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MAJOR ARTICLE

Maternal-Fetal Immunologic Response to SARS-CoV-2 Infection in a Symptomatic Vulnerable Population: A Prospective Cohort

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Background. Coronavirus disease 2019 (COVID-19) disproportionally affects pregnant women and their newborn; however, little is known about variables that modulate maternal-fetal immune response to infection.

Methods. We prospectively studied socioeconomic, biologic, and clinical factors affecting humoral immunity in 87 unvaccinated pregnant women hospitalized in Buenos Aires for symptoms consistent with COVID-19.

Results. The number of days between symptom onset and childbirth predicted maternal and newborn virus spike protein receptor binding domain (RBD)-specific immunoglobulin G (IgG). These findings suggest newborns may benefit less when mothers deliver soon after COVID-19 infection. Similarly, a longer time between symptom onset and birth predicted higher in utero transfer of maternal IgG and its concentration in cord blood. Older gestational age at birth was associated with lower maternal to cord blood IgG ratio. Of women with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, 87% developed RBD-specific IgA responses in breast milk within 96 hours of childbirth. IgA was not significantly associated with time from infection but correlated with maternal serum IgG and placental transfer.

Conclusions. These results demonstrate the combined role of biologic, clinical, and socioeconomic variables associated with maternal RBD-specific antibodies and supports early vaccination strategies for COVID-19 in socioeconomically vulnerable pregnant women.

Clinical Trials Registration. NCT04362956.

Keywords. antibody; COVID-19; newborn; pregnancy; SARS-CoV-2.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread globally since early 2020, infecting an immunologically naive population and causing significant morbidity and mortality. SARS-CoV-2 infection in pregnant women can result in severe complications, including an increased chance of hospitalization and intensive care unit (ICU) admission [1] and a requirement for mechanical ventilation to alleviate respiratory distress [2]. There is also a greater likelihood of fetal intrapartum distress [3] and preterm delivery [4].

The immune response to the virus in unvaccinated individuals includes both innate and adaptive immunity [5]. One immunological signature in recovered individuals is production of virus-specific antibodies, including those directed at the spike protein receptor binding domain (RBD) [6]. Seropositive recovered individuals have an estimated 89% protection from reinfection for at least 6 months [7]. Circulating resting memory B cells directed against SARS-CoV-2 have been detected in unvaccinated nonpregnant convalescent individuals, indicating establishment of a robust antigen-specific, long-lived humoral immune memory compartment [8]. The antibody response to the virus has a high degree of heterogeneity and correlates with disease severity [9]. Patterns of immunoglobulin G (IgG) production over time, by age, and according to sex vary in different populations [8]. IgA production is also significant during the early SARS-CoV-2–specific humoral immune response [10].

The neonatal immune defense against infection by several pathogens is mainly dependent on innate immune effectors, IgA-containing maternal milk, and IgG delivered by transplacental transport mechanisms [11]. Understanding the humoral response to SARS-CoV-2 infection in pregnant women, and the degree to which that response is transferred via the placenta and breast milk, is essential for understanding protection from coronavirus disease 2019 (COVID-19) in utero and in neonates.

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Recent studies have demonstrated that biologic and clinical factors encountered during pregnancy can affect the antibody delivery to the fetus [12, 13]. In human milk, studies have suggested the presence of virus-specific IgA in mothers previously infected with SARS-COV-2 [14], but little is known about the variables that modulate IgA concentrations in human milk.

Environmental factors and socioeconomic vulnerabilities are variables are known to modulate COVID-19 severity and risk of death [15]. Recently, in Peru, socioeconomic status and overcrowding have been associated with SARS-CoV-2 seroprevalence and disease severity [16–18]. Therefore, there is an urgent need to understand the biologic and socioeconomic variables that modulate humoral maternal-fetal immunity. Such information may inform the implementation of appropriate maternal vaccination strategies and strengthen the understanding of the association between public health and COVID-19.

METHODS

A prospective multicenter cohort study (ClinicalTrials.gov, NCT04362956) was performed in pregnant women admitted due to symptomatic COVID-19 in a network of 9 maternity hospitals in the metropolitan area of Buenos Aires, Argentina, from 10 July 2020 to 1 October 2020. Institutional review board approval was obtained from each institution.

Study Population

Consent was obtained from women upon admission to the hospital. Inclusion criteria included female sex, pregnancy at 24 or more weeks of gestation, and admission to the obstetric ward presenting with fever and 1 or more respiratory symptoms (cough, sore throat, and respiratory difficulty). Further criteria included a diagnosis of pneumonia with no other explainable cause. A SARS-CoV-2 infection diagnosis was achieved by reverse transcription polymerase chain reaction (RT-PCR) of nasopharyngeal swab samples. At the time of the study there were no clear guidelines on neonatal diagnostic protocols for infants born to women with COVID-19. For study purposes, nasopharyngeal swabs were obtained from newborns only once within 48 hours of life. The reported SARS-CoV-2 variants in Argentina during this time period were mostly Gamma and Lambda [19]. Samples were not collected and analyzed from recruitedwomen who continued with their pregnancy but had not given birth by the end of the study.

Study Definitions and Data and Sample Collection

Upon inclusion, demographic, socioeconomic, and clinical data were collected for 14 days for both the mother and the newborn or newborns in the case of multiple births. Maternal illness was classified as mild, moderate, severe, or critical based on the US National Institutes of Health guidelines for severity of clinical presentation [20]. Preterm delivery was defined as fewer than 37 weeks' gestation, and term was defined as 37 or more weeks' gestation.

Women had blood drawn (5 mL) and umbilical cord blood (3 mL) was obtained at the time of birth. After centrifugation, serum was frozen at −80°C until antibody titer determination. Human milk (1–5 mL) was obtained within 96 hours after childbirth using a standardized cleaning procedure in conjunction with pump or hand expression. Briefly, before antibody testing, milk samples were thawed, centrifuged at 800*g* for 15 minutes at room temperature, fat was removed, and supernatant transferred to a new tube following best practices for human milk study for COVID-19 research [21]. Skimmed acellular milk was aliquoted and frozen at −80°C until testing. Maternal serum samples and admission information were used as controls if women met the inclusion criteria but tested negative for SARS-CoV-2.

Antibody Measurements

To quantify SARS-CoV-2–specific IgG antibody concentrations in maternal serum and cord blood, 96-well enzyme-linked immunosorbent assay (ELISA) plates (Nunc, Thermo Scientific) were coated with recombinant SARS-CoV-2 spike protein RBD (Rankin Laboratory, Oklahoma Medical Research Foundation, Oklahoma City, OK) at a final concentration of 10 μg/mL in carbonate coating buffer and incubated overnight at 4°C. Wells were washed with phosphate-buffered saline-0.5% v/v Tween (PBST) then blocked with 0.1% w/v bovine serum albumin in PBS for 2 hours at room temperature. Wells were washed with PBST before adding sera diluted in PBS with 0.1% Tween at 4°C overnight. Wells were washed with PBST and then incubated for 1 hour with a 1000-fold dilution of horse radish peroxidase (HRP)-labeled goat anti-human IgG (Jackson Immunoresearch) in PBS. Wells were washed and developed for 2 minutes at room temperature with ABTS substrate (KPL). A 10% w/v sodium dodecyl sulfate solution was used to stop the reaction. IgG concentrations were determined by measuring the optical density at 405 nm and values were extrapolated from a standard curve. To generate the standard curve, a positive control SARS-CoV-2 spike-specific IgG (Active Motif) was serially diluted against a constant RBD coating concentration. This was done for each ELISA plate. Data were analyzed using Graphpad Prism 8.0 software.

SARS-CoV-2 RBD-specific IgA antibodies were detected in milk samples in a similar manner to serum IgG except that HRP-labeled goat anti-human serum IgA (Jackson Immunoresearch) was used as the detection antibody. A positive control RBD-specific IgA was not available for the study. Data were expressed as absorbance at 405 nm for a 1/16 dilution of serum. Extensive titrations of selected samples were used to show that absorbance at 405 nm at a 1/16 dilution correlated with end point titer.

Statistical Analysis

Outcome variables were examined for outliers and skewness, and descriptive statistics were computed. Data transformations in the Box-Cox family were applied to outcomes found to

depart severely from normality. To identify predictors for use in multiple regression, bivariate analyses were conducted using the following procedures: (1) for categorical predictors' effects on skewed outcome variables, we used nonparametric methods (Mann-Whitney and Kruskal-Wallis tests); (2) for continuous variables' relationships with the transformed variables, we used Pearson correlation coefficient; and (3) for relationships between binary predictors and continuous outcomes unaffected by skewness or outliers, we computed independent *t* tests for unequal sample sizes. Predictors detected as significantly related to IgG or IgA in bivariate analyses were included in hierarchical multiple regression analyses. More distal, socioeconomic variables were entered as the first block, then more proximal biologic and clinical factors were added to the model as the second block. Thus, the analysis tested the effect of biologic and clinical factors after accounting for socioeconomic variables. All maternal serum samples were used for maternal antibody studies, including those with undetectable IgG values. Matched maternal-newborn samples were used for cord blood antibody response and placental antibody transfer ratio (maternal serum IgG to cord blood IgG). To examine the effect of twins in the data, sensitivity analyses were conducted, randomly omitting data from 1 twin in each pair to determine whether dependence between the pairs had a notable effect on results. Analyses were performed in SAS version 9.4 and R version 4.1.1.

RESULTS

We recruited 112 women (Figure 1). Eighty-seven women tested positive for COVID-19, with 57 mothers' results being matched with cord blood sera from their 59 infants. Milk was obtained from 58 mothers, with 51 mothers (87.9%) also having blood test results. A total of 32 mothers with tested milk and blood sera were matched with their infants' data.

Sample Characteristics

Demographic results are presented in Table 1. Mothers were aged from 15 to 49 years (median, 30.8 years; 25th–75th percentile, 26.1–34.9 years). Sixteen mothers (18.4%) had obesity and 8 mothers (9.2%) smoked during pregnancy. Regarding the socioeconomic vulnerabilities, 14 women (17.5%) lived in crowded conditions, 12 (15.8%) lived far from the hospital, 13 (16.3%) had no sewage system at home, 27 (33.8%) were unemployed, and more than half (n = 42, 52.5%) had no medical insurance, reflecting the degree of vulnerability of this population. Median gestational age at maternal hospitalization was 36 6/7 weeks (25th–75th percentile, 32 4/7–39 0/7 weeks) with almost half (n = 38, 43.7%) presenting before term gestation. Preterm birth was unrelated to these socioeconomic variables.

Of the 59 infants, 35.6% (n = 21) were female and the incidence of cesarean delivery was 71.2% (n = 42), exceeding the national average rate 35.7% (28.4%–57.7%) [22], with almost half of these due to emergent cesarean delivery (n = 26). Twenty-three babies (38.9%) were born preterm compared to a local preterm rate of 8.8% [23].

Clinical Outcomes

The clinical outcomes are shown in Table 2. At the time of the study, all symptomatic women were hospitalized for observation. Eighty of the 87 women had disease severity ratings; 50 (62.5%) had mild disease, 14 (17.5%) had moderate, 12 (15%) had severe, and 4 (5%) had critical disease. One mother who was admitted 8 days after symptom onset was hospitalized in the intensive care unit (ICU) for 8–14 days and died of COVID-19; her late preterm baby survived. Forty-seven percent of women were admitted for more than a week; the rest had fewer than 7 days of hospitalization. The median days from symptom onset to childbirth was 14 days (25th–75th percentile, 5.5–45.5 days).

Seventeen babies (28.8%) were admitted to the neonatal intensive care unit (NICU). Among infants born from SARS-CoV-2 positive mothers only 1 infant tested positive, a full-term baby who stayed in the mother's hospital room. Fourteen infants required respiratory support. By the end of the study period, most babies (n = 52, 91.2%) were discharged to their home, 4 (7%) remained hospitalized, and 1 died of complications from preterm birth. The reasons for hospitalization of 2 babies after discharge were jaundice and a brief resolved unexplained event.

Maternal Antibody Concentration

Figure 2 shows the distributions of antibody responses, with $\log_{10}$ transformations on the maternal IgG, cord blood IgG, and maternal-cord blood IgG ratio to adjust for skewness. Time from symptom onset was positively correlated with maternal serum IgG concentration ($r = 0.48$, $P = .0002$); days of gestation at hospitalization trended toward a negative correlation with maternal antibody response ($r = -0.26$, $P = .0544$) (Supplemental Figures A and B); and mothers having a college education was associated with maternal IgG (Mann-Whitney test = 1.99, $P = .0464$). However, multiple regression analysis found that only time since symptom onset significantly predicted maternal IgG ($P = .0004$), with the model explaining 22.7% of the variance in IgG (model 1, Table 3). A greater numbers of days between symptom onset and delivery was associated with higher maternal IgG concentrations.

Cord Blood Antibody Concentration

Figure 2 shows the distribution of cord blood IgG concentration. Unlike the maternal IgG, gestational age had no relationship with IgG concentration in umbilical cord blood ($r = 0.06$, $P = .6404$). No socioeconomic variables were detected as significantly related to the log-transformed cord blood IgG concentrations, so only clinical variables were included in a 1-block regression analysis. Cord blood IgG was positively related to time from symptom onset to birth ($P = .0002$) (Supplemental

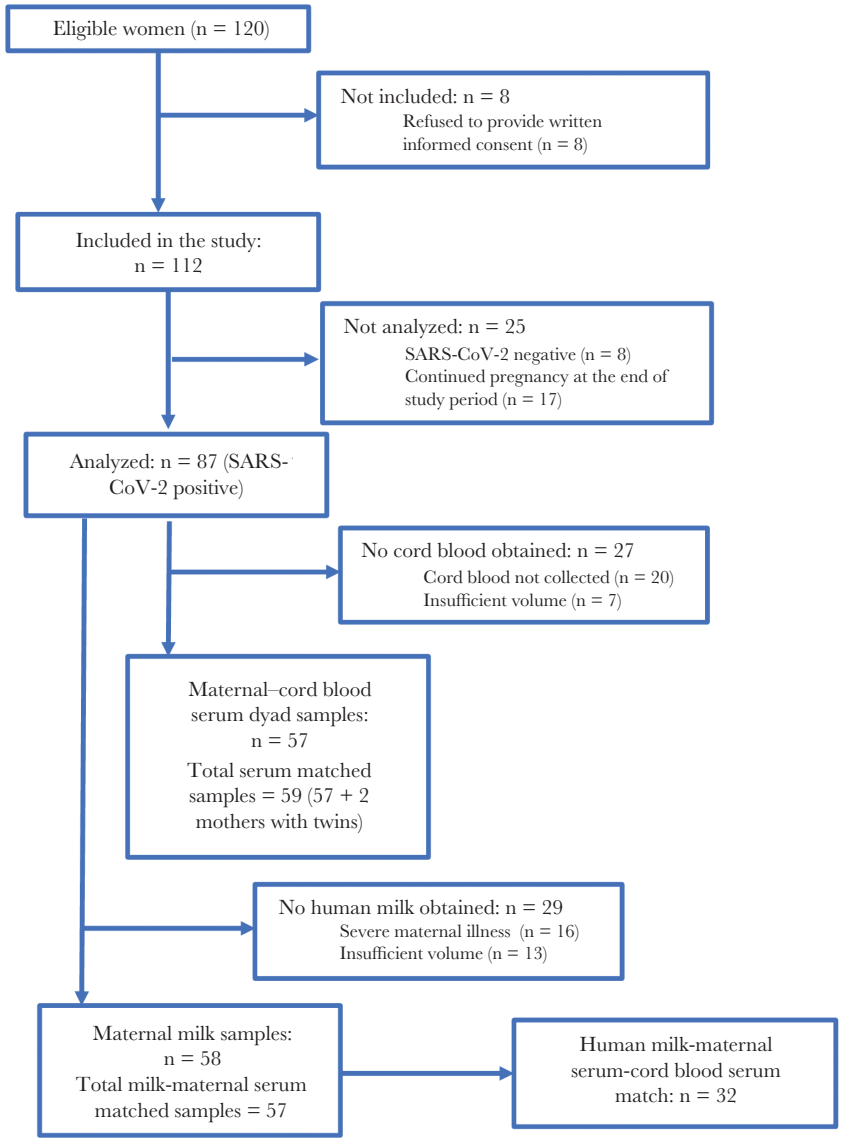

Figure 1. Study flow diagram. Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Figure C) and unrelated to mother's days of gestation at hospitalization ($P = .8485$) (model 2, Table 3). The model explained 23.9% of the variance in umbilical cord blood concentration. The positive regression coefficient suggests that newborns born after a recent maternal infection may carry low protection against SARS-CoV-2 infection.

Maternal-Fetal Antibody Transfer

The efficiency of the placenta in regulating maternal IgG transfer to the fetus is a fundamental biologic variable in neonatal immune protection. Thus, we investigated the ratio of maternal serum IgG levels at childbirth to IgG umbilical cord blood levels as an indication of maternal-fetal antibody transfer ability (Figure 2). Having maternal IgG levels similar to cord blood IgG (a lower mother to baby ratio) is interpreted as better antibody transfer ability. Model 3 Table 3 shows the results of the hierarchical regression analysis. The first block had crowded conditions as the only socioeconomic predictor that was significant in bivariate analysis (Mann-Whitney test = −1.99, $P = .0471$), with the second block consisting of time since symptom onset and gestational age at birth. Longer times since symptom onset trended toward predicting higher ratios of maternal serum IgG to cord blood IgG ratio ($P = .0524$) (Supplemental Figure D). Older gestational ages were associated with lower ratios ($P = .0307$). Although only 7 mothers reported living in crowded conditions, they had lower ratios ($P = .0259$) (Supplemental Figure E). These 3 variables explained 20.4% of the variance in the ratios. Supplemental Table A reflects results without log10 transformations. Overall, these results suggest that placental transfer becomes less efficient with time since infection and may be more efficient close to term gestation.

Table 1. Demographic Characteristics of Mothers (n = 87) and Infants (n = 59)

Characteristic	Value
Mother	
Age, y, median (25th–75th percentile)	30.4 (26.1–34.9)
Ethnicity	
European-Latin	50 (50.0)
European-Other	3 (2.8)
Argentinian native	38 (35.9)
Other	12 (11.3)
Highest education	
Some primary school	7 (8.5)
Completed primary school	22 (26.8)
High school	31 (37.8)
College	22 (26.8)
Obesity	16 (18.4)
Smoked during pregnancy	10 (8.9)
Crowded living conditions	14 (17.5)
Far from hospital	12 (15.8)
No sewage system	13 (16.3)
No running water	13 (16.5)
Unemployed	27 (33.8)
Uninsured	42 (52.5)
Infant	
Female sex	21 (35.6)
Preterm birth	23 (38.9)
Delivery type	
Vaginal	17 (28.8)
Scheduled cesarean delivery	16 (27.1)
Emergency cesarean delivery	26 (44.1)

Data are No. (%) except where indicated.

Percentages were calculated on available data, with number of missing observations ranging from 5 (highest education) to 11 (far from hospital). Percentages may not sum to 100% due to rounding.

Maternal Milk SARS-CoV-2–Specific IgA

RBD-specific IgA was measured in milk samples (Figure 3). Of the 58 samples obtained within 96 hours of childbirth, 51 (87%) had detectable RBD-specific IgA. The distribution of human milk RBD-specific IgA was symmetric without outliers and did not require transformation. SARS-CoV-2 in the milk samples was undetectable by RT-PCR.

Pearson correlation was used to analyze the relationships between milk IgA and (1) maternal serum IgG, (2) cord blood IgG, (3) the ratio of maternal IgG to cord blood IgG, (4) gestational age at birth, (5) time since symptom onset, and (6) maternal age (Figure 4). Maternal IgG serum production and IgA maternal milk presence were positively related ($r = 0.41$, $P = .0016$; Figure 4A). Figure 4B illustrates the nonsignificant relationship between cord blood IgG serum production and IgA maternal milk ($r = 0.16$, $P = .3961$). Human milk IgA was directly correlated with the maternal IgG to cord blood IgG ratio ($r = 0.53$, $P = .0018$; Figure 4C). IgA concentration was unrelated to days since maternal symptoms to childbirth ($r = 0.04$, $P = .7871$; Figure 4E) and maternal age ($r = -0.02$, $P = .8871$; Figure 4F). The sample size was deemed to be too small to support a multiple regression analysis. All analyses were repeated after randomly excluding data from 1 twin within each of the 2 sets. Results were consistent with the complete data set, and so we have reported the original results.

DISCUSSION

In this study 87 pregnant women admitted with COVID-19 were evaluated for variables associated with differential production of virus-specific IgA and IgG. Our study population presented with more severe disease than other cohorts of symptomatic pregnant women [24–26], with 20% having severe or critical disease. Our cohort had higher proportions of preterm birth (38.9%) and cesarean delivery (71.2%) than the national values (8.8% and 35.7%) [27], consistent with reports on COVID-19 during pregnancy [22]. None of the 14 neonates admitted to the NICU needing respiratory support were diagnosed with SARS-CoV-2 infection or pneumonia and all of them were born preterm. This suggests that the reason for respiratory distress was attributable to prematurity-associated lung disease or respiratory distress syndrome.

Although we did not evaluate the SARS-CoV-2 neutralizing capacity of IgG and IgA, several studies have documented a strong correlation between neutralizing antibody titers and RBD-specific antibody titers [28–30]. Like other reports, maternal and fetal antibody concentration was related to time elapsed from infection to delivery.

Maternal IgG is transported across the placenta by an active, neonatal Fc receptor (FcRn)-mediated process during pregnancy. This transport confers short-term passive immunity [31] and protect infants against infections during their first months of life. To design appropriate vaccination strategies, it is important to consider concentrations of IgG transferred from mother to infant during pregnancy and determine the biologic and environmental variables that affect it. We evaluated the efficiency of transfer according to gestational age at the time of birth at a single point in time. In our study, placental IgG antibody transfer was more efficient later in gestation (lower ratio of maternal serum IgG to cord blood IgG) and less efficient earlier in gestation (higher ratio). Our results at first appear to be contrary to results shown by Edlow et al [32]. In that study there was reduced IgG transport in maternal-fetal dyads during the third trimester in pregnant women with COVID-19. The Edlow study analyzed samples from 64 SARS-CoV-2–positive mothers in the United States, of which a third were asymptomatic and only 18% delivered a preterm baby [32]. Although the sample size of both studies is small, it is possible the apparently divergent findings may be reconciled by consideration of the socioeconomic background in both countries and the clinical severity of the disease. As indicated by our study, these factors may explain the differences in placental IgG transfer during gestation. The placental FcRn receptors are known to have differential affinity for the IgG subclasses [33] and IgG subclass

Table 2. Clinical Outcomes

Outcome (n = 87)	Value
Maternal	
No. of weeks' gestation at hospitalization, median (25th–75th percentile)	36 6/7 (32 4/7 to 39 0/7)
Admitted in active labor	8 (6.8)
Disease severity	
Mild	50 (62.5)
Moderate	14 (17.5)
Severe	12 (15.0)
Critical	4 (5.0)
Disposition	
Hospitalization < 1 wk	40 (52.6)
Hospitalization ≥ 1 wk	35 (46.1)
Death	1 (1.3)
Days between symptom onset and delivery, median (25th–75th percentile)	14 (5–45)
ICU days	
0	65 (82.3)
1–7	5 (6.3)
8–14	6 (7.6)
15 +	3 (3.8)
Infant (n = 59)	
NICU admission	17 (28.8)
Supplemental O_2	6 (35.3)[a]
Mechanical ventilation	5 (29.4)[a]
Noninvasive ventilation	3 (17.7)[a]
Disposition	
Home	52 (91.2)
Continued hospitalization	4 (7.0)
Death	1 (1.8)
Delayed cord clamping	49 (86.0)
Feeding, 15 d postdischarge (n = 36)	
Exclusive breast feeding	20 (46.5)
Formula	4 (9.3)
Combination of breast and formula feeding	10 (23.3)
Continued hospitalization	2 (4.7)
Feeding, 30 d postdischarge (n = 29)	
Exclusive breast feeding	14 (48.3)
Formula	3 (10.3)
Combination of breast and formula feeding	11 (37.9)
Continued hospitalization	1 (3.4)
Rehospitalization	2 (3.4)

Data are No. (%) except where indicated. Percentages were calculated on available data; 11 observations were missing from maternal disposition, 2 from infant disposition, 8 from maternal ICU days, 16 observations were missing for feeding 15 days postdischarge, and 30 observations were missing for feeding 30 days postdischarge. Percentages may not sum to 100% due to rounding.

[a]Percentage of the 17 babies admitted to neonatal intensive care unit (NICU).

levels can differ between 2 populations with specific genetic and socioeconomic backgrounds [34]. We speculate that this may explain, in part, the contrasting findings. Our findings reinforce the notion that pregnant women should be immunized as early as possible to allow sufficient time for development of a protective IgG response that can be transferred in utero. In addition, it is key to investigate further into immunologic details of not only the quantity of antibody placental transfer but the function and the influence of vaccination in IgG subclass and the protective consequences to the offspring.

Multiple small studies have demonstrated that human milk from mothers who had previously been infected contained SARS-CoV-2–specific antibodies and that these antibodies were capable of neutralizing the virus [35–37]. Recently, a large prospective study from the Netherlands showed that 524 of 2312 lactating mothers (23.1%) had SARS-CoV-2–specific IgA, with the median age of infants being 34 weeks [38]. Little is known about content and factors that modulate IgA in human milk early after childbirth when neonates are most vulnerable to infections. In our study, 87% of women had presence of IgA within the first 96 hours after

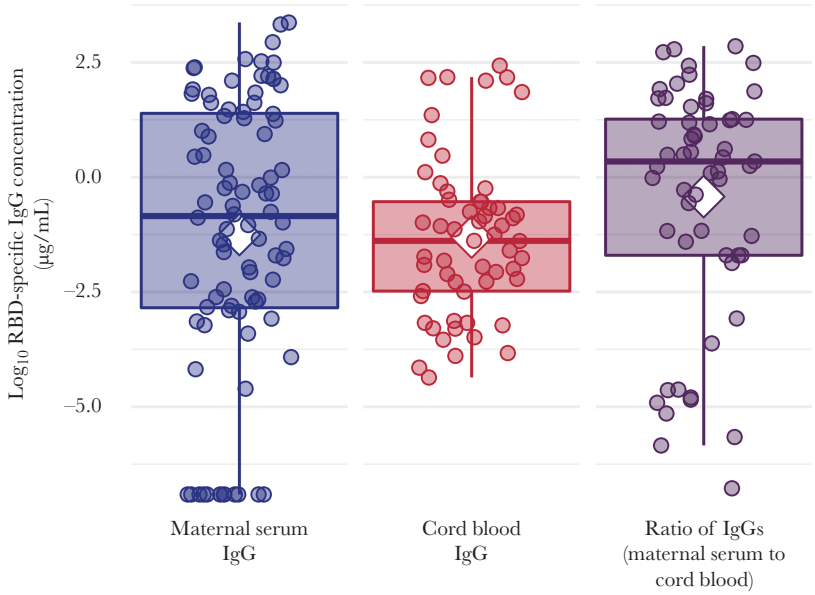

Figure 2. Distributions of antibody responses with log10 transformations to adjust for skewness and random horizontal variation added to points to reduce overlaps. Boxes contain 50% of scores, and any points beyond the whiskers represent outliers. Mother's serum SARS-CoV-2–specific IgG (n = 87), cord blood SARS-CoV-2–specific IgG (n = 59), and mother's and cord blood ratio (n = 59). Means are shown with diamond symbols, and medians are represented by the horizontal lines dividing the boxes. Abbreviations: IgG, immunoglobulin G; RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

childbirth, with higher levels of IgA in milk if children were delivered preterm. Studies on the IgA profile in breast milk from mothers delivering preterm infants have shown inconsistent results, with some showing no difference in total IgA [39] and others showing an elevated concentration [40]. In addition, SARS-CoV-2–specific IgA in milk was not strongly associated with time from infection, suggesting that breastfeeding may be even more important to protect the newborn

Table 3. Multiple Regression Coefficients

	Unstandardized Coefficients			
Model	β	Standard Error	*t*	*P*
Model 1: maternal IgG[a]				
Block 1				
(Constant)	−0.963	0.394	−2.44	.0168
College education	−0.982	0.760	−1.29	.2001
Block 2				
(Constant)	−0.146	2.716	−0.05	.9574
College education	−0.435	0.705	−0.62	.5393
Days since symptom onset	0.043	0.012	3.69	.0004*
Days gestation at hospitalization	−0.008	0.010	−0.79	.4303
Model 1: cord blood IgG[a]				
(Constant)	−2.303	1.833	−1.26	.2144
Days since symptom onset	0.030	0.007	4.00	.0002*
Days gestation at hospitalization	0.001	0.007	0.19	.8485
Model 3: transfer ratio[a]				
Block 1				
(Constant)	−0.023	0.376	−0.06	.9524
Crowding	−1.782	0.994	−1.79	.0793
Block 2				
(Constant)	6.519	3.170	2.06	.0456
Crowding	−2.189	0.950	−2.30	.0259*
Days since symptom onset	0.022	0.011	1.99	.0524
Gestational age at birth	−0.027	0.012	−2.23	.0307*

[a]Log10 transformation applied. *Statistically significant.

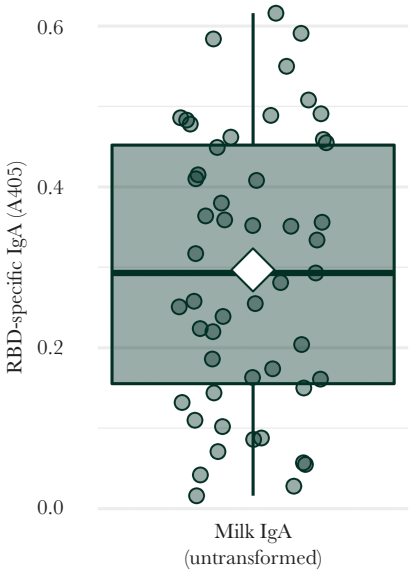

Figure 3. Distribution of RBD-specific IgA from milk samples (n = 51) with random horizontal variation added to points to reduce overlaps. The diamond symbol representing the mean lies on the line representing the median, illustrating the symmetry of the distribution. The box contains 50% of scores, and any points beyond the whiskers represent outliers. Abbreviations: A405, absorbance at 405 nm; IgA, immunoglobulin A; RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

in women who become infected or vaccinated closer to childbirth and lack the necessary time to achieve maternal-fetal antibody transfer.

Lastly, there are limited data reporting on socioeconomic variables that affect maternal-fetal SARS-COV-2 antibody response on pregnant women. Emeruwa et al showed that SARS-CoV-2 transmission among pregnant women in New York City was associated with neighborhood- and building-level markers of large household membership, household crowding, and low socioeconomic status [17]. In our study, women who did not finish college had a higher IgG concentration than women who had a complete college education, but this relationship did not persist when entered in a multiple regression analysis with days since symptom onset and days of gestation at hospitalization predicting maternal IgG. Although crowded living conditions were associated with a lower ratio of maternal serum IgG to cord blood IgG or a more efficient placental antibody transfer, we had only 7 mothers from crowded living conditions in this multivariable analysis. Taking all of this into account, it appears that a vulnerable environmental background may result in higher viral exposure that results in a higher antibody response and, in addition, improved placental antibody transfer that may benefit the newborn immunity.

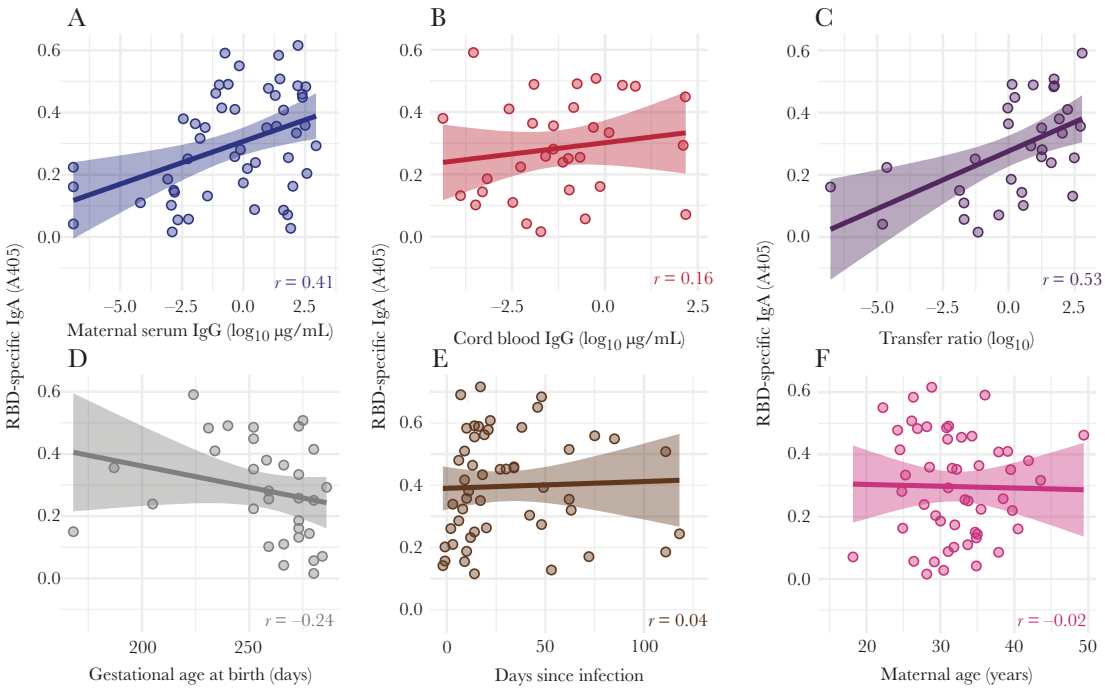

Figure 4. Correlation between human milk SARS-CoV-2–specific IgA and (*A*) maternal IgG (log_{10}), (*B*) baby's IgG (log_{10}), (*C*) transfer ratio (log_{10}), (*D*) gestational age at birth (square root transformation), (*E*) number of days from infection to delivery, and (*F*) maternal age. Human milk IgA was significantly related to (*A*) log_{10} maternal IgG and (*C*) log_{10} transfer ratio, but not (*B*) log_{10} baby's IgG, (*D*) gestational age, (*E*) days since infection, or (*F*) maternal age. Transfer ratio = maternal serum IgG to cord blood IgG. Abbreviations: A405, absorbance at 405 nm; IgA, immunoglobulin A; RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

A larger sample size and multiple postpartum observations would have allowed greater flexibility in assessing more complex models. In addition, longitudinal observations of antibody kinetics in single individuals should enhance the understanding of humoral response in this population. A portion of maternal sera could not be matched with umbilical cord serum due to limited research staff at the height of the pandemic and the ability to be present at childbirth. Ultimately, despite the limitations inherent in small studies, this work has demonstrated the potential effects of socioeconomic factors to explore in large-scale follow-up studies.

The results of this study help us understand the risk of infantile vulnerability and may inform maternal SARS CoV-2 vaccination strategies. In addition, our results confirm the potential for maternally derived SARS-CoV-2–specific antibodies to provide early neonatal protection from COVID-19.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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