

Maternal Antibody Response, Neutralizing Potency, and Placental Antibody Transfer After Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection

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OBJECTIVE: To characterize maternal immune response after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during pregnancy and quantify the efficiency of transplacental antibody transfer.

METHODS: We conducted a prospective cohort study of pregnant patients who tested positive for SARS CoV-2 infection at any point in pregnancy and collected paired maternal and cord blood samples at the time of delivery. An enzyme-linked immunosorbent assay (ELISA) and

neutralization assays were performed to measure maternal plasma and cord blood concentrations and neutralizing potency of immunoglobulin (Ig)G, IgA, and IgM antibodies directed against the SARS-CoV-2 spike protein. Differences in concentrations according to symptomatic compared with asymptomatic infection and time from positive polymerase chain reaction (PCR) test result to delivery were analyzed using nonparametric tests of significance. The ratio of cord to maternal anti-receptor-binding domain IgG titers was analyzed to assess transplacental transfer efficiency.

RESULTS: Thirty-two paired samples were analyzed. Detectable anti-receptor-binding domain IgG was detected in 100% (n=32) of maternal and 91% (n=29) of cord blood samples. Functional neutralizing antibody was present in 94% (n=30) of the maternal and 25% (n=8) of cord blood samples. Symptomatic infection was associated with a significant difference in median (interquartile range) maternal anti-receptor-binding domain IgG titers compared with asymptomatic infection (log 3.2 [3.5–2.4] vs log 2.7 [2.9–1.4], $P=.03$). Median (interquartile range) maternal anti-receptor-binding domain IgG titers were not significantly higher in patients who delivered more than 14 days after a positive PCR test result compared with those who delivered within 14 days (log 3.3 [3.5–2.4] vs log 2.67 [2.8–1.6], $P=.05$). Median (range) cord/maternal antibody ratio was 0.81 (0.67–0.88).

CONCLUSIONS: These results demonstrate robust maternal neutralizing and anti-receptor-binding domain IgG response after SARS-CoV-2 infection, yet a lower-than-expected efficiency of transplacental antibody transfer and a significant reduction in neutralization between maternal blood and cord blood. Maternal infection does confer some degree of neonatal antibody pro-

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tection, but the robustness and durability of protection require further study.

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Pregnancy is associated with an increased risk for severe coronavirus disease 2019 (COVID-19), including intensive care unit admission, mechanical ventilation, need for extracorporeal membrane oxygenation, and death, when compared with nonpregnant adults.¹ Severe disease in pregnancy is also associated with increased risk for obstetric complications, including cesarean delivery, preterm birth, and possibly stillbirth.² Neonates also represent a vulnerable population, susceptible to worse outcomes. Children younger than 1 year, an age group for which immunity predominantly occurs passively, comprise almost one third of pediatric COVID-19 hospitalizations.³ Mitigation strategies are urgently needed to protect pregnant persons and their newborns.

Describing the maternal immune response after natural infection is an important step in delineating maternal risks for infection, reinfection, treatment, and prevention. Evaluation of passive in utero antibody transfer after natural infection can help with understanding neonatal vulnerability to infection and whether risk can be mitigated by transplacental transfer of specific antibodies. In addition, studying the maternal immune response after natural infection may hold clues to understanding the maternal immune response and maternal and neonatal protection after vaccination. Although a number of studies have analyzed maternal serologic response after natural infection, they have primarily focused on immunoglobulin (Ig)G and IgM response, without measuring neutralizing potency, which is key to prevention of severe disease and long-term prevention of reinfection.^{4–7}

Therefore, we sought to characterize the maternal antibody and neutralizing response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during pregnancy, and to assess differences in maternal antibody concentrations according to symptomatic and asymptomatic infection, and the amount of time between confirmed SARS-CoV-2 positive polymerase chain reaction (PCR) test result and delivery. We also sought to characterize and to quantify transplacental transfer of SARS-CoV-2 antibodies.

METHODS

Pregnant patients aged 18 years or older who tested positive for SARS-CoV-2 infection by nasopharyn-

geal reverse transcription (RT) PCR between April and December 2020 and who planned to deliver at either Grady Memorial Hospital or Emory University Hospital-Midtown were offered enrollment into one of two studies: SPORE (Study of Pregnancy Outcomes in women with REspiratory illness due to suspected or confirmed coronavirus infection) at Grady Memorial Hospital or EmPOWR (Emory Prospective Opportunity for Women's Health Research Initiative) at Emory University Hospital Midtown, both in Atlanta, Georgia. During this time-frame, universal opt-out SARS-CoV-2 screening was performed on all pregnant individuals admitted to the labor and delivery units at both locations.⁸ Patients who did not speak either English or Spanish as their first language were not approached for the study (Appendix 1, available online at <http://links.lww.com/AOG/C319>).

Demographic and health information, including maternal age, race–ethnicity, insurance status, and medical comorbidities such as obesity, chronic hypertension, and pregestational diabetes were abstracted from the medical record by a trained medical abstractor and study author (N.T.J.). Clinical characteristics related to SARS-CoV-2 infection such as timing of infection, presence of symptoms as documented in the electronic medical record, clinical course, and hospitalization data were abstracted, as well as maternal, neonatal, and obstetric outcomes such as gestational age at birth, mode of delivery, neonatal birth weight, and neonates SARS-CoV-2 status. Neonatal SARS-CoV-2 testing was initially performed at the discretion of the pediatric or neonatal provider, but universal testing of neonates born to mothers with SARS-CoV-2 infection began in November 2020 based on American Academy of Pediatrics recommendations.⁹

After enrollment, maternal venous blood was collected into EDTA tubes when patients presented for clinical blood draws and at delivery hospitalization admission. The umbilical cord blood was collected into a cord blood kit using sterile technique at time of delivery; all samples were processed to obtain plasma and stored at -80°C .

The levels of anti-SARS-CoV-2 IgG, IgA, and IgM antibodies present in maternal and cord blood were assessed using an enzyme-linked immunosorbent assay (ELISA) developed in collaboration with the Emory Medical Lab.¹⁰ Log endpoint titers were calculated by imputation after sigmoidal fitting using GraphPad Prism software under clinically validated OD cutoffs (0.2 for IgG, 0.15 for IgA, and 0.35 for IgM), determined relative to prepandemic negative



controls and to convalescent plasma (Appendices 2 and 3, available online at <http://links.lww.com/AOG/C319>). Antibody end dilution titers were expressed as \log_{10} (value).

The SARS-CoV-2 neutralizing activity in maternal and cord blood was quantified using an assay developed by Crawford and colleagues, using the Wuhan-Hu-1 strain.^{11,12} To measure SARS-CoV-2 spike-specific neutralizing activity in plasma, a five-fold dilution series was prepared for each sample and incubated with a standard amount of the SARS-CoV-2 pseudovirus. The 50% inhibitory concentration–dilution (IC₅₀) for each plasma sample tested was determined by normalizing the luminescence signal in each sample dilution to the maximum signal in a pseudovirus alone control. The IC₅₀ log dilutions were then calculated by imputation after sigmoidal fitting of each neutralization curve using GraphPad Prism (Appendices 2 and 3, <http://links.lww.com/AOG/C319>).

Plasma samples were diluted 1:2 in Quanterix assay buffer before testing on a highly sensitive single molecule array immunoassay on a Quanterix HD-X instrument for the detection of SARS-CoV-2 nucleocapsid protein. Testing was performed as described by the manufacturer and validated from plasma.¹³

The underlying distribution of maternal antibody and cord antibody levels were assessed for normality. Median differences in maternal and cord blood median log endpoint antibody titers between those with asymptomatic and symptomatic infection and time from confirmed infection to delivery were evaluated using parametric tests and non-parametric tests of significance using 2-sided *P*-values where appropriate (*t* test for parametric tests, Mann-Whitney U test for nonparametric tests). Data sets that contained primarily null values were converted to binary variables and differences in presence or absence were analyzed using Fisher exact test.

The neonatal/maternal ratio was calculated as the ratio between cord blood and maternal plasma anti-receptor-binding domain IgG endpoint titers. Pearson correlation was used to analyze the relationship between maternal and cord blood antibody titers, and parametric tests were used to compare the fetal/maternal ratio between those with symptomatic and asymptomatic infection (two sample *t* test with equal variance) and by latency from infection to delivery. Univariate analysis to compare the difference in neonatal/maternal ratio samples amongst different categorical variables, specifically birth weight, neonatal sex assignment, and presence of maternal obe-

sity was performed using *t* tests or analysis of variance when appropriate.

A linear regression analysis was performed to analyze the relationship between log maternal anti-receptor-binding domain IgG titer (outcome) interval from maternal infection to delivery (natural logarithm days), symptomatic or asymptomatic infection, as well as to analyze the relationship between cord anti-receptor-binding domain IgG titers and maternal titers (Appendix 4, available online at <http://links.lww.com/AOG/C319>).

Analysis were performed using GraphPad Prism 9.0 statistical software and R-statistical software (<https://www.r-project.org>); *P* < .05 was considered statistically significant for all analyses.

This research was approved by the Emory University Institutional Review Board (Study IRB00101931, Study MOD003-STUDY 00000312) and the Grady Research Oversight Committee; all patients provided written informed consent for participation.

RESULTS

From April through December 2020, there were 83 pregnant patients enrolled in either SPORE (n=62) or EmPOWR (n=21); of these, 32 had paired maternal and cord blood samples available for analysis. All 32 paired samples were from pregnant patients with a positive SARS-CoV-2 RT-PCR test result. Demographics are reported in Table 1. The dominant comorbid conditions included obesity and asthma or other pulmonary conditions (Table 1).

The proportion of patients who were symptomatic is described in Table 2. The predominant symptoms in this group included cough (n=14; 82%), difficulty breathing (n=9; 53%), fever (n=5; 29%), and anosmia or ageusia (n=4; 24%). Delivery, maternal, and neonatal outcomes are also summarized in Table 2.

Anti-SARS-CoV-2 receptor-binding domain IgG, IgA, and IgM antibodies were present in 100% (n=32), 75% (n=24), and 94% (n=30) of maternal plasma samples and 91% (n=29), 3% (n=1), and 9% (n=3) of cord samples, respectively (Fig. 1). Functional neutralizing antibody was present in 94% (n=30) of the maternal plasma samples and 25% (n=8) of the cord serum samples. Paired patient-level data on disease severity and serologic response are provided in Appendix 5, available online at <http://links.lww.com/AOG/C319>.

The overall maternal plasma median antibody titers were calculated for the cohort. Median (interquartile range) maternal anti-receptor-binding



Table 1. Maternal Demographic and Clinical Characteristics of Patients With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Pregnancy (N=32)

Demographic	Value
Maternal age at delivery (y)	27.8±6.3
Race-ethnicity	
Non-Hispanic Black	23 (72)
Non-Hispanic White	1 (3)
Hispanic	8 (25)
Primary language	
English	29 (91)
Spanish	3 (9)
Insurance	
Uninsured	5 (16)
Medicaid or managed Medicaid	27 (84)
Private or commercial	4 (13)
Education (missing n=11)	
Less than 12th grade	7 (33)
High school	11 (52)
College	3 (14)
Parity*	
Nulliparous	10 (31)
Primiparous	6 (19)
Multiparous	16 (50)
Pregravid BMI (kg/m ²) (missing n=2)	
18–24.9	7 (23)
25–29.9	5 (17)
30.0–39.9	11 (37)
40 or higher	6 (20)
Medical comorbidities	
Obesity (BMI higher than 30)	17 (53)
Asthma, other pulmonary condition	9 (28)
Chronic hypertension [†]	7 (22)
Pregestational diabetes	4 (13)
Mental health	4 (13)
HIV	1 (3)

BMI, body mass index; HIV, human immunodeficiency virus. Data are mean±SD or n (%).

* Six women had history of miscarriage, termination, or ectopic pregnancy.

[†] Includes a patient with congestive heart failure.

domain IgG was log 2.77 (3.2–2.1), anti-receptor-binding domain IgA titer was log 1.83 (2.09–0), and anti-receptor-binding domain IgM was log 2.27 (2.8–1.9). The median (interquartile range) titer for which neutralizing activity was greater than 50% [IC50] was log 2.78 (3.2–0) for the cohort.

Receptor-binding domain IgM was detectable in three cord blood samples; all were from neonates whose mothers presented with symptoms in the third trimester and delivered 24, 38, and 96 days after the first SARS-CoV-2–positive test result. Two of these patients required hospitalization for SARS-CoV-2, although none required advanced support. All

Table 2. Timing of Infection and Clinical and Obstetric Course in Cohort of Pregnant Women With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection

Characteristic	Value
SARS-CoV-2 infection	
Gestational age at infection (wk)	34 (11–40)
Indications for testing	
Asymptomatic testing*	15 (47)
Person under investigation [†]	17 (53)
Time from positive PCR result to delivery (d)	
14 or less	13 (41)
More than 14	19 (59)
Timing of infection (trimester)	
1st	1 (3)
2nd	3 (9)
3rd	28 (88)
Neonate tested for SARS-CoV-2 [‡]	15 (47)
Neonate positive for SARS-CoV-2	0
Obstetric	
Gestational age at delivery (wk)	39 (34–40)
Neonate born before 37 wk	5 (16)
Spontaneous labor, PPRM	2 (40)
Mode of delivery	
Vaginal [§]	14 (44)
Cesarean	18 (56)
Neonatal sex assignment	
Female	20
Male	12
Neonatal birth weight (g)	3,084±437
Composite maternal morbidity [¶]	3
Composite neonatal morbidity [#]	3

SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; PCR, polymerase chain reaction; PPRM, preterm prelabor rupture of membranes.

Data are median (interquartile range), n (%), or mean±SD.

* On April 20, 2020, we implemented universal asymptomatic testing of all patients admitted for delivery and then expanded testing to all patients admitted for any indication on April 28, 2020.

[†] As testing protocols changed in our institution, persons under investigation included patients with any symptom of SARS-CoV-2 infection, suspicious clinical findings such as oxygen level lower than 95% or tachycardia greater than 120 bpm, or unexplained elevation in maternal white blood cell count.

[‡] Neonates underwent nasopharyngeal testing for SARS-CoV-2 infection at the discretion of the pediatric provider until implementation of universal testing of all neonates born to SARS-CoV-2–positive mothers.

[§] Includes two patients who underwent operative vaginal deliveries.

^{||} Includes five patients who underwent primary cesarean delivery for fetal distress.

[¶] Includes one patient admitted to the intensive care unit for respiratory failure and ventilatory support, one patient admitted to intermediate care for noninvasive ventilatory support, and one patient who underwent cesarean hysterectomy for uterine rupture after failed trial of labor after cesarean.

[#] Includes neonates admitted to the special care nursery or neonatal intensive care unit due to ventilatory support. One neonate was admitted with tetralogy of Fallot. No neonatal deaths occurred.



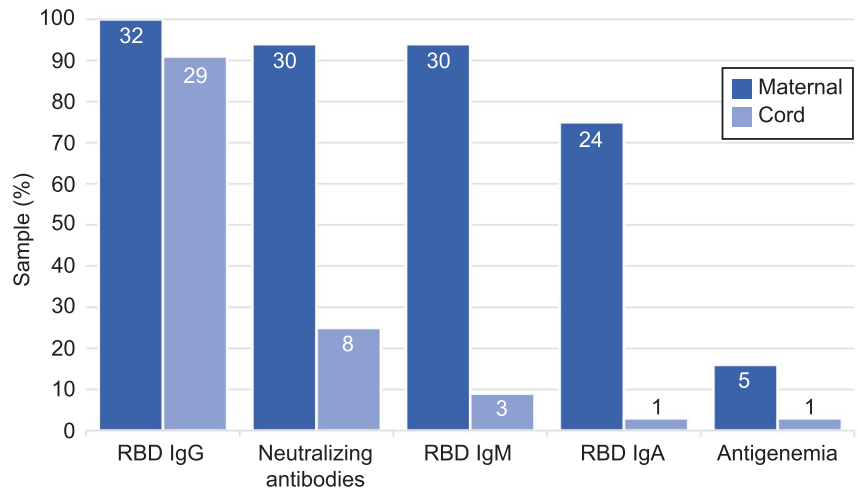


Fig. 1. Percentage of maternal and cord blood samples with detectable severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) receptor-binding domain (RBD) immunoglobulin (IgG, IgM, and IgA) antibody titers, neutralizing antibodies, and nucleocapsid antigen.

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patients had negative RT-PCR test results at time of delivery and two delivered by cesarean. None of these neonates were tested for SARS-CoV-2 at birth.

The median antibody concentrations were then analyzed according to the presence ($n=15$) or absence ($n=17$) of symptoms at the time of SARS-CoV-2 testing (Fig. 2). There was a statistically significant difference in median (interquartile range) anti-receptor-binding domain IgG titers between symptomatic and asymptomatic patients (log 3.2 [3.5–2.4] vs log 2.7 [2.9–1.4], $P=.03$) and in median (interquartile range) anti-receptor-binding domain IgA titers (log 2.09 [2.2–0.6] vs 1.3 [1.9–0], $P=.04$). However, no difference was seen in maternal neutralizing antibody concentrations or median IgM titers. Cord blood anti-receptor-binding domain IgG concentrations were also significantly different according to the presence or absence of symptoms at time of infection (log EDT 2.4 [2.9–1.8] vs 1.8 [2.2–0.6], $P=.02$) (Fig. 2). Mean differences are included in the Appendix 6, available online at <http://links.lww.com/AOG/C319>.

Patients were then categorized according to time from first positive PCR test result to delivery (14 days or less [$n=13$] vs more than 14 days [$n=19$]) (Fig. 3). Median (interquartile range) maternal anti-receptor-binding domain IgG titers were not significantly higher in patients who delivered more than 14 days after positive PCR test results compared with those who delivered within 14 days (log 3.3 [3.5–2.4] vs log 2.67 [2.8–1.6], $P=.05$). Although anti-receptor-binding domain cord IgG was higher in those delivering more than 14 days after diagnosis, this was not statistically significant (log 2.4 [2.9–1.7] vs log 1.8 [2.2–0.9], $P=.07$). A linear regression analysis was performed to analyze the relationship between log maternal receptor-binding domain IgG titer (out-

come) and the time from initial positive PCR test result as a continuous exposure (natural logarithm days). Each day was associated with a log 0.05 increase in maternal titers ($P=.049$).

Nucleocapsid antigen was present in 5 (16%) maternal plasma samples (3 from symptomatic patients, two from asymptomatic patients) and 1 cord blood sample (Appendix 5, <http://links.lww.com/AOG/C319>). The positive cord blood sample (18.15 pg/mL) was obtained after delivery in a patient who underwent urgent cesarean delivery after intubation for respiratory failure at 37 weeks of gestation; maternal plasma level was 1,780 pg/mL, and no IgM was detected in the cord blood from this patient. The neonate remained in the newborn nursery and was discharged home on day of life 3. The concentration in remaining maternal samples ranged from 0.3 to 11.3 pg/mL.

The relationship between maternal and cord anti-receptor-binding domain IgG titers was then analyzed and fetal/maternal ratio calculated for each paired sample. Overall, there was moderate correlation between maternal receptor-binding domain IgG concentrations and cord receptor-binding domain IgG, with higher maternal titers predicting higher cord blood titers [Pearson, $r(30)=0.78$, $P<.001$] (Appendix 7, available online at <http://links.lww.com/AOG/C319>). However, log latency of maternal infection was not predictive of log cord receptor-binding domain IgG titer ($P=.62$ for slope=0). The fetal/maternal ratio for anti-receptor-binding domain IgG ranged from 0 to 1.03 (median [interquartile range] 0.81 [0.67–0.88]), corresponding to an overall efficiency of 81%. There was no significant difference in transfer efficiency in symptomatic compared with asymptomatic infection ($P=.44$) or by latency in time from



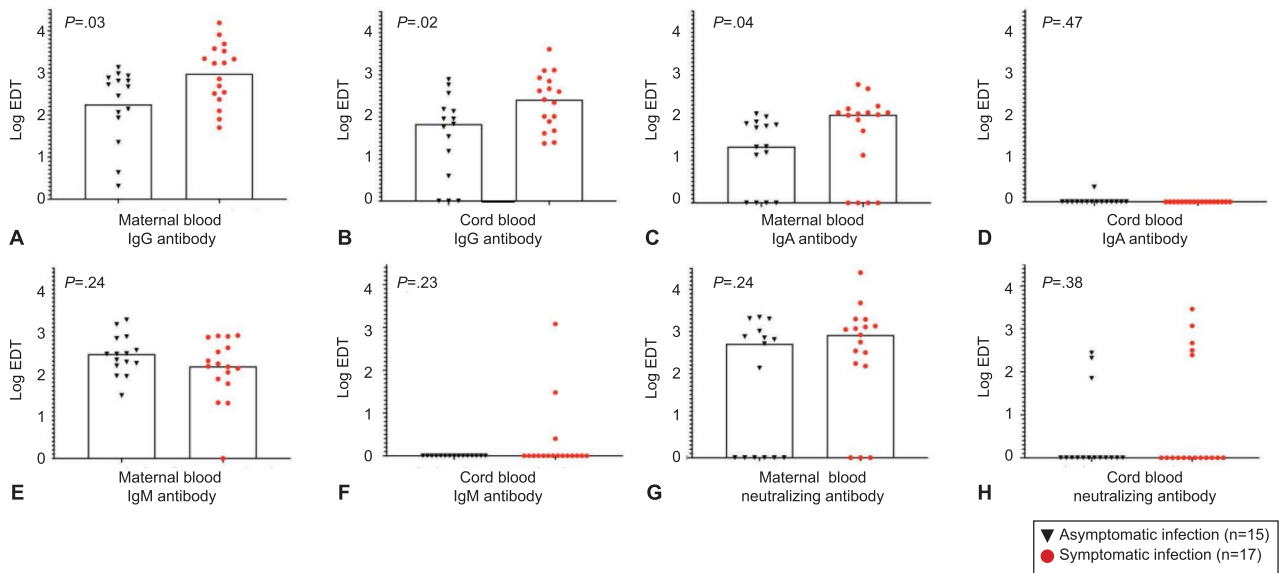


Fig. 2. Symptomatic maternal infection significantly alters the endpoint titers (EDT) of maternal (A) and cord blood, (B) anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) receptor-binding domain (RBD) immunoglobulin (Ig)G antibodies, as well as maternal (C) IgA antibodies, but does not alter the EDT of SARS-CoV-2 IgA (D) cord blood or IgM (E and F) and neutralizing antibodies (G and H). Differences in median EDT in maternal blood sera were analyzed using Mann-Whitney U two-tailed test for significance, with *P*-value set at $\leq .05$. There was a statistically significant difference in median anti-RBD IgG titers between symptomatic and asymptomatic patients in maternal plasma (log 3.2 [3.5, 2.4] vs log 2.7 [2.9, 1.4], *P*=.03) and in median anti-RBD IgA titers (log 2.09 [2.2, 0.6] vs 1.3 [1.9, 0], *P*=.04)]. However, no difference was seen in median maternal neutralizing antibody concentrations (IC50 2.9 [3.2, 1.1] vs 2.7 [3.0, 0], *P*=.24) or median IgM titers (log EDT 2.2 [2.7, 1.8] vs 2.3 [2.8, 1.9], *P*=.24) in symptomatic vs asymptomatic women. Cord RBD IgG concentrations were also significantly different according to the presence or absence of symptoms at time of infection (log EDT 2.4 [2.9, 1.8] vs 1.8 [2.2, 0.6], *P*=.02).

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infection to delivery (*P*=.82) (Fig. 4). Similarly, no differences were seen based on maternal body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) higher than 30 (*P*=.97), neonatal sex assignment (*P*=.98), or birth weight greater or less than 3,000 g (*P*=.80).

DISCUSSION

In this prospective sero-epidemiologic study, we demonstrate that SARS-CoV-2 infection during pregnancy generates a robust maternal immune response. Our analysis focused on the receptor-binding domain of the SARS-CoV-2 spike protein, which mediates viral entry,¹⁴ is highly correlated with antibody response to other SARS-CoV-2 proteins,¹⁵ and is the primary target for vaccine development.^{16,17} Median anti-receptor-binding domain IgG antibody concentrations were highest among pregnant patients with symptomatic infection; however, neutralizing potency did not differ significantly by symptoms or time from diagnosis to delivery. Although maternal IgG concentrations were moderately correlated with cord blood IgG, transfer

efficiency across the placenta was less than expected at 81%, and only 25% of cord blood samples demonstrated neutralizing potency.

Kubiak et al⁵ analyzed the antibody response (IgG, IgM) in 88 pregnant patients with SARS-CoV-2 infection and found that: 1) IgM peaked at 15 days, 2) IgG peaked within 30 days, 3) response was higher in symptomatic patients, and 4) maternal antibody levels correlated with cord blood levels. We similarly demonstrate a robust maternal immune response, correlation between maternal and cord blood IgG levels, and additionally demonstrate a robust maternal IgA and neutralizing response.

Anti-receptor-binding domain IgA was present in 74% of maternal samples. Previous studies indicate viral replication occurs in the GI tract and that IgA contributes an early neutralizing response at mucosal interfaces.^{18,19} The robust maternal response seen in our cohort may have implications for passive transfer through breastmilk. Additionally, the finding of a maternal neutralizing response is significant as a neutralizing response to SARS-CoV-2 prevents infection after vaccination and reinfection after natural



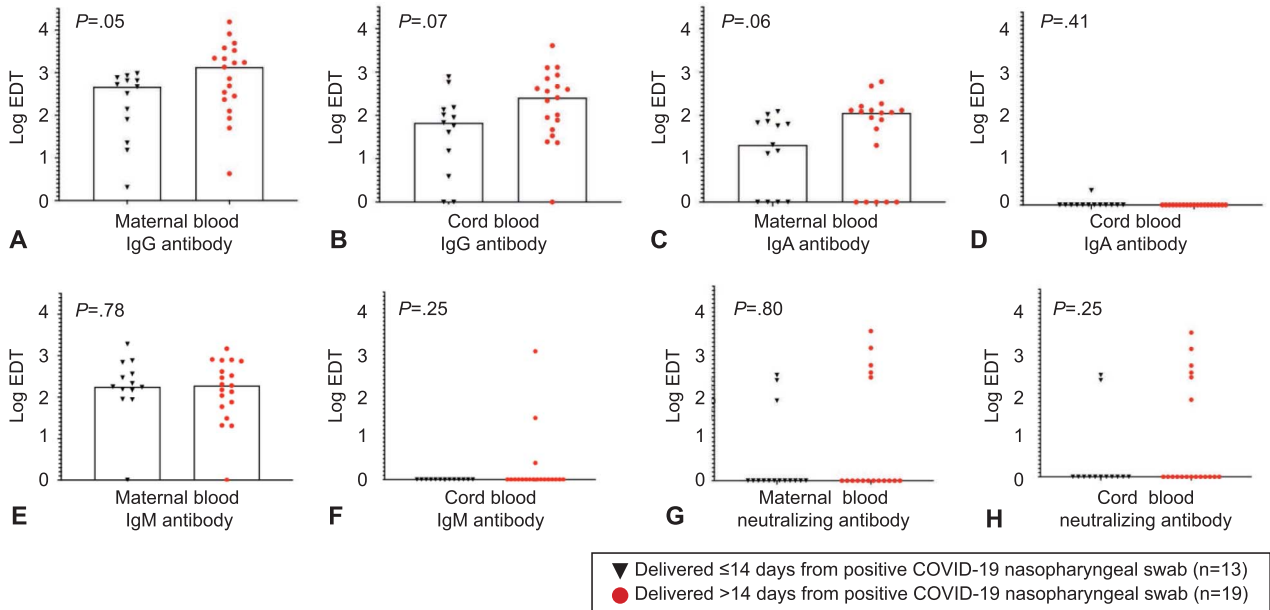


Fig. 3. The latency of maternal infection significantly alters the maternal endpoint titers (EDT) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulin (Ig)G antibodies but not cord blood IgG antibodies (A and B) or IgA (C and D), IgM (E and F), or neutralizing (F and H) maternal and cord blood antibodies. Differences in median endpoint titers in maternal blood sera were analyzed using Mann-Whitney U two-tailed test for significance, with *P*-value set at $\leq .05$. Median maternal anti-receptor-binding domain (anti-RBD) IgG titers were significantly higher in patients who delivered more than 14 days after a positive polymerase chain reaction test result vs those who delivered within 14 days (log 3.3 [3.5, 2.4] vs log 2.67 [2.8, 1.6], *P* = .05). Although anti-RBD cord IgG was also higher in those delivering more than 14 days after diagnosis, this was not statistically significant (log 2.4 [2.9, 1.7] vs log 1.8 [2.2, 0.9], *P* = .07). No between-group difference was seen in those delivering 14 days or less vs more than 14 days in maternal IgA (log 1.3 [1.8, 0] vs log 2.1 [2.1, 0], *P* = .06), maternal IgM (log 2.3 [2.7, 2.1] vs log 2.3 [2.9, 1.8], *P* = .78), and neutralizing response (log 2.7 [3.2, 0] vs log 2.8 [3.2, 0], *P* = .80). COVID-19, coronavirus disease 2019.

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infection. The neutralizing response also modulates disease severity, and reduces mortality.^{14,20,21}

The neonatal immune response is underdeveloped and relies on maternal antibodies transferred in utero.²² Anti-receptor-binding domain IgM was present in three cord blood samples and IgA in one. IgM has been reported in cord blood after maternal severe COVID-19 and in cases of suspected vertical transmission, which is known to occur, albeit rarely.²³ The finding of IgA in cord blood is difficult to explain. IgA is not known to cross the placental barrier although it has been reported²⁴; this may represent laboratory assay error or contamination from cord blood collection. Although anti-receptor-binding domain IgG was detected in 91% of cord blood samples, only 25% of cord blood samples had neutralizing potency. Cord blood levels of IgG were moderately correlated to maternal concentrations, however, the efficiency of in utero transfer was only 81%. This is significantly lower than seen after natural maternal infection of pertussis and influenza, where transfer efficiency is well above

300%.^{25,26} A reason for less efficient transfer compared with other viruses may be related to the effects of SARS-CoV-2 infection on the placenta. Placentas from pregnant patients with SARS-CoV-2 infection have been shown to have increased likelihood of maternal vascular malperfusion, particularly abnormal or injured maternal vessels, and intervillous thrombi.²⁷

Edlow et al⁶ published data on maternal immune response and transplacental antibody transfer efficiency. In their cohort of 37 maternal-neonatal dyads with confirmed infection, 65% of maternal plasma and 62% of paired cord blood samples from pregnant women had detectable anti-receptor-binding domain IgG, with mean (SD) antibody transfer ratio of 0.72 (0.57). These findings were also demonstrated in a second cohort by Flannery and colleagues, in which mean (SD) transplacental antibody ratio was 0.90⁴; both findings are similar to ours. It is not known what level of antibody transferred confers protection against SARS-CoV-2 infection or severe COVID-19. Additionally, whether transplacental passage of



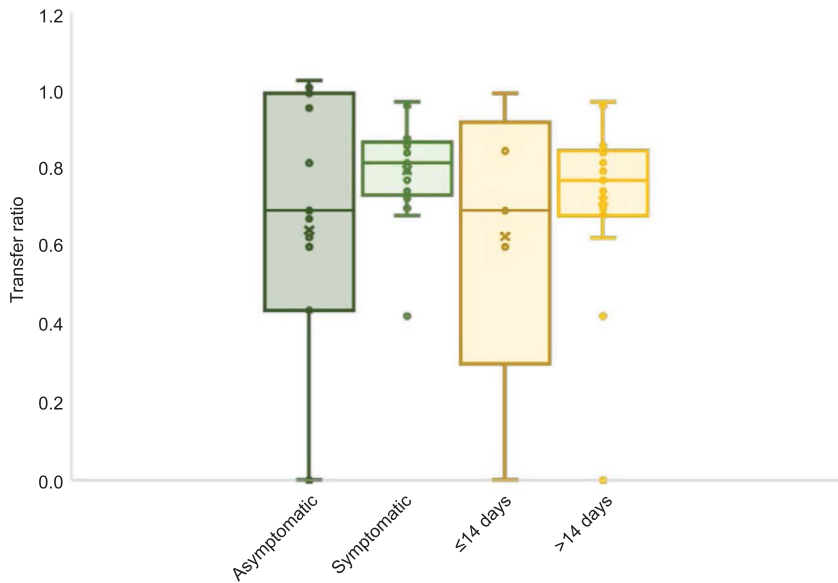


Fig. 4. Neonatal/maternal anti-receptor-binding domain (anti-RBD) immunoglobulin (Ig)G ratios in symptomatic vs asymptomatic paired patient samples and in paired patient samples with less than 14 days and more than 14 days after infection (positive polymerase chain reaction test result) to delivery. The fetal/maternal ratio (FMR) was calculated as the ratio between cord blood and maternal RBD IgG endpoint titers. The difference in FMR between groups was not statistically significant.

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antibodies after vaccine-induced immunity will occur with similar efficiency as was observed in our study remains an area of active investigation. A recent study by Gray and colleagues²⁸ demonstrates overall anti-receptor-binding domain IgG transfer efficiency of 91% in patients who had received either the Moderna or Pfizer SARS-CoV-2 vaccines, despite higher immune titers in vaccinated pregnant patients compared with those who had infection.

There are several limitations to our study. As enrollment in the study was based on clinician referral, we do not have data for patients who were offered and declined enrollment. We did not have a clinically similar, nonpregnant, reproductive age cohort as a control group. There was overlap between exposure variables (eg, patients with symptomatic infection also had duration of infection greater than 14 days) and we were underpowered to model the independent effect of these exposures on maternal and cord blood antibody response. Finally, we did not have sufficient longitudinal data to profile the serologic response over time.

The strengths of the study include a rigorous definition of exposure (all included patients had PCR confirmed infection). We analyzed paired maternal and cord blood samples at the time of delivery, providing uniform interpretation of the relationship between maternal and cord blood antibody concentrations. Finally, our cohort was comprised predominantly of Black patients with significant medical comorbidities, a population that has been disproportionately affected by COVID-19 yet understudied and underrepresented in the literature.^{8,29}

These data demonstrate that pregnant women are capable of consistently mounting a robust anti-receptor-binding domain IgG and neutralizing response to SARS-CoV-2 infection, even if asymptomatic at the time of diagnosis. Moreover, our data suggest that this response was durable, providing some support that vaccination in this population will be effective. However, transplacental antibody transfer was inefficient, at only 81% after infection. Further studies will be needed to determine whether or not vaccination will have similar antibody transfer across the placenta.

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