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Research Letter

SARS-CoV-2 Vaccine Booster Elicits Robust Prolonged Maternal Antibody Responses and Passive Transfer to the Offspring via the Placenta and Breastmilk

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The findings in the article will be presented at the 50th Annual Autumn Immunology Conference presented by Autumn Immunology, Inc. on November 18th-21st, 2022 in Chicago, Illinois.

INTRODUCTION

Infection during pregnancy can lead to adverse outcomes for both pregnant persons and offspring\(^1\) as observed during the SARS-CoV-2 global pandemic. Adverse outcomes can be mitigated by maternal vaccination, protecting the pregnant person and the neonate/infant via passive transfer of maternal antibodies either \textit{in utero} via the placenta or after birth via breastmilk.\(^2\) Immunoglobulins G (IgG) transfer from maternal to fetal circulation via neonatal plasma Fc receptors (FcRN) in the placenta and fetal intestines.\(^2\) The Centers of Disease Control and Prevention (CDC) recommend vaccination against SARS-CoV-2 for persons who are pregnant or plan to become pregnant.\(^3\) Despite this recommendation, there remains a high level of vaccine hesitancy among the pregnant population.\(^4\)

Vaccination decisions during pregnancy are often influenced by a primary goal of protecting neonatal health. Thus, the decision to vaccinate during pregnancy or to delay vaccination is shaped by knowledge about impact of vaccine timing and duration of protection. Previous studies investigating maternal SARS-CoV-2 vaccination included minimal longitudinal sampling and focused on one compartment (e.g., maternal blood, or breastmilk). In this study, we assessed the antibody response throughout gestation,
at birth, and up to 12 months post-partum in a cohort of 121 women in maternal circulation, cord blood (UCB), newborn blood (NB), and breastmilk.

**Study Design**

The study was approved by the IRB of Oregon Health & Science University and the University of Kentucky. From March 2021 until June 2022, maternal blood and breastmilk samples were obtained longitudinally from 121 SARS-CoV-2 vaccinated participants. The overwhelming majority (90.9%) of participants received the Pfizer BN162b2 vaccine (Table 1). Umbilical cord and maternal blood were collected at the time of delivery while newborn blood and colostrum were collected within 48 hours of delivery (Figure 1A). An indirect ELISA was used to determine the IgG (total and subclasses) end-point titer (EPT) of antibodies against SARS-CoV-2 receptor-binding domain (RBD) of the spike protein in plasma, whereas breastmilk antibody levels were reported as optical density (OD) values.

**Results**

Maternal plasma RBD-specific IgG titers strongly inversely correlated with time elapsed since first vaccination ($r=0.07043 \ p<0.0001$, half-life 56.45 days). (Figure 1B). After the booster dose, RBD-specific IgG titers increased significantly ($p<0.0001$) (Figure 1C) and exhibited a longer half-life of 128.12 days (Figure 1B, 1D). The booster produced a significant increase in all four IgG isotypes measured in maternal plasma (Figure 1E).

The initial 2-dose vaccination regimen resulted in detectable IgG antibody response in breastmilk (albeit reduced levels compared to maternal plasma) with a half-life of 61.34 days (Figure 1F). Comparable to maternal circulation, the booster produced a
significant increase in antibody levels ($p<0.0001$) (Figure 1G) and half-life (124.67 days) (Figure 1H). After the booster, IgG1 and IgG4 increased significantly, with IgG4 becoming dominant (Figure 1I).

RBD-specific IgG antibodies were detected in UCB plasma albeit at significantly lower levels than in maternal circulation at delivery ($p=0.0012$) (Figure 1J). Interestingly, there was no correlation between UCB RBD-specific IgG titers and maternal titers at delivery (Figure 1K) or time since maternal first vaccination (Figure 1L). Although UCB is often used as surrogate for newborn blood (NB), there may be differences in antibody transfer into UCB and fetal circulation. As described for UCB, titers in NB were lower than those in maternal circulation at delivery ($p=0.0200$) (Figure 1M). In contrast to UCB, a significant positive correlation was observed between paired NB and maternal plasma titers at delivery ($r=0.3782$ $p<0.0001$) (Figure 1N). Moreover, NB titers were inversely correlated with the time since initial maternal vaccination ($r=0.3130$ $p=0.0002$) (Figure 1O) with lower newborn IgG antibody titers in infants born to mothers vaccinated during early pregnancy.

Conclusion

Our results confirm the initial two dose vaccination series during gestation resulted in appreciable RBD-specific IgG response in maternal circulation, UCB, NB, and breastmilk. Longitudinal analysis of post-partum samples indicates the booster dose is essential for eliciting higher and more durable antibody levels in both maternal circulation and breastmilk. SARS-CoV-2-specific maternal antibodies generated via vaccination are passively transferred in utero and after birth via breastfeeding but wane within 6 months after first vaccination dose. Our longitudinal data indicate that
breastmilk antibody levels are dramatically increased by the booster. Therefore, the best neonatal protection against SARS-CoV-2 is for pregnant persons to receive the 3-dose vaccination series at any point during pregnancy to allow for placental antibody transfer, and to subsequently breastfeed their children for at least 6 months, at which point infants are eligible for SARS-CoV-2 vaccination. Continued breastfeeding throughout the first year of life is encouraged as SARS-CoV-2-specific maternal antibody levels persist in breastmilk following booster for at least 12 months.

REFERENCES


Table 1: Cohort Metadata

Subjects are stratified by the trimester of initial maternal SARS-CoV-2 vaccination. Maternal age and gestational age at delivery are mean ± standard deviation. There is no significant difference among maternal age nor gestational age of delivery within the cohort when stratified by vaccination timepoint.
<table>
<thead>
<tr>
<th></th>
<th>All (121)</th>
<th>Pre-pregnancy</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>Post-Partum</th>
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</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>15 (12.4%)</td>
<td>15 (12.4%)</td>
<td>36 (29.8%)</td>
<td>27 (22.3%)</td>
<td>28 (23.1%)</td>
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<tr>
<td>Maternal age (years)</td>
<td>34.9 ± 3.7</td>
<td>34.5 ± 3.1</td>
<td>34.2 ± 4.1</td>
<td>34.8 ± 4.7</td>
<td>33.6 ± 4.6</td>
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<tr>
<td>Gestational age at delivery (years)</td>
<td>38.9 ± 0.9</td>
<td>39.2 ± 1.2</td>
<td>38.9 ± 1.3</td>
<td>39.0 ± 2.0</td>
<td>39.0 ± 1.2</td>
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</tr>
<tr>
<td>Fetal sex (%) female</td>
<td>33%</td>
<td>40%</td>
<td>47%</td>
<td>52%</td>
<td>36%</td>
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<tr>
<td>Initial Vaccine Series</td>
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<td>13</td>
<td>34</td>
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<td>Moderna</td>
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<td>1</td>
<td>4</td>
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</tr>
<tr>
<td>Received booster</td>
<td>14</td>
<td>12</td>
<td>27</td>
<td>23</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Days post second dose that the booster was received</td>
<td>255 ± 29</td>
<td>275 ± 29</td>
<td>219 ± 33</td>
<td>234 ± 33</td>
<td>240 ± 31</td>
<td></td>
</tr>
</tbody>
</table>

FIGURE LEGEND
Figure 1:

(A) Experimental design to investigate the impact of maternal SARS-CoV-2 vaccination on passive transmission of RBD-specific IgG antibodies by assessing antibody titers in maternal plasma, UCB, newborn plasma, and...
breastmilk. (B) RBD-specific IgG antibody titers in maternal plasma relative to days post first vaccination (n=370 samples). (C) RBD-specific IgG antibody titers 50.59 ± 4.46 days before and 55.74 ± 4.14 days after booster dose (n=77 pairs). (D) RBD-specific IgG antibody titers in maternal plasma relative to days post booster dose (n=112). (E) IgG isotype levels 84.07 ± 12.34 days before and 58.47 ± 8.98 days after the booster dose (n=15 pairs). (F) RBD-specific IgG levels in breastmilk after the first and second vaccine doses (n=179). (G) Breastmilk IgG levels 37.84 ± 3.80 days prior to and 55.32 ± 5.30 days after booster (n=45 pairs). (H) RBD-specific IgG antibodies in breastmilk after maternal booster vaccination (n=123). (I) Levels of RBD specific IgG isotypes in breastmilk 57.50 ± 8.17 days before (n=28) and 117.23 ± 11.32 days after the booster dose (n=44). (J) RBD-specific IgG titers in maternal circulation and umbilical cord plasma at delivery (n=45 pairs). (K) Correlation between UCB and maternal RBD-specific IgG titers at delivery (n=45). (L) RBD-specific IgG titers in UCB relative to days since maternal first vaccine dose (n=48). (M) Overall comparison between maternal RBD-specific IgG antibodies at delivery and newborn RBD-specific IgG titers, independent of trimester of initial vaccination (n=35 pairs). (N) Correlation (n=35) of RBD-specific IgG titers in newborn and maternal plasma at delivery. (O) RBD-specific IgG titers in newborn plasma relative to days post maternal vaccination. Bar graphs show median values with the standard error of the mean (SEM). * p < 0.03, ** p < 0.002, *** p < 0.0002, **** p<0.0001.