Assessment of maternal and infant antibody response to COVID-19 and transplacental transfer ratios at labor & delivery

Christine Liu[1], Mary Catherine Cambou[2], Thalia Mok[3], Viviana Fajardo Martinez[4], Debika Battacharya[2], Tara Kerin[1], Francisco Javier Ibarrondo[2], Trevon Fuller[5], Sophia Paiola[1], Grace Aldrovandi[1], Rashmi Rao[3], Otto Yang[2], Karin Nielsen-Saines[1]

[1]Department of Pediatrics, Division of Infectious Diseases; David Geffen School of Medicine, University of California, Los Angeles; Los Angeles, CA; 90095; USA
[2]Department of Medicine, Division of Infectious Diseases; David Geffen School of Medicine, University of California, Los Angeles; Los Angeles, CA; 90095; USA
[3]Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine; David Geffen School of Medicine, University of California, Los Angeles; Los Angeles, CA; 90095; USA
[4]Department of Pediatrics, Division of Neonatology; David Geffen School of Medicine, University of California, Los Angeles; Los Angeles, CA; 90095; USA
[5]UCLA Institute for the Environment and Sustainability, Los Angeles, CA; 90095; USA

Contact: Christine Liu
David Geffen School of Medicine at UCLA
Email: cmliu@mednet.ucla.edu

Background

- Newborn protection from viral infection is dependent on both the neonatal innate immune response and transplacental transfer of maternal antibodies. When a woman is infected during pregnancy, the fetus can obtain specific maternally derived IgG, not IgM nor IgA, through placental transport[1].
- Understanding the maternal antibody responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during pregnancy at the time of labor & delivery (L&D) can elucidate the dynamics of placental transfer to the newborn as well as inform neonatal management and maternal vaccination strategies[2].
- There are limited data describing how coronavirus disease 2019 (COVID-19) disease severity shapes the maternal and infant serologic response at delivery. Evaluation by disease severity can better characterize the degree of protection conferred to the newborn.

Objectives

- To assess the association of COVID-19 diagnosis date-to-delivery interval with maternal IgG and transplacental transfer ratio in pregnant women with active or recovered SARS-CoV-2 infection at L&D
- To investigate SARS-CoV-2-specific antibody concentrations of pregnant women at L&D in relation to disease severity
- To compare infant serological response at birth when exposed to varying disease severity *in utero*

Methods

Study Design

- This study is a part of the COVID19 Outcomes in Mother-Infant Pairs (COMP) study, a prospective observational cohort of mother-infant dyads diagnosed with SARS-CoV-2 infection in pregnancy in the United States and in Brazil.
  - Data Collection: April 15, 2020 to May 28, 2021
  - Pregnant women >16 years of age with confirmed SARS-CoV-2 infection by nasopharyngeal (NP) reverse-transcription polymerase chain reaction (RT-PCR) or serology at any point during gestation were eligible for enrollment at the University of California, Los Angeles site.
  - Women with a history of COVID-19 vaccination were not eligible for enrollment.
  - Peripheral blood specimens were obtained from pregnant women at admission for delivery. This included mothers with active or recovered SARS-CoV-2 infection at L&D. Cord blood was collected at delivery when feasible, and infant blood specimens were collected between 24 to 48 hours of life.

Definitions

- Pregnancy was categorized into three trimesters according to the American College of Obstetrics and Gynecology (ACOG): first trimester (0 – 13 weeks), second trimester (14 – 27 weeks) and third trimester (≥28 weeks).
- Women with SARS-CoV-2 infections were grouped into the National Institutes of Health (NIH) COVID-19 severity of illness categories[3]. The clinical categories were collapsed into asymptomatic, mild/moderate and severe/critical for this analysis.

Clinical Demographics

Table 1: Demographics and clinical characteristics of mother-infant dyads infected with SARS-CoV-2 during pregnancy

Maternal Demographics and Medical History	All Women (N = 101)
Age, Median (Range)	33 (16-42)
Race/Ethnicity	**No. (%)**
Latina	46 (45.5)
White	27 (26.7)
Black/African American	8 (7.9)
Asian/Other	20 (19.8)
Insurance	**No. (%)**
Public	36 (35.6)
Private	65 (64.4)
Gravidity, Median (Range)	2 (1-10)
COVID-19 Severity	**No. (%)**
Asymptomatic	14 (13.9)
Mild / Moderate	76 (75.2)
Severe / Critical	11 (10.9)
Gestational Age at Diagnosis	**No. (%)**
First Trimester	10 (9.9)
Second Trimester	39 (38.6)
Third Trimester	52 (51.5)
Diagnosis Date-to-Delivery Interval, Median (IQR), Days	62 (32-120)
Medical History Prior to Pregnancy	**No. (%)**
Any Comorbidities	52 (51.5)
Obesity (Pre-Pregnancy BMI >30)	32 (31.7)
Diabetes Mellitus (Not Gestational)	3 (3.0)
Congenital Heart Disease	5 (5.0)
Asthma	12 (11.9)

Results

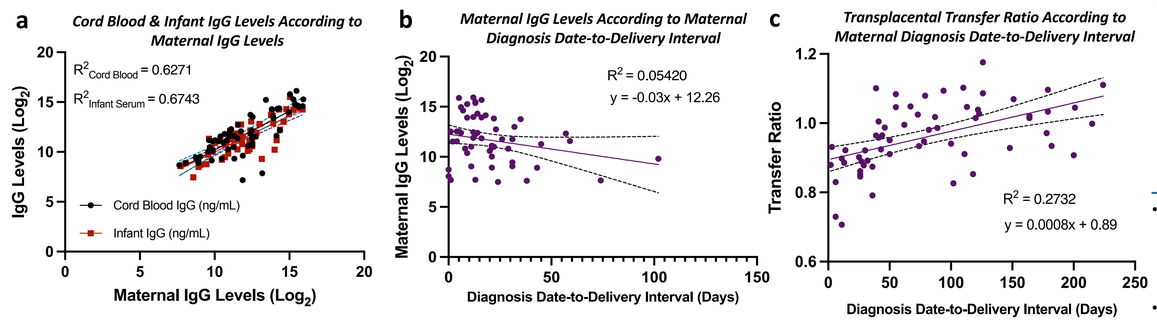

Figure 1: Correlations among anti-SARS-CoV-2 IgG levels at delivery from maternal sera (n = 101), matched cord blood (n = 72), infant sera (n = 86), and diagnosis date-to-delivery interval.
(a) Correlation between IgG levels from seropositive mother at L&D and matched cord blood serum (R^2 = 0.6271) and infant serum (R^2 = 0.6743). All concentrations (ng/mL) were log_2-transformed.
(b) Correlation between maternal IgG levels at L&D and COVID-19 diagnosis date-to-delivery interval (R^2 = 0.0542).
(c) Correlation between transplacental transfer ratio (log_2-transformed infant IgG / log_2-transformed-maternal IgG level) and COVID-19 diagnosis date-to-delivery interval (R^2 = 0.2732). Dotted lines represent 95% confidence intervals.

Table 2: Serology of mother-infant dyads infected with SARS-CoV-2 during pregnancy

	Maternal Serum at L&D	Cord Blood	Infant Serum at Delivery
Anti-SARS-CoV-2 IgG, IgM, and IgA	N = 101	N = 72	N = 86
	N (%)	**N (%)**	**N (%)**
IgG + Total	89 (88)	65 (90)	69 (80)
IgM+ Total	90 (89)	9 (13)	0 (0)
IgA+ Total	84 (83)	8 (11)	0 (0)
IgG (+) / IgM (+)/ IgA (+)	77 (76)	8 (11)	0 (0)
IgG (+) / IgM (-)/ IgA (-)	3 (3)	58 (81)	0 (0)
IgG (+) / IgM (+)/ IgA (-)	6 (6)	1 (1)	0 (0)
IgG (-) / IgM (+)/ IgA (-)	5 (5)	5 (7)	17 (20)
IgG (-) / IgM (+)/ IgA (-)	3 (3)	0 (0)	0 (0)
IgG (-) / IgM (+)/ IgA (+)	4 (4)	0 (0)	0 (0)
IgG (-) / IgM (-)/ IgA (+)	0 (0)	0 (0)	0 (0)

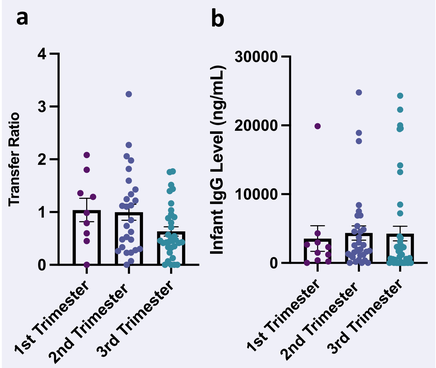

Figure 2: Neonatal IgG level (n = 84) and transplacental transfer ratio (n = 69) changes by trimester of COVID-19 diagnosis.
(a) Transplacental transfer ratio [infant IgG level (ng/mL) / maternal IgG level (ng/mL)] by trimester of pregnancy of diagnosis (P = 0.06).
(b) Infant IgG level (ng/mL) at birth by trimester of pregnancy of diagnosis (P = 0.99).
Data are presented as mean ± SEM. One-way ANOVA and Tukey's multiple comparisons test were performed.

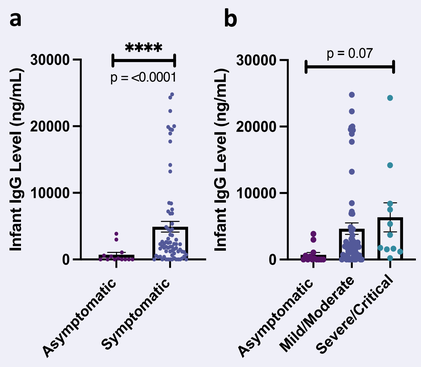

Figure 3: Neonatal antibody response at birth to maternal SARS-CoV-2 infection.
(a) Infant IgG levels (ng/mL) at birth in asymptomatic vs symptomatic mothers (****P < 0.0001).
(b) Infant IgG levels (ng/mL) at birth by maternal COVID-19 disease severity. Asymptomatic vs severe/critical disease exposure resulted in P = 0.07.
Data are presented as mean ± SEM. Welch's t test was performed for asymptomatic vs symptomatic. One-way ANOVA and Tukey's multiple comparisons test were performed for asymptomatic vs mild/moderate vs severe/critical groups. After performing a Log_2-transformation of infant IgG levels, P = 0.0661 for asymptomatic vs symptomatic. Of note, 7/13 asymptomatic infant sera and 10/71 symptomatic infant sera were 0 ng/mL and were lost in log_2-transformation.

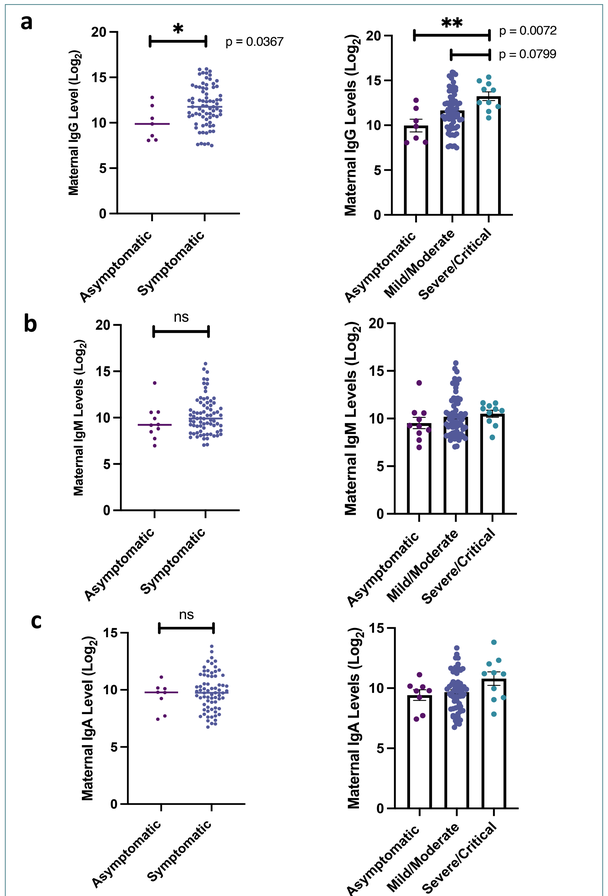

Figure 4: Maternal antibody response at L&D to SARS-CoV infection during pregnancy (n = 94).
(a) Log_2 of maternal IgG levels at L&D for asymptomatic vs symptomatic patients (*P < 0.05). Log_2 of maternal IgG levels at L&D by COVID-19 disease severity (**P < 0.01).
(b) Log_2 of maternal IgM levels at L&D for asymptomatic vs symptomatic patients (ns, not significant; P > 0.05). Log_2 of maternal IgM levels at L&D by COVID-19 disease severity (P > 0.05).
(c) Log_2 of maternal IgA levels at L&D for asymptomatic vs symptomatic patients (ns, not significant; P > 0.05). Log_2 of maternal IgA levels at L&D by COVID-19 disease severity(P > 0.05).
12/94 cases were 0 ng/mL and were lost in log_2-transformation. Data are presented as mean ± SEM. Welch's t test was performed for asymptomatic vs symptomatic. One-way ANOVA and Tukey's multiple comparisons test were performed for asymptomatic vs mild/moderate vs severe/critical groups.

Methods Cont.

Antibody Measurement

- All maternal and cord blood samples were tested for quantitative anti-SARS-CoV-2 IgA, IgG and IgM. Sera were analyzed by enzyme-linked immunosorbent assay (ELISA) to detect the spike receptor-binding domain (RBD) IgA, IgG and IgM[3,4].
- Transplacental Transfer Ratio = Log_2[Infant IgG Level at birth] / Log_2 [Maternal IgG Level at L&D]

Statistical Analysis:

- Correlations were studied using Pearson correlation analysis and linear regression. Standard descriptive analyses including Welch's t test and one-way ANOVA were used as appropriate to compare raw antibody concentrations, log_2-transformed antibody levels, and transplacental transfer ratios among categories divided by trimester of diagnosis or COVID-19 disease severity. Statistical significance was set at P < 0.05. Graphpad PRISM 9.0 software was used to conduct the analyses.

Results

- 101 women enrolled in the cohort delivered by May 28, 2021. Of these, 85% were diagnosed with SARS CoV-2 by PCR and 15% by SARS-CoV-2 serology. Cord blood was available for 72 deliveries, and infant specimens were available for 86 newborns (one triplet and two twins).
- 77% of the maternal cohort produced anti-SARS-CoV-2 IgG, IgM, and IgA isotypes; 93% of women had at least one antibody class positive for SARS-CoV-2; and 5% of women had no detectable antibody class. Infant serum at delivery only contained IgG, and neither IgM nor IgA was detected (**Table 2**). This is expected (in the absence of infant infection from mother-to-child transmission) considering that only maternal IgG can cross the placenta.
- In pregnant women with active infection or who had recovered from COVID-19, anti-SARS-CoV-2 IgG concentrations at delivery positively correlated with cord blood and infant IgG levels at birth (**Fig. 1a**), consistent with previous studies[5].
- Maternal IgG levels waned when further from the period of active infection (**Fig. 1b**); conversely, transplacental transfer ratios increased slightly with increased duration between onset of infection and delivery (**Fig. 1c**, R^2 = 0.27). As demonstrated by comparable studies[2,5], this finding may be an important factor when considering the timing of vaccination in pregnant women.
- Surprisingly, the transplacental transfer ratio (**Fig. 2a**, P = 0.06) and infant IgG levels at birth (**Fig. 2b**, P = 0.99) did not significantly differ by trimester of diagnosis, potentially due to the role of maternal disease severity in increasing antibody levels. However, there appeared to be a weak linear trend with the transfer ratio, as seen in Figure 1c.
- Maternal IgG levels increased with disease severity (**Fig. 4a**), suggestive of a more robust immunologic response. No significant difference was found in maternal IgM (**Fig. 4b**) or IgA (**Fig. 4c**) when grouped by COVID-19 severity, which is expected considering these are produced in early phases of infection.
- A significant increase in infant IgG levels at birth was observed in children born to women with symptomatic prenatal SARS-CoV-2 infection as opposed to infants born to asymptomatic mothers (p < 0.0001). A trend towards a more robust infant serological response was observed in infants with more severe/critical COVID-19 exposure *in utero*.

Conclusions

- Our findings demonstrate how altered maternal responses across distinct COVID-19 disease severity categories influence neonatal protection against SARS CoV-2.
- Future directions include neutralizing antibody studies to further characterize maternal and infant immune protection and evaluation of the role of T-cell immunity in mother-infant dyads following natural infection. Future studies should compare immune responses during pregnancy elicited by natural infection versus immunization during gestation.

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