The effect of gestational age at BNT162b2 mRNA vaccination on maternal and neonatal SARS-CoV-2 antibody levels

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Summary: Lower antibody titers were found after maternal vaccination at early pregnancy, suggesting considerable antibody waning throughout gestation, with a potential role of a third vaccine dose. The effect of immunization timing on the transplacental antibody transfer may influence neonatal seroprotection.

Abstract

Background

COVID-19 during pregnancy and early infancy can result in severe disease. Evaluating the effect of gestational age at the time of SARS-CoV-2 vaccination on maternal antibody levels and transplacental antibody transfer has important implications for maternal care and vaccination strategies.

Methods

Maternal and cord blood sera were collected from mother/newborn dyads (n=402), following term delivery after antenatal two-dose SARS-CoV-2 BNT162b2 mRNA vaccination. SARS-CoV-2 spike protein (S) and receptor binding domain (RBD)-specific IgG levels were evaluated in the samples collected.

Results Median anti-S and anti-RBD-specific IgG levels in maternal sera at the time of delivery were lowest following 1st trimester vaccination (n=90) (anti-S IgG: 76 AU/mL, anti-RBD-specific IgG: 478 AU/mL), intermediate in those vaccinated in the 2nd trimester (n=124) (anti-S IgG: 126 AU/mL, anti-RBD-specific IgG: 1263 AU/mL), and highest after 3rd trimester vaccination (n=188) (anti-S IgG: 240 AU/mL, anti-RBD-specific IgG: 5855 AU/mL). Antibody levels in neonatal sera followed a similar pattern and were lowest following antenatal vaccination in the 1st trimester (anti-S IgG: 126 AU/mL, anti-RBD-specific IgG: 1140 AU/mL). In a subgroup of parturients vaccinated in the 1st trimester (n=30), a third booster dose was associated with significantly higher maternal and neonatal antibody levels.

Conclusions These results suggest a considerable antibody waning throughout pregnancy in those vaccinated at early gestation. The observed boosting effect of a third vaccine dose, hints to its potential benefit in those who completed the two-dose vaccine series at early pregnancy or prior to conception. The impact of antenatal immunization timing on SARS-CoV-2 transplacental antibody transfer may influence neonatal seroprotection.

Keywords – pregnancy; vaccination; COVID-19; serology; 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]. By September 2021, over 270,000 pregnant women have been diagnosed with COVID-19 in the Americas, with more than 2600 resulting deaths [6]. It has also been shown that COVID-19 in pregnancy is associated with an increased risk of maternal and perinatal complications [1-5], and that infants are more vulnerable to severe illness upon SARS-CoV-2 infection compared to older children [7, 8]. Global efforts to combat COVID-19 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 [9, 10]. However, pregnant women and neonates were excluded from the pivotal vaccine trials due to enhanced safety concerns. 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 [11], considering the recognized adverse pregnancy outcomes associated with SARS-CoV-2 infection throughout gestation [1-5].

Antenatal BNT162b2 mRNA immunization was reported to be associated with reduced maternal risk of SARS-CoV-2 infection [12, 13]. Furthermore, in addition to its major role in preventing maternal illness, maternal immunization may potentially offer neonatal seroprotection in the early, vulnerable stages of life, when neonates rely on the transfer of maternal IgG antibodies across the placenta. Recently, we and others have demonstrated that antenatal vaccination leads to efficient transplacental transfer of maternally-derived anti-SARS-CoV-2 antibodies [14-17]. Nevertheless, data regarding the effect of gestational age at the time of SARS-CoV-2 vaccination on maternal and neonatal antibody levels are limited. Delineating the effect of antenatal SARS-CoV-2 immunization timing is crucial to optimize

maternal immunity and to maximize maternofetal antibody transfer. Toward this goal, we determined maternal and neonatal SARS-CoV-2 antibody levels at the time of delivery, following antenatal BNT162b2 mRNA vaccination in different stages of pregnancy.

Methods

Study Population

A prospective study following women admitted for delivery was performed during February-November 2021 at Hadassah Medical Center, a tertiary-care university affiliated hospital in Jerusalem, Israel with over 10,000 deliveries annually. Women who received the SARS-CoV-2 BNT162b2 mRNA vaccine during pregnancy were eligible for this study. 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). Women with prior history of SARS-CoV-2 infection were ineligible for this study. Demographic and clinical data were collected at the time of enrollment. 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. Spike protein (S) (Liaison SARS-CoV-2 S1/S2 IgG, DiaSorin, Saluggia, Italy) and 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/neonatal blood sera. Nucleocapsid (N) IgG assay (Architect SARS-CoV-2 IgG II Quant assay, Abbott Diagnostics, Chicago, USA) was also performed on maternal blood sera. Standard assay controls (negative, low-positive, and positive; supplied by the manufacturer and used in accordance with the manufacturer's specifications), along with internal quality controls

(prepared at the Hadassah Clinical Virology Laboratory from pooled sera, and established for statistically-based control limits in accordance with the lab's ISO 15189 accreditation requirements), were included in each assay. The controls' values were monitored by the Westgard rules for the specified ranges, to control for the system and assay performances.

For a subset of mother/newborn dyads (arbitrarily selected), neutralizing antibody titers against SARS-CoV-2 were defined using a wild-type SARS-CoV-2 virus microneutralization assay as previously described [18], with minor modifications. Briefly, serial two- fold dilutions of heat inactivated serum samples (starting from 1:10; 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 [19]). 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. 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 422 parturients who received the SARS-CoV-2 BNT162b2 mRNA vaccine throughout gestation and agreed to participate. Of them, 20 (4.7%) were excluded (preterm delivery [n=14], first vaccine dose >36 weeks [n=3], did not complete the two-dose vaccine series prior to delivery [n=2], twin gestation [n=1]). Thus, the final study cohort comprised 402 women including 90 (22.4%) who received the first vaccine dose at 1st trimester, 124 (30.8%) at 2nd trimester, and 188 (46.8%) at 3rd trimester (Figure 1).

Maternal and neonatal characteristics are summarized in Table S1. Median maternal age was 31 [IQR 27-35] years with a median gestational age of $39^{4/7}$ [IQR $38^{5/7}$-$40^{3/7}$] weeks at the time of delivery. The median time lapsed from the first vaccine dose administration until delivery was 92 [IQR 59-147] days. Baseline characteristics did not differ according to the time of maternal vaccination. All women included tested negative for SARS-CoV-2 anti-N antibodies.

Maternal SARS-CoV-2 anti-S and anti-RBD-specific IgG levels at the time of delivery were negatively correlated with the time lapsed since vaccination (r= -0.62; P <0.001 and r= -0.80; P <0.001, respectively; Figure 2A, B). Median anti-S and anti-RBD-specific IgG concentrations in maternal sera at the time of delivery were lowest in those vaccinated in the 1st trimester (anti-S IgG: 76 AU/mL, anti-RBD-specific IgG: 478 AU/mL), intermediate following 2nd trimester vaccination (anti-S IgG: 126 AU/mL, anti-RBD-specific IgG: 1263 AU/mL), and highest in those vaccinated in the 3rd trimester (anti-S IgG: 240 AU/mL, anti-RBD-specific IgG: 5855 AU/mL) (Figure 2C, D). The sequential decrease in anti-S and anti-

RBD-specific IgG maternal concentrations in relation to earlier gestational age at the time of vaccination is shown in Figure 2E, F.

All 402 neonates tested positive for SARS-CoV-2 anti S- and anti-RBD-specific IgG. Anti-S and anti-RBD-specific IgG levels in cord blood were positively correlated to their respective concentrations in maternal sera ($r = 0.81$; $P < 0.001$ and $r = 0.85$; $P < 0.001$, respectively; Figure 3A, B). Median anti-S and anti-RBD-specific IgG concentrations in neonatal sera were lowest following antenatal vaccination in the 1st trimester (anti-S IgG: 126 AU/mL, anti-RBD-specific IgG: 1140 AU/mL), intermediate after 2nd trimester vaccination (anti-S IgG: 204 AU/mL, anti-RBD-specific IgG: 3809 AU/mL), and highest after 3rd trimester vaccination (anti-S IgG: 255 AU/mL, anti-RBD-specific IgG: 8038 AU/mL) (Figure 3C, D). The temporal changes in anti-S and anti-RBD-specific IgG neonatal levels in relation to the gestational age at the time of vaccination, are shown in Figure 3E, F. Among neonates born to mothers who were vaccinated in the 3rd trimester, anti-RBD-specific IgG levels (median 9516 vs. 6811 AU/mL, $P=0.03$) and placental transfer ratio (2.4 vs. 0.8, $P<0.001$) were significantly higher following early 3rd trimester immunization (27-31 weeks gestation) as compared to late 3rd trimester immunization (32-36 weeks gestation). None of the neonates included experienced SARS-CoV-2 infection during the study period.

Neutralizing SARS-CoV-2 antibodies were assessed in 60 maternal-infant pairs following 1st trimester vaccination (n=20), 2nd trimester vaccination (n=20) and 3rd trimester vaccination (n=20). Neonatal sera neutralizing activity (as reflected by NT_{50} values) was positively correlated to maternal sera neutralizing activity ($r = 0.84$; $P<0.001$; Figure 4A). In addition, maternal and neonatal sera neutralizing activity was positively correlated to the respective anti-RBD concentration ($r = 0.93$; $P<0.001$; Figure 4B, $r = 0.90$; $P<0.001$; Figure 4C). Neutralizing SARS-CoV-2 antibody levels in maternal and neonatal sera were lowest following 1st trimester vaccination (median NT50: maternal 16, neonatal 34), intermediate

after 2nd trimester vaccination (median NT50: maternal 80, neonatal 191), and highest following 3rd trimester vaccination (median NT50: maternal 295, neonatal 391) (Figure 4D, E).

Maternal and cord blood sera were also collected from 30 additional parturients vaccinated in the 1st trimester, who further received a third booster dose of the BNT162b2 vaccine during the 3rd trimester. The booster dose administration was associated with significantly increased maternal and neonatal antibody levels (maternal: anti-S IgG: 1665 AU/mL, anti-RBD-specific IgG: 20,946 AU/mL, neonatal: anti-S IgG: 528 AU/mL, anti-RBD-specific IgG: 4225 AU/mL) as compared to those who completed the two-dose vaccine series in the 1st trimester and did not receive a third booster dose (Figure 5A-D, $P<0.001$ for all comparisons).

Discussion

In this prospective study, we characterized the association between the timing of antenatal SARS-CoV-2 BNT162b2 mRNA vaccination and maternal/neonatal antibody levels at the time of delivery. We showed that earlier gestational age at the time of vaccination was directly associated with lower maternal and neonatal SARS-CoV-2 IgG levels and neutralizing potency at term. A third vaccine dose administered antenatally in those who completed the two-dose series in the first trimester was able to significantly boost antibody levels in both the mother and the neonate.

Israel was one of the first countries to roll out its COVID-19 vaccination program, which resulted in a dramatic decline in COVID-19 cases across all age groups [20, 21]. Nevertheless, in July 2021, Israel has experienced a resurgence of COVID-19 driven by the highly contagious Delta variant. A substantial proportion of those infected in this fourth pandemic wave, were individuals who previously completed the two-dose series of the

SARS-CoV-2 BNT162b2 mRNA vaccine. In addition, the occurrence of these breakthrough infections among fully vaccinated subjects was found to correlate with the waning of neutralizing antibody titers and time lapsed since vaccination [22, 23]. These findings have led the Israeli Ministry of Health to recommend a third booster dose of the mRNA vaccine, starting from five months after the second vaccine dose, with gradual implementation, prioritizing the elderly and those at risk for severe COVID-19. This was followed by a significant decrease in the rates of breakthrough infection and severe SARS-CoV-2-related illness [24]. Despite the lack of supporting data, a third booster dose was also recommended for fully vaccinated pregnant women [25].

While the two SARS-CoV-2 mRNA vaccines of Pfizer and Moderna were shown to elicit a robust immune response among pregnant women [13], the durability of these vaccine-elicited antibodies across gestation has not been tested. In the current study, we demonstrated significantly lower maternal anti SARS-CoV-2 antibody levels and neutralizing titers at the time of delivery, in those who were immunized at early pregnancy, suggesting a considerable antibody waning throughout pregnancy. We also showed that in those who completed the two-dose vaccine series in the first trimester, the administration of a third booster dose was able to significantly augment antibody levels. Our observations, coupled with the aforementioned findings among non-pregnant fully-vaccinated subjects, may hint to the importance of a third booster dose during the antenatal course in those vaccinated at early stages of pregnancy or prior to conception. Implementing the administration of a booster dose would potentially maintain maternal immunity. Future studies are needed to examine the impact of a booster dose administration during pregnancy on preventing the maternal and neonatal COVID-19 related complications.

Antenatal SARS-CoV-2 immunization is primarily aimed at preventing maternal illness. An additional benefit of maternal vaccination is the potential ability to confer neonatal

seroprotection through transplacental transfer of vaccine-elicited antibodies. This concept is well-established for the prevention of other potentially life-threatening respiratory infections among infants (e.g., pertussis and influenza) [26-30]. IgG transplacental transfer, begins as early as 13 weeks of gestation and increases exponentially during pregnancy, culminating in the third trimester [31]. Interestingly, diminished transplacental transfer of anti–SARS-CoV-2 IgG among pregnant women with COVID-19, was reported after third-trimester infection as compared to second trimester infection [32]. In the current cohort, we found that third trimester immunization was associated with higher neonatal SARS-CoV-2 antibody levels and neutralizing activity, as compared to first and second trimester immunization. In addition, as we have recently demonstrated in a subgroup of the current cohort vaccinated in third trimester (n=171), neonatal anti-RBD specific IgG levels were highest following early third trimester vaccination (27-31 weeks gestation) [33], which concurs with previous studies evaluating the effect of maternal pertussis and influenza immunization [26-30]. The mechanisms underlying the differences observed in the transplacental transfer between infection- and vaccine- induced antibodies are still unclear. Moreover, whether passive immunization provided by these maternally-derived SARS-CoV-2 antibodies would enhance neonatal immunity and potentially decrease community transmission, requires further investigation.

Strengths and limitations

The major strengths of our study include its prospective design and its relatively large cohort size. Our study has several limitations. First, while we performed a robust analysis of the impact of antenatal immunization timing on antibody titers at the time of delivery, we lacked longitudinal measurements of antibody levels in each parturient and a control group of non-pregnant women, limiting our ability to detect differences in vaccine immunogenicity throughout pregnancy. Moreover, the different SARS-CoV-2 anti-S and anti-RBD-specific

IgG levels, may be accounted for by the assays used. In addition, as immune correlates of protection from SARS-CoV-2 are still largely undefined, the effects of antibody levels and the expected antibody decay on maternal immunity, remain to be determined. Furthermore, additional studies are warranted to better assess the effects of different SARS-CoV-2 vaccines in this regard. Finally, the durability of vaccine-induced maternally-derived antibodies transferred via the placenta, as well as their ability to confer neonatal seroprotection, are currently unknown.

Conclusions

The current study results indicate that antenatal BNT162b2 mRNA vaccination at an earlier gestational age is associated with substantially lower maternal and neonatal antibody levels and sera neutralizing activity at term. A third dose administration during the antenatal course was able to significantly boost maternal and neonatal antibody titers, hinting to its potential benefit in those who completed the two-dose vaccine series at early pregnancy or prior to conception. The observed effect of antenatal immunization timing on the transplacental transfer 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.

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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Declaration of interests:

The authors declare that they have no conflicts of interest.

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Figure Legends

Figure 1

Schematic flow chart of patient inclusion in the study

Figure 2

SARS-CoV-2 maternal anti-S (A) and anti-RBD-specific (B) IgG concentrations were negatively associated with the time lapsed since immunization (r= -0.62; P <0.001 and r=-0.80; P <0.001, respectively). Median anti-S (C) and anti-RBD-specific (D) IgG concentrations in maternal sera at the time of delivery were lowest in those vaccinated in the 1st trimester (anti-S IgG: 76 AU/mL, anti-RBD-specific IgG: 478 AU/mL), intermediate following 2nd trimester vaccination (anti-S IgG: 126 AU/mL, anti-RBD-specific IgG: 1263 AU/mL), and highest in those vaccinated in the 3rd trimester (anti-S IgG: 240 AU/mL, anti-RBD-specific IgG: 5855 AU/mL). Anti-S (E) and anti-RBD-specific (F) IgG concentrations in maternal sera in relation to gestational age (in weeks) at the time of immunization.

Figure 3

SARS-CoV-2 anti-S (A) and anti-RBD-specific (B) IgG levels in cord blood were positively correlated to their respective concentrations in maternal sera (r= 0.81; P <0.001 and r= 0.85; P <0.001, respectively). Median anti-S (C) and anti-RBD-specific (D) IgG concentrations in neonatal sera were lowest following antenatal vaccination in the 1st trimester (anti-S IgG: 126 AU/mL, anti-RBD-specific IgG: 1140 AU/mL), intermediate after 2nd trimester vaccination (anti-S IgG: 204 AU/mL, anti-RBD-specific IgG: 3809 AU/mL), and highest after 3rd trimester vaccination (anti-S IgG: 255 AU/mL, anti-RBD-specific IgG: 8038 AU/mL). Anti-S (E) and anti-RBD-specific (F) IgG concentrations in neonatal sera in relation to gestational age (in weeks) at the time of immunization.

Figure 4

Neonatal sera neutralizing activity (A) was positively correlated to maternal sera neutralizing activity ($r = 0.84$; $P<0.001$). In addition, maternal (B) and neonatal (C) sera neutralizing activity was positively correlated to the respective anti-RBD concentration ($r = 0.93$; $P<0.001$ and $r = 0.90$; $P<0.001$, respectively). Neutralizing SARS-CoV-2 antibody level in maternal (D) and neonatal (E) sera were lowest following 1st trimester vaccination (median NT50: maternal 16, neonatal 34), intermediate after 2nd trimester vaccination (median NT50: maternal 80, neonatal 191), and highest following 3rd trimester vaccination (median NT50: maternal 295, neonatal 391). Neutralizing activity is reflected by NT_{50} values (see Methods section).

Figure 5

Anti-S and anti-RBD-specific IgG concentrations in maternal (A, B) and neonatal (C, D) sera in women who completed the two-dose vaccine series in the 1st trimester. Maternal and neonatal antibody concentrations were significantly higher in those who received a third booster dose ($P<0.001$ for all comparisons).

Figure 1: Schematic flow chart of patient inclusion in the study

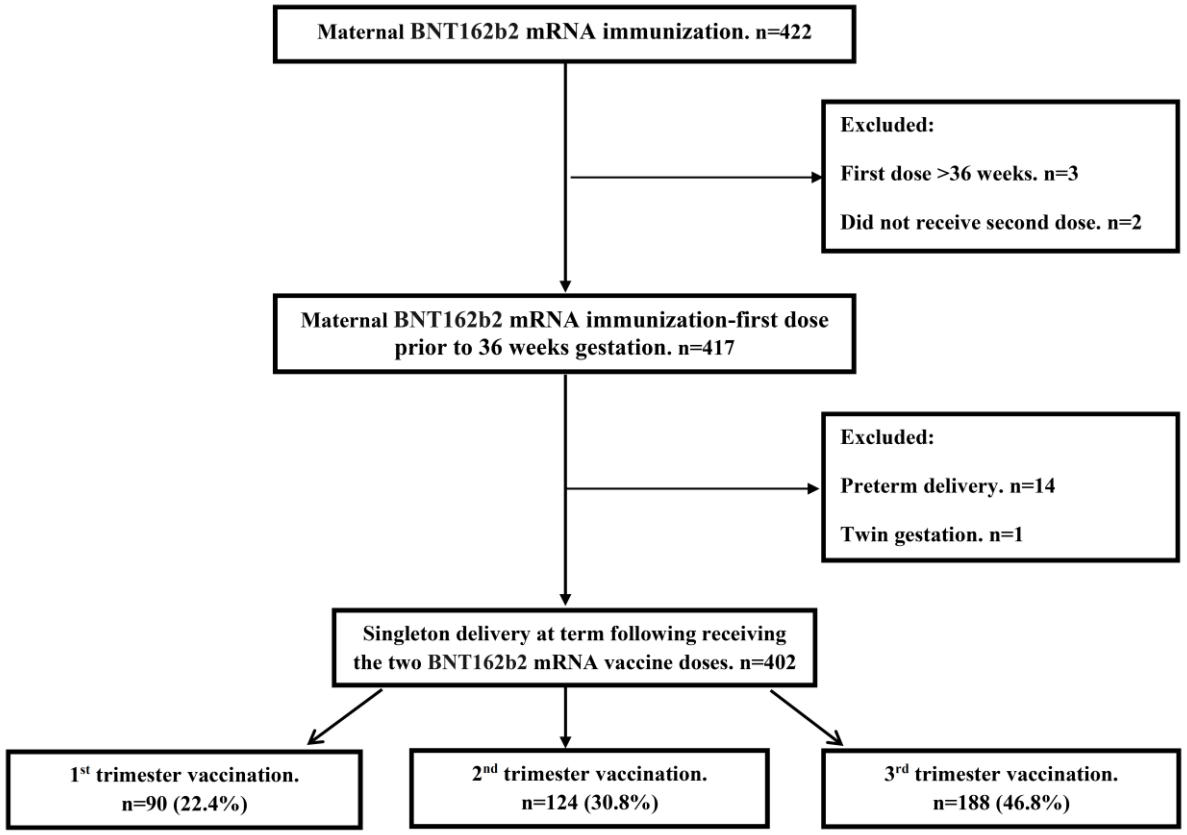

Figure 2

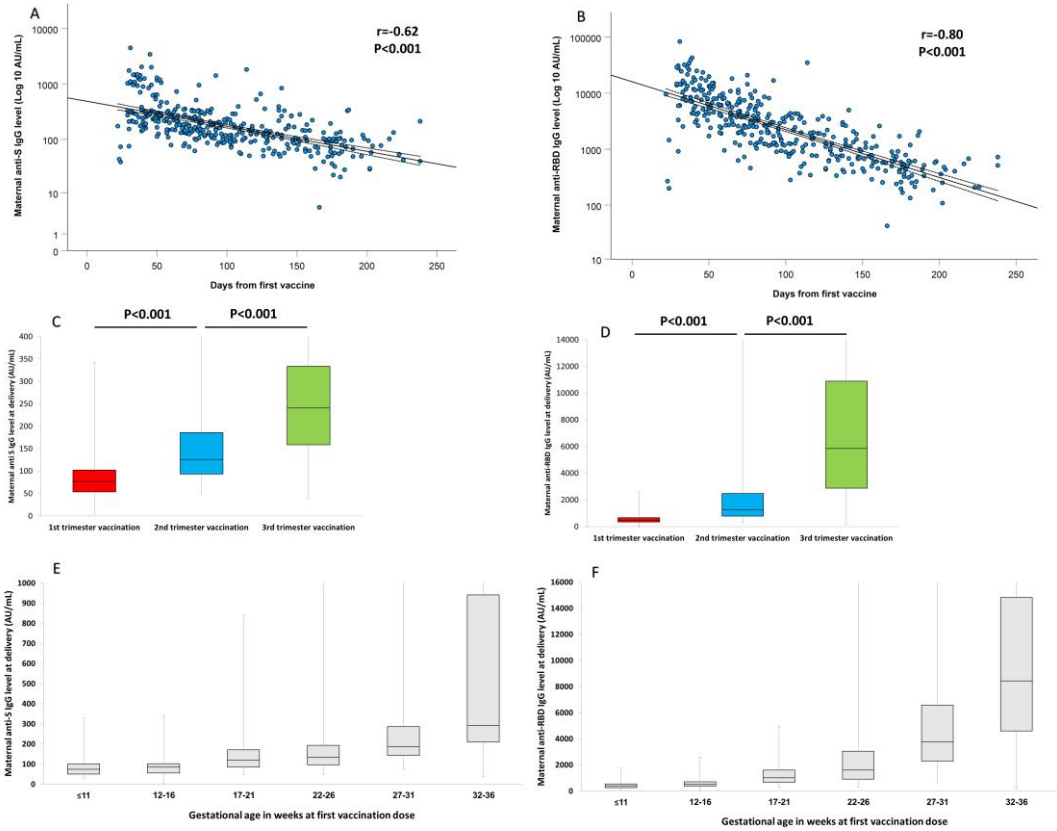

Figure 3

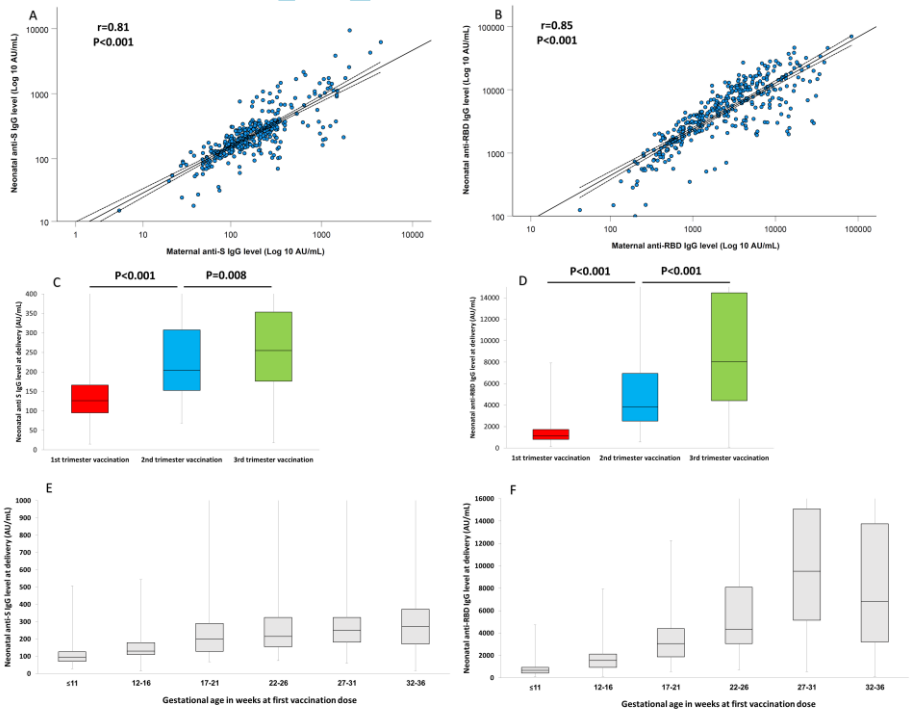

Figure 4

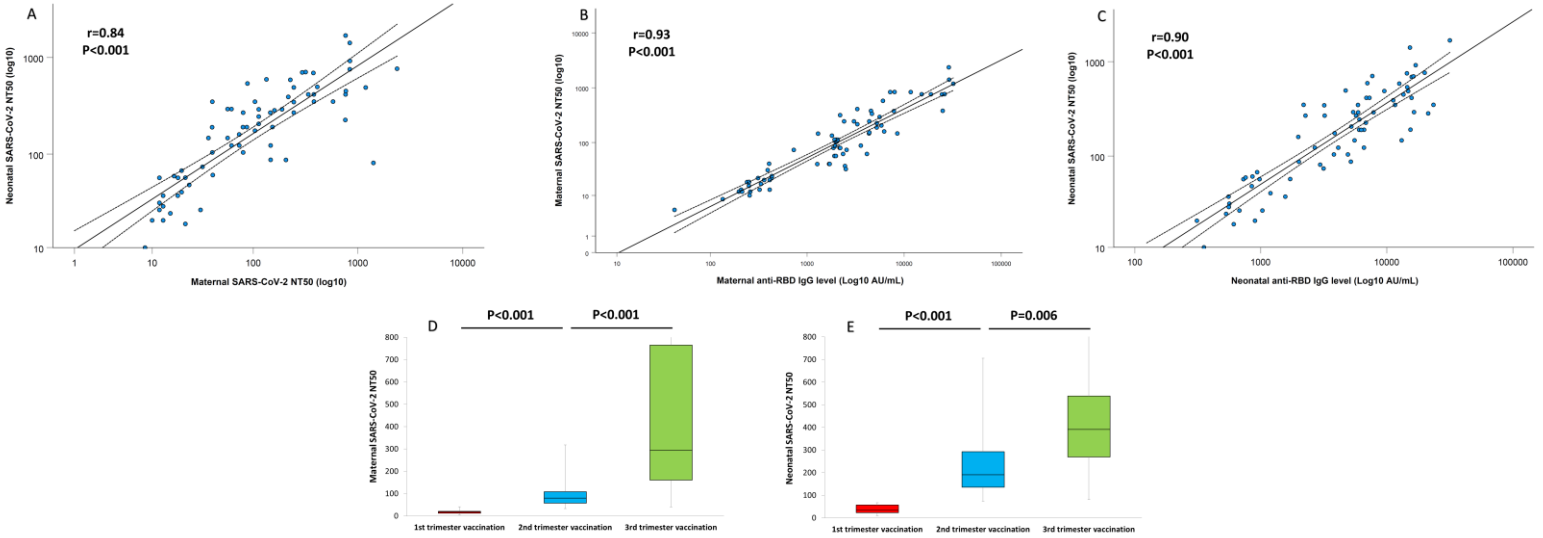
A
r=0.84
P<0.001
Neonatal SARS-CoV-2 NT50 (log10)
Maternal SARS-CoV-2 NT50 (log10)
B
r=0.93
P<0.001
Maternal SARS-CoV-2 NT50 (log10)
Maternal anti-RBD IgG level (Log10 AU/mL)
C
r=0.90
P<0.001
Neonatal SARS-CoV-2 NT50 (log10)
Neonatal anti-RBD IgG level (Log10 AU/mL)
D
P<0.001
P<0.001
Maternal SARS-CoV-2 NT50
1st trimester vaccination
2nd trimester vaccination
3rd trimester vaccination
E
P<0.001
P=0.006
Neonatal SARS-CoV-2 NT50
1st trimester vaccination
2nd trimester vaccination
3rd trimester vaccination

Figure 5