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Severe maternal morbidity in pregnant patients with SARS-CoV-2 infection

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BACKGROUND: Although the increased risk for severe illness and adverse pregnancy outcomes associated with SARS-CoV-2 infection during pregnancy is well described, the association of infection with severe maternal morbidity has not been well characterized.

OBJECTIVE: This study aimed to evaluate the risk for severe maternal morbidity associated with SARS-CoV-2 infection during pregnancy.

STUDY DESIGN: This was a multicenter retrospective cohort study of all pregnant patients who had a SARS-CoV-2 test done and who delivered in a New York health system between March 1, 2020 and March 1, 2021. Patients with missing test results were excluded. The primary outcome of severe maternal morbidity, derived from the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine example list of diagnoses and complications, was compared between the following 2 groups: patients who tested positive for SARS-CoV-2 during pregnancy and patients who tested negative. Secondary outcomes included subgroups of severe maternal morbidity. Multivariable logistic regression was used to adjust for potential confounders such as maternal demographics, neighborhood socioeconomic status, hospital location, and pregnancy-related complications. A subanalysis was performed to determine if the risk for severe obstetrical hemorrhage and hypertension-associated or neurologic morbidity differed based on the timing of SARS-CoV-2 infection between those who tested positive for SARS-CoV-2 at their delivery hospitalization (ie, active infection) and those who tested positive during pregnancy but negative at their delivery hospitalization (ie, resolved infection).

RESULTS: Of the 22,483 patients included, 1653 (7.4%) tested positive for SARS-CoV-2 infection. Patients with SARS-CoV-2 infection were more commonly Black, multiracial, Hispanic, non-English speaking, used Medicaid insurance, were multiparous, and from neighborhoods with a lower socioeconomic status. Patients with SARS-CoV-2 infection were at an increased risk for severe maternal morbidity when compared with those without infection (9.3 vs 6.5%; adjusted odds ratio, 1.52; 95% confidence interval, 1.21−1.88). Patients with SARS-CoV-2 infection were also at an increased risk for severe obstetrical hemorrhage (1.1% vs 0.5%; adjusted odds ratio, 1.78; 95% confidence interval, 1.04−2.88), pulmonary morbidity (2.0% vs 0.5%; adjusted odds ratio, 3.90; 95% confidence interval, 2.52−5.89), and intensive care unit admission (1.8% vs 0.5%; adjusted odds ratio, 3.29; 95% confidence interval, 2.09−5.04) when compared with those without infection. The risk for hypertension-associated or neurologic morbidity was similar between the 2 groups. The timing of SARS-CoV-2 infection (whether active or resolved at time of delivery) was not associated with the risk for severe obstetrical hemorrhage or hypertension-associated or neurologic morbidity when compared with those without infection.

CONCLUSION: SARS-CoV-2 infection during pregnancy was associated with an increased risk for severe maternal morbidity, severe obstetrical hemorrhage, pulmonary morbidity, and intensive care unit admission. These data highlight the need for obstetrical unit preparedness in caring for patients with SARS-CoV-2 infection, continued public health efforts aimed at minimizing the risk for infection, and support in including this select population in investigational therapy and vaccine trials.

Key words: COVID-19, intensive care unit admission, obstetrical hemorrhage, pregnancy, SARS-CoV-2, severe maternal morbidity

Introduction

Accumulating data have demonstrated that pregnant patients infected with SARS-CoV-2 are at increased risk for severe illness and death because of complications associated with COVID-19 when compared with nonpregnant patients infected with SARS-CoV-2.[1,2] Furthermore, SARS-CoV-2 infection during pregnancy and increased disease severity have been associated with a number of perinatal complications including hypertensive disorders of pregnancy, preterm birth, stillbirth, and cesarean delivery.[3−10] Consequently, public health efforts have highlighted the need to minimize the risk of infection and to support the inclusion of pregnant patients in investigational therapy and vaccine trials.[11,12]

Identifying health-impacting and unintended life-threatening outcomes that occur during labor and delivery has become an important initiative for healthcare organizations worldwide.[13−17] Quality committees often review these rare events, most commonly referred to as severe maternal morbidity, to address whether the outcome could have been avoided or if changes in the systems for care provision are needed.[15−17] Ultimately, employing strategies aimed at preventing or reducing the recurrence of these outcomes that may lead to maternal mortality helps to ensure quality obstetrical care.[15] Because of the increasing rates of severe maternal morbidity in the United States, several professional groups, including the American College of Obstetricians and Gynecologists (ACOG), the Society for Maternal-Fetal Medicine (SMFM), and the Centers for Disease Control and Prevention (CDC), have advocated for research aimed at identifying risk factors for severe maternal morbidity.[15]

Although the increased risk for severe illness and adverse pregnancy outcomes associated with SARS-CoV-2 infection during pregnancy are well described,[1−10]

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AJOG MFM at a Glance

Why was this study conducted?

The association of SARS-CoV-2 infection with severe maternal morbidity has not been well characterized for events other than intensive care unit (ICU) admission and ventilator use.

Key findings

SARS-CoV-2 infection during pregnancy was associated with an increased risk for composite severe maternal morbidity, severe obstetrical hemorrhage, pulmonary morbidity, and ICU admission. The timing of SARS-CoV-2 infection (whether active or resolved at the time of delivery) was not associated with the risk for severe obstetrical hemorrhage or hypertension-associated or neurologic morbidity.

What does this add to what is known?

Continuing to identify risk factors for severe maternal morbidity and implementing hospital guidelines to help reduce the incidence of severe maternal morbidity for those at risk remain important steps in promoting safe obstetrical care.

the association of infection with severe maternal morbidity has not been well characterized for events other than intensive care unit (ICU) admissions and ventilator use. Therefore, this study aimed to evaluate the association of severe maternal morbidity with SARS-CoV-2 infection during pregnancy.

Materials and Methods

This was a retrospective cohort study of all pregnant patients who underwent SARS-CoV-2 testing and who delivered at 1 of 7 hospitals within a large health system in New York between March 1, 2020 and March 1, 2021. Patients with missing test results were excluded. The Northwell Health institutional review board approved this study as minimal-risk research using data collected during routine clinical practice and waived the requirement for informed consent. A subset of these patients has been included in previous publications evaluating outcomes associated with SARS-CoV-2 infection in pregnancy within our health system.[18–22]

Two groups of patients were compared based on the results of their SARS-CoV-2 qualitative real-time polymerase chain reaction (PCR) test: those who tested positive for SARS-CoV-2 infection during pregnancy and those who tested negative. For the diagnosis of infection, qualitative real-time PCR was performed on maternal nasopharyngeal swab specimens. Universal testing for SARS-CoV-2 infection was implemented for all patients admitted to the labor and delivery and antepartum units in all participating sites on April 2, 2020.[23] Before April 2, 2020, owing to limited capabilities, testing was performed based on a clinical suspicion of SARS-CoV-2 infection (ie, fever, flu-like symptoms, travel history, and known or suspected exposure).

The primary outcome was a composite of severe maternal morbidity indicators listed in Table 1, derived from the ACOG and SMFM example list of diagnoses and complications.[15] Their obstetrical care consensus document, created in collaboration with multidisciplinary expert groups, is intended to outline the process of efficiently identifying cases of severe maternal morbidity and optimizing strategies to improve patient care through quality review.[15] Secondary outcomes included each classified subgroup of severe maternal morbidity, including severe obstetrical hemorrhage (patients who had at least 1 of the following: obstetrical hemorrhage requiring transfusion of ≥4 packed red blood cells, uterine artery embolization, or peripartum hysterectomy), hypertension-associated or neurologic morbidity (patients who had at least 1 of the following: eclampsia, stroke, severe hypertension [≥160 mmHg systolic blood pressure or ≥110 mmHg diastolic blood pressure] requiring intravenous antihypertensive therapy or hemolysis, elevated liver enzymes, and low platelet count syndrome), sepsis, pulmonary morbidity (patients who had at least 1 of the following: acute respiratory distress syndrome [ARDS], pulmonary edema, mechanical ventilation, or deep vein thrombosis or pulmonary embolism) cardiac morbidity (patients who had at least 1 of the following: myocardial infarction or peripartum cardiomyopathy), and ICU admission.[15]

Patient demographic information, clinical characteristics such as comorbid conditions (eg, cardiovascular disease [defined as patients with a history of cerebrovascular disorders, dysrhythmias, ischemic and nonischemic heart disease, pericarditis, myocarditis, valvular disease, heart failure, and thromboembolic disease]), pregnancy outcomes, and the presence of any of the defined severe maternal morbidity indicators were obtained from our institution's electronic health record system (Allscripts Sunrise Clinical Manager, Chicago, IL) (Table 2). Severe maternal morbidity events were identified from physician clinical documentation and the International Classification of Diseases, Tenth Revision (ICD-10), diagnosis and procedural codes. Race and ethnicity were self-reported from prespecified categories. Patient zone improvement plan codes were linked to neighborhood-level data (ie, annual household income, household size, proportions of occupants who are receiving supplemental income, have low education levels, and are in owner occupied or single parent housing) collected by the US Census Bureau's American Community Survey.[24]

Statistical analysis included the use of chi-square or Fisher's exact tests and Mann-Whitney U or Student's *t* tests for comparisons of categorical and continuous variables, respective, as appropriate. Backward stepwise multivariable logistic regression was performed to evaluate the association between SARS-CoV-2 infection and severe maternal morbidity while adjusting for the following potential confounders: maternal age, body mass index (BMI), race, ethnicity, parity, insurance type, neighborhood-level characteristics, hospital location, comorbid conditions (ie, chronic hypertension, asthma, cardiovascular

TABLE 1
Severe maternal morbidity indicators

Severe obstetrical hemorrhage	Obstetrical hemorrhage requiring transfusion of 4 or more packed red blood cells
	Uterine artery embolization
	Peripartum hysterectomy
Hypertension or neurologic morbidity	Eclampsia
	Stroke
	Severe hypertension (>160 mm Hg systolic blood pressure or >110 mm Hg diastolic blood pressure) requiring intravenous antihypertensive therapy
	Hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome
Sepsis	
Pulmonary	Acute respiratory distress syndrome
	Pulmonary edema
	Mechanical ventilation
	Deep vein thrombosis or pulmonary embolism
Cardiac	Myocardial infarction
	Peripartum cardiomyopathy
Intensive care unit admission	

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disease), gestational diabetes, hypertensive disorders of pregnancy (gestational hypertension or preeclampsia), mode of delivery, and gestational age at delivery (review Table 2 for categorization of each variable). The potential confounders included all baseline characteristics that were significantly different between the 2 groups and others, such as hospital location, because both tertiary care and community-based hospitals were included in our study. We then used backward stepwise logistic regression to select a model in which the least significant factors were removed. The best model was selected based on the fitness determined by the Akaike information criterion and log likelihood.

A subanalysis was performed to determine whether the risk for severe obstetrical hemorrhage and hypertension-associated or neurologic morbidity differed based on the timing of SARS-CoV-2 infection. For this analysis, patients with a positive SARS-CoV-2 PCR test result were further divided into the following 2 groups: those who tested positive for SARS-CoV-2 at their delivery hospitalization (ie, active infection) and those who tested positive during pregnancy but negative at their delivery hospitalization (ie, resolved infection). Patients who only had negative test results during their pregnancy and at delivery hospitalization represented the reference group. Only these 2 morbidity subgroups were selected because they most often present as peripartum complications, whereas others such as ICU admission, ARDS, and ventilator use may have occurred earlier in pregnancy. Data were presented as adjusted odds ratios (aORs) with 95% confidence intervals (95% CIs) and statistical significance was set at $P<.05$.

Results

During the study period, a total of 28,334 pregnant patients were admitted for delivery. Patients with missing SARS-CoV-2 test results (n=5896) were excluded. Of the remaining 22,483 patients included in our cohort, 1653 (7.4%) tested positive for SARS-CoV-2 infection during their pregnancy and 20,785 (92.6%) tested negative. A comparison of the baseline characteristics between the 2 groups is presented in Table 2. Patients with SARS-CoV-2 infection were more commonly Black, multiracial, Hispanic, non-English speaking, used Medicaid insurance, were multiparous, and from neighborhoods with a lower socioeconomic status (Table 2). There were also high rates of medical comorbidities such as pregestational diabetes and cardiac disease in the SARS-CoV-2−positive group (Table 2). Pregnancy-related complications such as gestational hypertension, preeclampsia, and gestational diabetes, and the mode of delivery was similar between the 2 groups (Table 2).

The risk for composite severe maternal morbidity was significantly higher among patients with SARS-CoV-2 infection than among those without infection (9.3% vs 6.5%; aOR, 1.52; 95% CI, 1.21−1.88) (Table 3). Patients with SARS-CoV-2 infection were also at an increased risk for severe obstetrical hemorrhage (1.1% vs 0.5%; aOR, 1.78; 95% CI, 1.04−2.88), pulmonary morbidity (2.0% vs 0.5%; aOR, 3.90; 95% CI, 2.52−5.89), and ICU admission (1.8% vs 0.5%; aOR, 3.29; 95% CI, 2.09−5.04) when compared with those without infection (Table 3). The risk for hypertension-associated or neurologic morbidity was similar between the 2 groups (Table 3). The incidences of cardiac morbidity (n=16) and sepsis (n=54) in our cohort were low and were thus not evaluated in our regression analysis.

A comparison of the baseline characteristics of patients with and those without composite severe maternal morbidity in each SARS-CoV-2 group (positive or negative) is presented in Table 4. Among patients with SARS-CoV-2 infection, those who had severe maternal morbidity were older, had a higher BMI, were more commonly Black or Asian, had higher rates of medical comorbidities such as cardiovascular disease, asthma, chronic hypertension, and pregestational diabetes, and delivered at an earlier median gestational age than those without severe maternal

TABLE 2
Baseline characteristics comparison between the 2 groups

Characteristics	SARS-CoV-2 positive (n=1653)	SARS-CoV-2 negative (n=20,785)	*P* value
Maternal age (y)	31.0 (27.0–34.0)	32.0 (28.0–35.0)	<.001
BMI (kg/m^2)	30.8 (27.3–34.8)	30.1 (26.8–34.1)	.001
Race			
Black	239 (14.5)	2641 (12.7)	<.001
White	633 (38.3)	9805 (47.2)	
Asian	151 (9.1)	2820 (13.6)	
American Native	7 (0.4)	149 (0.7)	
Other or multiracial	561 (33.9)	4667 (22.5)	
Unknown	62 (3.8)	703 (3.4)	
Ethnicity			
Hispanic	496 (30.0)	3686 (17.7)	<.001
Non-Hispanic	1098 (66.4)	16,322 (78.5)	
Unknown	59 (3.6)	777 (3.7)	
Insurance type			
Medicaid	893 (54.6)	7531 (36.7)	<.001
Private	740 (45.2)	12,959 (63.1)	
Self-pay or unknown	4 (0.2)	40 (0.2)	
Language			
English	1403 (84.9)	19,198 (92.4)	<.001
Non-English	249 (15.1)	1577 (7.6)	
Nulliparous	613 (39.8)	9343 (48.7)	<.001
Neighborhood characteristics			
Median annual household income ($)	39,349 (30,911–51,677)	46,375 (34,336–64,885)	<.001
Education less than high school (%)	12.5 (7.9–19.8)	9.1 (4.3–16.6)	<.001
Unemployment (%)	5.0 (4.2–6.5)	4.7 (3.9–6.3)	<.001
Households receiving supplemental income (%)	21.1 (10.2–31.9)	16.4 (7.3–27.5)	<.001
Single parent household (%)	27.3 (17.9–40.0)	23.0 (14.9–35.5)	<.001
Median household size	3.0 (2.8–3.4)	3.0 (2.7–3.2)	<.001
Owner occupied housing (%)	64.0 (35.9–75.8)	64.6 (36.3–81.2)	.001
Comorbidities			
Cardiovascular disease	110 (6.7)	1056 (5.1)	.007
Asthma	100 (6.0)	1312 (6.3)	.7
Chronic hypertension	64 (3.9)	789 (3.8)	.9
Gestational hypertension or preeclampsia	232 (14.0)	2833 (13.6)	.3
Pregestational diabetes	34 (2.1)	279 (1.3)	.02
Gestational diabetes	151 (9.1)	1994 (9.6)	.6
Gestational age at delivery (wk)	39.1 (38.1–40)	39.2 (38.3–40)	<.001
Mode of delivery			
Vaginal delivery	1099 (66.6)	13,834 (66.8)	.9
Cesarean delivery	551 (33.4)	6884 (33.2)	

Data are presented as median (interquartile range) or number (percentage).

Missing data for BMI (11.4%), parity (8.9%), insurance type (1.2%), median annual household income (3.1%), education less than high school (1.1%), median household size (1%), households receiving supplemental income (1%), single parent household (1%), owner occupied housing (1%), unemployment (1%), mode of delivery (0.3%), gestational age at delivery (0.3%), and language (<0.1%).

BMI, body mass index.

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TABLE 3
A comparison of the primary and secondary outcomes between pregnant patients with and without SARS-CoV-2 infection

Outcomes	SARS-CoV-2 positive (n=1653)	SARS-CoV-2 negative (n=20,785)	Adjusted OR[a] (95% CI)
Composite severe maternal morbidity,[b] n (%)	154 (9.3)	1345 (6.5)	1.52 (1.21−1.88)
Severe obstetrical hemorrhage,[c] n (%)	19 (1.1)	111 (0.5)	1.78 (1.04−2.88)
Hypertension/neurologic morbidity,[d] n (%)	100 (6.0)	1,103 (5.3)	1.08 (0.82−1.42)
Pulmonary morbidity,[e] n (%)	33 (2.0)	98 (0.5)	3.90 (2.52−5.89)
ICU admission, n (%)	30 (1.8)	101 (0.5)	3.29 (2.09−5.04)

CI, confidence interval; *HELLP*, hemolysis, elevated liver enzymes and low platelet count; *ICU*, intensive care unit; *OR*, odds ratio.

[a] Models adjusted for maternal age, body mass index, race, ethnicity, parity, insurance type, neighborhood-level characteristics, hospital location, comorbid conditions, gestational diabetes, hypertensive disorders of pregnancy (gestational hypertension or preeclampsia), mode of delivery, and gestational age at delivery; [b] Includes patients with at least 1 of the following complications during pregnancy: obstetrical hemorrhage requiring transfusion of ≥4 packed red blood cells, uterine artery embolization, peripartum hysterectomy, eclampsia, stroke, severe hypertension requiring antihypertensive therapy, HELLP syndrome, sepsis, acute respiratory distress syndrome, pulmonary edema, mechanical ventilation, venous thromboembolism, myocardial infarction, peripartum cardiomyopathy, or ICU admission; [c] Includes patients with at least 1 of the following: obstetrical hemorrhage requiring transfusion of ≥4 packed red blood cells, uterine artery embolization, or peripartum hysterectomy; [d] Includes patients with at least 1 of the following: eclampsia, stroke, severe hypertension requiring antihypertensive therapy, or HELLP syndrome; [e] Includes patients with at least 1 of the following: acute respiratory distress syndrome, pulmonary edema, mechanical ventilation, or venous thromboembolism.

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morbidity (Table 4). Similar differences in the baseline characteristics were also seen among patients without SARS-CoV-2 infection who had severe maternal morbidity when compared with those without severe maternal morbidity and without SARS-CoV-2 infection (Table 4).

A comparison of the rates of primary and secondary outcomes between the first and second half of the study period is displayed in Table 5. There was a significant increase in composite severe maternal morbidity during the second half of the study period when compared with the first half (7.4% vs 6.7%; *P*=.03) (Table 5). The rates of severe maternal morbidity subgroups were similar between the 2 groups (Table 5). Similarly, there was also a significant increase in the composite severe maternal morbidity among patients with SARS-CoV-2 infection when compared with those without infection during the first (10.1% vs 6.4%; *P*<.001) and second half (11.3% vs 7.3%; *P*=.003) of the study period.

In the subgroup analysis, of the 1653 patients who tested positive for SARS-CoV-2 infection during their pregnancy, 1047 (63.3%) had an active SARS-CoV-2 infection and 606 (36.7%) had a resolved SARS-CoV-2 infection. Timing of SARS-CoV-2 infection (whether active or resolved at time of delivery) was not associated with the risk for severe obstetrical hemorrhage or hypertension-associated or neurologic morbidity when compared with those without infection (Table 6).

Discussion

Principal findings

The results of this study illustrate that SARS-CoV-2 infection during pregnancy is associated with an increased risk for composite severe maternal morbidity and several subgroups of severe maternal morbidity, such as severe obstetrical hemorrhage, pulmonary morbidity, and ICU admission. The timing of SARS-CoV-2 infection, whether active or resolved at the time of delivery, was not associated with the risk for severe obstetrical hemorrhage or hypertension-associated or neurologic morbidity.

Results

Evaluations of the association between severe maternal morbidity and SARS-CoV-2 infection during pregnancy have been heterogeneous with respect to classification of the outcomes.[1,25,26] Our findings of an increased risk for pulmonary morbidity and ICU admission associated with SARS-CoV-2 infection during pregnancy are similar to previous reports from the CDC and other international cohort studies.[1,25,26] However, an assessment of the risk for severe maternal morbidity, defined according to indicators reported in national or international guidelines, has rarely been explored to date. In a prospective observational cohort of 2130 patients from 18 countries, the INTER-COVID study investigators reported an increased risk for composite maternal morbidity and mortality index associated with COVID-19 in pregnancy (31.9% vs 20.8%; relative risk, 1.54; 95% CI, 1.33−1.78).[25] Although the 12 maternal deaths (0.6% of total cohort) were included in their composite outcome, the much higher incidence of morbidity in their study compared with ours is likely secondary to their defined maternal morbidity index, which included relatively common complications such as third-trimester bleeding, pregnancy-induced hypertension, infections requiring antibiotics, and preterm labor.[25] Variation in the definitions of severe morbidity and proposed lists of conditions and complications that constitute severe morbidity among professional groups has made it challenging to develop a consensus definition of severe maternal morbidity.[15] Furthermore, given the rarity of many complications, large cohorts with data recorded in electronic databases that are reliable and generate reproducible data are required to evaluate this outcome. Future

research aimed at developing a single, comprehensive definition of severe maternal morbidity is needed.

Despite numerous studies characterizing the pregnancy outcomes associated with SARS-CoV-2 infection during pregnancy, few have evaluated the risk for obstetrical hemorrhage, and the results have been conflicting.[4,26,27] In a large population-based cohort study from France that included more than 244,000 births, Epelboin et al[26] reported that patients with COVID-19 had a significantly higher frequency of peripartum and postpartum hemorrhage (defined as the loss of >500 mL of blood within the first 22 hours following childbirth) than patients without COVID-19. Metz et al[4] evaluated the association of postpartum hemorrhage (defined as blood loss >1000 mL) with COVID-19 severity in a multicenter cohort of 1219 patients in the United States. In their primary adjusted analysis, increased COVID-19 severity was associated with a higher risk for postpartum hemorrhage.[4] These findings are in contrast with a smaller retrospective cohort study by Wang et al[27] who reported no association between obstetrical hemorrhage (defined as blood loss >1000 mL measured quantitatively at the time of delivery) and COVID-19 during pregnancy. Differences in the study design, definition of hemorrhage, and sample size likely contribute to the conflicting results reported in the literature.

Clinical implications

Or findings that SARS-CoV-2 infection during pregnancy represents a risk factor for severe maternal morbidity, defined based on the ACOG and SMFM's obstetrical care consensus document, highlight the importance of encouraging practices to reduce such risk. In addition, our findings of an increased risk for severe obstetrical hemorrhage associated with SARS-CoV-2 infection can be used to inform hospitals and clinicians caring for pregnant patients with SARS-CoV-2 infection to have blood products and medical interventions, such as uterotonics, available at the time of delivery. Furthermore, given this significant risk in addition to other severe morbidities associated with SARS-CoV-2 infection during pregnancy, patient transfer to higher-level care and alerting the appropriate surgical or interventional radiological consultants should be considered.

Classification of the novel SARS-CoV-2 primarily as a respiratory pathogen coupled with an increased susceptibility for hypoxemia as a consequence of pregnancy-associated anatomic and physiological changes likely contributes to the increased risk for pulmonary morbidity and ICU admission associated with SARS-CoV-2 infection.[28] The underlying etiology for severe obstetrical hemorrhage is less clear. Possible mechanisms include pathologic vascular changes, such as endothelial dysfunction, that are induced by the virus.[29,30] Furthermore, coagulopathy has been described in pregnant patients with severe illness.[31] It is possible that placental evaluation may provide additional insight into the pathophysiology of this association. However, placental evaluation in these cases was not performed, because placentas are not routinely sent to our pathology department for examination at our institution. Nevertheless, the potential contribution of these hypotheses to hemorrhage, along with the potential impact of the accompanying release of large amounts of pro-inflammatory cytokines after infection,[32] requires further study.

Research implications

Of note, we evaluated whether the timing of SARS-CoV-2 infection was associated with the risk for severe obstetrical hemorrhage or hypertension-associated or neurologic morbidity and found no such association. Although these data suggest earlier infection and subsequent resolution do not confer a higher risk and this may be reassuring, the incidence of these outcomes were relatively low, which may have limited the power to detect significant differences. Future studies exploring the association between timing of infection and adverse perinatal outcomes and severe morbidities are needed.

Strengths and limitations

This study has several strengths. We addressed the important topic of severe maternal morbidity, which contributes a significant burden to healthcare organizations around the world and for which efforts to develop interventions to reduce this risk are of importance. In addition, our severe maternal morbidity indicators were obtained from a joint document supported by the ACOG, SMFM, and the CDC.[15] Our multicenter cohort was derived from both tertiary care and community-based hospitals in New York and is diverse in terms of maternal demographics and neighborhood socioeconomic status, thus making our findings generalizable. Nearly 30,000 deliveries are performed annually in our healthcare system (1% of the US population of births), making our cohort one of the largest reported in the literature for which outcomes associated SARS-CoV-2 infection during pregnancy are described.

This study also has several limitations. Our analysis was retrospective and relied on identifying severe maternal morbidity events from physician clinical documentation and ICD-10 diagnosis codes. Consequently, the timing of the adjusted variables such as the diagnosis of preeclampsia or gestational hypertension may have occurred at the exact timing as severe maternal morbidity or earlier in pregnancy. We were also unable to assess the association between COVID-19 disease severity and our primary and secondary outcomes. Universal testing for SARS-CoV-2 infection was not performed throughout the entire study period. However, given that it was implemented across our health system in all the months except for one, it is likely that this would not have impacted the findings of our study. Our study period also includes more than 1 wave of SARS-CoV-2 infection during the COVID-19 pandemic. Although variants of SARS-CoV-2 infection may have different risk profiles in terms of disease severity and severe morbidity in pregnant patients, evaluation of this association was not the focus of our study. Although adjusted for in our multivariable analysis, there were several significant differences at baseline

TABLE 4

Baseline characteristics compared between patients with and without composite severe maternal morbidity in each SARS-CoV-2 group

	SARS-CoV-2 positive			SARS-CoV-2 negative		
Characteristics	SMM (n=154)	No SMM (n=1499)	*P* value	SMM (n=1345)	No SMM (n=19,440)	*P* value
Maternal age (y)	33.0 (28.0–36.0)	30.0 (26.0–34.0)	<.001	33.0 (29.0–37.0)	32.0 (28.0–35.0)	<.001
BMI (kg/m^2)	32.1 (28.7–36.9)	30.7 (27.1–34.7)	<.001	32.8 (28.7–37.4)	29.9 (26.6–33.9)	<.001
Race						
Black	36 (23.4)	203 (13.5)	.001	335 (24.9)	2306 (11.9)	<.001
White	43 (27.9)	590 (39.4)		450 (33.4)	9355 (48.1)	
Asian	22 (14.3)	129 (8.6)		181 (13.5)	2639 (13.6)	
American Native	1 (0.6)	6 (0.4)		13 (1.0)	136 (0.7)	
Other or multiracial	46 (29.9)	515 (34.4)		313 (23.3)	4354 (22.4)	
Unknown	6 (3.9)	56 (3.7)		53 (3.9)	650 (3.3)	
Ethnicity						
Hispanic	46 (29.9)	450 (30.0)	1.0	273 (20.3)	3413 (17.6)	.04
Non-Hispanic	102 (66.2)	996 (66.4)		1022 (76.0)	15,300 (78.7)	
Unknown	6 (3.9)	53 (3.5)		50 (3.7)	727 (3.7)	
Insurance type						
Medicaid	77 (50.7)	816 (54.9)	.5	520 (39.1)	7011 (36.5)	.1
Private	75 (49.3)	665 (44.8)		805 (60.6)	12,154 (63.3)	
Self-pay or unknown	0	4 (0.3)		4 (0.3)	36 (0.2)	
Language						
English	130 (84.4)	1273 (85.0)	.9	1225 (91.1)	17,973 (92.5)	.06
Non-English	24 (15.6)	225 (15.0)		120 (8.9)	1457 (7.5)	
Nulliparous	67 (46.2)	546 (39.1)	.1	731 (58.1)	8612 (48.1)	<.001
Neighborhood characteristics						
Median annual household income ($)	40,203 (31,202–49,784)	39,349 (30,910–51,677)	.7	42,569 (33,271–60,805)	46,410 (34,336–64,885)	<.001
Education less than high school (%)	12.1 (8.1–19.7)	12.5 (7.6–19.8)	.6	9.9 (5.3–17.4)	9.0 (4.3–16.6)	<.001
Unemployment (%)	5.2 (4.3–6.5)	5.0 (4.2–6.5)	.4	4.9 (3.9–6.5)	4.7 (3.9–6.2)	<.001
Households receiving supplemental income (%)	21.4 (12.9–30.7)	20.9 (9.7–31.9)	.7	17.8 (8.8–28.9)	16.4 (7.4–27.5)	<.001
Single parent household (%)	30.0 (19.7–40.6)	26.9 (17.9–40.0)	.2	26.5 (16.9–40.9)	22.6 (14.9–35.4)	<.001
Median household size	3.1 (2.7–3.4)	3.0 (2.8–3.4)	.7	3.0 (2.8–3.3)	3.0 (2.7–3.2)	<.001
Owner occupied housing (%)	62.1 (37.0–74.7)	64.0 (35.9–76.4)	.9	65.9 (39.1–81.5)	64.2 (36.3–81.2)	.06
Comorbidities						
Cardiovascular disease	29 (18.8)	81 (5.4)	<.001	148 (11.0)	908 (4.7)	<.001
Asthma	19 (12.3)	81 (5.4)	<.001	117 (8.7)	1195 (6.2)	<0.001
Chronic hypertension	28 (18.2)	36 (2.4)	<.001	323 (24.0)	466 (2.4)	<.001
Gestational hypertension or preeclampsia	91 (59.1)	141 (9.4)	<.001	936 (69.6)	1897 (9.8)	<.001
Pregestational diabetes mellitus	7 (4.6)	27 (1.8)	.02	77 (5.7)	202 (1.0)	<.001
Gestational diabetes mellitus	14 (9.1)	137 (9.1)	1.0	204 (15.2)	1790 (9.2)	<.001
Gestational age at delivery (wk)	37.3 (35.2–38.6)	39.2 (38.3–40)	<.001	37.5 (35.5–39.1)	39.2 (38.4–40.1)	<.001
Mode of delivery						
Vaginal delivery	69 (44.8)	1030 (68.9)	<.001	587 (43.9)	13,247 (68.3)	<.001
Cesarean delivery	85 (55.2)	466 (31.1)		749 (56.1)	6135 (31.7)	

Data are presented as median (interquartile range) and number (percentage).

Missing data for BMI (11.4%), parity (8.9%), insurance type (1.2%), median annual household income (3.1%), education less than high school (1.1%), median household size (1%), households receiving supplemental income (1%), single parent household (1%), owner occupied housing (1%), unemployment (1%), mode of delivery (0.3%), gestational age at delivery (0.3%), and language (<0.1%).

BMI, body mass index.

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TABLE 5
Differences in severe maternal morbidity compared between the first and second half of the study period

Outcome	First half of study period (n=10,545)	Second half of study period (n=11,893)	*P* value
Composite severe maternal morbidity,[a] n (%)	703 (6.7)	882 (7.4)	.03
Severe obstetrical hemorrhage,[b] n (%)	53 (0.5)	82 (0.7)	.07
Sepsis, n (%)	19 (0.2)	35 (0.3)	.08
Hypertension or neurologic morbidity,[c] n (%)	550 (5.2)	688 (5.8)	.06
Pulmonary morbidity,[d] n (%)	73 (0.7)	69 (0.6)	.3
Cardiac morbidity,[e] n (%)	8 (0.1)	8 (0.1)	.8
ICU admission, n (%)	65 (0.6)	66 (0.6)	.5

HELLP, hemolysis, elevated liver enzymes, low platelet count; *ICU*, intensive care unit.

[a] Includes patients with at least 1 of the following complications during pregnancy: obstetrical hemorrhage requiring transfusion of ≥4 packed red blood cells, uterine artery embolization, peripartum hysterectomy, eclampsia, stroke, severe hypertension requiring antihypertensive therapy, HELLP syndrome, sepsis, acute respiratory distress syndrome, pulmonary edema, mechanical ventilation, venous thromboembolism, myocardial infarction, peripartum cardiomyopathy, or ICU admission; [b] Includes patients with at least 1 of the following: obstetrical hemorrhage requiring transfusion of ≥4 packed red blood cells, uterine artery embolization, or peripartum hysterectomy; [c] Includes patients with at least 1 of the following: eclampsia, stroke, severe hypertension requiring antihypertensive therapy, or HELLP syndrome; [d] Includes patients with at least 1 of the following: acute respiratory distress syndrome, pulmonary edema, mechanical ventilation, or venous thromboembolism; [e] Includes patients with at least 1 of the following: myocardial infarction, peripartum cardiomyopathy.

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between the groups that independently have been associated with an increased risk for SARS-CoV-2 infection and may have contributed to our findings. Furthermore, there may have been potential factors, such as changes in patient population characteristics as a consequence of outmigration during the COVID-19 pandemic, that were not adjusted for and may have contributed to our findings. Lastly, our study period spans a year in which treatments for COVID-19 and interventions to help reduce the risk for infection, such as vaccination, were rapidly evolving. We were unable to examine the impact of these practices on severe maternal morbidity.

TABLE 6
Risk for severe obstetrical hemorrhage and hypertension-associated or neurologic morbidity based on the timing of SARS-CoV-2 infection

Outcome by timing of infection	Adjusted OR[a] (95% CI)
Severe obstetrical hemorrhage[b]	
Active SARS-CoV-2 infection	1.71 (0.85–3.10)
Resolved SARS-CoV-2 infection	1.89 (0.83–3.74)
SARS-CoV-2 negative	Ref
Hypertension-associated or neurologic morbidity[c]	
Active SARS-CoV-2 infection	1.09 (0.77–1.54)
Resolved SARS-CoV-2 infection	1.07 (0.69–1.60)
SARS-CoV-2 negative	Ref

Data are presented as adjusted odds ratios with 95% confidence intervals.

CI, confidence interval; *HELLP*, hemolysis, elevated liver enzymes, low platelet count; *OR*, odds ratio; *Ref*, reference interval.

[a] Models adjusted for maternal age, body mass index, race, ethnicity, parity, insurance type, neighborhood-level characteristics, hospital location, comorbid conditions, gestational diabetes, hypertensive disorders of pregnancy (gestational hypertension or preeclampsia), mode of delivery, and gestational age at delivery; [b] Includes patients with at least 1 of the following: obstetrical hemorrhage requiring transfusion of ≥4 packed red blood cells, uterine artery embolization, or peripartum hysterectomy; [c] Includes patients with at least 1 of the following: eclampsia, stroke, severe hypertension requiring antihypertensive therapy, or HELLP syndrome.

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Conclusions

Our findings illustrate that SARS-CoV-2 infection during pregnancy is associated with an increased risk for composite severe maternal morbidity, severe obstetrical hemorrhage, pulmonary morbidity, and ICU admission. As we enter another wave of the pandemic with record-setting infection rates, these data highlight the need for continued public health efforts aimed at minimizing the risk for infection and promoting vaccination and investigational therapies in this select patient population. Preliminary data evaluating the impact of vaccination on SARS-CoV-2 infection rates and COVID-19 disease severity in pregnancy have been reassuring.[33] Continuing to identify risk factors for severe maternal morbidity and implementing hospital guidelines to help reduce the incidence of severe maternal morbidity remain important steps in promoting safe obstetrical care and guiding patient counseling. ■

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