Kinetics of maternally-derived anti- SARS-CoV-2 antibodies in infants in relation to the timing of antenatal vaccination

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Running title: Kinetics of anti- SARS-CoV-2 antibodies in infants after maternal mRNA vaccination

Abstract

Background

SARS-CoV-2 infection during early infancy can result in severe disease. We evaluated the durability of maternally-derived anti-SARS-CoV-2 antibodies in infants and its relation to antenatal vaccination timing.

Methods

Sera were prospectively collected at birth and 3 months after delivery from mother-infant pairs following antenatal BNT162b2 vaccination. SARS-CoV-2 receptor binding domain (RBD)-specific IgG levels and neutralizing activity were evaluated.

Results

56 mother-infant pairs were included: 15 (26.8%) were vaccinated in the 1st trimester, 16 (28.6%) in the 2nd trimester, and 25 (44.6%) in the 3rd trimester.

At the time of delivery, all neonates were positive for anti-RBD-specific IgG with a median concentration of 4046 [IQR 2446-7896] AU/mL, with the highest concentration found after 3rd trimester vaccination (median 6763 [IQR 3857-12561] AU/mL). At 3 months after delivery, anti RBD-specific IgG levels in infants significantly waned with a median concentration of 545 [IQR 344-810] AU/mL (P<0.001). The half-life of anti-RBD-specific IgG was 66 days among mothers and 30 days among infants. While at the time of delivery, all neonates had detectable neutralizing activity regardless of gestational age at vaccination, at 3-months of age, a higher proportion of infants born to mothers vaccinated in 3rd trimester had persistent neutralizing activity as compared to those born to mothers vaccinated in 2nd trimester.

Conclusions

Maternal vaccination leads to efficient transplacental antibody transfer, with persistent anti-SARS-CoV-2 antibodies detected at 3 months of age in all infants. The observed effect of antenatal immunization timing on the kinetics of maternally-derived antibodies may have implications for SARS-CoV-2 vaccination strategies.

Keywords – pregnancy; vaccination; COVID-19; serology; infants; passive immunity; SARS-CoV-2.

Introduction

Pregnant women with SARS-CoV-2 infection are known to be at increased risk for severe coronavirus disease 19 (COVID-19) [1-5]. Since January 2020, the Centers for Disease Control and Prevention (CDC) has reported over 190,000 cases of COVID-19 among pregnant women, with more than 250 resulting deaths [6]. In addition, COVID-19 in pregnancy is associated with an increased risk of maternal and perinatal adverse outcomes [1-5].

Global efforts to combat the COVID-19 pandemic have led to the development of several vaccines including two novel mRNA-based vaccines, which were shown to be highly effective in preventing SARS-CoV-2- related illness [7, 8]. Further studies have shown the efficacy of these vaccines in the setting of pregnancy, coupled with favorable safety profile [9-12]. In Israel, a nationwide mass vaccination campaign against COVID-19 using the BNT162b2 (Pfizer/BioNTech) mRNA vaccine was launched in December 2020. Pregnant women were included in this campaign and were encouraged to receive the vaccine [13], considering the recognized adverse pregnancy outcomes associated with SARS-CoV-2 infection throughout gestation [1-5].

In addition to its major role in preventing maternal illness, antenatal SARS-CoV-2 immunization may provide neonatal protection in the early, vulnerable stages of life. During the first months of life, owing to their developing immune system, neonates are reliant on maternal IgG antibodies transferred across the placenta. Importantly, infants were reported to be more vulnerable to severe illness upon SARS-CoV-2 infection compared to older children [14-16]. We and others have shown that antenatal SARS-CoV-2 vaccination leads to efficient transplacental transfer of maternally-derived anti-SARS-CoV-2 antibodies [17-20]. Defining the durability of these passively acquired antibodies is crucial to understand their role in maintaining neonatal immunity and to design preventive strategies. Recently, Shook et al.

reported the persistence of anti-SARS-CoV-2 spike antibodies among infants after vaccination at 20-32 weeks of gestation [21]. However, neutralizing antibodies were not studied and women vaccinated at earlier or later gestational age were excluded. Finally, whether breastfeeding may contribute to the systemic levels of SARS-CoV-2 IgG antibodies remains unclear [22]. Given the high clinical relevance, we aimed to investigate the kinetics of anti-SARS-CoV-2 spike and neutralizing antibodies among infants following vaccination at different stages of pregnancy and in the early postpartum period.

Methods

Study Population

A prospective longitudinal study including mother-infant pairs following antenatal SARS-CoV-2 BNT162b2 mRNA vaccination, was performed between February and November 2021 at Hadassah Medical Center, a university affiliated hospital in Jerusalem, Israel. Parturients who delivered prematurely (<37 weeks gestation), multifetal gestations, those vaccinated later than 36 weeks gestation, and those who did not complete the two-dose vaccine series prior to delivery, were excluded. All women included completed the two-dose vaccine series within the recommended time frame (3-4 weeks), and more than 2 weeks prior to delivery. Women who received a third booster dose of the BNT162b2 vaccine and those with prior history of SARS-CoV-2 infection were ineligible for this study. All mothers were tested and found to be negative for nucleocapsid IgG. None of the women included received immunosuppressive treatment or had known immunodeficiency. Demographic and clinical data were collected at the time of enrollment. We also included an additional control group of fully breastfed 3-month-old infants born to mothers who were not vaccinated during pregnancy and completed the two-dose BNT162b2 vaccine series within the first month after delivery. The institutional review board of the Hadassah Medical Center approved this study (HMO-0064-21).

Laboratory Methods

Following delivery, maternal and cord blood sera were collected for antibody measurement. Maternal and infant blood sera were collected for repeat antibody measurement at 3 months after delivery.

Receptor binding domain (RBD)- specific (Architect SARS-CoV-2 IgG II Quant assay, Abbott Diagnostics, Chicago, USA) IgG levels were evaluated in maternal and cord/infant blood sera. Nucleocapsid (N) IgG assay (Architect SARS-CoV-2 IgG II Quant assay, Abbott Diagnostics, Chicago, USA) was also performed in maternal sera.

Neutralizing antibody titers against SARS-CoV-2 were determined using a wild-type SARS-CoV-2 virus microneutralization assay as previously described [23], with minor modifications. Briefly, serial two-fold dilutions of heat inactivated serum samples (starting from 1:20; diluted in DMEM in a total volume of 50 µl) were incubated with an equal volume of viral solution, containing 100 tissue culture infectious dose (TCID50) of SARS-CoV-2 isolate USA-WA1/2020 (NR-52281; obtained from BEI resources), for 1 hour in a 96-well plate (at 37°C in humidified atmosphere with 5% CO_2). The serum-virus mixtures (100 µL; 8 replicates of each serum dilution) were then added to a 96-well plate containing a semi-confluent Vero E6 cell monolayer (ATCC CRL-1586; maintained as described [24]). Following 3 days of incubation (at 37°C in a humidified atmosphere with 5% CO_2), the cells in each well were scored for viral cytopathic effect (CPE). The neutralization titer (NT_{50}) was defined as the reciprocal of the highest serum dilution that protected 50% of culture wells from CPE. Positive and negative serum controls, cell control, and a viral back-titration control were included in each assay.

Statistical analysis

Patient characteristics are described as proportions for categorical variables and medians and interquartile range (IQR) for continuous variables. Antibody levels and placental transfer ratios are expressed as medians and IQR. Significance between groups was assessed using the chi-square test and Fisher's exact test for categorical variables, while the Mann-Whitney U test was used for continuous variables. Correlations were reported using the Pearson's test with the correspondent R and P values. Decay rates of antibodies were calculated by a mixed linear regression model of log transformed antibody concentrations in relation to the time lapsed since delivery. Antibody half-life was calculated as the inverse reciprocal of the regression line slope, expressed in days [25, 26]. The data were analyzed using Software Package for Statistics and Simulation (IBM SPSS version 24, IBM Corp, Armonk, NY).

Results

During the study period, samples were collected from 56 mothers-infants dyads following antenatal SARS-CoV-2 BNT162b2 mRNA vaccination. Of the study group, 15 (26.8%) mothers were vaccinated in the 1st trimester, 16 (28.6%) in the 2nd trimester, and 25 (44.6%) in the 3rd trimester. All mothers included tested negative for SARS-CoV-2 anti-N antibodies. Maternal and infant characteristics are summarized in Table S1. Median neonatal birthweight age was 3257 [IQR 2898-3555] gram with a median gestational age of 39$^{5/7}$ [IQR 38$^{5/7}$-40$^{4/7}$] weeks at the time of delivery. None of the mothers and infants included experienced SARS-CoV-2 infection during the study period.

At the time of delivery, all neonates were positive for anti-RBD-specific IgG with a median concentration of 4046 [IQR 2446-7896] AU/mL. Median anti-RBD-specific IgG concentrations in neonatal sera at the time of delivery were lowest following antenatal vaccination in the 1st trimester (1595 [IQR 999-2482] AU/mL), intermediate following 2nd trimester vaccination (3809 [IQR 2980-6815] AU/mL), and highest after 3rd trimester

vaccination (6763 [IQR 3857-12561] AU/mL) (Figure 1A). Anti-RBD-specific IgG levels in cord blood were positively correlated to their respective concentrations in maternal sera (r= 0.80; P <0.001) (Figure 1B).

At 3 months after delivery, anti RBD-specific IgG levels in infants significantly waned with a median concentration of 545 [IQR 344-810] AU/mL (P<0.001). Antibody levels at 3 months of age were lowest following 1st trimester vaccination (median 220 [IQR 164-517] AU/mL) (P=0.002), whereas comparable levels were found after 2nd trimester (median 530 [IQR 453-929] AU/mL) and 3rd trimester (median 598 [IQR 503-1033] AU/mL) vaccination (P=0.62) (Figure 1C). Anti-RBD-specific IgG levels in infants' sera at 3 months of age were directly correlated to their respective concentrations in cord blood sera at the time of delivery (r= 0.91; P <0.001) (Figure 1D).

The half-life of anti-RBD-specific IgG was 66 days among mothers and 30 days among infants. Among mothers, the half-life did not differ according to gestational age at vaccination. In infants, the half-life was 38 days after 1st trimester vaccination, 39 days after 2nd trimester vaccination, and 25 days after 3rd trimester vaccination.

In a control group (n=10) of fully breastfed 3-month-old infants, born to mothers who were not vaccinated antenatally and completed the two-dose vaccine series within the first month after delivery, anti RBD-specific IgG antibodies were detected in none of the infants' sera.

Neutralizing antibody concentrations were also evaluated in infants following antenatal 2nd and 3rd trimester vaccination (Figure 2). At the time of delivery, all neonates had detectable neutralizing activity regardless of gestational age at vaccination, albeit the geometric mean concentration (GMC) was higher after 3rd trimester vaccination as compared to 2nd trimester vaccination (366 vs. 177 AU/mL, P=0.03). At 3-months of age, a higher proportion of infants born to mothers vaccinated in 3rd trimester had persistent neutralizing activity as compared to

those born to mothers vaccinated in 2nd trimester (16/18, 88.9% vs. 6/11, 54.5%, P=0.07), with an increased neutralizing antibodies concentration (GMC 35 vs. 16 AU/mL, P=0.08).

Discussion

In this prospective longitudinal study, we evaluated in detail the kinetics of SARS-CoV-2 BNT162b2-induced maternally-derived antibodies in neonates, in relation to the gestational timing of vaccination. We demonstrated that at birth, all neonates had detectable SARS-CoV-2 neutralizing activity regardless of gestational age at vaccination, followed by significant waning of antibody levels with an overall calculated half-life of just over four weeks. At 3-months of age, third-trimester antenatal vaccination was associated with a higher rate of persistent neutralizing activity and increased neutralizing antibodies concentration, as compared to vaccination at an earlier gestational age.

The current study results demonstrate the efficient placental transfer of IgG antibodies following maternal SARS-CoV-2 vaccination and their durability in the early months of life. The ability to provide seroprotection to infants via maternal vaccination, is also supported by recent data showing reduced risk for COVID-19-related hospitalization among infants aged <6 months after SARS-CoV-2 mRNA vaccination during pregnancy [27]. These findings highlight the important role of antenatal SARS-CoV-2 immunization to protect both the mother and the infant. This may be of paramount importance as current trials evaluating COVID-19 vaccination in pediatric population, only involve subjects older than 6 months of age. Moreover, we also showed that breastfeeding likely does not contribute to the systemic levels of SARS-CoV-2 IgG antibodies, further underscoring the advantage of transplacental antibody transfer in this regard.

We also characterized the effect of vaccination timing throughout gestation on the kinetics of maternally-derived SARS-CoV-2 antibodies. At the time of delivery, higher anti-RBD-specific IgG and neutralizing antibodies concentrations were found following 3rd trimester

vaccination as compared to immunization at early pregnancy. Interestingly, at 3-months of age, anti-RBD specific IgG levels were comparable between infants born to mothers immunized in the 2nd and 3rd trimesters. However, 3rd trimester maternal vaccination remained associated at 3-months of age with a higher rate of persistent neutralizing activity and increased neutralizing antibodies concentration. This is in accordance with the aforementioned CDC publication, in which the reduced risk for COVID-19-associated hospitalization among infants, was more pronounced after vaccination later in pregnancy [27]. These findings further support our and others' previous observations [28-31] that third trimester SARS-CoV-2 immunization has the potential to maximize maternofetal transplacental antibody transfer thereby affording longer-lasting seroprotection during early infancy. While antenatal SARS-CoV-2 vaccination is primarily aimed at preventing maternal illness, the optimal immunization regimen (i.e. number of doses and timing) to maintain maternal immunity throughout gestation is still unclear. Immunization at early pregnancy could potentially provide maternal protection through the longer course of pregnancy. However, the far-reaching potential to confer enhanced neonatal protection against COVID-19 via maternal immunization at a later gestational age raises critical questions concerning the optimal timing of antenatal vaccination.

The calculated half-life of SARS-CoV-2 anti-RBD specific IgG in our cohort of infants was 30 days, which is similar to that of pertussis-specific antibodies after antenatal vaccination [25, 32]. Nevertheless, the half-life found among infants was over two-times shorter from that found among their mothers during the same time period. Moreover, in contrast to the mothers, the antibody half-life among infants differed according to gestational age at the time of vaccination, with longer half-life after 1st and 2nd trimester vaccination as compared to 3rd trimester vaccination. The mechanisms underlying the differential antibody decay rate between mothers and infants, as well as its relation to gestational age at vaccination, remain

largely unclear. A deeper understanding of the distinct kinetics of maternally-acquired IgG in infants is critical to guide the development of strategies to increase their durability.

Strengths and limitations

The major strengths of our study are its prospective design including longitudinal follow-up of the same maternal-infant pairs and the ability to evaluate the effect of gestational age at vaccination on study outcomes. However, this study has several caveats, which mainly include its relatively small sample size and the lack of follow-up beyond 3-months of age. Furthermore, while the presence of nucleocapsid IgG was excluded in all study participants, as the levels of this antibody wane throughout time, the potential occurrence of prior remote infection remains possible. In addition, the impact of a third booster dose and other SARS-CoV-2 vaccines in this regard could not be assessed. Moreover, whether passive immunization provided by these maternally-derived SARS-CoV-2 antibodies would potentially decrease community transmission and contribute to herd immunity, requires further investigation. Finally, vaccine-induced maternally-derived antibodies might blunt the infant humoral immune response to future SARS-CoV-2 vaccination; while the clinical significance of this interference effect is largely unknown [33], it should be acknowledged and further explored.

Conclusions

The current study results indicate that antenatal BNT162b2 mRNA vaccination leads to efficient transplacental transfer of SARS-CoV-2 antibodies, with persistent anti-RBD-specific IgG detected at 3 months of age in all infants. Higher antibody concentrations and neutralizing activity were detected following 3rd trimester vaccination. The observed effect of antenatal immunization timing on the kinetics of maternally-derived SARS-CoV-2 antibodies provides insights into the optimal time window in which maternal immunization may bolster

seroprotection at the early stages of life, and thus may have implications for developing vaccination strategies.

NOTES

Contributors:

Dr Rottenstreich had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Porat, Rottenstreich, Wolf.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Rottenstreich, Zigron, Zarbiv, Porat, Wolf.

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All authors read and approved the final manuscript.

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Data sharing

Individual-level data will not be made publicly available with this Article. Requests for sharing of deidentified individual-level participant data for scientific research can be directed to the corresponding author. All proposals will be subject to scientific review and institutional review board approval at Hadassah Medical Center.

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Declaration of interests:

The authors declare that they have no conflicts of interest.

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Legends for tables and figures-

Table 1

Maternal and neonatal characteristics among SARS-CoV-2 BNT162b2 immunized pregnant women

Figure 1

Median anti-RBD-specific IgG concentrations in neonatal sera at the time of delivery were lowest following antenatal vaccination in the 1st trimester (1595 [IQR 999-2482] AU/mL), intermediate following 2nd trimester vaccination (3809 [IQR 2980-6815] AU/mL), and highest after 3rd trimester vaccination (6763 [IQR 3857-12561] AU/mL) (A). Anti-RBD-specific IgG levels in cord blood were positively correlated to their respective concentrations in maternal sera ($r = 0.80$; $P < 0.001$) (B). At 3 months after delivery, anti RBD-specific IgG level in infants significantly waned with a median concentration of 545 [IQR 344-810] AU/mL. Antibody levels at 3 months of age were lowest following 1st trimester vaccination (median 220 [IQR 164-517] AU/mL) ($P=0.002$), whereas comparable levels were found after 2nd trimester (median 530 [IQR 453-929] AU/mL) and 3rd trimester (median 598 [IQR 503-1033] AU/mL) vaccination ($P=0.62$) (C). Anti-RBD-specific IgG levels in infant's sera at 3 months of age were directly correlated to their respective concentrations in cord blood sera at the time of delivery ($r = 0.91$; $P < 0.001$) (D).

Figure 2

Neutralizing antibody titers at the time of birth and 3-months after delivery among infants born to mothers who completed the two-dose vaccine series in the second and third trimesters of pregnancy. Neutralizing efficiency is reflected by NT_{50} values, measured in live virus microneutralization assay (see Methods section). The I bars represent 95% confidence intervals, and the circles represent the values in individual participants. The dashed line indicates the lower limit of detection of the assay.

Table S1.

Maternal and neonatal characteristics among SARS-CoV-2 BNT162b2 immunized pregnant women

Characteristics	**1st trimester two-dose vaccination n=15**	**2nd trimester two-dose vaccination n=16**	**3rd trimester two-dose vaccination n=25**
Age (years)	33 [30-35] (32)	33 [29-36] (33)	32 [29-37] (32)
Nulliparous	4 (26.7%)	3 (18.8%)	5 (20.0%)
Maternal pre-pregnancy weight (kg)	71 [66-84] (73)	70 [68-76] (73)	74 [69-79] (74)
Maternal pre-pregnancy body mass index (kg/m^2)	27 [24-32] (28)	26 [24-28] (27)	28 [25-30] (28)
Gestational age at delivery (weeks)	$39^{5/7}$ [$38^{6/7}$ -$40^{3/7}$] ($39^{4/7}$)	$39^{1/7}$ [$38^{4/7}$ -$39^{4/7}$] ($38^{6/7}$)	$40^{1/7}$ [$38^{5/7}$ -$40^{6/7}$] ($39^{5/7}$)
Gestational age at 1st dose immunization (weeks)	12 [10-14] (12)	22 [20-23] (22)	31 [29-33] (31)
1st vaccine dose-to-delivery interval (days)	190 [178-208] (193)	118 [105-138] (118)	64 [40-71] (59)
2nd vaccine dose-to-delivery interval (days)	169 [157-187] (172)	97 [84-117] (97)	43 [19-50] (38)
Mode of delivery Vaginal Cesarean	 13 (86.7%) 2 (13.3%)	 15 (83.7%) 1 (6.3%)	 22 (88.0%) 3 (12.0%)
Neonatal Birthweight (grams)	3310 [3061-3475] (3367)	3170 [2798-3410] (3046)	3420 [2890-3710] (3234)
Male gender (%)	8 (53.3%)	8 (50.0%)	12 (48.0%)

All continuous variables are expressed as medians [interquartile range] (means).

None of the women included received immunosuppressive treatment or had known immunodeficiency.

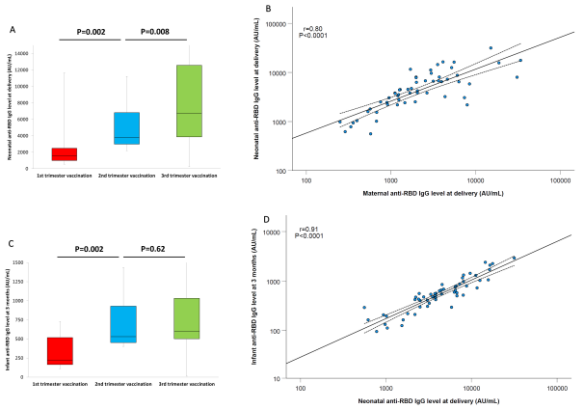

Figure 1
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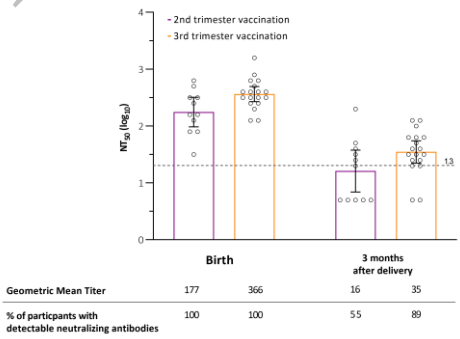

Geometric Mean Titer	177	366	16	35
% of particpants with detectable neutralizing antibodies	100	100	55	89

Figure 2
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