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OBSTETRICS

Pregnant women with severe or critical coronavirus disease 2019 have increased composite morbidity compared with nonpregnant matched controls



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BACKGROUND: In March 2020, as community spread of severe acute respiratory syndrome coronavirus 2 became increasingly prevalent, pregnant women seemed to be equally susceptible to developing coronavirus disease 2019. Although the disease course usually appears mild, severe and critical cases of coronavirus disease 2019 seem to lead to substantial morbidity, including intensive care unit admission with prolonged hospital stay, intubation, mechanical ventilation, and even death. Although there are recent reports regarding the impact of coronavirus disease 2019 on pregnancy, there is a lack of information regarding the severity of coronavirus disease 2019 in pregnant vs nonpregnant women.

OBJECTIVE: We aimed to describe the outcomes of severe and critical cases of coronavirus disease 2019 in pregnant vs nonpregnant, reproductive-aged women.

STUDY DESIGN: This is a multicenter, retrospective, case-control study of women with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 infection hospitalized with severe or critical coronavirus disease 2019 in 4 academic medical centers in New York City and 1 in Philadelphia between March 12, 2020, and May 5, 2020. The cases consisted of pregnant women admitted specifically for severe or critical coronavirus disease 2019 and not for obstetrical indications. The controls consisted of reproductive-aged, nonpregnant women admitted for severe or critical coronavirus disease 2019. The primary outcome was a composite morbidity that includes the following: death, a need for intubation, extracorporeal membrane oxygenation, noninvasive positive pressure ventilation, or a need for high-flow nasal cannula O₂ supplementation. The secondary outcomes included intensive care unit admission, length of stay, a need for discharge to long-term acute care facilities, and discharge with a home O₂ requirement.

RESULTS: A total of 38 pregnant women with severe acute respiratory syndrome coronavirus 2 polymerase chain reaction-confirmed infections were admitted to 5 institutions specifically for coronavirus disease 2019, 29

(76.3%) meeting the criteria for severe disease status and 9 (23.7%) meeting the criteria for critical disease status. The mean age and body mass index were markedly higher in the nonpregnant control group. The nonpregnant cohort also had an increased frequency of preexisting medical comorbidities, including diabetes, hypertension, and coronary artery disease. The pregnant women were more likely to experience the primary outcome when compared with the nonpregnant control group (34.2% vs 14.9%; $P=.03$; adjusted odds ratio, 4.6; 95% confidence interval, 1.2–18.2). The pregnant patients experienced higher rates of intensive care unit admission (39.5% vs 17.0%; $P<.01$; adjusted odds ratio, 5.2; 95% confidence interval, 1.5–17.5). Among the pregnant women who underwent delivery, 72.7% occurred through cesarean delivery and the mean gestational age at delivery was 33.8±5.5 weeks in patients with severe disease status and 35±3.5 weeks in patients with critical coronavirus disease 2019 status.

CONCLUSION: Pregnant women with severe and critical coronavirus disease 2019 are at an increased risk for certain morbidities when compared with nonpregnant controls. Despite the higher comorbidities of diabetes and hypertension in the nonpregnant controls, the pregnant cases were at an increased risk for composite morbidity, intubation, mechanical ventilation, and intensive care unit admission. These findings suggest that pregnancy may be associated with a worse outcome in women with severe and critical cases of coronavirus disease 2019. Our study suggests that similar to other viral infections such as severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus, pregnant women may be at risk for greater morbidity and disease severity.

Key words: coronavirus, critical disease, disease course, intensive care, intubation, maternal morbidity, pandemic, pregnancy, preterm birth, respiratory distress syndrome, severe acute respiratory syndrome, severe acute respiratory syndrome coronavirus 2, severe disease

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Introduction

The novel coronavirus disease 2019 (COVID-19), caused by infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global public health emergency with 21,294,845 infected people and 761,779 related deaths worldwide at the time of this writing.¹ In the United States alone, 5,258,565 cases have been reported with 167,201 related deaths.¹

Based on the early reports in pregnant women, the clinical course of COVID-19 is typically mild (86%), severe (9%), or critical (5%),² which is similar to the clinical course distribution seen in the nonpregnant population, which is mild (81%), severe (14%), or critical (5%).³

SARS-CoV-2 infections seem to cause serious pulmonary manifestations, including pneumonia, which is the most prevalent nonobstetrical infection that

AJOG at a Glance

Why was this study conducted?

This study aimed to improve our understanding of how pregnancy affects the clinical course of severe and critical cases of coronavirus disease 2019 (COVID-19) in pregnant vs nonpregnant controls.

Key findings

Pregnant women are more likely to experience a composite morbidity including death, the need for intubation, extracorporeal membrane oxygenation, noninvasive positive pressure ventilation, and a need for high-flow nasal cannula supplementation when compared with the nonpregnant control group.

What does this study add to what is known?

This study adds to the existing data by comparing the clinical characteristics and outcomes of severe and critical cases of COVID-19 in pregnant and nonpregnant women. Our data suggest that the clinical course and severity of COVID-19 in hospitalized pregnant women is worse than in nonpregnant controls.

occurs in pregnancy,⁴ acute respiratory distress syndrome, pervasive microemboli, and coagulation perturbations,⁵ and therefore an increase in morbidity and mortality among pregnant women is a reasonable concern. As with other infectious diseases, the normal maternal physiological changes that accompany pregnancy, including hypercoagulability, altered cell-mediated immunity,⁶ and the changes in pulmonary function, which cause a reduced total lung capacity at term and an inability to clear pulmonary secretions effectively,⁷ have been hypothesized to effect both the susceptibility to and clinical severity of pneumonia in pregnant women. The changes to the immune and respiratory systems that occur during pregnancy can increase their vulnerability to severe infection and hypoxic compromise. Common symptoms in pregnancy, such as physiological dyspnea, may delay a diagnosis when the pathologic dyspnea secondary to COVID-19 is not distinguished.⁸

There is a paucity of information regarding the outcomes of COVID-19 in pregnant women compared with nonpregnant women. A report from the Centers for Disease Control and Prevention (CDC) found that hospitalization was substantially higher among SARS-CoV-2–infected pregnant women when compared with nonpregnant women. Pregnant women were more

frequently admitted to the intensive care unit (ICU) (1.5% vs 0.9%) and 0.5% of pregnant women required mechanical ventilation when compared with 0.3% of nonpregnant women. A total of 16 deaths (0.2%) were reported among pregnant women and 208 (0.2%) among nonpregnant women.⁹ However, in this report, data to distinguish between hospitalizations for COVID-19–related illness and admission for pregnancy-related conditions were not available. Knowledge of the course of the disease in pregnant vs nonpregnant women is essential to better understand the risk to our pregnant population. This study aimed to compare the clinical outcomes of severe and critical cases of COVID-19 in pregnant vs nonpregnant control women of reproductive age. We hypothesized that the clinical course and outcomes are worse in pregnant women, as has been demonstrated with other respiratory pathogens.^{10–12}

Materials and Methods

This was a multicenter, case-control study of women with polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infections who met the admission criteria for severe and critical COVID-19. We explored the clinical course and outcomes of pregnant women admitted with severe and critical COVID-19 status compared with nonpregnant control women of reproductive age. The data

were collected from patients admitted to 4 hospitals in New York City and 1 in Philadelphia between March 12, 2020, and May 5, 2020. Our primary outcome variable was a composite morbidity that included death, a need for intubation, extracorporeal membrane oxygenation (ECMO), noninvasive positive pressure ventilation, including bilevel positive airway pressure (BiPAP) and continuous positive airway pressure (CPAP), and a need for high-flow nasal cannula supplementation. Other treatment interventions, including medications used and the use of prone positioning, were also collected. Secondary outcomes included ICU admission, length of stay, frequency of discharge to home with O₂ supplementation, and frequency of discharge to a long-term care facility. During admission, delivery was performed for the usual obstetrical indications, however, beyond this, decisions about delivery was up to the individual providers' discretion.

The inclusion criteria were defined as pregnant and nonpregnant women between 18 and 50 years of age who met the admission criteria for a diagnosis of severe or critical COVID-19 as defined by the World Health Organization and the Chinese Center for Disease Control and Prevention. Severe COVID-19 was defined as the presence of dyspnea (patient reported), a respiratory rate of ≥ 30 breaths per minute, blood O₂ saturation of $\leq 93\%$ on room air, a partial pressure of arterial O₂ to the fraction of inspired oxygen of < 300 , and findings consistent with pneumonia on a chest x-ray.^{13–15} Critical COVID-19 was defined as respiratory failure requiring intubation or mechanical ventilation, septic shock, and multiple organ dysfunction or failure.^{13–15} Respiratory failure was defined as a need for invasive mechanical ventilation. Septic shock was defined as a need for vasopressors to maintain a mean arterial pressure (MAP) of ≥ 65 and serum lactate levels of > 2 mmol/L despite a sufficient volume resuscitation along with ≥ 2 sepsis-related organ failure assessment criteria which include the following: a decline in the partial pressure of O₂ or fraction of inspired O₂, decline in platelet counts, rising

bilirubin levels, decline in MAP, decline in the Glasgow Coma Scale, and a rise in serum creatinine.¹⁶ Multiple organ dysfunction or failure was defined as the presence of at least 2 of the following: renal impairment or failure (defined as a 3-fold increase in the baseline creatinine or need for dialysis¹⁷), liver failure (defined as an international normalized ratio of >1.5), a diagnosis of refractory hypoglycemia by the treating institution, or hepatic encephalopathy.¹⁸ A test result was considered positive for SARS-CoV-2 infection if the quantitative reverse transcription PCR (qRT-PCR) analysis of the specimen acquired from the respiratory tract in the form of a nasopharyngeal swab was positive for the presence of SARS-CoV-2. This method of confirming SARS-CoV-2 infection, in addition to the criteria used to define severe COVID-19 and critical COVID-19 cases, were uniform across all institutions. We excluded patients with comorbidities that are associated with an immunocompromised state including the following: an active malignancy, a history of transplant, a history of developmental delay, cerebral palsy, and trisomy 21 or other known aneuploidies. Regardless of a clinical suspicion, women with inconclusive or negative SARS-CoV-2 laboratory results were excluded. The variables of the obstetrical comorbidity index that is validated for use during labor and delivery to predict the risk of severe maternal morbidity were also collected.¹⁹ Severe maternal morbidity was classified according to the guidelines of the American College of Obstetricians and Gynecologists, the Society for Maternal Fetal Medicine, and the CDC.²⁰ According to the CDC National Center for Health Statistics, preterm birth rate was defined as a singleton livebirth at <37 weeks' gestation and early preterm birth as a singleton livebirth at <34 weeks of gestation.

The institutional review board at each institution approved this study. Data use agreements were obtained for collaboration among the sites. Data from each medical center's electronic medical record (EMR) were abstracted by means of a Research Electronic Data Capture form. De-identified data were then

Demographics	Pregnant cases (n=38)			Nonpregnant controls (n=94)			P value
	n	Mean±SD	Range	n	Mean±SD	Range	
Maternal age (y)	38	34.7±4.3	25–42	94	37.9±6.7	23–50	<.01
BMI at admission (kg/m ²)	38	31.7±5.2	20.2–41	94	33.4±6.6	22–55	.15
	n/N (%)			n/N (%)			
Race or ethnicity							.16
Non-Hispanic white	9/38 (23.7)			9/94 (9.6)			
Non-Hispanic black	7/38 (18.4)			13/94 (13.8)			
Hispanic or Latina	15/38 (39.5)			35/94 (37.2)			
Asian	3/38 (7.9)			8/94 (8.5)			
American Indian or Alaska Native	0/38 (0.0)			1/94 (1.1)			
Other	2/38 (5.3)			11/94 (11.7)			
Unknown or not recorded	2/38 (5.3)			17/94 (18.1)			
Insurance type							.41
Private or commercial	16/38 (42.1)			36/94 (38.3)			
Medicaid or managed Medicaid	20/38 (52.6)			55/94 (58.5)			
Medicare	0/38 (0.0)			2/94 (2.1)			
Uninsured or self-pay	2/38 (5.3)			1/94 (1.1)			
Tobacco use							.23
Current smoker	0/38 (0.0)			0/94 (0.0)			
Former smoker	1/38 (2.6)			10/94 (10.6)			
Never smoker	35/38 (92.1)			75/94 (79.8)			
Not recorded	2/38 (5.3)			9/94 (9.6)			
Disease severity at admission							.23
Severe	29/38 (76.3)			80/94 (85.1)			
Critical	9/38 (23.7)			14/94 (14.9)			
Preexisting conditions ^a							
Preexisting pulmonary disease	4/38 (10.5)			21/94 (22.3)			.12
Preexisting cardiac disease	4/38 (10.5)			27/94 (28.7)			.03
Preexisting diabetes	4/38 (10.5)			26/94 (27.7)			.03

BMI, body mass index; SD, standard deviation.

^a Pulmonary disease is defined as asthma, obstructive sleep apnea, chronic obstructive pulmonary disease, and chronic bronchitis. Cardiac disease is defined as hypertension, coronary artery disease, hyperlipidemia, valvular disease, and congenital heart disease. Diabetes is defined as type 1 and type 2 diabetes mellitus.

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merged into 1 data set managed by the primary author at Mount Sinai Hospital. We obtained data on the demographics, socioeconomic factors, presenting signs and symptoms, and the results of the laboratory and radiology tests that were

performed. When applicable, the delivery data, including the maternal complications and neonatal outcomes, were obtained. Relevant COVID-19–related clinical information, including disease severity, was also collected.

TABLE 2
Primary outcome by group

Outcome	Pregnant cases (n=38), n/N (%)	Nonpregnant controls (n=94), n/N (%)	Adjusted Pvalue	Adjusted OR (95% CI)
Composite morbidity ^a	13/38 (34.2)	14/94 (14.9)	.03	4.6 (1.2–18.2)
High-flow nasal cannula	8/38 (21.1)	6/94 (6.4)	---	---
BiPAP or CPAP	3/38 (7.9)	4/94 (4.3)	---	---
Intubation or mechanical ventilation	10/38 (26.3)	10/94 (10.6)	.22	3.3 (0.5–21.1)
ECMO	0/38 (0.0)	0/94 (0.0)	---	---
Death	0/38 (0.0)	3/94 (3.2)	---	---

BiPAP, bilevel positive airway pressure; CI, confidence interval; CPAP, continuous positive airway pressure; ECMO, extracorporeal membrane oxygenation; OR, odds ratio.

^a Composite morbidity includes need for high-flow nasal cannula supplementation, noninvasive positive pressure ventilation, intubation or mechanical ventilation, extracorporeal membrane oxygenation, and death.

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Cases were defined as pregnant women requiring admission for severe or critical COVID-19. Controls were defined as nonpregnant women of reproductive age requiring admission for severe or critical COVID-19. We initially sought to match 3 controls to every 1 case based on age ranges (ie, 18–30, 31–40, and 41–50 years), body mass index (BMI) class (ie, under 30, class I obesity [30–34.9], class II obesity [35–39.9], class III obesity [≥ 40] kg/m²) and severity of illness (ie, severe

[dyspnea, O₂ saturation of $\leq 93\%$, respiratory rate of ≥ 30 , imaging with $>50\%$ lung involvement] vs critical [respiratory failure, shock, and multi-organ dysfunction]). However, as only 96 of the 132 patients were successfully matched, a covariate adjusted analysis was conducted without accounting for matching.

Demographic, pregnancy, and neonatal characteristics were compared between the groups using *t* tests or Wilcoxon rank sum tests for continuous

measures and chi-square or Fisher's exact tests for the categorical measures as appropriate. The primary outcome was assessed using a logistic regression model of the composite outcomes, adjusted for age, BMI, severity of illness, preexisting cardiac disease (hypertension, coronary artery disease, hyperlipidemia, valvular disease, and congenital heart disease), and preexisting diabetes. The secondary outcomes were evaluated using logistic or linear regression analyses adjusted for age, BMI, severity of illness, preexisting cardiac disease, and preexisting diabetes. Hospital length of stay was log transformed before the analysis. In a subgroup analysis, the primary and secondary outcomes were also assessed only for those patients who met the criteria for severe COVID-19 status on admission using a logistic regression model of the composite outcomes, adjusted for age, BMI, preexisting cardiac disease, and preexisting diabetes. The outcomes were not assessed for those patients meeting the admission criteria for critical COVID-19 status alone because of the small number of patients available for the analysis. Available pregnancy and neonatal outcomes were presented descriptively based on the severity of illness. Presented *P* values were 2-sided and values of $<.05$ were considered statistically significant. All analyses were conducted using SAS software version 9.4 (SAS Institute Inc, Cary, NC).

Results

A total of 38 pregnant women with SARS-CoV-2 PCR-confirmed infections were admitted to 5 institutions for severe or critical COVID-19. Of note, 13 pregnant patients (34.2%) were admitted to NYU Langone Health, 10 patients to Mount Sinai Hospital (26.3%), 7 patients to Elmhurst Hospital (18.4%), 5 patients to Montefiore Medical Center (13.2%), and 3 patients to Thomas Jefferson University Hospital (7.9%). Of the 38 pregnant patients admitted for COVID-19, 29 (76.3%) met the criteria for severe disease status and 9 (23.7%) met the criteria for critical disease status. A total of 94 reproductive-aged, nonpregnant women admitted for

TABLE 3
Primary outcome by group among patients with severe cases of COVID-19

Outcome	Pregnant cases (n=29), n/N (%)	Nonpregnant controls (n=80), n/N (%)	Adjusted Pvalue	Adjusted OR (95% CI)
Composite morbidity ^a	4/29 (13.8)	4/80 (5.0)	.09	3.8 (0.8–18.1)
High-flow nasal cannula	2/29 (6.9)	2/80 (2.5)	---	---
BiPAP or CPAP	1/29 (3.5)	2/80 (2.5)	---	---
Intubation or mechanical ventilation	2/29 (6.9)	1/80 (1.3)	---	---
ECMO	0/29 (0.0)	0/80 (0.0)	---	---
Death	0/29 (0.0)	0/80 (0.0)	---	---

BiPAP, bilevel positive airway pressure; CI, confidence interval; COVID-19, coronavirus disease 2019; CPAP, continuous positive airway pressure; ECMO, extracorporeal membrane oxygenation; OR, odds ratio.

^a Composite morbidity includes the need for high-flow nasal cannula supplementation, noninvasive positive pressure ventilation, intubation or mechanical ventilation, extracorporeal membrane oxygenation, and death.

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TABLE 4
Secondary outcomes by group

Secondary outcomes	Pregnant cases (n=38)				Nonpregnant controls (n=94)				Adjusted <i>P</i> value	Ratio of means (95% CI)
	N	Mean±SD	Median (IQR)	Range	N	Mean±SD	Median (IQR)	Range		
Length of stay										
Hospital length of stay (d)	38	8.7±8.1	5.5 (4–10)	2–42	94	7.1±8.2	5 (3–9)	1–53	.08	0.8 (0.6–1.0) ^b
ICU length of stay (d) ^a	15	6.4±6.9	4 (1–9)	0–26	16	9.3±11.8	5.5 (2–12)	0–45	—	—
			n/N (%)				n/N (%)	Adjusted OR (95% CI)		
ICU admission				15/38 (39.5)				16/94 (17.0)	<.01	5.2 (1.5–17.5)
Discharge disposition										.77
Home without O ₂ requirement				35/38 (92.1)				77/94 (81.9)	Ref	
SNF or LTAC or home with O ₂ or other requirements				3/38 (7.9)				14/94 (14.9)	0.8 (0.3–2.8)	
Morbidity during admission										
Any morbidity				12/38 (31.6)				20/94 (21.3)	.57	
Sepsis				2/38 (5.3)				7/94 (7.4)		
Cardiac arrest				1/38 (2.6)				3/94 (3.2)		
ARDS				6/38 (15.8)				7/94 (7.4)		
Ventilation				10/38 (26.3)				10/94 (10.6)		
Tracheostomy				3/38 (7.9)				1/94 (1.1)		
Blood product transfusion				2/38 (5.3)				1/94 (1.1)		
AKI				0/38 (0.0)				3/94 (3.2)		
Shock				2/38 (5.3)				4/94 (4.3)		
Other morbidity				0/38 (0.0)				3/94 (3.2)		

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; LTAC, long-term acute care; OR, odds ratio; Ref, referend; SD, standard deviation; SNF, skilled nursing facility.

^a ICU length of stay is only calculated for those 31 patients who were admitted to the ICU (15 pregnant cases and 16 nonpregnant controls); ^b Hospital length of stay was log transformed and modeled using linear regression. The beta coefficient for the cases was exponentiated to estimate the ratio of the geometric means.

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severe or critical COVID-19 were identified as controls across the institutions. Of note, 22 (23.4%) women admitted to NYU Langone Health, 30 (31.9%) patients to Mount Sinai Hospital, 21 (22.3%) patients to Elmhurst Hospital, 15 (16.0%) patients to Montefiore Medical Center, and 6 (6.4%) patients to Thomas Jefferson University Hospital comprised the control cohort, 80 (85.1%) of these meeting the criteria for severe disease status and 14 (14.9%) meeting the criteria for critical disease status.

The patient demographics are outlined in Table 1. The mean age (in years) was significantly higher in the nonpregnant controls compared with the

pregnant cases (37.9±6.7 vs 34.7±4.3 years; *P*<.01) (Table 1). The mean BMI on admission was also higher in the nonpregnant controls compared with the pregnant cases (33.4±5.2 vs 31.7±6.6 kg/m²; *P*=.15) (Table 1). Pre-existing diabetes (27.7% vs 10.5%; *P*=.03) (Table 1) and preexisting cardiac disease (28.7% vs 10.5%, *P*=.03) (Table 1) were both noted to be significantly higher in the control group.

Pregnant women were more likely to experience the composite morbidity, including death, a need for intubation, ECMO, noninvasive positive pressure ventilation, including BiPAP and CPAP, and a need for high-flow nasal cannula supplementation when compared with

the nonpregnant control group (34.2% vs 14.9%; *P*=.03; adjusted odds ratio [aOR], 4.2; 95% confidence interval [CI], 1.2–18.2) (Table 2). A greater percentage of pregnant women received mechanical ventilation compared with the nonpregnant controls (26.3% vs 10.6%; *P*=.22; aOR, 3.3; 95% CI, 0.5–21.1) (Table 2). However, death and the need for ECMO did not contribute to the primary composite outcome in the pregnant cases. There were no cases of mortality among the pregnant women, whereas death occurred in 3 of the 94 nonpregnant women. In those with severe COVID-19, the pregnant women remained more likely to experience the composite morbidity compared with the

TABLE 5
Secondary outcomes by group among patients with severe COVID-19

Secondary outcome	Pregnant cases (n=29)				Nonpregnant controls (n=80)				Adjusted <i>P</i> value	Ratio of means (95% CI)
	N	Mean±SD	Median (IQR)	Range	N	Mean±SD	Median (IQR)	Range		
Length of Stay										
Hospital length of stay (d)	29	7.3±7.8	5 (4–6)	2–42	80	5.3±4.1	4 (3–7)	1–23	.04	0.7 (0.5–1.0) ^b
ICU length of stay (d) ^a	6	6.2±10.1	1 (1–8)	0–26	6	2.5±2.9	1.5 (1–3)	0–8	—	—
			n/N (%)				n/N (%)			Adjusted OR (95% CI)
ICU admission			6/29 (20.7)				6/80 (7.5)		.03	4.9 (1.2–19.5)
Discharge disposition									.98	
Home without O ₂ requirement			27/29 (93.1)				70/80 (87.5)			Ref
SNF or LTAC or home with O ₂ or other requirement			2/29 (6.9)				10/80 (12.5)			9.8 (0.2–5.7)
Morbidity during admission										
Any morbidity			3/29 (10.3)				9/80 (11.3)		.72	1.3 (0.3–6.2)
Sepsis			0/29 (0.0)				3/80 (3.8)			
Cardiac arrest			1/29 (3.5)				0/80 (0.0)			
ARDS			1/29 (3.5)				1/80 (1.3)			
Ventilation			2/29 (6.9)				2/80 (2.5)			
Tracheostomy			1/29 (3.5)				0/80 (0)			
Blood product transfusion			1/29 (3.5)				1/80 (1.3)			
AKI			0/29 (0.0)				2/80 (2.5)			
Shock			0/29 (0.0)				0/80 (0.0)			
Other morbidity			0/29 (0.0)				2/80 (2.5)			

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CI, confidence interval; COVID-19, coronavirus disease 2019; ICU, intensive care unit; IQR, interquartile range; LTAC, long-term acute care; OR, odds ratio; Ref, referend; SD, standard deviation; SNF, skilled nursing facility.

^a ICU length of stay is only calculated for those 12 patients who were admitted to the ICU (6 pregnant cases and 6 nonpregnant controls); ^b Hospital length of stay was log transformed and modeled using linear regression. The beta coefficient for the cases was exponentiated to estimate the ratio of the geometric means.

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nonpregnant control group, although this finding was not statistically significant (13.8% vs 5.0%; *P*=.09) (Table 3). Secondary outcomes are presented in Tables 4 and 5. The hospital length of stay and ICU length of stay were similar between the groups. However, the rate of ICU admission was higher among the pregnant patients vs the nonpregnant controls (39.5% vs 17.0%; *P*<.01; aOR, 5.2; 95% CI, 1.5–17.5) (Table 4). Pregnant women admitted with severe COVID-19 also had higher rates of ICU admission (20.7% vs 7.5%; *P*=.03; aOR, 4.9; 95% CI, 1.2–19.5) (Table 5) and a longer hospital length of stay (7.3±7.8 vs

5.3±4.1 days, *P*=.04; aOR, 0.7; 95% CI, 0.5–1) (Table 5). Although there were no statistically significant differences in other treatment interventions between the groups (Table 6), there was a trend toward increased use of antivirals, including lopinavir-ritonavir, oseltamivir, and remdesivir in the pregnant cohort.

The pregnancy and neonatal outcomes are outlined in Table 7 and Table 8. At the time of analysis, 22 of 38 (58%) patients underwent delivery. The majority of women were delivered through cesarean delivery, regardless of the severity of disease. Worsening

maternal status was most often noted to be the indication for delivery in patients with both severe and critical COVID-19 (60.0% and 85.7%, respectively). The mean gestational age at delivery was 33.8±5.5 weeks' gestation for the severe cases and 35±3.5 weeks' gestation for the critical cases.

Discussion

Principal findings

In this case-control study comparing pregnant vs reproductive age, nonpregnant women admitted with severe or critical COVID-19, pregnant women were more likely to experience the

composite morbidity compared with nonpregnant controls. Our sample size was not large enough to make conclusions regarding the mortality among the pregnant patients and nonpregnant control women.

Results

In previous outbreaks of respiratory pathogens, pregnant populations experienced an increased severity of illness and mortality,^{10–12} and our data suggest a similar pattern for COVID-19. Most notably, we found higher rates of ICU admission in our pregnant cohort (39.5% vs 17.0%) and higher rates of intubation and mechanical ventilation (26.3% vs 10.6%), which are distinct surrogates for the severity of illness. Other interventions, including prone positioning and medication use, were similar between the groups. A trend of increased antiviral use in the pregnant patients was noted, which was potentially secondary to the increased rate of critical disease status. These findings suggest that pregnant women admitted to the hospital with COVID-19 are at an increased risk for these and other complications. However, death and the use of ECMO did not contribute to the composite morbidity in our pregnant cohort because pregnant women did not experience either of these outcomes.

In the subset of patients admitted with severe disease status, the pregnant women displayed a trend toward an increased composite morbidity and a considerable increase in ICU admission and longer hospital length of stay compared with the nonpregnant control group. Although an analysis comparing the pregnant women to the nonpregnant women with critical disease was not performed because of the small sample size, 100% of the pregnant women in this subset experienced the composite morbidity and ICU admission vs 71.4% of the controls, as shown in [Supplemental Table 1](#) and [Supplemental Table 2](#). The lack of statistical significance for the primary outcome in the severe disease subset is most likely because of a combination of a small sample size and removal of those patients with a critical

TABLE 6
Other intervention by group

Intervention	Pregnant cases (n=38), n/N (%)	Nonpregnant controls (n=94), n/N (%)	P value
Hydroxychloroquine	34/38 (89.5)	76/94 (80.9)	.23
Azithromycin	25/38 (65.8)	56/94 (59.6)	.51
Antivirals ^a	7/38 (18.4)	6/94 (6.4)	.05
Tocilizumab	3/38 (7.9)	4/94 (4.3)	.41
Systemic steroids ^b	4/38 (10.5)	15/94 (16.0)	.42
Convalescent plasma	2/38 (5.3)	4/94 (4.3)	>.99
Therapeutic anticoagulation ^c	8/38 (21.1)	20/94 (21.3)	.98
Prophylactic anticoagulation ^c	24/38 (63.2)	61/94 (64.9)	.85
Prone positioning	5/38 (13.2)	7/94 (7.4)	.30

^a Antivirals included remdesivir, lopinavir-ritonavir, and oseltamivir; ^b Systemic steroids included prednisone, methylprednisolone, and dexamethasone; ^c Anticoagulation therapy included unfractionated heparin, low molecular weight heparin, fondaparinux, and apixaban.

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COVID-19 status, all of whom experienced the composite morbidity.

Among the pregnant women who delivered during their hospitalization, the majority underwent a cesarean delivery (72.7%) and delivered preterm (68.2%). Of those who delivered preterm, one-third occurred before 34 weeks' gestation. Among those who delivered, there was only 1 case of spontaneous preterm delivery (4.5%), which is similar to the reported spontaneous preterm birth rate of 6.1% in a case series by Yan et al.²¹

Our findings suggest that among women of reproductive age (18–50 years) with severe or critical cases of COVID-19, pregnancy is associated with an increased risk for ICU admission in addition to intubation and mechanical ventilation, but there was no evidence of an increased mortality risk, because the event rates and sample sizes were too low to substantiate this. Our findings are in agreement with a recent study in Sweden, which included 53 reproductive-aged women admitted to the ICU, and in which all of the pregnant and recently postpartum (within 1 week) women with COVID-19 were admitted to the ICU and 7 of the 13 pregnant or recently postpartum women received mechanical ventilation (53.8%). Using a sensitivity analysis,

pregnant women were at an increased risk for ICU admission for a laboratory-confirmed SARS-CoV-2 infection (relative risk, 2.59; 95% CI 1.13–5.91).²² Blitz et al²³ did not find an increased risk for ICU admission among 82 pregnant women hospitalized with COVID-19, 8 of which were admitted to the ICU for worsening respiratory status (9.8%) when compared with 332 nonpregnant women, 50 of which were admitted to the ICU for worsening respiratory status (15.1%).²³ However, the reason for admission included those admitted for either delivery or symptoms related to COVID-19, and in our cohort of women admitted specifically for severe and critical disease status, we did in fact see an increased rate of ICU admission and need for mechanical ventilation. Although the recent CDC *Morbidity and Mortality Weekly Report (MMWR)* of June 26, 2020, did not specify the reason for admission to the hospital in their pregnant cohort, their findings were in agreement with our study, suggesting that pregnancy is associated with an increased risk for surrogate markers of disease severity.⁹

Clinical implications

The current challenge lies in the prediction of patients presenting with

TABLE 7
Pregnancy outcomes by case severity

Outcome	Pregnant severe cases (n=29), n/N (%)	Pregnant critical cases (n=9), n/N (%)
Mode of delivery^a		
Cesarean delivery	10/15 (66.7)	6/7 (85.7)
Vaginal delivery	5/15 (33.3)	1/7 (14.3)
Indication for delivery^a		
Maternal status	9/15 (60.0)	6/7 (85.7)
Fetal status	1/15 (6.7)	0/7 (0.0)
Obstetrical indications	5/15 (33.3)	1/7 (14.3)
Prenatal complications		
Pregnancy-related hypertensive disorders	0/29 (0.0)	1/9 (11.1)
Gestational diabetes	1/29 (3.4)	0/9 (0.0)
Other prenatal complications	4/29 (13.8)	0/9 (0.0)
Obstetrical complications		
Hypertensive disorder of pregnancy	2/29 (6.9)	1/9 (11.1)
Presumed IAI	1/29 (3.4)	0/9 (0.0)
Preterm labor	1/29 (3.4)	0/9 (0.0)
Other obstetrical complications	2/29 (6.9)	0/9 (0.0)
Maternal Morbidity		
Postpartum hemorrhage	0/29 (0.0)	1/9 (11.1)
Blood product transfusion	0/29 (0.0)	1/9 (11.1)
Other outcomes		
Fetal demise ^a	2/15 (13.3)	0/7 (0.0)
Betamethasone for fetal lung maturity	5/29 (17.2)	1/9 (11.1)
Magnesium sulfate for fetal neuroprotection	2/29 (6.9)	2/9 (22.2)
Magnesium sulfate for PEC or HTN	2/29 (6.9)	0/9 (0.0)

HTN, hypertension; IAI, intraamniotic infection; PEC, preeclampsia.

^a At the time of data analysis, 22 (58%) pregnant patients underwent delivery (15 patients in the severe group and 7 patients in the critical group).

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COVID-19 who will progress to develop critical disease status. Across the studies in nonpregnant populations, the risk of adverse outcomes consistently increased with age and underlying illness, and the majority of hospitalized patients were men.²⁴ The most prevalent comorbidities associated with the severity of COVID-19 in the nonpregnant population are hypertension and diabetes, followed by cardiovascular disease and respiratory disease.²⁵ When compared with nonpregnant women with mild COVID-19, the pooled odds ratio for

hypertension was 2.36 (95% CI, 1.46–3.83), for respiratory system disease it was 2.46 (95% CI, 1.76–3.44), and for cardiovascular disease it was 3.42 (95% CI, 1.88–6.22) in those with severe COVID-19.¹⁹ Patients requiring ICU care were more likely to have comorbid hypertension, cardiovascular disease, diabetes, and cerebrovascular disease.^{26–28} Obesity with a BMI of >30 was also found to be a risk factor for disease severity in the pregnant populations.^{29,30} As COVID-19 pneumonia rapidly progresses from focal to diffuse

consolidation of lung parenchyma, the reduced total lung capacity at term as a result of diaphragmatic splinting by the gravid uterus, may predispose pregnant women to hypoxemic respiratory failure leading to increased morbidity.⁸ Although pregnant women are often young with a lower frequency of preexisting medical comorbidities, we have yet to completely comprehend how SARS-CoV-2 infection manifests in pregnancy. In our cohort, we sought to identify a comparative control group, including only women up to the age 50 years admitted with severe and critical COVID-19. At baseline, our nonpregnant cohort had increased rates of preexisting diabetes, cardiovascular disease, and a higher BMI. These findings suggest that pregnancy itself may potentially be a risk factor for severe and critical COVID-19.

Research implications

Larger case-control studies and prospective cohort studies are needed to determine whether pregnancy alone places patients at an increased risk for developing severe or critical COVID-19 to guide future management for our obstetrical population. Studies with a larger cohort of patients will be needed to determine whether mortality is higher among pregnant women with COVID-19 than that of the nonpregnant population. As long-term follow-ups occur and more data are acquired, studies focusing on the pregnancy and neonatal outcomes could be performed to better understand the disease process and its effects on pregnancy.

Strengths and limitations

Currently, we are not aware of a large cohort study examining the outcomes of severe and critical cases of COVID-19 in pregnant women compared with nonpregnant, reproductive-aged controls, all of whom were admitted specifically for COVID-19. Although management of COVID-19 varied across institutions, the multicenter nature of our study resulted in a highly diverse patient population with regards to demographics, including race, ethnicity, and other social determinants of health.

TABLE 8
Neonatal outcomes by case severity

Neonatal outcomes	Neonates from severe cases (n=15)				Neonates from critical cases (n=7)			
	N	Mean±SD	Median (IQR)	Range	N	Mean±SD	Median (IQR)	Range
Gestational age at delivery (wk)	15	33.8±5.5	36.3 (30.4–37)	17.6–39.1	7	35±3.5	35.9 (34.1–37.3)	27.9–38.4
Birthweight (g)	15	2307.7±889.7	2530 (1705–3065)	65–3315	7	2495±774.2	2485 (2110–3230)	1160–3500
NICU length of stay (d) ^a	4	15.0±15.3	11 (3–27)	3–35	4	7.0±3.2	6.5 (4.5–9.5)	4–11
				n/N (%)				n/N (%)
Neonatal complications								
RDS				2/15 (13.3)				2/7 (28.6)
Prematurity				6/15 (40.0)				2/7 (28.6)
Other				1/15 (6.7)				1/7 (14.3)
Neonatal mortality				0/13 (0.0)				0/7 (0.0)

IQR, interquartile range; NICU, neonatal intensive care unit; RDS, respiratory distress syndrome; SD, standard deviation.

^a NICU length of stay is only calculated for those 8 of the 12 neonates who were admitted to the NICU who had both NICU admission and discharge date (4 neonates in the severe group and 4 neonates in the critical group).

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We are unable to currently report on the long-term pregnancy or neonatal outcomes at this time.

Our study has several limitations. Although a control group was assessed, we noted difficulty in the ability to match the cases and controls as initially planned. We sought to match the cases on the basis of age range (18–30, 31–40, and 41–50 years), BMI class (under 30, class I obesity [30–34.9], class II obesity [35–39.9], class III obesity [≥ 40] kg/m²), and disease severity (critical vs severe) upon admission. All patients were, however, matched based on the reproductive age range between 18 and 50 years. We also noted difficulty in finding a 3:1 ratio of controls to cases, because many nonpregnant, reproductive-aged females did not meet the inclusion criteria for severe or critical COVID-19 status upon hospital admission. Overall, our pregnant cases were younger and had a lower BMI than the nonpregnant controls. Although it is well documented that persons of nonwhite race have worse outcomes, there was no statistically significant difference in the distribution of race and ethnicity between our 2 cohorts. We are unable to comment on the differences in race and ethnicity in our current study and how this difference

has impacted the primary outcome. These data are either not reported or reported as “other” or “unknown” for 4/38 (10.5%) of the pregnant patients and 28/94 (29.8%) of the nonpregnant controls, which is, unfortunately, a limitation of how race and ethnicity data are captured and reported in the EMR.

An inherent bias may exist, because pregnant women at baseline may be more likely to be admitted to the ICU compared with nonpregnant women with the same disease severity. To sufficiently oxygenate the uteroplacental unit, a lower threshold to initiate oxygen supplementation may be necessary. Pregnancy may lead to increased rates of high-flow nasal cannula and noninvasive positive pressure ventilation. However, the marked increase in mechanical ventilation and intubation is unlikely to be subject to bias based on the pregnancy status. Our study is also limited by a small sample size, and thus we cannot draw conclusions about the difference in mortality among pregnant and nonpregnant women. Data on the relationship between maternal mortality rates and COVID-19 in the literature are conflicting. Although some case series report lower rates of mortality in pregnant women, others report mortality

rates that are similar to those seen previously in severe acute respiratory syndrome and Middle East respiratory syndrome infections.^{31,32}

A recent systematic review by Allotey et al³³ which included 11,432 pregnant and recently postpartum women describes an increased risk for ICU admission and mechanical ventilation among those with confirmed or suspected COVID-19. In this review, the control group consisted of nonpregnant, reproductive-aged women and pregnant women without COVID-19.³³ Similar to the *MMWR* of the CDC, the reason for admission was not distinguished in these patients, including patients admitted for delivery and incidentally found to have SARS-CoV-2 documented infections. A strength of our study is that all participants analyzed were admitted to the hospital specifically for COVID-19-related symptoms and met the criteria for severe or critical COVID-19 status upon admission. The difficulty in attempting to match our cohort, speaks to the lack of nonpregnant young female patients being admitted for COVID-19, further suggesting that pregnancy may be a contributing factor for developing severe or critical cases of COVID-19.

Conclusions

Pregnant women with severe and critical cases of COVID-19 are at an increased risk for morbidity when compared with reproductive-aged, nonpregnant controls. The hospital and ICU lengths of stay were similar between our cohorts. Preexisting comorbidities such as hypertension, diabetes, and coronary artery disease were increased in our nonpregnant controls, in addition to increased age and BMI, however, despite these differences, the pregnant women with severe and critical COVID-19 remained at an increased risk for ICU admission, intubation, and mechanical ventilation. These findings suggest that pregnancy itself may manifest increased complications and morbidities among women with severe and critical COVID-19. Complications such as preterm birth and need for delivery are common for women with severe and critical cases of COVID-19.^{34,35} Our study suggests that the known respiratory complications associated with severe and critical COVID-19 may lead to greater numbers of maternal ICU admissions, intubation, and mechanical ventilation and may likely result in an increased number of preterm births and cesarean deliveries in the setting of worsening maternal respiratory status. This information is important in counseling pregnant women diagnosed at the early stage of the disease on the potential for progression to a severe or critical stage. ■

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SUPPLEMENTAL TABLE 1

Primary outcome by group among patients with critical disease

Outcome	Pregnant cases (n=9), n/N (%)	Nonpregnant controls (n=14), n/N (%)
Composite morbidity ^a	9/9 (100)	10/14 (71.4)
High-flow nasal cannula	6/9 (66.7)	4/14 (28.6)
BiPAP or CPAP	2/9 (22.2)	2/14 (14.3)
Intubation or mechanical ventilation	8/9 (88.9)	9/14 (64.3)
ECMO	0/9 (0.0)	0/14 (0.0)
Death	0/9 (0.0)	3/14 (21.4)

BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; ECMO, extracorporeal membrane oxygenation.

^a Composite morbidity includes need for high-flow nasal cannula supplementation, noninvasive positive pressure ventilation, intubation or mechanical ventilation, extracorporeal membrane oxygenation, and death.

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SUPPLEMENTAL TABLE 2

Secondary outcomes by group among patients with critical disease

Secondary outcome	Pregnant cases (n=29)				Nonpregnant controls (n=80)			
	N	Mean±SD	Median (IQR)	Range	N	Mean±SD	Median (IQR)	Range
Length of stay								
Hospital length of stay (d) ^a	9	13.3±7.9	12 (6–21)	4–25	14	17.5±15.7	13 (7–25)	2–53
ICU length of stay (d) ^b	9	6.6±4.2	7 (4–9)	1–13	10	13.4±13.3	9.5 (5–17)	2–45
			n/N (%)				n/N (%)	
ICU admission			9/9 (100.0)				10/14 (71.4)	
Discharge disposition								
Home without O ₂ requirement			8/9 (88.9)				7/14 (50.0)	
SNF or LTAC or home with O ₂ or other requirement			1/9 (11.1)				4/14 (28.6)	
Death			0/9 (0.0)				3/14 (21.4)	
Morbidity during admission								
Any morbidity			9/9 (100.0)				11/14 (78.6)	
Sepsis			2/9 (22.2)				4/14 (28.6)	
Cardiac arrest			0/9 (0.0)				3/14 (21.4)	
ARDS			5/9 (55.6)				6/14 (42.9)	
Ventilation			8/9 (88.9)				7/14 (50.0)	
Tracheostomy			2/9 (22.2)				1/14 (7.1)	
Blood product transfusion			1/9 (11.1)				0/14 (0.0)	
AKI			0/9 (0.0)				1/14 (7.1)	
Shock			2/9 (22.2)				4/14 (28.6)	
Other morbidity			0/9 (0.0)				1/14 (7.1)	

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; IQR, interquartile range; LTAC, long-term acute care; SD, standard deviation; SNF, skilled nursing facility.

^a Hospital length of stay was log transformed and modeled using linear regression. The beta coefficient for cases was exponentiated to estimate the ratio of geometric means; ^b ICU length of stay is only calculated for those 19 patients who were admitted to the ICU (pregnant cases and 10 nonpregnant controls).

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