleocapsid antibodies indicate that over 50% of the U.S. adult population had a previous infection with SARS-CoV-2 [22]. As the world shifts from the pandemic phase of SARS-CoV-2 to endemicity [23], characterization of the humoral antibody response of SARS-CoV-2 infection in pregnancy may inform maternal vaccination schedules in order to optimize both maternal and neonatal protection.

The COVID-19 Outcomes in Mother-Infant Pairs (COMP) study is a large, longitudinal cohort of mother-infant dyads diagnosed with SARS-CoV-2 during pregnancy [21]. Study participants were recruited from one site in the United States and another in Brazil, countries disproportionately impacted by the COVID-19 pandemic [24-28]. Here, we describe the

persistence of anti-SARS-CoV-2 antibodies among mother-infant pairs enrolled in the COMP study, ranging from time of diagnosis in pregnancy up to 6 months postpartum.

METHODS

Study Participants and Data Collection

Study procedures have been described previously [21]. Pregnant women ≥16 years of age with confirmed SARS-CoV-2 by nasopharyngeal (NP) reverse transcription polymerase chain reaction (RT-PCR) during gestation were eligible for enrollment. Participants were recruited primarily through the obstetric services at the David Geffen School of Medicine at the University of California, Los Angeles, and Maternidade do Hospital Estadual Adão Pereira Nunes in Rio de Janeiro, Brazil. The recruitment period was from April 15, 2020 to August 31, 2021, in the U.S., and April 15, 2020 to November 15, 2020 in Brazil. The majority of participants were recruited in 2020, although participants were followed until February 28, 2022. Beginning in April 2020, all women admitted to UCLA for labor and delivery (L&D) were screened for SARS-CoV-2 infection via NP RT-PCR. Women admitted to Maternidade do Hospital Estadual Adão Pereira Nunes for L&D were screened for SARS-CoV-2 via NP RT-PCR based on symptoms. Healthy pregnant controls without COVID-19 or upper respiratory infection symptoms and negative NP RT-PCR were concurrently recruited for validation studies. Peripheral blood specimens (5.0 mL) were collected in BD Gold top serum separator tubes at each time point from pregnant women at enrollment (acute infection), admission for delivery, and 6 months post-partum. Cord blood specimens (5.0 mL) were collected in BD Gold top serum separator tubes at delivery when feasible. Infant peripheral blood specimens (0.5 mL) were collected in BD Red top tubes between 24 and 48 hours of life at the time of routine bilirubin checks (to minimize blood draws), and at 6 months of age when possible. Serum aliquots were stored at –80^{o}C. All infants born to mothers with active SARS-CoV-2 infection at the time of delivery were tested by NP-PCR between 24-48 hours of life according to the local standard of care.

Clinical, obstetrical, and laboratory results were abstracted from medical records. Demographics included age at the time of enrollment, maternal race/ethnicity (White, Black, U.S. Latina/Hispanic, Mixed/Biracial, Asian/Other), and country of enrollment (U.S., Brazil). While we acknowledge that race is a social construct, we chose to include it in the analysis given the higher risk of severe and critical COVID-19 among women of color. Women with SARS-CoV-2 infections were grouped into the following NIH COVID-19 severity of illness categories [29]: asymptomatic, mild, moderate, severe, and critical. The clinical categories were collapsed into asymptomatic, mild/moderate and severe/critical for the analyses. Participants who completed a COVID-19 vaccine series (one Ad26.COV2.S or two messenger RNA (mRNA) vaccines, BNT162b2 or mRNA-1273) were categorized as either: 1) vaccinated following recovery and prior to delivery, or 2) vaccinated following recovery and postpartum (prior to 6 months). Maternal clinical characteristics included gravidity, trimester at diagnosis, medical comorbidities, including pre-pregnancy body mass index (BMI) >30 kg/m^2, diabetes mellitus (type 1 or type 2), congenital heart disease, and history of asthma. Pregnancy was categorized into three trimesters: first trimester (0 – 13 weeks), second trimester (14 – 27 weeks) and third trimester (≥28 weeks). Obstetrical complications included hypertensive disorders or pregnancy (chronic hypertension, gestational hypertension, preeclampsia/eclampsia, and chronic hypertension with superimposed preeclampsia), preeclampsia as a separate category, hemolysis elevated liver enzymes and low platelets (HELLP) syndrome, and gestational diabetes (separate from pre-gestational diabetes). Birth outcomes were categorized as vaginal delivery, Caesarean section, termination, miscarriage, stillbirth, maternal death, and delivered at outside facilities. For the neonates, gestational age at delivery and birthweight (in grams) were collected. Preterm delivery was stratified by <37 weeks and <35 weeks, low birth weight by <2500 grams (g), and small for gestational age (SGA) was categorized based on infant weight <10^{th} percentile for gestational age based on the WHO Growth Curve. Clinical, lab and hospital data were

abstracted from the chart by a multidisciplinary team of infectious disease specialists, maternal-fetal medicine specialists, and neonatologists.

Nasopharyngeal SARS-CoV-2 PCR Quantification

As previously described [21], maternal NP SARS-CoV-2 PCR testing was performed at with one of three assays: 1) The TaqPath COVID19 Combo Kit (Thermo Fisher Scientific Inc), which uses probes targeting the ORF1ab, N and S genes; 2) The DiaSorin Simplexa COVID19 Direct RT-PCR (DiaSorin Molecular LLC), which targets the ORF1ab and S genes, or 3) The US Centers for Disease Control and Prevention (CDC) 2019-nCoV RT-PCR Diagnostic Panel Protocol which probes the N1 and N2 genes.

Detection of Anti-SARS-CoV-2 Spike IgG, IgM, and IgA

All maternal, cord and infant blood samples were tested for quantitative anti-SARS-CoV-2 spike immunoglobulin G (IgG), immunoglobulin M (IgM), and immunoglobulin A (IgA). Sera were analyzed by enzyme-linked immunosorbent assay (ELISA) for IgG, IgM and IgA targeting the receptor binding domain (RBD) of the SARS-CoV-2 spike protein, as previously described [21]. A total of 22 healthy controls (18 pre-pandemic and 4 current maternal controls with negative SARS-CoV-2 NP RT-PCR) were tested for validation of the serologic assays. Negative was defined as values under the lowest point of the linear range of the standard curves. Limits of detection for IgG, IgM, and IgA were set as 148 ng/mL, 148 ng/mL, and 185 ng/mL, respectively.

Statistical Analysis

Descriptive analysis of the demographics and clinical characteristics of mother-infant dyads were performed. Correlations between log-transformed maternal IgG levels at delivery, and matched cord blood IgG as well as infant blood IgG, were evaluated by Pearson correlation.

Correlations between transplacental transfer ratios (TTR) of IgG (Log_2[Infant IgG at Birth+1]/[Maternal IgG at L&D+1]) and diagnosis date-to-delivery time intervals were evaluated by Pearson correlation. Log-transformed maternal IgG, IgM and IgA levels were stratified by severity of illness categories. Differences across groups were evaluated by analysis of variance followed by Tukey's post-hoc. Log-transformed maternal IgG, IgM and IgA levels were stratified by maternal vaccination following recovery and prior to delivery. Differences in antibody levels were evaluated by unpaired, two-sided Mann-Whitney U tests. Stepwise regression was used to construct the final model for predictors of detectable IgG in infants at delivery and 6 months of age. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. The Haldane-Anscombe adjustment was applied to correct for zero cell values. Statistical analyses were conducted using R version 4.1.0 and Prism version 9.0, with statistical significance defined using a two-sided α<0.05.

Informed consent for study participation was obtained for all participants prior to enrollment. If the participant was incapacitated during an acute hospitalization and consented by a surrogate, the participant was re-consented once they regained capacity. The study was approved by both the University of California, Los Angeles and Fiocruz Institutional Review Boards.

RESULTS

A schema of the study design is shown in Figure 1: a total of 256 women and 135 infants were enrolled in the study. At delivery, 148 maternal and 122 neonatal specimens were collected, and 45 maternal and 48 infant specimens were collected at 6 months postpartum. Table 1 describes maternal and neonatal demographics and clinical characteristics of the cohort. The median maternal age was 32, with 62.1% participants recruited from the U.S. site. Over half of the participants were either U.S. Latina/Hispanic (31.0%) or Mixed/Biracial (26.6%); 83% of the population were women of color. The majority of participants had mild/moderate COVID-19

(69.9%), followed by severe/critical disease (20.0%). Of the 148 women with specimens at delivery, 23 (15.5%) had severe/critical disease, and 16 (10.8%) were vaccinated following recovery and prior to delivery: 5 were vaccinated in the 1st, 2 in the 2nd, and 9 in the 3rd trimester of pregnancy. One participant received only one mRNA shot prior to maternal specimen collection, and only one participant received Ad26.COV2.S. A total of 14 women were vaccinated postpartum prior to 6 months post-delivery. None of the pregnant participants received the vaccine pre-gestation. The majority of participants were diagnosed with SARS-CoV-2 during the 2nd (41.3%) and 3rd trimester (44.4%) of pregnancy. Nearly a quarter of the participants had a pre-pregnancy BMI >30 kg/m^2. The most common obstetrical complication was hypertensive disorder of pregnancy (26.7%), with a diagnosis of preeclampsia among 13.4% of the cohort. Nearly half of the cohort had a vaginal delivery (47.0%). There was one case of maternal death followed by an intrauterine fetal demise (listed as maternal-fetal demise in Table 1). For the neonates, the median gestational age was 38 weeks, and 30.4% were preterm. While the prevalence of SGA was low (8.8%), the median birthweight was 3010 g, and 27.4% were considered low birthweight.

The majority (68%) of the cohort produced all three anti-SARS-CoV-2 isotypes (IgG, IgM and IgA) at delivery, and 96% had at least one SARS CoV-2 isotype present. There was one case of a possible vertical transmission in a term neonate who was transferred at 48 hours to UCLA with respiratory distress and found to have a weakly positive SARS CoV-2 RT-PCR (Ct value 32.4) at 24 hours of life. Anti-SARS-CoV-2 IgM was detected in maternal blood, although maternal nasopharyngeal PCR for SARS CoV-2 was negative. The infant did clinically well and was discharged with one week of life. We did not observe any other potential cases of vertical transmission in our cohort, however, only infants born to SARS CoV-2 positive mothers at the time of delivery underwent SARS CoV-2 RT-PCR testing. Maternal IgG levels were significantly higher at 6 months compared to enrollment (Figure 2a), although infant levels were significantly

lower at 6 months of age compared to birth (Figure 2b). A total of 95 of 122 infants (77.9%) had anti-SARS CoV-2 IgG antibodies at delivery, while only 25 of 48 infants (52.1%) had detectable IgG at 6 months. No infants had IgA or IgM levels at birth, but 7 (14.6%) had detectable IgA, and 1 (2.0%) had detectable IgM at 6 months.

Figure 3 depicts the correlation of maternal and infant antibody responses and transplacental transfer ratios. The mean time from the diagnosis date to blood draw at enrollment was 16 days (95% confidence interval [CI], 12-19), while the mean time interval from diagnosis date to collection at L&D was 68 days (95% CI, 55-81). Maternal anti-SARS-CoV-2 spike IgG levels correlated with neonatal anti-SARS-CoV-2 IgG levels at birth ($r = 0.51$, $P<0.001$), and with cord blood anti-SARS-CoV-2 spike IgG levels ($r = 0.66$, $P<0.001$). There was a weak positive correlation between the time interval of diagnosis date-to-delivery and transplacental transfer ratios ($r = 0.18$, $P<0.01$).

Maternal anti-SARS-CoV-2 spike antibody responses at delivery were stratified by maternal COVID-19 disease severity (Figure 4). A more robust immunologic response was observed across all immunoglobulin subtypes with worsening disease severity: maternal IgG, IgM, and IgA levels were significantly higher among women with symptomatic disease (severe/critical or mild/moderate) in pregnancy compared to women with asymptomatic disease.

Maternal antibody responses were stratified by vaccination status following recovery and prior to delivery (Figure 5). Recovered pregnant women who received the vaccine prior to delivery had significantly higher median anti-SARS-CoV-2 spike IgG levels at L&D compared to unvaccinated mothers (15.5[14.5-16.1] vs 13.6 [11.6-14.5] ng/mL; $P<0.001$, Figure 5a). All infants born to recovered mothers vaccinated prior to delivery had detectable IgG at birth.

In the multivariate analysis to explore factors associated with detectable IgG in infants at delivery (Table 2a), significant predictors were 3rd trimester infection (OR 4.02, 95% CI 1.37 – 11.87), mild/moderate disease (OR 4.86, 95% CI 1.41 – 16.72), severe/critical disease (OR 6.35, 95% CI 1.20 – 33.69), and maternal vaccination prior to delivery (OR 18.89, 95% CI 1.11 – 322.60). No factors were shown to be significant in the multivariate analysis at 6 months of age (Table 2b).

DISCUSSION

To our knowledge, this is the largest, longitudinal cohort to monitor antibody persistence among mother-infant dyads diagnosed with COVID-19 in pregnancy. Transplacental transfer of anti-SARS-CoV-2 spike IgG was high following infection in pregnancy, and weakly correlated with increasing duration between diagnosis date and delivery, as previously described in smaller cohorts of mother-infant dyads diagnosed with SARS-CoV-2 in pregnancy [1, 2, 5, 11, 30]. Most of the women enrolled in the study were women of color, underscoring the role played by social inequities in the pandemic in both the U.S. and Brazil [24-28]. The high frequency of adverse obstetrical and neonatal complications due to COVID-19 have been reported [31]. Our cohort was no exception, with hypertensive disorders of pregnancy present in 26.7% of women, surgical deliveries in 40.1% of cases, preterm deliveries in nearly one-third of the cohort, and low birth weight present in over a quarter of the neonatal study population, a higher frequency of adverse complications than seen in pre-pandemic populations [31-33].

Anti-SARS-CoV-2 spike IgG levels dropped significantly in infants by 6 months as previously described [13], consistent with the waning of passively acquired maternal IgG from transplacental transfer. Nevertheless, epidemiologic studies suggest that completion of the mRNA COVID-19 vaccine series during pregnancy may prevent COVID-19 related hospitalizations among infants <6 months of age [6]. The presence of detectable IgM was

observed in only one infant at 6 months of age, which might have represented an active infection, although we were not able to confirm with NP RT-PCR at the time. The specificity of IgM is lower than IgG, and may reflect cross-reaction with another beta-coronavirus. Therefore, in the absence of a detectable NP PCR, a detectable SARS CoV-2 IgM is difficult to interpret. The increased detection of IgA in infants at 6 months likely represents passive immunity transfer from breastmilk, which has been described [34, 35]. Early in the pandemic, there was concern that breastfeeding shortly after COVID-19 may lead to SARS-CoV-2 transmission via breastmilk. Studies have demonstrated that SARS-CoV-2 cannot be transmitted via breastmilk, and , breastfeeding is safe following SARS-CoV-2 infection [36].

A more robust immunologic response was observed across all maternal immunoglobulin subtypes with symptomatic compared to asymptomatic disease, consistent with smaller cohort studies [37]. Infant IgG levels at birth reflected this pattern as well: asymptomatic maternal disease was associated with lower odds of detectable infant IgG at birth, pointing to lower IgG transfer with asymptomatic disease, likely due to lower levels in maternal circulation. Recovered pregnant individuals with a history of asymptomatic COVID-19 in pregnancy may benefit from subsequent vaccination in order to enhance transplacental IgG transfer.

While several studies suggest vaccination in the second or third trimester among women without a history of SARS-CoV-2 produces the highest levels of maternal and cord anti-SARS-CoV-2 spike IgG levels [3, 9, 38-40], few studies have evaluated vaccination prior to delivery following recovery of SARS-CoV-2 infection in pregnancy [10, 14, 38, 41]. In a large retrospective cohort of pregnant women with self-reported COVID-19 vaccination, maternal and cord anti-SARS-CoV-2 spike IgG levels among the subset of those with a history of SARS-CoV-2 infection who initiated or completed the vaccine series in pregnancy did not significantly differ depending on the trimester of vaccination [38]. In a cohort of 228 pregnant individuals,

significantly higher levels of anti-SARS-CoV-2 antibody levels were detected in convalescent infected mothers who received a single BNT162b2 mRNA booster compared to both non-boosted convalescent infected individuals and naïve vaccinated mothers [10]. In our cohort, the strongest predictor of detectable IgG at birth was maternal vaccination prior to delivery, although this was no longer significant at 6 months of age.

Our study has several strengths. First, to our knowledge, this is the largest longitudinal cohort of mother-infant dyads with a history of SARS-CoV-2 in pregnancy. While several studies implemented a cross-sectional design, our ability to follow mothers and infants up to 6 months of age allows us to monitor changes in antibody patterns over time. Second, few studies analyzed differential maternal and neonatal antibody responses based not only on maternal COVID-19 disease severity and timing of infection, but also subsequent vaccination following recovery. Nevertheless, our study has limitations. First, due to the observational design, associations do not necessarily imply causation. Second, we did not have vaccinated controls without a history of SARS-CoV-2, although several other studies have addressed this question [12, 38, 39, 41-43]. Last, we had a high rate of attrition by 6 months, limiting out ability to maximize our longitudinal design. Nevertheless, we had a sizeable number of linked maternal-infant specimens at both delivery and 6 months.

Growing evidence points toward efficient transplacental IgG transfer following either symptomatic, natural SARS-CoV-2 infection or vaccination in pregnancy [4, 9, 12-14, 38, 43]. Our findings indicate that transplacental IgG transfer was high following SARS-CoV-2 infection in pregnancy and weakly correlated with increasing duration between diagnosis date and delivery. While maternal IgG levels at delivery and 6 months were not significantly different, IgG levels in infants waned significantly by 6 months of age. COVID-19 vaccination in this age group can provide additional and much-needed protection. Symptomatic maternal COVID-19 and

vaccination prior to delivery were associated with higher maternal and neonatal IgG levels at birth. Our data further supports vaccinating pregnant women post COVID-19 recovery and prior to delivery given the high anti-SARS-CoV-2 antibody levels generated by vaccination to both mothers and infants at delivery. Ongoing longitudinal research is needed to characterize the kinetics and sterilizing immunity of maternal and infant antibody responses elicited by COVID-19 mRNA vaccination in recovered pregnant women.

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REFERENCES

1. Edlow AG, Li JZ, Collier AY, et al. Assessment of Maternal and Neonatal SARS-CoV-2 Viral Load, Transplacental Antibody Transfer, and Placental Pathology in Pregnancies During the COVID-19 Pandemic. JAMA Netw Open **2020**; 3:e2030455.

2. Flannery DD, Gouma S, Dhudasia MB, et al. Assessment of Maternal and Neonatal Cord Blood SARS-CoV-2 Antibodies and Placental Transfer Ratios. JAMA Pediatr **2021**; 175:594-600.

3. Mithal LB, Otero S, Shanes ED, Goldstein JA, Miller ES. Cord blood antibodies following maternal coronavirus disease 2019 vaccination during pregnancy. Am J Obstet Gynecol **2021**; 225:192-4.

4. Prabhu M, Murphy EA, Sukhu AC, et al. Antibody Response to Coronavirus Disease 2019 (COVID-19) Messenger RNA Vaccination in Pregnant Women and Transplacental Passage Into Cord Blood. Obstet Gynecol **2021**; 138:278-80.

5. Song D, Prahl M, Gaw SL, et al. Passive and active immunity in infants born to mothers with SARS-CoV-2 infection during pregnancy: prospective cohort study. BMJ Open **2021**; 11:e053036.

6. Halasa NB, Olson SM, Staat MA, et al. Effectiveness of Maternal Vaccination with mRNA COVID-19 Vaccine During Pregnancy Against COVID-19-Associated Hospitalization in Infants Aged <6 Months - 17 States, July 2021-January 2022. MMWR Morb Mortal Wkly Rep **2022**; 71:264-70.

7. Marchant A, Sadarangani M, Garand M, et al. Maternal immunisation: collaborating with mother nature. Lancet Infect Dis **2017**; 17:e197-e208.

8. Atyeo C, Pullen KM, Bordt EA, et al. Compromised SARS-CoV-2-specific placental antibody transfer. Cell **2021**; 184:628-42.e10.

9. Beharier O, Plitman Mayo R, Raz T, et al. Efficient maternal to neonatal transfer of antibodies against SARS-CoV-2 and BNT162b2 mRNA COVID-19 vaccine. J Clin Invest **2021**; 131.

10. Nevo L, Cahen-Peretz A, Vorontsov O, et al. Boosting maternal and neonatal humoral immunity following SARS-CoV-2 infection using a single mRNA vaccine dose. Am J Obstet Gynecol **2022**.

11. Poon LC, Leung BW, Ma T, et al. Relationship between viral load, infection-to-delivery interval and mother-to-child transfer of anti-SARS-CoV-2 antibodies. Ultrasound Obstet Gynecol **2021**; 57:974-8.

12. Rottenstreich A, Zarbiv G, Oiknine-Djian E, et al. Timing of SARS-CoV-2 vaccination during the third trimester of pregnancy and transplacental antibody transfer: a prospective cohort study. Clin Microbiol Infect **2021**.

13. Shook LL, Atyeo CG, Yonker LM, et al. Durability of Anti-Spike Antibodies in Infants After Maternal COVID-19 Vaccination or Natural Infection. Jama **2022**.

14. Collier AY, McMahan K, Yu J, et al. Immunogenicity of COVID-19 mRNA Vaccines in Pregnant and Lactating Women. Jama **2021**; 325:2370-80.

15. Ellington S, Strid P, Tong VT, 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.

16. Zambrano LD, Ellington S, Strid P, 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.

17. Delahoy MJ, Whitaker M, O'Halloran A, et al. Characteristics and Maternal and Birth Outcomes of Hospitalized Pregnant Women with Laboratory-Confirmed COVID-19 - COVID-NET, 13 States, March 1-August 22, 2020. MMWR Morb Mortal Wkly Rep **2020**; 69:1347-54.

18. Fenizia C, Biasin M, Cetin I, et al. Analysis of SARS-CoV-2 vertical transmission during pregnancy. Nat Commun **2020**; 11:5128.

19. Woodworth KR, Olsen EO, Neelam V, et al. Birth and Infant Outcomes Following Laboratory-Confirmed SARS-CoV-2 Infection in Pregnancy - SET-NET, 16 Jurisdictions, March 29-October 14, 2020. MMWR Morb Mortal Wkly Rep **2020**; 69:1635-40.

20. DeSisto CL, Wallace B, Simeone RM, et al. Risk for Stillbirth Among Women With and Without COVID-19 at Delivery Hospitalization - United States, March 2020-September 2021. MMWR Morb Mortal Wkly Rep **2021**; 70:1640-5.

21. Foo SS, Cambou MC, Mok T, et al. The systemic inflammatory landscape of COVID-19 in pregnancy: Extensive serum proteomic profiling of mother-infant dyads with in utero SARS-CoV-2. Cell Rep Med **2021**; 2:100453.

22. Clarke KEN, Jones JM, Deng Y, et al. Seroprevalence of Infection-Induced SARS-CoV-2 Antibodies - United States, September 2021-February 2022. MMWR Morb Mortal Wkly Rep **2022**; 71:606-8.

23. Murray CJL. COVID-19 will continue but the end of the pandemic is near. Lancet **2022**; 399:417-9.

24. Macias Gil R, Marcelin JR, Zuniga-Blanco B, Marquez C, Mathew T, Piggott DA. COVID-19 Pandemic: Disparate Health Impact on the Hispanic/Latinx Population in the United States. J Infect Dis **2020**; 222:1592-5.

25. Clark E, Fredricks K, Woc-Colburn L, Bottazzi ME, Weatherhead J. Disproportionate impact of the COVID-19 pandemic on immigrant communities in the United States. PLoS Negl Trop Dis **2020**; 14:e0008484.

26. Simon P, Ho A, Shah MD, Shetgiri R. Trends in Mortality From COVID-19 and Other Leading Causes of Death Among Latino vs White Individuals in Los Angeles County, 2011-2020. Jama **2021**; 326:973-4.

27. Castro MC, Gurzenda S, Turra CM, Kim S, Andrasfay T, Goldman N. Reduction in life expectancy in Brazil after COVID-19. Nat Med **2021**; 27:1629-35.

28. Castro MC, Kim S, Barberia L, et al. Spatiotemporal pattern of COVID-19 spread in Brazil. Science **2021**; 372:821-6.

29. COVID-19 Treatment Guidelines: Clinical Spectrum of SARS-CoV-2 Infection. Available at: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/. Accessed May 10, 2022.

30. Gee S, Chandiramani M, Seow J, et al. The legacy of maternal SARS-CoV-2 infection on the immunology of the neonate. Nat Immunol **2021**; 22:1490-502.

31. Metz TD, Clifton RG, Hughes BL, et al. Association of SARS-CoV-2 Infection With Serious Maternal Morbidity and Mortality From Obstetric Complications. Jama **2022**; 327:748-59.

32. Abbasi J. The COVID Heart-One Year After SARS-CoV-2 Infection, Patients Have an Array of Increased Cardiovascular Risks. Jama **2022**; 327:1113-4.

33. Vouga M, Favre G, Martinez-Perez O, et al. Maternal outcomes and risk factors for COVID-19 severity among pregnant women. Sci Rep **2021**; 11:13898.

34. Pullen KM, Atyeo C, Collier AY, et al. Selective functional antibody transfer into the breastmilk after SARS-CoV-2 infection. Cell Rep **2021**; 37:109959.

35. Fox A, Marino J, Amanat F, et al. Robust and Specific Secretory IgA Against SARS-CoV-2 Detected in Human Milk. iScience **2020**; 23:101735.

36. Krogstad P, Contreras D, Ng H, et al. No infectious SARS-CoV-2 in breast milk from a cohort of 110 lactating women. Pediatr Res **2022**.

37. Buckley A, Mills A, Paul K, et al. SARS-CoV-2 Antibody Response among Women Infected during Pregnancy. Am J Perinatol **2021**.

38. Yang YJ, Murphy EA, Singh S, et al. Association of Gestational Age at Coronavirus Disease 2019 (COVID-19) Vaccination, History of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection, and a Vaccine Booster Dose With Maternal and Umbilical Cord Antibody Levels at Delivery. Obstet Gynecol **2022**; 139.

39. Rottenstreich A, Zarbiv G, Oiknine-Djian E, et al. The effect of gestational age at BNT162b2 mRNA vaccination on maternal and neonatal SARS-CoV-2 antibody levels. Clin Infect Dis **2022**.

40. Kugelman N, Nahshon C, Shaked-Mishan P, et al. Maternal and Neonatal SARS-CoV-2 Immunoglobulin G Antibody Levels at Delivery After Receipt of the BNT162b2 Messenger RNA COVID-19 Vaccine During the Second Trimester of Pregnancy. JAMA Pediatrics **2022**; 176:290-5.

41. Conti MG, Terreri S, Terrin G, et al. SARS-CoV-2 infection versus vaccination in pregnancy: Implications for maternal and infant immunity. Clin Infect Dis **2022**.

42. Blakeway H, Prasad S, Kalafat E, et al. COVID-19 vaccination during pregnancy: coverage and safety. Am J Obstet Gynecol **2022**; 226:236.e1-.e14.

43. Gray KJ, Bordt EA, Atyeo C, et al. Coronavirus disease 2019 vaccine response in pregnant and lactating women: a cohort study. Am J Obstet Gynecol **2021**; 225:303.e1-.e17.

Table 1. Demographics and clinical characteristics of all pregnant women diagnosed with SARS-CoV-2 (N = 256), and their infants enrolled in the COMP Study (N = 135).

N	256
Median Maternal Age (IQR)	32 (25-35)
Country of Enrollment	n (%)
U.S.	159 (62.1)
Brazil	97 (37.9)
Race/Ethnicity	n (%)
White	44 (17.2)
Black	22 (8.6)
U.S. Latina/Hispanic	79 (31.0)
Mixed/Biracial	68 (26.6)
Asian/Other	43 (16.8)
COVID-19 Severity	n (%)
Asymptomatic	31 (12.1)
Mild/Moderate	179 (69.9)
Severe/Critical	46 (20.0)
Vaccinated Following Recovery and Prior to Delivery	16 (6.3)
Vaccinated Following Recovery and Postpartum	14 (5.5)
Median Gravida (IQR)	2 (1-3)
Trimester at Diagnosis	n = 252
1st	36 (14.3)
2nd	104 (41.3)
3rd	112 (44.4)
Medical Comorbidities	n = 237

Pre-Pregnancy BMI>30 kg/m^2	55 (23.2)
Diabetes (Type I or Type II)	6 (2.5)
Congenital Heart Disease	6 (2.5)
Asthma	22 (9.3)
Obstetrical Complications	n = 202
Hypertensive Disorder of Pregnancy	54 (26.7)
Preeclampsia	27 (13.4)
HELLP	4 (2.0)
Gestational Diabetes	28 (13.9)
Birth Outcome	n = 202
Vaginal Delivery	95 (47.0)
C-Section	81 (40.1)
Termination	2 (1.0)
Miscarriage	8 (4.0)
Stillbirth	6 (3.0)
Maternal-Fetal Demise	1 (0.4)
Delivered at Outside Facilities	9 (4.5)
Maternal Specimens Collected at Delivery	148 (57.8)
Maternal Specimens Collected at 6 Months	45 (17.6)
N	135
Median Gestational Age in Weeks (IQR)	38 (36-39)
Preterm Delivery	n (%)
<37 Weeks	41 (30.4)
<35 Weeks	31 (23.0)
Small for Gestational Age	12 (8.8)

Low Birthweight (<2500 grams)	37 (27.4)
Median Birthweight in Grams (IQR)	3010 (2414-3518)
Neonatal Specimens Collected at Birth	122 (91.0)
Infant Specimens Collected at 6 Months of Age	48 (35.6)

1
2

Table 2. Predictors of SARS-CoV-2 IgG levels in infants at birth and 6 months of age*

Variable	OR (95% CI)	*p*
A. Delivery (N = 122)		
Constant	0.56	0.304
3rd Trimester Infection	4.02 (1.37-11.87)	0.011
Mild/Moderate COVID-19	4.86 (1.41-16.72)	0.012
Severe/Critical COVID-19	6.35 (1.20-33.69)	0.03
Maternal Vaccination Prior to Delivery	18.89 (1.11-322.6)	0.0016
B. Six Months (N = 48)		
Constant	0.45	0.21
3rd Trimester Infection	1.72 (0.5-5.9)	0.39
Mild/Moderate COVID-19	2.35 (0.57-9.98)	0.24
Severe/Critical COVID-19	3.1 (0.2-48.9)	0.42
Maternal Vaccination Prior to Delivery	5.44 (0.25-119.63)	0.47

*Stepwise regression was used to construct the final model for predictors of detectable IgG in infants at delivery and 6 months of age. A. Third trimester infection, symptomatic maternal infection, and maternal vaccination following recovery and prior to birth increased the probability that IgG antibodies would be detectable in the newborn at delivery. Maternal vaccination prior to delivery was the strongest predictor of infant IgG at birth B. Third trimester infection, symptomatic maternal infection, and maternal vaccination following recovery and prior to birth was associated with an increased odds of detectable infant IgG, although none were statistically significant. The Haldane-Anscombe adjustment was applied to maternal vaccination to correct for zero cell values.

FIGURE LEGENDS

Figure 1. Schema of the study design.

*Five women who received monoclonal antibodies prior to specimen collection were excluded

†Includes one twin gestation stillbirth, and one neonatal death immediately after delivery

Figure 2. Maternal and infant anti-SARS-CoV-2 spike IgG responses over time.

Figured legend: a. Maternal IgG levels at different timepoints following SARS-CoV-2 infection during pregnancy. b. Neonatal IgG response at birth and 6 months of age after maternal SARS-CoV-2 infection during pregnancy. The boxplots in a and b show medians (middle line) and third and first quartiles (boxes), while the whiskers depict minimum and maximum. Dotted line denotes limit of detection. Numbers of participants (*N*) are shown underneath. *P* values and differences across groups were assessed by analysis of variance followed by Tukey's post-hoc.

Figure 3. Correlation of maternal and infant antibody responses and transplacental transfer ratios.

Figure legend: a. Correlations between anti-SARS-CoV-2 spike IgG levels from mothers at delivery and matched cord blood and infant sera at birth. b. Pearson correlation between transplacental transfer ratio (Log_2[Infant IgG at Birth+1] / [Maternal IgG at L&D+1]) and diagnosis date-to-delivery time interval in days.

Figure 4. Comparison of maternal anti-SARS-CoV-2 spike IgG (a), IgM (b) and IgA (c) antibody responses at L&D, stratified by maternal COVID-19 disease severity.

Figure legend: All antibody levels are log2-scaled. For boxplots, box extends from the 25th to 75th percentile, whiskers depict minimum and maximum, and horizontal line depicts the median. Dotted lines denote limit of detection. Numbers of participants (*N*) are shown underneath. *P*

values and differences across groups were assessed by analysis of variance followed by Tukey's post-hoc.

Figure 5. Comparison of maternal anti-SARS-CoV-2 spike IgG (a), IgM (b) and IgA (c) antibody responses at L&D, stratified by maternal vaccination status prior to delivery.

Figure legend: All antibody levels are log2-scaled. All mothers were infected with SARS-CoV-2 during pregnancy. Maternal vaccination was defined as receiving one AD26.COV2.S, or two mRNA vaccines, BNT162b2 or mRNA-1273, prior to delivery. For boxplots, box extends from the 25^{th} to 75^{th} percentile, whiskers depict minimum and maximum, and horizontal line depicts the median. Dotted lines denote limit of detection. Numbers of participants (*N*) are shown underneath. *P* values were determined by unpaired, two-sided Mann-Whitney U test.

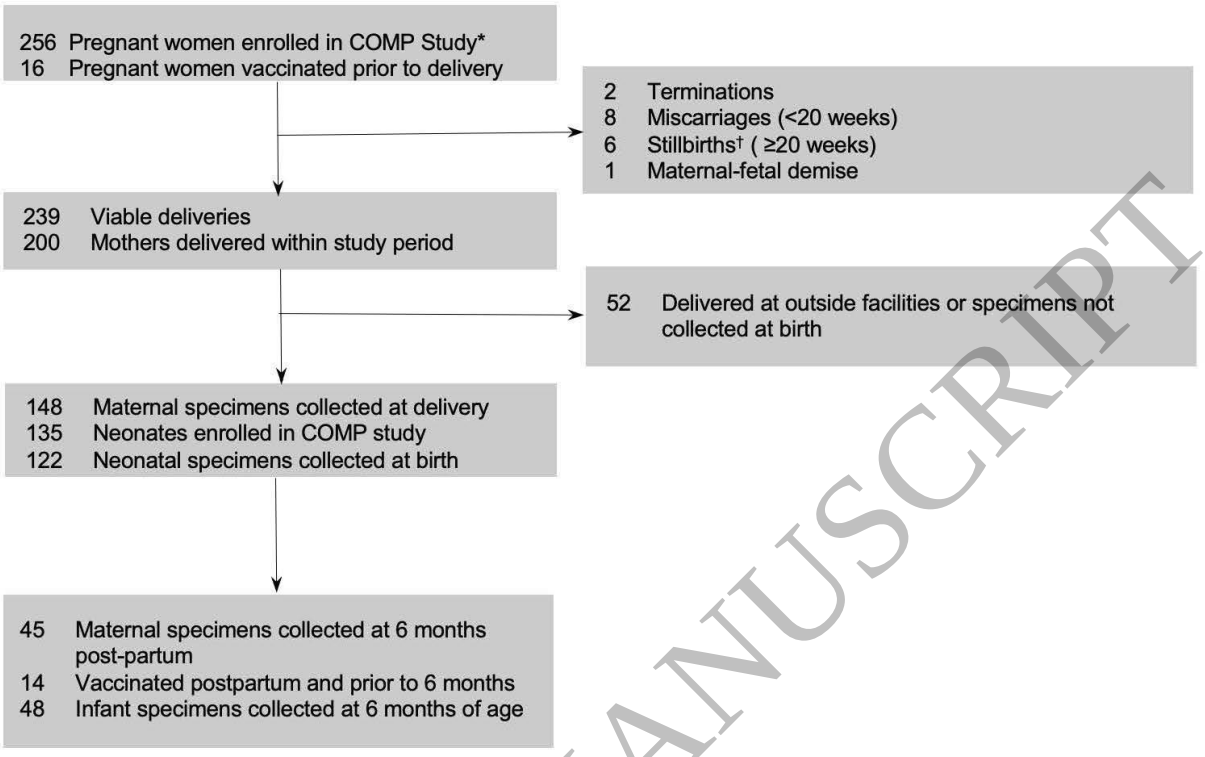

Figure 1
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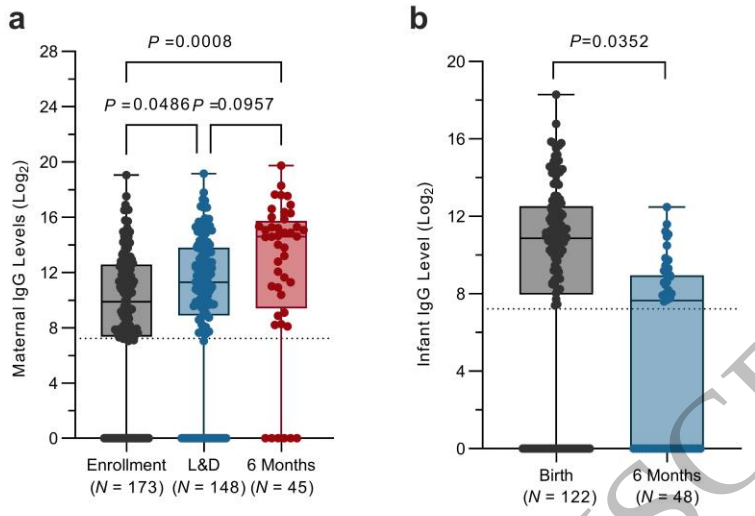

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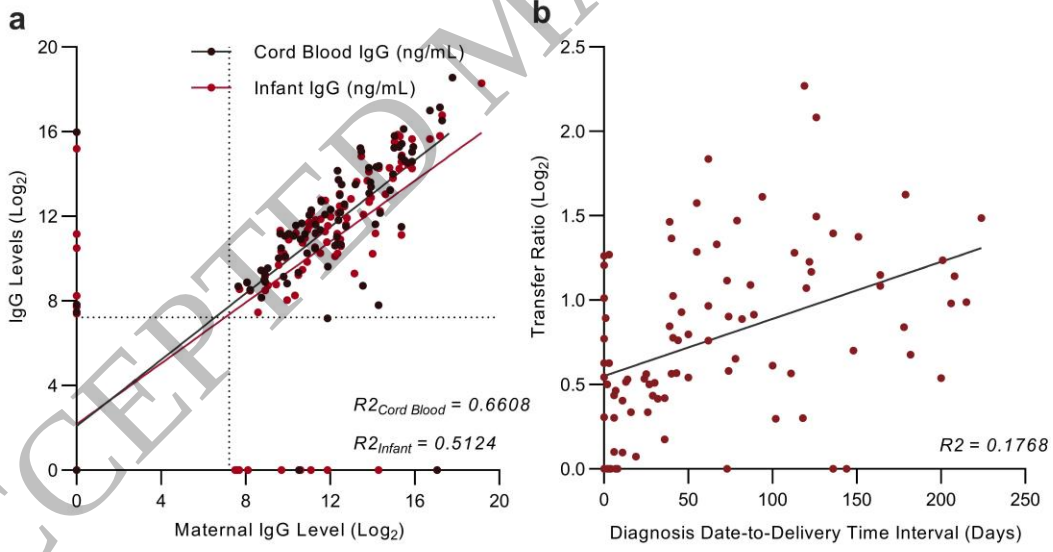

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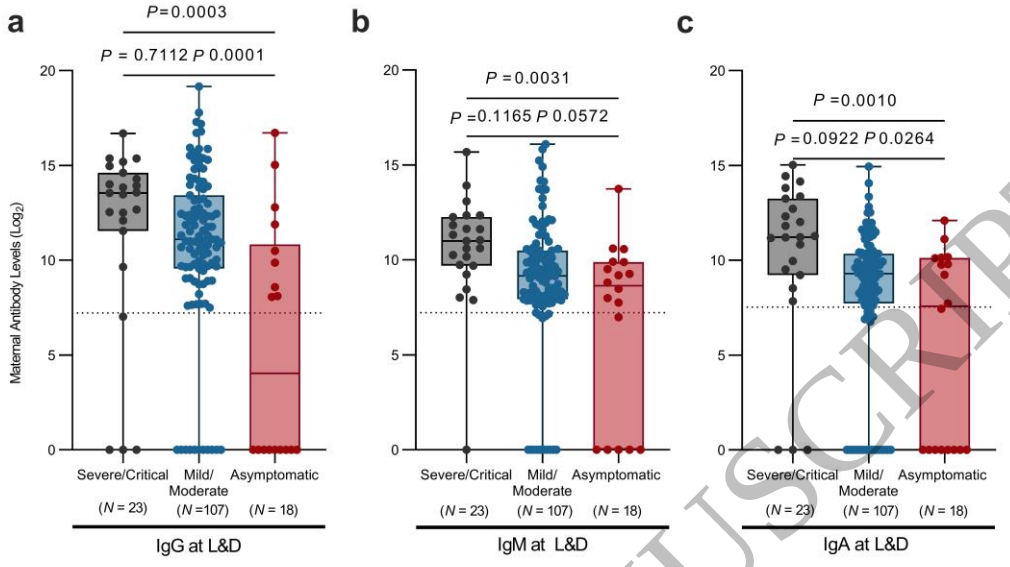

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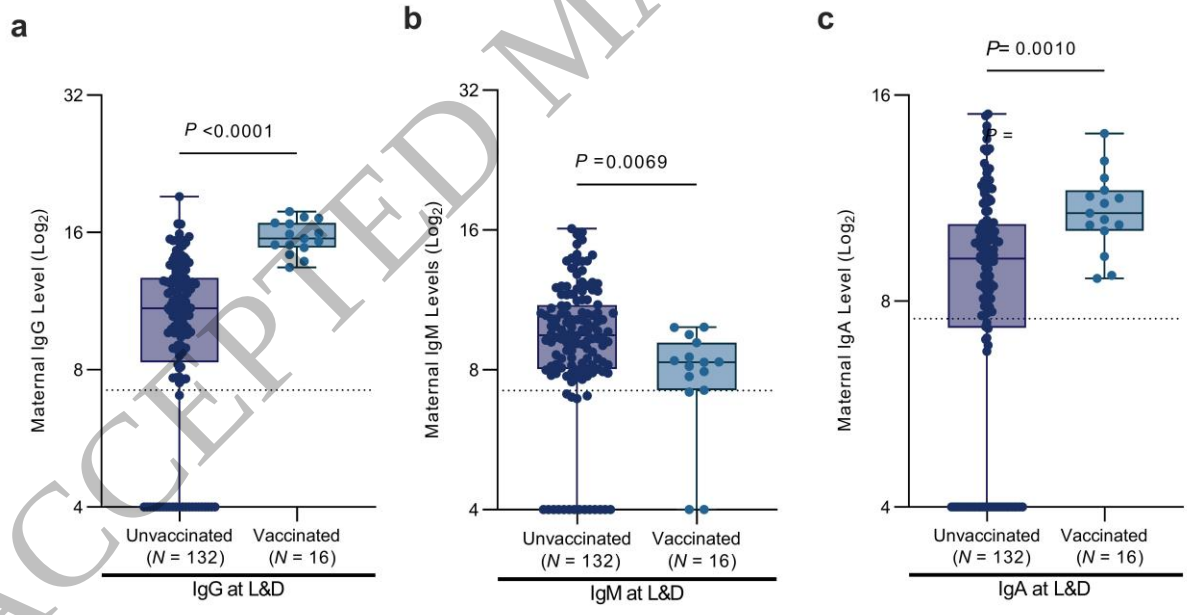

Figure 5
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