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ORIGINAL ARTICLE

Predictors of severe and critical disease in pregnant women with SARS-CoV-2

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ABSTRACT

Background/Objective: SARS-CoV-2 continues to spread widely in the US and worldwide. Pregnant women are more likely to develop severe or critical illness than their non-pregnant counterparts. Known risk factors for severe and critical disease outside of pregnancy, such as asthma, diabetes, and obesity have not been well-studied in pregnancy. We aimed to determine which clinical and pregnancy-related factors were associated with severe and critical COVID illness in pregnancy.

Study design: This was a retrospective cohort study of women with confirmed intrauterine pregnancy and positive nasopharyngeal swab for SARS-CoV-2 who presented to an academic medical center in New York City from 1 March 2020 to 1 July 2020. Severe and critical COVID-19 disease was defined by World Health Organization criteria. Women with severe/critical disease were compared to women with asymptomatic/mild disease. Continuous variables were compared with Mann–Whitney or *t*-test and categorical variables were compared using chi-square and Fisher's exact. Statistical significance was set at $p < .05$. Multivariable logistic regression was performed including variables that were significantly different between groups.

Results: Two hundred and thirty-three patients were included, 186 (79.8%) with asymptomatic/mild disease and 47 (20.2%) with severe/critical disease. Women with asymptomatic/mild disease were compared to those with severe/critical disease. Women with severe/critical disease were more likely to have a history of current or former smoking (19.6 *vs.* 5.4%, $p = .004$), COVID-19 diagnosis in the 2nd trimester (42.6 *vs.* 11.8%, $p = .001$), and asthma or other respiratory condition (21.3 *vs.* 7.0%, $p = .01$). Women with severe/critical disease were more likely to have cesarean delivery (35.5 *vs.* 15.6%, $p < .01$) and preterm delivery <37 weeks (25.8 *vs.* 3.8%, $p < .01$). After adjustment, history of smoking remained significantly predictive of severe/critical disease [aOR 3.84 (95% CI, 1.25–11.82)].

Conclusion: Pregnant women with a history of smoking, asthma, or other respiratory condition, and COVID-19 diagnosis in the second trimester of pregnancy were more likely to develop severe/critical disease. These findings may be useful in counseling women on their individual risk of developing the severe or critical disease in pregnancy and may help determine which women are good candidates for vaccination during pregnancy.

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COVID 19; pregnancy; infection; severe disease; infectious disease

Introduction

In March 2020, widespread community transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, became a global public health crisis. As of 24 April 2021, more than 32 million people in the US and 146 million people globally had been infected [1]. Despite increasing rates of vaccination, widespread transmission is ongoing and hospitalizations and deaths continue to rise. It remains unclear why some develop a severe infection while others remain asymptomatic. Risk factors for severe disease outside pregnancy include obesity, smoking, preexisting conditions, such as asthma, diabetes, and kidney disease, and age >65, and similar risk factors have been implicated in pregnancy as well [2,3]. Additionally, women infected in pregnancy are more likely to develop severe or critical disease than non-pregnant counterparts [4–6]. We aimed to determine which factors were associated with severe and critical COVID disease in pregnancy in a cohort of pregnant women infected with SARS-CoV-2 in New York City, an early epicenter of the pandemic. We hypothesized that medical comorbidities, such as obesity and asthma, as well as trimester of diagnosis and pregnancy-specific comorbidities, such

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as preeclampsia and gestational diabetes, would impact the severity of disease in pregnancy.

Methods

We performed an IRB-approved retrospective cohort study of women ages 14–55 with confirmed intrauterine pregnancy and positive nasopharyngeal swab for SARS-CoV-2 who presented to NYU Langone Health-Tisch, NYU Langone Health-Brooklyn, or Bellevue Hospital Center from 1 March 2020 to 1 July 2020. Clinical and demographic characteristics, as well as maternal and neonatal outcomes of included patients, were collected. Charts were reviewed at least 6 weeks after the date of the last positive nasopharyngeal swab in the cohort. Initially, only symptomatic patients were tested for SARS-CoV-2. Universal screening of all patients admitted to labor and delivery was implemented on 14 April 2020 at Bellevue Hospital Center and 4 May 2020 at the two NYU Langone sites. Testing was performed using cobas SARS-CoV-2 assay (Roche), Cepheid Xpert Xpress assay, and BioReference.

Severe COVID-19 infection was defined per World Health Organization criteria as patients with dyspnea, respiratory rate of $\geq$30 breaths per minute, or blood oxygen concentration $<$93% on room air [7,8]. Critical disease was defined as respiratory failure requiring intubation, septic shock, and/or multiple organ dysfunction or failure [7,8]. Patients with asymptomatic/mild disease were compared to those with severe/critical disease. Continuous variables were compared with Mann–Whitney or *t*-test and categorical variables were compared using chi-square and Fisher's exact. Statistical significance was set at $p < .05$. Multivariable logistic regression was performed including variables that were significantly different between the asymptomatic/mild and severe/critical groups in the univariate analysis. Analysis was performed using SPSS Version 25 (Armonk, NY, USA).

Results

Two hundred and thirty-three patients were included in the analysis. One hundred and forty-two women were tested because of provider suspicion for COVID or symptoms, before the implementation of universal screening on labor and delivery. One hundred and eighty-six (79.8%) had asymptomatic/mild disease and 47 (20.2%) developed severe/critical disease. 36.5% of patients were asymptomatic on presentation, 18.9% reported anosmia or ageusia, 17.6% dyspnea, and 36.1% fever. Two neonates had nasopharyngeal swabs positive for SARS-CoV-2. Eight women (3.4%) required intubation and there were no maternal deaths. Pregnancy outcomes included 191 (82.0%) live births, 4 (1.7%) stillbirths, 7 (3%) first trimester miscarriages or terminations, and 29 (12.4%) ongoing pregnancies at the time of analysis. Two women did not have pregnancy outcomes available. Two stillbirths, at 18 and 36 weeks, occurred in the setting of significant fetal anomalies. Another stillbirth at 27 weeks occurred in pregnancy also complicated by poorly controlled diabetes. All of these patients were asymptomatic for COVID-19 and diagnosed on universal screening. One stillbirth occurred at 36 weeks in a patient with mild COVID-19 in pregnancy with poorly controlled diabetes.

When women with asymptomatic/mild disease were compared to those with severe/critical disease, there were no differences in demographic characteristics, including race/ethnicity and insurance status (Table 1).

Table 1. Demographic characteristics of study population.

Demographic characteristics	Asymptomatic or mild disease ($N = 186$)	Severe or critical disease ($N = 47$)	*p*-Value
Age*	30 (9)	33 (8)	.11†
Race/ethnicity			.15§
Black	17 (9.1)	6 (12.8)	
Asian	3 (1.6)	2 (4.3)	
White	85 (45.7)	15 (31.9)	
Hispanic	59 (31.7)	21 (44.7)	
Other/not recorded	22 (11.8)	3 (6.4)	
Interpreter used	46 (24.7)	9 (19.1)	.42‖
Insurance status			.26‖
Medicaid	108 (58.1)	29 (61.7)	
Private	76 (40.9)	16 (34.0)	
Uninsured	2 (1.1)	2 (4.3)	
Parous	131 (70.4)	32 (68.1)	.75‖
BMI at time of diagnosis*	28.9 (6.7)	29.3 (7.3)	.92†
BMI $>$ 30 at time of diagnosis	77 (42.1)	20 (45.5)	.68‖

All data presented as *n* (%) unless otherwise stated.
*Data presented as median (IQR).
†Mann–Whitney test used.
§Fisher's exact test used.
‖Chi-square test used.

Table 2. Medical and pregnancy-specific comorbidities with possible impact on severity of COVID-19 disease.

Comorbidities	Asymptomatic or mild disease ($N = 186$)	Severe or critical disease ($N = 47$)	p-Value
Age > 35	55 (29.6)	16 (34.0)	.55‖
Age > 40	15 (8.1)	2 (4.3)	.54§
Trimester of diagnosis			<.001§
<14 weeks	13 (7)	2 (4.3)	
14–27 weeks	22 (11.8)	20 (42.6)	
28–40 weeks	151 (81.2)	25 (53.2)	
Current or former smoker	10 (5.4)	9 (19.6)	.004§
Chronic hypertension	4 (2.2)	4 (8.5)	.06§
Cardiac disease	3 (1.6)	3 (6.4)	.1§
Asthma or other respiratory condition	13 (7)	10 (21.3)	.01§
Thrombophilia	3 (1.6)	1 (2.1)	1.0§
Rheumatologic disorder	4 (2.2)	1 (2.1)	1.0§
Anemia	39 (21)	12 (25.5)	.50‖
Multiple gestation	2 (1.1)	0 (0)	1.0§
Pregestational diabetes	6 (3.2)	2 (4.3)	.66§
GDMA (1 or 2)	8 (4.3)	5 (10.6)	.15§
Preeclampsia	15 (8.1)	6 (12.8)	.32‖
Blood type	($N = 182$)	($N = 45$)	.76§
A	58 (31.9)	12 (26.7)	
B	29 (15.9)	9 (20)	
AB	8 (4.4)	1 (2.2)	
O	87 (47.8)	23 (51.1)	
Home medications used			
Plaquenil	3 (1.6)	1 (2.1)	1.0§
Steroids	4 (2.2)	2 (4.3)	.35§
Antihypertensive	3 (1.6)	2 (4.3)	.27§
Aspirin	27 (14.5)	11 (23.4)	.14‖

All data presented as n (%) unless otherwise stated.
*Data presented as median (IQR).
†Mann–Whitney test used.
§ Fisher's exact test used.
‖Chi-square test used.

The impact of medical and pregnancy comorbidities on the severity of COVID-19 disease was compared between the two groups (Table 2). Notably, women with severe/critical disease were more likely to have a history of current or former smoking, COVID-19 diagnosis in the 2nd trimester, and asthma or other respiratory condition. Women with obesity and hypertension were no more likely to develop severe/critical disease. There were no differences in blood type, medication use, or hypertensive disease of pregnancy between the groups. Women with severe/critical disease were more likely to have cesarean delivery (35.5 *vs.* 15.6%, $p < .01$) and preterm delivery <37 weeks (25.8 *vs.* 3.8%, $p < .01$).

Multivariable logistic regression was performed including trimester at diagnosis, history of smoking, and asthma or other respiratory condition. After adjustment, history of smoking remained significantly predictive of severe/critical disease [aOR 3.84 (95%CI 1.25–11.82), $p < .01$]. The overall model was significant (Hosmer-Lemeshow goodness of fit = 0.85), and correctly predicted 81% of the severe and critical cases.

Discussion

We found that pregnant women with a history of smoking, asthma, or other respiratory condition, and diagnosis in the second trimester of pregnancy were more likely to develop severe/critical disease. Other medical comorbidities, such as obesity and other pregnancy-associated comorbidities including preeclampsia and gestational diabetes were not associated with the development of severe/critical disease. While asthma and a history of smoking are risk factors for severe/critical disease outside of pregnancy and have been implicated in pregnancy as well [2,3,9], our data suggest a novel finding of increased severity of disease in pregnancy during the second trimester. There may be a biological basis for increased severity in the second trimester, such as changes in lung function and volume or immune system activation as pregnancy progresses, which should be investigated further. We did not find obesity to be a risk factor for severe/critical illness as has been seen in other studies [3,10–12], which may have been related to our small sample size or lower incidence of obesity in New York City. Of note, 33/47 women who developed severe/critical illness did not have a history of asthma or smoking, suggesting that there may be other risk factors for the development of severe/critical illness that has not yet been identified.

This study has several strengths. We included a large cohort of women with SARS-CoV-2 infection in

pregnancy and used manual chart review rather than ICD10 codes to obtain reliable and detailed information about patient clinical characteristics. Data were collected from three centers with a diverse patient population and payer mix, making our findings generalizable. We are limited by the relatively small cohort size, which may lead to an inability to detect some risk factors that could have contributed to severe/critical illness.

This study also had several limitations. Universal testing for SARS-CoV-2 was not available in the first weeks of data collection, and therefore only symptomatic women were tested initially. This may have increased the proportion of women with severe/critical illness in our cohort. The increased severity of disease in women diagnosed in the second trimester may have been due to selection bias, as universal screening likely led to an overrepresentation of asymptomatic women in the third trimester. Asymptomatic women or those with mild symptoms were likely not well-represented in our cohort since they were not screened in the first few weeks of the pandemic or were encouraged to remain at home. However, women who developed severe/critical COVID-19 disease in any trimester were included and therefore our evaluation of prediction of this level of disease should be robust.

Additionally, this study was performed based on patient data from early in the pandemic, when fewer treatments for severe and critical COVID-19 disease, such as remdesivir and dexamethasone were recommended. This may have contributed to the high rate of severe/critical disease (20.2%) seen in this cohort. Due to the testing strategy that was utilized, this rate should not be interpreted as the overall risk of developing severe/critical disease in pregnancy. However, the risk factors for the development of severe and critical diseases described here remain applicable.

Conclusions

In conclusion, we found that women infected with SARS-CoV-2 in pregnancy were more likely to develop severe or critical disease if they were diagnosed in the second trimester or had a history of smoking or respiratory disease. In our cohort, severity of disease was not impacted by obesity and age. Despite the rollout of multiple effective vaccines, pregnant women are less likely to be vaccinated and remain at risk for contracting COVID-19. The risk factors described here may be useful in counseling pregnant women on their individual risk of developing the severe or critical disease, and may help providers counsel women for vaccination during pregnancy.

Disclosure statement

The authors report no conflict of interest.

Author contributions

All authors contributed to the study conception and design. Data collection and analysis were performed by Megan E. Trostle, Meghana Limaye, Pooja Venkatesh, Meralis Lantigua Martinez, Lili Wei, Parita Sahani, Tracy B. Grossman, and Jessica A. Meyer. The first draft of the manuscript was written by Meghana Limaye and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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