

Rh-Negative Blood Type Associated with Less Risk for COVID-19 Infection in an Observational Cohort of Pregnant Women

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Received: 21 Sep 2026; Accepted: 29 Sep 2026; Published: 04 Oct 2026

Citation: J. Brooks Jackson, Linder H Wendt, Kimberly A Kenne, et al. Rh-Negative Blood Type Associated with Less Risk for COVID-19 Infection in an Observational Cohort of Pregnant Women. J Med - Clin Res & Rev. 2026; 10(10): 1-3.

Keywords

COVID-19, Rh blood type, Pregnant women.

Introduction

Recent studies suggest certain ABO and Rh-negative blood types may be associated with stronger immunity to infectious diseases such as COVID-19 [1]. Several studies have reported a significant association between Rh-negative blood type and a lower risk for COVID-19 infection and/or less severe COVID-19 disease in the general population [2-5]. Other studies have reported that Rh-negative blood type is associated with an increased COVID-19 associated mortality risk and longer hospital stay [6,7]. Rh-blood type has also been associated with an enhanced IFN gamma mediated immune response to influenza A virus [8]. The objective of this study was to determine the association between Rh-negative blood type and COVID-19 infection in pregnant women at delivery compared to women with Rh-positive blood type.

Methods

This prospective observational study included all 2497 pregnant patients who delivered or underwent procedures for a spontaneous or induced second-trimester abortion on the labor and delivery unit at University of Iowa Hospitals and Clinics between May 1, 2020, and April 30, 2021, as part of a study of COVID-19 in pregnancy. All delivering patients were included in the study and none were excluded. The primary outcome of the original study was the prevalence of COVID-19 and the maternal and fetal outcomes

in COVID-19 positive delivering women; this is a secondary analysis of data from the same cohort [9,10]. The Institutional Review Board of the University of Iowa approved this study (IRB #202004278).

Excess plasma from routine blood samples for ABO/Rh typing was collected and frozen at -18° C within 3 days of admission and used to determine the prevalence of COVID-19 antibodies using the Elecsys Anti-SARS-CoV-2 assay (Roche Diagnostics) and the LIASON SARS-CoV-2 S1/S2 IgG assay (DiaSorin, Inc.). Women were considered positive for antibodies to COVID-19 if both the DiaSorin and Roche assays yielded positive results. None of the women who tested positive by both assays had received a COVID-19 vaccine. Routine COVID-19 respiratory testing was not being performed during the study period; the two positive antibodies are considered a marker of past infection. COVID-19 antibody testing and Rh blood type was performed at time of admission. Patient BMI (kg/m²) was calculated based on measured height and weight at the time of admission for delivery. Pearson's Chi squared tests were used to test for differences among categorical variables, while Wilcoxon rank sum tests were used for continuous variables. Additionally, a logistic regression model using RH positivity, race, and their interaction as independent variables was used to examine whether patient race alters the impact of RH positivity on the likelihood of a patient testing positive for COVID-19. R, version 4.5.1 was used for all analyses and p-values less than 0.05 were considered statistically significant throughout the manuscript.

Results

Among 2497 women, 351 (14.1%) were Rh-negative and 284 (11.4%) were positive for COVID-19 antibody. The median ages of 351 Rh-negative women and 2146 Rh-positive women were 30 (IQR 26-34) and 30 (IQR 26-33) years, respectively ($p=0.3$). The median body mass index (BMI) values of Rh-negative women and Rh-positive women were 31 (IQR 28-37) and 32 (IQR 28-38) respectively ($p=0.3$). Of the 2497 women, 1766 were white and 731 were non-white. Of 351 Rh-negative women, 23 (6.6%) were positive for COVID antibody vs 261 (12.2%) of 2146 Rh-positive women ($\chi^2=8.87$, $p=0.002$). In the regression analysis, we observed that the impact of Rh status differed significantly based on the individual's race. For white individuals, Rh status did not significantly impact their likelihood of being COVID positive (estimated 7.8% for Rh-positive and 6.7% for Rh-negative). For non-white individuals, RH status made a large, significant difference on their likelihood of being COVID positive (estimated 21.6% for Rh-positive and 5.9% for Rh-negative). We have statistically significant evidence that Rh-positivity impact white and non-white patients differently (OR 3.738, $p = 0.043$). We did evaluate whether Rh-status was different among COVID-19 positive women who were symptomatic vs asymptomatic, but found no difference between the two groups.

Discussion

We found that Rh-negative blood type is associated with less risk for COVID-19 infection in pregnant women, similar to other reports in different populations. However, when analyzed by race, there was significantly less risk only for Rh-negative non-white women. A plausible biological mechanism for such a difference in our study and others is not obvious. In theory, it is conceivable that the Rh-positive protein may enhance COVID-19 viral transmission to certain virus receptors, particularly specific to certain populations like pregnant women, but there are no data we are aware of to support this mechanism. There are also other possible confounders in the interpretation of the data. For example, nearly all the Rh-negative pregnant women would have received Rh immune globulin at 28 weeks gestation as standard practice, though we did not specifically collect data on whether all women had received the Rh immune globulin as part of our study. Rh immune globulin has a number of different immune globulins (which might vary from manufacturer and lot) besides anti-D antibody that could provide protection to COVID-19 infection. Additionally, there is a wide variation in the gestational ages at which the cohort of patients delivered, which is a limitation of the study. As always with observational studies, there are possible other unknown confounders that may make interpretation difficult.

It is also possible that the use of COVID antibody testing in this study underestimated past COVID infection since detectable COVID antibody can wane over time to undetectable which is also dependent on the sensitivity of the assay. However, given the women tested in this study delivered during the first year of the COVID epidemic, this underestimate is likely minimal. Using antigen or PCR testing for COVID infection would not have

detected past COVID infection that had resolved.

Despite these limitations, strengths of the study include the capturing and testing consecutively for COVID-19 antibody of each pregnant woman at delivery for a one-year period at a large academic medical center with a population of pregnant women who had not yet been vaccinated for COVID-19. The overall significant association between Rh-negative blood type and COVID-19 infection in our relatively young healthy population of pregnant women is consistent with a number of other studies with different, older, and less healthy populations who would not have received Rh immune globulin. Our study and others suggest that Rh-negative individuals may have enhanced immunity against COVID-19 and other viral infections, or the converse that Rh-positive individuals are at greater risk, or the possibility that Rh immune globulin provides some protection against COVID-19 infection. Clinically, the implication is that Rh-positive pregnant women may be at increased risk for COVID-19 infection and its sequelae during pregnancy. Further research into this area is worth pursuing if pregnant women and others could be better protected against COVID-19 and potentially other infections.

Funding

Statistical Support was provided by the University of Iowa Clinical and Translational Science Award from the NIH (UM1TR004404).

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