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SPECIAL ISSUE: INFECTIONS DURING PREGNANCY

SARS-CoV-2 during pregnancy and associated outcomes: Results from an ongoing prospective cohort

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Abstract

Background: The COVID-19 pandemic is an ongoing global health threat, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Questions remain about how SARS-CoV-2 impacts pregnant individuals and their children.

Objective: To expand our understanding of the effects of SARS-CoV-2 infection during pregnancy on pregnancy outcomes, regardless of symptomatology, by using sero-logical tests to measure IgG antibody levels.

Methods: The Generation C Study is an ongoing prospective cohort study conducted at the Mount Sinai Health System. All pregnant individuals receiving obstetrical care at the Mount Sinai Healthcare System from 20 April 2020 onwards are eligible for participation. For the current analysis, we included participants who had given birth to a liveborn singleton infant on or before 22 September 2020. For each woman, we tested the latest prenatal blood sample available to establish seropositivity using a SARS-CoV-2 serologic enzyme-linked immunosorbent assay. Additionally, RT-PCR testing was performed on a nasopharyngeal swab taken during labour. Pregnancy outcomes of interest (i.e., gestational age at delivery, preterm birth, small for gestational

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age, Apgar scores, maternal and neonatal intensive care unit admission, and length of neonatal hospital stay) and covariates were extracted from medical records. Excluding individuals who tested RT-PCR positive at delivery, we conducted crude and adjusted regression models to compare antibody positive with antibody negative individuals at delivery. We stratified analyses by race/ethnicity to examine potential effect modification.

Results: The SARS-CoV-2 seroprevalence based on IgG measurement was 16.4% (95% confidence interval 13.7, 19.3; n=116). Twelve individuals (1.7%) were SARS-CoV-2 RT-PCR positive at delivery. Seropositive individuals were generally younger, more often Black or Hispanic, and more often had public insurance and higher prepregnancy BMI compared with seronegative individuals. None of the examined pregnancy outcomes differed by seropositivity, overall or stratified by race/ethnicity.

Conclusion: Seropositivity for SARS-CoV-2 without RT-PCR positivity at delivery (suggesting that infection occurred earlier during pregnancy) was not associated with selected adverse maternal or neonatal outcomes among live births in a cohort sample from New York City.

KEYWORDS

COVID-19, infection, pregnancy outcomes, neonatal outcomes, SARS-CoV-2, seroepidemiologic studies

1 | BACKGROUND

The COVID-19 pandemic is an ongoing global health threat, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Despite the widespread prevalence of the virus, questions remain about how SARS-CoV-2 impacts vulnerable populations, including pregnant individuals. Previous findings suggest that in the New York City area, up to 16% of pregnant individuals have been infected with SARS-CoV-2.^{1,2}

Although the absolute risks for severe SARS-CoV-2-related outcomes among pregnant individuals are low, research indicates that pregnant individuals with SARS-CoV-2 infection have a higher mortality risk and are more likely to require intensive care unit admission and invasive ventilation compared with age-matched nonpregnant individuals.³⁻⁷ In addition, existing studies find associations between SARS-CoV-2 infection during pregnancy and adverse pregnancy outcomes, with the most commonly reported adverse outcomes being preterm delivery and low birthweight.^{1,5,7-11} Other obstetric complications and outcomes previously reported include maternal and neonatal admission to the intensive care unit, as well as maternal death.^{7,9} However, these findings are mostly based on reverse transcription polymerase chain reaction (RT-PCR) testing to establish SARS-CoV-2 infection. RT-PCR testing is limited; it is designed to identify active infections (although prolonged SARS-CoV-2 RNA shedding has been reported in some individuals¹²) and is usually performed based on clinical indication which may lead to an overrepresentation of symptomatic cases in scientific studies. For pregnant individuals, RT-PCR nasopharyngeal testing may be universally

Synopsis

Study question

What are the effects of prenatal SARS-CoV-2 infection on pregnancy outcomes (i.e., gestational age at delivery, preterm birth, small for gestational age, mode of delivery, Apgar score, ICU/NICU admission and length of neonatal hospital stay), regardless of symptomatology.

What is already known

The absolute risks for severe SARS-CoV-2-related outcomes among pregnant individuals are low. Yet, pregnant individuals with SARS-CoV-2 infection are more likely to require intensive care compared with age-matched nonpregnant individuals and to experience adverse pregnancy outcomes such as preterm birth.

What this study adds

The current understanding of the effects of prenatal SARS-CoV-2 infection on pregnancy outcomes predominantly relies on data derived from acute symptomatic infections. We show that SARS-CoV-2 seropositivity without RT-PCR positivity at delivery was not associated with selected adverse maternal or neonatal outcomes in our New York City sample. Serological testing identifies individuals previously infected with SARS-CoV-2, regardless of symptomatology.

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performed upon admission for labour and delivery, but not earlier in pregnancy. Unless RT-PCR testing is frequently and routinely administered to all pregnant individuals, many infections will be missed.

In the current study, we determined IgG antibody levels, of individuals infected with SARS-CoV-2, and examined the associations between serostatus and the pregnancy outcomes gestational age at delivery, preterm birth, small for gestational age, 5-min Apgar scores, maternal and neonatal intensive care unit (ICU) admission, and length of neonatal hospital stay. These outcomes were selected due to their potential association with SARS-CoV-2 infection as observed in previous studies^{1,5,8-10} and their general indication of neonatal health.¹³

2 | METHODS

2.1 | Study design and cohort

The Generation C Study is a prospective cohort study designed to examine the impact of SARS-CoV-2 infection and immune response in pregnant individuals (symptomatic and asymptomatic) on maternal, foetal and neonatal outcomes. Throughout this paper, we refer to outcomes of pregnant and birthing individuals as "maternal" outcomes, while acknowledging that not all pregnant and birthing individuals choose this label. To test for IgG antibodies to SARS-CoV-2, the Generation C Study utilises existing infrastructures to collect blood samples from pregnant individuals at their prenatal visits throughout pregnancy and at delivery. The study is being conducted at the Mount Sinai Health System (MSHS), the largest healthcare system in NYC, which has over 14,000 deliveries each year. All pregnant individuals receiving obstetrical care at the Mount Sinai Hospital and Mount Sinai West Hospital (two MSHS hospital campuses located in Manhattan) during the study period are eligible for participation. MSHS patients are approached for study participation at one of their prenatal visits or at Labour and Delivery. Recruitment and sampling started on 20 April 2020 and are currently ongoing. Given that patients are seen multiple times during pregnancy and blood is drawn during routine prenatal care, some individuals have more than one blood sample available. An extra 4cc of blood (EDTA tube) are obtained by medical assistants as part of routine blood draws. The tube is centrifuged and plasma aliquoted into 500 µl vials. Samples are stored at -80°C. Patients are informed about the study before their obstetrical care appointment through printed materials, emails, an online hospital platform, clinical coordinators and their physicians. At one of their regular prenatal visits, pregnant individuals are consented to providing an extra tube of blood as part of regular blood draws, for extraction of their clinical data from the EMR and for permission to be re-contacted for future studies. Study participants provide informed consent.

2.2 | Exposure: Serology testing

To understand the consequences of SARS-CoV-2 infection during pregnancy for pregnant individuals and their newborns, outcomes

should be examined in patients with and without SARS-CoV-2 infection at any point during pregnancy, regardless of their symptomatology. One of the methods to detect SARS-CoV-2 infection is by using serological tests to measure IgG antibody levels. Although not without limitations, the advantage of serological testing is that it can identify individuals previously infected with SARS-CoV-2, even if they were asymptomatic and/or never underwent testing while acutely infected.

The Generation C Study employs a serologic enzyme-linked immunosorbent assay (ELISA) developed at the Icahn School of Medicine at Mount Sinai.¹⁴ This assay is based on the soluble receptor-binding domain and the trimerised, stabilised full-length spike protein. The assay used in this study is for research purposes, but closely resembles an assay established in the MSHS CLIA-certified Clinical Pathology Laboratory, which received New York State Department of Health (NYSDOH) and Food and Drug Administration (FDA) emergency use authorisation (EUA) in early 2020.^{14,15} The test has high sensitivity (95.0%) and specificity (100%), as determined with an initial validation panel of samples, with a positive predictive value of 100% and a negative predictive value of 97.0%.¹⁶ We measure IgG antibodies because this type of antibody is produced for at least 3 months and potentially longer after exposure.¹⁷⁻¹⁹ Whereas some studies with small numbers of participants have shown rapid decay of SARS-CoV-2 antibodies over time,^{20,21} a recent examination of the assay being used in the Generation C study found that the vast majority of infected individuals with mild-to moderate COVID-19 experienced robust IgG antibody responses against the viral spike protein and that the titres were relatively stable for at least 5 months.²² By using a low dilution (1:50) for the screening assay, we test for SARS-CoV-2 seropositivity. Positive samples are further diluted and tested in an assay using the full-length spike protein to determine the antibody endpoint titre.

2.3 | Molecular testing

Beginning 27 March 2020, MSHS implemented universal molecular testing for all pregnant individuals admitted to labour and delivery. A nucleic acid RT-PCR test to detect SARS-CoV-2 is routinely performed on a nasopharyngeal RT-PCR swab sample obtained at the time of labour and delivery admission.

2.4 | Outcomes: Electronic medical record data

Electronic medical record (EMR) data are extracted for each participant through the Mount Sinai Data Warehouse. This study collects data on all prenatal diagnoses as established with ICD-10 codes, clinical laboratory values and medication use. We also obtain all EMR record data on diagnosis, laboratory and medication use for both the mother and the baby up to 6 months postpartum. Collecting all these variables enables us to explore the effects of SARS-CoV-2 infection on a multitude of outcomes, while correcting for potentially confounding factors. For the current interim analysis, we focussed on participants who gave birth to a liveborn singleton infant on or before 22 September 2020; we excluded (from this interim analysis) participants with other outcomes (e.g., miscarriage, abortion, stillbirth) due to limited statistical power (n = 3) (Figure 1). Since widespread community transmission of SARS-CoV-2 in NYC began in March 2020, we theorised that for any woman who gave birth before or in mid- to late-September, the infection must have occurred at some point during pregnancy. Serostatus was established using blood samples collected during pregnancy. We only included individuals whose latest blood sample was collected during a second or third trimester prenatal visit or upon admission to labour and delivery to prevent misclassification of individuals as seronegative. Information on COVID-19 symptomatology

was not available for these individuals. Pregnancy outcomes of interest and covariates were extracted from the electronic medical records (EMR) of participants. The selected outcomes examined were gestational age at delivery and preterm birth (<37 weeks' gestation), small for gestational age (10th sex-specific percentile), Apgar score at 5 min, maternal ICU admission, neonatal ICU (NICU) admission, neonatal hospital length of stay, and maternal and neonatal mortality during hospitalisation (or known follow-up up to 6 months among those continuing care at MSHS). These were selected due to their general indication of neonatal health and their potential association to SARS-CoV-2 infection as observed in other studies. The analyses were adjusted for the following covariates, which are potential risk factors for both SARS-CoV-2 seropositivity or infection severity²³⁻²⁸ and adverse pregnancy outcomes²⁹⁻³⁴: maternal age, parity, race/ethnicity, insurance status, tobacco use during pregnancy,



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alcohol use during pregnancy, illicit drug use during pregnancy (e.g., marijuana, cocaine), pre-pregnancy body mass index (BMI), pre-pregnancy diabetes and pre-pregnancy hypertension. Patients report their race and ethnic background when presenting for care in the health system. The Mount Sinai Data Warehouse categorises these measures using U.S. Office of Management and Budget categories. SARS-CoV-2 disproportionately affects groups that have been economically/socially marginalised.³⁵⁻³⁸ In addition, research has also documented disparities in maternal and neonatal outcomes by race/ethnicity and SES.³⁹⁻⁴¹

First, we calculated the SARS-CoV-2 seroprevalence in our sample as the number of individuals with SARS-CoV-2 spike IgG antibodies divided by the total number of individuals in the sample and constructed a 95% confidence interval around the estimate. We then estimated the proportion of individuals testing RT-PCR positive at delivery. Given the small number of individuals testing RT-PCR positive at delivery (n = 12) and the likelihood that these patients received differential care potentially resulting in altered outcomes, these individuals were excluded from analyses of associations between serostatus and selected adverse pregnancy outcomes (Figure 1); we hope to include these individuals in future analyses. We then categorised all RT-PCR negative individuals into one of two groups: (1) antibody negative [reference group]; or (2) antibody positive. Antibody status was not known to clinicians at time of delivery.

To examine the effect of SARS-CoV-2 seropositivity during pregnancy on outcomes of interest among live births, we conducted crude and adjusted linear, quantile and Poisson regression models (depending on the nature of the outcome variable) to compare seropositive individuals with seronegative individuals. To account for potential effect modification, we additionally stratified models by race/ethnicity. We further assessed the relative excess risk due to interaction (RERI) between serostatus and race/ethnicity for Black and Hispanic individuals compared to White individuals because White individuals made up the largest SARS-CoV-2 antibody negative group (Table S1).

2.6 | Missing data

In our cohort, 7.6% of individuals had missing RT-PCR test result data at delivery. Moreover, in the SARS-CoV-2 IgG antibody negative group, pre-pregnancy BMI data were missing in 5.1%. For these variables with more than 5% missing data, we applied 50 imputations using the Markov Chain Monte Carlo technique.

2.7 | Sensitivity analyses

We performed sensitivity analyses excluding participants with a missing RT-PCR result at delivery (Table S2). In a second series of sensitivity analyses, we excluded those participants for whom the time between their latest collected blood sample and delivery was

more than 30 days to avoid misclassification of individuals with SARS-CoV-2 infection later in pregnancy as seronegative (Table S3). Stata 15 was used for data analysis .

2.8 | Ethics approval

The institutional review board (IRB) at the Icahn School of Medicine at Mount Sinai reviewed and approved the study protocol (protocol IRB-20-03352, April 15, 2020).

3 | RESULTS

A total of 708 Generation C participants had given birth by 22 September 2020. Mean gestational age at time of serosample collection was 37 weeks (SD 27.3 days), and mean time between serosample collection and delivery was 13.5 days (SD 24.7). Most serosamples (n = 448, 63.3%) were taken upon admission to labour and delivery, 255 serosamples (36.0%) were taken during a prenatal visit in the third trimester, and only five serosamples (0.7%) were taken during a prenatal visit in the second trimester. The overall SARS-CoV-2 seroprevalence based on IgG measurement (regardless of SARS-CoV-2 RT-PCR test result at delivery) was 16.4% (n = 116, 95% confidence interval (CI) 13.7, 19.3). Additionally, 12 individuals (1.7%) were SARS-CoV-2 RT-PCR positive at delivery (11 of these individuals were also seropositive). Sample characteristics for seronegative and seropositive individuals, excluding those individuals with RT-PCR positivity at delivery, are shown in Table 1. Seronegative and seropositive individuals differed by maternal age, race/ethnicity, insurance status and pre-pregnancy BMI. Seropositive individuals were generally younger, more often Black or Hispanic, and more often had public insurance and higher pre-pregnancy BMI compared with seronegative individuals.

3.1 | Pregnancy outcomes

Pregnancy outcomes for seropositive and seronegative individuals are summarised in Table 2. Most delivery outcomes did not differ between groups, before or after adjustment (Table 3). We observed no maternal or neonatal mortality while in care at the MSHS. Only one maternal ICU admission occurred after birth, in a woman who was SARS-CoV-2 seronegative without RT-PCR positivity.

Additionally, seropositive individuals without RT-PCR positivity at delivery had slightly lower Apgar scores at 5 min (adjusted β -0.11, 95% CI -0.21, 0.00), of which the clinical relevance is limited given the overall high Apgar scores. Stratified by race/ethnicity, we found no differences between seropositive and seronegative individuals with regard to 5 min Apgar scores. Associations between seropositivity and the other outcome variables did not vary by race/ethnicity. Similarly, we did not find relative excess risk due to interaction

TABLE 1 Characteristics of women delivering a singleton infant according to SARS-CoV-2 IgG antibody status ^a , Mount Sinai Health System, 20 April 2020–22 September 2020	Characteristic	SARS-CoV-2 IgG antibody negative (n = 591)	SARS-CoV-2 lgG antibody positive (n = 105)
	Maternal age in years, mean (SD)	33.3 (5.2)	31.8 (5.9)
	Nulliparous, n (%)	306 (51.8)	44 (41.9)
	Race/Ethnicity, n (%)		
	Asian	72 (12.2)	4 (3.8)
	Black, non-Hispanic	85 (14.4)	25 (23.8)
	Hispanic	133 (22.5)	45 (42.9)
	Other	25 (4.2)	3 (2.9)
	White, non-Hispanic	267 (45.2)	26 (24.8)
	Missing	9 (1.5)	2 (1.9)
	Insurance, n (%)		
	Private	449 (76.0)	59 (56.2)
	Public	133 (22.5)	43 (41.0)
	Self-pay	9 (1.5)	3 (2.9)
	Tobacco use during pregnancy, n (%)	29 (4.9)	2 (1.9)
	Alcohol use during pregnancy, n (%)	176 (29.8)	25 (23.8)
	Illicit drug use during pregnancy, n (%)	30 (5.1)	5 (4.8)
	Pre-pregnancy BMI		
	Median (range)	25.2 (16.6-59.7)	28.0 (18.1-45.2)
	Missing n (%)	30 (5.1)	3 (2.9)
	Pre-pregnancy diabetes, n (%)	4 (0.7)	1 (1.0)
	Pre-pregnancy hypertension, n (%)	13 (2.2)	1 (1.0)

Note: Antibody results based on testing latest available blood samples. Percentages shown are column percentages. Unless specified in the table, data were not missing.

^aExcluding individuals with RT-PCR positivity, as tested using a nasopharyngeal swab at time of delivery (n = 12).

TABLE 2	Neonatal outcomes of participants delivering a singleton infant according to SARS-CoV-2 IgG antibody status ^a , N	∕Iount Sinai
System, 20) April 2020-22 September 2020	

Outcome	SARS-CoV-2 IgG antibody negative (n = 591)	SARS-CoV-2 lgG antibody positive (n = 105)
Gestational age in week+days, mean (SD in days)	39+0 (10.4)	38+6 (14.5)
Preterm birth (<37 weeks), n (%)	37 (6.3)	8 (7.6)
Small for gestational age, n (%)	43 (7.3)	9 (8.6)
Apgar score 5 min		
Median (range)	9 (2-9)	9 (3-9)
Missing n (%)	2 (0.34)	O (-)
NICU admission, n (%)	53 (9.0)	11 (10.5)
Length of neonatal hospital stay in days, median (range)	2 (1-64)	2(1-41)

Note: Unless specified in the table, data were not missing.

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^aExcluding individuals with RT-PCR positivity, as tested using a nasopharyngeal swab at time of delivery (n = 12).

for Black or Hispanic individuals for any of the assessed outcomes (Table S1).

4 | COMMENT

The sensitivity analyses, which excluded (1) participants with a missing RT-PCR result at delivery and (2) participants with more than 30 days between serosample collection and delivery, produced similar results (Tables S2 and S3).

4.1 | Principal findings

Our analyses from a prospective pregnancy cohort study show that SARS-CoV-2 seropositivity in the absence of RT-PCR-detected

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TABLE 3 Association between SARS-CoV-2 IgG antibody positivity and neonatal outcomes^a

Outcome	Unadjusted coefficient (95% CI)	Adjusted coefficient ^b (95% CI)
Gestational age in days ^c	-1.80 (-4.10, 0.52)	-1.00 (-3.32, 1.31)
Apgar score 5 min ^d	-0.02 (-0.04, -0.00)	-0.02 (-0.03, 0.00)
Neonatal hospital length of stay ^d	-0.08 (-0.20, 0.04)	-0.10 (-0.21, 0.02)
	Unadjusted RR (95% CI)	Adjusted RR ^b (95% CI)
Preterm birth (<37 weeks) ^e	Unadjusted RR (95% CI) 1.20 (0.58, 2.54)	Adjusted RR ^b (95% CI) 1.06 (0.50, 2.23)
Preterm birth (<37 weeks) ^e Small for gestational age ^e	Unadjusted RR (95% CI) 1.20 (0.58, 2.54) 1.18 (0.59, 2.34)	Adjusted RR ^b (95% Cl) 1.06 (0.50, 2.23) 1.16 (0.58, 2.35)

^aExcluding individuals with RT-PCR positivity, as tested using a nasopharyngeal swab at time of delivery (n = 12).

^bAdjusted for: maternal age, parity, race/ethnicity, and insurance status, tobacco use during pregnancy, alcohol use during pregnancy, illicit drug use during pregnancy, pre-pregnancy BMI, pre-pregnancy hypertension and pre-pregnancy diabetes.

^cLinear regression

^dQuantile regression

^ePoisson regression

infection at delivery (suggesting that infection occurred earlier, at some point during pregnancy) was not associated with selected adverse pregnancy outcomes among live births in our sample from NYC. Moreover, we found that SARS-CoV-2 disproportionately affects Black and Hispanic patients, as well as patients with public insurance.

4.2 | Strengths of the study

The strengths of this study are that we measured antibodies with a highly sensitive SARS-CoV-2 IgG antibodies test right after the start of the pandemic in an ethnically and socially diverse sample of pregnant individuals. Furthermore, we collected information on pregnancy and neonatal outcomes as part of a prospective pregnancy cohort using routine clinical care, meaning that all measurements are free of researcher bias.

4.3 | Limitations of the data

We measured SARS-CoV-2 seropositivity in the second and third trimester during antenatal care or at labour and delivery. Consequently, we cannot be certain when these individuals were infected with SARS-CoV-2 or precisely how long SARS-CoV-2 IgG antibodies are present in individuals. However, since widespread community transmission of SARS-CoV-2 began in March 2020, the infection must have occurred at some point during pregnancy given that all participants included in this study delivered by mid-September. Future analyses should repeat measures of seropositivity within each trimester to better pinpoint when each woman became infected and how timing impacts pregnancy outcomes. Research indicates that inflammatory responses earlier in pregnancy might produce more marked adverse effects on the foetus than those that occur later.^{42–44}

Due to the putative decay of SARS-CoV-2 IgG antibodies in milder COVID-19 cases over time,²¹ we cannot preclude potential misclassification of participants as seronegative who were infected earlier in pregnancy but no longer produced antibodies at the time of blood sampling. Although our study was designed to collect multiple blood samples from participants during each trimester of pregnancy, very few participants in the current analysis had repeat blood samples; this precluded us from examining potential seroconversion throughout pregnancy. However, recent findings about the serologic assay used in our study indicate that robust antibodies to SARS-CoV-2 infection persist for at least 5 months in the majority of the people.²² We were unable to obtain information on symptoms which may impact pregnancy outcomes, but we plan to investigate this in the full sample in the future. Although our cohort was a convenience sample, it included a diverse sample of pregnant individuals. We were unable to assess the representativeness of our cohort because recruitment procedures precluded our ability to determine the proportion of eligible individuals who enrolled, or compare characteristics of eligible individuals who enrolled versus who did not. Lastly, our sample may have been underpowered to detect smaller effects and research in larger samples is warranted.

4.4 | Interpretation

We found no indication of adverse pregnancy outcomes among live births related to SARS-CoV-2 seropositivity during pregnancy among our cohort from NYC. These findings contrast with systematic reviews which found SARS-CoV-2 infection to be associated with increased risk of preterm birth.^{8,9,45} However, most previous research used a single RT-PCR test to confirm SARS-CoV-2 infection, when indicated or as part of universal screening at delivery. Symptomatic individuals and individuals with active infection at delivery might be over-represented in these studies, whereas individuals with resolved infections or ongoing infections who are no longer testing positive by RT-PCR may be missing. By measuring SARS-CoV-2 IgG antibodies, we were able to study SARS-CoV-2 exposure earlier in pregnancy irrespective of symptomatology and testing for acute infection. One other study, in which SARS-CoV-2 infection during pregnancy was evaluated using antibody testing, did not find a difference in pregnancy outcomes between antibody positive and negative individuals in Denmark.⁴⁶

Similar to previous work in both the general and pregnant populations,³⁵⁻³⁸ we show that SARS-CoV-2 disproportionately affects groups that have been economically/socially marginalised. Black and Hispanic patients, as well as patients with public insurance, had higher proportions of SARS-CoV-2 seropositivity compared with non-Hispanic White patients and patients with private insurance. These findings may be explained by various factors disproportionally impacting Black and Hispanic individuals and individuals with an occupation as essential worker and/or are related to conditions associated with disparities of socioeconomic status (SES), such as segregated neighbourhoods, crowded housing and discrimination.^{47,48} In addition to an increased risk of contracting SARS-CoV-2, research has also documented disparities in maternal and neonatal outcomes by race/ethnicity and SES.³⁹⁻⁴¹ Our findings suggest that the presence of SARS-CoV-2 IgG antibodies do not add to an already elevated risk of adverse maternal and neonatal outcomes.

Our findings, therefore, provide some reassurance regarding the effects of SARS-CoV-2 infection during pregnancy. However, since these findings are based on a potentially underpowered sample and a selection of key maternal and neonatal outcomes, further research is needed to strengthen the evidence base on the effects of SARS-CoV-2 infection during pregnancy. Research indicates that inflammatory responses earlier in pregnancy might produce more marked adverse effects on the foetus (e.g., on neurodevelopment) than those that occur later.⁴²⁻⁴⁴ Future analyses should also measure seropositivity within each trimester of pregnancy to better pinpoint when each individual became infected and how this timing may impact the outcome of pregnancy and the health of the baby.

5 | CONCLUSIONS

Seropositivity for SARS-CoV-2 without RT-PCR positivity at delivery, indicative of an infection earlier during pregnancy, was not associated with selected adverse maternal or neonatal outcomes among live births in a cohort sample from New York City. While Black and Hispanic participants in our cohort had a higher rate of SARS-CoV-2 seropositivity compared with non-Hispanic White participants, we found no increase in adverse maternal or neonatal outcomes among these groups due to infection.

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CONFLICT OF INTEREST

Mount Sinai has licenced serological assays to commercial entities and has filed for patent protection for serological assays. D.S and F.K. are listed as inventors on the pending patent application. The other authors have nothing to report.

AUTHOR CONTRIBUTIONS

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

- 1. Prabhu M, Cagino K, Matthews KC, et al. Pregnancy and postpartum outcomes in a universally tested population for SARS-CoV-2 in New York City: a prospective cohort study. *BJOG*. 2020;127(12):1548-1556. 10.1111/1471-0528.16403
- Haizler-Cohen L, Davidov A, Blitz MJ, Fruhman G. Severe acute respiratory syndrome coronavirus 2 antibodies in pregnant women admitted to labor and delivery units. *Am J Obstet Gynecol.* 2020;224(1):112-114. 10.1016/j.ajog.2020.09.022
- Zambrano LD, Ellington S, Strid P, et al. Update: characteristics of symptomatic women of reproductive age with laboratoryconfirmed SARS-CoV-2 infection by pregnancy status – United States, January 22–October 3, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(44):1641-1647. 10.15585/mmwr.mm6944e3
- DeBolt C, Bianco A, Limaye M, et al. Pregnant women with severe or critical COVID-19 have increased composite morbidity compared to non-pregnant matched controls. *Am J Obstet Gynecol.* 2020;224:510.e1-510.e12. 10.1016/j.ajog.2020.11.022
- Karimi L, Makvandi S, Vahedian-Azimi A, Sathyapalan T, Sahebkar A. Effect of COVID-19 on mortality of pregnant and postpartum women: a systematic review and meta-analysis. J Pregnancy. 2021;5:8870129.
- Hudak ML, Getzlaff T, Cs BS, Townson J, Barnette K. Pregnancy and neonatal outcomes of COVID-19 - coreporting of common outcomes from the PAN-COVID and AAP SONPM registry. *medRxiv*. 2021:2021.01.06.21249325. 10.1101/2021.01.06.21249325
- WAPM (World Association of Perinatal Medicine) Working Group on COVID-19. Maternal and perinatal outcomes of pregnant women with SARS-CoV-2 infection. Ultrasound Obstet Gynecol. 2021;57(2):232-241. 10.1002/UOG.23107
- Khalil A, Kalafat E, Benlioglu C, et al. SARS-CoV-2 infection in pregnancy: a systematic review and meta-analysis of clinical features and pregnancy outcomes. *EClinicalMedicine*. 2020;25:100446. 10.1016/j.eclinm.2020.100446
- Allotey J, Stallings E, Bonet M, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ. 2020;370:m3320. 10.1136/bmj.m3320
- Woodworth KR, Olsen M, Neelam V, et al. Birth and infant outcomes following laboratory-confirmed SARS-CoV-2 infection in pregnancy – SET-NET, 16 jurisdictions, March 29–October 14, 2020. MMWR Morb Mortal Wkly Rep. 2020;69:1635–1640.
- Di Mascio D, Sen C, Saccone G, et al. Risk factors associated with adverse fetal outcomes in pregnancies affected by Coronavirus disease 2019 (COVID-19): a secondary analysis of the WAPM study on COVID-19. J Perinat Med. 2020;48(9):950-958. 10.1515/ JPM-2020-0355
- Li N, Wang X, Lv T. Prolonged SARS-CoV-2 RNA shedding: not a rare phenomenon. J Med Virol. 2020;92(11):2286-2287. 10.1002/ jmv.25952
- Thorngren-Jerneck K, Herbst A. Low 5-minute Apgar score: a population-based register study of 1 million term births. *Obstet Gynecol.* 2001;98(1):65-70. 10.1016/S0029-7844(01)01370-9
- Amanat F, Stadlbauer D, Strohmeier S, et al. A serological assay to detect SARS-CoV-2 seroconversion in humans. *Nat Med.* 2020;26:1033-1036. 10.1038/s41591-020-0913-5
- Stadlbauer D, Amanat F, Chromikova V, et al. SARS-CoV-2 seroconversion in humans: a detailed protocol for a serological assay, antigen production, and test setup. *Curr Protoc Microbiol*. 2020;57(1):e100. 10.1002/cpmc.100

- Stadlbauer D, Tan J, Jiang K, et al. Repeated cross-sectional sero-monitoring of SARS-CoV-2 in New York City. Nature. 2020;590(7844):146-150. 10.1038/s41586-020-2912-6
- Bettencourt P, Fernandes C, Gil A, Almeida A, Alvelos M. Qualitative serology in patients recovered from SARS CoV 2 infection. *Int J Pharm.* 2020;81(2):e120-e121. 10.1016/j.jinf.2020.05.057
- Wang Y, Zhang L, Sang L, et al. Kinetics of viral load and antibody response in relation to COVID-19 severity. J Clin Invest. 2020;130:5235-5244. 10.1172/JCI138759
- Seow J, Graham C, Merrick B, et al. Longitudinal evaluation and decline of antibody responses in SARS-CoV-2 infection. *medRxiv*. 2020:2020.07.09.20148429. 10.1101/2020.07.09.20148429
- Self WH, Tenforde MW, Stubblefield WB, et al. Decline in SARS-CoV-2 antibodies after mild infection among frontline health care personnel in a multistate hospital network 12 States, April-August 2020. MMWR Morb Mortal Wkly Rep. 2020;69(47):1762-1766. 10.15585/mmwr.mm6947a2
- Ibarrondo FJ, Fulcher JA, Goodman-Meza D, et al. Rapid decay of anti-SARS-CoV-2 antibodies in persons with mild Covid-19. N Engl J Med. 2020;383(11):1085-1087. 10.1056/nejmc2025179
- Wajnberg A, Amanat F, Firpo A, et al. Robust neutralizing antibodies to SARS-CoV-2 infection persist for months. *Science*. 2020;370(6521):1227-1230. 10.1126/science.abd7728
- Zheng Z, Peng F, Xu B, et al. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. *J Infect*. 2020;81(2):e16-e25. 10.1016/j.jinf.2020.04.021
- 24. Zhang J, Wang X, Jia X, et al. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. *Clin Microbiol Infect*. 2020;26(6):767-772. 10.1016/j. cmi.2020.04.012
- 25. Jordan RE, Adab P, Cheng KK. Covid-19: risk factors for severe disease and death. *BMJ*. 2020;368:m1198. 10.1136/bmj.m1198
- Rod JE, Oviedo-Trespalacios O, Cortes-Ramirez J. A brief-review of the risk factors for covid-19 severity. *Rev Saude Publica*. 2020;54:60. 10.11606/S1518-8787.2020054002481
- 27. Finer N, Garnett SP, Bruun JM. COVID-19 and obesity. *Clin Obes*. 2020;10(3):e12365. 10.1111/cob.12365
- Hamer M, Kivimäki M, Gale CR, Batty GD. Lifestyle risk factors, inflammatory mechanisms, and COVID-19 hospitalization: a community-based cohort study of 387,109 adults in UK. Brain Behav Immun. 2020;87:184-187. 10.1016/j.bbi.2020.05.059
- 29. Jaddoe VWV, Troe EJWM, Hofman A, et al. Active and passive maternal smoking during pregnancy and the risks of low birthweight and preterm birth: the generation R study. *Paediatr Perinat Epidemiol*. 2008;22(2):162-171. 10.1111/j.1365-3016.2007.00916.x
- Catalano PM, Shankar K. Obesity and pregnancy: mechanisms of short term and long term adverse consequences for mother and child. BMJ. 2017;356:j1. 10.1136/bmj.j1
- Macintosh MCM, Fleming KM, Bailey JA, et al. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. *Br Med J.* 2006;333(7560):177-180. 10.1136/ bmj.38856.692986.AE
- Maselli DJ, Adams SG, Peters JI, Levine SM. Management of asthma during pregnancy. *Ther Adv Respir Dis*. 2013;7(2):87-100. 10.1177/1753465812464287
- Lean SC, Derricott H, Jones RL, Heazell AEP. Advanced maternal age and adverse pregnancy outcomes: a systematic review and meta-analysis. *PLoS One.* 2017;12(10):e0186287. 10.1371/journ al.pone.0186287
- Adam K. Pregnancy in women with cardiovascular diseases. Methodist Debakey Cardiovasc J. 2017;13(4):209-215. 10.14797/ mdcj-13-4-209
- COVID-19 Cases in New York City, a Neighborhood-Level Analysis
 NYU Furman Center. https://furmancenter.org/thestoop/entry/

covid-19-cases-in-new-york-city-a-neighborhood-level-analysis. Accessed April 21, 2020.

- Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and mortality among black patients and white patients with Covid-19. N Engl J Med. 2020;382(26):2534-2543. 10.1056/NEJMsa2011686
- Grechukhina O, Greenberg V, Lundsberg LS, et al. Coronavirus disease 2019 pregnancy outcomes in a racially and ethnically diverse population. *Am J Obstet Gynecol MFM*. 2020;2(4):100246. 10.1016/j.ajogmf.2020.100246
- Flannery DD, Gouma S, Dhudasia MB, et al. SARS-CoV-2 seroprevalence among parturient women. *medRxiv*. 2020:2020.07.08.20149179. 10.1101/2020.07.08.20149179
- Tangel V, White RS, Nachamie AS, Pick JS. Racial and ethnic disparities in maternal outcomes and the disadvantage of peripartum black women: a multistate analysis, 2007–2014. *Am J Perinatol.* 2019;36(8):835-848. 10.1055/s-0038-1675207
- Grobman WA, Parker CB, Willinger M, et al. Racial disparities in adverse pregnancy outcomes and psychosocial stress. *Obstet Gynecol.* 2018;131(2):328-335. 10.1097/AOG.00000000002441
- Crawford S, Joshi N, Boulet SL, et al. Maternal racial and ethnic disparities in neonatal birth outcomes with and without assisted reproduction. *Obstet Gynecol.* 2017;129(6):1022-1030. 10.1097/ AOG.00000000002031
- Atladóttir HÓ, Thorsen P, Østergaard L, et al. Maternal infection requiring hospitalization during pregnancy and autism spectrum disorders. J Autism Dev Disord. 2010;40(12):1423-1430. 10.1007/ s10803-010-1006-y
- Meyer U, Nyffeler M, Yee BK, Knuesel I, Feldon J. Adult brain and behavioral pathological markers of prenatal immune challenge during early/middle and late fetal development in mice. *Brain Behav Immun.* 2008;22(4):469-486. 10.1016/j.bbi.2007.09.012
- 44. Meyer U, Nyffeler M, Engler A, et al. The time of prenatal immune challenge determines the specificity of inflammation-mediated

brain and behavioral pathology. J Neurosci. 2006;26(18):4752-4762. 10.1523/JNEUROSCI.0099-06.2006

- Han Y, Ma H, Suo M, et al. Clinical manifestation, outcomes in pregnant women with COVID-19 and the possibility of vertical transmission: a systematic review of the current data. J Perinat Med. 2020;48(9):912-924. 10.1515/jpm-2020-0431
- Egerup P, Olsen LF, Christiansen A-MH, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies at delivery in women, partners, and newborns. *Obstet Gynecol.* 2020;137(1):49-55.
- Abrams EM, Szefler SJ. COVID-19 and the impact of social determinants of health. Lancet Respir Med. 2020;8(7):659-661. 10.1016/ S2213-2600(20)30234-4
- Janevic T, Zeitlin J, Egorova N, Hebert PL, Balbierz A, Howell EA. Neighborhood racial and economic polarization, hospital of delivery, and severe maternal morbidity. *Health Aff.* 2020;39(5):768-776. 10.1377/hlthaff.2019.00735

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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