Assessment of timing of transplacental antibody transfer after SARS-CoV-2 vaccination against the Omicron variant: A prospective cohort study

Chia-Jung Chiang[1], Wei-Lun Hsu[1], Meitsz Su[1], Wen-Chien Ko[1], Keng-Fu Hsu[1], and Pei-Yin Tsai[1]

[1]National Cheng Kung University Hospital

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Abstract

Objective To determine the optimal timing of SARS-CoV-2 vaccination during pregnancy by investigating the transplacental transfer of SARS-CoV-2 antibodies from maternal SARS-CoV-2 vaccination or infection. **Design** Prospective cohort study **Setting** Samples were collected between June 6, 2022 and September 20, 2022 in Taiwan. **Sample** Seventy-five maternal-cord pairs, including 38 pairs with a primary maternal SARS-CoV-2 infection by the Omicron variant (BA.2.3.7) and 37 pairs without maternal infection. **Methods** SARS-CoV-2 antibodies against the nucleocapsid (anti-N), receptor-binding domain of the spike protein (anti-S), and the neutralizing antibody (nAb) titers against different SARS-CoV-2 variants were measured for the maternal-cord pairs. The participants were categorized based on the timing of their last vaccination, including during the third (T3) and second trimesters (T2) and before/during the first trimester (T1). Comparison of anti-spike protein antibody and neutralizing antibody concentrations was analyzed using the Kruskal-Wallis test followed by a post-hoc Mann-Whitney U test. **Main Outcome Measures** Anti-S concentrations of maternal and cord serum among T1, T2, and T3 groups. **Results** Among participants without SARS-CoV-2 infection, the highest anti-S levels (p value for anti-S levels in maternal and cord plasma were <0.001 and <0.001, respectively) and highest nAb potency against both the Wuhan and Omicron strains (p value for nAb against Omicron strain were both <0.001 for maternal and cord plasma) were observed in maternal and cord plasma in the T3 group. **Conclusions** A booster vaccine dose during the third trimester can provide maximum transplacental protection against the Wuhan wild-type strain and Omicron variant. Pregnant women are encouraged to receive vaccinations during pregnancy, ideally in the third trimester, for the highest level of neonatal protection.

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Chia-Jung Chiang, MD[*1]; Wei-Lun Hsu, MD[*1]; Mei-Tsz Su, MD, PhD[1] Wen-Chien Ko, MD[2,3]; Keng-Fu Hsu, MD, PhD[1]; Pei-Yin Tsai, MD[1]

[*] Chia-Jung Chiang and Wei-Lun Hsu contributed equally to this paper.

[1] Department of Obstetrics and Gynecology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

[2] Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

[3] Center for Infection Control, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

*** Correspondence to: Pei-Yin Tsai, MD**

Department of Obstetrics and Gynecology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

Address: 138 Sheng-Li Road, Tainan, Taiwan 704, ROC

Phone numbers: +886-6-2353535 (5221)

E-mail address: tsaipy@ncku.edu.tw

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Disclosure of interest

The authors have declared no conflicts of interest.

Contribution to Authorship

CJC involved in conceptualization, methodology, and writing the original draft, which was reviewed and critically revised by all authors. WLH involved in analysis and visualization. PYT involved in conceptualization, validation, review of manuscript, and funding acquisition. MTS, WCK, KFH involved in resources and review of manuscript. All authors approved the final manuscript as submitted.

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Details of Ethics Approval

The study was approved by the Institutional Review Board of NCKUH (IRB: B-ER-111-164), and all the participants provided informed consent.

Abstract

Objective

To determine the optimal timing of SARS-CoV-2 vaccination during pregnancy by investigating the transplacental transfer of SARS-CoV-2 antibodies from maternal SARS-CoV-2 vaccination or infection.

Design

Prospective cohort study

Setting

Samples were collected between June 6, 2022 and September 20, 2022 in Taiwan.

Sample

Seventy-five maternal-cord pairs, including 38 pairs with a primary maternal SARS-CoV-2 infection by the Omicron variant (BA.2.3.7) and 37 pairs without maternal infection.

Methods

SARS-CoV-2 antibodies against the nucleocapsid (anti-N), receptor-binding domain of the spike protein (anti-S), and the neutralizing antibody (nAb) titers against different SARS-CoV-2 variants were measured for the maternal-cord pairs. The participants were categorized based on the timing of their last vaccination, including during the third (T3) and second trimesters (T2) and before/during the first trimester (T1).

Comparison of anti-spike protein antibody and neutralizing antibody concentrations was analyzed using the Kruskal-Wallis test followed by a post-hoc Mann-Whitney U test.

Main Outcome Measures

Anti-S concentrations of maternal and cord serum among T1, T2, and T3 groups.

Results

Among participants without SARS-CoV-2 infection, the highest anti-S levels (p value for anti-S levels in maternal and cord plasma were <0.001 and <0.001, respectively) and highest nAb potency against both the Wuhan and Omicron strains (p value for nAb against Omicron strain were both <0.001 for maternal and cord plasma) were observed in maternal and cord plasma in the T3 group.

Conclusions

A booster vaccine dose during the third trimester can provide maximum transplacental protection against the Wuhan wild-type strain and Omicron variant. Pregnant women are encouraged to receive vaccinations during pregnancy, ideally in the third trimester, for the highest level of neonatal protection.

Keywords

SARS-CoV-2 vaccine, COVID-19, Omicron, Pregnancy, Transplacental antibody transfer

Introduction

The global outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019 has been a worldwide concern. Taiwan, being an isolated island in East Asia, had a low incidence of SARS-CoV-2 infection until 2020.(1, 2) In Taiwan, the pandemic surged in April 2022 with the Omicron variant (BA.2.3.7) being identified as the major lineage.(3)

Pregnant individuals are encouraged to receive the SARS-CoV-2 vaccine because of the higher risk of adverse outcomes, such as death, intubation, admission to an intensive care unit, preterm birth, preeclampsia, venous thromboembolism, and other severe comorbidities.(4-6) The safety of SARS-CoV-2 vaccination during pregnancy has been supported by current evidence.(7, 8)

Newborns have immature immune systems and are vulnerable to infectious diseases. Neonatal passive immunity mainly depends on the maternal concentration of respective antibodies for most viral diseases.(9) Low or early disappearance of maternal-derived antibody concentrations can lead to insufficient protection for newborns. Maternal-derived, vertically transferred immunity provides protection for newborns against vaccine-preventable infectious diseases, such as measles, mumps, and rubella, which cannot be administered to infants before 12 months.(10) Similarly, no SARS-CoV-2 vaccine is currently available for newborns. For the window period before routine vaccination of the newborn, passive immunization for neonates from vertical transmission can be present for up to six months.(11)

Transplacental transfer of SARS-CoV-2 antibodies, specifically against the receptor binding domain (RBD) of the spike protein (anti-S) and nucleocapsid antigen (anti-N), has been observed in previous studies of both infected pregnant individuals and those vaccinated against COVID-19.(12-17) However, the relationship between the timing of vaccination or infection and transplacental antibody transfer is unclear.

Given that newborn protection from infectious diseases depends on antibodies acquired transplacentally,(9) we investigated the timing of transplacental passage of SARS-CoV-2 antibodies through vaccines and maternal infections. We focused on a specific, highly vaccinated pregnant population with or without SARS-CoV-2 infection, solely by the Omicron strain.

Methods

A prospective cohort study was conducted at the National Cheng Kung University Hospital (NCKUH), a medical center in Southern Taiwan, between June 6, 2022 and September 20, 2022. Eligible participants

included the following: pregnant women who delivered at the NCKUH; women with or without a primary SARS-CoV-2 infection officially reported to the Central Epidemic Command Center (CECC) of Taiwan; women with cord blood sample available upon delivery and maternal blood sample available within three days from delivery; and participants who provided informed consent. Our study population did not have a second SARS-CoV-2 infection.

The participants were categorized based on the timing of their last vaccination, including during the third trimester (T3), second trimester (T2), and before and during the first trimester (T1). The diagnosis of SARS-CoV-2 was confirmed by real-time polymerase chain reaction (RT-PCR) or antigen testing of respiratory tract specimens, according to the guidelines of the CECC of Taiwan. The study was approved by the Institutional Review Board of NCKUH (IRB: B-ER-111-164), and all the participants provided informed consent.

Clinical and laboratory data were collected using questionnaires and electronic medical records. Cord blood was obtained from the umbilical cord immediately after delivery. Blood samples were centrifuged at 1000 g for 10 min at room temperature, and plasma samples were aliquoted into dedicated pre-coded tubes and stored at –80°C until analysis.

Serological Testing

Severe acute respiratory syndrome coronavirus 2 antibody levels were measured in the maternal and fetal cord plasma using the Elecsys Anti-SARS-CoV-2 and Anti-SARS-CoV-2 S kits (Roche Diagnostics, Switzerland). Immunoglobulin M and G antibodies against the nucleocapsid (anti-N) and receptor-binding domain of the spike (anti-S) of SARS-CoV-2 were detected. The cut-off for positivity was [?]1.0 or the anti-N assay and [?]0.8 U/mL for the anti-S_RBD assay. The value of the anti-S_RBD assay between 0.4–250 U/mL represents the linear range, and samples >250 U/mL were diluted with a Diluent Universal provided by the kit. The cPass^{TM} surrogate virus neutralization test (GenScript Biotech Corp., USA) was conducted to measure neutralizing antibody (nAb) titers against different SARS-CoV-2 variants. Ninety-six-well plates coated with recombinant hACE2 and recombinant S-RBD from Wuhan and Omicron BA.2 variants were used in the experiments, according to the manufacturer's instructions. An inhibition percentage [?]30% was considered seropositive for SARS-CoV-2 nAbs. Additionally, the percent inhibition of the Wuhan strain was converted to IU/mL using a previously proposed formula.(18)

Statistics

Differences between participants with and without SARS-CoV-2 infection were analyzed using the Mann-Whitney U and chi-square tests with a two-sided P value. Demographic variables and antibody responses were also evaluated. Continuous outcome measures are summarized as median and interquartile range (IQR), and antibody concentrations were log10-transformed for the analysis. A P value of <0.05 was considered significant.

The comparison of anti-S antibody and neutralizing antibody concentrations was analyzed using the Kruskal-Wallis test followed by a post-hoc Mann-Whitney U test. Statistical analysis was conducted using SPSS version 28 and Prism version 7 (GraphPad). Temporal relationships between antibody concentrations were plotted as quadratic curves using a polynomial regression approach.

Results

Between June 6, 2022 and September 20, 2022, there were 89 women admitted to the NCKUH Maternal Unit for delivery. Of these, 46 were either previously diagnosed with SARS-CoV-2 infection during pregnancy or had a positive nasopharyngeal RT-PCR test result upon admission. Of the 46 women with SARS-CoV-2 infection, 42 had paired maternal and cord blood samples available for the analysis. Four women without SARS-CoV-2 vaccination had negative maternal plasma anti-S antibody levels; therefore, they were not eligible for further analysis of transplacental antibody transfer and were excluded from the SARS-CoV-2 infection group. Of the 89 women, 43 had no history of SARS-CoV-2 infection and had negative nasopharyngeal RT-PCR test results upon admission with paired maternal and cord blood samples. Six

women were excluded from the SARS-CoV-2 negative group due to reactive anti-N antibody levels, which indicated a possible previous asymptomatic SARS-CoV-2 infection without documentation. Ultimately, 75 maternal-cord pairs were enrolled for analysis, including 38 pairs from the SARS-CoV-2 infection group and 37 pairs from the SARS-CoV-2 negative group (Fig. S1).

Demographic, obstetric, and clinical characteristics of the participants are summarized in Table 1. The median ages of the participants in the SARS-CoV-2 and SARS-CoV-2 negative group were 32.5 (IQR, 29.75–38) and 34 (IQR, 30–37), respectively. Both groups had similar profiles in terms of body mass index (BMI), gravidity, and gestational age at birth. Cesarean section rate was higher in the SARS-CoV-2 negative group (49% vs. 21%, p=0.012).

Both groups had similar vaccination profiles, and all the participants included in the analysis received a vaccine. Approximately 60% of the patients from both groups (58% in the SARS-CoV-2 group and 60% in the non-SARS-CoV-2 group) were fully vaccinated with a primary series plus one booster dose. Most of the patients (58% in the SARS-CoV-2 group and 62% in the non-SARS-CoV-2 group) received various types of vaccines, including mRNA (NT162b2, Pfizer/BioNTech, or mRNA-1273, Moderna), viral vector (ChAdOx1 nCoV-19, Oxford-AstraZeneca), and protein subunit (MVC-COV1901, Medigen) vaccines. The difference in median intervals from the last vaccination to delivery was not significant with median intervals of 125 days in the SARS-CoV-2 group and 105 days in the non-SARS-CoV-2 group (p=0.824). (Table 1)

The participants were categorized based on the timing of their last vaccination: during the T3, T2, and before/during the T1 (Fig. 1). The highest concentration of maternal and cord plasma anti-S antibodies was observed in the T3 group among all the participants (median 10627.5 U/mL, IQR 6102.75–18021.5 U/mL in maternal plasma; median 16082.5, IQR 10805.5–19823.75 U/mL in cord plasma; p<0.001 and <0.001, respectively) (Fig. 1A). For the SARS-CoV-2 negative pregnant women, the anti-S titer was significantly higher in the T3 group (median 10442 U/mL, IQR 9535–13033 U/mL for maternal plasma; median 14999 U/mL, IQR 12085–19042 U/mL for cord plasma; p<0.001 and <0.001, respectively) than in the T1 (median 578.5 U/mL, IQR 160.25–6425 U/mL for maternal plasma; median 576.1 U/mL, IQR 184–3757 U/mL for cord plasma) and T2 (median 4565 U/mL, IQR 1749–10213.25 U/mL for maternal plasma; median 6017 U/mL, IQR 3838.75–11717.25 U/mL for cord plasma) groups (p<0.001 for maternal plasma and <0.001 for cord plasma) (Fig. 1B). However, the significance of vaccine timing on both maternal and cord plasma anti-S titer was diminished when comparing the SARS-CoV-2 positive T1, T2, and T3 groups (Fig. 1C), which emphases the effect of recent infection on the anti-S titer. (Table S1)

The nAbs response at different times after the last vaccination were similar to those of anti-S antibodies. Maximum neutralizing responses against both the Wuhan wild-type strain and Omicron variant were found in the maternal and cord sera of the T3 group (Fig. 1D, 1G). The neutralizing responses of the SARS-CoV-2 vaccine against the Omicron variant were more pronounced in the SARS-CoV-2 negative participants, and the neutralizing responses increased significantly across the T1, T2, and T3 groups (T3 group of cord sera with median 98.15%, IQR 98.04–98.22% for the Wuhan strain; median 88.94, IQR 79.36–91.98% for the Omicron strain; p <0.001) (Fig. 1E, 1H). However, the nAb response rates in both maternal and cord sera were not significant for participants with SARS-CoV-2 infection across the T1, T2, and T3 groups (Fig. 1F, 1I). (Table S2)

The levels of maternal and cord serum anti-S antibody concentrations increased significantly seven days after SARS-CoV-2 infection (Fig. S2) (Table S3) and peaked around 50 days from the day of the last vaccination (Fig 2A) or SARS-CoV-2 infection (Fig. 2B). Delayed peaks and declines were observed in the cord sera of both groups. The anti-S antibodies were measurable in maternal and cord sera up to one year after the last vaccination (Fig. 2A). A delayed appearance of anti-N antibody in cord sera was also found following SARS-CoV-2 diagnosis. While the anti-N antibodies were detected in 5 out of the total 46 maternal serum samples within 7 days from diagnosis, a delayed response was observed in cord serum, with a rise in anti-N antibodies not observed until 18 days after SARS-CoV-2 diagnosis. (Figure S3)

The transplacental transfer ratio (TR), which was calculated as the cord serum antibody concentration

divided by the maternal serum antibody concentration measured the transplacental transfer of antibodies. Time variable was presented as the time interval from delivery to the last antigen exposure, either the last vaccination or infection, which ever occurred last. The TRs of anti-S from the post-infection and non-infection groups and anti-N from the post-infection group showed a similar linear correlation with the time variable before 100 days (Fig. 3). The TRs peaked at approximately 100 days, reaching as high as 3–4, then plateaued at approximately 1–2 after 150 days.

Discussion

Main Findings

Our study has shown that a booster dose of the SARS-CoV-2 vaccine during the third trimester can help achieve maximum transplacental protection against SARS-CoV-2.

Strengths and Limitations

Our study presents some significant advantages. First, the study population was unique in that it enabled us to analyze only patients infected with the Omicron variant and without any previous SARS-CoV-2 exposure. Second, our study cohort of pregnant women differed from those of previous studies with an extremely high rate (95.5%) of vaccine coverage. (7) All of the included 85 pregnant women had received one or more vaccinations. Third, a clear temporal relationship was established between maternal and cord serum antibodies. Both the timing of maternal SARS-CoV-2 infection and maternal SARS-CoV-2 vaccination were well documented in all our included cases. Fourth, a similar rising trend in the TR was observed in both the anti-S and anti-N from vaccinated or infected maternal-fetal pairs, suggesting that the previously proposed lower TRs in the third trimester or in infected individuals may be influenced by time. Lastly, our results showed that mothers and newborns would receive the greatest protection at birth if the mother received her last vaccination during the third trimester, as indicated by maternal and cord serum anti-S antibody levels and neutralizing antibodies.

However, our study has some limitations. The sample size was relatively small, and data on serial follow-up of antibody titers were not available; therefore, we could not address the dynamic changes in antibody titers in individuals. Additionally, maternal-acquired passive immunity includes not only immunoglobulin but also cellular responses, such as the vertical transfer of pathogen-specific T cells.(9) Our focus was solely on the measurable immunoglobulin titer from maternal and cord serum. Further research that specifically examines cellular level and on functional activity may provide additional insights into the neonatal immunity.

Interpretation

The safety of SARS-CoV-2 vaccination during pregnancy has been established in current short-term reports.(7, 8) Despite this, more than 50% of pregnant women have reported hesitancy towards COVID-19 vaccination,(19, 20) and the coverage rate among this population is only approximately 30–50%.(7, 21)

Our study focused on a highly vaccinated pregnant population, where only four out of 89 participants were unvaccinated and excluded from the analysis. Seventy-two participants received one or more vaccinations during pregnancy, and half of them completed the primary series with a booster dose. All the participants received first-generation vaccines designed for the Wuhan strain.

Participants with and without SARS-CoV-2 infection showed similar characteristics in terms of vaccination history and type. Our high vaccination coverage rate allowed for a focused analysis of the effects of vaccination and infection in the pregnant population. Other characteristics, including gestational age, maternal general condition, comorbidities, patient age, and BMI, were similar between the two groups. The cesarean rates differed because our hospital serves as a tertiary center where patients without SARS-CoV-2 infection were mostly admitted because of high-risk pregnancy.

The timing of vaccination is a critical factor that affects the level of cord serum antibodies, particularly in pregnant individuals without prior SARS-CoV-2 infection. Previous reports have demonstrated the safety of SARS-CoV-2 vaccination during the third trimester and its ability to reduce the risk of neonatal adverse

outcomes.(7) However, optimal trimester for maternal vaccination remains a topic of discussion due to limited cord samples and follow-up intervals in previous studies.(22) Our study, on the other hand, revealed that neonates born to mothers who received a booster dose of SARS-CoV-2 vaccine during the third trimester, especially those without prior SARS-CoV-2 infection, had the highest level of cord serum anti-S concentration (Fig. 2) and the most effective protection against both Wuhan and Omicron strains. (Fig. 3)

In the immunocompetent general population, anti-S and anti-N antibodies appear 8–14 days after the onset of symptoms.(23) In our study, delay in the elevation of cord serum anti-S antibody levels was also observed in comparison to maternal serum levels, both following vaccination and infection. Our study found that the transmission ratios of both anti-S and anti-N in maternal-fetal pairs had a comparable association with the time variable, up to 150 days from the last vaccination or infection. Previous observations of a negative correlation between transmission ratios and viral load (12, 24) may be attributed to the decline in viral load over time. Based on these findings, we can conclude that recent SARS-CoV-2 infection may induce a booster vaccine-like effect on antibody titers in pregnant women and their fetuses. Furthermore, our study suggests that the interval between antigen exposure and blood sampling may be the primary determinant of the transplacental antibody transmission ratio.

Our results are consistent with previous experience with the combined tetanus-diphtheria-pertussis vaccine. Tetanus-diphtheria-pertussis immunization 8–12 weeks prior to delivery provides newborns with the highest antibody titer,(25) similar to the suggestion for optimal timing of SARS-CoV-2 vaccination in the third trimester. We believe that our results can be replicated for future variants of the SARS-CoV-2.

Conclusion

Our findings showed that the level of antibody peaked at two months after either vaccination or infection, and a booster-like effect was observed following a recent SARS-CoV-2 infection. Our results suggest that a booster dose of the vaccine during the third trimester can provide maximum transplacental protection against both the Wuhan wild-type strain and Omicron variant. Based on these results, we encourage pregnant women to receive vaccination during pregnancy with a focus on the third trimester for optimal protection.

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Conflicts of interest

The authors have declared no conflicts of interest.

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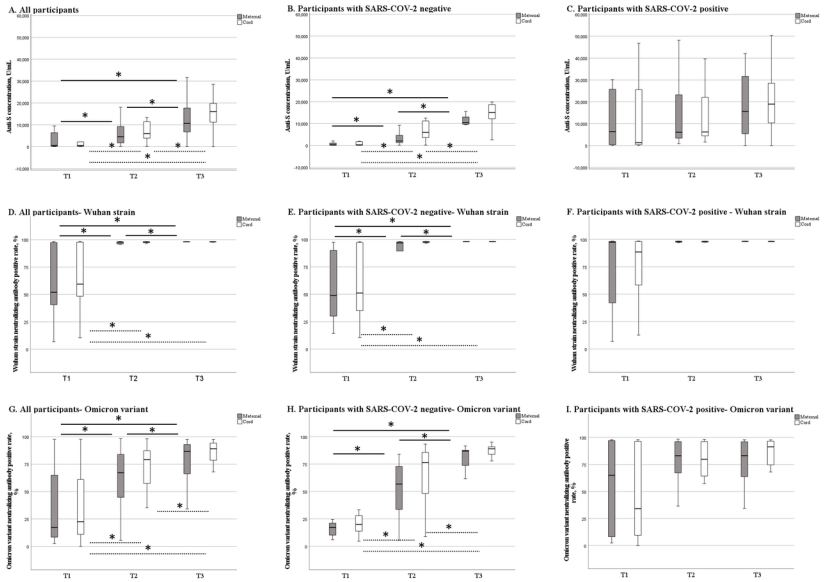

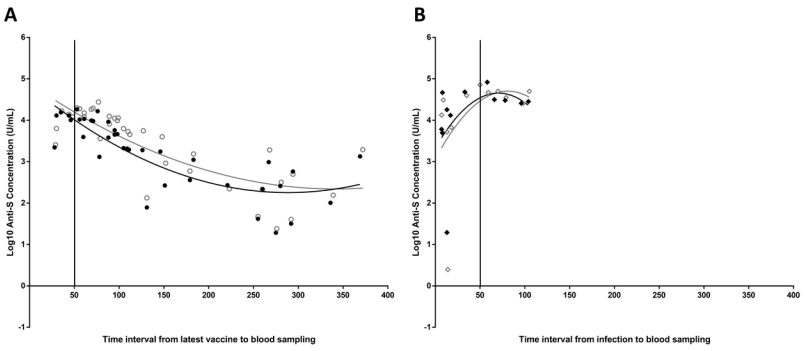

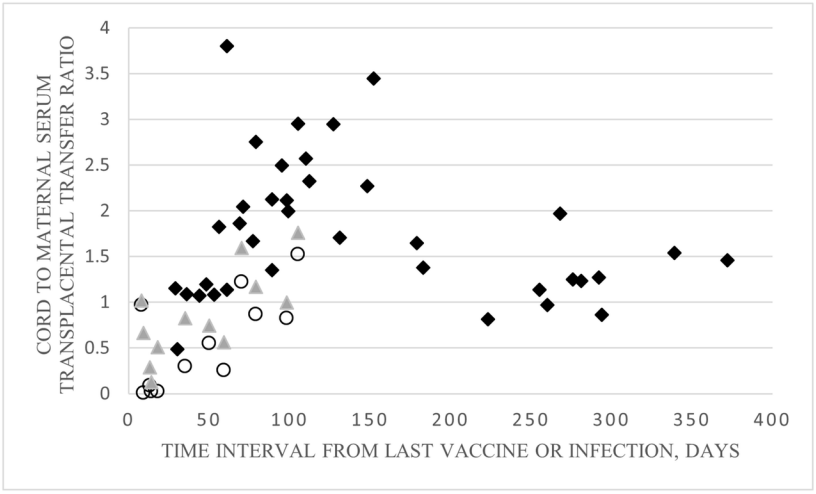

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Fig. 1 Box Plot Showing Anti-S Antibody Concentration and Neutralizing Antibody Response Rate Against the Wuhan Strain and Omicron Variant in Participants Receiving Latest Vaccine Dose During Different Trimesters

(A) Concentration of maternal and cord blood anti-S antibody in all participants. **(B)** Concentration of maternal and cord blood anti-S antibody in participants with SARS-CoV-2 negative. **(C)** Concentration of maternal and cord blood anti-S antibody in participants with SARS-CoV-2 positive. **(D)** Concentration of maternal and cord blood neutralizing antibodies against Wuhan strain in all participants. **(E)** Concentration of maternal and cord blood neutralizing antibodies against Wuhan strain in participants who were SARS-CoV-2 negative. **(F)** Concentration of maternal and cord blood neutralizing antibodies against Wuhan strain in participants who were SARS-CoV-2 positive. **(G)** Concentration of maternal and cord blood neutralizing antibodies against Omicron variant in all participants. **(H)** Concentration of maternal and cord blood neutralizing antibodies against Omicron variant in participants who were SARS-CoV-2 negative. **(I)** Concentration of maternal and cord blood neutralizing antibodies against Omicron variant in participants who were SARS-CoV-2 positive. Significance was determined using the Mann-Whitney U test. *$p<0.05$

T1, before pregnancy and during first trimester; T2, during second trimester; T3, during third trimester; *SARS-COV-2,* severe acute respiratory syndrome coronavirus 2

Fig. 2 Scatter Plot Presenting Correlation Between the Time Interval from Latest Vaccine or Infection to Blood Sampling and Log10 Transformed Maternal and Cord Blood Anti-S Concentration

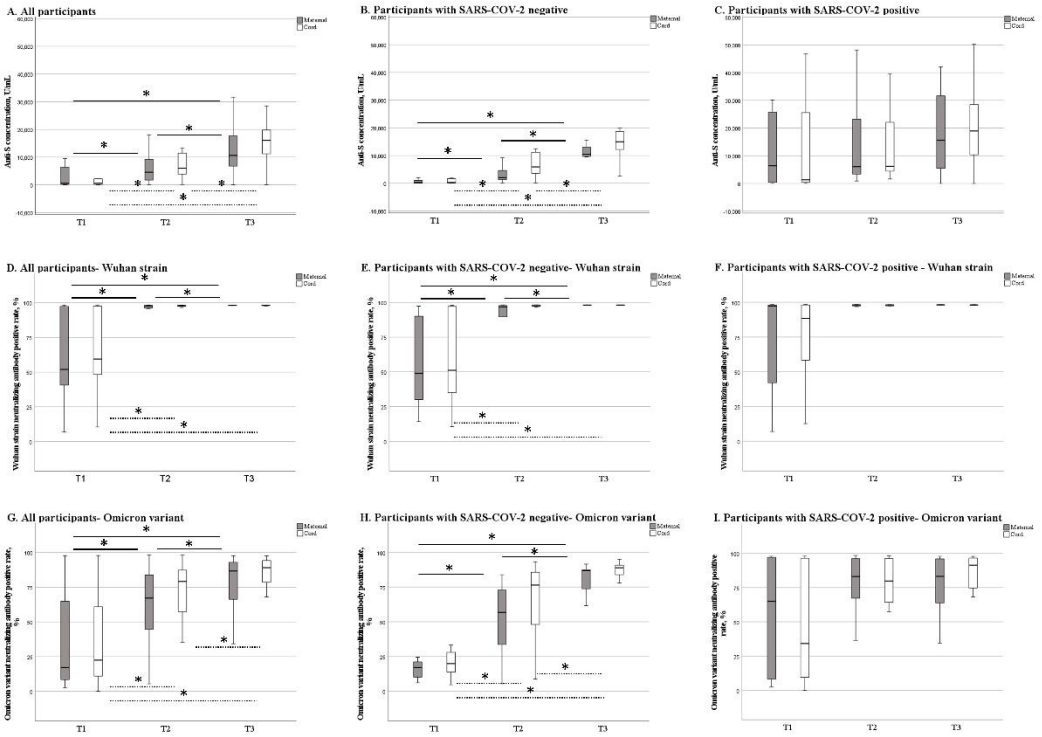
(A) Correlation between the time interval from latest vaccine dose to blood sampling and log10 transformed maternal blood (●) and cord blood (○) anti-S concentration in participants with SARS-COV-2 negative (n=37).

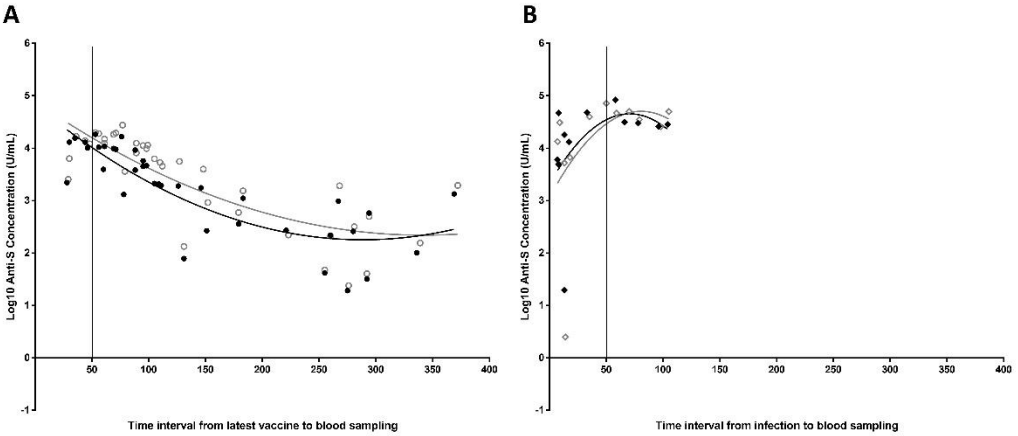
(B) Correlation between the time interval from infection to blood sampling and log10 transformed maternal blood (◆) and cord blood (◇) anti-S concentration in participants with SARS-CoV-2 positive >7 days (n=12).

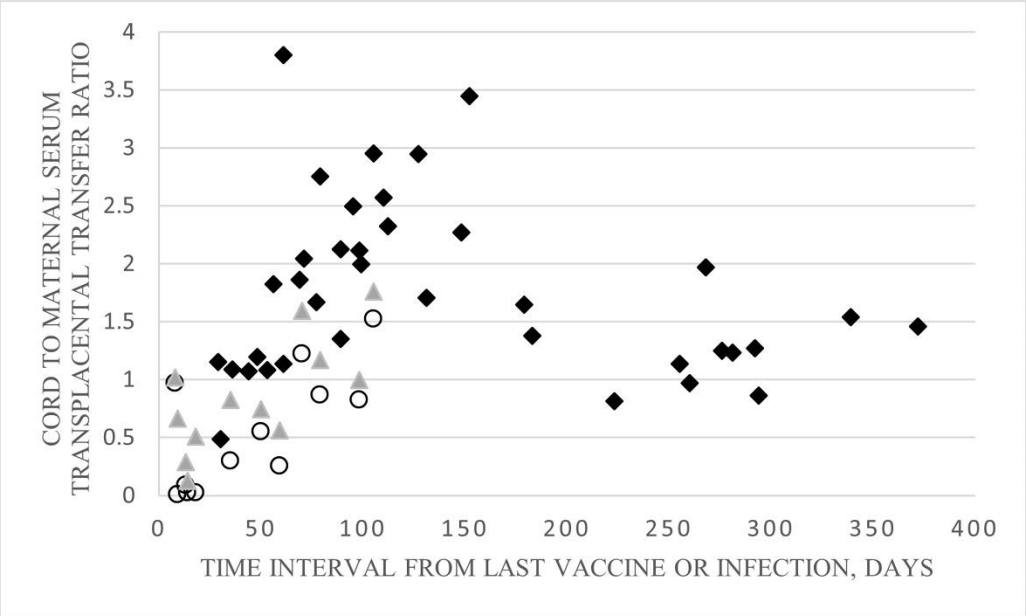
Fig. 3 Scatter Plot Presenting the Correlation of Time Interval from Last Vaccine or Infection and Transplacental Transfer Ratio of Anti-S and Anti-N Antibodies

Anti-S antibody transplacental ratio of participants with SARS-CoV-2 negative (n= 37) were depicted in the scatter plot as triangle marker (▲). Anti-N and anti-S antibodies transplacental ratio of participants with SARS-CoV-2 infection >7 days (n=12) were depicted as circle (○) and filled diamond- shaped marker (◆), respectively.

Anti-S, anti-S RBD antibody; Anti-N, anti-nucleocapsid antibody.


A. All participants
B. Participants with SARS-COV-2 negative
C. Participants with SARS-COV-2 positive
D. All participants- Wuhan strain
E. Participants with SARS-COV-2 negative- Wuhan strain
F. Participants with SARS-COV-2 positive - Wuhan strain
G. All participants- Omicron variant
H. Participants with SARS-COV-2 negative- Omicron variant
I. Participants with SARS-COV-2 positive- Omicron variant
Maternal
Cord
T1
T2
T3


A
B
Log10 Anti-S Concentration (U/mL)
Time interval from latest vaccine to blood sampling
Time interval from infection to blood sampling


CORD TO MATERNAL SERUM TRANSPLACENTAL TRANSFER RATIO
4
3.5
3
2.5
2
1.5
1
0.5
0
0
50
100
150
200
250
300
350
400
TIME INTERVAL FROM LAST VACCINE OR INFECTION, DAYS