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Association of SARS-CoV-2 Infection With Serious Maternal Morbidity and Mortality From Obstetric Complications

Torri D. Metz, MD, MS; Rebecca G. Clifton, PhD; Brenna L. Hughes, MD, MS; Grecio J. Sandoval, PhD; William A. Grobman, MD, MBA; George R. Saade, MD; Tracy A. Manuck, MD, MS; Monica Longo, MD, PhD; Amber Sowles, BSN, RN; Kelly Clark, BSN, RN; Hyagriv N. Simhan, MD; Dwight J. Rouse, MD; Hector Mendez-Figueroa, MD; Cynthia Gyamfi-Bannerman, MD, MS; Jennifer L. Bailit, MD, MPH; Maged M. Costantine, MD; Harish M. Sehdev, MD; Alan T. N. Tita, MD, PhD; George A. Macones, MD; for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units (MFMU) Network

IMPORTANCE It remains unknown whether SARS-CoV-2 infection specifically increases the risk of serious obstetric morbidity.

OBJECTIVE To evaluate the association of SARS-CoV-2 infection with serious maternal morbidity or mortality from common obstetric complications.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study of 14 104 pregnant and postpartum patients delivered between March 1, 2020, and December 31, 2020 (with final follow-up to February 11, 2021), at 17 US hospitals participating in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development's Gestational Research Assessments of COVID-19 (GRAVID) Study. All patients with SARS-CoV-2 were included and compared with those without a positive SARS-CoV-2 test result who delivered on randomly selected dates over the same period.

EXPOSURES SARS-CoV-2 infection was based on a positive nucleic acid or antigen test result. Secondary analyses further stratified those with SARS-CoV-2 infection by disease severity.

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of maternal death or serious morbidity related to hypertensive disorders of pregnancy, postpartum hemorrhage, or infection other than SARS-CoV-2. The main secondary outcome was cesarean birth.

RESULTS Of the 14 104 included patients (mean age, 29.7 years), 2352 patients had SARS-CoV-2 infection and 11 752 did not have a positive SARS-CoV-2 test result. Compared with those without a positive SARS-CoV-2 test result, SARS-CoV-2 infection was significantly associated with the primary outcome (13.4% vs 9.2%; difference, 4.2% [95% CI, 2.8%-5.6%]; adjusted relative risk [aRR], 1.41 [95% CI, 1.23-1.61]). All 5 maternal deaths were in the SARS-CoV-2 group. SARS-CoV-2 infection was not significantly associated with cesarean birth (34.7% vs 32.4%; aRR, 1.05 [95% CI, 0.99-1.11]). Compared with those without a positive SARS-CoV-2 test result, moderate or higher COVID-19 severity (n = 586) was significantly associated with the primary outcome (26.1% vs 9.2%; difference, 16.9% [95% CI, 13.3%-20.4%]; aRR, 2.06 [95% CI, 1.73-2.46]) and the major secondary outcome of cesarean birth (45.4% vs 32.4%; difference, 12.8% [95% CI, 8.7%-16.8%]; aRR, 1.17 [95% CI, 1.07-1.28]), but mild or asymptomatic infection (n = 1766) was not significantly associated with the primary outcome (9.2% vs 9.2%; difference, 0% [95% CI, −1.4% to 1.4%]; aRR, 1.11 [95% CI, 0.94-1.32]) or cesarean birth (31.2% vs 32.4%; difference, −1.4% [95% CI, −3.6% to 0.8%]; aRR, 1.00 [95% CI, 0.93-1.07]).

CONCLUSIONS AND RELEVANCE Among pregnant and postpartum individuals at 17 US hospitals, SARS-CoV-2 infection was associated with an increased risk for a composite outcome of maternal mortality or serious morbidity from obstetric complications.

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Torri D. Metz, MD, MS, University of Utah Health, 30 N 1900 E, SOM 2B200, Salt Lake City, UT 84132 (torri.metz@hsc.utah.edu).

Pregnant individuals with COVID-19 are at increased risk of intensive care unit (ICU) admission, mechanical ventilation, and death compared with both pregnant individuals without SARS-CoV-2 infection and nonpregnant adults with SARS-CoV-2 infection.[1-3] While COVID-19 increases the risk of maternal morbidity related to the virus (eg, as a result of severe acute respiratory syndrome), it remains unknown whether pregnant individuals with SARS-CoV-2 infection experience higher risk of serious morbidity from obstetric complications.

In aggregate, hypertensive disorders of pregnancy, postpartum hemorrhage, and other infections affect 10% to 20% of pregnancies in the United States and are leading causes of serious obstetric morbidity.[4-7] Prevention of serious morbidity related to these common complications relies on timely presentation to care, as well as appropriate monitoring and rapid intervention including delivery for severe hypertension, uterotonics to treat atony, and antibiotics for bacterial infections. Care modifications for pregnant individuals with SARS-CoV-2, such as limitations on in-person visits, isolation of infected individuals, and time for hospital staff to don necessary personal protective equipment, could all plausibly delay evaluation and treatment resulting in disease progression and morbidity. In addition, COVID-19 can result in aberrations in coagulation and hypertension, which could also result in obstetric morbidity.

The objective of this study was to evaluate whether SARS-CoV-2 infection was associated with increased risk of serious maternal morbidity or mortality from hypertensive disorders of pregnancy, postpartum hemorrhage, and infections other than SARS-CoV-2 overall and when stratified by disease severity. The secondary aim was to evaluate whether SARS-CoV-2 was associated with cesarean birth and adverse maternal and neonatal outcomes.

Key Points

Question Among pregnant and postpartum individuals, is SARS-CoV-2 infection associated with increased risk of maternal mortality or serious morbidity from obstetric complications?

Findings In this retrospective cohort study that included 14 104 patients, a composite outcome of maternal death or serious morbidity related to hypertensive disorders of pregnancy, postpartum hemorrhage, or infection other than SARS-CoV-2 occurred significantly more frequently in individuals with SARS-CoV-2 infection compared with individuals without SARS-CoV-2 infection (13.4% vs 9.2%, respectively).

Meaning Among pregnant and postpartum individuals, SARS-CoV-2 infection was associated with increased risk of a composite outcome of maternal mortality or serious morbidity from obstetric complications.

Methods

Study Design

This was a retrospective cohort study of pregnant or postpartum patients with a singleton or twin gestation who delivered at 1 of 17 US hospitals participating in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units (MFMU) Network's Gestational Research Assessments for COVID-19 (GRAVID) Study. The 17 included hospitals are affiliated with 1 of 12 MFMU Network centers. All hospitals are in close geographic proximity to the main center, and all except 1 are academic medical centers. Patients with SARS-CoV-2 infection were compared with patients without known SARS-CoV-2 infection who delivered at the same hospitals over the same period. The study was considered exempt from institutional review board review at all participating institutions and performed under waiver of consent. The study protocol and statistical analysis plan are available in Supplement 1 and Supplement 2, respectively. A subset (n = 833) of these patients was included in a prior publication.[8]

Participants and Exposure

Patients with a positive nucleic acid or antigen test result for SARS-CoV-2 during pregnancy or within 6 weeks postpartum were considered infected. All inpatients and outpatients with positive SARS-CoV-2 test results were included if they delivered at a participating site between March 1, 2020, and December 31, 2020. Patients with a negative SARS-CoV-2 test result or those with no documented SARS-CoV-2 infection at any time in pregnancy who delivered on randomly selected dates over the same period at the same hospital sites were considered not to have SARS-CoV-2 infection. All of the MFMU sites used the same randomly selected delivery dates. Random selection was based on a uniform distribution in which each weekday and each weekend day would have equal probability of random selection. Both weekdays and weekend days were sampled intentionally because staffing and delivery volumes were anticipated to differ. The protocol was created early in the pandemic. Therefore, 6 weekdays and 2 weekend days per month were sampled from March to May 2020 when we anticipated the largest surge of COVID-19, and 3 weekdays and 1 weekend day per month were randomly selected from June to December 2020.

Data regarding symptoms and severity of COVID-19 were abstracted from the medical record. Patients with SARS-CoV-2 were classified as having asymptomatic, mild, moderate, severe, or critical illness based on National Institutes of Health guidelines.[9] Classification was based on the patient's worst clinical status from their presentation for SARS-CoV-2 testing through 6 weeks postpartum.

Outcomes

The primary outcome was a composite of death from any cause or serious maternal morbidity related to common obstetric complications: hypertensive disorders of pregnancy, postpartum hemorrhage, or infection other than SARS-CoV-2. Serious morbidity was defined by maternal-fetal medicine subspecialists a priori as clinically significant end points that could be affected by the pathophysiology of COVID-19 or result from disease progression related to delays in care. Serious morbidity related to hypertensive

disorders of pregnancy included eclampsia; hemolysis, elevated liver enzymes, and low platelets syndrome[3]; pulmonary edema on chest x-ray; severe hypertension (>160/110 mm Hg) with acute administration of antihypertensive therapy; hepatic rupture; impaired liver function (>2 times the upper limit of normal); kidney insufficiency (creatinine ≥1.2 mg/dL [to convert to μmol/L, multiply by 88.4]); thrombocytopenia (platelets <100 000/μL); or placental abruption. Serious morbidity related to postpartum hemorrhage included transfusion of 4 or more units of packed red blood cells, surgical or radiologic interventions to control bleeding, and related complications. Serious morbidity related to infection included sepsis (infection with end organ dysfunction), bacteremia, endometritis requiring intravenous antibiotic therapy for more than 24 hours, deep incisional surgical site infection, or pelvic abscess.

The major secondary outcome was cesarean birth. An adverse maternal composite outcome of severe maternal morbidity defined as recommended by the American College of Obstetricians and Gynecologists and Society for Maternal-Fetal Medicine was also evaluated.[10] Adverse maternal outcomes related to COVID-19 also included ICU admission, ventilator support, extracorporeal membrane oxygenation, vasopressor support, cardiomyopathy, venous thromboembolism, arterial thrombosis, cerebral venous sinus thrombosis, kidney failure requiring dialysis, encephalopathy, multisystem inflammatory syndrome (patients <18 years), or superficial or deep incisional surgical site infection. Maternal outcomes were collected through 6 weeks postpartum.

Neonatal secondary outcomes included fetal or neonatal death, positive SARS-CoV-2 test result, preterm birth (<37 weeks' gestation), small for gestational age,[11] major congenital malformations, and both a preterm and term adverse neonatal composite outcome. The preterm composite included death, severe bronchopulmonary dysplasia, grade III or IV intraventricular hemorrhage, Bell stage 2A or greater necrotizing enterocolitis, periventricular leukomalacia, stage III or IV retinopathy of prematurity, or neonatal sepsis with positive blood cultures. The term composite outcome included death, respiratory support within the first 72 hours, Apgar score less than or equal to 3 at 5 minutes, hypoxic ischemic encephalopathy, seizure, infection (sepsis or pneumonia), birth trauma, meconium aspiration syndrome, intracranial or subgaleal hemorrhage, or hypotension requiring vasopressor support. Neonatal outcomes were collected during the delivery hospitalization. A post hoc outcome of preterm birth at less than 32 weeks' gestation was also included.

Utilization of inpatient health care resources was evaluated based on total maternal inpatient hospitalization and ICU days during pregnancy through 6 weeks postpartum, neonatal length of stay, and days in the neonatal ICU (NICU) or special care nursery that were not simply due to isolation from a mother with COVID-19.

Data Abstraction

All data were abstracted from the medical record by centrally trained and certified perinatal research staff using a standardized data collection form. Ongoing data quality checks were performed by an independent data coordinating center, which also performed the statistical analyses. Race and ethnicity data were based on patient self-report. Race and ethnicity data were collected because this study evaluated the exposure of SARS-CoV-2 infection, which has been found to be more common among patients who identify as Black or Hispanic,[12] and was therefore considered an important descriptive characteristic. All patients who identified as Hispanic ethnicity, regardless of race, were categorized as Hispanic. Non-Hispanic patients were categorized as American Indian or Alaska Native, Asian, Black, Native Hawaiian or Pacific Islander, White, or more than 1 self-reported race in the medical record. Races with low frequency were collapsed to make statistical comparisons.

Sample Size Calculation

Data from the MFMU Network's Assessment of Perinatal Excellence (APEX) cohort study were used to provide estimates on outcome rates for the sample size calculation.[13] The rate of serious maternal morbidity in APEX was 5.1%. Assuming 50% of the sites (45 000 deliveries annually) had a SARS-CoV-2 incidence of 5% over 3 months and the other 50% had an incidence of 1% to 2% over 9 months, the anticipated number of individuals with SARS-CoV-2 during the study period was 1000. With at least 1000 individuals with confirmed SARS-CoV-2 and 13 800 individuals without SARS-CoV-2 infection, the study had more than 85% power to detect a 50% increase in the primary composite maternal morbidity end point, from 5% to 7.5% with a 2-sided alpha of .05. The study would still have more than 85% power to detect a 50% increase if the number of individuals without SARS-CoV-2 infection was as low as 10 000.

Statistical Analyses

For the primary analysis, individuals infected with SARS-CoV-2 were compared with individuals without a positive SARS-CoV-2 test result. Bivariable comparisons were made using χ^2 or Fisher exact tests for categorical variables and Wilcoxon test for continuous variables. For the secondary analysis, the SARS-CoV-2–infected group was subdivided by COVID-19 severity. The group without a positive SARS-CoV-2 test result was compared with those with asymptomatic or mild COVID-19 and with those with moderate, severe, or critical COVID-19. Baseline demographics across disease severity were compared using Cochran-Armitage trend test for binary variables, score test from multinomial logistic regression for multinomial variables, or Jonckheere-Terpstra trend test for continuous variables. To account for random sampling of individuals without SARS-CoV-2, weighted analyses were performed for maternal and neonatal outcomes.

For maternal outcomes, modified Poisson regression models were used to estimate relative risks and 95% CIs. For continuous outcomes, generalized linear models were used to estimate difference in means and 95% CIs. To account for patients with twin gestations, models based on a generalized estimating equations framework with exchangeable correlation structure were used to estimate relative risk and difference in means for neonatal outcomes. For skewed continuous variables, the natural log-transformed value was used in

Figure 1. Cohort Development in a Study of SARS-CoV-2 Infection Among Pregnant and Postpartum Individuals

Bpm indicates beats per minute; Fio_2, fraction of inspired oxygen; and Spo_2, oxygen saturation as measured by pulse oximetry.

[a] First positive SARS-CoV-2 test result (molecular or antigen).

[b] Includes patients with no positive SARS-CoV-2 result any time during pregnancy through 42 days postpartum in the inpatient or outpatient setting.

[c] COVID-19 severity classification based on data during pregnancy through 42 days postpartum defined by National Institutes of Health guidelines for disease severity. Multiple signs and symptoms may be listed for each patient.

[d] Respiratory failure is use of any of the following: extracorporeal membrane oxygenation, continuous positive airway pressure, bilevel positive airway pressure, or ventilation.

[e] Multiple organ dysfunction or failure is 2 or more of the following: cardiac arrest, impaired liver function, kidney insufficiency (serum creatinine >1.2 mg/dL), kidney failure requiring dialysis, encephalopathy, any need for pressor support, or thrombocytopenia (platelets <100 000/μL).

[f] Other symptoms include fever, fatigue, chills, back pain, nausea, vomiting, joint pain, conjunctivitis, confusion, diarrhea, or other. Symptoms are not mutually exclusive.

the regression model to estimate differences in the means of the log-transformed values.

Covariates for models were selected a priori based on clinical importance. All multivariable models included MFMU center, maternal age, body mass index (BMI), and major medical comorbidity (chronic hypertension, pregestational diabetes, asthma, or chronic obstructive pulmonary disease). Models for the primary morbidity and mortality outcome, preterm birth, and hypertensive disorders of pregnancy also included obstetric history categorized as no prior deliveries at more than 20 weeks' gestation, prior delivery with a hypertensive disorder or preterm birth, or prior delivery without hypertensive disorder or preterm birth. The model for cesarean birth also included prior route of delivery categorized as prior vaginal birth, prior cesarean birth, or no prior pregnancy. Multivariable modeling was not performed for outcomes with low frequencies.

A planned sensitivity analysis was performed for the primary and major secondary outcomes in which those with no SARS-CoV-2 testing were excluded from analysis because it is possible these patients were asymptomatic but SARS-CoV-2 positive. A sensitivity analysis was also performed in which missing BMI values were imputed based on a generalized linear model and adjusted models were re-run. The imputation modeled the natural-log scale BMI with linear, quadratic, and cubic natural-log scale BMI at delivery calculated from the most recent pregnancy weight before delivery. For patients with BMI at delivery and without prenatal (or prepregnancy) BMI, imputed BMI values were the back-transformed predicted values based on the model. No other variables had missing data at a level that resulted in a need for multiple imputation.

Subgroup analyses were conducted to determine whether the association or lack thereof prevailed throughout particular subgroups of patients. Score tests were used to evaluate interactions between the exposure and a prespecified subgroup. For each subgroup (race and ethnicity, parity, and insurance status), stratified analyses were only conducted for outcomes if there was evidence of a significant interaction.

Statistical significance was defined as $P < .05$ and all tests were 2-tailed. All analyses were performed in SAS version 9.4 (SAS Institute Inc). Adjustments were not made for multiple comparisons. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory.

Results

Overall, 2352 patients tested positive for SARS-CoV-2 during pregnancy or within 6 weeks of delivery, and delivered from March through December 2020. During this time, 11 752 patients without a positive SARS-CoV-2 test result delivered on randomly selected delivery dates (**Figure 1**). Among patients who were SARS-CoV-2 positive in pregnancy, most (80.1%) tested positive in the third trimester, with 17.6% in the second trimester and 2.3% in the first trimester. Among the 103 patients (4.4%) with their first positive test result postpartum, the median timing was 18 days after delivery (IQR, 7-29). Among individuals with a positive SARS-CoV-2 test result, only 58 (2.47%) tested positive more than 2 weeks after delivery.

Patients with SARS-CoV-2 were significantly more likely to have had a previous pregnancy, be younger, of higher BMI, Hispanic, and to have public or no insurance compared with those without a positive SARS-CoV-2 test result (**Table 1**). The prevalence of preexisting major medical comorbidities is displayed in Table 1.

Primary Outcome

Compared with those without a positive SARS-CoV-2 test result, SARS-CoV-2 infection was significantly associated with the primary serious maternal morbidity and mortality outcome (13.4% vs 9.2%; difference, 4.2% [95% CI, 2.8%-5.6%); adjusted relative risk [aRR], 1.41 [95% CI, 1.23-1.61]) (**Table 2**). All 5 maternal deaths were in the SARS-CoV-2 group. In sensitivity analyses with imputation for missing BMI and in which those with no testing for SARS-CoV-2 were removed, results were similar (eTables 1 and 2 in Supplement 3).

Secondary Maternal Outcomes

Previous cesarean birth was the indication for the current cesarean birth in 28.9% of those with a positive SARS-CoV-2 test result vs 28.6% of those without a positive SARS-CoV-2 test result. Among those with SARS-CoV-2 infection, 2.3% of the cesarean births were noted to be indicated for COVID-19. Compared with patients without SARS-CoV-2 infection, those with SARS-CoV-2 were not at significantly increased risk of cesarean birth (34.7% vs 32.4%; aRR, 1.05 [95% CI, 0.99-1.11]) (Table 2).

SARS-CoV-2 infection was significantly associated with severe maternal morbidity or mortality[10] and ICU admission (Table 2). Other maternal adverse outcomes, including need for mechanical ventilation, vasopressor support, cardiomyopathy, and venous thromboembolism, were significantly more frequent among those infected with SARS-CoV-2 (eTable 3 in Supplement 3). There were no cases of multisystem inflammatory syndrome. All 4 cases of extracorporeal membrane oxygenation were among those with SARS-CoV-2 infection. In sensitivity analyses with imputation for missing BMI and in which those with no testing for SARS-CoV-2 were removed, results were similar (eTables 4 and 5 in Supplement 3).

Planned Subanalyses

There was no significant interaction between parity, insurance status, or race and ethnicity and SARS-CoV-2 infection for any of the outcomes. Subgroup analyses are reported in eTables 6 to 8 in Supplement 3.

Secondary Neonatal Outcomes

Overall, there were 14 471 neonates included in the analysis (2297 delivered by patients who were SARS-CoV-2 positive during pregnancy and 12 017 delivered by patients without SARS-CoV-2) (Figure 1). SARS-CoV-2 exposure was significantly associated with preterm birth at less than 37 weeks' gestation

Table 1. Baseline Demographics and Clinical Characteristics of Pregnant and Postpartum Patients With and Without a Positive SARS-CoV-2 Test Result

Characteristic	SARS-CoV-2 positive, No. (%)[a]	
	Yes (n = 2352)	No (n = 11 752)
Age, mean (SD), y	28 (6.2)	30 (5.8) [n = 11 749]
Body mass index, mean (SD)[b]	30.0 (7.75)	28.3 (7.64)
≥30	890/2080 (42.8)	3441/10 678 (32.2)
≥40	207/2080 (10.0)	808/10 678 (7.6)
Race and ethnicity		
No.	2259	11 178
American Indian/Alaska Native	4 (0.2)	43 (0.4)
Asian	49 (2.2)	575 (5.1)
Hispanic	1209 (53.5)	2626 (23.5)
Native Hawaiian/Pacific Islander	18 (0.8)	29 (0.3)
Non-Hispanic		
Black	536 (23.7)	2535 (22.7)
White	438 (19.4)	5310 (47.5)
>1 Self-reported race in medical record	5 (0.2)	60 (0.5)
Private insurance	683/2328 (29.3)	6389/11 674 (54.7)
Obstetric history		
No prior pregnancy 20 wk or longer	783/2350 (33.3)	4792/11 740 (40.8)
Previous preterm birth (20 to <37 wk)	260/2350 (11.1)	1088/11 740 (9.3)
Previous cesarean birth	503/2350 (21.4)	2156/11 740 (18.4)
Previous hypertensive disorder of pregnancy	243/2350 (10.3)	928/11 740 (7.9)
Substance use during this pregnancy[c]		
Smoked tobacco	100 (4.3)	853 (7.3)
Any substance use	132 (5.6)	975 (8.3)
Medical comorbidity[d]		
Asthma or chronic obstructive pulmonary disease	301 (12.8)	1558 (13.3)
Chronic hypertension	163 (6.9)	649 (5.5)
Neurocognitive disorder	146 (6.2)	1559 (13.3)
Thyroid disease	92 (3.9)	795 (6.8)
Pregestational diabetes	90 (3.8)	268 (2.3)
Immunocompromising condition	34 (1.4)	162 (1.4)
Seizure disorder	32 (1.4)	147 (1.3)
Chronic cardiovascular disease	26 (1.1)	175 (1.5)
Chronic liver disease	13 (0.6)	108 (0.9)
Thrombophilia	10 (0.4)	79 (0.7)
Inflammatory bowel disease	9 (0.4)	129 (1.1)
Chronic kidney disease	9 (0.4)	60 (0.5)
Neuromuscular disorder	9 (0.4)	52 (0.4)
Any comorbidity (asthma/chronic obstructive pulmonary disease, pregestational diabetes, or chronic hypertension)	485 (20.6)	2231 (19.0)
Twin pregnancy	53 (2.3)	265 (2.3)

[a] Data are mean (SD), No. (%), or No./total (%) unless otherwise specified.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Includes any use of alcohol, marijuana, opiates, cocaine, crack, amphetamines, hallucinogens, or benzodiazepines at any time during the pregnancy by either self-report or clinical urine toxicology in the medical record.

[d] Medical comorbidities were abstracted from the medical record.

(17.7% vs 14.1%; difference, 3.7% [95% CI, 2.1%-5.4%]; aRR, 1.15 [95% CI, 1.02-1.30]) and NICU admission (22.0% vs 17.8%; difference, 4.7% [95% CI, 2.9%-6.5%]; aRR, 1.15 [95% CI, 1.04-1.27]) (Table 2; eTable 9 in Supplement 3). Most of the preterm births among patients with SARS-CoV-2 were medically indicated or not resulting from spontaneous preterm labor (58.8%). COVID-19 was the indication for preterm birth in 8.3% of those with SARS-CoV-2 who had a medically indicated preterm birth. Maternal SARS-CoV-2 test positivity was not significantly associated with any other adverse neonatal outcome (Table 2; eTable 9 in Supplement 3). Among live births in the exposed group with a SARS-CoV-2 test (n = 1323), 1.2% (95% CI, 0.6%-1.8%) of neonates tested positive for SARS-CoV-2 before discharge.

Table 2. Maternal and Neonatal Outcomes for Individuals With and Without a Positive SARS-CoV-2 Test Result

	SARS-CoV-2 positive, No. (%)				
	Yes (n = 2352)	No (n = 11 752)	Difference (95% CI)	Relative risk (95% CI)	Adjusted relative risk (95% CI)
Maternal outcomes					
Primary composite outcome of death or serious morbidity from hypertensive disorders of pregnancy, postpartum hemorrhage, or non-SARS-CoV-2 infection	316 (13.4)	1076 (9.2)	4.2 (2.8 to 5.6)	1.45 (1.29 to 1.64)	1.41 (1.23 to 1.61)[a]
Death (any cause)	5 (0.2)	0			
Hypertensive disorders of pregnancy[b]	238 (10.1)	761 (6.5)	3.6 (2.4 to 4.8)	1.56 (1.35 to 1.79)	1.53 (1.31 to 1.79)[a]
Postpartum hemorrhage[c]	61 (2.6)	282 (2.4)	0.1 (−0.5 to 0.8)	1.06 (0.81 to 1.40)	1.13 (0.83 to 1.53)[a]
Infection other than SARS-CoV-2[d]	55 (2.3)	103 (0.9)	1.4 (0.8 to 2.1)	2.61 (1.88 to 3.63)	2.08 (1.41 to 3.05)[a]
Maternal secondary outcomes					
Cesarean birth	817 (34.7)	3811 (32.4)	2.1 (0.2 to 4.1)	1.06 (1.00 to 1.13)	1.05 (0.99 to 1.11)[e]
ACOG and SMFM-defined severe morbidity or mortality[f]	90 (3.8)	163 (1.4)	2.4 (1.7 to 3.2)	2.74 (2.12 to 3.55)	4.39 (3.15 to 6.12)[g]
ICU admission	86 (3.7)	139 (1.2)	2.5 (1.7 to 3.2)	3.12 (2.38 to 4.09)	5.82 (4.09 to 8.29)[g]
Neonatal Secondary Outcomes					
No.	2405	12 017			
Fetal or neonatal death	59 (2.5)	218 (1.8)	0.8 (0.1 to 1.4)	1.44 (1.08 to 1.93)	1.38 (0.98 to 1.95)[g]
Miscarriage at <20 wk	28 (1.2)	63 (0.5)			
Stillbirth at ≥20 wk	13 (0.5)	89 (0.7)			
Neonatal death (prior to discharge)	18 (0.7)	66 (0.5)			
Preterm birth at <37 wk[h]	425 (17.7)	1698 (14.1)	3.7 (2.1 to 5.4)	1.29 (1.16 to 1.43)	1.15 (1.02 to 1.30)[g]
Spontaneous	175 (41.2)	816 (48.1)			
Medically indicated[i]	250 (58.8)	882 (51.9)			
Preterm birth at <32 wk[j]	114 (4.7)	431 (3.6)	1.2 (0.3 to 2.1)	1.36 (1.10 to 1.68)	1.23 (0.95 to 1.60)[g]
Major congenital malformations[k]	108 (4.5)	584 (4.9)	−0.3 (−1.2 to 0.6)	0.94 (0.76 to 1.15)	0.91 (0.72 to 1.13)[g]
Perinatal preterm composite[l]	84 (3.5)	312 (2.6)	1.1 (0.3 to 1.9)	1.43 (1.12 to 1.82)	1.31 (0.98 to 1.75)[g]
Perinatal term composite[m]	169 (7.0)	768 (6.4)	0.9 (−0.3 to 2.0)	1.14 (0.97 to 1.34)	0.97 (0.81 to 1.16)[g]

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; ICU, intensive care unit; MFMU, Maternal-Fetal Medicine Units Network; SMFM, Society for Maternal-Fetal Medicine.

[a] Adjusted for MFMU center, maternal age, body mass index, any comorbidity (asthma/chronic obstructive pulmonary disease [COPD], pregestational diabetes, or chronic hypertension), and obstetric history (no prior pregnancy, prior pregnancy without preterm birth/preeclampsia, or prior pregnancy with preterm birth/preeclampsia).

[b] Includes eclampsia; hemolysis, elevated liver enzymes, and low platelets syndrome; pulmonary edema; severe hypertension (blood pressure ≥160/110 mm Hg) with acute administration of antihypertensive medication; hepatic rupture; impaired liver function (blood concentrations of liver enzymes 2 × upper limit of normal); kidney insufficiency (serum creatinine ≥1.2 mg/dL); thrombocytopenia (platelets <100 000/μL); or placental abruption.

[c] Includes transfusion of 4 or more units of packed red blood cells and surgical or radiologic interventions to control bleeding and related complications (eg, uterine packing, intrauterine balloon tamponade, uterine artery ligation, uterine compression sutures, hysterectomy, laparotomy, evacuation of hematoma, arterial embolization, and uterine evacuation).

[d] Includes sepsis (infection with organ dysfunction), bacteremia, endometritis requiring intravenous antibiotic therapy for more than 24 hours, deep incisional surgical site infection, or pelvic abscess.

[e] Adjusted for MFMU center, maternal age, body mass index, any comorbidity (asthma/COPD, pregestational diabetes, or chronic hypertension), and prior delivery route (no prior pregnancy, vaginal only, or cesarean).

[f] Includes death from any cause, ICU admission, or transfusion of 4 or more units of blood.

[g] Adjusted for MFMU center, maternal age, body mass index, and any comorbidity (asthma/COPD, pregestational diabetes, or chronic hypertension).

[h] Includes both live and stillbirths at greater than 20 weeks' gestation but less than 37 weeks' gestation.

[i] Preterm births that did not result from spontaneous preterm labor.

[j] Includes both live and stillbirths at greater than 20 weeks' gestation but less than 32 weeks' gestation.

[k] Includes cardiac (eg, major congenital heart disease), abdominal wall (eg, gastroschisis, omphalocele), central nervous system (eg, holoprosencephaly, myelomeningocele), chest (eg, congenital cystic adenomatoid malformation), gastrointestinal tract (eg, tracheoesophageal fistula), genitalia (eg, hypospadias or ambiguous genitalia), limbs (eg, limb reduction defect), and other clinically significant malformations.

[l] Includes fetal or neonatal death, severe bronchopulmonary dysplasia (grade 3), intraventricular hemorrhage (grades III or IV), necrotizing enterocolitis (Bell stage 2A or greater), periventricular leukomalacia, retinopathy of prematurity (stage III-IV), or proven sepsis (early or late).

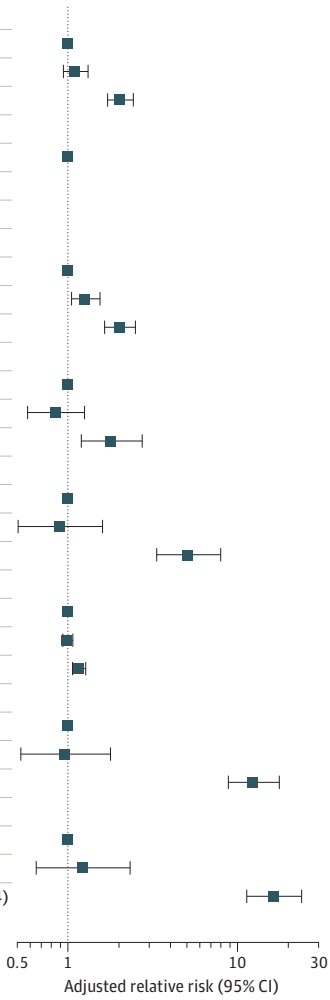
[m] Includes fetal or neonatal death, respiratory support within first 72 hours, Apgar score of 3 or less at 5 minutes, hypoxic ischemic encephalopathy, seizure, infection (sepsis or pneumonia), birth trauma, meconium aspiration syndrome, intracranial or subgaleal hemorrhage, or hypotension requiring vasopressor support. Additional maternal and neonatal outcomes can be found in eTables 3 and 9 in Supplement 3.

Secondary Analyses Stratified by COVID-19 Severity

In secondary analyses, COVID-19 was classified by severity (eTable 10 in Supplement 3). COVID-19 severity was categorized as critical in 59 patients (2.5%), severe in 180 (7.7%), moderate in 347 (14.8%), mild in 728 (31.0%), and asymptomatic in 1038 (44.1%). Baseline demographic characteristics differed

Figure 2. Maternal Outcomes Stratified by COVID-19 Severity

Maternal outcomes	No./total (%)	Difference (95% CI)	Relative risk (95% CI)	Adjusted relative risk (95% CI)
Primary composite outcome of death or serious morbidity from hypertensive disorders of pregnancy, postpartum hemorrhage, or non-SARS-CoV-2 infection				
Not SARS-CoV-2 positive	1076/11 752 (9.2)	0 [Reference]	1 [Reference]	1 [Reference]
Asymptomatic or mild	163/1766 (9.2)	0.0 (-1.4 to 1.4)	1.00 (0.85 to 1.17)	1.11 (0.94 to 1.32)
Moderate, severe, or critical	153/586 (26.1)	16.9 (13.3 to 20.4)	2.83 (2.44 to 3.28)	2.06 (1.73 to 2.46)
Death (any cause)				
Not SARS-CoV-2 positive	0	0 [Reference]	1 [Reference]	1 [Reference]
Asymptomatic or mild	0	NA	NA	NA
Moderate, severe, or critical	5/586 (0.9)	NA	NA	NA
Hypertensive disorders of pregnancy[a]				
Not SARS-CoV-2 positive	761/11 752 (6.5)	0 [Reference]	1 [Reference]	1 [Reference]
Asymptomatic or mild	126/1766 (7.1)	0.6 (-0.6 to 1.8)	1.10 (0.91 to 1.32)	1.28 (1.05 to 1.56)
Moderate, severe, or critical	112/586 (19.1)	12.6 (9.4 to 15.8)	2.94 (2.45 to 3.53)	2.05 (1.66 to 2.53)
Postpartum hemorrhage[b]				
Not SARS-CoV-2 positive	282/11 752 (2.4)	0 [Reference]	1 [Reference]	1 [Reference]
Asymptomatic or mild	31/1766 (1.8)	-0.7 (-1.3 to -0.1)	0.72 (0.50 to 1.04)	0.85 (0.58 to 1.26)
Moderate, severe, or critical	30/586 (5.1)	2.7 (0.9 to 4.5)	2.09 (1.45 to 3.03)	1.83 (1.20 to 2.77)
Infection other than SARS-CoV-2[c]				
Not SARS-CoV-2 positive	103/11 752 (0.9)	0 [Reference]	1 [Reference]	1 [Reference]
Asymptomatic or mild	16/1766 (0.9)	0.0 (-0.4 to 0.5)	1.01 (0.60 to 1.71)	0.90 (0.51 to 1.61)
Moderate, severe, or critical	39/586 (6.7)	5.8 (3.7 to 7.8)	7.43 (5.16 to 10.69)	5.25 (3.39 to 8.15)
Cesarean birth				
Not SARS-CoV-2 positive	3811/11 752 (32.4)	0 [Reference]	1 [Reference]	1 [Reference]
Asymptomatic or mild	551/1766 (31.2)	-1.4 (-3.6 to 0.8)	0.96 (0.89 to 1.03)	1.00 (0.93 to 1.07)
Moderate, severe, or critical	266/586 (45.4)	12.8 (8.7 to 16.8)	1.39 (1.27 to 1.53)	1.17 (1.07 to 1.28)
ACOG and SMFM–defined severe morbidity or mortality[d]				
Not SARS-CoV-2 positive	163/11 752 (1.4)	0 [Reference]	1 [Reference]	1 [Reference]
Asymptomatic or mild	12/1766 (0.7)	-0.7 (-1.1 to -0.3)	0.49 (0.27 to 0.88)	0.97 (0.52 to 1.80)
Moderate, severe, or critical	78/586 (13.3)	11.9 (9.2 to 14.7)	9.55 (7.35 to 12.40)	12.84 (9.05 to 18.21)
ICU admission				
Not SARS-CoV-2 positive	139/11 752 (1.2)	0 [Reference]	1 [Reference]	1 [Reference]
Asymptomatic or mild	11/1766 (0.6)	-0.6 (-0.9 to -0.2)	0.53 (0.29 to 0.98)	1.23 (0.65 to 2.35)
Moderate, severe, or critical	75/586 (12.8)	11.6 (8.9 to 14.3)	10.91 (8.30 to 14.35)	16.98 (11.65 to 24.74)



NA indicates not applicable.

[a] Includes eclampsia; hemolysis, elevated liver enzymes, and low platelets syndrome; pulmonary edema; severe hypertension (blood pressure at least 160/110 mm Hg) with acute administration of antihypertensive medication; hepatic rupture; impaired liver function (blood concentrations of liver enzymes 2 times the upper limit of normal); kidney insufficiency (serum creatinine at least 1.2 mg/dL); thrombocytopenia (platelets <100 000/μL); or placental abruption.

[b] Includes transfusion of 4 or more units of packed red blood cells and surgical or radiologic interventions to control bleeding and related complications (eg, uterine packing, intrauterine balloon tamponade, uterine artery ligation, uterine compression sutures, hysterectomy, laparotomy, evacuation of hematoma, arterial embolization, and uterine evacuation).

[c] Includes sepsis (infection with organ dysfunction), bacteremia, endometritis requiring intravenous antibiotic therapy for more than 24 hours, deep incisional surgical site infection, or pelvic abscess.

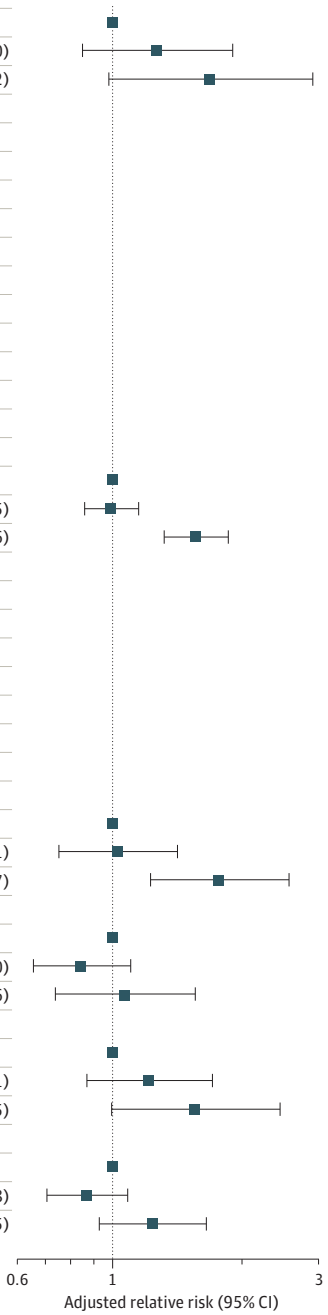
[d] American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal-Fetal Medicine (SMFM)–defined severe morbidity and mortality includes death from any cause, intensive care unit (ICU) admission, or transfusion of 4 or more units of blood.

significantly by COVID-19 severity (eTable 11 in Supplement 3). Those with moderate or higher disease severity were at significantly increased risk of the primary serious maternal morbidity and mortality composite (26.1% vs 9.2%; difference, 16.9% [95% CI, 13.3%-20.4%]; aRR, 2.06 [95% CI, 1.73-2.46]), cesarean birth (45.4% vs 32.4%; difference, 12.8% [95% CI, 8.7%-16.8%]; aRR, 1.17 [95% CI, 1.07-1.28]), severe maternal morbidity and mortality (13.3% vs 1.4%; difference, 11.9% [95% CI, 9.2%-14.7%]; aRR, 12.84 [95% CI, 9.05-18.21]), and ICU admission (12.8% vs 1.2%; difference, 11.6% [95% CI, 8.9%-14.3%]; aRR, 16.98 [95% CI, 11.65-24.74]) when compared with those without SARS-CoV-2 infection (**Figure 2**).

Outcomes for those with mild or asymptomatic COVID-19 were not significantly different from those without SARS-CoV-2 infection for the primary outcome (9.2% vs 9.2%; difference, 0% [95% CI, −1.4% to 1.4%]; aRR, 1.11 [95% CI, 0.94-1.32]) or the main secondary outcome of cesarean birth (31.2% vs 32.4%; difference, −1.4% [95% CI, −3.6% to 0.8%]; aRR, 1.00 [95% CI, 0.93-1.07]). However, mild or asymptomatic infection was significantly associated with a higher risk

Figure 3. Neonatal Outcomes Stratified by COVID-19 Severity

Neonatal outcomes	No./total (%)	Difference (95% CI)	Relative risk (95% CI)	Adjusted relative risk (95% CI)
Fetal or neonatal death				
Not SARS-CoV-2 positive	218/12 017 (1.8)	0 [Reference]	1 [Reference]	1 [Reference]
Asymptomatic or mild	38/1803 (2.1)	0.4 (-0.3 to 1.2)	1.26 (0.89 to 1.78)	1.27 (0.85 to 1.90)
Moderate, severe, or critical	21/602 (3.5)	1.7 (0.2 to 3.2)	2.00 (1.27 to 3.15)	1.69 (0.98 to 2.92)
Miscarriage at <20 wk[a]				
Not SARS-CoV-2 positive	63			
Asymptomatic or mild	20			
Moderate, severe, or critical	8			
Fetal loss at ≥20 wk[a]				
Not SARS-CoV-2 positive	89			
Asymptomatic or mild	7			
Moderate, severe, or critical	6			
Neonatal death[a]				
Not SARS-CoV-2 positive	66			
Asymptomatic or mild	11			
Moderate, severe, or critical	7			
Preterm birth at <37 wk				
Not SARS-CoV-2 positive	1698/12 017 (14.1)	0 [Reference]	1 [Reference]	1 [Reference]
Asymptomatic or mild	263/1803 (14.6)	0.6 (-1.1 to 2.4)	1.05 (0.92 to 1.19)	0.99 (0.86 to 1.15)
Moderate, severe, or critical	162/602 (26.9)	13.0 (9.4 to 16.6)	2.00 (1.73 to 2.32)	1.56 (1.32 to 1.86)
Spontaneous[a]				
Not SARS-CoV-2 positive	816/1698 (48.1)			
Asymptomatic or mild	123/263 (46.8)			
Moderate, severe, or critical	52/162 (32.1)			
Medically indicated[a]				
Not SARS-CoV-2 positive	882/1698 (51.9)			
Asymptomatic or mild	140/263 (53.2)			
Moderate, severe, or critical	110/162 (67.9)			
Preterm birth at <32 wk				
Not SARS-CoV-2 positive	431/12 017 (3.6)	0 [Reference]	1 [Reference]	1 [Reference]
Asymptomatic or mild	67/1803 (3.7)	0.2 (-0.8 to 1.1)	1.05 (0.80 to 1.36)	1.03 (0.75 to 1.41)
Moderate, severe, or critical	47/602 (7.8)	4.3 (2.1 to 6.5)	2.29 (1.70 to 3.09)	1.77 (1.22 to 2.57)
Major congenital malformations				
Not SARS-CoV-2 positive	584/12 017 (4.9)	0 [Reference]	1 [Reference]	1 [Reference]
Asymptomatic or mild	77/1803 (4.3)	-0.5 (-1.6 to 0.5)	0.88 (0.70 to 1.12)	0.85 (0.65 to 1.10)
Moderate, severe, or critical	31/602 (5.1)	0.4 (-1.4 to 2.3)	1.09 (0.77 to 1.56)	1.07 (0.74 to 1.56)
Perinatal preterm composite				
Not SARS-CoV-2 positive	312/12 017 (2.6)	0 [Reference]	1 [Reference]	1 [Reference]
Asymptomatic or mild	54/1803 (3.0)	0.6 (-0.3 to 1.4)	1.24 (0.93 to 1.66)	1.22 (0.87 to 1.71)
Moderate, severe, or critical	30/602 (5.0)	2.5 (0.7 to 4.3)	2.01 (1.38 to 2.92)	1.56 (0.99 to 2.45)
Perinatal term composite				
Not SARS-CoV-2 positive	768/12 017 (6.4)	0 [Reference]	1 [Reference]	1 [Reference]
Asymptomatic or mild	113/1803 (6.3)	0.1 (-1.1 to 1.4)	1.02 (0.84 to 1.24)	0.87 (0.70 to 1.08)
Moderate, severe, or critical	56/602 (9.3)	3.0 (0.6 to 5.4)	1.48 (1.14 to 1.93)	1.24 (0.93 to 1.65)



[a] Statistical comparisons were not made for subcategories of prespecified outcomes. Data for subcategories are presented for descriptive purposes.

for superficial or deep surgical site infection (1.8% vs 0.7%; difference, 1.1% [95% CI, −0.02% to 2.2%]; RR, 2.55 [95% CI, 1.23-5.27]) and hypertensive disorders of pregnancy (7.1% vs 6.5%; difference, 0.6% [95% CI, −0.6% to 1.8%]; aRR, 1.28 [95% CI, 1.05-1.56]) (Figure 2; eTable 12 in Supplement 3). Sensitivity analyses with imputation for missing BMI and which removed those with no testing for SARS-CoV-2 yielded similar results (eTables 13 and 14 in Supplement 3).

For neonatal outcomes stratified by maternal COVID-19 severity, patients with moderate or higher disease severity were at significantly increased risk of preterm birth at less than 37 weeks' gestation, preterm birth at less than 32 weeks' gestation (post hoc outcome), and NICU admission compared with those without SARS-CoV-2 infection (**Figure 3**; eTable 15 in Supplement 3). The outcomes for patients with asymptomatic or mild COVID-19 were not significantly different from

those without SARS-CoV-2 infection. Sensitivity analyses with imputation for missing BMI and which removed those with no testing for SARS-CoV-2 yielded similar results (eTables 16 and 17 in Supplement 3).

Discussion

In this study from 17 US hospitals, pregnant and postpartum patients with SARS-CoV-2 were at significantly increased risk of a composite of death and serious obstetric morbidity related to hypertensive disorders of pregnancy, postpartum hemorrhage, and infections other than SARS-CoV-2 when compared with individuals without SARS-CoV-2 infection.

Neonates of individuals with SARS-CoV-2 were at increased risk of preterm delivery and NICU admission. In secondary analyses, the observed maternal and neonatal risks could be attributed primarily to those with moderate or higher COVID-19 disease severity. Conversely, those with asymptomatic or mild COVID-19 had largely similar outcomes to the comparison group without SARS-CoV-2 infection.

Data from the Centers for Disease Control and Prevention (CDC) and other studies have shown increased risks of mechanical ventilation, ICU admission, and death from COVID-19 in pregnancy.[1,14,15] However, evidence about the relationship between SARS-CoV-2 and morbidity and mortality from obstetric complications is limited and mixed. Son and colleagues[16] found no association between SARS-CoV-2 and adverse pregnancy outcomes including preterm birth, hypertensive disorders of pregnancy, cesarean birth, or postpartum hemorrhage using administrative data from a large health care database. In contrast, using billing data, Jering and colleagues[2] found an association between SARS-CoV-2 and several of these outcomes. Neither study could assess risk by COVID-19 severity or whether there was increased morbidity following development of these common complications.

For a variety of obstetric complications, timely intervention is critical for prevention of serious morbidity and mortality. During the COVID-19 pandemic, it is plausible that changes in obstetric care could increase serious morbidity. The INTERCOVID study group similarly demonstrated an increased risk of morbidity and mortality in pregnant patients with SARS-CoV-2 infection, which was driven largely by a diagnosis of hypertensive disorders of pregnancy, preterm labor, or vaginal bleeding.[17] Overall, 32% of the COVID-19-positive group (n = 706) and 21% of the COVID-19-negative group (n = 1424) met the morbidity end point in INTERCOVID. The current study evaluated less common but significant morbidity that may reflect progression of disease without early intervention, as well as those adverse outcomes that may result from COVID-19. Patients with early SARS-CoV-2 infection in the first or second trimester were included in this study given the biologic plausibility for inflammation associated with viral infection to adversely affect the placenta. Prior reports demonstrated higher rates of placenta vascular malperfusion, thrombosis, and inflammation among individuals with SARS-CoV-2 infection compared with those without SARS-CoV-2 infection.[18,19] These changes may increase the risk of adverse pregnancy outcomes including hypertensive disorders of pregnancy, fetal growth restriction, and fetal loss.[20]

Planned subanalyses were performed to evaluate whether there was an interaction between race and ethnicity, parity, or insurance status and SARS-CoV-2 infection for the primary and major secondary outcomes. These subanalyses were planned because patients of certain races and ethnicities and of lower socioeconomic status are known to be at increased risk for both SARS-CoV-2 infection[12] and a number of the included outcomes, such as death and serious morbidity,[21] due to social determinants of health. There were no significant interactions detected with these subanalyses; yet, because of the overall association between SARS-CoV-2 and adverse pregnancy outcomes demonstrated in this study, it is worth noting that those individuals at higher risk of acquiring SARS-CoV-2 are also at higher risk of pregnancy complications.

A strength of this study is detailed data abstraction from the medical record by trained perinatal research staff, allowing for assessment of morbidity that cannot be extracted using administrative or billing data alone. In addition, patients were classified by COVID-19 severity and a sensitivity analysis was performed after excluding those with no testing, which yielded similar results. SARS-CoV-2-exposed individuals were identified in both the inpatient and outpatient settings to ensure the cohort was not biased with only those requiring hospitalization. The cohort was diverse and generalizable to the US population.

Limitations

This study has several limitations. First, data were collected in 2020 prior to wide circulation of the B.1.617.2 (Delta) variant of SARS-CoV-2, which may result in increased disease severity in pregnancy.[22-24] The association between the more recent Omicron variant and morbidity from obstetrical complications similarly could not be assessed. Second, while there was sufficient sample size to examine a composite outcome of serious morbidity or death, there was not sufficient power to examine rare outcomes such as death. Third, most SARS-CoV-2–infected individuals acquired the virus in the third trimester; therefore, the observed morbidity may be related to virus acquisition surrounding the time of delivery. Fourth, while pregnancy losses at less than 20 weeks' gestation were collected when available, ascertainment was incomplete because many of these patients would not require medical intervention. Fifth, 16 of the 17 included sites were academic centers, which may limit generalizability. Sixth, the study was conducted almost entirely prior to the availability of SARS-CoV-2 vaccination in December 2020.

Conclusions

Among pregnant and postpartum individuals at 17 US hospitals, SARS-CoV-2 infection was associated with an increased risk for a composite outcome of maternal mortality or serious morbidity from obstetric complications.

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Author Affiliations: Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Utah Health, Salt Lake City (Metz, Sowles); George Washington University Biostatistics Center, Washington, DC (Clifton, Sandoval); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of North Carolina at Chapel Hill (Hughes, Manuck, Clark); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Northwestern University, Chicago, Illinois (Grobman); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Texas Medical Branch, Galveston (Saade); *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, Maryland (Longo); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Pittsburgh, Pittsburgh, Pennsylvania (Simhan); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Brown University, Providence, Rhode Island (Rouse); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Texas Health Science Center at Houston, Children's Memorial Hermann, Hospital, Houston (Mendez-Figueroa); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Columbia University, New York, New York (Gyamfi-Bannerman); MetroHealth Medical Center, Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Case Western Reserve University, Cleveland, Ohio (Bailit); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Ohio State University, Columbus (Costantine); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Pennsylvania, Philadelphia (Sehdev); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Alabama at Birmingham (Tita); Department of Women's Health, University of Texas at Austin (Macones).

Author Contributions: Drs Metz and Clifton had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Metz, Clifton, Hughes, Grobman, Manuck, Longo, Sowles, Clark, Mendez-Figueroa, Gyamfi-Bannerman, Costantine, Tita, Macones.
Acquisition, analysis, or interpretation of data: Metz, Clifton, Hughes, Sandoval, Grobman, Saade, Manuck, Sowles, Clark, Simhan, Rouse, Mendez-Figueroa, Gyamfi-Bannerman, Bailit, Costantine, Sehdev, Tita, Macones.
Drafting of the manuscript: Metz, Clifton, Sandoval.
Critical revision of the manuscript for important intellectual content: All authors.
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Supervision: Metz, Clifton, Manuck, Clark, Rouse, Bailit, Sehdev, Tita, Macones.

Conflict of Interest Disclosures: Dr Metz reported receiving personal fees from Pfizer for her role as a medical consultant for a study of SARS-CoV-2 vaccination in pregnancy and grants from Pfizer for her roles as a site principal investigator [PI] for a study of SARS-CoV-2 vaccination in pregnancy and as a site PI for a study of respiratory syncytial virus vaccination in pregnancy, and from Gestvision for her role as a site PI for a preeclampsia study outside the submitted work. Dr Hughes reported receiving personal fees from Merck outside the submitted work. Dr Simhan reported being the co-founder of Naima Health LLC and receiving personal fees from UpToDate outside the submitted work. Dr Costantine reported relationships with Baxter International, Momenta Pharmaceuticals, Progenity, AMAG Pharmaceuticals, and ObsEva. Dr Tita reported receiving grants from Pfizer for a COVID-19 in pregnancy trial outside the submitted work. No other disclosures were reported.

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