Pregnant women with severe or critical COVID-19 have increased composite morbidity compared to non-pregnant matched controls

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PII: S0002-9378(20)31312-0

DOI: https://doi.org/10.1016/j.ajog.2020.11.022

Reference: YMOB 13603

To appear in: *American Journal of Obstetrics and Gynecology*

Received Date: 9 September 2020

Revised Date: 9 November 2020

Accepted Date: 11 November 2020

Please cite this article as: DeBolt CA, Bianco A, Limaye MA, Silverstein J, Penfield CA, Roman AS, Rosenberg HM, Ferrara L, Lambert C, Khoury R, Bernstein PS, Burd J, Berghella V, Kaplowitz E, Overbey JR, Stone J, Pregnant women with severe or critical COVID-19 have increased composite morbidity compared to non-pregnant matched controls, *American Journal of Obstetrics and Gynecology* (2020), doi: https://doi.org/10.1016/j.ajog.2020.11.022.

American Journal of Obstetrics & Gynecology

STATEMENT OF AUTHORSHIP

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Date: 9/8/2020 **Manuscript # (if available):** _____

Manuscript title: Pregnant women with severe or critical COVID-19 have increased composite morbidity compared to non-pregnant matched controls

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Authors may either sign the same form or submit individually

I am an author on this submission, have adhered to all editorial policies for submission as described in the Information for Authors, attest to having met all authorship criteria, and all potential conflicts of interest / financial disclosures appears on the title page of the submission.

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The authors report no conflicts of interest or financial disclosures.

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Word count:

Abstract: 473

Main text: 3822

Condensation

A case-control study comparing pregnant versus non-pregnant reproductive aged women with severe/critical COVID-19 to better understand the effect of pregnancy on the disease process.

Short Title: Severe and critical COVID-19 in pregnant vs. non-pregnant control women

AJOG at a Glance

A. Why was the study conducted?

To improve our understanding of how pregnancy impacts the clinical course of severe and critical COVID-19 in pregnant versus non-pregnant controls.

B. What are the key findings?

Pregnant women are more likely to experience the composite morbidity including death, need for intubation, ECMO, non-invasive positive pressure ventilation, as well as need for high flow nasal cannula supplementation when compared to the non-pregnant control group.

C. What does this study add to what is already known?

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

Abstract

Background: In March 2020, as community spread of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) became increasingly prevalent, pregnant women appeared to be equally susceptible to developing Coronavirus Disease 2019 (COVID-19). While the disease course usually appears mild, severe and critical COVID-19 appears to lead to significant morbidity including ICU admission with prolonged hospital stay, intubation, mechanical ventilation and even death. Although there are recent reports regarding the impact of COVID-19 on pregnancy, information regarding the severity of COVID-19 in pregnant versus non-pregnant women remains unknown.

Objective: We aim to describe the outcomes of severe and critical COVID-19 infection in pregnant versus non-pregnant reproductive aged women.

Study Design: This is a multi-center retrospective case-control study of women with laboratory confirmed SARS-CoV-2 infection hospitalized with severe or critical COVID-19 in four academic medical centers in NYC and one in Philadelphia between March 12 and May 5, 2020. The cases consist of pregnant women admitted specifically for severe or critical COVID-19 and not for obstetric indication. The controls consist of reproductive aged, non-pregnant women admitted for severe or critical COVID-19. The primary outcome is a composite morbidity including: death, need for intubation, extracorporeal membrane oxygenation (ECMO), non-invasive positive pressure ventilation or need for high flow nasal cannula oxygen supplementation. Secondary outcomes include ICU admission, length of stay, need for discharge to long term acute care facility and discharge with home oxygen requirement.

Results: Thirty-eight pregnant women with SARS-CoV-2 polymerase chain reaction (PCR) confirmed infection were admitted to five institutions specifically for COVID-19, 29 (76.3%) meeting criteria for severe disease and 9 (23.7%) meeting criteria for critical disease. The mean age and BMI were significantly higher in the non-pregnant control group. The non-pregnant cohort was also noted to have increased frequency of pre-existing medical comorbidities, including diabetes, hypertension and coronary artery disease. Pregnant women were more likely to experience the primary outcome when compared to the non-pregnant control group (34.2% vs. 14.9%, p=0.03, adjusted OR 4.6 [95% CI 1.2-18.2]). Pregnant patients experienced higher rates of ICU admission (39.5% vs. 17.0%, p<0.01, adjusted OR 5.2 [95% CI 1.5-17.5]). Among pregnant women that underwent delivery, 72.7% occurred via cesarean delivery and mean gestational age at delivery was 33.8 ±5.5 weeks in patients with severe disease and 35 ±3.5 weeks in patients with critical COVID-19.

Conclusions: Pregnant women with severe and/or critical COVID-19 are at increased risk for certain morbidities when compared to non-pregnant controls. Despite the higher comorbidities of diabetes and hypertension in the non-pregnant controls, the pregnant cases were at increased risk for composite morbidity, intubation, mechanical ventilation and ICU admission. These findings suggest that pregnancy may be associated with a worse outcome in women with severe and critical COVID-19. Our study suggests that similar to other viral infections such as SARS-CoV and MERS-CoV, pregnant women may be at risk for greater morbidity and disease severity.

Keywords: coronavirus, critical disease, disease course, intensive care, intubation, maternal morbidity, pandemic, pregnancy, preterm birth, respiratory distress syndrome, SARS-CoV-2, SARS, severe disease

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 resulting in 21,294,845 infected people and 761,779 deaths worldwide at the time of this writing.[1] In the United States alone, 5,258,565 cases have been reported with 167,201 deaths.[1] Based on 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 non-pregnant population, mild (81%), severe (14%) or critical (5%).[3]

SARS-CoV-2 appears to cause serious pulmonary manifestations, including pneumonia, which is the most prevalent non-obstetric infection occurring in pregnancy,[4] acute respiratory distress syndrome, pervasive micro-emboli and coagulation perturbations,[5] therefore increased morbidity and mortality among pregnant women is a reasonable concern. As with other infectious diseases, the normal maternal physiologic changes that accompany pregnancy, including hypercoagulability, altered cell-mediated immunity[6] and changes in pulmonary function, resulting in 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. Changes to the immune and respiratory systems that occur during pregnancy can increase vulnerability to severe infection and hypoxic compromise. Common symptoms in pregnancy, such as physiologic dyspnea, may delay diagnosis when pathologic dyspnea secondary to COVID-19 is not distinguished.[8]

There is a paucity of information regarding outcomes of pregnant women with COVID-19 compared to non-pregnant women. A report from the CDC found that hospitalization was substantially higher among SARS-CoV-2 infected pregnant women compared to non-pregnant women. Pregnant women were more frequently admitted to the ICU (1.5% vs. 0.9%) and 0.5% of pregnant women required mechanical ventilation when compared to 0.3% of non-pregnant women. Sixteen deaths (0.2%) were reported among pregnant women and 208 (0.2%) among non-pregnant women.[9] However in this report, data was not available to distinguish between hospitalizations for COVID-19 related illness versus admission for pregnancy-related conditions. Knowledge of the course of disease in pregnant versus non-pregnant women is essential to better understand the risk for our pregnant population. The aim of this study was to compare the clinical outcomes of severe and critical COVID-19 in pregnant versus non-pregnant 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 is a multi-center case-control study of women with polymerase chain reaction (PCR) confirmed SARS-CoV-2 infection who met admission criteria for severe and/or critical COVID-19. We explored the clinical course and outcomes of pregnant women admitted with severe and critical COVID-19 compared to non-pregnant control women of reproductive age. Data was collected on patients admitted to four hospitals in New York City and one in Philadelphia between March 12, 2020 and May 5, 2020. Our primary outcome was a composite morbidity including death, need for intubation,

extracorporeal membrane oxygenation (ECMO), non-invasive positive pressure ventilation, including bilevel positive airway pressure (BiPAP) and continuous positive airway pressure (CPAP), as well as need for high flow nasal cannula supplementation. Other treatment interventions, including medications used and use of prone positioning were also collected. Secondary outcomes included ICU admission, length of stay, frequency of discharge to home with oxygen supplementation and frequency of discharge to long term care facility. During admission, delivery was performed for the usual obstetric indications, however beyond this, decision for delivery was up to the individual providers' discretion.

Inclusion criteria were defined as pregnant and non-pregnant women between 18-50 years of age meeting admission criteria for diagnosis of severe or critical COVID-19 as defined by the WHO and Chinese Center for Disease Control and Prevention. Severe COVID-19 was defined as dyspnea (patient reported), respiratory rate of ≥30 breaths per minute, blood oxygen saturation ≤ 93% on room air, partial pressure of arterial oxygen to fraction of inspired oxygen <300, and/or findings consistent with pneumonia on chest x-ray.[13-15] Critical COVID-19 was defined as respiratory failure requiring intubation or mechanical ventilation, septic shock, and/or multiple organ dysfunction or failure.[13-15] Respiratory failure was defined as a need for invasive mechanical ventilation. Septic shock was defined as need for vasopressors to maintain mean arterial pressure $\geq$ 65 and serum lactate >2 mmol/L despite sufficient volume resuscitation along with ≥2 Sepsis-related Organ Failure Assessment (SOFA) criteria which include: decline in partial pressure of oxygen/fraction of inspired oxygen, decline in platelets, rising bilirubin, decline in MAP, decline in Glasgow Coma Scale (GCS), and

rise in serum creatinine.[16] Multiple organ dysfunction or failure was defined by the presence of at least 2 of the following: renal impairment or failure (defined as a threefold increase in baseline creatinine or need for dialysis[17]), liver failure (defined as INR >1.5), diagnosis of refractory hypoglycemia by the treating institution, or hepatic encephalopathy.[18] A test result was considered positive for SARS-CoV-2 infection if there was presence of SARS-CoV-2 on quantitative reverse transcription polymerase chain reaction (qRT-PCR) analysis of specimens acquired from the respiratory tract in the form of a nasopharyngeal swab. This method of confirming SARS-CoV-2 infection as well as the criteria used to define severe COVID-19 and critical COVID-19 were uniform across all institutions. We excluded patients with comorbidities that are associated with an immunocompromised state including those with: active malignancy, history of transplant, history of developmental delay, cerebral palsy, Trisomy 21 or other known aneuploidy. Regardless of clinical suspicion, women with inconclusive or negative laboratory testing for SARS-CoV-2 were excluded. The variables in the obstetric comorbidity index validated for use on labor and delivery to predict the risk of severe maternal morbidity were collected.[19] Severe maternal morbidity was classified according to the guidelines of the American College of Obstetricians and Gynecologists (ACOG), Society for Maternal Fetal Medicine (SMFM) and Centers for Disease Control (CDC).[20] Per the CDC National Center for Health Statistics, preterm birth rate was defined as singleton livebirth <37 weeks and early preterm as <34 weeks of gestation.

The institutional review board at each institution approved this study. Data use agreements were obtained for collaboration between sites. Data from each medical center's electronic medical record (EMR) were abstracted by means of a Research

Electronic Data Capture (REDCap) form. De-identified data were then merged into one dataset managed by the primary author at Mount Sinai Hospital. We obtained data on demographics, socio-economic factors, presenting signs and symptoms, as well as results of laboratory and radiologic testing performed. When applicable, delivery data including maternal complications and neonatal outcomes were obtained. Relevant COVID-19 related clinical information including disease severity was also collected.

Cases were defined as pregnant women requiring admission for severe or critical COVID-19. Controls were defined as non-pregnant 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 range (18-30, 31-40 and 41-50), BMI class (under 30, class I obesity [30-34.9], class II obesity [35-39.9], class III obesity [40 and greater]) and severity of illness (severe [dyspnea, O2 sat less than or equal to 93%, RR greater than or equal to 30, imaging with >50% lung involvement] vs. critical [respiratory failure, shock, multi-organ dysfunction]). However, as only 96 of the 132 patients were successfully matched, covariate adjusted analysis was conducted without accounting for matching.

Demographic, pregnancy, and neonatal characteristics were compared between groups using T-tests or Wilcoxon-Rank Sum tests for continuous measures and Chi-square or Fisher's exact tests for 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, pre-existing cardiac disease (hypertension, coronary artery disease [CAD], hyperlipidemia [HLD], valvular disease and/or congenital heart disease) and pre-existing diabetes. The secondary outcomes were evaluated

using logistic or linear regression adjusted for age, BMI, severity of illness, pre-existing cardiac disease and pre-existing diabetes. Hospital length of stay was log-transformed prior to analysis. In a subgroup analysis, the primary and secondary outcomes were also assessed only for those patients who met criteria for severe COVID-19 on admission using a logistic regression model of the composite outcomes, adjusted for age, BMI, pre-existing cardiac disease and pre-existing diabetes. The outcomes were not assessed for those patients meeting admission criteria for critical COVID-19 alone because of the small number of patients available for analysis. Available pregnancy and neonatal outcomes were presented descriptively based upon severity of illness. Presented p-values were two sided and values <0.05 were considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Thirty-eight pregnant women with SARS-CoV-2 PCR confirmed infection were admitted to five institutions for severe or critical COVID-19. Thirteen 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 criteria for severe disease and 9 (23.7%) met criteria for critical disease. Ninety-four reproductive aged, non-pregnant patients admitted for severe or critical COVID-19 were identified as controls across institutions. Twenty-two (23.4%) women admitted to NYU Langone Health, 30 (31.9%) patients at Mount Sinai Hospital, 21 (22.3%) patients at Elmhurst Hospital, 15

(16.0%) patients at Montefiore Medical Center and 6 (6.4%) patients at Thomas Jefferson University Hospital comprised the control cohort, 80 (85.1%) meeting criteria for severe disease and 14 (14.9%) meeting criteria for critical disease.

Patient demographics are outlined in Table 1. The mean age in years was significantly higher in the non-pregnant controls compared to the pregnant cases (37.9±6.7vs. 34.7±4.3 years, p<0.01, Table 1). Mean BMI on admission was also higher in the non-pregnant controls compared to the pregnant cases (33.4±5.2 vs. 31.7±6.6 kg/m^2, p=0.15, Table 1). Pre-existing diabetes and pre-existing cardiac disease were both noted to be significantly higher in the control group (Table 1).

Pregnant women were more likely to experience the composite morbidity including death, need for intubation, ECMO, non-invasive positive pressure ventilation, including BiPAP and CPAP, as well as need for high flow nasal cannula supplementation when compared to the non-pregnant control group (34.2% vs. 14.9%, p=0.03, aOR 4.2 [95% CI 1.2-18.2], Table 2a). A greater percentage of pregnant women received mechanical ventilation compared to non-pregnant controls (26.3% vs. 10.6%, p=0.22, aOR 3.3 [95% CI 0.5-21.1], Table 2a). However, death and 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, while death occurred in 3 of the 94 non-pregnant women. Hospital length of stay and ICU length of stay were similar between groups. However, the rate of ICU admission was higher in pregnant patients versus non-pregnant controls (39.5% vs. 17.0%, p <0.01, aOR 5.2 [95% CI 1.5-17.5], Table 3a). In Tables 2b and 3b, the primary and secondary outcomes are presented for the

patients meeting admission criteria for severe disease alone. In those with severe COVID-19, the pregnant women remained more likely to experience the composite morbidity compared to the non-pregnant control group, although this finding was not statistically significant (13.8% vs. 5.0%, p=0.09, Table 2b). Pregnant women admitted with severe COVID-19 had higher rates of ICU admission (20.7% vs. 7.5%, p=0.03, aOR 4.9 [95% CI 1.2-19.5], Table 3b) and a longer hospital length of stay (7.3±7.8 vs. 5.3± 4.1, p=0.04, aOR 0.7 [95% CI 0.5-1], Table 3b). While there were no statistically significant differences in other treatment interventions between groups (Table 3c), there was a trend toward increased use of antivirals, including lopinavir-ritonavir, oseltamivir and remdesivir in the pregnant cohort.

Pregnancy outcomes and neonatal outcomes are outlined in Tables 4 and 5. At the time of analysis, 22 of 38 (58%) patients underwent delivery. The majority of women were delivered via cesarean, regardless of severity of disease. Worsening maternal status was most often noted to be the indication for delivery in patients with both severe and critical illness (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 for the critical cases.

Discussion

Principal findings

In this case-control study comparing pregnant versus reproductive age non-pregnant women admitted with severe or critical COVID-19, pregnant women were more likely to experience the composite morbidity compared to non-pregnant controls.

Our sample size was not large enough to make conclusions regarding mortality among pregnant patients and non-pregnant control women.

Results

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

In the subset of patients admitted with severe disease, pregnant women experienced a trend toward increased composite morbidity and a significant increase in ICU admission and longer hospital length of stay compared to the non-pregnant control group. While analysis comparing pregnant women to non-pregnant 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 Appendix Tables I and II. The lack of statistical

significance for the primary outcome in the severe disease subset is most likely due to a combination of small sample size and removal of those patients with critical COVID-19, all of which experienced the composite morbidity.

Among the pregnant women who delivered during their hospitalization, the majority underwent cesarean delivery (72.7%) and delivered preterm (68.2%). Of those that delivered preterm, one third occurred prior to 34 weeks gestation. Among those that delivered, there was only one 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 COVID-19, pregnancy is associated with an increased risk for ICU admission, as well as intubation and mechanical ventilation, but there was no evidence of an increased mortality risk, however event rates and sample sizes were too low to substantiate this. Our findings are in agreement with a recent study in Sweden, including 53 reproductive aged women admitted to the ICU, 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 increased risk of ICU admission for laboratory confirmed SARS-CoV-2 (RR 2.59; 95% CI 1.13-5.91).[22] Blitz et al. did not find an increased risk of 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 to 332 non-pregnant 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/or critical disease, we did in fact see an increased rate of ICU admission and need for mechanical ventilation. While the recent CDC MMWR from June 26, 2020, did not distinguish 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 increased risk for surrogate markers of disease severity.[9]

Clinical implications

A current challenge lies in the prediction of patients presenting with COVID-19 infection who will progress to develop critical disease. Consistently across studies in non-pregnant populations, the risk of adverse outcomes increases with age and underlying illness, and the majority of hospitalized patients are men.[24] The most prevalent comorbidities associated with the severity of COVID-19 in the non-pregnant population are hypertension and diabetes, followed by cardiovascular disease and respiratory disease.[25] When compared to non-pregnant women with mild COVID-19, those with severe disease, the pooled OR for hypertension was 2.36 (95% CI: 1.46–3.83), respiratory disease system was 2.46 (95% CI: 1.76–3.44) and cardiovascular disease was 3.42 (95% CI: 1.88–6.22).[19] Patients requiring ICU care were more likely to have comorbid hypertension, cardiovascular disease, diabetes, and cerebrovascular disease[26-28]. Obesity with a BMI >30 was also found to be a risk factor for disease severity in 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 to

hypoxemic respiratory failure leading to increased morbidity in pregnancy.[8] Though pregnant women are often young with a significantly lower frequency of pre-existing 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 age 50 admitted with severe and/or critical COVID-19. At baseline our non-pregnant cohort had increased rates of pre-existing 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 if pregnancy alone places patients at increased risk for developing severe or critical COVID-19, in order to guide future management for our obstetric population. Studies with a larger cohort of patients will be needed in order to determine if mortality is higher among pregnant women with COVID-19 compared to the non-pregnant population. As long term follow up occurs and more data is acquired, studies focusing on pregnancy and neonatal outcomes could be performed in order 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 COVID-19 in pregnant women as they compare to non-pregnant reproductive aged controls, all of whom were admitted specifically for COVID-19. While management of COVID-19 varied across institutions, the multi-center nature of our

study resulted in a highly diverse patient population in relation to demographics including race, ethnicity and other social determinants of health. We are unable to currently report on long term pregnancy or neonatal outcomes at this time.

Our study has several limitations. While a control group was assessed, we noted difficulty in the ability to match the cases and controls as initially planned. We sought to match based upon age range (18-30, 31-40, 41-50), BMI class (under 30, class I obesity [30-34.9], class II obesity [35-39.9], class III obesity [40 and greater]) and admission disease severity, critical vs. severe. All patients were, however, matched based upon reproductive age range between 18 and 50 years. We also noted difficulty in finding a 3:1 ratio of controls to cases, as many non-pregnant reproductive aged females did not meet inclusion criteria for severe or critical COVID-19 or hospital admission. Overall, our pregnant cases were younger and had a lower BMI compared to non-pregnant controls. While, it is well documented that persons of non-White race have worse outcomes, there was no statistically significant difference in distribution of race and ethnicity between our two cohorts. We are unable to comment on differences in race and ethnicity in our current study and how this difference has impacted the primary outcome. This data is 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 non-pregnant controls, which is unfortunately, a limitation of how race and ethnicity data is captured and reported in the EMR.

An inherent bias may exist, as pregnant women at baseline may be more likely to be admitted to the ICU compared to non-pregnant women with the same disease severity. In order to sufficiently oxygenate the uteroplacental unit, a lower threshold to

initiate oxygen supplementation may occur. Pregnancy may lead to increased rates of high flow nasal cannula and non-invasive positive pressure ventilation. However, the significant increase in mechanical ventilation and intubation is unlikely to be subject to bias based on pregnancy status. Our study is also limited by a small sample size, thus we cannot conclude about the difference in mortality among pregnant and non-pregnant women. Data regarding maternal mortality and COVID-19 in the literature is conflicting. While some case series report lower rates of mortality in pregnant women, others report rates of mortality similar to rates previously seen in SARS and MERS.[31,32]

A recent systematic review by Allotey et al. including 11,432 pregnant and recently postpartum women describes an increased risk of ICU admission and mechanical ventilation among those with confirmed or suspected COVID-19. In this review, the control group consisted of non-pregnant reproductive aged women and pregnant women without COVID-19[33]. Similar to the MMWR from the CDC, reason for admission was not distinguished in these patients, including patients admitted for delivery and incidentally found to have SARS-CoV-2 documented infection. A strength of our study is that all participants analyzed were admitted to the hospital specifically for COVID-related disease and met criteria for severe or critical COVID-19 upon admission. The difficulty in attempting to match our cohort, speaks to the lack of non-pregnant young female patients being admitted for COVID-19, further suggesting that pregnancy may be a contributing factor for developing severe or critical disease.

Conclusions

Pregnant women with severe and critical COVID-19 are at increased risk for morbidity when compared to reproductive aged non-pregnant controls. The hospital and ICU lengths of stay are similar between our cohorts. Pre-existing comorbidities, such as hypertension, diabetes and coronary artery disease were increased in our non-pregnant controls, along with increased age and BMI, however despite these differences, pregnant women with severe and critical COVID-19 remained at increased risk of ICU admission, need for 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/or critical COVID-19 infection.[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 likely resultant 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 disease on the potential for progression to a severe or critical stage.

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Table 1. Maternal Demographics by Group

	Pregnant Cases (n=38)			Non-Pregnant Controls (n=94)			P-Value
	N	Mean ±SD	Range	N	Mean ±SD	Range	
Maternal age (years)	38	34.7 ± 4.3	25-42	94	37.9 ± 6.7	23-50	<0.01
BMI at admission (kg/m2)	38	31.7 ± 5.2	20.2-41	94	33.4 ± 6.6	22-55	0.15
	No. / No. observed (%)			No. / No. observed (%)			
Race/Ethnicity							0.16
Non-Hispanic White	9/38 (23.7)			9/94 (9.6)			
Non-Hispanic Black	7/38 (18.4)			13/94 (13.8)			
Hispanic/Latina	15/38 (39.5)			35/94 (37.2)			
Asian	3/38 (7.9)			8/94 (8.5)			
American Indian/Alaska Native	0/38 (0)			1/94 (1.1)			
Other	2/38 (5.3)			11/94 (11.7)			
Unknown/Not Recorded	2/38 (5.3)			17/94 (18.1)			
Insurance Type							0.41
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)			2/94 (2.1)			
Uninsured/Self-pay	2/38 (5.3)			1/94 (1.1)			
Tobacco Use							0.23
Current Smoker	0/38 (0)			0/94 (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 on Admission							0.23
Severe	29/38 (76.3)			80/94 (85.1)			
Critical	9/38 (23.7)			14/94 (14.9)			
Pre-existing Conditions*							
Pre-existing pulmonary disease	4/38 (10.5)			21/94 (22.3)			0.12
Pre-existing cardiac disease	4/38 (10.5)			27/94 (28.7)			0.03
Pre-existing diabetes	4/38 (10.5)			26/94 (27.7)			0.03

*Pulmonary disease is defined as asthma, obstructive sleep apnea (OSA), chronic obstructive pulmonary disease (COPD), and/or chronic bronchitis. Cardiac disease is defined as hypertension (HTN), coronary artery disease (CAD), hyperlipidemia (HLD), valvular disease, and/or congenital heart disease (CHD). Diabetes is defined as type 1 and type 2 diabetes mellitus (T1DM, T2DM).

Table 2a. Primary Outcome by Group

	Pregnant Cases (n=38)	Non-Pregnant Controls (n=94)	Adjusted P-Value	Adjusted OR (95% CI)
	No. / No. observed (%)	No. / No. observed (%)		
Composite Morbidity*	13/38 (34.2)	14/94 (14.9)	0.03	4.6 (1.2-18.2)
High flow nasal cannula (HFNC)	8/38 (21.1)	6/94 (6.4)	-	-
BiPAP/CPAP	3/38 (7.9)	4/94 (4.3)	-	-
Intubation/mechanical ventilation	10/38 (26.3)	10/94 (10.6)	0.22	3.3 (0.5-21.1)
ECMO	0/38 (0)	0/94 (0)	-	-
Death	0/38 (0)	3/94 (3.2)	-	-

*Composite morbidity includes need for high flow nasal cannula supplementation (HFNC), non-invasive positive pressure ventilation (BiPAP/CPAP), intubation/mechanical ventilation, extracorporeal membrane oxygenation (ECMO), and death.

Table 2b. Primary Outcome by Group among Patients with Severe Disease

	Pregnant Cases (n=29)	Non-Pregnant Controls (n=80)	Adjusted P-Value	Adjusted OR (95% CI)
	No. / No. observed (%)	No. / No. observed (%)		
Composite Morbidity*	4/29 (13.8)	4/80 (5.0)	0.09	3.8 (0.8-18.1)
High flow nasal cannula (HFNC)	2/29 (6.9)	2/80 (2.5)	-	-
BiPAP/CPAP	1/29 (3.5)	2/80 (2.5)	-	-
Intubation/mechanical ventilation	2/29 (6.9)	1/80 (1.3)	-	-
ECMO	0/29 (0)	0/80 (0)	-	-
Death	0/29 (0)	0/80 (0)	-	-

*Composite morbidity includes need for high flow nasal cannula supplementation (HFNC), non-invasive positive pressure ventilation (BiPAP/CPAP), intubation/mechanical ventilation, extracorporeal membrane oxygenation (ECMO), and death.

Table 3a. Secondary Outcomes by Group

	Pregnant Cases (n=38)				Non-Pregnant Controls (n=94)				Adjusted P-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 (days)	38	8.7 ± 8.1	5.5 (4-10)	2-42	94	7.1 ± 8.2	5 (3-9)	1-53	0.08	0.8 (0.6-1.0)**
ICU length of stay (days)*	15	6.4 ± 6.9	4 (1-9)	0-26	16	9.3 ± 11.8	5.5 (2-12)	0-45	-	-
	No. / No. observed (%)				No. / No. observed (%)					Adjusted OR (95% CI)
ICU Admission	15/38 (39.5)				16/94 (17.0)				<0.01	5.2 (1.5-17.5)
Discharge Disposition									0.77	
Home w/o O_2 requirement	35/38 (92.1)				77/94 (81.9)					Ref.
SNF/LTAC or home w/ O_2 or other req.	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)				0.57	1.4 (0.4-5.0)
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)				3/94 (3.2)					
Shock	2/38 (5.3)				4/94 (4.3)					
Other morbidity	0/38 (0)				3/94 (3.2)					

*ICU length of stay is only calculated for those 31 patients who were admitted to the ICU (15 pregnant cases and 16 non-pregnant controls).

**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.

Table 3b. Secondary Outcomes by Group among Patients with Severe Disease

	Pregnant Cases (n=29)	Non-Pregnant Controls (n=80)	Adjusted P-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 (days)	29	7.3 ± 7.8	5 (4-6)	2-42	80	5.3 ± 4.1	4 (3-7)	1-23	0.04	0.7 (0.5-1.0)**
ICU length of stay (days)*	6	6.2 ± 10.1	1 (1-8)	0-26	6	2.5 ± 2.9	1.5 (1-3)	0-8	-	-
	No. / No. observed (%)				No. / No. observed (%)					Adjusted OR (95% CI)
ICU Admission	6/29 (20.7)				6/80 (7.5)				0.03	4.9 (1.2-19.5)
Discharge Disposition									0.98	
Home w/o O_2 requirement	27/29 (93.1)				70/80 (87.5)					Ref.
SNF/LTAC or home w/ O_2 or other req.	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)				0.72	1.3 (0.3-6.2)
Sepsis	0/29 (0)				3/80 (3.8)					
Cardiac arrest	1/29 (3.5)				0/80 (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)				2/80 (2.5)					
Shock	0/29 (0)				0/80 (0)					
Other morbidity	0/29 (0)				2/80 (2.5)					

*ICU length of stay is only calculated for those 12 patients who were admitted to the ICU (6 pregnant cases and 6 non-pregnant controls).

**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.

Table 3c. Other Intervention by Group

	Pregnant Cases (n=38)	Non-Pregnant Controls (n=94)	P-Value
	No. / No. observed (%)	No. / No. observed (%)	
Hydroxychloroquine	34/38 (89.5)	76/94 (80.9)	0.23
Azithromycin	25/38 (65.8)	56/94 (59.6)	0.51
Antivirals*	7/38 (18.4)	6/94 (6.4)	0.05
Tocilizumab	3/38 (7.9)	4/94 (4.3)	0.41
Systemic steroids**	4/38 (10.5)	15/94 (16.0)	0.42
Convalescent plasma	2/38 (5.3)	4/94 (4.3)	>0.99
Therapeutic anticoagulation***	8/38 (21.1)	20/94 (21.3)	0.98
Prophylactic anticoagulation***	24/38 (63.2)	61/94 (64.9)	0.85
Prone positioning	5/38 (13.2)	7/94 (7.4)	0.30

*Antivirals included remdesivir, lopinavir-ritonavir, oseltamivir
**Systemic steroids included prednisone, methylprednisolone, dexamethasone
***Anticoagulation included unfractionated heparin, low molecular weight heparin, fondaparinux, apixaban

Table 4. Pregnancy Outcomes by Case Severity

	Pregnant Severe Cases (n=29)	Pregnant Critical Cases (n=9)
	No. / No. observed (%)	No. / No. observed (%)
Mode of delivery*		
Cesarean delivery	10/15 (66.7)	6/7 (85.7)
Vaginal delivery	5/15 (33.3)	1/7 (14.3)
Indication for delivery*		
Maternal status	9/15 (60.0)	6/7 (85.7)
Fetal status	1/15 (6.7)	0/7 (0)
Obstetric indications	5/15 (33.3)	1/7 (14.3)
Prenatal Complications		
Pregnancy related hypertensive disorders	0/29 (0)	1/9 (11.1)
Gestational diabetes	1/29 (3.4)	0/9 (0)
Other prenatal complications	4/29 (13.8)	0/9 (0)
Obstetric Complications		
Hypertensive disorder of pregnancy	2/29 (6.9)	1/9 (11.1)
Presumed IAI	1/29 (3.4)	0/9 (0)
Preterm labor	1/29 (3.4)	0/9 (0)
Other obstetric complications	2/29 (6.9)	0/9 (0)
Maternal Morbidity		
Postpartum hemorrhage	0/29 (0)	1/9 (11.1)
Blood product transfusion	0/29 (0)	1/9 (11.1)
Other Outcomes		
Fetal demise*	2/15 (13.3)	0/7 (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/HTN	2/29 (6.9)	0/9 (0)

*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).

686 *Table 5*. Neonatal Outcomes by Case Severity

	Neonates of Severe Cases (n=15)				Neonates of Critical Cases (n=7)			
	N	Mean ±SD	Median (IQR)	Range	N	Mean ±SD	Median (IQR)	Range
Gestational age at delivery (weeks)	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
Birth weight (grams)	15	2307.7 ±889.7	2530 (1705-3065)	65-3315	7	2495 ±774.2	2485 (2110-3230)	1160-3500
NICU length of stay (days)*	4	15.0 ±15.3	11 (3-27)	3-35	4	7.0 ±3.2	6.5 (4.5-9.5)	4-11
	No. / No. observed (%)				No. / No. observed (%)			
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)				0/7 (0)			

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

689 Appendix.
690
691 *Appendix Table I*. Primary Outcome by Group among Patients with Critical Disease

	Pregnant Cases (n=9)	**Non-Pregnant Controls (n=14)**
	No. / No. observed (%)	No. / No. observed (%)
Composite Morbidity*	9/9 (100)	10/14 (71.4)
High flow nasal cannula (HFNC)	6/9 (66.7)	4/14 (28.6)
BiPAP/CPAP	2/9 (22.2)	2/14 (14.3)
Intubation/mechanical ventilation	8/9 (88.9)	9/14 (64.3)
ECMO	0/9 (0)	0/14 (0)
Death	0/9 (0)	3/14 (21.4)

692 *Composite morbidity includes need for high flow nasal cannula supplementation (HFNC), non-invasive
693 positive pressure ventilation (BiPAP/CPAP), intubation/mechanical ventilation, extracorporeal membrane
694 oxygenation (ECMO), and death.
695
696 *Appendix Table II*. Secondary Outcomes by Group among Patients with Critical Disease

	Pregnant Cases (n=29)				**Non-Pregnant Controls (n=80)**			
	N	Mean ±SD	Median (IQR)	Range	N	Mean ±SD	Median (IQR)	Range
Length of Stay								
Hospital length of stay (days)	9	13.3 ± 7.9	12 (6-21)	4-25	14	17.5 ± 15.7	13 (7-25)	2-53
ICU length of stay (days)*	9	6.6 ± 4.2	7 (4-9)	1-13	10	13.4 ± 13.3	9.5 (5-17)	2-45
	No. / No. observed (%)				No. / No. observed (%)			
ICU Admission	9/9 (100)				10/14 (71.4)			
Discharge Disposition								
Home w/o O_2 requirement	8/9 (88.9)				7/14 (50)			
SNF/LTAC or home w/ O_2 or other req.	1/9 (11.1)				4/14 (28.6)			
Death	0/9 (0)				3/14 (21.4)			
Morbidity During Admission								
Any Morbidity	9/9 (100)				11/14 (78.6)			
Sepsis	2/9 (22.2)				4/14 (28.6)			
Cardiac arrest	0/9 (0)				3/14 (21.4)			
ARDS	5/9 (55.6)				6/14 (42.9)			
Ventilation	8/9 (88.9)				7/14 (50)			
Tracheostomy	2/9 (22.2)				1/14 (7.1)			
Blood product transfusion	1/9 (11.1)				0/14 (0)			
AKI	0/9 (0)				1/14 (7.1)			
Shock	2/9 (22.2)				4/14 (28.6)			
Other morbidity	0/9 (0)				1/14 (7.1)			

697 *ICU length of stay is only calculated for those 19 patients who were admitted to the ICU (pregnant cases
698 and 10 non-pregnant controls).
699 **Hospital length of stay was log transformed and modeled using linear regression. The beta coefficient
700 for cases was exponentiated to estimate the ratio of geometric means.