Journal Pre-proof

Pregnancy as a risk factor for severe coronavirus 2019 (COVID-19) disease using standardized clinical criteria

Megan C. OAKES MD , Annessa S. KERNBERG MD , Ebony B. CARTER MD MPH , Megan E. FOELLER MD , Arvind PALANISAMY MD FRCA , Nandini RAGHURAMAN MD MS , Jeannie C. KELLY MD MS

PII: S2589-9333(21)00014-8
DOI: https://doi.org/10.1016/j.ajogmf.2021.100319
Reference: AJOGMF 100319

To appear in: *American Journal of Obstetrics & Gynecology MFM*

Received date: 22 November 2020
Revised date: 2 January 2021
Accepted date: 19 January 2021

Please cite this article as: Megan C. OAKES MD , Annessa S. KERNBERG MD , Ebony B. CARTER MD MPH , Megan E. FOELLER MD , Arvind PALANISAMY MD FRCA , Nandini RAGHURAMAN MD MS , Jeannie C. KELLY MD MS , Pregnancy as a risk factor for severe coronavirus 2019 (COVID-19) disease using standardized clinical criteria, *American Journal of Obstetrics & Gynecology MFM* (2021), doi: https://doi.org/10.1016/j.ajogmf.2021.100319

TITLE:

Pregnancy as a risk factor for severe coronavirus 2019 (COVID-19) disease using standardized clinical criteria

AUTHORS:

Megan C. OAKES MD[1], Annessa S. KERNBERG MD[1], Ebony B. CARTER MD MPH[1], Megan E. FOELLER MD[1], Arvind PALANISAMY MD FRCA[2], Nandini RAGHURAMAN MD MS[1], Jeannie C. KELLY MD MS[1]

AFFILIATIONS:

[1]Washington University in St. Louis School of Medicine, Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, St. Louis, MO

[2]Washington University in St. Louis School of Medicine, Department of Anesthesiology, Division of Obstetric Anesthesiology, St. Louis, MO

CORRESPONDING AUTHOR:

Megan C. Oakes, MD

Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine

4901 Forest Park Avenue, Suite 710

St. Louis, MO 63108

Cell phone: 626-8620-0984 Email: mcoakes@wustl.edu

DISCLOSURE OF FINANCIAL SUPPORT AND FUNDING: The authors have no financial support or funding to disclose.

CLINICAL TRIAL REGISTRATION: Not applicable.

PRESENTATION: Not applicable.

ACKNOWLEDGEMENTS: None.

CONDENSATION: Pregnancy significantly increases the risk for severe COVID-19 disease when using non-admission based, clinical criteria to define severe disease.

SHORT TITLE: Severe COVID-19 and pregnancy

AJOG AT A GLANCE:

A. Why was the study conducted?

To improve understanding of the risk for severe COVID-19 in pregnant and non-pregnant patients using non-admission based, clinical criteria.

B. What are the key findings?

After adjusting for ethnicity and insurance type, pregnancy is associated with a significantly higher risk for severe COVID-19 among symptomatic women age 13-45 years using two different sets of clinical criteria.

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

This study adds to the existing literature by applying two sets of widely accepted clinical criteria defining severe COVID-19 to investigate the association of pregnancy and severe disease in a cohort of inpatient and outpatient women age 13-45 years with symptomatic COVID-19.

KEYWORDS: COVID-19, SARS-CoV-2, SARS, coronavirus, severe COVID-19, pregnancy

ABSTRACT:

BACKGROUND: As of November 18, 2020, over 11 million people have been infected with coronavirus disease 2019 (COVID-19) and almost 250,000 people have died from the disease in the US, less than one year since its discovery. Although literature is beginning to emerge on pregnancy as a risk factor for severe COVID-19, these studies are heterogeneous and use primary outcomes such as intensive care unit admission or hospitalization as surrogate markers that may subject analyses to misclassification bias in pregnant patients.

OBJECTIVE: We aim determine the risk of severe COVID-19 among pregnant women with symptomatic COVID-19 compared to non-pregnant women using non-admission based, standardized clinical criteria for severe disease.

STUDY DESIGN: This is a retrospective cohort study of women aged 13-45 years and diagnosed with symptomatic COVID-19 between May 28-July 22, 2020. The primary outcome was severe COVID-19 as defined by two sets of non-admission based, clinical criteria: the World Health Organization Ordinal Scale for Clinical Improvement and the Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. Adjusted risk ratios were estimated using multivariable logistic regression analyses.

RESULTS: Of 262 women aged 13-45 years with symptomatic COVID-19, 22 (8.4%) were pregnant and 240 (91.6%) were non-pregnant. After adjusting for covariates potentially associated with the primary outcome, symptomatic pregnant women were at significantly increased risk for severe COVID-19 compared to non-pregnant women using both the World Health Organization Ordinal Scale for Clinical Improvement (aRR 3.59, 95% CI 1.49-7.01) and Novel Coronavirus Pneumonia Emergency Response Epidemiology Team (aRR 5.65, 95% CI 1.36-17.31) criteria.

CONCLUSION: Pregnancy significantly increases the risk for severe COVID-19 as defined by non-admission based, clinical criteria.

INTRODUCTION

As of November 18, 2020, over 11 million people have been infected with coronavirus disease 2019 (COVID-19) and 247,834 have died from the disease in the US, less than one year since its discovery.[1] Of the many clinical characteristics that make combatting COVID-19 challenging is the varied and sometimes rapid progression of COVID-19 infection, representing a spectrum

ranging from persistently asymptomatic infection to acute respiratory failure. Among pregnant women admitted for delivery, asymptomatic infection appears to be the most common presentation of COVID-19; however, up to one-third may progress to symptomatic disease, including critical illness, during a single admission.[2]

With limited therapeutic options and no vaccine yet widely available to the general population, the focus of pandemic control has been on primary prevention and identifying those at greatest risk for severe disease. In June 2020, the Centers for Disease Control and Prevention (CDC) included pregnancy as a risk factor for severe COVID-19 based on hospitalization rates; although their data was limited, as pregnancy status was not available for 71% of patients and admission indication was not specified.[3] Recent literature continues to support pregnancy as a risk factor for severe COVID-19.[4,5] However, the diagnosis of severe COVID-19 in these studies is heterogeneous, using primary outcomes such as intensive care unit admission or hospitalization as surrogate markers that are subject to misclassification bias in pregnant patients. While there is no gold standard, twodefinitions of severe COVID-19 have been published previously. Shortly after the identification of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and the classification of COVID-19 as a Class B notifiable disease in China, the Novel Coronavirus Pneumonia Emergency Response Epidemiology Team (NCPERET) set specific clinical criteria defining severe disease as a way to better describe the emerging viral illness.[6] Notably, the NCPERET criteria is the same recommended by the Society of Maternal-Fetal Medicine (SMFM) to define severe disease with the exception that dyspnea is excluded.[7] More recently, the World Health Organization (WHO) proposed an ordinal scale of clinical endpoints to facilitate interpretation and combination of results across studies and trials (https://www.who.int/teams/blueprint/covid-19). Contemporary clinical studies regarding

COVID-19 have widely adopted ordinal scales similar to the WHO Ordinal Scale for Clinical Improvement (WHOOSCI) to define severe disease in non-pregnant individuals.[8-11]

To better describe the relationship between pregnancy and severe COVID-19, we tested the hypothesis that pregnancy is associated with a higher risk of severe disease in symptomatic COVID-19 positive patients using two sets of standardized clinical criteria recommended by the NCPERET and WHO, rather than inpatient or intensive care unit admission, to define severe disease.

MATERIALS AND METHODS

This is a retrospective cohort study of all women aged 13-45 years who had a positive SARS-CoV-2 test by polymerase chain reaction (PCR) or rapid antigen testing and were symptomatic with COVID-19 between May 28-July 22, 2020 at a single, urban tertiary hospital. The Washington University School of Medicine Human Research Protection Office granted exemption as part of a quality improvement initiative. Patients with asymptomatic COVID-19, such as those found to have a positive test result as a part of universal testing prior to delivery or surgery, were excluded.

The primary outcome was severe COVID-19 defined in two ways: NCPERET criteria,[6] and the WHOOSCI (https://www.who.int/teams/blueprint/covid-19). Severe COVID-19 using the NCPERET criteria is defined as: dyspnea, respiratory rate of $\geq$ 30 breaths per minute, blood oxygen saturation of $\leq$ 93%, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) of <300, or lung infiltrates involving >50% on imaging (Table 1). Disease severity using the WHOOSCI is determined by oxygen and organ support requirements. Scores of 5-7 are classified as severe disease (Table 1).

All patients with a positive SARS-CoV-2 test during the study period were identified, then the cohort narrowed by sex and age. A detailed chart review of clinical notes, medical history, pregnancy status, vital signs, laboratory studies, and imaging pertaining to the index encounter following a positive test was performed by trained staff. Patients were deemed to have severe disease based upon the presence of any criteria for severe disease by either the NCPERET or WHOOSCI during the index encounter. Patients meeting criteria for severe disease were only counted once for each set of criteria, regardless of the number of criteria present for severe disease.

The primary outcome of severe disease was compared between pregnant and non-pregnant women.The presence of medical co-morbidities deemed by the Centers for Disease Control and Prevention (CDC) as risk factors for severe disease (with the exception of pregnancy) was determined by chart review. Co-morbidities were assessed individually, summed to generate a composite co-morbidity risk score, and compared between pregnant and non-pregnant women.[12] Baseline patient characteristics were compared using χ^2 or Fisher's exact for categorical variables and Student's t-test or Wilcoxon rank-sum for continuous variables, as appropriate. Normality of distribution for continuous variables was tested using the Kolmogorov-Smirnov test. Relative risk (RR) and 95% confidence intervals (95% CI) were calculated for the primary outcome using each set of clinical criteria separately. Multivariable logistic regression was used to adjust for confounders, identified as variables which had at least a 10% effect size on the RR. The Zhang method was used to approximate an adjusted relative risk from the adjusted odds ratio given the frequency of our primary outcome.[13] The final model was tested with the Hosmer-Lemeshow goodness-of-fit test. No *a priori* sample size estimation was performed, as all patients

who met inclusion criteria during the study period were included. Statistical analyses were performed using STATA software, version 16.1 (StataCorp LLC, College Station, TX).

RESULTS

A total of 301 patients who met inclusion criteria tested positive for SARS-CoV-2 within the study period. Of those, 39 were asymptomatic (n=26, 66.6% pregnant; n=13, 33.3% non-pregnant) and excluded. Of the remaining 262 symptomatic women, 22 (8.4%) were pregnant and 240 (91.6%) were not pregnant at the time of positive test (Figure 1). Pregnant patients were more likely to be Hispanic/Latina (36.4% vs 9.6%, *P*=0.001) and publicly insured (72.7% vs 38.3%, *P*=0.002) (Table 2). The median gestational age of pregnant patients with symptomatic COVID-19 at diagnosis was 32.4 weeks (range 15.7-39.6). There was no difference in gestational age between patients who had non-severe (median 33.1 weeks, range 15.7-39.6) and severe COVID-19 (median 33.2 weeks, range 24.3-35.4; *P*=0.57). There were no postpartum patients in our cohort. Non-pregnant patients were older than pregnant patients (31.0 $\pm$ 7.8 years vs. 29.4 $\pm$ 5.9 years, respectively), although this was not statistically significant (*P*=0.35). Non-pregnant patients also had a higher composite co-morbidity risk score compared to pregnant women that did not reach statistical significance (1.0 $\pm$ 1.1 vs. 0.6 $\pm$ 0.7, *P*=0.06). The duration of clinical follow-up after a positive test was similar between pregnant and non-pregnant patients (median and interquartile range 15 [3-15] and 15 [0-15] days, respectively).

Among symptomatic women, 7 (31.8%) pregnant and 17 (7.1%) non-pregnant patients were classified as having severe COVID-19 using the NCPERET criteria. Using the WHOOSCI criteria, 3 (13.6%) pregnant and 6 (2.50%) non-pregnant patients were classified as having severe COVID-19. Composite co-morbidity, ethnicity, and insurance type were selected as covariates for the multivariable logistic regression model given clinical and statistical

significance; however, only when ethnicity and insurance remained in the final model did the Hosmer-Lemeshow goodness-of-fit test reach a $P>0.05$, meaning no significant difference between observed and expected values within the final model. After adjusting for these covariates, pregnant patients were significantly more likely to have severe disease compared to non-pregnant patients using both the NCPERET criteria and the WHOOSCI (aRR 3.59, 95% CI 1.49-7.01 and aRR 5.65, 95% CI 1.36-17.31, respectively) (Table 3). While there was no significant difference in the length of stay between pregnant and non-pregnant patients, more pregnant patients with severe COVID-19 were admitted to an intensive care unit (7 (100%) vs 9 (50%), $P=0.03$, and 3 (100%) vs 5 (83.3%), $P=1.00$), by NCPERET and WHOOSCI criteria, respectively). There were no deaths in either group.

DISCUSSION

Principal finding

Among women presenting with symptomatic COVID-19, pregnancy was associated with a significantly higher risk of severe disease by standardized NCPERET and WHOOSCI criteria compared to non-pregnant counterparts.

Results

Our results mirror the described clinical course of pregnant women infected with both COVID-19 and other respiratory viral illnesses (namely, influenza).[2,5,14-17] During the 2009 influenza pandemic (H1N1), pregnant women accounted for 5% of all deaths yet only represented 1% of the population, a marked disproportion in distribution of severe disease.[15] In a systematic review of H1N1, pregnancy was demonstrated to be a risk factor for hospitalization, intensive care unit admission, and death when compared to non-pregnant women of similar age.[16] While many pregnant women with H1N1 had severe disease, pregnant women with additional co-morbidities

identified by the Advisory Committee on Immunization Practices (ACIP) as risk factors for severe disease were more likely to develop severe disease than those without additional risk factors. This is in contrast to findings from a recently published multi-center case control study, in which pregnant women were found to have a greater risk for severe COVID-19 independent of select co-morbidities.[17]

Our finding of pregnancy as a risk factor for severe COVID-19 is similar to several recently published studies.[5,17] In multi-center matched case-control study, Badr et al found that, compared to non-pregnant controls, pregnant women were significantly more likely to require oxygen supplementation (36.04% vs 17.24%, *P*=0.006) and endotracheal intubation (10.16% vs 1.67%, *P*=0.022).[5] Although these select end-points differ from our study, we note a similar proportion of pregnant and non-pregnant women requiring ventilation with organ support in our study, which is classified as WHOOSCI score 7 (9.1% and 1.3%, respectively). In a multi-center case-control study, Debolt et al found that pregnant women were more likely to experience the composite primary outcome of death, need for intubation, extracorporeal membrane oxygenation (ECMO), non-invasive positive pressure ventilation or supplemental oxygen via high flow nasal cannula compared to non-pregnant women (aOR 4.6, 95% CI 1.2-18.2).[17] Importantly, the authors highlight that while non-pregnant controls had a higher prevalence of select co-morbidities, pregnancy still emerged as a risk factor for the composite primary outcome. Similarly, in our study, non-pregnant women had a higher composite co-morbidity risk score than pregnant women (1.0 $\pm$ 1.1 vs 0.6 $\pm$ 0.7, *P*=0.06). Although this was not included in the final multivariable logistic regression model, we conclude that pregnancy is a risk factor for severe COVID-19 in symptomatic women that is likely independent of other co-morbidities.

Our results add to the growing body of literature describing pregnancy as a risk factor for severe disease; however, there are important distinctions to consider. The primary outcome of severe COVID-19 was defined by two sets of clinical criteria in our study. Although similar findings are noted, using admission to an intensive care unit as the primary outcome for severe disease may have subjected results from previously published studies to misclassification bias given inability to account for obligatory hospitalization during pregnancy for delivery, and differential hospital protocols for admitting pregnant patients with COVID-19 to an intensive care unit.[5,18] We see this reflected in our own data, with a greater proportion of pregnant patients with severe COVID-19 defined by either the NCPERET or WHOOSCI criteria being admitted to an intensive care unit compared to non-pregnant patients without a significant difference in length of stay. Additionally, a majority of pregnant women positive for COVID-19 during our study period were asymptomatic compared to non-pregnant patients (54.2% vs 5.1%, respectively). This is consistent with findings prior observational studies of pregnant patients with COVID-19, likely attributed to the widespread universal testing policies on obstetric units.[19-23] We specifically included only women symptomatic with COVID-19 in our study in order to minimize the risk of sampling bias, which may have affected prior studies.[5]

Clinical Implications

One of the major challenges in management of the COVID-19 pandemic is the wide spectrum in severity of disease and urgent need to better predict risk factors for progression.[2] Biologic plausibility of our finding of pregnancy as an independent risk factor for severe COVID-19 can be drawn from known immunologic and physiologic modulations in pregnancy. The number of CD3+ T lymphocytes (CHD4+ and CD8+), as well as Th1 and Th2 responses to mitogentic or antigenic lymphocyte stimulation, decrease during pregnancy.[24,25] Following infection and

replication within cells infected with SARS-CoV-2, pyroptosis (inflammation-mediated programmed cell death in response to a pathogenic stimulus) occurs, releasing damage-associated molecular proteins and stimulating a pro-inflammatory response.[26] T cells are attracted to the site of infection; however, as the response is modulated in the context of pregnancy, altered clearance of infected cells may favor severe disease.

Further, the immunomodulatory properties of progesterone may also be implicated in the increased risk for severe disease in pregnancy. Progesterone has been shown to suppress the maternal immune response and alter the balance between Th1 and Th2 responses.[27] This shift to Th2-dominant, cell-mediated immunity is thought to be implicated in increased severity of respiratory viral illnesses. In one mouse model of influenza A infection, treatment with progesterone resulted in a decrease of both virus-specific antibody levels and circulating CD8+ T cells.[28] When challenged with influenza A following progesterone treatment, increased severe disease was noted. Additionally, physiologic changes of the maternal respiratory system complicate the response to infection. Increases in minute ventilation, oxygen consumption, and chest wall compliance; reduction in expiratory reserve volume, functional residual capacity, and residual volume; and upward displacement of the maternal diaphragm all result in a decreased ability to compensate for respiratory disease.[29,30]

Together, these decreases in adaptive immunity and physiologic changes of pregnancy help to explain the observed increase risk for severe COVID-19. As the rising number of cases continues to put a strain on the demands of healthcare providers, refining the prediction of which patients are at high risk for the development of severe disease is ever important. Pregnant women who develop symptoms from COVID-19 should be closely monitored given the risk for severe disease.

Research Implications

Larger, prospective studies are needed to continue to understand the implications of severe COVID-19 in pregnancy on both maternal and neonatal outcomes. Currently, clinical criteria for defining severe COVID-19 are neither universal, nor specific to pregnancy. A two-fold difference in the absolute number of patients classified as having severe disease between the NCPERET and WHOOSCI (7 vs 3 and 17 vs 6, respectively) in both the pregnant and non-pregnant groups underscores the importance of developing universally standardized definitions inclusive of pregnant women to determine the true prevalence of severe COVID-19 and to better interpret and combine results of future studies. Notably, certain NCPERET parameters were unavailable for almost half of the patients otherwise defined as having severe disease by some other criteria. The WHOOSCI was specifically introduced as criteria that do not require extensive laboratory data or radiologic information for assessment of disease severity. Pragmatically, using such an ordinal scale will likely lead to better uniform clinical classification, and thus could be more widely utilized across many populations

Strengths and Limitations

Our study used clinical criteria, not admission data, to determine severe COVID-19. We included symptomatic women with COVID-19 women who were followed both in the inpatient and outpatient setting, improving the generalizability of our findings. We assessed for the presence of all co-morbidities considered to be risk factors for severe disease by the CDC in evaluating the characteristics of our cohort. Most women were followed for >14 days, which decreased the likelihood of misclassification bias.

This study has potential limitations that should be considered. While generation of results from a single, tertiary care center decreased the variability in the management of women with severe

COVID-19 in our study, this may limit the broad application of our findings. Given the retrospective nature of the study design, all cases meeting inclusion criteria were included in the analyses. Although we detected a difference in the primary outcome using both sets of clinical criteria between pregnant and non-pregnant women, larger studies are needed to validate our findings.

Both the NCPERET and WHOOSCI have been applied to diverse populations in the literature; however, these clinical criteria are not without their limitations.[7-11] Lower scores on the WHOOSCI involve subjective assessment (for example, score 2=limitation of activity); however, we limited our assessment to women with scores of $\geq$ 5, which do not include assessment of activity limitation or hospitalization without requiring oxygen. The NCPERET criteria partially relies on laboratory data and radiologic assessment in qualifying severe disease, which not every patient underwent. Notably, 4/22 (18.1%) of pregnant were missing Pa/FiO_2 information, versus only 8/240 (3.3%) of non-pregnant women. The missing data, due to lack of arterial blood gas results, demonstrates a limitation of using the NCPERET criteria broadly to define severe disease. Using available data, there was a significant difference with more pregnant women having a Pa/FiO_2 <300 (11.1% vs 3.4%, P=0.04), suggesting that pregnant women are more likely to have severe COVID-19 by NCPERET criteria. Further, the application of both sets of criteria to the same population allowed for a detailed investigation of the relationship between pregnancy and severe COVID-19. Larger studies are needed to analyze the two sets of criteria for convergent validity.

Conclusions

In conclusion, pregnancy is an independent risk factor for severe COVID-19 in symptomatic, women aged 13-45 years using clinical criteria irrespective of admission status. The results from

this study highlight the need of careful surveillance for the development of COVID-19 symptoms in pregnant patients diagnosed with COVID-19, and close clinical follow-up if symptoms develop for progression to severe disease. Future work in developing and validating universal criteria for the classification of severe disease, inclusive of pregnant women, is critically needed.

REFERENCES

1. CDC COVID Data Tracker. at https://covid.cdc.gov/covid-data-tracker/#cases_casesper100klast7days.)
2. Khoury R, Bernstein PS, Debolt C, et al. Characteristics and Outcomes of 241 Births to Women With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection at Five New York City Medical Centers. Obstet Gynecol 2020;136:273-82.
3. CDC updates, expands list of people at risk of severe COVID-19 illness. at https://www.cdc.gov/media/releases/2020/p0625-update-expands-covid-19.html.)
4. Ellington S, Strid P, Tong VT, et al. Characteristics of Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status - United States, January 22-June 7, 2020. MMWR Morb Mortal Wkly Rep 2020;69:769-75.
5. Badr DA, Mattern J, Carlin A, et al. Are clinical outcomes worse for pregnant women >/= 20 weeks' gestation infected with COVID-19? A multicenter case-control study with propensity score matching. Am J Obstet Gynecol 2020.
6. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. [The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China]. Zhonghua Liu Xing Bing Xue Za Zhi 2020;41:145-51.
7. Management considerations for pregnant patients with COVID-19. at https://s3.amazonaws.com/cdn.smfm.org/media/2334/SMFM_COVID_Management_of_COVID_pos_preg_patietns_4-29-20_final.pdf.)
8. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med 2020.
9. Laing AG, Lorenc A, Del Molino Del Barrio I, et al. A dynamic COVID-19 immune signature includes associations with poor prognosis. Nat Med 2020;26:1623-35.
10. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. JAMA 2020;324:1048-57.
11. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395:1569-78.
12. Coronavirus Disease 2019 (COVID-19): People with Certain Medical Conditions. at https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html.)
13. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA 1998;280:1690-1.

14. Jamieson DJ, Honein MA, Rasmussen SA, et al. H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet 2009;374:451-8.
15. Siston AM, Rasmussen SA, Honein MA, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. JAMA 2010;303:1517-25.
16. Mosby LG, Rasmussen SA, Jamieson DJ. 2009 pandemic influenza A (H1N1) in pregnancy: a systematic review of the literature. Am J Obstet Gynecol 2011;205:10-8.
17. DeBolt CA BA, Limaye MA, Silverstein J, Penfiled CA, Roman AS, Rosenberg HM, Ferrara L, Lambert C, Khoury R, Bernstein PS, Burd J, Berghella V, Kaplowits E, Overby JR, Stone J. Pregnant women with severe or critical COVID-19 have increased composite morbidity compared to non-pregnant matched controls. Am J Obstet Gynecol 2020.
18. Collin J, Bystrom E, Carnahan A, Ahrne M. Public Health Agency of Sweden's Brief Report: Pregnant and postpartum women with severe acute respiratory syndrome coronavirus 2 infection in intensive care in Sweden. Acta Obstet Gynecol Scand 2020;99:819-22.
19. Kelly JC, Raghuraman N, Carter EB, Palanisamy A, Stout MJ. Preprocedural asymptomatic coronavirus disease 2019 cases in obstetrical and surgical units. Am J Obstet Gynecol 2020.
20. Bianco A, Buckley AB, Overbey J, et al. Testing of Patients and Support Persons for Coronavirus Disease 2019 (COVID-19) Infection Before Scheduled Deliveries. Obstet Gynecol 2020;136:283-7.
21. Sutton D, Fuchs K, D'Alton M, Goffman D. Universal Screening for SARS-CoV-2 in Women Admitted for Delivery. N Engl J Med 2020;382:2163-4.
22. Miller ES, Grobman WA, Sakowicz A, Rosati J, Peaceman AM. Clinical Implications of Universal Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Testing in Pregnancy. Obstet Gynecol 2020;136:232-4.
23. Delahoy MJ, Whitaker M, O'Halloran A, et al. Characteristics and Maternal and Birth Outcomes of Hospitalized Pregnant Women with Laboratory-Confirmed COVID-19 - COVID-NET, 13 States, March 1-August 22, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1347-54.
24. Zoller AL, Schnell FJ, Kersh GJ. Murine pregnancy leads to reduced proliferation of maternal thymocytes and decreased thymic emigration. Immunology 2007;121:207-15.
25. Clarke AG, Kendall MD. The thymus in pregnancy: the interplay of neural, endocrine and immune influences. Immunol Today 1994;15:545-51.
26. Wastnedge EA, Reynolds RM, van Boeckel SR, et al. Pregnancy and COVID-19. Physiol Rev 2020.
27. Kourtis AP, Read JS, Jamieson DJ. Pregnancy and infection. N Engl J Med 2014;370:2211-8.
28. Hall OJ, Klein SL. Progesterone-based compounds affect immune responses and susceptibility to infections at diverse mucosal sites. Mucosal Immunol 2017;10:1097-107.
29. American College of O, Gynecologists' Committee on Practice B-O. Practice Bulletin No. 170: Critical Care in Pregnancy. Obstet Gynecol 2016;128:e147-54.
30. Goodnight WH, Soper DE. Pneumonia in pregnancy. Crit Care Med 2005;33:S390-7.

Figure 1. Flow chart of study participants

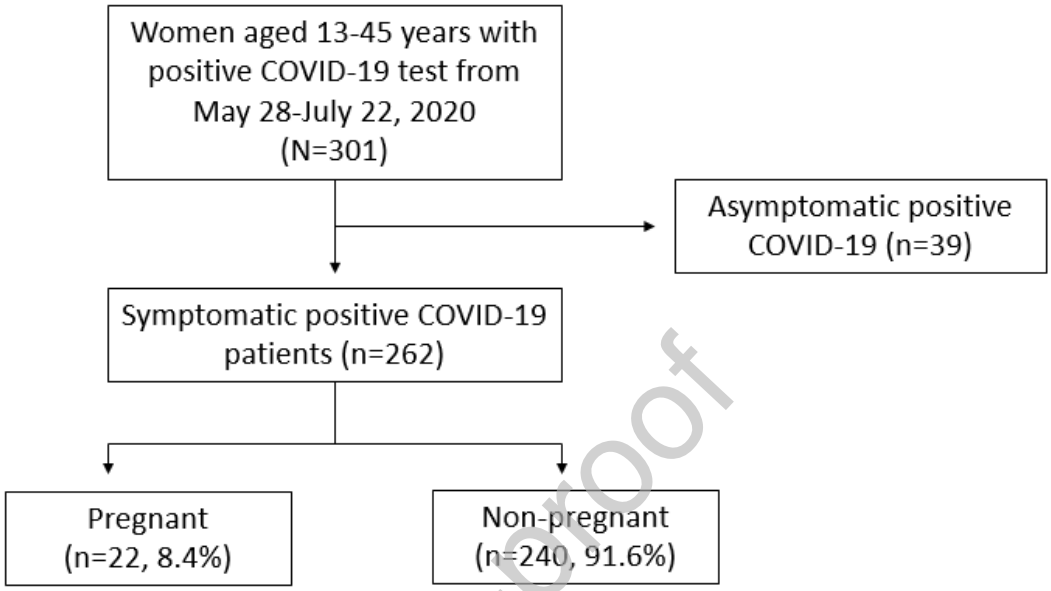

Table 1. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team (NCPERET) and World Health Organization Ordinal Scale for Clinical Improvement (WHOOSCI) criteria for severe COVID-19.

NCPERET: severe disease defined as the presence of any of the following	WHOOSCI: severe disease defined as a score of $\geq$5-7
Dyspnea Respiratory rate $\geq$ 30 breaths per minute Blood oxygen saturation $\leq$ 93% PaO_2/FiO_2 <300	1 – No limitation of activity 2 – Limitation of activities 3 – Hospitalized, no oxygen therapy 4 – Oxygen by mask or nasal prongs

Lung infiltrates involving >50% on imaging	5 – Non-invasive ventilation or high-flow oxygen use 6 – Intubation and mechanical ventilation 7 – Ventilation with additional organ support (ECMO, RRT, vasopressor use)

* Abbreviations: ECMO, extracorporeal mechanical oxygenation; RRT, renal replacement therapy

Table 2. Background characteristics of pregnant and non-pregnant patients with symptomatic COVID-19

	Symptomatic pregnant patients with COVID-19 (N=22)	Symptomatic non-pregnant patients with COVID-19 (N=240)	*P**
Age, years	29.4 ± 5.9	31.0 ± 7.8	0.35
Race			
White	10 (45.4)	99 (41.3)	
Black	11 (50.0)	124 (51.7)	
Asian/Pacific Islander	1 (4.6)	2 (0.8)	0.56
American Indian	0	1 (0.4)	
Other	0	1 (0.4)	
Unable to obtain	0	13 (5.4)	
Ethnicity			
Non-Hispanic/Latina	14 (63.6)	194 (80.8)	**0.001**
Hispanic/Latina	8 (36.4)	23 (9.6)	

Unable to obtain	0	23 (9.6)	
Insurance type Public Private	 16 (72.7) 6 (27.3)	 92 (38.3) 148 (61.7)	**0.002**
Area deprivation index[4], decile	6.3 ± 2.9	5.9 ± 3.3	0.60
Obese[†]	8 (36.4)	119 (49.6)	0.23
Cancer	0	4 (1.7)	0.70
Renal disease[‡]	1 (4.5)	7 (2.9)	0.51
Transplant	0	4 (1.7)	0.70
Cerebrovascular disease[§]	0	3 (1.2)	0.77
Cardiovascular disease[‖]	2 (9.1)	36 (15.0)	0.35
Sickle cell disease	0	2 (0.8)	0.84
Thalessemia	0	1 (0.4)	0.92
Diabetes	1 (4.5)	17 (7.1)	0.54
HIV	0	1 (0.4)	0.92
Liver disease[¶]	0	1 (0.42)	0.92
Pulmonary disease[#]	1 (4.5)	44 (18.3)	0.08
Tobacco use	0	13 (5.4)	0.31
Composite co-morbidity risk score	0.6 ± 0.7	1.0 ± 1.1	0.06
Duration of follow-up, days	15 (3-15)	15 (0-15)	0.06
Gestational age at diagnosis, weeks Non-severe COVID-19	32.4 (15.7-39.6)	N/A	

Severe COVID-19	33.2 (24.3-35.4) 33.1 (15.7-39.6)		

Data are presented as n(%), mean ± standard deviation, or median (range). Bold indicates significant values. Abbreviations: COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus. *Based on χ^2 or Fisher's exact for categorical variables and Student's t-test for parametric continuous variables. †Obese, BMI ≥30 kg/m^2. ‡Renal disease, chronic kidney disease. §Cerebrovascular disease, stroke, dementia. ||Cardiovascular disease, heart failure, coronary artery disease, cardiomyopathy, pulmonary hypertension, hypertension. ¶Liver disease, alcohol related liver disease, nonalcoholic fatty liver disease, cirrhosis. #Pulmonary disease, moderate to severe asthma, chronic obstructive pulmonary disease, cystic fibrosis, pulmonary fibrosis, other chronic lung disease.

Table 3. Comparison of severe disease between pregnant and non-pregnant patients with symptomatic COVID-19

Clinical criteria for severe disease	Symptomatic pregnant patients with COVID-19 (N=22)	Symptomatic non-pregnant patients with COVID-19 (N=240)	RR (95% CI)	aRR* (95% CI)
Novel Coronavirus Pneumonia Emergency Response Epidemiology Team criteria (NCPERET)[6]	7 (31.8)	17 (7.1)	**4.49** (2.09-9.64)	**3.59** (1.49-7.01)
Dyspnea	7	18		
Respiratory rate ≥ 30	7	15		
Blood oxygen saturation ≤93%	6	15		

Pa/FiO_2 <300[†]	2	8		
Lung infiltrates >50% on imaging	6	15		
WHO Ordinal Scale for Clinical Improvement (WHOOSCI)[‡]	3 (13.6)	6 (2.50)	**5.45** (1.46-20.32)	**5.65** (1.36-17.31)
Score 5: Non-invasive ventilation or high-flow oxygen	1	4		
Score 6: Intubation and mechanical ventilation.	0	0		
Score 7: Ventilation with additional organ support (extracorporeal mechanical oxygenation, renal replacement therapy, vasopressors)	2	2		
			P[§]	
Length of stay, days	5 (1-15)	6 (1-25)	0.77	
Severe COVID-19 (NCPERET)	8 (1-15)	7 (1-29)	0.94	
Severe COVID-19 (WHOOSCI)	11 (8-15)	16 (1-29)	0.70	
ICU admission	8 (36.4)	9 (3.75)	**<0.01**	
Severe COVID-19 (NCPERET)	7 (100.0)	9 (50.0)	**0.03**	
Severe COVID-19 (WHOOSCI)	3 (100.0)	5 (83.3)	1.00	

Death	0	0	-	

Data are presented as n(%) or median (range). Bold indicates significant values. Abbreviations: COVID-19, coronavirus disease 2019; RR, relative risk; aRR, adjusted relative risk; Pa/FiO_2, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; WHO, World Health Organization (https://www.who.int/teams/blueprint/covid-19); ICU, intensive care unit.

*Determined using multivariable logistic regression adjusting for ethnicity and insurance type.

†Values not available for 4 pregnant (4/22, 18.1%) and 8 non-pregnant (8/240, 3.3%) patients. ‡ https://www.who.int/teams/blueprint/covid-19. §Based on Wilcoxon rank-sum or Fisher's exact, as appropriate.