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## **COVID-19 in Pregnancy: Occupations with Higher Density of Population Exposure Associated with More Severe Disease**

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Running Head Title: Occupational Risk and COVID-19 in Pregnancy

## Clinical Significance

This study describes clinical presentations and risk factors for disease severity for individuals diagnosed with SARS-CoV-2 infection during pregnancy. Increased age and occupations with high intensity contact with others (including healthcare work) were found to be associated with more severe COVID-19 infection.

### Abstract:

**Objective:** To define the symptomatology of SARS-CoV-2 infection in pregnancy and associations between occupation, sociodemographic factors, and comorbidities with the severity of COVID-19 disease in pregnancy in all trimesters, regardless of hospitalization.

**Methods:** We studied a retrospective cohort of a public health surveillance sample of persons with COVID-19 infection diagnosed during pregnancy. Data was collected March 2020-August 2020 regarding symptoms, disease severity, comorbidities, obstetric history, and occupation.

**Results:** 163 individuals were identified. Constitutional (64%) and lower respiratory symptoms (61%) were most common. Seventeen individuals (13.6%) were hospitalized, and one person (0.7%) died due to COVID-19. Risk factors for severe disease were age and an occupation that had high intensity exposure to people.

**Conclusions:** Occupational exposure is a risk factor for severe COVID-19 disease in pregnancy, justifying policy measures to ensure protection of this vulnerable population.

**Keywords:** COVID-19; SARS-CoV-2; Pregnancy; Occupation; Health Personnel; Symptomatology

## Introduction

COVID-19 (SARS-CoV-2) infection was first described in December 2019 in Wuhan, Hubei Province, China<sup>1</sup>, and was declared a global pandemic by WHO on March 11, 2020.<sup>2</sup> To date, there have been over 170 million cases and 3.8 million deaths due to COVID-19 worldwide.<sup>3</sup>

Considering the vulnerability of pregnant persons to severe complications of other viral infections, especially other coronaviruses (SARS and MERS, in which maternal case-fatality rate was 25% and 27%, respectively)<sup>4,5</sup>, characterizing the symptomatology and factors associated

with the severity of maternal COVID-19 disease is a public health priority. Early in the pandemic, there were case series describing the clinical course in hospitalized pregnant patients, with reports in which the majority of subjects had mild to moderate disease<sup>6,7,8</sup> and a case series of 9 pregnant women in Iran, of which 7 expired.<sup>9</sup> An analysis of 400,000 women of reproductive age with symptomatic COVID-19 infection from Centers for Disease Control (CDC) data, demonstrated a higher likelihood of intensive care unit admission, extracorporeal membrane oxygenation (ECMO), mechanical ventilation, and mortality in pregnant versus non-pregnant women.<sup>10</sup> A meta-analysis that included 77 studies of pregnant women with SARS-CoV-2 infection demonstrated increased odds of Intensive Care Unit (ICU) admission, mechanical ventilation, and extracorporeal membrane oxygenation (ECMO) in pregnant women with COVID-19 infection versus non-pregnant women of reproductive age with COVID-19 infection.<sup>11</sup> This meta-analysis also demonstrated increased odds of all-cause mortality, ICU admission, preterm birth (<37 weeks), stillbirth, and admission of the neonate to the neonatal intensive care unit in pregnant women with COVID-19 infection as compared to pregnant women without COVID-19 infection.<sup>11</sup> With the exception of the CDC study, these studies primarily included hospitalized women and women in the second or third trimesters.<sup>6-9,11</sup> There are sparse data outlining the symptoms and clinical course of COVID-19 in the first trimester in the literature, and most studies describe only hospitalized women.

The goal of this retrospective cohort study was to identify occupational, sociodemographic, and clinical characteristics associated with COVID-19 disease severity, and to describe symptomatology and disease severity of in all trimesters of pregnancy.

## **Methods**

This was a retrospective cohort study of a public health surveillance sample of pregnant women primarily from the Cuyahoga County Board of Health (CCBH) jurisdiction in the Greater Cleveland, OH area. CCBH is the local health jurisdiction for Cleveland-area suburbs and covers a population of approximately 854,000.<sup>12</sup> The remainder of the subjects were either residents of the city of Cleveland or the surrounding counties. The subjects were identified either via mandated reporting of COVID-19 cases as documented in the CCBH COVID-19 Surveillance Database, through communications with the Cleveland Department of Public Health (the local health department for the City of Cleveland), or from local obstetric providers referring their patients to the study. Women who were identified as having COVID-19 infection during any gestational age of their pregnancy were included. SARS-CoV2 infection was defined by either a positive SARS-CoV-2 RT-PCR nasopharyngeal test or having had close contact with a lab-confirmed case in conjunction with symptoms consistent with COVID-19 infection. Subjects with illness onset dates from March 13<sup>th</sup>, 2020 through August 21<sup>st</sup>, 2020 were included in the analysis. Data were obtained via case interviews conducted as part of routine surveillance that typically occurred within days of COVID-19 diagnosis. The research team conducted follow-up

interviews to collect additional data in the days to weeks following the initial case interview data collection.

Data regarding trimester, race, ethnicity, home address, symptomatology, comorbidities, health care worker status, hospitalization (including need for intensive care admission, mechanical ventilation, ECMO), chest x-ray findings, presence of pneumonia, acute respiratory distress syndrome (ARDS), and COVID-19 exposure history were collected at the time of the original case interview performed by the local public health department, as per standard protocol. The subject would then be contacted via telephone by a study physician for another interview, at which time obstetric history, in-depth occupational history, and body mass index data were obtained. The interview consisted of questions regarding the subject's specific occupation and intensity of exposure to other individuals in the course of their work. The physicians would also assess for high-risk medical conditions or concerning symptoms that would require closer monitoring.

Outcomes assessed were severity of clinical illness, the frequency of individual symptoms, hospitalization, and death. Illness severity was defined based on National Institutes of Health criteria for the clinical spectrum of SARS-CoV-2 infection.<sup>13</sup> COVID-19 illness was categorized as: 1) asymptomatic (SARS-CoV-2 PCR testing positive but no symptoms consistent with COVID-19 infection), 2) mild (symptoms present but no dyspnea), 3) moderate (lower respiratory disease as evidenced by dyspnea but no hypoxia present), and 4) severe (need for supplemental oxygen). Case interviews documented the presence of any of twenty individual symptoms that were grouped into broader categories of constitutional, upper respiratory, lower respiratory, gastrointestinal, neurological, and other symptoms. Information regarding hospitalization was obtained via self-report from the subjects or through communications with local obstetric providers.

Sociodemographic characteristics and potential predictors of disease severity were examined. Home addresses were geocoded to the census tract level using the US Census online geocoder<sup>14</sup>, and household median income was determined for the census tract using Integrated Public Use Microdata Series (IPUMS USA).<sup>15</sup> Age, race/ethnicity, presence of at least one high-risk comorbidity, and occupation were assessed as predictors of disease severity. Comorbidities present in our sample considered to be high-risk based on previous studies were obesity ( $\geq 30 \text{ kg/m}^2$ )<sup>16-18</sup> and pregestational Diabetes Mellitus.<sup>19-20</sup> Asthma, hypertension, liver disease, immune deficiencies, and being overweight were not considered to have strong enough evidence to include as high-risk conditions, based on the summary of available evidence for high-risk conditions provided by the CDC.<sup>20</sup> Additionally, gestational diabetes was not considered a high-risk condition. Occupation at time of diagnosis was categorized based on density of exposure to other individuals, adapted from a description of high-density work settings provided by the CDC.<sup>21</sup> The occupation categories were as follows: 1) unemployed, 2) persons working from home, 3) low population density work, 4) high population density work, and 5) direct patient care. High population density work was defined as per the CDC definition of persons who are working shifts of 8-12 hours duration in close contact (within 6 feet) of coworkers for prolonged

(15 minutes or more) duration.<sup>21</sup> Examples of high population density occupations were workers in food service, factories, warehouses, correctional facilities, retail, and daycare settings. Those persons considered to fall into the low population density workforce included those working administrative positions in offices and persons in cosmetology that did not have long shifts or prolonged interaction with co-workers.

Ethical approval was obtained from the Institutional Review Board of University Hospitals Cleveland Medical Center .

All analyses were undertaken in R software version 4.0.3.<sup>22</sup> Continuous variables were reported using mean and standard deviation. Categorical variables were reported as frequencies and percentages. Bivariate analyses were performed using Welch's t-test for continuous variables and Fisher's Exact or Pearson Chi Square for categorical variables. All p values reported are two-sided and  $p < 0.05$  was considered significant. Multivariable logistic regression was used to describe the effect of age, race/ethnicity, occupation category, and presence of at least one high risk comorbid condition on COVID-19 illness severity. Logistic regression models that included subsets of this model were evaluated, as well as a model that included all four variables in addition to trimester of pregnancy.

## Results

A total of 163 pregnant women with COVID-19 infection were identified and included in the analysis, the majority of whom resided in the CCBH jurisdiction, and 113 women (76.7% of subjects) were able to be reached for a follow-up interview. The baseline characteristics of the study participants are presented in Table 1. Symptom data were available for 147 of the subjects and are presented in Table 2, categorized by organ system. The most frequently reported types of symptoms were constitutional (64%) and lower respiratory (61%). Anosmia was reported in 46% of subjects. Asymptomatic subjects comprised 10.9% of the sample, with all these subjects diagnosed in the third trimester through active screening for COVID-19 at the time of delivery. Mild illness was demonstrated in 54.7% of the study sample. Seventeen individuals (13.6%) were hospitalized, and one person (0.7%) died due to COVID-19.

The results of bivariate analyses are presented in Table 3. Median age was found to be higher in the moderate to severe illness group compared to the asymptomatic-mild group (28 years versus 29 years,  $p=0.04$ ). There was an association between high-risk occupational exposure group (high population density work and direct patient care) and moderate to severe disease severity ( $p=0.02$ ). There were no statistically significant differences in the two severity groups with respect to race/ethnicity, presence of at least one high-risk comorbidity, or trimester of diagnosis.

A multivariable logistic regression assessed for the effect of age, race/ethnicity, occupation, and presence of at least one high-risk comorbidity on odds of moderate to severe illness (see Table 4). Validation statistics favored the model that included the four predictors

(corrected Nagelkerke's  $R^2$  was 0.11 in the model with four predictors vs 0.09 for the model with five) and was therefore selected as the final model. Holding the other three variables constant, the odds of moderate to severe illness in a person with a high-risk occupation were 4.41 times that of a person with a low-risk occupation (95% confidence interval 1.70-12.81). There was no statistically significant effect found for the other predictors.

A sensitivity analysis was performed, in which the asymptomatic subjects were excluded. This demonstrated no substantive differences in findings, compared to an analysis of the full set of subjects, thus the final analysis included all subjects.

## Discussion

Among women diagnosed with SARS-CoV-2 infection during pregnancy in a public health surveillance sample, increasing age and high-risk occupation were associated with moderate to severe illness in pregnancy. Hospitalization and death were uncommon overall. Race/ethnicity, presence of at least one high-risk comorbid condition, and trimester of pregnancy did not have an association with disease severity. In the multivariable logistic regression, we found that pregnant women working in a high-risk occupation had four times the odds of moderate to severe COVID-19 disease than those who were in a low-risk occupation or unemployed. Age, race/ethnicity, and presence of at least one high-risk comorbidity did not have an effect on disease severity in multivariable analysis.

A major strength is that we included non-hospitalized pregnant women with COVID-19, whereas most of the literature describes COVID-19 in pregnancy in hospitalized individuals.<sup>11</sup> Also, 23.3% of our subjects were diagnosed in the first trimester, while other reports feature COVID-19 infection in women diagnosed predominantly in the second and third trimesters of pregnancy.<sup>7,8,24-30</sup> A unique feature of our study is the granular description of subjects' sociodemographic characteristics, in particular the occupational history and census tract median income.

The finding that occupations in which persons are in prolonged, frequent contact with others place workers at risk for worse COVID-19 severity was also demonstrated in a study of COVID-19 disease severity in essential versus non-essential workers in the general population.<sup>29</sup> This phenomenon may be explained by the concept of a viral inoculum, which refers to a dose of viral particles over time.<sup>30</sup> This effect has been documented for various respiratory viruses.<sup>30</sup> For SARS-CoV-2, a potential inoculum effect has been demonstrated by a study of Swiss soldiers, in which a cohort of subjects infected with SARS-CoV-2 following initiation of social distancing and masking measures had less severe illness as compared to a cohort infected prior to adoption of these practices.<sup>31</sup> Evidence for this effect was also shown in a case-contact study from Spain, in which development of symptomatic COVID-19 infection in contacts was primarily driven by viral load of the index case.<sup>32</sup>

Our study's findings differ from those demonstrated in others' work. D'Ambrosi et al reported on social determinants of COVID-19 disease acquisition in pregnant women in Northern Italy.<sup>33</sup> The population of this study was different from ours in that only hospitalized women were included and the vulnerable population consisted of immigrants who were likely to be unemployed and live in households with large numbers of family members.<sup>33</sup> The authors found that younger age (less than 35 years old), unemployment, and having a partner who was unemployed were each associated with higher odds of SARS-CoV-2 infection.<sup>33</sup> The authors attributed the association of younger age with increased odds of SARS-CoV-2 infection to the predominance of younger women in the immigrant population, who were also more likely to have SARS-CoV-2 infection. In comparison, our study found that younger age and unemployment were each associated with decreased COVID-19 disease severity. Also, a prospective national population-based observational cohort study from the UK using the UK Obstetric Surveillance System (UKOSS) demonstrated that the majority of pregnant women admitted to the hospital with SARS-CoV-2 infection were black or from other minority groups, were overweight or obese, were age 35 or over, or had comorbidities.<sup>34</sup> In contrast, we did not find an association between comorbidities or BMI and disease severity. It is possible that our study was underpowered and couldn't detect small effects of these factors on COVID-19 disease, as the UK study was larger (n=427). As with the Italian study, the UK study included only hospitalized women, while ours included both hospitalized and non-hospitalized women. Also, other than the Italian study examining unemployment status, neither study examined specific occupation type and its relationship to COVID-19 infection severity.

The chief limitation of the study is the relatively modest sample size, potentially limiting the ability to detect additional effects and raising the possibility of overestimation of effect size<sup>35</sup> for occupation type. This data nonetheless represents a substantial and inclusive sample of a large population of an urban county over an approximately five-month period. Even if the effect size for occupation is substantially overestimated (even if by 100%), the significant association of occupation type with disease severity is noteworthy. A second limitation is that clinical data was not verifiable through medical records. However, the use of follow-up calls by physicians to supplement initial case report data collected by public health personnel likely improves the accuracy of symptom elicitation. Finally, of a non-pregnant control group would have provided a valuable comparison, but the extended timetable and additional subject burden this would have entailed led us to proceed without such a group.

These findings emphasize the importance of further research into occupational risk in pregnancy and policy measures to protect pregnant women against COVID-19 in high-risk occupations. A logical next step would be a larger study, with an age- and race-matched comparator group of infected non-pregnant women, to determine if the effect of high exposure occupation is again demonstrated and whether pregnancy modifies the effect. If the occupational risk findings from this study are replicated in large studies, arguments could be made for policies ensuring that pregnant workers are able to avail themselves of adequate PPE, social distancing

(and perhaps non-public facing roles), and COVID-19 vaccination pregnant workers. In the meantime, additional caution and protections for pregnant women in the workplace are warranted.

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**Table 1: Sample Description**

<b>Demographic Characteristics</b>	<b>N=163</b>
Age: Mean (SD)	28 (5.65)
Race (%)	
African-American	78 (47)
Caucasian	69 (41.6)
Asian	2 (1.2)
Other	5 (3)
Unknown	9 (7.2)
Ethnicity (%)	
Non-Hispanic	152 (99.3)
Hispanic	7 (4.3)
Unknown	4 (2.5)
Occupation (%)	
Direct Patient Care	47(37.6)
High population density work environment	23 (18.4)
Low population density work environment	9 (7.2)
Work from Home	27 (21.6)
Unemployed	19 (15.2)
Census tract median household income category (%)	
<\$25,000	19 (11.7)
\$25,000-\$49,999	58 (35.6)
\$50,000-\$74,999	56 (34.4)
\$75,000-\$99,999	16 (9.8)
\$100,000+	7 (4.3)
Unknown	7 (4.3)
Comorbidities*	
Chronic Lung Disease	20 (15.9)

DM**	3 (3.9)
Hypertension	7 (6.1)
Cardiac disease other than HTN	4 (3.2)
Other Chronic Disease	11 (8.9)
Obesity	42 (51.9)
Immunocompromise	1 (0.8)
Chronic Liver Disease	1 (0.8)
Trimester of COVID-19 Diagnosis (%)	N=119
1st	28 (23.3)
2nd	34 (28.3)
3rd	58 (48.3)

\*percentages are row percentages

\*\* 3 pregestational DM cases (2 additional Gestational DM cases)

**Table 2 Symptomatology and Clinical Outcomes**

Symptoms Present (%)	
<b>Constitutional</b>	<b>92 (64)</b>
Fever	32 (21.6)
Chills	21 (14.4)
Fatigue	33 (22.4)
Myalgias	40 (27.4)
Headache	47 (32.4)
Backache	11 (7.7)
Loss of appetite	8 (5.6)
<b>Lower Respiratory</b>	<b>89 (61.0)</b>
Cough	71 (48.6)
Dyspnea	44 (29.9)
<b>Neurological</b>	<b>68 (47.5)</b>
Anosmia	67 (46.2)
Ageusia	45 (31)
Other neurological symptoms*	1 (0.7)
Nasal Congestion	36 (25)
<b>Gastrointestinal</b>	<b>34 (23.7)</b>
Nausea	18 (12.6)
Vomiting	16 (11.1)
Abdominal Pain	5 (3.5)
Diarrhea	20 (13.8)
<b>Other Symptoms</b>	
Other symptoms	16 (11.2)
Severity of Symptoms (%)	N=150
Asymptomatic	16 (10.7)
Mild	82 (54.6)
Moderate	49 (32.7)
Severe	3 (2.0)
Hospitalization due to COVID-19 (%) n=125	17 (13.6)
Death (%)	1 (0.7)

\*Syncope

**Table 3 Severity of Illness by Demographic and Clinical Characteristics**

	Asymptomatic/Mild	Moderate-Severe	P value
Median Age (IQR)	28 (23-31)	29 (25-33.25)	
Mean Age	27.6	29.6	0.04
Race			0.37
Non-Hispanic Black	50 (51)	21 (53.8)	
All others	45 (45.9)	27 (30.8)	
Unknown	3 (3.1)	4 (15.4)	
Occupation			0.02
Low Risk Exposure	44 (44.9)	11 (21.2)	
High Risk Exposure	40 (40.8)	27 (51.9)	
Unknown	14 (14.3)	14 (26.9)	
Presence of High-Risk Condition	27 (27.6)	17 (32.7)	0.43
Trimester at diagnosis			0.46
1	21 (21.4)	7 (13.5)	
2	18 (18.4)	12 (23.1)	
3	38 (38.8)	17 (32.7)	
Unknown	21 (21.4)	16 (30.8)	

**Table 4: Multivariable Logistic Regression Analysis of Risk for Moderate to Severe Disease**

Variable	OR of Moderate-Severe Disease	95% CI
Age > 29	0.68	0.26- 1.74
Non-hispanic black race	0.45	0.16- 1.17
Presence of at least one comorbidity	2.11	0.83- 5.51
High Population Density Occupation	4.41	1.70-12.81