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MAJOR ARTICLE

# Coronavirus Disease 2019 (COVID-19) Disease Severity: Pregnant vs Nonpregnant Women at 82 Facilities

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***Background.*** Pregnancy has been reported to be a risk factor for severe COVID-19. We evaluated the impact of pregnancy on severe COVID-19 and mortality in an electronic medical record (EMR) database that enabled exclusion of labor and delivery (L&D) encounters.

***Methods.*** In this retrospective cohort study, EMRs from 82 healthcare facilities in the Cerner COVID-19 Datamart were analyzed. The study comprised 38 106 individuals aged 18–45 years old with COVID-19 who had emergency department, urgent care, or inpatient encounters from December 2019 to September 2020. Subgroups were balanced through propensity score weights for age, race, smoking status, and number of comorbidities. The primary outcome was COVID-19–related mortality; secondary outcomes were markers of severe COVID-19: intubations, mechanical ventilation, use of vasopressors, diagnosis of sepsis, and diagnosis of acute respiratory distress syndrome.

***Results.*** In comparing pregnant and nonpregnant women, no statistical differences were found for markers of severe COVID-19, after adjusting for age, smoking, race, and comorbidities. The adjusted odds of an inpatient encounter were higher for pregnant vs nonpregnant women (adjusted odds ratio [aOR], 13.2; 95% confidence interval [CI], 11.6–15.3; $P < .001$), but notably lower after excluding L&D encounters (aOR, 2.3; 95% CI, 1.89–2.88; $P < .001$). In comparison to women without L&D encounters, hospitalization was significantly more likely for men.

***Conclusions.*** We did not find an increased risk of severe COVID-19 or mortality in pregnancy. Hospitalization does not necessarily indicate severe COVID-19 in pregnancy, as half of pregnant patients with COVID-19 were admitted for L&D encounters in this study.

**Keywords.** COVID-19; pregnancy; severe COVID-19; COVID-19 mortality.

Over 30 million confirmed coronavirus disease 2019 (COVID-19) cases and over a half-million COVID-19 deaths have occurred in the United States [1]. Using national surveillance data, symptomatic pregnant women with COVID-19 have been reported to be at increased risk for severe illness, compared with nonpregnant women [2–5]. However, several limitations are noted, including voluntary reporting to the national surveillance database, lack of information on reasons for hospitalization (such as labor and delivery), unknown pregnancy status for the majority of COVID-19–positive cases in 1 study, and a large proportion of missing data on comorbidities, age, and race [2–5]. Contrary to the aforementioned studies, recent meta-analyses report clinical similarities between COVID-19–positive pregnant and nonpregnant women [6, 7]. In this study, we evaluated the effect of pregnancy on severe COVID-19 and mortality using a large patient electronic medical record (EMR) database that enabled identification of labor and delivery (L&D) encounters, age, race, and comorbidities.

## METHODS

### Database Description

We performed a retrospective cohort study using de-identified EMR data in the Cerner HealtheDataLab platform (Cerner Corporation) [8] including 82 healthcare facilities, from December 2019 to September 2020, and using R Statistical Computing Language. This is a national database with medical facilities located throughout the United States [9]. University of Missouri Institutional Review Board exemption was granted (IRB #2050882).

### Study Population

Cohorts of interest included pregnant women, nonpregnant women, and men aged 18 to 45 years who were COVID-19

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positive. The Cerner COVID-19 Datamart includes over 100 LOINC (Logical Observation Identifiers Names and Codes) codes for different types of COVID-19 screening tests. Selection of eligible participants for the COVID Datamart included a positive test for at least 1 of these LOINC codes. COVID-19–positive status was determined either at the encounter or within 2 weeks prior to the encounter. Pregnancy encounter reasons (eg, vaginal delivery, preterm labor, etc) were identified through International Classification of Diseases, 10 Revision (ICD-10), condition codes (see Supplementary Appendix). Patients with tubal, ectopic, or molar pregnancies were removed from the pregnancy analysis (n = 28) but not the gender analysis. Condition descriptions for each pregnant woman (up to 14 per patient) were reviewed by our clinical researchers to verify appropriate group assignments.

ICD-10 or procedure codes were used to classify markers of COVID-19 severity (intubation, mechanical ventilation, use of vasopressors, acute respiratory distress syndrome [ARDS], and sepsis), inpatient encounters, and mortality dichotomously. For 16 selected comorbidities, 3 categories (0, 1, or ≥2) were used. Smoking status was coded dichotomously, while race was classified into 5 categories (see Supplementary Appendix for variable descriptions).

### Statistical Analysis

Univariate analyses were performed for demographics, markers of COVID-19 severity, mortality, and inpatient encounters. A test for independence was performed on all covariates; *P* values for a 2-sided test were reported using Fisher's exact test and a 2-sample *t* test to compare subgroups. After balancing subgroups through propensity score weights [10] for age, race, count of comorbidities, and smoking status, adjusted odds ratios (aORs) for markers of severe COVID-19 and mortality were estimated using multivariable logistic regression with covariates and a penalized maximum likelihood approach to reduce bias from small samples and rare events [11], with statistical significance at $\alpha = 0.05$.

## RESULTS

Of 3042 pregnant women, over half (53.3%) were hospitalized for L&D reasons. Of patients with identifiable trimester codes (n = 2617), 74.3% of all pregnant women were in their third trimester; when excluding L&D, 38.3% were in their second and 43.7% were in their third trimester. Baseline characteristics (age, race, smoking status, number of comorbidities) showed significant differences between groups, supporting propensity weighting (Table 1). Men (n = 16 947) were approximately 1 year older as well as more likely to smoke and to have 2 or more comorbidities than women (n = 21 159). Pregnant women (n = 3042) were 3 years younger as well as less likely to smoke (1.2% vs 3.2%) and to have 2 or more comorbidities than nonpregnant women (n = 18 089).

For pregnant and nonpregnant women, death was the least frequent outcome (0.1–0.8%), while ARDS was the most common marker of severe COVID-19 (3.6–7.1%) (Table 2). Pregnant women had lower odds of mortality (aOR, .28; 95% confidence interval [CI], .06–.83; $P = 0.02$) compared with nonpregnant women after adjusting for age, smoking status, race, and number of comorbidities. After excluding L&D encounters, there was no longer a statistically significant difference in aOR of mortality for pregnant versus nonpregnant women. No marker of severe disease was significantly different between pregnant and nonpregnant women. Pregnant women were 12 times as likely to be admitted to the hospital versus nonpregnant women, but after excluding L&D, they were only twice as likely to be admitted (Table 3).

**Table 1. Baseline Characteristics of Groups (Univariate Analysis of Covariates: Full Sample)**

| | Women (n = 21 159) | Men (n = 16 947) | NP Women (n = 18 089) | P Women (n = 3042) | Men vs Women, *P* | P vs NP Women, *P* | P Women Excluding L&D Encounters (n = 1420) | P Women L&D vs non-L&D Encounters, *P* |
|---|---|---|---|---|---|---|---|---|
| Age, years | 31.18 (7.54) | 32.10 (7.58) | 31.69 (7.67) | 28.23 (5.94) | <.001 | <.001 | 28.16 (5.93) | .60 |
| Comorbidities | | | | | <.001 | <.001 | | .10 |
| 0 | 16 771 (79.3) | 12 905 (76.2) | 13 988 (77.3) | 2758 (90.7) | | | 1276 (89.9) | |
| 1 | 2418 (11.4) | 1952 (11.5) | 2196 (12.1) | 221 (7.3) | | | 107 (7.5) | |
| 2+ | 1970 (9.3) | 1233 (12.3) | 1905 (10.5) | 63 (2.7) | | | 37 (2.6) | |
| Smoker | | | | | <.001 | <.001 | | .66 |
| Yes | 624 (2.9) | 864 (5.1) | 587 (3.2) | 36 (1.2) | | | 15 (1.1) | |
| Race | | | | | <.001 | <.001 | | <.001 |
| AI/AN | 555 (2.6) | 439 (2.6) | 511 (2.8) | 44 (1.4) | | | 22 (1.5) | |
| Asian/PI | 393 (1.9) | 359 (2.1) | 331 (1.8) | 61 (2.0) | | | 25 (1.8) | |
| Black | 4318 (20.4) | 3091 (18.2) | 3847 (21.3) | 465 (15.3) | | | 258 (18.2) | |
| Other/unknown | 4525 (21.4) | 4099 (24.2) | 3735 (20.6) | 785 (25.8) | | | 318 (22.4) | |
| White | 11 368 (53.7) | 8959 (52.9) | 9665 (53.4) | 1687 (55.5) | | | 797 (56.1) | |

Quantitative variables report the mean (SD) with the *P* value from a 2-sample unpaired *t* test. Categorical variables report the count (%) with the *P* value from Fisher's exact test. Abbreviations: AI/AN, American Indian/American Native; Asian/PI, Asian/Pacific Islander; L&D, labor and delivery; NP, nonpregnant; P, pregnant.

**Table 2. COVID-19 Mortality and Disease Severity (Emergency Room and Hospitalized Patients, Aged 18–45 Years)**

| | All Women | | | | Excluding L&D Encounters[a] | |
|---|---|---|---|---|---|---|
| | NP Women (n = 18 089) | | P Women (n = 3042) | | P women (n = 1420) | |
| | n | (%) | n | (%) | n | (%) |
| Death | 137 | (0.8%) | 3 | (0.1%) | 3 | (0.1%) |
| Inpatient | 3140 | (17.4%) | 1909 | (62.8%) | 334 | (23.5%) |
| Intubation | 219 | (1.2%) | 13 | (0.4%) | 4 | (0.3%) |
| Ventilation | 260 | (1.4%) | 15 | (0.5%) | 5 | (0.4%) |
| ARDS | 1286 | (7.1%) | 108 | (3.6%) | 59 | (4.2%) |
| Vasopressors | 233 | (1.3%) | 24 | (0.8%) | 6 | (0.4%) |
| Sepsis | 314 | (1.7%) | 19 | (0.6%) | 9 | (0.6%) |
| | Full Sample | | | | Excluding L&D Encounters[a] | |
| | Women (n = 21 159) | | Men (n = 16 947) | | Women (n = 19 536) | |
| | n | (%) | n | (%) | n | (%) |
| Death | 140 | (0.6) | 277 | (1.6) | 140 | (0.7) |
| Inpatient | 5054 | (23.9) | 4001 | (23.6) | 3479 | (17.8) |
| Intubation | 232 | (1.1) | 394 | (2.3) | 223 | (1.1) |
| Ventilation | 275 | (1.3) | 486 | (2.9) | 265 | (1.4) |
| ARDS | 1394 | (6.6) | 1937 | (11.4) | 1345 | (6.9) |
| Vasopressors | 258 | (1.2) | 411 | (2.4) | 240 | (1.2) |
| Sepsis | 333 | (1.6) | 504 | (3.0) | 323 | (1.7) |

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; L&D, labor and delivery; NP, nonpregnant; P, pregnant.
[a]Ectopic pregnancies are removed from the pregnancy analysis (n = 28); 1 woman had coding for both an ectopic pregnancy and an L&D encounter, and so that encounter was also removed from analysis.

To validate our database, we also compared markers of severe COVID-19 and mortality in men versus women. After adjusting for age, smoking, race, and comorbidities, men were twice as likely to die as women. Men also had significantly increased odds of intubation, mechanical ventilation, use of vasopressors, and diagnoses of sepsis and ARDS (Table 3). Men

**Table 3. Adjusted Odds Ratios for COVID-19 Mortality and Disease Severity**

| | Pregnant Women (Reference: Nonpregnant Women) | | | | | |
|---|---|---|---|---|---|---|
| | All Pregnant Women | | | All Women, Excluding L&D Encounters | | |
| | aOR | (95% CI) | *P* | aOR | (95% CI) | *P* |
| Death | .28 | (.06–.83) | .02 | .56 | (.11–2.01) | .31 |
| Inpatient | 13.2 | (11.57–15.27) | <.001 | 2.32 | (1.89–2.88) | <.001 |
| Intubation | .81 | (.38–1.69) | .55 | .57 | (.14–1.76) | .29 |
| Ventilation | .78 | (.39–1.53) | .45 | .59 | (.17–1.64) | .28 |
| ARDS | .93 | (.71–1.22) | .61 | 1.09 | (.74–1.60) | .67 |
| Vasopressors | 1.44 | (.78–2.78) | .22 | .77 | (.25–2.15) | .57 |
| Sepsis | .72 | (.39–1.28) | .25 | .72 | (.29–1.66) | .41 |
| | Men (Reference All Women) | | | Men (Reference: All Women, Except Those With L&D Encounters) | | |
| | aOR | 95% CI | *P* | aOR | 95% CI | *P* |
| Death | 2.24 | (1.81–2.78) | <.001 | 2.16 | (1.75–2.68) | <.001 |
| Inpatient | .90 | (.86–.95) | <.001 | 1.37 | (1.29–1.45) | <.001 |
| Intubation | 1.88 | (1.59–2.24) | <.001 | 1.89 | (1.60–2.25) | <.001 |
| Ventilation | 1.97 | (1.69–2.31) | <.001 | 1.98 | (1.69–2.32) | <.001 |
| ARDS | 1.65 | (1.53–1.79) | <.001 | 1.63 | (1.51–1.77) | <.001 |
| Vasopressors | 1.77 | (1.51–2.10) | <.001 | 1.84 | (1.56–2.18) | <.001 |
| Sepsis | 1.64 | (1.42–1.90) | <.001 | 1.62 | (1.41–1.88) | <.001 |

aORs adjusted for age, smoking status, race, and number of comorbidities through propensity score weighting and multivariate logistic regression.
Abbreviations: aOR, adjusted odds ratio; ARDS, acute respiratory distress syndrome; CI, confidence interval; COVID-19, coronavirus disease 2019; L&D, labor and delivery.

with COVID-19 had a lower risk of inpatient admission; after excluding L&D encounters, however, men with COVID-19 had a greater risk of inpatient admission compared with women.

## DISCUSSION

In this large retrospective cohort study of mortality and markers of severe COVID-19, we did not find any significant differences between pregnant and nonpregnant women, regardless of whether or not encounters for L&D were excluded. This null finding has previously been reported in some systematic reviews and meta-analyses [7, 12, 13]. Hospitalization was more likely for pregnant women compared with nonpregnant women; precautionary hospital admission for pregnant women was reasonable and expected, especially early in the pandemic, given the uncertain impacts of COVID-19 on maternal and fetal health. However, hospitalization does not necessarily indicate severe COVID-19 symptoms in pregnancy. Inpatient status in pregnancy is a poor metric for severe disease; indeed, half of pregnant patients with COVID-19 in our study were admitted for L&D.

Given the physiological changes during pregnancy (including increased heart rate and oxygen consumption, decreased lung capacity, and altered cell immunity [14]), it was hypothesized that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may disproportionally affect pregnant women. In New York City, an early US location significantly affected by COVID-19, initial reports in spring of 2020 suggested that, compared with nonpregnant women, pregnant women were not at increased risk of hospitalization or intensive care unit (ICU) admission [13]. These reports were followed by surveillance studies using the National Notifiable Diseases Surveillance System (NNDSS) that added a new event code for COVID-19 [15]; these publications consistently noted increased risks of severe COVID-19, ICU admission, and mechanical ventilation in pregnant women, although with several limitations noted (including unbalanced subgroups and unknown reasons for ICU admission) [2–5].

In our study, when L&D encounters were excluded, men were at increased risk of hospitalization compared with all women. Consistent with prior literature [16], men in our study were also at increased risk of severe COVID-19 and mortality compared with women. Our confidence in our study findings is supported by use of a large EMR dataset of patients with COVID-19 with known pregnancy status from 82 health systems across the United States, meticulous classification of reasons for patient encounters, statistical adjustment for risk factors associated with COVID-19 severity, and findings of increased mortality and severe COVID-19 for men compared with women. Given the breadth of our dataset, we also have no reason to believe that pregnant women, nonpregnant women, or men had systemic differences in their types of COVID-19 screening tests.

Limitations of our study include our inability to review medical charts (to assess ICU status and to determine clinical reasons for admitting patients and ordering procedures) and heterogeneity among 82 health systems' policies regarding COVID-19 encounters and screening protocols. Evaluation of health outcomes using billing codes is necessary for this analysis but is a limitation. Additionally, the low number of deaths limited our statistical power.

Sensible and prudent behavior to limit exposure among pregnant women, especially amid emerging COVID-19 "variants of concern," continues to be important. Further studies to determine birth outcomes and COVID-19 disease severity in pregnant women will be critical for these women, their families, and healthcare providers to appropriately weigh risks and benefits of COVID-19 vaccinations for this vulnerable population.

### Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

### Notes

***Author Contributions.*** A. L. H., A. M. O., and J. A. M.: concept and analytical plan. A. M. O. and J. A. M. had full access to the data in the study, through project approval for data access from Cerner. A. M. O. performed the data analyses and these analyses were reviewed by A. L. H., A. M. O., and J. A. M. All authors, except for A. M. O. and X.-F. W., evaluated ICD-10 codes to classify pregnancy encounters and labor and delivery encounters. All authors assisted in the interpretation of data and manuscript production.

***Potential conflicts of interest.*** The authors: No reported potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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