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Short communication

Longitudinal analysis of antibody response following SARS-CoV-2 infection in pregnancy: From the first trimester to delivery

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ABSTRACT

We report herein the longest-lasting study of SARS-CoV-2 antibody profile in pregnancy, from first trimester-infection to delivery. Seventeen out of 164 pregnant women tested positive for COVID-19. Throughout pregnancy, the neutralizing antibody titer remained stable, whilst a significant decline in the non-neutralizing antibodies was observed after 16 weeks of gestation. All the newborns of women who developed IgG antibodies showed the presence of the same antibodies in arterial cord blood. Knowledge on the longevity and type of SARS-CoV-2 antibody response may help to guide vaccination strategies in pregnancy.

1. Introduction

The rapid spread of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), raises particular concern for the health of a potentially vulnerable population: pregnant women (Cosma et al., 2020a, 2020b). Data on the immune response to SARS-CoV-2 during pregnancy are lacking and the potential role of SARS-CoV-2 vaccination in pregnancy is yet to be investigated, although the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) support the benefit of vaccination in high-risk pregnancy patients. Indeed, maternal-fetal immunization is known to reduce morbidity and mortality from infectious diseases (Benedetto et al., 2019).

Most individuals with a diagnosis of SARS-CoV-2 infection confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) develop immunoglobulins against different virally encoded proteins within 1–2 weeks after the onset of symptoms. Anti-surface spike (S) glycoprotein-binding titer correlates with neutralization of SARS-CoV-2 and the magnitude of the titer peak depends on disease severity (Seow et al., 2020). As asymptomatic or pauci-symptomatic patients have a weaker immune response to SARS-CoV-2, the duration of humoral immunity is uncertain in many such patients, including those that are pregnant (Long et al., 2020).

The type of antibody response and its longevity in pregnancy is currently unknown, although its knowledge is essential for planning a global vaccination program.

To fill this gap, we wanted to study the antibody response in pregnant women with COVID-19 during the first trimester of pregnancy and to measure how antibody titration varies during pregnancy, until delivery. The secondary aim was to evaluate transplacental antibody transfer to the neonate.

2. Methods

For this study, consecutive 12-week pregnant patients attending our institution for noninvasive prenatal diagnosis or admitted to the care

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units for COVID-19-related symptoms between April and June 2020 were invited to participate. The study protocol was approved by the Institutional Review Board (IRB) of the City of Health and Science of Turin (no. 00171/2020).

Nasopharyngeal swabs were taken for RT-PCR assay to detect SARS-CoV-2, and blood samples were used for the detection of antibodies against SARS-CoV-2. Semi-quantitative detection of IgG/IgM non-neutralizing antibodies (nNAbs) against the nucleocapsid (N) viral proteins was performed with an automated (AFIAS™ COVID-19, Boditech Med Inc, Gang-won-do, Korea) lateral flow immunochromatographic assay, expressing the results as a cut-off index (COI), where a COI of > 1.1 indicates a positive result. Chemiluminescent immunoassay technology was used for semi-quantitative determination of anti-S (S1 and S2) specific IgG neutralizing antibodies (NAbs) to SARS-CoV-2 (Liaison® SARS-CoV-2 S1/S2 IgG, Diasorin, Italy), expressing antibody concentration as arbitrary units (AU/mL) and grading the results as positive when ≥ 15 AU/mL.

Only women with last menstruation at latest 1 month after the date of the first reported case of COVID-19 infection in Piedmont (February 22nd, 2020) were eligible for inclusion in the study, so as to exclude the possibility of COVID-19 seroconversion before pregnancy. The entire cohort was tested a second time at 16 weeks of pregnancy, a third time at 21 weeks, and a fourth and final time at delivery. Arterial umbilical cord blood samples were tested for nNAbs and NAbs immediately after delivery.

Variables were compared with the Wilcoxon matched-pairs signed-rank test. Differences were considered statistically significant if $p < 0.05$. Statistical analysis was performed using SAS software version 9.4 for Windows (SAS Institute, Carey, NC, USA).

3. Results and discussion

A total of 164 women in their first trimester of pregnancy were included. Of these 164 women, 17 (10.4 %) tested positive for anti-SARS-CoV-2 antibodies at 12 weeks gestation or had a positive nasopharyngeal swab for SARS-CoV-2. The mean gestational age at delivery of the affected patients was 38.8 weeks (median: 39 weeks, range: 34.3–41 weeks) with a mean follow-up of 188.17 days of gestation after the determination of the first antibody profile.

Five of the 17 (29.4 %) patients, tested positive for SARS-CoV-2 at RT-PCR before 12 weeks of pregnancy and self-reported as being symptomatic; 9/17 (52.9 %) had self-misrecognized symptoms and reported symptoms only at history taking, whilst 3/17 (17.6 %) were asymptomatic; symptoms included fever, anosmia and ageusia, cough, arthralgia, diarrhea, and dyspnea; no pneumonia or hospital admission was observed.

Sixteen (16/17, 94.1 %) tested positive for nNAbs: 10/16 (62.5 %), 4/16 (25 %), and 2/16 (12.5 %) were positive for SARS-CoV-2 nNIgG, IgM, or both IgG and IgM, respectively; in 1 patient the nasopharyngeal swab tested positive but no antibody response was detected.

Nine of the 17 (52.9 %) patients of the entire cohort and 9 of the 12 who seroconverted to nNIgG antibodies (10 positive for nNIgG + 2 positive for both nNIgG and nNIgM) expressed IgG NAbs (75 %), regardless of the presence or severity of symptoms. In particular, 7 women suffered from mild cases of COVID-19 and 2 were asymptomatic.

The mean antibody titer at admission was 19.82 ± 2.79 COI and 1.18 ± 0.40 COI for anti-SARS-CoV-2 IgG and IgM nNAbs, respectively, and 43.72 ± 29.13 AU/mL for anti-SARS-CoV-2 IgG NAbs. Longitudinal analysis across sequential samples (Fig. 1) showed a decrease in the nNIgG response over the weeks of gestation, which was statistically significant after 16 weeks ($p < 0.05$). There was a statistically significant decrease in the COI between the first sample and the COI at delivery (19.82 ± 2.79 and 6.09 ± 7.04, respectively) ($p < 0.05$). Differently, there was no significant decrease in neutralizing antibody titers measured between the first (43.72 ± 29.13 AU/mL) and the fourth (53.43 ± 43.15 AU/mL) time point ($p = 0.58$).

All the newborns of women who developed IgG antibodies showed the presence of the same antibodies in arterial cord blood and tested negative at the nasopharyngeal swab for SARS-CoV-2. The mean maternal titer of NAbs at delivery was 53.43 ± 43.15 AU/mL, the neonatal titer 58.51 ± 49.02 AU/mL ($p = 0.81$); the mean maternal titer of nNAbs was 6.09 ± 7.04 COI, the neonatal titer 8.61 ± 8.82 COI ($p = 0.44$).

The present report is the longest-lasting study of SARS-CoV-2 antibody profile throughout pregnancy. NAbs were detectable only in 52.9 % of our cohort; as the affected women were asymptomatic or mildly symptomatic, this finding appears in agreement with the previous observation that neutralizing antibody response correlates with COVID-19 severity (Long et al., 2020).

Neutralizing antibody titers in the study cohort remained stable throughout pregnancy, whereas nNAbs progressively declined from 12 weeks to delivery. The longevity of neutralizing antibody titers

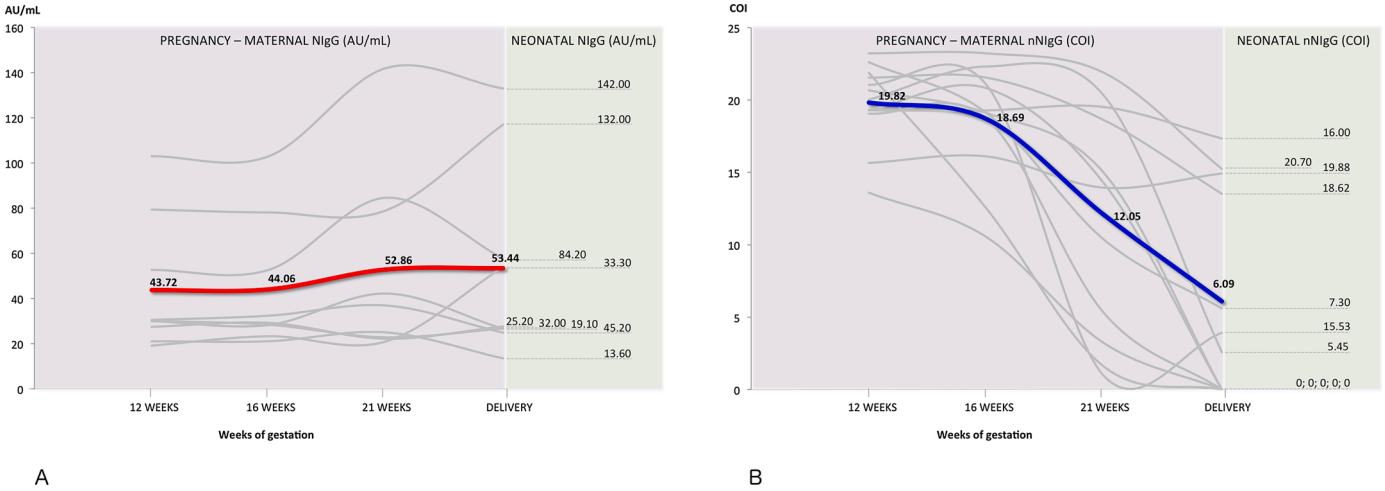

Fig. 1. Dynamics of neutralizing and non-neutralizing IgG antibodies during pregnancy (purple box) and their vertical transmission to the infant (green box) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).
A. Individual (grey line) and mean (red line) IgG neutralizing antibody (NIgG) profile.
B. Individual (grey line) and mean (blue line) IgG non-neutralizing antibody (nNIgG) profile.
AU denotes arbitrary units; COI, cut-off index; dotted orange line, umbilical cord blood sample at delivery; dotted grey line, neonatal sampling paired with the corresponding maternal sampling

throughout pregnancy is a brand new finding; it is known that these antibodies are persistent, but to date there is only one long-term follow-up study (8 months) on SARS-CoV-2 infection in the general population (Choe et al., 2020).

However, recent studies have shown that the neutralizing antibody titers of patients with mild SARS-CoV-2 infection decline more quickly than those reported for Severe Acute Respiratory Syndrome Coronavirus 1 (SARS-CoV-1) patients (Long et al., 2020). As the average duration of human pregnancy is nine months, it is questionable whether the antibody response to SARS-CoV-2 infection is sufficient to ensure immunity for the entire length of gestation and to limit the risk of re-infection. In light of our results, careful evaluation of the type of antibodies developed in early pregnancy is necessary to identify women at potential risk of re-infection. However, the observation that many individuals with asymptomatic or mild COVID-19, lacking detectable circulating specific antibodies, had highly durable memory T cell responses directed against the internal (nucleocapsid) and surface proteins (membrane and/or spike), suggests that natural exposure or infection could prevent recurrent episodes of severe COVID-19 (Sekine et al., 2020).

Knowledge about the duration of immunity against SARS-CoV-2 is essential in maternal-fetal medicine, since maternal immunization can protect the newborn from COVID-19 infection during the first months of life (Carosso et al., 2020). We found transplacental passage of SARS-CoV-2 antibodies higher than previously reported in affected patients of the second/third trimester, but still in line with the expected cord-to-maternal antibody ratio typically observed for other pathogens (Edlow et al., 2020). This is particularly important because the neonatal immune system in the first months of life is immature and potentially ineffective in mounting an adequate humoral response.

Our findings may help to guide global COVID-19 vaccination program in pregnancy. Published data on COVID-19 vaccines show that they are approximately 95 % effective in preventing development of the disease (Polack et al., 2020) but at time of writing there are no vaccine efficacy and safety studies involving pregnant women. Requests by international societies of obstetrics and gynecology that pregnant and lactating women be included in ongoing vaccine trials and research have not been met, unfortunately. The longevity of the neutralizing response detected in our study suggests that vaccination in the first trimester would be sufficient to ensure adequate protection throughout gestation, without the need for vaccine boosters to provide long-lasting protection. Furthermore, our findings suggest that SARS-CoV-2-infected pregnant patients who have only seroconverted to nNAbs, and not to NAbs, should still be considered for immunization with vaccines.

In summary, in sequential samples collected up to at least 6 months after SARS-CoV-2-infection in pregnant patients, we detected a typical antibody response after an acute viral infection. In those who developed a neutralizing antibody response, the titers were maintained for the entire length of pregnancy and transmitted to the newborn.

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