Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Adverse perinatal outcomes in pregnancies affected by severe COVID-19 infection

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BACKGROUND: Severe COVID-19 infection in pregnancy has been associated with an increase in adverse perinatal outcomes, although studies differ regarding which outcomes are affected. Increased characterization of obstetrical and neonatal outcomes is needed, including details on indications for preterm delivery and additional neonatal adverse outcomes.

OBJECTIVE: This study aimed to determine whether there is a higher rate of adverse perinatal outcomes with severe-to-critical COVID-19 infection compared with nonsevere COVID-19 diagnosed during pregnancy.

STUDY DESIGN: This was a retrospective observational cohort study that compared rates of adverse perinatal outcomes between patients with severe-to-critical and those with nonsevere (asymptomatic, mild, or moderate) COVID-19 infection. Patients had singleton pregnancies and a positive laboratory polymerase chain reaction result for COVID-19. Primary outcomes included hypertensive disorders of pregnancy, cesarean delivery, fetal growth restriction, preterm birth, and neonatal intensive care unit admission. Additional neonatal outcomes analyzed included need for cardiopulmonary resuscitation, low birthweight (<2500 g), 1- or 5-minute Apgar score <7, need for supplemental oxygen, need for intubation, intraventricular hemorrhage, sepsis, respiratory distress syndrome, bronchopulmonary dysplasia, blood transfusion, necrotizing enterocolitis, hypoxic-ischemic encephalopathy, birth trauma, or neonatal death. Appropriate bivariate analyses were used to compare groups. Logistic regression was used to examine primary outcomes while adjusting for confounders.

RESULTS: A total of 441 participants were identified and confirmed via detailed chart review to be pregnant with a singleton pregnancy while diagnosed with COVID-19. Of these, 44 (10%) met National Institutes of Health criteria for severe-to-critical COVID-19 infection. The median gestational age at the time of maternal COVID-19 diagnosis was 36.4 weeks (interquartile range, 29.6–38.6). Severe-to-critical COVID-19 infection had a higher risk of a composite adverse neonatal outcome (36.4% vs 21.4%; P=.03). There was a high incidence of hypertensive disorders of pregnancy overall (20.6%), but this outcome was not higher in the severe-to-critical vs nonsevere group. There were no maternal deaths. There was a low incidence of neonatal COVID-19 test positivity among those tested (1.8%). When adjusting for presence of heart disease and gestational age at COVID-19 diagnosis, severe-to-critical COVID-19 was strongly associated with fetal growth restriction (adjusted odds ratio, 2.73; confidence interval, 1.03–7.25) and neonatal intensive care unit admission (adjusted odds ratio, 3.50; confidence interval, 1.56–7.87). Preterm delivery was more common but was no longer significant after adjustment (adjusted odds ratio, 2.23; confidence interval, 0.99–5.05).

CONCLUSION: Severe-to-critical COVID-19 infection during pregnancy is associated with higher rates of adverse neonatal outcomes and strongly associated with neonatal intensive care unit admission and fetal growth restriction compared with nonsevere disease. There is a high rate of hypertensive disorders of pregnancy overall in all those affected by COVID-19, regardless of severity. Pregnant persons should be counseled on these risks to encourage vaccination, and those with infection during pregnancy should be monitored for fetal growth disorders.

Key words: coronavirus, COVID-19, fever, morbidity, mortality, pandemic, pregnancy, preterm birth, respiratory distress syndrome, SARS-CoV, SARS-CoV-2, sepsis, virus

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Why was this study conducted?

This was a retrospective cohort study conducted to investigate the impact of severe COVID-19 infection on obstetrical and neonatal outcomes.

Key findings

Our study demonstrated increased rates of adverse neonatal outcomes including neonatal intensive care unit admission and increased risk of fetal growth restriction in severe COVID-19 infection compared with nonsevere COVID-19. There was a high rate of hypertensive disorders of pregnancy among all pregnancies affected by COVID-19.

What does this add to what is known?

Our study included detailed characterization of obstetrical and neonatal outcomes in pregnancies with severe COVID-19 disease across a >1-year time span, confirmed findings of increased rates of adverse neonatal outcomes, added details of indications for preterm birth, and found a strong association with fetal growth restriction.

Introduction

The impact of SARS-CoV-2 (COVID-19) during pregnancy has been an ongoing area of investigation with varying results regarding the characterization of maternal outcomes, disease severity, and perinatal and obstetrical outcomes. After several conflicting early reports on rates of maternal adverse outcomes,[1–7] the largest body of data from the Centers for Disease Control and Prevention ultimately confirmed substantially higher rates of hospitalization, intensive care unit (ICU) admission, and mechanical ventilation among pregnant women with COVID-19 compared with nonpregnant persons.[5] This was a large and informative data set but was subject to reporting bias, and pregnancy status was only available for some women. In addition, obstetrical and neonatal outcomes were not available. Studies examining the effect of COVID-19 on obstetrical and neonatal outcomes have also been conflicting.[8–12] The most robust study by Metz et al[9] examined 1219 pregnant persons positive for COVID-19 and found an increased risk of cesarean delivery, hypertensive disorders of pregnancy, and preterm birth in those with severe-to-critical COVID-19 compared with asymptomatic patients. They did not find an increase in adverse outcomes in the mild-to-moderate group compared with asymptomatic patients.

We sought to elucidate maternal and neonatal outcomes in further detail and confirm these more recent findings of increased adverse perinatal outcomes in those with severe-to-critical COVID-19. We investigated these outcomes through a retrospective observational cohort study examining all pregnant persons with confirmed COVID-19 infection within a large health system. We hypothesized that we would find higher rates of adverse perinatal and neonatal outcomes among severe-to-critical than among nonsevere COVID-19 infections during pregnancy.

Materials and Methods

This was a retrospective observational cohort study examining pregnant persons with polymerase chain reaction (PCR) laboratory-confirmed COVID-19 infection diagnosed between March 1, 2020 and May 5, 2021 across a large hospital system. This hospital system includes a major academic tertiary-care center and 12 regional hospitals. Patients were screened for eligibility if they had a confirmed pregnancy diagnosis and simultaneous diagnosis of COVID-19 using the services of Health Data Compass, an enterprise health data warehouse that integrates patient clinical data from the electronic health record. We identified any patient with a prenatal or delivery encounter using International Classification of Diseases (ICD)-9, ICD-10, Current Procedural Terminology, and positive COVID-19 laboratory codes. Detailed electronic medical record review and data abstraction were performed to ensure that patients met the inclusion criteria of a diagnosis of COVID-19 during a clinically confirmed pregnancy. All study sites had a universal screening process for testing patients on admission to the labor and delivery unit. Additional COVID-19 testing was obtained for inpatients and outpatients presenting with symptoms. Patients were excluded if they did not have a laboratory-confirmed PCR diagnosis of COVID-19, or if they had a multifetal gestation or a known major fetal anomaly. Study data were collected and managed using REDCap (Vanderbilt University, Nashville, TN) electronic data capture tools hosted at the University of Colorado.[13] The study was approved by the institutional review board.

Data abstraction included demographics, medical and obstetrical history, COVID-19 treatment, laboratory findings, imaging studies, and birth outcomes. Neonatal outcomes were reviewed for the duration of the neonate's delivery admission. Data accuracy was ensured by detailed chart review and/or reviewed for accuracy by the primary author who is a trained obstetrician. The accuracy of a PCR-confirmed laboratory diagnosis of COVID-19 was verified, including if external laboratory results were available for review. The gestational age at the time of COVID-19 diagnosis was determined using the clinically established estimated due date.

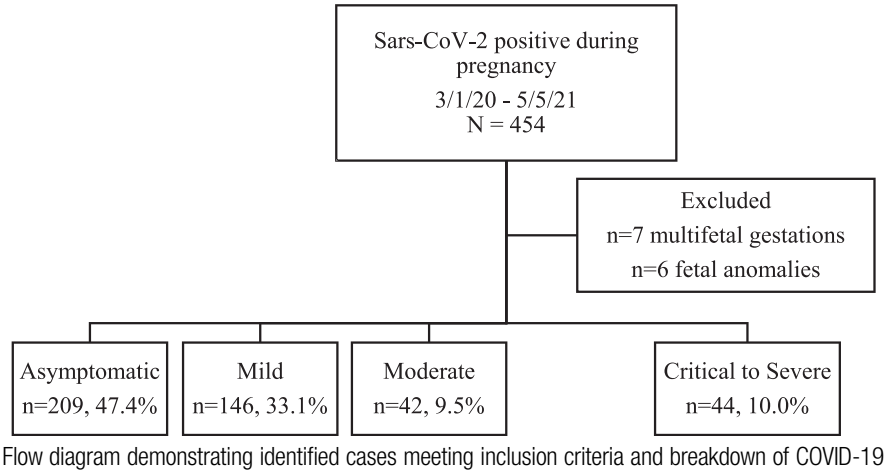
Classification of COVID-19 severity was based on the established National Institutes of Health (NIH) guidelines.[14] According to these guidelines, severe COVID-19 disease is defined as peripheral oxygen saturation (SpO_2) <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates on imaging >50% of lung fields. Critical disease is defined as respiratory failure, septic shock, and/or multiorgan dysfunction. The "nonsevere COVID-19" cohort included those meeting NIH criteria for asymptomatic disease, mild disease (defined as any

signs or symptoms of COVID-19 excluding shortness of breath/dyspnea, or abnormal chest imaging), or moderate illness (defined as evidence of lower respiratory disease during clinical assessment or imaging and an SpO2 ≥94% on room air at sea level). The NIH criteria specify SpO_2 criteria at sea level, whereas our study cohort was at approximately 5000 ft of elevation; thus, we translated an SpO_2 level of <94% on room air at sea level to any need for oxygen supplementation, which is typically set at a threshold of an SpO2 <92% for pregnant persons at altitude.

Rates of adverse perinatal and neonatal outcomes were compared between those meeting NIH criteria for severe or critical COVID-19 and those with nonsevere disease (asymptomatic, mild, or moderate). Primary perinatal outcomes included cesarean delivery, preterm delivery (<37 weeks), and the placentally mediated disorders of fetal growth restriction and hypertensive disorders of pregnancy. Fetal growth restriction was defined as either an estimated fetal weight or abdominal circumference measuring <10th centile. Hypertensive disorders of pregnancy included gestational hypertension, chronic hypertension with superimposed preeclampsia, preeclampsia with or without severe features, HELLP syndrome, and eclampsia and were classified according to the criteria by the American College of Obstetricians and Gynecologists.[15] Secondary perinatal outcomes included rates of pregnancy loss (defined as spontaneous miscarriage at any gestational age or intrauterine fetal demise), blood transfusion, postpartum hemorrhage (defined as >1000 mL of estimated blood loss), venous thromboembolism (VTE), maternal ICU admission, endometritis, and clinically diagnosed chorioamnionitis.

Neonatal outcomes included NICU admission, NICU length of stay, and a composite adverse neonatal outcome defined as the incidence of at least one of the following: NICU admission, incidence of birthweight <2500 g, 1- or 5-minute Apgar score <7, use of supplemental oxygen, intubation, cardiopulmonary resuscitation, incidence of sepsis, respiratory distress syndrome, bronchopulmonary dysplasia, blood transfusion, necrotizing enterocolitis, hypoxic-ischemic encephalopathy, birth trauma, or neonatal death. The incidence of positive neonatal COVID-19 testing was also examined. NICU admission and neonatal testing were not universal for all maternal cases of COVID-19 but provided at the clinical discretion of the neonatal care team. Similarly, placental pathology was not universally sent but performed when clinicians considered it appropriate on the basis of neonatal outcomes.

FIGURE 1
COVID-19 severity in the study cohort



Flow diagram demonstrating identified cases meeting inclusion criteria and breakdown of COVID-19 severity classifications.

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Descriptive statistics including tests of normality were computed to assess the study variables. Appropriate bivariate analyses were used to compare baseline demographic data and medical history and secondary outcomes including Student *t* or Mann−Whitney U tests for continuous variables and chi-square or Fisher exact tests for categorical outcomes. Logistic regression was used to identify predictors of primary perinatal outcomes associated with placental disorders (preterm delivery, fetal growth restriction, and hypertensive disorders of pregnancy), and NICU admission, adjusting for any baseline variables found to be associated with severe COVID-19 ($P \leq .05$).

Results

A total of 441 participants were identified and confirmed to have a singleton pregnancy while diagnosed with COVID-19 via laboratory-confirmed PCR. Among these, 397 met criteria for asymptomatic, mild, or moderate infection, and 44 met criteria for critical-to-severe disease (Figure 1). The rates of characteristics defining disease severity for symptomatic patients and rates of specific symptoms are presented in Table 1. Specific symptoms that were more common in the severe-to-critical group included dyspnea, cough, fever, and muscle aches (Table 1).

The location of diagnosis varied, with most cases diagnosed in the labor and delivery unit (47.9%). The second most common location was an outpatient clinic (40.1%), with the remainder being recognized in the emergency department, a different inpatient setting (such as ICU or medicine floor), or an urgent care setting (9.3%, 2.5%, and 0.2%, respectively). The median gestational age at time of COVID-19 diagnosis across the entire cohort was 36.4 weeks (interquartile range, 29.6−38.6), with 52.4% of participants being diagnosed with COVID-19 preterm (<37 weeks). There was a low incidence of COVID-19 diagnosis in the first trimester (<12 weeks), with a total of 9 participants (2.0%).

Baseline demographics and clinical characteristics were overall similar between those with severe-to-critical

TABLE 1
Disease severity classification

	Mild/moderate COVID-19 (n=188)		Critical/severe COVID-19 (n=44)		
	N	%	n	%	*P* value
Respiratory failure (ECMO, CPAP, BiPap, ventilation)	0	0.0	8	18.2	
Nasal cannula[a]	1	0.3	27	61.4	
HFNC	0	0.0	1	2.3	
BiPap or CPAP	0	0.0	0	0.0	
Mechanical ventilation	0	0.0	8	18.2	
ECMO	0	0.0	1	2.4	
Septic shock	1	0.5	0	0.0	
Death	0	0	0	0.0	
Abnormal CXR or chest CT	10	5.3	38	86.4	
Self-reported dyspnea	35	18.6	33	75.0	
Other symptoms:					
Cough	101	53.7	33	75.0	.01
Fever	57	30.3	25	56.8	<.01
Chest pain or tightness	13	6.9	6	13.6	.14
Headache	45	23.9	9	20.5	.62
Nausea	25	13.3	8	18.2	.40
Vomiting	14	7.5	7	15.9	.08
Diarrhea	10	5.3	3	6.8	.70
Loss of smell	45	23.9	6	13.6	.14
Loss of taste	38	20.2	5	11.4	.17
Joint pain	0	0.0	0	0.0	—
Muscle aches	41	21.8	17	38.6	.02
Nasal congestion	55	29.3	2	4.6	<.01
Runny nose	18	9.6	1	2.3	.14
Sore throat	36	19.2	3	6.8	.05
Fatigue	28	14.9	11	25.0	.11
Conjunctivitis	1	0.5	0	0	1.0

BiPAP, bilevel positive airway pressure; *CPAP*, continuous positive airway pressure; *CT*, computed tomography; *CXR*, chest x-ray; *ECMO*, extracorporeal membrane oxygenation; *HFNC*, high-flow nasal cannula.

[a]One patient required nasal cannula and remained in the mild group category because the nighttime oxygen requirement was suspected to be secondary to obstructive sleep apnea and the patient had otherwise only mild symptoms.

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and those with nonsevere disease (Table 2). Notably, there were no differences in age, body mass index, history of preterm birth, cesarean delivery, or history of hypertensive disorders. Those with severe-to-critical infection had a higher incidence of underlying heart disease (4.6% vs 0.3%; *P*<.01) and a lower median gestational age at diagnosis (31.5 vs 37 weeks; *P*<.01).

Table 3 demonstrates primary and secondary perinatal outcomes. Those with severe-to-critical COVID-19 infection demonstrated higher rates of preterm birth (25% vs 10.2%; *P*<.01) and fetal growth restriction (13.6% vs 5.3%; *P*=.03). There was a high but similar rate of hypertensive disorders of pregnancy in both groups (22.7% vs 20.4%; *P*=.72). The overall cesarean rate and primary cesarean rate were also similar between the groups. Secondary outcomes were significant for earlier gestational age at delivery (38.4 vs 39.1 weeks; *P*=.04), higher incidence of delivery for nonreassuring fetal status (15.9% vs 5.6%; *P*<.01), higher maternal ICU admission (31.8 vs 0%; *P*<.001), and higher rates of VTE (4.6 vs 0.3%; *P*=.03) in the severe-to-critical group (Table 3).

Table 4 demonstrates primary and secondary neonatal outcomes. The primary neonatal outcome of NICU admission was significantly higher in the severe-to-critical group (27.3% vs 7.9%; $P<.01$). A composite of neonatal adverse outcomes was also significantly higher in the severe-to-critical group (36.4% vs 21.4%; $P=.03$). Individual secondary neonatal outcomes that were higher in the severe-to-critical group included rates of low birthweight <2500 g (20.9 vs 10.0%; $P=.03$), 1-minute Apgar <7 (20.5 vs 9.5%; $P=.03$), use of supplemental oxygen (27.3 vs 11.2%; $P<.01$), intubation (6.8 vs 1.5%; $P=.02$), and respiratory distress syndrome (15.9 vs 4.6%; $P<.01$) (Table 4).

There were no maternal or neonatal deaths in our cohort. There was an overall low incidence of neonatal COVID-19 test positivity among those tested (2/111; 1.8%). No differences in rates of pregnancy loss were noted, with a total of 4 pregnancy losses that were all in the nonsevere COVID-19 group (Table 3). These losses included a 15-week, 20-week, and 21-week spontaneous delivery, and one 26-week intrauterine fetal demise. Two losses had evidence of acute chorioamnionitis on placental pathologic examination, and 2 of the spontaneous deliveries presented with a clinical picture consistent with cervical insufficiency.

Table 5 presents the final logistic regression models. Severe-to-critical COVID-19 was predictive of fetal growth restriction (adjusted odds ratio [aOR], 2.73; 95% confidence interval [CI], 1.03−7.25) and NICU admission (aOR, 3.50; 95% CI, 1.56−7.87) when adjusting for gestational age at diagnosis and history of heart disease. Preterm delivery was no longer significant in the severe-to-critical group (aOR, 2.23; 95% CI, 0.99−5.05). Of note, 81.8% of preterm deliveries in the severe-to-critical group were indicated (vs spontaneous), whereas only 27.5% of preterm deliveries were indicated in the nonsevere group. Of the 9 indicated preterm deliveries in the severe group, most occurred during the time of COVID-19 hospitalization (88.9%), and most were secondary to nonreassuring fetal assessment (77.8%). Among the indicated deliveries in the nonsevere group, most were secondary to a hypertensive diagnosis of pregnancy (63.6%). There was a high incidence of hypertensive disorders of pregnancy in the cohort overall (20.6%), but severe-to-critical disease was not associated with this outcome (aOR, 1.30; 95% CI, 0.61−2.76). In addition, severe-to-critical disease was not associated with cesarean delivery (aOR, 1.18; 95% CI, 0.52−2.71) nor primary cesarean delivery (aOR, 0.09; 95% CI, 0.44−1.87).

Comment

Principal findings

Our study found higher rates of adverse perinatal outcomes among pregnancies affected by severe-to-critical COVID-19 than among those with nonsevere disease. These outcomes included higher rates of fetal growth restriction, NICU admission, and a composite adverse neonatal outcome. Preterm birth was more common in the severe-to-critical group, and this difference neared significance when adjusting for confounders. We did not find higher rates of cesarean delivery or hypertensive disorders in the severe-to-critical group, but there was an overall high rate of hypertensive disorders in the entire cohort (20.6%). Our findings expand the body of evidence supporting the association of COVID-19 with worsened pregnancy outcomes and add additional details on fetal and neonatal outcomes.

Results in the context of what is known

Preterm birth was more common in the severe-to-critical group (25% vs 10.2%; $P\leq.01$). Although this was no longer significant after adjusting for gestational age at diagnosis and heart disease, we suspect that many of the additional adverse neonatal outcomes were driven by the high rate of preterm birth in the severe group. It is also noteworthy that preterm birth was largely driven by indicated deliveries in the severe-to-critical group (81.8%), similarly to what was found by Metz et al.[9] Our study adds additional detail on delivery indication, noting that 77.8% were because of nonreassuring fetal status. There was also a high rate of indicated preterm births in the nonsevere group (27.5%). This may be partially explained by the higher incidence of comorbid diagnoses such as hypertensive disorders of pregnancy in all pregnancies affected by COVID-19 regardless of severity, which was indeed the most common indication for preterm delivery in the nonsevere group (63.6%). Although higher rates of adverse neonatal outcomes and low birthweight are expected in the setting of high rates of preterm delivery and NICU admission, these are clinically significant comorbidities.

Our finding that fetal growth restriction was more common in the severe-to-critical COVID-19 group is notable. Aside from isolated case reports,[16] previous studies evaluating fetal growth restriction have not shown a consistent correlation with COVID-19 infection; however, these previous studies did not account for severity of infection.[17−19] Although we are cautious about interpreting this finding because of lack of obtained data regarding Doppler studies or other indicators of severe fetal growth restriction, growth restriction is known to be more common in inflammatory states in pregnancy,[20] and higher levels of inflammation are a hallmark of severe COVID-19. Because of the retrospective nature of this research, it was difficult to ascertain the timing of COVID-19 infection in relation to the onset of fetal growth restriction. However, we attempted to obtain a general idea of the temporal relationship of COVID-19 diagnosis among the 28 participants with a diagnosis of fetal growth restriction. We did not find a significant difference in the rate of fetal growth restriction diagnosed at any time before a COVID-19 diagnosis. This increased the likelihood of a true difference between the groups, but a causative relationship could not be fully established.

We were surprised not to find a higher rate of hypertensive disorders of pregnancy in the severe group because of the

TABLE 2
Baseline demographic and clinical characteristics

Characteristic	Asymptomatic, mild, or moderate infection (n=397; 90.0%) Median (IQR) or n (%)	Critical-severe (n=44; 10.0%) Median (IQR) or n (%)	*P* value
Age (y)	27.5 (22–32)	28 (25–33.5)	.15
Gravidity			
1	133 (33.5%)	14 (31.8%)	.68
2–4	212 (53.4%)	26 (59.1%)	
≥5	52 (13.1%)	4 (9.1%)	
Parity			
Nulliparous	159 (40.1%)	14 (31.8%)	.29
Multiparous	238 (59.9%)	30 (68.2%)	
Previous cesarean delivery[a]	67 (17.1%)	4 (9.1%)	.17
Gestational age at diagnosis	37 (30.1–39)	31.5 (27.5–34.8)	<.01
Body mass index (kg/m^2)	31.5 (27.1–36)	32.4 (28–37.1)	.71
Race-ethnicity			
Non-Hispanic White	142 (36.1%)	10 (23.3%)	.17
Non-Hispanic Black	33 (8.4%)	2 (4.7%)	
Non-Hispanic Other	38 (9.7%)	7 (16.3%)	
Hispanic	180 (45.8%)	24 (55.8%)	
History of preterm birth	28 (7.1%)	6 (13.6%)	.12
History of any hypertensive disorder of pregnancy	32 (8.1%)	3 (6.8%)	1.00
Tobacco use during pregnancy	23 (5.8%)	2 (4.6%)	1.00
Illicit substance use during pregnancy	29 (7.3%)	2 (4.6%)	.76
History of stroke	0	0	—
History of thrombosis	1 (0.3%)	1 (2.3%)	.19
HIV infection	1 (0.3%)	1 (2.3%)	.19
Asthma	41 (10.3%)	8 (18.2%)	.12
Diabetes mellitus			.19
Preexisting	8 (2.0%)	3 (6.8%)	
Gestational	33 (8.3%)	2 (4.6%)	

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(continued)

TABLE 2
Baseline demographic and clinical characteristics *(continued)*

Characteristic	Asymptomatic, mild, or moderate infection (n=397; 90.0%) Median (IQR) or n (%)	Critical-severe (n=44; 10.0%) Median (IQR) or n (%)	*P* value
Chronic hypertension	19 (4.8%)	4 (9.1%)	.28
Seizure disorder	9 (2.3%)	1 (2.3%)	1.00
Immunosuppression[b]	2 (0.5%)	0 (0.0%)	1.00
Any psychiatric or mood disorder	93 (23.4%)	14 (31.8%)	.22
Chronic kidney disease	1 (0.3%)	0 (0%)	1.00
Rheumatologic disease	3 (0.8%)	1 (2.3%)	.34
Thyroid disease	19 (4.8%)	0 (0.0%)	.24
Heart disease[c]	1 (0.25%)	2 (4.6%)	.03
Chronic liver disease	1 (0.3%)	0 (0.0%)	1.00

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

IQR, interquartile range.

[a]Excluding patients with pregnancy loss in COVID-19–affected pregnancy

[b]HIV, chronic steroid use, or other immunosuppressants

[c]Heart disease included 1 patient with arrhythmia and 2 patients with rheumatic heart disease.

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known effect of inflammation in pregnancy on the rates of these disorders.[20] Although the lack of increase in rates of hypertensive disorders of pregnancy in the severe-to-critical COVID-19 group differs from the findings of Metz et al,[9] it may be explained by the high rate of hypertensive disorders of pregnancies in both severe and nonsevere COVID-19 groups overall (20.6%), which is higher than the background rate of approximately 8.6% in the United States and the rate of 11.1% reported within our health system between 2019 and 2020.[21] Hypertensive disorders are emerging as more common with the diagnosis of COVID-19 in pregnancy in general, thus we may have been underpowered to find a difference between the groups.[10]

We found a higher rate of VTE in the severe COVID-19 group, although the incidence was low overall (3 in the entire cohort). This outcome is difficult to interpret in the context of small numbers and variation in local VTE prophylaxis strategies that changed over time and may have differed among the local and regional hospitals. In addition, although our rate of neonatal test positivity (2/111; 1.8%) is similar to previously published rates,[9] it should be interpreted with caution because of lack of uniformity for neonatal testing approaches across sites.

Clinical implications

Our finding of increased adverse neonatal outcomes is particularly useful in counseling patients on the continued risks of COVID-19 infection in pregnancy, especially now that preventative intervention with vaccines is available. Although many of the risks are associated with immediately acute concerns in severe-to-critically ill patients (such as increased indicated preterm birth for nonreassuring fetal status), we additionally confirmed a high rate of hypertensive diagnosis in both groups.[9,10] Lastly, our study found an increase in the rate of fetal growth restriction and supports the practice of increased fetal growth surveillance, especially for those who suffer severe-to-critical COVID-19 infection.

Research implications

Continued research into timing of infection and adverse perinatal outcomes would be beneficial. There were limited numbers of participants in the first trimester in our study, and the effect of COVID-19 during this pregnancy time frame remains understudied. Lastly, because of the rarity of stillbirth and pregnancy loss, we were unable to further examine their relationship with COVID-19.

Strengths and limitations

Our study's greatest limitation is its retrospective nature, which limits the ability to draw conclusive relationships between COVID-19 severity and outcomes. Our results were likely skewed toward later gestational ages at time of diagnosis because universal screening protocols for planned admission to labor and delivery are more likely to occur at later gestational ages, which also explains the gestational age difference between our 2 groups, although we did adjust for this in our logistic regressions. There was also potential for confounding between the outcomes of hypertensive disorders of pregnancy and fetal growth restriction that frequently co-occur, although it is biologically plausible that both were caused by the inflammatory nature of COVID-19.[20,22] Our study was limited in its ability to separate these 2 outcomes. Overall, there was a low rate of adverse outcomes in our cohort because of a large proportion of

TABLE 3
Perinatal outcomes

Characteristic	Asymptomatic, mild, or moderate infection (n=397; 90.0%) Median (IQR) or n (%)	Critical-severe (n=44; 10.0%) Median (IQR) or n (%)	*P* value
Delivery mode:			
Cesarean delivery	107 (27.2%)	12 (27.3%)	.99
Vaginal delivery (spontaneous or operative)	286 (72.8%) Operative: n=4	32 (72.7%) Operative: n=2	
Primary cesarean delivery	60 (56.1%)	9 (75.0%)	.24
Gestational age at delivery (wk)	39.1 (37.5–39.4)	38.4 (36.8–39.4)	.04
Indication for delivery			
Spontaneous	194 (49.6%)	14 (31.8%)	<.01
Worsening maternal status	1 (0.26%)	1 (2.3%)	
Nonreassuring fetal heart tones	22 (5.6%)	7 (15.9%)	
Other obstetrical indication	174 (44.5%)	22 (50%)	
Preterm birth (<37 wk)	40 (10.2%)	11 (25%)	<.01
Indicated	27.5% (11/40)	81.8% (9/11)	
Gestational age at preterm delivery			
<28 wk	3 (7.5%)	1 (9.1%)	1.00
28–36.6 wk	37 (92.5%)	10 (91.0%)	
Fetal growth restriction	21 (5.3%)	6 (13.6%)	.03
Pregnancy outcome			
Live birth	393 (99.0%)	44 (100%)	.50
Pregnancy loss[a]	4 (1.0%)	0 (0.0%)	
Preterm premature rupture of membranes	19 (4.8%)	1 (2.3%)	.71
Endometritis	8 (2.0%)	1 (2.3%)	1.00
Chorioamnionitis	14 (3.5%)	0 (0%)	.38
Hypertensive disorder of pregnancy			
Any hypertensive disorder of pregnancy	81 (20.4%)	10 (22.7%)	.72
Gestational hypertension	29 (7.3%)	5 (11.4%)	.90
Preeclampsia without severe features	31 (7.8%)	3 (6.8%)	
Preeclampsia with severe features	20 (5.0%)	2 (4.6%)	
Eclampsia	1 (0.3%)	0 (0.0%)	
HELLP syndrome	0 (0.0%)	0 (0.0%)	
Uterine rupture	0 (0.0%)	0 (0.0%)	1.00
Blood transfusion	2 (0.5%)	0 (0.0%)	1.00
Postpartum hemorrhage	29 (7.4%)	1 (2.3%)	.34
Maternal intensive care unit admission	0 (0.0%)	14 (31.8%)	<.01
Venous thromboembolism	1 (0.3%)	2 (4.6%)	.03

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

IQR, interquartile range.

[a]Pregnancy loss defined as spontaneous miscarriage at any gestational age or intrauterine fetal demise.

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TABLE 4
Neonatal outcomes

Outcome	Asymptomatic, mild, or moderate infection (n=397; 90.0%) Median (IQR) or n (%)	Critical-severe (n=44; 10.0%) Median (IQR) or n (%)	*P* value
Composite adverse neonatal outcome[a]	85 (21.4%)	16 (36.4%)	.03
Neonatal ICU admission	31 (7.9%)	12 (27.3%)	<.01
Neonatal ICU length of stay (d)	14 (6–27)	21.5 (7–40)	.39
Birthweight (g)	3186.5 (2840–3480)	3125 (2715–3410)	.24
Birthweight <2500 g	39 (10.0%)	9 (20.9%)	.03
1-min Apgar score <7	37 (9.5%)	9 (20.5%)	.03
5-min Apgar score <7	9 (2.3%)	3 (6.8%)	.08
Use of supplemental oxygen	44 (11.2%)	12 (27.3%)	<.01
Required intubation	6 (1.5%)	3 (6.8%)	.02
Required CPR	2 (0.5%)	0 (0%)	1.00
Intraventricular hemorrhage	0	0	—
Sepsis	1 (0.3%)	0 (0%)	1.00
Respiratory distress syndrome	18 (4.6%)	7 (15.9%)	<.01
Bronchopulmonary dysplasia	2 (0.5%)	1 (2.3%)	.27
Blood transfusion	1 (0.3%)	1 (2.3%)	.19
Necrotizing enterocolitis	0	0	—
Hypoxic-ischemic encephalopathy	1 (0.3%)	0 (0%)	1.00
Birth trauma	1 (0.3%)	0 (0%)	1.00
Neonatal death	0 (0%)	0 (0%)	—
Neonatal+COVID-19 PCR[b]	2 (0.5%)	0 (0%)	1.00

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

CPR, cardiopulmonary resuscitation; *ICU*, intensive care unit; *IQR*, interquartile range; *PCR*, polymerase chain reaction.

[a]Composite adverse neonatal outcome includes at least 1 of the following: neonatal ICU admission, need for CPR, low birthweight (<2500 g), 1- or 5-minute Apgar score <7, need for supplemental oxygen, need for intubation, intraventricular hemorrhage, sepsis, respiratory distress syndrome, bronchopulmonary dysplasia, blood transfusion, necrotizing enterocolitis, hypoxic-ischemic encephalopathy, birth trauma, or neonatal death

[b]Calculated out of n=111 neonates tested for COVID-19.

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TABLE 5
Adjusted odds ratios of adverse perinatal and neonatal outcomes in severe-to-critical vs nonsevere COVID-19

Outcomes	Adjusted odds ratios (95% CI)
All preterm delivery <37 wk	2.23 (0.99–5.05)
Spontaneous preterm delivery	0.46 (0.09–2.20)
Fetal growth restriction	2.73 (1.03–7.25)[a]
NICU admission	3.50 (1.56–7.87)[a]
Risk of cesarean delivery	0.90 (0.44–1.87)
Risk of primary cesarean delivery	1.18 (0.51–2.71)
Risk of hypertensive disorders of pregnancy	1.30 (0.61–2.76)

Adjusted for gestational age at the time of COVID-19 diagnosis and preexisting heart disease.

CI, confidence interval; *NICU*, neonatal intensive care unit.

[a]Significant *P* values defined as *P*<.05.

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asymptomatic positive individuals. Lastly, there were changes in standard-of-care treatments (increased use of steroids and remdesivir) and vaccine availability across the time span of our study, which may have affected outcomes. Because of the timeline of our study within the pandemic, we were unable to assess vaccine status or use of monoclonal antibodies, which were rarely used in this time frame at our system.

There are several strengths of our study. Although this analysis was limited to a single region, it did include a major academic tertiary-care center and outlying regional hospitals, which adds to the generalizability of the results beyond the limitations of studying a single referral site. Our detailed analysis

reviews a large number of pertinent clinical outcomes and spans over a year of the pandemic. Our data across this time span reflect that adverse perinatal outcomes remained elevated with COVID-19 even as knowledge of its optimal treatment increased. We were able to perform a detailed chart review and examine a variety of neonatal outcomes in significantly more detail. In addition, different variants of concern have existed during this expanded time frame, thus our review enables a comprehensive updated overview of the effects of COVID-19 on pregnancy.

Conclusions

Severe-to-critical COVID-19 disease is associated with increased risk of fetal growth restriction, NICU admission, and a composite of adverse neonatal outcomes. Indicated preterm birth owing to fetal distress was common. Our study adds additional strength to the existing literature on adverse perinatal outcomes in pregnancy with further detail on neonatal risks, which can aid in counseling patients on the risks of COVID-19 while vaccine hesitancy in this population remains high. ■

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