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Adverse perinatal outcomes in a large United States birth cohort during the COVID-19 pandemic

Ethan A. Litman, MD; Ying Yin, PhD; Stuart J. Nelson, MD; Emily Capbarat, MD; Daniel Kerchner, MS; Homa K. Ahmadzia, MD, MPH

BACKGROUND: The impact of coronavirus disease 2019 (COVID-19) on adverse perinatal outcomes remains unclear.

OBJECTIVE: This study aimed to investigate whether COVID-19 is associated with adverse perinatal outcomes in a large national dataset and to examine the rates of adverse outcomes during the pandemic compared with the rates of adverse outcomes during the prepandemic period.

STUDY DESIGN: This observational cohort study included 683,905 patients, between the ages of 12 and 50, hospitalized for childbirth and abortion between January 1, 2019, and May 31, 2021. During the prepandemic period, 271,444 women were hospitalized for childbirth. During the pandemic, 308,532 women were hospitalized for childbirth, and 2708 women had COVID-19. The associations between COVID-19 and inhospital adverse perinatal outcomes were examined using propensity score—adjusted logistic regression.

RESULTS: Women with COVID-19 were more likely to experience both early and late preterm birth (adjusted odds ratios, 1.38 [95% confidence interval, 1.1–1.7] and 1.62 [95% confidence interval, 1.3–1.7], respectively), preeclampsia (adjusted odds ratio, 1.2 [95% confidence interval, 1.0–1.4]), disseminated intravascular coagulopathy (adjusted odds ratio, 1.57 [95% confidence interval, 1.1–2.2]), pulmonary edema (adjusted odds ratio, 2.7 [95% confidence interval, 1.1–6.3]), and need for mechanical ventilation (adjusted odds ratio, 8.1 [95% confidence interval, 3.8–17.3]) than women without COVID-19. There was no significant difference in the prevalence of stillbirth among women with COVID-19 (147 [95% confidence interval, 3.0–292.0] vs 2.5 [95% confidence interval, 0.0–7.5] deaths per 100,000 women). Women diagnosed with COVID-19 within 30 days before hospitalization were more likely to experience early preterm birth, placental abruption, and mechanical ventilation than women diagnosed with COVID-19 >30 days before hospitalization for childbirth (4.0% vs 2.4% for early preterm birth [adjusted odds ratio, 1.7; 95% confidence interval, 1.1–2.7]; 2.2% vs 1.2% for placental abruption [adjusted odds ratio, 1.86; 95% confidence interval, 1.0–3.4]; and 0.9% vs 0.1% for mechanical ventilation [adjusted odds ratio, 13.7; 95% confidence interval, 1.8–107.2]).

CONCLUSION: Women with COVID-19 had a higher prevalence of adverse perinatal outcomes and increased in-hospital mortality, with the highest risk occurring when the diagnosis was within 30 days of hospitalization, raising the possibility of a high-risk period.

Key words: adverse perinatal outcomes, COVID-19, high-risk pregnancy

Introduction

Scientific consensus has yet to be achieved regarding the clinical impact of COVID-19 in pregnancy. A recent meta-analysis of a global population demonstrated worsened maternal and fetal outcomes during the COVID-19 pandemic, with large disparities between high- and low-resource countries. Although some studies support this meta-analysis, other studies have demonstrated a mixed effect of the impact of COVID-19 on pregnancy. Of note, one of the largest US study showed a significant difference in mortality rates, intensive care unit admission, and preterm birth among women with COVID-19. However, most US studies were smaller in size and were conducted during the first few months of the pandemic, before the largest increase in COVID-19 case numbers and fatalities in the United States, during fall and winter of 2020. We used a large cohort to study the effect of COVID-19 on perinatal outcomes. We investigated the relationship between the timing of COVID-19 diagnosis and childbirth to adverse perinatal outcomes. In addition, we examined the change in adverse perinatal outcomes by comparing the 14-month pandemic period to the 13 months before the pandemic.

Methods

Women who gave birth between January 1, 2019, and May 31, 2021, were identified by International Statistical Classification of Disease and Related Health Problems, Tenth Revision (ICD-10) codes from Cerner Real-World Data, which is extracted from the electronic health records of hospitals with which Cerner has a data use agreement. Childbirth during the pandemic was defined as occurring between March 1, 2020, and May 31, 2021, whereas childbirth before the pandemic (prepandemic period) was defined as occurring between January 1, 2019, and February 28, 2020. Race and ethnicity were self-reported, body mass index was calculated using measured height and weight, COVID-19 status was determined using the COVID-19 polymerase chain reaction (PCR) test result, and comorbidities and inhospital outcomes were identified using the ICD-10 and billing codes (Appendix 1). The cohort with COVID-19 included only women with a positive PCR result during pregnancy. The cohort without COVID-19 included women with a negative PCR result on admission who never had a positive PCR result during pregnancy. The
difference between the date of hospitalization and PCR test result was used to calculate the days since COVID-19. Early and late preterm births were defined as live births between 24 and 33 and 34 and 36 completed weeks of gestation, respectively. Stillbirth was defined as fetal death >19 completed weeks of gestation.

The percentage of women with COVID-19 by first, second, and third trimesters of pregnancy were 12.7%, 26.1%, and 61.2%, respectively. Of note, 877 pregnant women with a positive COVID-19 PCR result were excluded (592 women did not have a documented gestational age, and 285 women had a positive result before pregnancy). Most COVID-19 diagnoses occurred near hospitalization, with 49.5% within 0 to 30 days, 10.2% within 31 to 60 days, 17.6% within 61 to 120 days, and 22.6% >120 days before hospitalization.

The institutional review board approved the study protocol and waived the requirement for patient informed consent. Multivariable logistic regression was used to derive a propensity score of COVID-19 based on baseline conditions to estimate the probability of developing COVID-19 as a function of 17 baseline covariates, including age, ethnicity, race, single-digit zip code, trimester, asthma, autoimmune disease, chronic hypertension, chronic kidney disease, gestational hypertension, gestational diabetes mellitus, major mental illness, morbid obesity, obesity, pregestational diabetes mellitus, pulmonary disease, and tobacco use. The associations between COVID-19 and in-hospital outcomes were examined using propensity score–adjusted regression. Analyses were conducted using scikit-learn and statsmodels Python Library, with a 2-tailed P value of <.05 considered significant. Categorical variables, such as demographics, preexisting conditions, and outcomes, were compared using the chi-squared test. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.11

**Results**

During the pandemic, 308,532 women were hospitalized for childbirth. Of those tested, 39,562 had a negative COVID-19 PCR result, and 2708 (6.4%) had COVID-19. Of those who tested positive, 1342 (49.5%) were diagnosed with COVID-19 within 30 days before hospitalization for childbirth. Women with COVID-19 were younger, more likely to identify as Hispanic, and more likely to have comorbid asthma, pulmonary disease, hypertension, gestational hypertension, diabetes mellitus, gestational diabetes mellitus, obesity, or morbid obesity than women without COVID-19 (Table 1).

Women with COVID-19 were more likely to experience preterm birth (early preterm birth, 3.2% vs 2.2%; adjusted odds ratio [aOR], 1.38; 95% confidence interval [CI], 1.1–1.7), late preterm birth (9.0% vs 5.8%; aOR, 1.62; 95% CI, 1.3–1.7), preeclampsia (8.0% vs 6.1%; aOR, 1.2; 95% CI, 1.0–1.4), placental abruption (1.7% vs 0.9%; aOR, 1.86; 95% CI, 1.4–2.5), disseminated intravascular coagulopathy [DIC] (1.3% vs 0.8%; aOR, 1.57; 95% CI, 1.1–2.2), and pulmonary edema (0.3% vs 0.1%; aOR, 2.67; 95% CI, 1.0–6.3) and require mechanical ventilation (0.5% vs 0.05%; aOR, 8.12; 95% CI, 3.8–17.3) (Table 2).

Women diagnosed with COVID-19 within 30 days of hospitalization for childbirth had the highest prevalence of adverse perinatal outcomes (Appendix 2). Among women diagnosed with COVID-19 in pregnancy, women diagnosed with COVID-19 within 30 days of hospitalization for childbirth had the highest risk of early preterm birth (4.0% vs 2.4%; aOR, 1.7; 95% CI, 1.1–2.6), placental abruption (2.2% vs 1.2% aOR, 1.8; 95% CI, 1.0–3.4), and need for mechanical ventilation (0.9% vs 0.1%; aOR, 13.7; 95% CI, 1.8–107.1) (Table 2).

In-hospital mortality was significantly higher for women with COVID-19 than women without COVID-19 (147 [95% CI, 3.0–292] vs 2.5 [95% CI, 0.0–7.5] deaths per 100,000 women; P<.0001). Most in-hospital deaths among women with COVID-19 occurred in women who were diagnosed with COVID-19 within 30 days of hospitalization (Appendix 2).

There was no significant difference in the prevalence of stillbirth between women with and without COVID-19 (0.6% vs 0.5%; aOR, 1.46; 95% CI, 0.8–2.4) (Table 2). However, the prevalence of stillbirths occurring in women diagnosed with COVID-19 within the previous 30 days was significantly greater than women diagnosed with
COVID-19 31 to 60, 60 to 120, or >120 days before hospitalization (11/16 [68.8%], 0/16 [0%], 3/16 [18.7%], and 2/16 [12.5%], respectively; \( P < .001 \)) (Appendix 2). A similar pattern was observed for the prevalence of placental abruption, DIC, preterm premature rupture of membranes (PPROM), and need for mechanical ventilation (Appendix 2).

During the prepandemic period, 271,444 women were hospitalized for childbirth. Women hospitalized for childbirth during the pandemic period were more likely to have comorbid...
### TABLE 2
Comparison of inhospital outcomes of pregnant woman during the COVID-19 pandemic based on COVID-19 status

| Outcome                  | Without COVID-19 (n=39,562) | COVID-19 positive (n=2708) | COVID-19 within 30 d (n=1342) |
|--------------------------|------------------------------|---------------------------|------------------------------|
| Early preterm birth      | 84 (2.2)                     | 84 (3.2)                  | 52 (4.0)                     |
| Late preterm birth       | 2230 (5.8)                   | 239 (9.0)                 | 113 (8.6)                    |
| Term birth               | 35,646 (92.3)                | 2349 (9.0)                | 1151 (87.7)                  |
| Cesarean delivery        | 12,916 (33.4)                | 826 (31.1)                | 419 (31.9)                   |
| Birthweight (g)          | 3400 (2950–3785)             | 3418 (3093–3780)          | 3396 (2698–3769)             |
| PPROM                    | 814 (2.2)                    | 84 (3.2)                  | 52 (4.0)                     |
| Stillbirth               | 174 (0.5)                    | 16 (0.6)                  | 11 (0.8)                     |
| Blood product transfusion| 237 (0.6)                    | 23 (0.9)                  | 15 (1.1)                     |
| Sepsis                   | 71 (0.2)                     | 22 (0.8)                  | 19 (1.4)                     |
| Shock                    | 2313 (5.9)                   | 161 (6.0)                 | 91 (6.8)                     |
| Preeclampsia             | 2407 (6.1)                   | 215 (7.9)                 | 103 (7.7)                    |
| Eclampsia                | 21 (0.1)                     | 7 (0.3)                   | 2 (0.2)                      |
| DIC                      | 345 (0.9)                    | 35 (1.3)                  | 21 (1.6)                     |
| HELLP                    | 76 (0.2)                     | 6 (0.2)                   | 4 (0.3)                      |
| Myocardial infarction    | 8 (0.0)                      | 4 (0.2)                   | 2 (0.2)                      |
| VTE                      | 55 (0.1)                     | 5 (0.2)                   | 3 (0.2)                      |
| Mechanical ventilation   | 18 (0.1)                     | 13 (0.5)                  | 12 (0.8)                     |
| Length of stay           | 3 (3–4)                      | 3 (3–4)                   | 3 (3–4)                      |
| Discharge disposition    |                              |                           |                              |
| Home                     | 38,117 (96.4)                | 2610 (96.4)               | 1299 (96.8)                  |
| Postacute care           | 324 (0.8)                    | 37 (1.4)                  | 12 (0.9)                     |
| Death                    | 1 (0.0)                      | 4 (0.1)                   | 3 (0.2)                      |
| Rehab                    | 209 (0.5)                    | 10 (0.4)                  | 8 (0.6)                      |
| Hospice                  | 49 (0.1)                     | 1 (0.0)                   | 1 (0.1)                      |
| Other                    | 862 (2.2)                    | 46 (1.7)                  | 19 (1.4)                     |

ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulopathy; HELLP, hemolysis, elevated liver enzymes, low platelet count; IQR, interquartile range; OR, odds ratio; PPROM, preterm premature rupture of membranes; VTE, venous thromboembolism.

* Trimester-specific information was missing for 10.4% of patients with COVID. ** Adjusted for propensity score, which estimates the probability of developing COVID-19 as a function of 17 baseline covariates, including age, race, ethnicity, single-digit zip code, trimester, chronic kidney disease, asthma, pulmonary disease, autoimmune disease, chronic hypertension, gestational hypertension, pregestational diabetes mellitus, gestational diabetes mellitus, major mental illness, morbid obesity, obesity, and tobacco use. The propensity score was defined as the logistic regression of the predicted probability of COVID-19 status; ` Statistically significant outcomes, \( P < 0.05 \); ' Birthweight in grams reported as median (IQR); " Myocardial infarction was defined as the composite of myocardial infarction and cardiac arrest; ' Length of stay in days reported as median (IQR).

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gestational diabetes mellitus, gestational hypertension, hypertension, obesity, morbid obesity, and major mental illness than women hospitalized for childbirth during the prepandemic period (Appendix 3). Compared with women who delivered during the prepandemic period, there was no significant difference in the number of stillbirths, the prevalence of early or late preterm birth, or in-hospital mortality among women who delivered during the pandemic period (Table 3).

**Discussion**

**Principal findings**

In a large cohort of US women hospitalized for childbirth, we found that inhospital mortality, preterm birth, preeclampsia, placental abruption, and DIC were statistically significantly higher among women with COVID-19 than women without COVID-19. Women with COVID-19 who were diagnosed within 30 days of hospitalization had the highest prevalence of in-hospital mortality, stillbirth, placental abruption, PPROM, DIC, early and late preterm births, and need for mechanical ventilation.

**Results**

To date, this is the third-largest US cohort of pregnancies during the COVID-19 pandemic and the second-largest US cohort of patients with COVID-19. The use of a large childbirth cohort enabled us to detect statistically significant differences in mortality and adverse outcomes, even though absolute rates of death and adverse perinatal outcomes were low overall. Moreover, we could demonstrate a temporal effect of COVID-19 on adverse perinatal outcomes, suggesting a high-risk period.

Our findings of increased risk of preterm birth, preterm labor, and development of preeclampsia among women found to have COVID-19 who were hospitalized for childbirth have not been consistently reported in previous US studies, which may be because of a longer study period, larger sample size in the current study, and the development of novel variants during the study period. Interestingly, in the largest reported US cohort to date, Chinn et al demonstrated a greater degree of risk of preterm birth among women diagnosed with COVID-19 and hospitalized for childbirth than the current study. However, unlike Chinn et al, our study accounted for differences in preexisting comorbid conditions in the cohort, which may account for the variation.

This study did not demonstrate a difference between the prevalence of adverse perinatal outcomes in the year preceding the pandemic and the first 16 months of the pandemic, which was surprising, given the disruptive nature of the COVID-19 pandemic. Some studies have reported decreased prematurity birth rates during the pandemic; however, smaller sample sizes and shorter study periods may have biased

| Outcome                      | Prepandemic \(n=271,444\) | Pandemic \(n=308,532\) | \(P\) value |
|------------------------------|----------------------------|-------------------------|-------------|
| Early preterm                | 7848 (2.9)                 | 9059 (2.9)              | .317        |
| Late preterm                 | 8,182 (6.9)                | 21,573 (7.0)            | .373        |
| Term                         | 221,135 (81.5)             | 252,190 (81.7)          | .252        |
| Cesarean delivery            | 70,008 (25.8)              | 81,556 (26.4)           | .001        |
| Birthweightb                 | 3332 (2885–3760)           | 3327 (2888–3740)        |             |
| PPROM                        | 8115 (2.5)                 | 8999 (2.5)              | .183        |
| Stillbirth                   | 1697 (0.6)                 | 2018 (0.7)              | .170        |
| Blood product transfusion    | 3044 (0.9)                 | 3665 (1.0)              | .012        |
| Sepsis                       | 561 (0.2)                  | 598 (0.1)               | .308        |
| Shock                        | 19,416 (6.1)               | 22,069 (6.1)            | .663        |
| Preeclampsia                 | 19,131 (6.0)               | 22,895 (6.3)            | <.001       |
| Eclampsia                    | 241 (0.1)                  | 330 (0.1)               | .024        |
| DIC                          | 1933 (0.6)                 | 2289 (0.6)              | .143        |
| HELLP                        | 755 (0.2)                  | 840 (0.2)               | .733        |
| Myocardial infarctionc       | 58 (0.0)                   | 96 (0.0)                | .021        |
| VTE                          | 378 (0.1)                  | 465 (0.1)               | .229        |
| Mechanical ventilation       | 80 (0.0)                   | 133 (0.0)               | .006        |
| Length of stayd              | 3 (2–4)                    | 3 (2–4)                 |             |
| Discharge disposition        |                            |                         |             |
| Home                         | 246,659 (90.6)             | 281,286 (91.2)          |             |
| Postacute care               | 9259 (3.4)                 | 9811 (3.1)              |             |
| Death                        | 27 (0.0)                   | 39 (0.0)                | .231        |
| Hospice                      | 39 (0.0)                   | 132 (0.0)               |             |
| Rehabilitation               | 815 (0.3)                  | 916 (0.3)               |             |
| Other or unknown             | 14,645 (5.3)               | 16,348 (5.2)            |             |

DIC, disseminated intravascular coagulopathy; HELLP, hemolysis, elevated liver enzymes, low platelet count; IQR, interquartile range; PPROM, preterm premature rupture of membranes; VTE, venous thromboembolism.

* a The prepandemic period includes hospitalizations between January 01, 2019, and February 28, 2020. The pandemic period includes hospitalizations between March 01, 2020, and May 31, 2021. b Birthweight in grams reported as median (IQR). c Myocardial infarction was defined as the composite of myocardial infarction and cardiac arrest. d Length of stay in days reported as median (IQR).

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Lastly, low case rates and residual confounding may have experienced selection bias toward more frequent testing. Furthermore, this study was unable to provide information about the severity of COVID-19 among patients who tested positive. This study was unable to differentiate iatrogenic preterm birth from spontaneous preterm birth, which may be an important driver of preterm birth. Lastly, low case rates and residual confounding may further impact the clinical significance of the results.

Clinical implications
Despite the limitations, our study, which focused on a longer peak period of COVID-19, demonstrated that women hospitalized for childbirth with a history of COVID-19 have a higher prevalence of adverse perinatal outcomes and increased in-hospital mortality, consistent with previously reported global results. Future investigation is warranted and should include the delineation of a high-risk period for adverse perinatal outcomes after COVID-19 diagnosis, as enhanced antenatal surveillance may be warranted for women recently diagnosed with COVID-19.

Conclusion
Women with COVID-19 had a higher prevalence of adverse perinatal outcomes and increased in-hospital mortality, with the highest risk period occurring when a COVID-19 test positive result was present within 30 days of hospitalization for childbirth.

Supplementary materials
Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ajogmf.2022.100577.

References
1. Cmielewskia B, Barratt I, Townsend R, et al. Effects of the COVID-19 pandemic on maternal and perinatal outcomes: a systematic review and meta-analysis. Lancet Glob Health 2021;9: e759–72.
2. Jering KS, Claggett BL, Cunningham JW, et al. Clinical characteristics and outcomes of hospitalized women giving birth with and without COVID-19. JAMA Intern Med 2021;181:714–7.
3. Chinn J, Sedighim S, Kirby KA, et al. Characteristics and outcomes of women with COVID-19 giving birth at US academic centers during the COVID-19 pandemic. JAMA Netw Open 2021;4:e2120456.
4. Janjevic T, Glazer KB, Vieira L, et al. Racial/ethnic disparities in very preterm birth and preterm birth before and during the COVID-19 pandemic. JAMA Netw Open 2021;4:e211816.
5. Handley SC, Mullin AM, Elovitz MA, et al. Changes in preterm birth phenotypes and stillbirth at 2 Philadelphia hospitals during the SARS-CoV-2 pandemic, March–June 2020. JAMA 2021;325:87–9.
6. Huntley BJF, Mulder IA, Di Mascio D, et al. Adverse pregnancy outcomes among individuals with and without severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): a systematic review and meta-analysis. Obstet Gynecol 2021;137:585–96.
7. Adhikari EH, Moreno W, Zofkie AC, et al. Pregnancy outcomes among women with and without severe acute respiratory syndrome coronavirus 2 infection. JAMA Netw Open 2020;3:e2029256.
8. Johns Hopkins University of Medicine. Coronavirus resource center. 2021. Available at: https://coronavirus.jhu.edu/map.html. Accessed June 1, 2021.
9. Pedregosa F, Varoquaux G, Gramfort A, et al. Scikit-learn: machine learning in Python. J Mach Learn Res 2011;12:2825–30.
10. Seabold S, Statmodelsp J. Econometric and statistical modeling with Python. Proc 9th Python Sci Conf 2010;57:61.
11. Vandenbergroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Ann Intern Med 2007;147:W163–94.
12. Webb Hooper M, Nápoles AM, Pérez-Stable EJ. COVID-19 and racial/ethnic disparities. JAMA 2020;323:2466–7.
13. Kim SJ, Bostwick W. Social vulnerability and racial inequality in COVID-19 deaths in Chicago. Health Educ Behav 2020;47:509–13.
14. Wadhera RK, Wadhera P, Gaba P, et al. Variation in COVID-19 hospitalizations and deaths across New York City boroughs. JAMA 2020;323:2192–5.
15. Hedermann G, Hedley PL, Bakvd-Hansen M, et al. Danish premature birth rates during the COVID-19 lockdown. Arch Dis Child Fetal Neonatal Ed 2021;106:93–5.
16. Meyar R, Bart T, Tsur A, et al. A marked decrease in preterm deliveries during the coronavirus disease 2019 pandemic. Am J Obstet Gynecol 2021;224:234–7.

Author and article information
From the Department of Obstetrics and Gynecology, George Washington University, Washington, DC (Els Litman and Capbarat); Biomedical Informatics Center, George Washington University, Washington, DC (Drs Yin and Nelson); George Washington University Libraries, George Washington University, Washington, DC (Mr Kerchner); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, George Washington University, Washington, DC (Dr Ahmadzia).
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Corresponding author: Ethan A Litman, MD. elitman@gwu.edu

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