SHORT COMMUNICATION

The impact of maternal SARS-CoV-2 vaccination and first trimester infection on feto-maternal immune responses

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Abstract

Problem: COVID-19 infection during pregnancy increases maternal and fetal morbidity and mortality. Infection in the second or third trimester leads to changes in the decidual leukocyte populations. However, it is not known whether COVID-19 infection in the first trimester or COVID-19 vaccination during pregnancy alters the decidual immune environment.

Method of study: We examined decidual biopsies obtained at delivery from women who had COVID-19 in the first trimester (n = 8), were fully vaccinated against COVID-19 during pregnancy (n = 17), or were neither infected nor vaccinated during pregnancy (n = 9). Decidual macrophages, NK cells, and T cells were quantified by immunofluorescence. Decidual IL-6, IL-10, and IP-10 were quantified by ELISA.

Results: There were no differences in decidual macrophages, NK cells, T cells, or cytokines between the first trimester COVID-19 group and the control group. The vaccinated cohort had lower levels of macrophages and NK cells compared to the control group. There were no differences in cytokines between the vaccinated and control groups.

Conclusions: COVID-19 infection in the first trimester did not cause significant decidual leukocyte or cytokine changes at the maternal-fetal interface. Additionally, vaccination was not associated with decidual inflammation, supporting the safety of SARS-CoV-2 vaccination during pregnancy.

KEYWORDS
COVID-19, decidual immunity, pregnancy, vaccination

1 INTRODUCTION

COVID-19 infection of pregnant persons (PP) is commonplace and associated with increased disease severity and mortality compared to non-PP.1–3 COVID-19 during pregnancy also increases the risk for pregnancy complications including preterm delivery, pre-eclampsia, and perinatal death.4–6 Most of the perinatal morbidity is derived from maternal critical illness rather than fetal infection.1 However, COVID-19 viremia during pregnancy can lead to the rare complication of SARS-CoV-2 placentitis, which is associated with stillbirth and neonatal death.7

Given this, COVID-19 vaccines have the potential to decrease disease burden and untoward outcomes in PP. However, vaccine uptake during pregnancy has been lower than in the general public,8 which
may be due to concerns regarding the safety of vaccine for the developing fetus, concerns regarding future fertility difficulties, and general vaccine hesitancy.

Regarding COVID-19 vaccine safety, multiple epidemiologic studies and national registries of vaccine safety have seen no evidence of vaccine-associated pregnancy, perinatal, or neonatal adverse effects.\textsuperscript{5–13} COVID-19 vaccination leads to similar antibody titers between pregnant and non-pregnant groups, higher titers than natural infection during pregnancy, and similar clinical efficacy to the general population.\textsuperscript{11,14,15} Anti-Spike IgG antibodies cross the placenta and are present in cord blood at birth,\textsuperscript{14,15} and cord blood antibody titers are maximal following late second or early third-trimester vaccination.\textsuperscript{16} Preliminary clinical evidence suggests that vaccines prevent hospitalization from COVID-19 in infants less than 6 months of age.\textsuperscript{17} Taken as a whole, studies thus far support the safety and efficacy of COVID-19 vaccination during pregnancy.

However, mRNA vaccines remain a novel platform for vaccine delivery and cause systemic side effects in all groups, including PP.\textsuperscript{18} While studies thus far support the safety of vaccination in terms of perinatal complications, it is possible that the immune response to COVID-19 vaccination affects the decidua basalis of the placenta and therefore may lead to as-yet undiscovered negative consequences to the fetus. There are no reported differences in placental pathology following COVID-19 vaccination during pregnancy,\textsuperscript{19} but it remains unknown whether there are changes in the decidual immune response. This is particularly important to consider given the growing knowledge that COVID-19 infection impacts the placental immune environment, including the decidua, even in the absence of SARS-CoV-2 placentitis.

Our laboratory recently demonstrated that COVID-19 during the second or third trimester of pregnancy leads to decidual accumulation of T cells, and that COVID-19 during the third trimester leads to increases in decidual NK cells and macrophages.\textsuperscript{20} Work from other groups have confirmed that late-gestation COVID-19 leads to changes in the decidual immune response, including local activation of maternal decidual NK cells and T cells.\textsuperscript{21,22} In terms of early gestation COVID-19 infections, there are reports that first-trimester COVID-19 can lead to fetal loss\textsuperscript{23} and immune infiltration\textsuperscript{24} of the decidua. Importantly, whether there are lasting changes to the decidual immune environment following COVID-19 infection in the first trimester when the pregnancy is carried to term remains less well studied.

The overall goal of this study was to improve understanding of the decidual immune response to COVID-19 infection and vaccination by investigating the impact of first-trimester infection and COVID-19 vaccination on decidual leukocytes and inflammation at delivery.

2 MATERIALS AND METHODS

2.1 Study enrollment

The study cohort was recruited at Boston Medical Center (BMC) and all patient enrollment/tissue collection was approved by the BMC Institutional Review Board. Parent-infant dyads were consented in a prospective cohort study (July 2020 – November 2021). Inclusion criteria included age minimum of 18 years, singleton pregnancy, full-term (gestational age ≥ 37 weeks) delivery, and English/Spanish speaking. For the COVID-19 First-Tri group, PP had a positive SARS-CoV-2 nasopharyngeal qRT-PCR test and symptoms of COVID-19 between weeks 2 and 12 of pregnancy. For the control group, PP must not have had a documented SARS-CoV-2 infection at any point during pregnancy. For the vaccinated group, PP must have been fully vaccinated (including two doses of mRNA vaccines) during pregnancy and must not have had a documented SARS-CoV-2 infection at any point during pregnancy. An electronic REDCap vaccination survey was administered to participants in the vaccinated group at the time of delivery, confirming their date and type of COVID-19 vaccination, any other vaccinations during the pregnancy, and any vaccine adverse reactions. Demographic and clinical variables were obtained from the electronic medical record (EMR) and recorded in a secure, de-identified RedCap Database (www.project-redcap.org).

2.2 Sample collection

Fresh placental tissue was collected and processed within 6 h after delivery. Cytokine analysis: Dissected decidual tissue biopsies were obtained according to established methods,\textsuperscript{25} flash-frozen with dry ice, and stored at −80°C. We have previously published that samples obtained using these methods have high expression of the decidual markers IGF-BP1 and HLA-A.\textsuperscript{20} Immune cell analysis: Placental full-thickness biopsies were fixed with formaldehyde/sucrose for 72 h, embedded in OCT (Fisher), frozen at −80°C, and cryosectioned at 10 μM thickness. Serum antibody analysis: All delivery specimens were collected by bedside clinical staff and/or trained research staff. Five milliliter of maternal blood and 5 ml of cord blood were collected during the delivery hospitalization. An infant blood sample of 0.5 – 1 ml was collected during the delivery hospitalization if cord blood could not be obtained. All samples were then transported to our BLS-2 plus research laboratory. Blood samples were centrifuged and plasma was extracted and frozen at −80°C in aliquots until analysis.

2.3 Immune cell analysis

2.3.1 Immunohistochemistry

Immune cell analysis of the decidual basalis was performed as previously published by our group.\textsuperscript{20} Briefly, full-thickness placental tissue sections containing decidua basalis were washed, permeabilized, and incubated with Histostain Plus Broad Spectrum Blocking Solution (#859043, Novex by Life Technologies). The following primary antibodies were used at 1:100 dilution: CD14 (mouse anti-human, 14-149-82, Invitrogen), CD56 (mouse anti-human, 14-0567-82, Invitrogen), CD3 (mouse anti-human, 14-0038-82, Invitrogen), SARS-CoV-2 spike glycoprotein (rabbit anti-human, ab272504 Abcam). Fluorescently labeled secondary antibodies (Alexa 594 anti-mouse, ab150108 Abcam or
AlexaFluor 647 anti-rabbit, A21244, Life Technologies) were used at 1:500 dilution. Control slides were incubated with secondary antibody alone. Washed slides were cover slipped with Prolong Gold with DAPI (ThermoFisher).

2.3.2 Microscopy

Images were acquired on a Nikon deconvolution wide-field epifluorescence microscope using NIS-Elements Software (Nikon). Decidua basalis areas were identified by manual survey at 100× followed by automated acquisition at 200× with standardized exposure times of four tiled images from five randomized areas per slide.

2.3.3 Quantitative Image Analysis

Image area and integrated density were measured via ImageJ software (imagej.net) for each immunofluorescent 200× image (n=5/slide). Corrected total cell fluorescence (CTCF) and a final Fluorescence Ratio (target antigen CTCF/secondary only control CTCF) were calculated per published protocols. All ImageJ analysis and calculations were performed on blinded samples.

2.4 Cytokine protein analysis

2.4.1 Protein isolation

Tissue lysates were prepared from frozen decidua basalis biopsies (100–300 mg) via mechanical homogenization in NP-40 Lysis Buffer (ThermoFisher #J60766) with Pierce Protease inhibitor (ThermoFisher #A32953). Homogenates were centrifuged at 20,000×g for 30 min at 4°C. Supernatants were collected and frozen at −80°C. Protein concentrations were determined using Pierce BCA Protein Assay (ThermoFisher #23225).

2.4.2 ELISA

IL-10 (Invitrogen #EHI101), IL-6 (Invitrogen #KHC0061), and IP-10 (Invitrogen #KAC2361) ELISA were performed on decidua basalis biopsy lysates according to the manufacturer’s instructions. Cytokine/chemokine concentrations were normalized to total protein as measured by BCA. The IP-10 ELISA was repeated to ensure reproducibility with consistent results and results across the 2 days of experiments were averaged.

2.5 Serum antibody quantification

Antibodies reactive to SARS-CoV-2 receptor binding domain (RBD) of the spike protein and nucleocapsid protein (N-protein) were assayed from plasma following the BU ELISA protocol as previously described. Subject maternal or infant (cord/neonatal) serum or dilutions of monoclonal SARS-CoV-2 reactive antibodies (RBD IgG, clone CR3022, gift from the Alter lab at Ragon Institute) were added to 96-well plates coated with the appropriate SARS-CoV-2 protein. The secondary antibody was anti-human horseradish peroxidase (HRP)-conjugated antibody against IgG (cat#A18817, Thermo Fisher, 1:2000), and detection was performed with 3,3′,5,5′-Tetramethylbenzidine (TMB)-ELISA substrate solution (Thermo Fisher Scientific, cat# 34029) with accompanying stop solution for TMB (Thermo Fisher Scientific, cat#N600). Optical density was measured 450 nm (OD 450 nm) on a Synergy HT Multi-Detection Microplate reader (BioTek Instruments) using the accompanying Gen5 software. Arbitrary units (AU) on a ng/ml scale were calculated as previously described.

2.6 Statistical analysis

All statistical analyses were performed using Prism 9 software (GraphPad). Differences were considered significant at α = 0.05. Specific statistical tests are described in the respective Figure or Table legend.

3 RESULTS AND DISCUSSION

3.1 Cohort demographic and clinical information

Our cohort included PP who had mild-to-moderate symptomatic COVID-19 that did not require hospitalization during their first trimester of pregnancy (COVID−first Tri, n = 8), PP who were fully vaccinated with mRNA-1273 (Moderna/Spikevax) or BNT162b2 (Pfizer/Comirnaty) (Vaccinated, n = 17), or PP who had neither a documented COVID-19 infection nor vaccination during pregnancy (Control, n = 9). All tissue specimens were collected at the time of delivery in these full-term pregnancies (Figure S1). Table 1 presents clinical and demographic information for all maternal-fetal dyads. There were no significant differences in maternal age, race, ethnicity, chronic health conditions, or pregnancy complications. There were also no significant differences in infant gestational age, birth measurements, or NICU admission. Placental pathology was reviewed for all participants for whom pathology was obtained for a clinical indication, and the findings are summarized in Table S1. An important limitation of this study is that only term deliveries were enrolled.

3.2 Decidual leukocyte analysis following COVID-19 in first trimester

We previously demonstrated that COVID-19 infection in the third trimester of pregnancy leads to increased macrophage and NK cell immunofluorescence in the decidua basalis at delivery, and COVID-19 infection in the second and third trimester is associated with increased
| Variable                                           | Control group | COVID-First Tri | p-Value (compared to Control) | Vaccinated group | p-Value (compared to control) |
|----------------------------------------------------|---------------|----------------|------------------------------|-----------------|------------------------------|
| Maternal age at delivery (years)                   | N = 9         | N = 8          | .46^c                        | N = 17          | .44^d                        |
| Maternal race                                      |               |                |                              |                 |                              |
| Black                                               | 3 (33.3%)     | 2 (25%)        |                              | 3 (17.6%)       |                              |
| White                                               | 0 (0%)        | 1 (12.5%)      |                              | 8 (47.1%)       |                              |
| Asian                                               | 1 (11.1%)     | 1 (12%)        |                              | 1 (5.9%)        |                              |
| Other                                               | 5 (55.6%)     | 4 (50%)        |                              | 3 (17.6%)       |                              |
| Unknown                                             | 2 (11.7%)     |                |                              |                 |                              |
| Maternal ethnicity                                 |               |                | > .99                        |                 | .50                          |
| Hispanic                                            | 5 (55.6%)     | 4 (50%)        |                              | 3 (17.6%)       |                              |
| Non-Hispanic                                       | 4 (44.4%)     | 4 (50%)        |                              | 13 (76.5%)      |                              |
| Unknown                                             | 1 (5.9%)      |                |                              |                 |                              |
| Maternal primary language                           |               |                | .64                          |                 | .08                          |
| English                                             | 4 (44.4%)     | 5 (62.5%)      |                              | 3 (17.6%)       |                              |
| Spanish                                             | 5 (55.6%)     | 3 (37.5%)      |                              | 14 (82.4%)      |                              |
| Maternal chronic health condition\(^a\)            | 5 (55.6%)     | 3 (37.5%)      | > .99                        | 12 (71%)        | .67                          |
| All pregnancy co-morbidities\(^b\)                 | 7 (77.8%)     | 6 (75%)        | > .99                        | 15 (88.2%)      | .59                          |
| Chorioamnionitis                                    | 0             | 1 (12.5%)      | -                            | 3 (17.6%)       | -                            |
| Gestational diabetes                                | 1 (11.1%)     | 1 (12.5%)      | -                            | 3 (17.6%)       | -                            |
| Hypertensive disorder of pregnancy                  | 6 (66.7%)     | 1 (12.5%)      | -                            | 8 (47.1%)       | -                            |
| Hypertensive disorder of pregnancy with severe features | 0             | 1 (12.5%)      | -                            | 0               | -                            |
| Fetal growth restriction                            | 1 (11.1%)     | 1 (12.5%)      | -                            | 4 (23.5%)       |                              |
| Preterm labor                                       | 0             | 1 (12.5%)      | -                            | 0               | -                            |
| Unexplained vaginal bleeding                        | 1 (11.1%)     | 1 (12.5%)      | -                            | 0               | -                            |
| Delivery mode                                       |               |                | > .99                        |                 | .67                          |
| Vaginal                                             | 7 (77.8%)     | 6 (75%)        |                              | 11 (64.7%)      |                              |
| Caesarian section                                   | 2 (22.2%)     | 2 (25%)        |                              | 6 (35.3%)       |                              |
| Gestational age (weeks) at time of COVID-19 infection | N/A           | 7.5 (3.8)      | -                            | N/A             | -                            |
| Maternal symptoms of COVID-19                      | N/A           | 8 (100%)       | -                            | N/A             | -                            |
| Maternal hospitalization for COVID-19               | N/A           | 0 (0%)         | -                            | N/A             | -                            |
| Gestational age at delivery (weeks)                | 39.0 (1.7)    | 38.7 (1.9)     | .76^c                        | 38.9 (9)        | .87^c                        |
| Infant birth weight (grams)                        | 3243 (722)    | 3158 (709)     | .81^c                        | 3083 (895)      | .75^d                        |
| Birth length (cm)                                  | 49.6 (2.9)    | 50.1 (3.2)     | .75^c                        | 50.0 (1.6)      | .71^c                        |
| Birth head circumference (cm)                      | 34.3 (1.8)    | 33.7 (1.9)^c   | .47                          | 34.0 (1.4)      | .44^d                        |
| Infant sex                                          |               |                | > .99                        |                 | .68                          |
| Male                                                | 5 (55.6%)     | 4 (50%)        |                              | 7 (41.2%)       |                              |
| Female                                              | 4 (44.4%)     | 4 (50%)        |                              | 10 (58.8%)      |                              |
| NICU admission                                      | 1 (11.1%)     | 1 (12.5%)      | > .99                        | 0               | -                            |

(Continues)
Decidual cytokine analysis following COVID-19

We next evaluated decidual cytokines following COVID-19 infection in the first trimester. Adults with COVID-19 have elevations of IP-10, IL-6, and IL-10\(^{21,31,32}\) and we previously demonstrated that cord blood IP-10 levels are higher in pregnancies complicated by COVID-19.\(^{33}\) Therefore, we chose to evaluate decidual protein levels of IP-10, IL-6, and IL-10. There were no differences in cytokine levels between the COVID-first tri or Control cohorts (Figure 2A–C). Taken together, the findings of similar cytokine levels and decidual leukocyte immunofluorescence in our small cohort suggest that early COVID-19 infection does not lead to decidua basalis inflammation that remains evident months later at delivery. During pregnancy, Th2-associated anti-inflammatory mechanisms may function to blunt proinflammatory cytokine release.\(^{34}\) Viruses associated with severe congenital defects often are the most deleterious when infection occurs in the first trimester,\(^{35}\) and the lack of immunopathology in the decidua following COVID-19 infection in the first trimester is in line with the epidemiological evidence that COVID-19 does not cause congenital defects. There are several important limitations to these results. Foremost, the cohort is very limited in sample size and only includes PP who carried the pregnancy until term. The immediate effect of COVID-19 infection on the decidua during first-trimester infection is not investigated in this work.

### Decidual cytokine analysis following COVID-19 in first trimester

We next evaluated decidual cytokines following COVID-19 infection in the first trimester. Adults with COVID-19 have elevations of IP-10, IL-6, and IL-10\(^{21,31,32}\) and we previously demonstrated that cord blood IP-10 levels are higher in pregnancies complicated by COVID-19.\(^{33}\) Therefore, we chose to evaluate decidual protein levels of IP-10, IL-6, and IL-10. There were no differences in cytokine levels between the COVID-first tri or Control cohorts (Figure 2A–C). Taken together, the findings of similar cytokine levels and decidual leukocyte immunofluorescence in our small cohort suggest that early COVID-19 infection does not lead to decidua basalis inflammation that remains evident months later at delivery. During pregnancy, Th2-associated anti-inflammatory mechanisms may function to blunt proinflammatory cytokine release.\(^{34}\) Viruses associated with severe congenital defects often are the most deleterious when infection occurs in the first trimester,\(^{35}\) and the lack of immunopathology in the decidua following COVID-19 infection in the first trimester is in line with the epidemiological evidence that COVID-19 does not cause congenital defects. There are several important limitations to these results. Foremost, the cohort is very limited in sample size and only includes PP who carried the pregnancy until term. The immediate effect of COVID-19 infection on the decidua during first-trimester infection is not investigated in this work.
FIGURE 1  Decidual immune cells following SARS-CoV-2 vaccination during pregnancy in comparison to first trimester infection and uninfected, unvaccinated controls. (A, C, E) Representative images (200×) of decidual areas stained for (A) CD14, (C) CD56, or (E) CD3 immunofluorescence. White scale bar = 50 μm. Dashed insets are higher magnification, with green scale bar = 12.5 μm. Solid insets: secondary-only controls. (B, D, F) Graphical analysis of comparative fluorescence quantitation of (B) CD14, (D) CD56, or (F) CD3. n = 16 (vaccinated), n = 8 (first trimester COVID infection), n = 9 (control). **p < .01; ****p < .0001.

cohort. Similarly, there was significantly less CD56 fluorescent staining in the vaccinated cohort compared to the Control group (NK cell marker, Figure 1C,D). There was no difference in CD3 fluorescence between groups (T cell marker, Figure 1E,F). SARS-CoV-2 Spike protein was not detected in any sample (data not shown). There was no correlation between immune cell fluorescence and duration of time from vaccination and delivery (Figure S3A-C), nor were there significant differences in decidual immune cell fluorescence by vaccine type (BNT162b2 or mRNA-1273, Figure S4A-C). Therefore, using the same methods in the same laboratory, we can confirm that second or third trimester COVID-19 vaccination leads to leukocyte accumulation in the decidua, but vaccination does not.

The finding of decreased decidual NK cells and macrophages was surprising and should be investigated in larger clinical cohorts to determine if it is a direct effect of vaccination. There appears to be a lack of studies in the literature evaluating the impact of other common vaccinations during pregnancy (influenza, Tdap) on decidual leukocytes, and future studies should investigate this area.
3.5 Decidual cytokines analysis following COVID-19 vaccination during pregnancy

We next assayed the levels of IL-6, IL-10, and IP-10 in the decidua for the vaccinated cohort and saw no significant differences in comparison with the control cohort (Figure 2A-C). Timing of vaccination did not alter levels of IL-6, IL-10, or IP-10 (Figure S3D-F), and neither did the type of mRNA vaccine administered (Figure S4D-F). This provides evidence that there is not lasting decidual inflammation following COVID-19 vaccination pregnancy, although it is possible that there is a brief inflammatory response immediately following vaccination, which we did not investigate.

It is important to understand the immune response because of the potential consequences on the developing neonatal immune system. A recent study demonstrated that the neonatal immune system was altered by recent or ongoing maternal COVID-19 infection during pregnancy. Neonates had increased plasma cytokine levels, NK cells, regulatory T cells, and γδ T cells.36 One might surmise that these immune cell changes could cause long-term consequences, such as altered neurodevelopmental outcomes37 or other yet unrecognized
long-term immune response changes. It is reassuring that there is no signal for increased inflammation at the maternal-fetal interface following vaccination.

### 3.6 Seroconversion following COVID-19 vaccination does not correlate with increased decidual leukocytes or cytokines

COVID-19 vaccination causes a local and systemic inflammatory response, but whether an effective vaccine response causes inflammation in the decidua is less well known. Antibody production against the SARS-CoV-2 Spike protein is the best studied surrogate of protection following COVID-19 vaccination. We quantified the maternal and infant serum levels of anti-Spike receptor-binding domain IgG and nucleocapsid protein NP (Figure S5). All participants except one had high Spike IgG levels at delivery. We also noted that three individuals had high levels of NP IgG levels, indicating a history of natural infection with COVID-19, although whether this occurred during pregnancy or prior to pregnancy could not be evaluated. We correlated maternal and infant IgG levels with decidual CD14, CD56, and CD3 fluorescence (Figure S3). There was no signal of higher antibody levels correlating with increased decidual leukocytes. In contrast, there was a significant negative correlation between CD56 fluorescence and maternal IgG (Figure S8), as well as a significant negative correlation between CD3 fluorescence and maternal IgG (Figure S3C). There were no differences in decidual cell fluorescence or decidual cytokines in PP with serological evidence of natural COVID-19 infection (Figure S6). These results provide evidence that successful vaccination is not associated with decidual inflammation.

Of note, our cohort was enrolled and samples were collected prior to COVID-19 vaccine boosters and prior to the emergence of SARS-CoV-2 variants in our region. Another important limitation is that this study only includes participants who received a mRNA vaccine. This is not a significant drawback as the majority of PP are vaccinated with a mRNA vaccine. An additional limitation to our results is that COVID-19 antibodies were not assessed in the control group, and therefore asymptomatic or occult infection during pregnancy cannot be ruled out. Taken together, this study demonstrated that COVID-19 infection in the first trimester did not cause significant decidual leukocyte or cytokine changes at the maternal-fetal interface, that vaccination was not associated with increased inflammation at the maternal-fetal interface, and further supports the safety of COVID-19 vaccination during pregnancy.

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### CONFLICTS OF INTEREST

None to declare.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

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