Relationship between viral load, infection-to-delivery interval and mother-to-child transfer of anti-SARS-CoV-2 antibodies

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CONTRIBUTION

What are the novel findings of this work?
In pregnant women who have recovered from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, anti-SARS-CoV-2 immunoglobulin G (IgG) concentrations at delivery increased with increasing viral load during infection and decreased with increasing infection-to-delivery interval. The median transplacental transfer ratio of IgG was 1.3 and it decreased with increasing viral load during infection.

What are the clinical implications of this work?
Even though high viral load during SARS-CoV-2 infection is associated with higher concentration of anti-SARS-CoV-2 IgG antibodies in recovered mothers, it affects negatively the transplacental transfer of IgG to the fetuses.

ABSTRACT

Objective To investigate the association of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load and infection-to-delivery interval with maternal and cord serum concentrations of anti-SARS-CoV-2 immunoglobulin G (IgG) antibodies and transplacental transfer ratio in pregnant women with active or recovered SARS-CoV-2 infection.

Methods This was a prospective case series of consecutive pregnant women with laboratory-confirmed SARS-CoV-2 infection between 27 March 2020 and 24 January 2021. We collected information regarding deep throat saliva or nasopharyngeal swab (NPS) reverse transcription polymerase chain reaction (RT-PCR) test results, serial cycle threshold (Ct) values at and after diagnosis, demographic, clinical and outcome data, and neonatal NPS RT-PCR results. Qualitative and quantitative analysis of IgG and immunoglobulin M (IgM) antibodies against SARS-CoV-2 was performed in maternal and cord blood serum samples obtained at delivery. Correlation of maternal Ct values, infection-to-delivery interval, infection duration and viral load area under the curve (AUC) with gestational age (GA) at diagnosis, maternal and cord serum IgG concentrations and transplacental transfer ratio of IgG were evaluated using Pearson’s correlation.

Results Twenty pregnant women who consented to participate and who had delivered their babies by 31 January 2021 were included in the study, comprising 14 who had recovered from coronavirus disease 2019 (COVID-19) and six with active infection at delivery. The median GA at clinical manifestation was 32.7 (range, 11.9–39.4) weeks. The median infection-to-delivery interval and infection duration were 41.5 (range, 2–187) days and 10.0 (range, 1–48) days, respectively. The median GA at delivery was 39.1 (range, 32.4–40.7) weeks and the median seroconversion interval was 14 (range, 1–19) days. Of 13 neonates born to seropositive mothers with recovered infection at delivery, 12

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tested positive for anti-SARS-CoV-2 IgG. All neonatal NPS samples were negative for SARS-CoV-2 and all cord sera tested negative for IgM. The median transplacental transfer ratio of IgG was 1.3 (interquartile range, 0.9–1.6). There was a negative correlation between infection-to-delivery interval and anti-SARS-CoV-2 IgG concentrations in maternal serum and viral load AUC \( (r = -0.6693, P = 0.0087) \) and cord serum \( (r = -0.6554, P = 0.0068) \) serum and a positive correlation between IgG concentration in maternal and cord serum and viral load AUC \( (r = 0.5109, P = 0.0310) \). A negative correlation was observed between transfer ratio and viral load AUC \( (r = -0.4757, P = 0.0409) \).

Conclusions In pregnant women who have recovered from COVID-19, anti-SARS-CoV-2 IgG concentrations at delivery increased with increasing viral load during infection and decreased with increasing infection-to-delivery interval. The median transplacental transfer ratio of IgG was 1.3 and it decreased with increasing viral load during infection. © 2021 International Society of Ultrasound in Obstetrics and Gynecology.

INTRODUCTION

Newborn protection from infection is dependent primarily on the neonatal innate immune response and transplacentally acquired antibodies from the mother. Understanding the dynamics of maternal antibody response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during pregnancy and subsequent transplacental antibody transfer could help inform neonatal management as well as maternal vaccination strategies. There are limited data with regard to the immune status of babies born to mothers who have recovered from coronavirus disease 2019 (COVID-19). In this study, we aimed to investigate the association of SARS-CoV-2 viral load and infection-to-delivery interval with maternal and cord serum anti-SARS-CoV-2 immunoglobulin G (IgG) antibody levels and transplacental transfer ratio in pregnant women with active or recovered SARS-CoV-2 infection.

METHODS

This was a prospective case series of consecutive pregnant women with laboratory-confirmed SARS-CoV-2 infection by reverse transcription polymerase chain reaction (RT-PCR) testing of deep throat saliva (DTS) or nasopharyngeal swab (NPS), between 27 March 2020 and 24 January 2021, who gave written informed consent to participate in the study. Women who tested positive for SARS-CoV-2 at any gestational age and continued the pregnancy beyond 24 weeks’ gestation were included. As per hospital clinical protocols, SARS-CoV-2 infection was assessed using the cycle threshold (Ct) values obtained from the RT-PCR assay of the DTS or NPS samples. The Ct value represents the number of amplification cycles required for the target gene to reach a detectable level. A higher viral load in the sample can be detected in fewer amplification cycles and thus is indicated by a lower Ct value. Ct value ≥35 was defined as a negative result. Approval for the study was obtained from the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (CREC reference number: 2020.210). The study was registered with ClinicalTrials.gov (identifier: NCT044645474).

Demographic, clinical and outcome data, DTS or NPS RT-PCR results, serial Ct values at and after diagnosis, and neonatal NPS RT-PCR results were collected from the medical records of the patients. In all women, a blood sample was obtained at the time of delivery and cord blood was collected immediately after delivery.

Analysis of serum antibodies against SARS-CoV-2 was performed using two serological assays. Qualitative detection of the anti-SARS-CoV-2 antibodies (IgG and immunoglobulin M (IgM)) directed against the nucleocapsid protein (N-protein) of the virus was carried out using the Elecsys® Anti-SARS-CoV-2 assay (Roche Diagnostics, Rotkreutz, Switzerland) on a Cobas® e411 analyzer (Roche Diagnostics). The result was expressed as negative for anti-SARS-CoV-2 antibodies when the cut-off index (COI) was <1.0 and positive for anti-SARS-CoV-2 antibodies when COI was ≥1.0. Quantitative measurement of the IgG and IgM antibodies against the SARS-CoV-2 spike protein (S1) was performed using enzyme linked immunosorbent assays (ELISA) (ImmunoDiagnostics Limited, Hong Kong). All tests were performed in duplicate according to the manufacturer’s instructions. Results were interpreted as negative when the optical density (OD) was <0.2 and as positive when OD was ≥0.2. For samples with a positive result, anti-S1 concentrations (ng/mL) were further calculated.

Continuous variables were expressed as median with interquartile range (IQR) and/or range. Categorical variables were summarized as counts and percentages. Infection duration was determined from the time of manifestation of symptoms or a positive RT-PCR test until a negative RT-PCR test or delivery. Viral load during the infection period was calculated by \( 2^{\Delta C_t} \) values and presented as \( \log_{10} \) copies/mL. We also calculated the viral load area under the curve (AUC), which indicates the total amount of virus shed over the duration of the infection, i.e. the infectiousness and severity of the infection. Transplacental transfer ratio of IgG was calculated as cord serum IgG concentration divided by maternal serum IgG concentration. The correlation of maternal Ct values, infection-to-delivery interval, infection duration and viral load AUC with the gestational age (GA) at diagnosis, maternal and cord serum IgG concentrations and transfer ratio were evaluated using Pearson’s correlation. The statistical software SPSS for Windows version 26 (SPSS Inc., Chicago, IL, USA) was used for data analysis.
RESULTS

Of 33 pregnancies with confirmed SARS-CoV-2 infection, 25 (75.8%) agreed to participate in the study. Of these, two women withdrew from the study because they returned to their home country for delivery, one had a spontaneous miscarriage, one underwent termination of pregnancy for social reasons and one was undelivered at the time of reporting. Therefore, 20 women who delivered their babies by 31 January 2021 were included in the analysis, comprising 14 who had recovered from COVID-19 and six with active infection at delivery. Their median maternal age was 35.5 (IQR, 31.0–38.8) years, the median prepregnancy body mass index was 22.9 (IQR, 21.6–27.1) kg/m² and the median GA at clinical manifestation (development of symptoms or positive RT-PCR test) was 32.7 (IQR, 26.0–35.0; range, 11.9–39.4) weeks. The median GA at delivery was 39.1 (IQR, 37.1–40.1; range, 32.4–40.7) weeks.

The results of the qualitative and quantitative methods for detection of anti-SARS-CoV-2 antibodies were concordant in all cases. In total, 15 (75%) women were seropositive at delivery, of which two had active infection (median anti-SARS-CoV-2 IgG, 299.1 (IQR, 291.6–306.5) ng/mL) and 13 had recovered from SARS-CoV-2 infection at delivery (median anti-SARS-CoV-2 IgG, 295.5 (IQR, 37.1–40.1; range, 32.4–40.7) weeks. The median infection-to-delivery interval was 14 (IQR, 7.5–17.0; range, 1–19) days. The median seroconversion interval and infection duration were 41.5 (IQR, 8.0–100.25; range, 2–187) days and 10.0 (IQR, 4–20; range, 1–48) days, respectively. The median GA at delivery was 39.1 (IQR, 37.1–40.1; range, 32.4–40.7) weeks.

The cord serum and maternal serum IgG concentrations at delivery were positively correlated ($r = 0.68$, $P < 0.001$) (Figure 2). There was a negative correlation between infection-to-delivery interval and anti-SARS-CoV-2 IgG concentrations in maternal ($r = -0.63$, $P = 0.04$) and cord serum ($r = -0.59$, $P = 0.04$) (Figure 3b). A positive correlation was observed between IgG concentrations in maternal serum and viral load AUC ($r = 0.51$, $P = 0.03$) (Figure 3d). In addition, a significant negative correlation was noted between transplacental transfer ratio and viral load AUC ($r = -0.46$, $P = 0.04$) (Figure 4d).

DISCUSSION

Our findings demonstrate that, in pregnant women who have recovered from COVID-19, the higher the viral load during infection and the shorter the infection-to-delivery interval, the higher is the anti-SARS-CoV-2 IgG concentration in maternal serum at delivery. The median transplacental transfer ratio of anti-SARS-CoV-2 IgG was 1.3 and it decreased with increasing viral load AUC. Similar to most pathogens, maternal infection with SARS-CoV-2 leads to higher concentration of IgG in umbilical cord serum than in maternal blood. Our observation that the transfer ratio of anti-SARS-CoV-2 IgG decreases with increasing viral load is in agreement with the findings of Atyeo et al. who reported that maternal SARS-CoV-2 infection reduces transplacental transfer of SARS-CoV-2 receptor-binding-domain-specific, spike-specific and nucleocapsid-specific antibodies. However, we did not find reduced transplacental transfer of anti-SARS-CoV-2 IgG in pregnancies with third-trimester
Transplacental transfer of anti-SARS-CoV-2 antibodies

Figure 3 Correlation between anti-SARS-CoV-2 immunoglobulin G (IgG) concentration at delivery in serum of 12 seropositive mothers (Δ: ---) and matched cord blood serum of their seropositive newborns (●: ---) and: (a) maternal cycle threshold (Ct) values at diagnosis (mothers: \( r = -0.2633, P = 0.2042 \); newborns: \( r = -0.2030, P = 0.2635 \)); (b) infection-to-delivery interval (mothers: \( r = -0.6693, P = 0.0087 \); newborns: \( r = -0.6554, P = 0.0068 \)); (c) infection duration (mothers: \( r = 0.3812, P = 0.1245 \); newborns: \( r = 0.3792, P = 0.0952 \)); and (d) viral load area under the curve (AUC) (mothers: \( r = 0.5109, P = 0.0310 \); newborns: \( r = 0.3798, P = 0.1117 \)).

Figure 4 Correlation between transplacental transfer ratio of anti-SARS-CoV-2 immunoglobulin G (IgG) in 12 mother/newborn dyads and: (a) gestational age at diagnosis of SARS-CoV-2 infection (\( r = -0.1608, P = 0.3088 \)); (b) infection-to-delivery interval (\( r = 0.1823, P = 0.2853 \)); (c) infection duration (\( r = -0.3335, P = 0.1447 \)); and (d) viral load area under the curve (AUC) (\( r = -0.4757, P = 0.0409 \)).
infection but rather that the transfer ratio was constant across GA at diagnosis. It is unclear whether the compromised transfer of SARS-CoV-2-specific antibodies during third-trimester infection, reported by Atyeo et al., is related to the infection status of the patients, i.e. active infection vs recovered.

In contrast to the findings of Flannery et al. who demonstrated, based on 72 mother/newborn dyads who were seropositive at delivery, that the transfer ratio of anti-SARS-CoV-2 IgG correlated positively with the interval between onset of infection and delivery, we did not find a significant change in transplacental transfer ratio with increasing infection-to-delivery interval. Our study additionally evaluated the effect of viral load on transplacental IgG transfer and showed that, even though a high viral load leads to higher concentrations of anti-SARS-CoV-2 IgG antibodies in mothers, it affects negatively the transplacental transfer of IgG to the fetuses. The transplacental transfer of IgG in pregnancies with SARS-CoV-2 infection is related to trophoblast Fc glycosylation and FCGR3A expression. Our findings raise the question regarding the potential impact of vaccine-induced immune response on mother-to-baby transfer of anti-SARS-CoV-2 IgG. There is an urgent need to generate clinical data on the efficacy and safety of the different available COVID-19 vaccines in pregnant women, as well as to determine the vaccine technology and timing of vaccination which can deliver the maximum potential benefits to pregnant women and their babies.

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