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Longitudinal antibody response kinetics following SARS-CoV-2 messenger RNA vaccination in pregnant and nonpregnant persons

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BACKGROUND: For some vaccine-preventable diseases, the immunologic response to vaccination is altered by a pregnant state. The effect of pregnancy on SARS-CoV-2 vaccine response remains unclear.

OBJECTIVE: We sought to characterize the peak and longitudinal anti-S immunoglobulin G, immunoglobulin M, and immunoglobulin A responses to messenger RNA-based SARS-CoV-2 vaccination in pregnant persons and compare them with those in nonpregnant, reproductive-aged persons.

STUDY DESIGN: We conducted 2 parallel prospective cohort studies among pregnant and nonpregnant persons who received SARS-CoV-2 messenger RNA vaccinations. Blood was collected at the time of first and second vaccine doses, 2 weeks post second dosage, and with serial longitudinal follow-up up to 41.7 weeks post vaccination initiation. Anti-S immunoglobulin M, immunoglobulin G, and immunoglobulin A were analyzed by enzyme-linked immunosorbent assay. We excluded those with previous evidence of SARS-CoV-2 infection by history or presence of anti-nucleocapsid antibodies. In addition, for this study, we did not include individuals who received a third or booster vaccine dosage during the study period. We also excluded pregnant persons who were not fully vaccinated (14 days post receipt of the second vaccine dosage) by time of delivery and nonpregnant persons who became pregnant through the course of the study. We studied the effect of gestational age at vaccination on the anti-S response using Spearman correlation. We compared the peak anti-S antibody responses between pregnant and nonpregnant persons using a Mann-Whitney U test. We visualized and studied the longitudinal anti-S antibody response using locally weighted scatterplot smoothing, Mann-Whitney U test, and mixed analysis of variance test.

RESULTS: Data from 53 pregnant and 21 nonpregnant persons were included in this analysis. The median (interquartile range) age of the pregnant and nonpregnant participants was 35.0 (33.3–37.8) years and 36.0 (33.0–41.0) years, respectively. Six (11.3%) participants initiated vaccination in the first trimester, 23 (43.3%) in the second trimester, and 24 (45.3%) in the third trimester, with a median gestational age at delivery of 39.6 (39.0–40.0) weeks. The median (interquartile range) follow-up time from vaccine initiation to the last blood sample collected was 25.9 (11.9) weeks and 28.9 (12.9) weeks in the pregnant and nonpregnant cohort, respectively. Among pregnant persons, anti-S immunoglobulin G, immunoglobulin A, and immunoglobulin M responses were not associated with gestational age at vaccine initiation (all P > .05). The anti-S immunoglobulin G response at 2 weeks post second dosage was not statistically different between pregnant and nonpregnant persons (P > .05). However, the anti-S immunoglobulin M and immunoglobulin A responses at 2 weeks post second dosage were significantly higher in pregnant compared with nonpregnant persons (P < .001 for both). The anti-S immunoglobulin G and immunoglobulin M levels 6 to 8 months after vaccine initiation fell to comparable proportions of the peak 2 weeks post second dosage antibody levels between pregnant and nonpregnant persons (immunoglobulin G P = .77; immunoglobulin M P = .51). In contrast, immunoglobulin A levels 6 to 8 months after vaccine initiation fell to statistically significantly higher proportions of peak 2 weeks post second dosage antibody levels in pregnant compared with nonpregnant persons (P = .002). Maternal anti-S immunoglobulin G levels were strongly correlated with umbilical cord anti-S immunoglobulin G levels (R = 0.8, P < .001).

CONCLUSION: The anti-S immunoglobulin A, immunoglobulin M, and immunoglobulin G response to SARS-CoV-2 vaccination in pregnancy is independent of gestational age of vaccine initiation. Maintenance of the immunoglobulin G response is comparable between pregnant and nonpregnant persons. The differential peak response of immunoglobulin M and immunoglobulin A and the differential decline of anti-S immunoglobulin A between pregnant and nonpregnant persons requires further investigation.

Key words: COVID-19 vaccination, immunoglobulin A, immunoglobulin M, immunoglobulin G, immune response, maternal, neonate, passive immunity, postpartum, pregnancy, spike protein, titers, umbilical cord blood

Introduction

COVID-19 is associated with adverse pregnancy outcomes including preterm delivery, stillbirth, maternal intensive care unit admission, mechanical ventilation, and maternal death. Vaccination against COVID-19 is recommended in pregnancy. However, data on vaccination in pregnancy are limited, as pregnant persons were excluded from the initial SARS-CoV-2 messenger RNA (mRNA) vaccine trials. Vaccination with the mRNA-lipid nanoparticle (LNP) platform has been demonstrated to result in a robust maternal immune response. Whether the immunologic milieu of pregnancy alters the longitudinal vaccine response to mRNA-based immunization...
Pregnancy induces an immunologic shift to a Th2-mediated immunity. These changes are responsible for differential susceptibilities to infections during pregnancy and differential responses to some vaccinations in pregnancy and across gestational ages in pregnancy. When considering COVID-19 vaccination in pregnancy, a study of 30 pregnant and 57 nonpregnant persons who received an mRNA-based SARS-CoV-2 vaccine demonstrated similar anti-spike (S) immunoglobulin (Ig) G titers between groups 2 weeks after the second dosage of the vaccine. Similar findings were noted in a separate cohort comparing 17 pregnant persons with 16 nonpregnant persons 2 to 6 weeks after the second dosage of an mRNA-based SARS-CoV-2 vaccine. A recent study evaluating differences in immune response by trimester did not identify differences in anti-S titers by trimester of vaccine initiation. The long-term durability and kinetics of the vaccine-elicited antibody responses between pregnant and nonpregnant persons was not assessed.

In this study, we sought to describe the peak and longitudinal antibody response kinetics to the 2-dosage mRNA-LNP-based SARS-CoV-2 vaccination across various gestational ages of vaccination initiation in pregnancy and to compare the vaccine-elicited antibody response of pregnant persons with that of nonpregnant persons.

**Materials and Methods**

We conducted dual prospective cohort studies at a single academic medical center with regard to SARS-CoV-2 vaccination. Participants received vaccinations between December 18, 2020 and June 26, 2021.

The first cohort prospectively recruited pregnant participants between 18–45 years of age who were planning to (1) deliver at this institution and (2) receive mRNA-based SARS-CoV-2 vaccination (Pfizer-BioNTech BNT162b2; New York, NY, USA or Moderna mRNA-1273; Cambridge, MA, USA) at any gestational age. Information about the study was distributed at sites of care and vaccination sites within the hospital and at our network care facilities. Interested participants completed a questionnaire, and only participants who had yet to receive any doses of the SARS-CoV-2 vaccinations were included in the study. Sampling was conducted close to: time at first vaccine dosage (t0), time at second vaccine dosage (t1), 2 weeks post second vaccine dosage (t2), delivery, and longitudinal serial follow-ups at approximately 6 weeks and 6 months postpartum. Blood samples were collected prospectively for all visits except for the maternal blood sample at delivery and neonatal umbilical cord blood sample, which were collected from discarded clinical specimens used for routine clinical testing. These prospective samples were taken between March 2, 2021 and December 3, 2021. Written informed consent was obtained before study participation. All participants were consented for the collection and testing of samples and for collecting of pertinent patient information and clinical history via self-report or the electronic health record. Screening for an updated history of COVID-19 infections continued throughout the participation of the study.

The second cohort prospectively recruited nonpregnant adults between 18 and 80 years of age who were planning to receive mRNA-based SARS-CoV-2 vaccination (Pfizer-BioNTech BNT162b2, Moderna mRNA-1273). Information about the study was distributed at sites of care and vaccination sites within the hospital and at our network care facilities. Interested participants completed a questionnaire, and only participants who had yet to receive any doses of the SARS-CoV-2 vaccinations were included in the study. For the purposes of this analysis, we only included females under the age of 45 years to age-match a comparison population of reproductive-aged nonpregnant persons. Participants who became pregnant through the course of the study were excluded from analysis. Sampling was conducted close to: time at first vaccine dosage (t0), time at second vaccine dosage (t1), 2 weeks post second vaccine dosage (t2), and longitudinal serial follow-ups at approximately 3 months, 6 months, and 9 months after the first vaccine dosage. All blood samples were prospectively collected between December 31, 2020 and
We enrolled 78 participants in the pregnant cohort and excluded 25 participants for the following reasons: 19 had a history of COVID-19 at t0, 5 were not fully vaccinated by the time of delivery, and 1 received a non-mRNA-based vaccine. Among the 53 pregnant persons included, all delivered liveborn infants between April 13, 2021, and November 29, 2021. The median (interquartile range [IQR]) maternal age at the time of delivery was 35.0 (33.3–37.8) years, and the median (IQR) gestational ages at vaccine initiation and delivery were 26.3 (19.1–30.7) weeks and 39.6 (39.0–40.0) weeks, respectively (Table 1). No participant had an immunosuppressing condition or used an immunosuppressing medication. The 53 pregnant participants delivered 53 live-born neonates, from whom 49 umbilical cord blood samples were analyzed for this study. At the date of last sample collection included in this study (December 3, 2021), 48 participants reached the 6 week postpartum time point, and all had samples collected; 29 participants reached the 6 month postpartum time point, and samples were
TABLE 1

Demographic characteristics of the pregnant and nonpregnant cohort

| Characteristics                          | Pregnant cohort (n=53) | Nonpregnant cohort (n=21) |
|------------------------------------------|------------------------|---------------------------|
| Demographics                             |                        |                           |
| Age, median (IQR) (y)                    | 35.0 (33.3−37.8)       | 36.0 (33.0−41.0)          |
| Gestational age at t0, n (%)             |                        |                           |
| <14 wk                                   | 6 (11%)                | NA                        |
| 14−<28 wk                                | 23 (43%)               | NA                        |
| ≥28 wk                                   | 24 (45%)               | NA                        |
| Gestational age at delivery, median (IQR) (wk) | 39.6 (39.0−40.0)       | NA                        |
| Liveborn neonates, n (%)                 | 53 (100%)              | NA                        |
| Umbilical cord blood captured, n (%)     | 49 (92%)               | NA                        |
| Vaccine type received, n (%)             |                        |                           |
| Pfizer-BioNTech BNT162b2                 | 42 (79%)               | 15 (71%)                  |
| Moderna mRNA-1273                        | 11 (21%)               | 6 (29%)                   |

NA, not applicable; t0, blood collected at first time.

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collected from 25 participants. The median (IQR) follow-up was 25.9 (11.9) weeks.

From the nonpregnant cohort, we included data from 21 participants who did not self-identify as pregnant before or throughout the course of the study and who did not have an immunosuppressed condition or used an immunosuppressing medication. The median (IQR) age of the participants was 36.0 (33.0−41.0) years. The median (IQR) follow-up was 28.9 (12.9) weeks.

Among pregnant participants, the magnitudes of the anti-S IgA, IgG, and IgM responses at time points t1 and t2 were not significantly associated with gestational age of vaccine initiation (Figure 1). Because the maternal anti-S responses appeared independent of gestational age, we then compared the anti-S IgM, IgG, and IgA responses between all pregnant and nonpregnant participants at time points t0, t1, and t2. The IgM response was significantly higher in the nonpregnant cohort at t2 (P=.00045), whereas the IgG response was not statistically different between the pregnant and nonpregnant cohorts at t0, t1, or t2 (Figure 2). The IgA response was significantly higher in the nonpregnant cohort at t1 (P=.016) and t2 (P=.00022) (Figure 2). The highest magnitude response for all antibody isotypes occurred at t2 for both cohorts (Figure 2).

The anti-S IgG, IgM, and IgA levels declined over time, and there were no significant differences in the slope of the decline for all antibodies between pregnant and nonpregnant persons (IgG, P=.099; IgM, P=.088; IgA, P=.274) (Figure 3). The anti-S IgG and IgM levels 6–8 months after vaccine initiation fell to comparable proportions of the t2 antibody levels between pregnant and nonpregnant persons (IgG response among pregnant persons, 75.2% of t2; IgG response among nonpregnant persons, 75.4% of t2, P=.77; IgM response among pregnant persons, 77.4% of t2; IgM response among nonpregnant persons, 72.1% of t2, P=.51). In contrast, IgA levels 6–8 months after vaccine initiation fell to statistically significantly larger proportions of t2 antibody levels in pregnant compared with nonpregnant persons (IgA among pregnant persons, 74.3% of t2; IgA among nonpregnant persons, 63.3% of t2, P=.002) (Figure 4).

We also analyzed the relationship between maternal and umbilical cord blood plasma anti-S IgM, IgG, and IgA levels. Maternal anti-S IgG levels were strongly correlated with umbilical cord anti-S IgG levels (R=0.8, P<.001). All umbilical cord samples were negative for IgM, and 96% (47/49) of umbilical cord samples were negative for IgA (Figure 5).

Discussion

Principal findings

We demonstrated that the anti-S IgA, IgM, and IgG responses to SARS-CoV-2 mRNA-LNP vaccination in pregnancy are independent of gestational age of vaccine initiation. These findings suggest that the immunologic changes of pregnancy do not affect initial vaccine response based on gestational age at immunization and support the clinical recommendation for COVID-19 vaccination at any point in pregnancy. These findings are substantiated by the noted clinical efficacy of SARS-CoV-2 vaccination in pregnancy in other cohorts that is comparable to the efficacy in nonpregnant individuals.3,16 In addition, the peak and longitudinal anti-S IgG response among pregnant participants at 6 to 8 months post peak is similar to the response in nonpregnant participants. Overall, our findings demonstrate that the immunologic milieu of pregnancy does not influence the durability of the anti-S IgG response to SARS-CoV-2 vaccination.

Results in the context of what is known

Data on the impact of SARS-CoV-2 vaccination in pregnancy on antibody levels are emerging and thus far provide a snapshot in time of the immune response, often after the second dosage or at the time of delivery. One study demonstrated lower anti-S IgG levels in pregnant persons 2 weeks to 2 months after vaccine dosage.17 In contrast, 2 other studies demonstrated no difference in anti-S IgG levels 2 to 6 weeks
Maternal anti-S IgM, IgG, and IgA levels at the time of vaccine dosage 1 (t0, light green), vaccine dosage 2 (t1, turquoise), and 2 weeks post vaccine dosage 2 (t2, blue) represented at the gestational age of vaccine initiation. Each horizontal linear line for t0 (light green), t1 (turquoise), and t2 (blue), respectively, represents the linear smoothed line for all samples from all participants captured at that time point. The gray dotted line connecting a point from t0 to t1 to t2 is indicative of serial sampling from the same participant. The horizontal dotted line represents the cutoff for positive serology results. The Spearman rho ($\rho$) was calculated and showed no significant association between antibody levels and gestational age at vaccine initiation. The results are from 53 participants, totaling 144 samples.

Ig, immunoglobulin; t0, blood collected at first time; t1, blood collected at second time; t2, 2 weeks post second dosage.

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The anti-S IgM, IgG, and IgA levels were compared within 7 days before vaccine dosage 1 (t0), 7 days before or after vaccine dosage 2 (t1), and 1–3 weeks post vaccine dosage 2 (t2) between pregnant (red) and nonpregnant persons (blue) using a Mann-Whitney U test. The count is the number of samples captured for the time point. The mean is mean antibody levels. The horizontal dotted line represents the cutoff for positive serology results; ns indicates not significant. The medians (interquartile range) in weeks of samples since dosage 1 are as follows: t0 pregnant, 0.14 (0.0029); t0 nonpregnant, 0 (0); t1, pregnant, 3.07 (1.14); t1 nonpregnant, 5.14 (0.61); t2, pregnant, 5.22 (1.17).

Ig, immunoglobulin; t0, blood collected at first time; t1, blood collected at second time; t2, 2 weeks post second dosage.

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Anti-S IgM, IgG, and IgA response in weeks since t0 (vaccine dosage 1) in the cohort vaccinated in pregnancy (red) and the cohort of nonpregnant persons (blue). A. Data points within each cohort are visualized with a locally weighted scatterplot smoothing (LOESS) smoothed line. B. Only data points within each cohort that fall between T2 and the end of sample collection are analyzed with a linear regression model. The horizontal dotted line represents the cutoff for positive serology results. The pregnant cohort includes 53 participants and 274 samples; the nonpregnant cohort includes 21 participants and 72 samples. All participants completed the 2-dosage messenger RNA vaccination course and received the second dosage between 3 and 4.1 weeks post first dosage. The follow-up medians (interquartile range) in weeks are as follows: pregnant, 25.9 weeks (11.9 weeks) and nonpregnant, 28.9 weeks (12.9 weeks). The longest follow-up periods from vaccination initiation are as follows: pregnant, 38.4 weeks and nonpregnant, 41.7 weeks. The differences in the slopes of the decline between pregnant and nonpregnant persons are as follows: IgG, $P=0.099$; IgM, $P=0.088$; IgA, $P=0.274$.

Ig, immunoglobulin; t0, blood collected at first time.

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FIGURE 4
Decrease of antibody levels by 6–8 months post vaccination initiation between pregnant and nonpregnant persons

Ratio of antibody levels 6–8 months post vaccination initiation to antibody levels at t2 for anti-S IgM, IgG, and IgA for pregnant (red) and nonpregnant persons (blue). IgG levels at 6–8 months post vaccination initiation fell to 75.2% of t2 (pregnant) and 75.4% of t2 (nonpregnant). IgM levels at 6 to 8 months post vaccination initiation fell to 77.4% of t2 (pregnant) and 72.1% of t2 (nonpregnant). IgA levels at 6–8 months post vaccine initiation fell to 74.3% of t2 (pregnant) and 63.3% of t2 (nonpregnant).

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has demonstrated that 57% of infants 6 months of age have detectable anti-S antibodies derived from maternal vaccination.21 Now that infant vaccination is not recommended to begin until 6 months, maternal vaccination resulting in transplacental IgG transfer is likely the most effective route to confer clinical benefit to neonates from birth to 6 months.

Clinical implications
The anti-S IgG response from initiation of vaccination through peak response in the pregnant cohort was similar to that in nonpregnant persons. In addition, the decline in anti-S IgG response was comparable between pregnant and nonpregnant persons. IgG has been shown to be the most abundant and potent antibody in the serum following mRNA-LNP vaccination, mediating neutralizing activity against SARS-CoV-2. Thus, the comparable IgG levels between pregnant and nonpregnant persons at initiation of vaccination and longitudinal follow-up provide additional support for the strong immunogenicity and consequently efficacy of SARS-CoV-2 vaccination in pregnancy.1,16,23–25 These findings support the clinical recommendations for COVID-19 vaccination at any point in pregnancy for optimal maternal protection.

In addition, the peak mRNA-vaccine-elicited antibody response occurred approximately 2 weeks post vaccine dosage 2 (or 5–6 weeks post vaccination initiation). However, by 6 to 8 months post vaccination initiation, all antibody levels fell to 63.3%–77.4% of the peak antibody levels. This waning of vaccine-elicited antibody levels strengthens the clinical recommendation for COVID vaccine booster administration after the completion of the primary vaccination series.

Research implications
In contrast, the pregnant cohort demonstrated significantly lower anti-S IgA and IgM responses at the time of peak antibody response and a differential decrease in IgA levels over time. The biological significance of the difference in IgA and IgM antibody response is not clear. A serum IgA response to infection has been shown to be less potent than an IgG equivalent against SARS-CoV-2.24 In addition, SARS-CoV-2-specific monomeric IgA is also less potent than dimeric IgA found mostly in the mucosal surfaces of the nasopharynx at the site of initial infection.24 Thus the impact of serum IgA response on the level of protection against SARS-CoV-2 remains to be determined.24,26

Data presented in this study are also in the absence of a booster dosage as recommended by the Centers for Disease Control and Prevention (although not recommended during the time frame for recruitment for this study). The impact of a booster dosage on the peak and durability of the initial antibody response from vaccination in pregnancy is another area of further investigation.

Strengths and limitations
Several strengths exist for this study. First, we prospectively recruited pregnant and nonpregnant participants, allowing us to accurately describe the response to vaccination at prespecified time intervals. We recruited participants at different time points in pregnancy, allowing us to describe vaccination response across gestational ages. We also prospectively followed the participants for up to 42 weeks post vaccination initiation, which allowed us to study the long-term maintenance of serum antibody levels.

Our study also has limitations. First, information about vaccination was self-reported, as participants sought vaccination wherever an appointment was available early in the pandemic. Although our sample size is limited, it is comparable to other studies evaluating antibody response in this unique population. We are not able to comment on neutralization or functional antibody response in this study. However, other studies have demonstrated a correlation between plasma anti-S IgG levels and neutralization and functional response and between anti-S IgG levels and immune correlates of protection.27 We are unable to directly comment on adult or neonatal immune correlates of protection, as pregnant persons and neonates did not have known exposures to COVID-19. Finally, we cannot comment on differential vaccine response after a booster dosage, in case of maternal immunosuppressed conditions, or
Conclusions

Pregnancy does not alter the mRNA-LNP vaccine-elicited anti-S IgG peak response and the kinetics of the response. The clinical implications of lower serum vaccine-elicited IgA and IgM response in pregnant persons and whether these differences may affect immune protection are areas of active investigation. This study supports the current recommendation for SARS-CoV-2 vaccination of pregnant persons at any point during pregnancy and booster dose(s) after the initial 2 dosage series. Furthermore, this strategy results in robust passive antibody transfer to the neonate.

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