OBSTETRICS

Epidemiology of coronavirus disease 2019 in pregnancy: risk factors and associations with adverse maternal and neonatal outcomes

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BACKGROUND: Coronavirus disease 2019 may be associated with adverse maternal and neonatal outcomes in pregnancy, but there are few controlled data to quantify the magnitude of these risks or to characterize the epidemiology and risk factors.

OBJECTIVE: This study aimed to quantify the associations of coronavirus disease 2019 with adverse maternal and neonatal outcomes in pregnancy and to characterize the epidemiology and risk factors.

STUDY DESIGN: We performed a matched case-control study of pregnant patients with confirmed coronavirus disease 2019 cases who delivered between 16 and 41 weeks' gestation from March 11 to June 11, 2020. Uninfected pregnant women (controls) were matched to coronavirus disease 2019 cases on a 2:1 ratio based on delivery date. Maternal demographic characteristics, coronavirus disease 2019 symptoms, laboratory evaluations, obstetrical and neonatal outcomes, and clinical management were chart abstracted. The primary outcomes included (1) a composite of adverse maternal outcome, defined as preeclampsia, venous thromboembolism, antepartum admission, maternal intensive care unit admission, need for mechanical ventilation, supplemental oxygen, or maternal death, and (2) a composite of adverse neonatal outcome, defined as respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, 5-minute Apgar score of <5, persistent category 2 fetal heart rate tracing despite intrauterine resuscitation, or neonatal death. To quantify the associations between exposure to mild and severe or critical coronavirus disease 2019 and adverse maternal and neonatal outcomes, unadjusted and adjusted analyses were performed using conditional logistic regression (to account for matching), with matched-pair odds ratio and 95% confidence interval based on 1000 bias-corrected bootstrap resampling as the effect measure. Associations were adjusted for potential confounders.

RESULTS: A total of 61 confirmed coronavirus disease 2019 cases were enrolled during the study period (mild disease, n=54 [88.5%]; severe disease, n=6 [9.8%]; critical disease, n=1 [1.6%]). The odds of adverse composite maternal outcome were 3.4 times higher among cases than controls (18.0% vs 8.2%; adjusted odds ratio, 3.4; 95% confidence interval, 1.2—13.4). The odds of adverse composite neonatal outcome were 1.7 times higher in the case group than to the control group (18.0% vs 13.9%; adjusted odds ratio, 1.7; 95% confidence interval, 0.8—4.8). Stratified analyses by disease severity indicated that the morbidity associated with coronavirus disease 2019 in pregnancy was largely driven by the severe or critical disease phenotype. Major risk factors for associated morbidity were black and Hispanic race, advanced maternal age, medical comorbidities, and antepartum admissions related to coronavirus disease 2019.

CONCLUSION: Coronavirus disease 2019 during pregnancy is associated with an increased risk of adverse maternal and neonatal outcomes, an association that is primarily driven by morbidity associated with severe or critical coronavirus disease 2019. Black and Hispanic race, obesity, advanced maternal age, medical comorbidities, and antepartum admissions related to coronavirus disease 2019 are risk factors for associated morbidity.

Key words: adverse maternal outcomes, adverse neonatal outcomes, case-control study, coronavirus disease in pregnancy, coronavirus disease 2019, epidemiology, morbidity, novel coronavirus, pandemic, pregnancy, risk factors, severe acute respiratory syndrome coronavirus 2, virus

Introduction

Pregnant women are more susceptible to viral respiratory infections owing to immunologic and physiological adaptations of pregnancy.[1] An early Chinese

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report of coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), found that the risk of severe disease in pregnant patients was similar to the general population.[2] This was also observed in initial studies in the United States, including a report from New York[3] and Washington.[4]

Recent data from the National Notifiable Diseases Surveillance System, reported by the Centers for Disease Control and Prevention (CDC) on June 25, 2020, compared outcomes of 8207 pregnant and 83,205 nonpregnant women with COVID-19 (January 22 to June 7, 2020).[5] The authors included all laboratory-confirmed infections with SARS-CoV-2 among women at the age of 15 to 44 years from all of the United States and Washington, DC. The main findings were that pregnant women with COVID-19 were more likely to be hospitalized, require intubation and mechanical ventilation, and be admitted to an intensive care unit (ICU) than nonpregnant women. The authors concluded that pregnant women should be counseled about the potential for severe COVID-19 disease, despite a low absolute risk of ICU admissions and the need for mechanical ventilatory support.

AJOG at a Glance

Why was this study conducted?

This study aimed to quantify the magnitude of the risk of adverse maternal and neonatal outcomes associated with coronavirus disease 2019 (COVID-19) in pregnancy vs unaffected pregnant women and characterize the epidemiology and risk factors for adverse outcomes.

Key findings

COVID-19 in pregnancy is associated with adverse maternal and neonatal outcomes, and this association is primarily driven by morbidity associated with severe or critical disease. Black and Hispanic patients with obesity, advanced maternal age, medical comorbidities, and antepartum admissions related to COVID-19 have the greatest risk of associated complications.

What does this add to what is known?

The study quantifies the magnitude of adverse maternal and neonatal outcomes associated with severe or critical COVID-19 compared with unaffected pregnant women during pregnancy.

This report, which generated substantial press,[6,7] could not distinguish hospitalizations related to COVID-19 from obstetrical indications and could not ascertain whether complications from COVID-19 or pregnancy resulted in the escalation of medical care and increased morbidity.[1]

To date, medical care and guidance from professional societies during the pandemic have been largely based on case reports and case series and epidemiologic studies that compared outcomes of pregnant women with COVID-19 with nonpregnant women. Most of these studies lacked an appropriate control group, a common limitation that has complicated our understanding of COVID-19's impact on pregnancy. Therefore, to quantify the maternal and neonatal risks associated with COVID-19 in pregnancy and to describe the epidemiology and risk factors for morbidity associated with COVID-19, we undertook a matched case-control study. Associations were evaluated for all COVID-19 patients and for diseases classified as mild vs severe or critical diseases.[2] We also characterized the epidemiology and identified risk factors for morbidity associated with COVID-19 in pregnancy.

Materials and Methods

We performed a matched case-control study at the Robert Wood Johnson University Hospital, a regional perinatal center in New Brunswick, NJ. The Institutional Review Board of the Rutgers Robert Wood Johnson Medical School, NJ, granted the ethics approval under a waiver of informed consent (PRO2020000854). The study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline for case-control studies.

Consecutive pregnant patients with COVID-19 who were admitted to the hospital were enrolled from March 11 to June 11, 2020; this period corresponds to the first 3 months of the SARS-CoV-2 pandemic.[8] COVID-19 testing to detect SARS-CoV-2 infection was performed by nasopharyngeal swab and quantitative polymerase-chain-reaction test. Before April 10, 2020, patients admitted to the labor and delivery unit were tested if they had symptoms of SARS-CoV-2 infection, had a recent travel to high-risk countries with a prevalent disease, or had a direct contact with someone who traveled to high-risk countries or who had COVID-19 (eg, considered to have a high-risk exposure). On April 10, 2020, we implemented universal COVID-19 testing for all pregnant patients at the time of hospital admission, regardless of symptoms or exposure history.

Consecutive patients with COVID-19 were prospectively identified in a clinical database. Patients were considered to be cases if they had a positive COVID-19 test result and delivered between 16.0 and 41.6 weeks' gestation. Cases were categorized as mild, severe, or critical disease according to previously published criteria.[9] Mild disease was defined as nonpneumonia and mild pneumonia; severe disease was defined as dyspnea, respiratory rate of ≥30/minute, blood oxygen saturation of ≤93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio of <300, and lung infiltrates of >50% on chest X-ray; and critical disease was defined as respiratory failure, septic shock, and multiple organ failure. Patients were eligible to be cases if the initial COVID-19 testing was negative, but the subsequent testing during the delivery hospitalization became positive. Patients were excluded if they were persons under investigation (PUIs) without confirmatory testing or had a negative COVID-19 test result or if they were hospitalized but discharged before delivery.

Each COVID-19 case was matched to 2 controls by delivery date. Before April 10, controls were selected as the first 2 patients who delivered between 16.0 and 41.6 weeks' gestation on the same date as the cases if they were asymptomatic or had a negative COVID-19 test result. After April 10, controls were selected if they had a negative COVID-19 test result and delivered on the same date as the cases. On days with 2 or more cases, we identified the next 2 eligible controls as potential matches.

All patient data were abstracted from the electronic medical record. The primary outcomes were composites of adverse maternal outcomes and adverse neonatal outcomes. The maternal composite included preeclampsia (defined according to the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy[10]), venous thromboembolism, antepartum admission (defined as hospital admission for obstetrical or nonobstetrical indications for inpatient management for >48 hours), ICU admission, need for mechanical ventilation, supplemental oxygen, or maternal death. The neonatal composite included respiratory distress

syndrome (RDS; defined as the need for supplemental oxygen and the presence of typical radiographic findings in the absence of other causes for respiratory distress), intraventricular hemorrhage (IVH; defined as grade 1–4 hemorrhages), necrotizing enterocolitis (defined as radiographic or operative findings consistent with perforation), 5-minute Apgar score of <5, persistent category 2 fetal heart rate tracing despite intrauterine resuscitation, or neonatal death. The primary maternal and neonatal outcomes were examined as a composite owing to a small number of patients with the specific complication, and importantly, all of the individual outcomes were regarded as "competing risks."

Secondary maternal outcomes included components of the composite outcome and preterm delivery (defined as delivery before 37 weeks' gestation, <34 weeks' gestation, and <28 weeks' gestation), mode of delivery (cesarean or vaginal delivery), intrauterine fetal demise, length of hospital stay, and chorioamnionitis. Other neonatal outcomes included birthweight, neonatal ICU (NICU) admission, 1- and 5-minute Apgar scores, and length of hospital stay. Per institutional policy, all babies born to COVID-19–positive mothers during the study period were considered PUI; these babies were admitted to the NICU until a negative COVID-19 test result at 36 hours of life. Persistent category 2 fetal heart rate tracing despite intrauterine resuscitation, chorioamnionitis, and other clinical outcomes were defined by the providers managing each patient. If the provider believed that the patient met the criteria for 1 of these diagnoses, it was noted in the medical record.

Gestational age was based on the best obstetrical estimate.[11] Maternal demographics were abstracted from the electronic medical record, including age, gravidity, parity, body mass index at delivery, race, and medical comorbidities. Renal disease was defined as baseline proteinuria of >300 mg/24 hours or creatinine of >1.1 mg/dL. An immunocompromised state was defined as HIV infection or chronic steroid use. Anemia

was defined as admission hemoglobin of <10.5 mg/dL.

Data related to COVID-19 symptoms, laboratory evaluations, and clinical management were also abstracted. Maternal symptoms included fever (defined as temperature of >100.4°F), cough, shortness of breath, chest pain, diarrhea, myalgias, and sore throat. Laboratory evaluation included the results of routine complete blood counts and comprehensive metabolic panels (the latter when ordered for clinical purposes). Clinical management included supplemental oxygen, hydroxychloroquine, remdesivir, antibiotic agents, bronchodilators, mechanical ventilation, steroids, and ICU admission.

Statistical analysis

Demographic characteristics of COVID-19 cases and controls were compared using descriptive statistics, including mean and standard deviation for normally distributed continuous variables and median (interquartile range) for nonnormally distributed continuous variables. To quantify the associations between exposure to mild and severe or critical COVID-19 and adverse maternal and neonatal outcomes, we fit conditional logistic regression models from which we estimated matched-pair odds ratios (ORs) and 95% confidence interval (CI). Analyses were adjusted for confounders, including advanced maternal age, obesity, maternal race, and comorbid medical problems (specifically diabetes mellitus, chronic hypertension, renal disease, immunocompromised state, asthma, and anemia). Owing to a small study size, we estimated the variance of ORs (and by extension, 95% CIs) based on 1000 bias-corrected bootstrap resampling. All analyses were performed with Stata version 10.1 (StataCorp LLC, College Station, TX).

Results

During the 3-month study period, there were 61 pregnant patients diagnosed as having COVID-19 who delivered at our institution and met the inclusion criteria (cases). Each case was matched to 2 controls by delivery date; 11 cases (18%) were enrolled in the first month, 28

(45.9%) were enrolled in the second, and 22 (36.1%) were enrolled in the third. Among the cases, disease severity was mild (n=54 [88.5%]), severe (n=6 [9.8%]), and critical (n=1 [1.6%]). Demographic characteristics for cases and controls are presented in Table 1. Overall, the groups were well matched, but there were more white women with COVID-19 (58.3% vs 42.7%). Notably, 142 (77.6%) patients were healthy and without medical comorbidities. However, compared with controls, patients with severe or critical disease had higher rates of medical comorbidities (42.9% vs 24.6%), such as a diabetes mellitus (28.6% vs 16.4%), chronic hypertension (28.6% vs 4.9%), renal disease (14.4% vs 0%), and anemia (14.3% vs 3.3%). In addition, cases with severe or critical disease were more likely to be Hispanic (57.1% vs 26.2%) and black (14.1% vs 6.6%).

Overall, 61.1% of patients with mild COVID-19 were asymptomatic. Of the 11 patients who were enrolled during the first month of the study period, 1 patient (9.1%) was asymptomatic; testing of the asymptomatic patient was because of a high-risk exposure. During the latter 2 months of the study period, 32 patients (64%) were asymptomatic. The most common symptoms for mild disease were cough, fever, and myalgias (Table 2). In contrast, all patients with severe or critical disease reported symptoms, with cough, shortness of breath, and fever being the most common symptoms. All patients with severe or critical disease required supplemental oxygen, and some also received other interventions such as hydroxychloroquine (n=4 [57.1%]) in the early part of the study period and corticosteroids (n=4 [57.1%]) in the latter part. In contrast, only 1 patient with mild disease received treatment; the patient was treated with antibiotic agents for a bacterial pneumonia.

Laboratory results are presented in Table 3. Patients with mild disease had similar mean white blood cell and platelet counts and median lymphocyte counts and transaminases. In contrast, cases with severe or critical COVID-19 had higher risks of white blood cell

Demographic characteristics of COVID-19 cases vs matched controls

	COVID-19 cases (n=61)	Controls (n=122)
Maternal age,[a] y	30.3 (6.4)	30.9 (6.3)
Maternal age of ≥35 y	17 (27.9)	37 (30.3)
Gravidity[b]	3 (2–4)	2 (2–4)
Parity[b]	2 (1–3)	1 (1–3)
Prepregnancy BMI,[a] kg/m²	31.5 (7.3)	30.1 (5.7)
Normal BMI (<25.0)	10 (16.4)	15 (12.3)
Overweight (25.0–29.0)	23 (37.7)	59 (48.4)
Obese	28 (45.9)	48 (39.3)
Class 1 obese (30.0–34.9)	11 (18.0)	27 (22.1)
Class 2 obese (35.0–39.9)	8 (13.1)	12 (9.8)
Class 3 obese (≥40)	9 (14.8)	9 (7.4)
Maternal race		
White	35 (58.3)	47 (42.7)
Black	2 (3.3)	8 (7.3)
Hispanic	21 (35.0)	32 (29.1)
Asian or Indian	2 (3.3)	23 (20.9)
No medical history	50 (82.0)	92 (75.4)
Comorbid medical condition	11 (18.0)	30 (24.6)
Diabetes	7 (11.5)	20 (16.4)
Chronic hypertension	2 (3.3)	6 (4.9)
Renal disorder	1 (1.6)	0
Immunocompromised	2 (3.3)	1 (0.8)
Asthma	2 (3.3)	4 (3.3)
Anemia	2 (3.3)	4 (3.3)
Twins	0	1 (0.8)

Data are presented as number (percentage) unless noted otherwise.

BMI, body mass index; *COVID-19*, coronavirus disease 2019.

[a] Data are presented as mean (standard deviation); [b] Data are presented as median (interquartile range).

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count of <9.5 cells/L, platelets of <150,000/mm³, lymphocytes of <10⁹ cells/L, and elevated alanine aminotransferase of >45 units/L or aspartate transaminase of >35 units/L than controls.

Obstetrical and neonatal outcomes are presented in Table 4. Cases with mild disease had similar obstetrical outcomes compared with controls. However, cases with severe or critical disease had more adverse obstetrical outcomes, including earlier gestational age of delivery (34.0 vs 38.7 weeks; mean difference, 4.8 weeks;

95% CI, 2.6–6.9). Cases were more likely to deliver preterm at <37, <34, and <28 weeks' gestation than controls. Patients with severe or critical COVID-19 also had higher risks of antepartum admissions, cesarean delivery, chorioamnionitis, preeclampsia, and persistent category 2 fetal heart rate tracing despite intrauterine resuscitation and required longer hospital stays than controls.

Notably, 4 patients with severe or critical disease required antepartum admissions compared with 1 control

patient. All 4 cases were admitted for COVID-19 management and required delivery during their admissions. One was admitted at 38 weeks' gestation with COVID-19 symptoms and severe disease. After a period of maternal stabilization, she required cesarean delivery at 39 weeks' gestation for a worsening respiratory status. The other 3 patients had clinician-initiated preterm deliveries at 26 weeks' gestation (critical disease with emergent cesarean delivery in the ICU for refractory hypotension and persistent category 2 fetal heart rate tracing despite intrauterine resuscitation), at 29.3 weeks' gestation (repeat cesarean delivery for severe COVID-19 in the context of superimposed preeclampsia with severe features), and at 34.6 weeks' gestation (induction of labor for severe COVID-19 with worsening respiratory status). The control patient was admitted with preeclampsia with severe features and hemolysis, elevated liver enzymes, and a low platelet count syndrome at 28 weeks' gestation. She underwent inpatient expectant monitoring for 48 hours and then had a successful induction of labor.

Driven primarily by the gestational age at delivery, the offspring of pregnant patients with severe or critical COVID-19 had lower birthweights and higher rates of NICU admission, RDS, and IVH than controls (Table 4). Neonatal outcomes were similar for pregnant patients with mild COVID-19 vs controls.

Associations of COVID-19 and composites of adverse maternal and neonatal outcomes are presented in Table 5. Comparing all COVID-19 cases with controls, the unadjusted ORs of adverse maternal and neonatal outcome were 2.7 (95% CI, 1.0–10.0) and 1.4 (95% CI, 0.6–3.6), respectively. After adjusting for advanced maternal age, obesity, race, and comorbid medical problems, the adjusted odds of adverse maternal and neonatal outcomes were 3.4 (95% CI, 1.2–13.4) and 1.7 (95% CI, 0.8–4.8), respectively. In analyses stratified by disease severity, the odds of adverse maternal and neonatal outcome were similar for mild COVID-19 cases vs controls (Table 5). These results suggest that the morbidity associated with

COVID-19 in pregnancy is largely driven by the severe or critical phenotype.

Comment
Principal findings
We evaluated the risk factors that drive the associations between COVID-19 and adverse maternal and neonatal outcomes. In this matched case-control study, we demonstrated that pregnant women with mild COVID-19 have similar outcomes compared with pregnant controls matched by delivery date whereas pregnant patients with severe or critical disease have worse outcomes. Black and Hispanic race; advanced maternal age; obesity; medical comorbidities, such as diabetes mellitus and chronic hypertension; and antepartum admission related to COVID-19 are risk factors for adverse maternal and neonatal outcomes.

Results of the study in context
The main finding of this study is that severe or critical disease drive morbidity associated with COVID-19 in pregnancy. Because a broader testing for COVID-19 becomes available, the prevalence of asymptomatic and mild disease has increased. The results of this study can provide some reassurance for most pregnant patients.

After implementation of universal testing, we found that 64% of cases were asymptomatic. Our rate of asymptomatic disease was lower than other reports of asymptomatic presentation on labor and delivery. For example, in the initial experience of Columbia with a universal testing, 87.9% of labor and delivery admissions with COVID-19 were asymptomatic.[12] Although the reason for higher rates of self-reported symptoms is uncertain in this study, there is still a large burden of asymptomatic positive patients with COVID-19. The public health threat that this poses—both for the transmission in the greater community and for the risk to healthcare providers—underscores the importance of access to universal testing for COVID-19 on labor and delivery.

Among the COVID-19 cases, disease severity was mild (n=54 [88.5%]), severe (n=6 [9.8%]), and critical (n=1

[1.6%]). These proportions are comparable with what has been observed in nonpregnant patients.[2]

Clinical implications
The results of this study provide a risk profile associated with maternal and neonatal complications associated with COVID-19 in pregnancy. Although limited by small numbers, patients with severe or critical disease were more likely to be older (advanced maternal age), obese, and black and Hispanic and have medical comorbidities. Although young and healthy patients may have

manifestations of severe COVID-19, the results of this study suggest that specific risk factors are the driver of risk.

CDC surveillance data suggest that pregnancy is associated with an increased risk of hospitalization, ICU admission, and mechanical ventilation.[5] The CDC study found low absolute rates of ICU admission and mechanical ventilation, but was limited by incomplete data. The study could not explain whether COVID-19 or obstetrical complications were responsible for higher rates of ICU and mechanical ventilation. In this context, the results

TABLE 2
Characteristics of COVID-19 symptoms among cases and controls matched by delivery date, stratified by disease severity

	COVID-19 cases (n=61)	
	Mild (n=54)	**Severe or critical (n=7)**
COVID-19 disease		
Mild disease	54 (100)	0
Severe disease	0	6 (85.7)
Critical disease	0	1 (14.3)
COVID-19 symptoms		
None	33 (61.1)	0
Fever	13 (24.1)	5 (71.4)
Cough	14 (25.9)	7 (100)
Shortness of breath	2 (3.7)	6 (85.7)
Chest pain	0	1 (14.3)
Diarrhea	0	1 (14.3)
Myalgias	5 (9.3)	1 (14.3)
Sore throat	1 (1.9)	0
COVID-19 treatment		
Any treatment	1 (1.9)	7 (100)
Supplemental O$_2$	0	7 (100)
Hydroxychloroquine	0	4 (57.1)
Remdesivir	0	2 (28.6)
Antibiotic agents	1 (1.9)	3 (42.9)
Bronchodilators	0	3 (42.9)
Mechanical ventilation	0	1 (14.3)
Steroid use	0	4 (57.1)
ICU admission	0	1 (14.3)

Data are presented as number (percentage).

COVID-19, coronavirus disease 2019; *ICU*, intensive care unit.

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TABLE 3
Laboratory findings of patients with COVID-19 stratified by disease severity vs controls matched by delivery date

| Laboratory findings | COVID-19 cases (n=61) | | Controls (n=122) | Severe or critical vs controls (OR [95% CI]) |
	Mild (n=54)	Severe or critical (n=7)		
WBC, cells/L[a]	10.4 (3.3)	7.9 (3.6)	10.0 (2.7)	—
WBC of <9.5 cells/L	24 (44.4)	5 (71.4)	54 (44.3)	2.(0.3—∞)
Platelets,[a] 10^3/mm^3	212.8 (56.8)	214.6 (75.3)	209.5 (55.6)	—
Platelets of <150,000/mm^3	3 (5.6)	2 (28.6)	14 (11.5)	4.0 (0.5—∞)
Lymphocytes,[b] cells/L (n=54)	195 (171—242)	230 (147—294)	204 (163—241)	—
Lymphocytes of <10^9, cells/L	1 (3.0)	2 (40.0)	2 (4.1)	—
AST, units/L[b] (n=35)	22 (19—26)	34 (21—54)	23 (17—25)	—
ALT, units/L[b] (n=35)	14 (12—20)	17 (13—45)	34 (21—54)	—
Elevated ALT of >45 units/L or AST of >35 units/L	2 (13.3)	2 (33.3)	3 (10.3)	—

Data are presented as number (percentage) unless noted otherwise.

ALT, alanine aminotransferase; *AST*, aspartate aminotransferase; *CI*, confidence interval; *COVID-19*, coronavirus disease 2019; *OR*, odds ratio; *WBC*, white blood count.

[a] Data presented as mean (standard deviation); [b] Data presented as median (interquartile range).

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TABLE 4
Obstetrical and neonatal outcomes stratified by disease severity vs controls matched by delivery date

| | COVID-19 cases (n=61) | | Controls (n=122) | Severe or critical vs controls (OR [95% CI]) |
	Mild (n=54)	Severe or critical (n=7)		
Obstetrical outcomes				
Length of stay, d[a]	3 (2—3)	6 (5—17)	3 (3—3)	—
Antepartum admission	0	4 (57.1)	1 (0.8)	—
Cesarean delivery	9 (16.7)	5 (71.4)	40 (32.8)	4.6 (0.7—∞)
Gestational age at testing, wk[b]	38.8 (2.8)	33.6 (5.8)	38.8 (2.5)	—
Gestational age at delivery, wk[b]	39.0 (2.7)	34.0 (5.8)	38.7 (2.5)	—
Preterm delivery				
<37 wk	3 (5.6)	4 (57.1)	10 (8.2)	4.6 (0.4—∞)
<34 wk	1 (1.9)	3 (42.9)	4 (3.3)	6.0 (0.7—∞)
<28 wk	1 (1.9)	1 (14.3)	1 (0.8)	2.0 (0.5—4.0)
Chorioamnionitis	1 (1.9)	1 (14.3)	2 (1.6)	—
Venous thromboembolism	0	0	0	—
Persistent category 2 fetal heart rate tracing	3 (5.6)	3 (42.9)	9 (7.4)	—
Preeclampsia	4 (7.4)	2 (28.6)	10 (8.2)	—
Intrauterine fetal demise	0	0	0	—
Neonatal outcomes				
Birthweight, g[b]	3230 (549)	2293 (1104)	3246 (605)	
1-min Apgar[a]	9 (9—9)	9 (1—9)	9 (9—9)	—
5-min Apgar[a]	9 (9—9)	9 (5—9)	9 (9—9)	—

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TABLE 4
Obstetrical and neonatal outcomes stratified by disease severity vs controls matched by delivery date (continued)

| | COVID-19 cases (n=61) | | Controls (n=122) | Severe or critical vs controls (OR [95% CI]) |
	Mild (n=54)	Severe or critical (n=7)		
NICU admission	46 (85.2)	7 (100.0)	14 (11.5)	—
NICU length of stay, d[a]	2 (2—3)	9 (5—49)	0-0	—
Respiratory distress syndrome	1 (1.9)	4 (57.1)	6 (4.9)	—
Intraventricular hemorrhage	0	2 (28.6)	1 (0.8)	—
Necrotizing enterocolitis	0	0	0	—
Neonatal death	1 (1.9)	0	1 (0.8)	—

Data are presented as number (percentage) unless noted otherwise.

Apgar, appearance, pulse, grimace, activity, and respiration; *CI*, confidence interval; *COVID-19*, coronavirus disease 2019; *OR*, odds ratio; *NICU*, neonatal intensive care unit.

[a] Data are presented as median (interquartile range); [b] Data are presented as mean (standard deviation).

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presented in this case-control study shed light on the risk factors and associations that drive morbidity associated with COVID-19. Pregnant patients who require ICU admission and mechanical ventilation are more likely to have severe or critical COVID-19.

It remains debated whether vertical transmission of SARS-CoV-2 occurs, and current CDC guidelines call for treating offspring of COVID-19 patients as PUI, which typically involves isolation precautions and COVID-19 testing.[13] The guidelines further suggest that shared decision making should be used to determine the extent of social distancing between the patient and the neonate. All neonates of COVID-19 patients in the study had testing at 36 hours of life, and all results were negative.

We found an increased risk of preterm delivery among severe or critical patients affected by COVID-19 compared with controls. These findings are similar to other studies that suggest the preterm birth risk is primarily clinician-initiated rather than spontaneous.[14,15] This observation is notable during the pandemic lockdown, when some countries have noted a reduction in spontaneous preterm birth rates.[16]

Strengths and limitations

Our study has several strengths. As a matched case-control study, maternal and neonatal outcomes of patients with COVID-19 could be compared with matched controls. Other influential

TABLE 5
Associations of COVID-19 and composites of adverse maternal and neonatal outcomes

| | COVID-19 cases (n=61) | | | Controls (n=122) | Odds ratio (95% confidence interval) | |
	All cases (n=61)	Mild (n=54)	Severe or critical (n=7)		Unadjusted	Adjusted
					All cases vs controls	
Maternal composite	11 (18.0)	—	—	10 (8.2)	2.7 (1—10)	3.4 (1.2—13.4)
Neonatal composite	11 (18.0)	—	—	17 (13.9)	1.4 (0.6—3.6)	1.7 (0.8—4.8)
					Mild cases vs controls	
Maternal composite	—	4 (7.4)	7 (100)	10 (8.2)	0.7 (<0.01—3.3)	1.1 (<0.01—6.0)
Neonatal composite	—	5 (9.3)	6 (85.7)	17 (13.9)	1.0 (0.1—7.7)	1.0 (0.1—7.7)

Data are presented as number (percentage) unless noted otherwise. The analyses for severe and critical cases vs controls were not estimable owing to small numbers and the lack of convergence of the conditional logistic regression model.

Composite maternal outcome includes venous thromboembolism, preeclampsia, intensive care unit admission, mechanical ventilation, antepartum admission, supplemental oxygen, and death.

Composite neonatal outcome includes respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, 5-minute Apgar score of <5, persistent category 2 fetal heart rate tracing, and neonatal death

Odds ratios were adjusted for advanced maternal age, obesity, race, and comorbid medical problem; 95% CIs were based on 1000 bias-corrected bootstrap resampling method.

COVID-19, coronavirus disease 2019.

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studies that have informed our knowledge of COVID-19 in pregnancy have lacked control groups, including case reports,[17,18] case series,[19–21] and epidemiologic studies.[5,15]

Although the study was robust and included maternal and neonatal outcomes that were rigorously abstracted, the data were abstracted from delivery hospitalizations. We recognize that some patients with COVID-19 in the community may not have required hospitalization or were hospitalized, but remained undelivered over the course of this project. These patients were not included in this study. As such, the current analysis may bias toward more severe phenotype for patients with severe or critical COVID-19 during the first 3 months of the pandemic.

The study's sample size was relatively small, leading to imprecision in the effect measure estimates. We included 2 matched controls per COVID-19 case (which may have resulted in improved power), but the small sample size limited conclusions about rare outcomes. For example, a large retrospective cohort study that included 3309 births found higher rates of intrauterine fetal demise during the pandemic than a prepandemic period,[22] but we were underpowered for rare outcomes such as this. There is a great need for robust research on this topic, which is why we have presented these data at this time, but we intend to continue data collection for the purposes of larger studies in the future.

Finally, whether the findings reported in this study permits generalizability remains uncertain. Hospital-based studies are guided by referrals to the institution and may not reflect the prevailing landscape of patients seen in other hospital settings or the general population.

Conclusions

The CDC recommends that pregnant patients take steps to minimize acquisition of the infection that causes COVID-19 owing to the potential for a severe disease compared with nonpregnant patients.[5] Most pregnant patients with COVID-19 have mild disease, and this is not associated with a substantial risk of adverse maternal and neonatal outcomes. However, the results of this matched case-control study show the driver for the risk in pregnancy is severe or critical disease. Moreover, specific risk factors are associated with the severe or critical disease phenotype, including black and Hispanic race, advanced maternal age, obesity, medical comorbidities, and antepartum admission related to COVID-19. Although the results of this study support the CDC's conclusion, the main findings suggest disease severity and specific risk factors drive the risk associated with COVID-19 during pregnancy. ∎

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