ARTICLE

Titers of SARS CoV-2 antibodies in cord blood of neonates whose mothers contracted SARS CoV-2 (COVID-19) during pregnancy and in those whose mothers were vaccinated with mRNA to SARS CoV-2 during pregnancy

Lior Kashani-Ligumsky1,2, Miriam Lopian1,2, Ronnie Cohen1,2, Hila Senderovich1,2, Shelly Czeiger1,2, Ariel Halperin2,3, Adina Bar Chaim4, Irit Kremer4, Joseph B. Lessing1,2, Eli Somekh2,3 and Ran Neiger5

OBJECTIVE: We compared neonatal immunity after vaccination against SARS-CoV-2 during pregnancy to that achieved after maternal infection.

STUDY DESIGN: We tested cord blood from women infected with SARS-CoV-2 during pregnancy (group 1, n = 29), women who were vaccinated during pregnancy (group 2, n = 29) and from women not infected and not vaccinated (Group 3, n = 21) for titers of antibodies to both SARS-CoV-2 spike and ‘N’ proteins.

RESULTS: Seventy-nine women were included: Antibodies against SARS-CoV-2 spike protein were detected in all samples from Group 1 and 2. Antibodies to the ‘N’ protein were detected in 25/29 samples in Group 1. None of the samples from Group 3 had antibodies to either protein. Mean titers of SARS-CoV-2 antibodies were significantly higher in Group 2 than in Group 1 (p < 0.05).

CONCLUSIONS: Neonates born to mothers vaccinated during pregnancy have higher antibody titers and may therefore have more prolonged protection than those born to women infected during pregnancy.

Journal of Perinatology (2021) 41:2621–2624; https://doi.org/10.1038/s41372-021-01216-1

INTRODUCTION

The novel coronavirus (SARS-CoV-2) pandemic, declared in March 2020, has been responsible for more than 3 million deaths globally [1]. Several vaccines against the SARS-CoV-2 virus have been developed. In December 2020, the United States Food and Drug Administration (FDA) granted an emergency use authorization for SARS-CoV-2 vaccines developed by Pfizer and Moderna for individuals over the age of sixteen [2]. Both vaccines are based on the production of the SARS-CoV-2 Spike protein (‘S’ protein) via mRNA to “educate” the immune system and produce immunoglobulins (IgG) antibodies against the virus [3]. Due to the lack of clinical data regarding the safety and efficacy of these vaccines in pregnant and lactating women, in January 2021 the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine advised to allow pregnant women to decide whether they be vaccinated after counselling about the risks and benefits of vaccination during pregnancy [4]. Since then, studies have shown that mRNA SARS-CoV-2 vaccines are safe and effective in pregnant women and provide the same level of immunity as to they do in the general population [5].

There is limited data regarding the effect on neonatal immunity to SARS-CoV-2 in women vaccinated during pregnancy. Researchers showed that maternal IgG antibodies that were produced in response to vaccination of pregnant women against influenza and pertussis crossed the placenta and significantly decreased neonatal morbidity and mortality due to these infections [6, 7]. Similarly, Flannery et al. reported that neonates born to mothers infected by SARS-CoV-2 during pregnancy were born with IgG antibodies to SARS-CoV-2 as a result of transfer across the placenta [8]. Additional publications regarding transplacental transfer of maternal SARS-CoV-2-specific antibodies to newborns after vaccination of the mother are limited to case reports [5, 9].

We studied cord blood for the presence of IgG to both SARS-CoV-2 ‘S’ protein and the Nucleocapsid Protein (‘N’) protein. Anti-‘S’ protein antibodies can be detected in both infected and vaccinated women. Nucleocapsid Protein of SARS-CoV-2 is located in the viral core, therefore IgG antibodies against the ‘N’ protein are detectable only in the serum of infected women; these antibodies may disappear over a period of 18 months [10].

The aim of our study was to compare the titers of IgG antibodies to SARS-CoV-2 in umbilical cord blood in women who received the SARS-CoV-2 BNT162b2 mRNA vaccine during gestation and in women who were infected with SARS-CoV-2 during gestation.
RESULTS
Between February 28th and March 8th, 2021 there were 181 singleton livebirths in our institution. We collected 83 cord blood samples and divided them into three groups: Group 1 included 29 samples (37%) from women who were infected with SARS-CoV-2 during pregnancy. Twelve had RT-PCR confirmed Covid-19 infection: three were infected in the first trimester, three in the second trimester and six in the third trimester. The other 17 had no clinical signs of SARS-CoV-2 infection during pregnancy and had a positive serologic test on admission. None of the 17 women had active SARS-CoV-2 infection at the time of delivery. Group 2 included 29 samples (37%) from women who were vaccinated against SARS-CoV-2. Group 3 included 21 women (34%) and served as controls. Four women were excluded; three of them contracted SARS-CoV-2 infection during pregnancy and were later vaccinated prior to delivery. The other one had a clinical infection that was confirmed by a positive RT-PCR test during the first trimester. Two had antibody titer of 250 U/ml and one woman had a titer of 27.6 U/ml. The fourth woman was excluded since she had received only a single dose of the vaccine; her titer was 250 U/ml. Aside from slight differences in age and a higher parity in Group 2, there were no significant differences in the demographic characteristics among the three groups (Table 1).

There were no cases of neonatal SARS-CoV-2 infections, neonatal sepsis, NICU admissions, RDS, sepsis or neonatal death. All umbilical cord samples from groups 1 and 2 were seropositive for the SARS-CoV-2 IgG ‘S’ protein (100%). Twenty-five were also positive for the N protein. Of the four who were not, three had asymptomatic infection and one had a clinical infection that was confirmed by a positive RT-PCR test during the first trimester. The mean titers of SARS-CoV-2 ‘S’ antibodies in these four samples were lower than the titers in the rest of the group (33.9 U/ml compared with 91.6 U/ml) but this difference did not reach statistical significance (p = 0.41). None of the samples from group 2 were positive for the SARS-CoV-2 ‘N’ protein. None of the samples from Group 3 were seropositive for antibodies to the SARS-CoV-2 IgG ‘S’ or ‘N’ protein. The mean antibody titer of group 1 was 83.7 ± 91.6 U/ml compared with 224.7 ± 64.3 U/ml in group 2, a statistically significant difference (p < 0.05).

Maternal SARS-CoV-2 antibody titers at delivery were available for 39 women: 13 in group 1, 17 in group 2, and 9 women from the control group (Group 3, who were all seronegative). There was a strong correlation between the maternal antibody titers and the
Our results support the current recommendation for pregnant women to receive the SARS-CoV-2 vaccination [4]. We report that vaccination during gestation results in a robust IgG antibody response in the mother and that this response is significantly greater than the immune response in women who contracted SARS-CoV-2 infection during pregnancy. Given the higher antibody titers found among women who were vaccinated, we can speculate that boosting immunity during pregnancy translates into measurable serological benefits and might determine milder courses of the neonatal disease.

It is likely that this immunity is transient in both groups; among the women who contracted SARS-CoV-2 infection during pregnancy, as cord blood samples from four women were seronegative for the ‘N’ Protein. These women most likely contracted infection during the early stage of pregnancy. The implications of declining antibody titers in both those who contracted SARS-CoV-2 infection and those vaccinated against this virus are not clear since other immune mechanisms such as cellular mediated immunity and rapid boosting can afford sufficient protection against virus infection. However, immunization during pregnancy is important since the transplacental transfer of antibodies is the only means of protection from SARS-CoV-2 available to newborns. The magnitude of antibody titer is probably directly correlated to the duration of postnatal protection. We assume that the higher antibody titers detected in cord blood of babies born to mothers vaccinated during the third trimester, compared with the lower titers found in samples from those born to mothers who were previously infected with SARS-CoV-2, result in a longer protection period during the first months of life. These findings can be used to encourage pregnant women to vaccinate against SARS-CoV-2. Our findings also support the recent recommendation by health organizations to vaccinate people previously infected with SARS-CoV-2 to boost their immunity [13]. This recommendation is the subject of debate when pertaining to pregnant women and is supported by the findings of the current study. However, the decision whether or not to vaccinate pregnant women who had previously contracted SARS-CoV-2 infection in order to enhance the protection of their babies (similarly to the practice of protection against infantile pertussis) [7] also depends on the local epidemiology of SARS-CoV-2 infection: this measure may be considered in communities where there is a high rate of SARS-CoV-2 infections.

Our study is among the first that evaluated antibody titers in cord blood of newborns born to women who were vaccinated during pregnancy and compared them to titers in babies born to women who contracted SARS-CoV-2 infection during pregnancy. The limitations of our study include the relatively small cohort size, the low availability of the samples adequate for quantification of anti-SARS-CoV-2 antibodies and the lack of correlation to the presence of antibodies in breastfeeding. Another limitation was that data regarding the timing of SARS-CoV-2 infection was available only for 12 of the 29 women in Group 1 (17 women were interviewed and had no known SARS-CoV-2 infection). We were unable to assess the latency period between acute infection to the appearance of antibodies, the highest antibodies level and the rate of decline. However, since the majority of women in group 1 (17 of 29) had asymptomatic infections, it is unlikely this information can be determined without periodically testing a very large cohort of pregnant women.

CONCLUSIONS

Titer of IgG antibodies against SARS-CoV-2 in umbilical cord blood samples were significantly higher in a cohort of newborns born to women vaccinated against SARS-CoV-2 during their third trimester than among those born to women who contracted SARS-CoV-2 during pregnancy. Cord blood antibody concentrations correlated with maternal antibody concentrations. These findings demonstrate that boosting immunity during pregnancy confers serological benefits to the offspring. Due to the small number of subjects and the short follow-up period, this study should be considered a primarily hypothesis generating; larger studies and longer follow up are required in order to recommend a clinical practice such as vaccination during pregnancy.

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AUTHOR CONTRIBUTIONS
Concept and design: K-L, ES. Acquisition, analysis or interpretation of the data: K-L, ML, RC, HS, SC, AH, ABC, IK, JBL, RN. Drafting and paper: K-L, ML, RN, ES. Critical revision of the paper for important intellectual content: ML, K-L, SC, RN, RC, JBL, ES. Statistical analysis: RC. Supervision: K-L, ES, RN.

COMPETING INTERESTS
The authors declare no competing interests.

ADDITIONAL INFORMATION
Correspondence and requests for materials should be addressed to Lior Kashani-Ligumsky.

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