Original Research

Coronavirus Disease 2019 (COVID-19) Pandemic and Pregnancy Outcomes in a U.S. Population

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OBJECTIVE: To examine whether the coronavirus disease 2019 (COVID-19) pandemic altered risk of adverse pregnancy-related outcomes and whether there were differences by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection status among pregnant women.

METHODS: In this retrospective cohort study using Epic's Cosmos research platform, women who delivered during the pandemic (March–December 2020) were compared with those who delivered prepandemic (matched months 2017–2019). Within the pandemic epoch, those who tested positive for SARS-CoV-2 infection were compared

with those with negative test results or no SARS-CoV-2 diagnosis. Comparisons were performed using standardized differences, with a value greater than 0.1 indicating meaningful differences between groups.

RESULTS: Among 838,489 women (225,225 who delivered during the pandemic), baseline characteristics were similar between epochs. There were no significant differences in adverse pregnancy outcomes between epochs (standardized difference<0.10). In the pandemic epoch, 108,067 (48.0%) women had SARS-CoV-2 testing available; of those, 7,432 (6.9%) had positive test results. Compared with women classified as negative for SARS-CoV-2 infection, those who tested positive for SARS-CoV-2 infection were less likely to be non-Hispanic White or Asian or to reside in the Midwest and more likely to be Hispanic, have public insurance, be obese, and reside in the South or in high social vulnerability ZIP codes. There were no significant differences in the frequency of preterm birth (8.5% vs 7.6%, standardized difference=0.032), stillbirth (0.4% vs 0.4%, standardized difference=−0.002), small for gestational age (6.4% vs 6.5%, standardized difference=−0.002), large for gestational age (7.7% vs 7.7%, standardized difference=−0.001), hypertensive disorders of pregnancy (16.3% vs 15.8%, standardized difference=0.014), placental abruption (0.5% vs 0.4%, standardized difference=0.007), cesarean birth (31.2% vs 29.4%, standardized difference=0.039), or postpartum hemorrhage (3.4% vs 3.1%, standardized difference=0.019) between those who tested positive for SARS-CoV-2 infection and those classified as testing negative.

CONCLUSION: In a geographically diverse U.S. cohort, the frequency of adverse pregnancy-related outcomes did not differ between those delivering before compared with during the pandemic, nor between those classified as positive compared with negative for SARS-CoV-2 infection during pregnancy.

See related editorial on page 539.

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected millions of people in the United States,[1] and the coronavirus disease 2019 (COVID-19) pandemic has created an enormous health burden, significantly affecting health care delivery and utilization.[2,3] It is unknown whether the stressors and disruptions associated with the COVID-19 pandemic altered the risk of adverse pregnancy outcomes for women as a whole or if risk for such outcomes was conferred only to women acquiring SARS-CoV-2 infection during pregnancy.

To date, most studies examining pregnancy outcomes related to the COVID-19 pandemic compare birth outcomes among all pregnant women in the prepandemic and pandemic periods without assessing the SARS-CoV-2 infection status of included individuals.[4–11] Studies specifically assessing pregnant women with and without SARS-CoV-2 infection[12–14] are limited by their inability to distinguish outcomes between those with true-negative results and those untested for infection. This is a noteworthy limitation because there may be selectivity in the pregnant women referred for testing. In addition, the current literature has not yet distinguished between the downstream effects of societal disruptions caused by the pandemic and SARS-CoV-2 infection on pregnancy-related outcomes.

To address these limitations, this study had two main objectives: 1) to compare pregnant women who delivered before the COVID-19 pandemic with those who delivered during the COVID-19 pandemic to investigate whether the pandemic and its disruptions were associated with changes in adverse pregnancy-related outcomes independent of individual SARS-CoV-2 infection status; and 2) among those with evidence of SARS-CoV-2 testing during pregnancy, to examine whether SARS-CoV-2 infection was associated with adverse pregnancy-related outcomes compared with those classified as negative for SARS-CoV-2 infection.

METHODS

This retrospective cohort study was performed using data in Epic's Cosmos research platform.[15] Epic Systems Corporation provides electronic health record (EHR) software and related services to roughly one third of the hospitals in the United States. Currently, 117 Epic health systems and their combined 100 million patients have contributed data to Cosmos. Cosmos collects a Health Insurance Portability and Accountability Act–defined limited data set from participating health systems that use Epic's software and aggregates these data to support research, public health, and health care operations activities. Patients with records at more than one health care organization are deduplicated across participating organizations in Cosmos. For this study, all hospital departments with more than 100 births annually that are part of health systems that had at least 3 years of prepandemic data in Cosmos were included, representing 79% of the health systems participating in Cosmos. All women who delivered after 24 weeks of gestation were included. Women with multiple gestation pregnancies and those with missing outcome data were excluded.

Two epochs were created: the pandemic epoch, spanning March 1, 2020 (when COVID-19 cases first became widely reported in the United States), to December 31, 2020; and the prepandemic epoch, inclusive of matched months (to account for seasonality) in the 3 years before the pandemic (2017–2019). Two comparisons were made: 1) all eligible pregnant women who delivered in the 3 years before the pandemic compared with all those who delivered during the COVID-19 pandemic; and 2) within the COVID-19 epoch, women classified as positive for SARS-CoV-2 infection compared with those classified as negative for SARS-CoV-2 infection during their pregnancies or their delivery hospitalizations.

Baseline patient and area-level characteristics were obtained, including maternal age, race and ethnicity, insurance type, prepregnancy body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), pre-existing medical comorbidities, overall Social Vulnerability Index, urbanicity, and Census region. Age was defined as the mother's age on the date she gave birth. Given the data that certain racial and ethnic groups are at increased risk for COVID-19 and its sequelae,[16–18] race and ethnicity were examined as documented in the EHR. Race and ethnicity were classified as Non-Hispanic White, Non-Hispanic Black, Hispanic, Asian, or Other. The "Other" category was inclusive of "American Indian or Alaskan Native," "Native Hawaiian or Other Pacific Islander," or "Other," which is a selectable category for some included hospital systems. Patients with public insurance were defined as those who had at least one insurance carrier with a financial class of Medicare or Medicaid documented at the birth admission. If the prepregnancy BMI was not available, it was estimated by subtracting the recommended weight gain during pregnancy per week in each trimester[19] from the earliest weight obtained during pregnancy. Pre-existing medical comorbidities were determined using International Classification of Diseases, Tenth Revision, Clinical

Modification (ICD-10-CM) diagnostic codes (Appendix 1, available online at http://links.lww.com/AOG/C409). Each patient's home address ZIP code was used to determine the Social Vulnerability Index, urbanicity, and Census region. The Centers for Disease Control and Prevention's Social Vulnerability Index[20] comprises indicators of socioeconomic status, household composition, disability, minority status, and language. For each ZIP code, the weighted average of composite Social Vulnerability Index across all Census tracts overlapping the ZIP code was calculated based on relative population. For urbanicity, mapping of ZIP codes to rural-urban commuting area codes was obtained from the U.S. Department of Agriculture.[21] Rural-urban commuting area codes 1 through 3 were considered urban.

In the COVID-19 pandemic epoch, women were considered tested for SARS-CoV-2 infection during pregnancy if at least one SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) test result was available or if the presence of the ICD-10-CM code for confirmed COVID-19 (U07.1) was observed from the date of estimated conception through the delivery hospitalization encounter. Women without either of these indicators were considered untested for SARS-CoV-2 infection during pregnancy. Among those who were tested for SARS-CoV-2 infection during pregnancy, a woman was classified as positive if there was any positive RT-PCR result, independent of the number of tests performed during pregnancy, or if the ICD-10-CM code U07.1 was observed. If at least one negative RT-PCR test result and no positive RT-PCR test results were identified and no ICD-10-CM code U07.1 was recorded, the woman was considered tested negative.

The pregnancy-related outcomes were hypertensive disorders of pregnancy inclusive of gestational hypertension, preeclampsia, eclampsia, and hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome; placental abruption; cesarean birth; and postpartum hemorrhage. The neonatal outcomes were preterm birth at less than 37 weeks of gestation, stillbirth, and birth weights small or large for gestational age. Small for gestational age was defined as birth weight less than the 10th percentile for gestational age at birth; large for gestational age was defined as birth weight greater than the 90th percentile for gestational age at birth.[22] Gestational age at birth, mode of delivery, and neonatal birth weight were available discretely in the EHR. The other outcome measures were determined using ICD-10-CM diagnostic codes recorded in the EHR (Appendix 1, http://links.lww.com/AOG/C409).

All comparisons between groups were made using standardized differences. Standardized differences compare the proportions–formulated as a series of one-vs-rest comparisons for categorical variables–in units of the pooled standard deviation.[23,24] A standardized difference with an absolute value greater than 0.1 indicates meaningful difference between groups.[23] With a large sample, hypothesis testing (eg, χ^2 test) is likely to demonstrate a significant P value even when the difference in outcome between groups is negligible or meaningless (due to chance).[25,26] Standardized differences are not influenced by sample size and have been used to evaluate meaningful differences between groups in large cohort studies.[27–29]

Both comparisons (prepandemic vs pandemic epochs, positive vs negative for SARS-CoV-2 infection) were also stratified by race and ethnicity, high-risk Social Vulnerability Index, and public insurance type to test whether there were changes in the observed outcomes due to potential effect modification by these covariates.

Although standardized difference analyses were favored for interpretation in this study, given the smaller cohort of women who had evidence of testing, χ^2 tests (two-sided with $P=.01$) were also performed to compare women positive for SARS-CoV-2 infection with those negative for SARS-CoV-2 infection. Two post hoc mixed-effects logistic regression models were used to further examine the association between women with SARS-CoV-2 positivity during pregnancy and the risk for preterm birth at less than 37 weeks of gestation and the risk for cesarean birth, because these associations were found to have P-values less than .01 with χ^2 analyses. The models were adjusted for relevant baseline characteristics ($P<.01$) and included hospital system as a random intercept.

Among women who were classified as positive for SARS-CoV-2 infection during pregnancy, we also compared women who were classified as positive during the first two trimesters of pregnancy (from estimated date of conception to 28 weeks of gestation) with those classified as positive during the third trimester of pregnancy (28 weeks of gestation and greater). For the outcome of preterm birth at less than 37 weeks of gestation, comparison between groups was made after excluding women who could not have reached term (37 0/7 weeks) gestation by the end of the study period and women who tested positive for SARS-CoV-2 infection at 37 weeks of gestation or later, because they could not have experienced the outcome of preterm birth after the exposure. Comparisons were made using standardized differences.

All calculations were based on the number of valid observations. Analysis was completed using Python v.3.8.5 (numpy v.1.19.1, pandas v.1.0.5, scipy v.1.5.0). This study was considered exempt from the Yale University Institutional Review Board because all data were deidentified.

RESULTS

A total of 838,489 women delivering at 465 U.S. hospitals were included in this analysis (Fig. 1). Overall 613,264 women delivered during the prepandemic epoch and 225,225 delivered during the pandemic epoch. Baseline sociodemographic characteristics and chronic medical comorbidities were similar between epochs (Table 1). There were no significant standardized differences in adverse pregnancy-related outcomes between the two epochs (Table 2).

Among the 225,225 women who delivered during the COVID-19 pandemic, 108,067 (48.0%) had evidence of at least one RT-PCR test performed for SARS-CoV-2 infection or an ICD-10-CM code for confirmed COVID-19 present in their EHR. There was no evidence of SARS-CoV-2 testing in the antenatal or delivery encounter records for 52.0% of pregnant women delivering during the COVID-19 pandemic. Women with evidence of testing were more likely to live in ZIP codes in the top 25th percentile Social Vulnerability Index (the most vulnerable population) compared with those without evidence of testing (15.0% vs 11.2% respectively, standardized difference=0.112). Women who had evidence of testing during pregnancy were less likely to live in the South compared with those without evidence of testing (32.1% vs 44.8%, standardized difference=−0.262).

Of those with evidence of SARS-CoV-2 testing (n=108,067), 7,432 (6.9%) had a positive test result or a COVID-19 diagnosis code in their EHR and 100,635 (93.1%) had only negative test results and no recorded COVID-19 diagnosis code. Women positive for SARS-CoV-2 infection were more likely to be Hispanic, less likely to be non-Hispanic White or Asian, more likely to have public insurance, more likely to be socially vulnerable, more likely to live in the South, less likely to live in the Midwest, and more likely to be obese compared with those considered negative for SARS-CoV-2 infection (Table 3). There were no significant standardized differences in adverse pregnancy-related outcomes between women considered positive compared with negative for SARS-CoV-2 infection in pregnancy (Table 4). With logistic regression modeling, after adjustment for potential confounders, there was similarly no significant association between SARS-CoV-2 positivity and preterm birth or cesarean birth (Table 5).
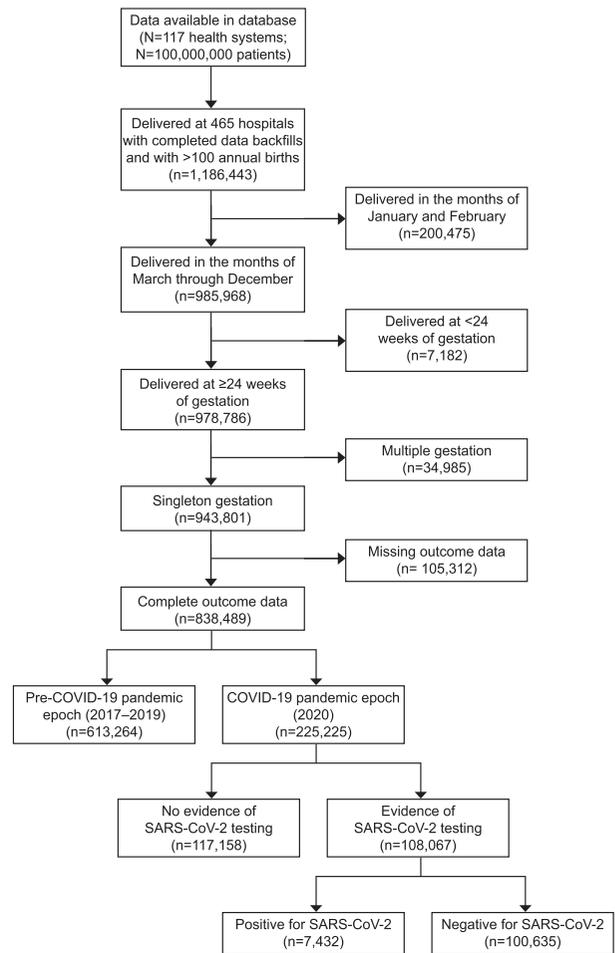

Fig. 1. Study cohort identification flow diagram. COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Son. COVID-19 Pandemic and Pregnancy Outcomes. Obstet Gynecol 2021.

Of the 7,432 women positive for SARS-CoV-2 infection, the majority (n=6,842, 92%) were tested during the third trimester of pregnancy compared with the first or second trimesters (n=590, 8%). Compared with women positive for SARS-CoV-2 infection during the third trimester, those who were positive in the first or second trimester of pregnancy were more likely to have private insurance, more likely to be obese, more likely to have asthma or chronic obstructive pulmonary disease or pregestational diabetes, more likely to live in the Midwest, and less likely to live in an urban area (Appendix 2, available online at http://links.lww.com/AOG/C409). Women positive for SARS-CoV-2 infection during the first or second trimester were less likely to experience preterm birth at less than 37 weeks of gestation compared with those who were positive in the third trimester of pregnancy

Table 1. Maternal Characteristics Before and During the Coronavirus Disease 2019 (COVID-19) Pandemic

	Epoch		
	Pre–COVID-19 Pandemic (n=613,264)	COVID-19 Pandemic (n=225,225)	Standardized Difference*
Maternal age (y)			
Younger than 20	29,616 (4.8)	10,294 (4.6)	0.012
20-34	479,359 (78.2)	174,754 (77.6)	0.014
35 or older	104,289 (17.0)	40,177 (17.8)	−0.022
Race and ethnicity[†]			
Non-Hispanic White	348,018 (56.7)	126,082 (56.0)	0.015
Non-Hispanic Black	101,030 (16.5)	38,033 (16.9)	−0.011
Hispanic	83,938 (13.7)	31,772 (14.1)	−0.012
Asian	26,285 (4.3)	10,224 (4.5)	−0.001
Other	23,192 (3.8)	8,036 (3.6)	0.003
Missing	30,801 (5.0)	4,908 (2.2)	0.006
Insurance type			
Public	129,478 (21.1)	52,990 (23.5)	−0.058
Private	423,854 (69.1)	165,284 (73.4)	−0.094
None, self-pay, or other	59,932 (9.8)	5,304 (2.4)	**0.275**
BMI (kg/m²)			
30 or higher (obese)	170,667 (27.8)	66,783 (29.7)	−0.040
Lower than 30 (nonobese)	408,754 (66.7)	148,830 (66.1)	0.012
Missing	33,843 (5.5)	9,612 (4.3)	0.058
Smoking status during pregnancy			
Current	51,095 (8.3)	13,888 (6.2)	0.084
Former	100,413 (16.4)	36,048 (16.0)	0.010
Never	436,006 (71.1)	166,396 (73.9)	−0.062
Missing	25,750 (4.2)	8,893 (3.9)	0.013
Asthma or COPD	56,015 (9.1)	22,768 (10.1)	−0.033
Chronic hypertension	29,051 (4.7)	12,860 (5.7)	−0.044
Pregestational diabetes	13,849 (2.3)	5,357 (2.4)	−0.008
Heart disease	25,266 (4.1)	10,077 (4.5)	−0.017
High-risk SVI[‡§]	85,583 (14.0)	29,386 (13.0)	0.027
Urban area[§]	549,906 (89.7)	201,322 (89.4)	0.009
Census region[§]			
Northeast	88,879 (14.5)	31,672 (14.1)	0.012
Midwest	188,824 (30.8)	71,291 (31.7)	−0.019
South	218,600 (35.6)	87,210 (38.7)	−0.064
West	116,650 (19.0)	35,010 (15.5)	0.092

COVID-19, coronavirus disease 2019; BMI, body mass index; COPD, chronic obstructive pulmonary disease; SVI, Social Vulnerability Index.

Data are n (%) unless otherwise specified.

* Any absolute value greater than 0.1 was considered significant imbalance and is bolded.

[†] Race or ethnic group was based on documentation in the electronic health record. This characteristic was examined because certain racial and ethnic groups have been identified to be at increased risk populations during the COVID-19 pandemic. The "Other" category is inclusive of "American Indian or Alaskan Native," "Native Hawaiian or Other Pacific Islander," or "Other," which is a selectable category for some included hospital systems.

[‡] High-risk SVI is the top quartile of SVI values across the cohort.

[§] Data are missing for 353 women (311 in the prepandemic epoch group and 42 in the pandemic epoch group, of whom 25 were in the tested group and 17 were in the untested group).

(12.9% vs 23.7%, standardized difference=−0.283) (Appendix 3, available online at http://links.lww.com/AOG/C409). There were no other significant differences in adverse pregnancy outcomes in the comparison between trimester of infection.

Analyses stratified by race and ethnicity, high-risk Social Vulnerability Index, and public insurance type did not show evidence of effect modification in adverse pregnancy outcomes across both comparisons (data not shown).

DISCUSSION

In this large, diverse U.S. cohort, the frequency of adverse pregnancy outcomes did not meaningfully

Table 2. Neonatal and Adverse Pregnancy Outcomes Before and During the Coronavirus Disease 2019 (COVID-19) Pandemic

Outcome	Epoch		Standardized Difference
	Pre–COVID-19 Pandemic (n=613,264)	COVID-19 Pandemic (n=225,225)	
Preterm birth*	47,286 (7.7)	17,205 (7.6)	0.003
Stillbirth	2,039 (0.3)	772 (0.3)	−0.002
Birth weight category			
SGA	41,760 (6.8)	14,657 (6.5)	0.012
AGA	525,152 (85.6)	193,075 (85.7)	−0.003
LGA	46,352 (7.6)	17,493 (7.8)	−0.008
HDP	83,764 (13.7)	34,573 (15.4)	−0.048
Placental abruption	2,355 (0.4)	907 (0.4)	−0.003
Cesarean birth	189,080 (30.8)	66,042 (29.3)	0.033
PPH	14,280 (2.3)	6,137 (2.7)	−0.025

COVID-19, coronavirus disease 2019; SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age; HDP, hypertensive disorders of pregnancy; PPH, postpartum hemorrhage.
Data are n (%) unless otherwise specified.
* Preterm birth is defined as birth before 37 weeks of gestation.

differ between those who delivered before compared with during the COVID-19 pandemic. Notably, in this study, nearly half of women who delivered during the pandemic had SARS-CoV-2 testing, and there were no differences between those positive compared with negative for SARS-CoV-2 infection during pregnancy.

Our finding that there was no meaningful difference in the frequency of preterm birth between women who delivered before compared with during the COVID-19 pandemic is consistent with much of the existing literature.[4–8] However, prior studies were limited in that they lacked data regarding SARS-CoV-2 testing status or included only those who tested positive for SARS-CoV-2 infection when making comparisons before and during the COVID-19 pandemic. Thus, this study is a significant contribution because we have SARS-CoV-2 testing results and diagnostic codes for almost half of the women who delivered in the pandemic epoch.

We found no significant changes in the frequency of other adverse pregnancy outcomes such as stillbirth during the COVID-19 pandemic. Although earlier case series and single-center data[4,30] suggested a higher frequency of stillbirth during the pandemic, a larger cohort using National Health Service data in England[31] did not find any increase in stillbirth frequency regionally or nationally. Notably, this larger cohort study did not have data available on maternal SARS-CoV-2 infection status, sociodemographic attributes, or access to medical care. With our large sample size inclusive of more than 7,000 women with

SARS-CoV-2 infection and availability of more comprehensive data, we were able to more rigorously evaluate infrequent outcomes such as stillbirth.

Our data indicate that many U.S. hospitals were not employing universal SARS-CoV-2 screening for pregnant women during the pandemic. Still, almost half of the women who delivered during the COVID-19 epoch in our cohort had evidence of SARS-CoV-2 testing during pregnancy. We found that pregnant women living in ZIP codes with a high-risk (top 25th percentile) overall Social Vulnerability Index were significantly more likely to have evidence of testing for SARS-CoV-2 during their pregnancies or delivery hospitalizations. Selective testing patterns may have been influenced by the awareness that those who are socioeconomically vulnerable are at disproportionately higher risk of SARS-CoV-2 infection.[32,33] Alternatively, hospitals that serve socially vulnerable populations may have prioritized or been better equipped to perform testing. Pregnant women delivering in the South were less likely to be tested for SARS-CoV-2 infection; those in the Northeast and Midwest were more likely to be tested. Regional testing patterns may have been influenced by the shifting geographical surges of SARS-CoV-2 infection during the study period, and there may have been regional differences in the prioritization or availability of resources for testing.

Among women who had evidence of SARS-CoV-2 testing, the positivity rate was 7%, which is consistent with previous work from multiple hospitals with varying sampling rates.[12] Many of the differences

Table 3. Maternal Characteristics of the Coronavirus Disease 2019 (COVID-19) Pandemic Epoch Group by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection Status

Characteristic	SARS-CoV-2 Infection Status		Standardized Difference*
	Positive (n=7,432)	Negative (n=100,635)	
Maternal age (y)			
Younger than 20	402 (5.4)	4,356 (4.3)	0.050
20-34	5,784 (77.8)	77,416 (76.9)	0.021
35 or older	1,246 (16.8)	18,863 (18.7)	−0.052
Race and ethnicity[†]			
Non-Hispanic White	3,404 (45.8)	58,413 (58.0)	**−0.247**
Non-Hispanic Black	1,456 (19.6)	16,529 (16.4)	0.082
Hispanic	1,584 (21.3)	15,097 (15.0)	**0.164**
Asian	212 (2.9)	4,900 (4.9)	**−0.105**
Other	351 (4.7)	3,667 (3.6)	0.054
Missing	425 (5.7)	2,029 (2.0)	**0.193**
Insurance type			
Public	2,292 (30.8)	22,832 (22.7)	**0.185**
Private	4,934 (66.4)	75,357 (74.9)	**−0.187**
None, self-pay, or other	206 (2.8)	2,446 (2.4)	0.021
BMI (kg/m^2)			
30 or higher (obese)	2,613 (35.2)	29,512 (29.3)	**0.125**
Lower than 30 (nonobese)	4,583 (61.7)	67,986 (67.6)	**−0.123**
Missing	236 (3.2)	3,137 (3.1)	0.003
Asthma or COPD	774 (10.4)	10,325 (10.3)	0.005
Chronic hypertension	498 (6.7)	5,391 (5.4)	0.056
Pregestational diabetes	258 (3.5)	2,326 (2.3)	0.069
Heart disease	417 (5.6)	4,598 (4.6)	0.047
High-risk SVI[‡][§]	1,416 (19.1)	14,815 (14.7)	**0.116**
Urban area[§]	6,866 (92.4)	90,727 (90.2)	0.079
Census region[§]			
Northeast	997 (13.4)	16,371 (16.3)	−0.080
Midwest	1,863 (25.1)	36,706 (36.5)	**−0.249**
South	3,514 (47.3)	31,227 (31.0)	**0.338**
West	1,057 (14.2)	16,307 (16.2)	−0.055

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; BMI, body mass index; COPD, chronic obstructive pulmonary disease; SVI, Social Vulnerability Index.

Data are n (%) unless otherwise specified.

* Any absolute value greater than 0.1 was considered significant and is bolded.

[†] Race or ethnic group was based on documentation in the electronic health record. This characteristic was examined because certain racial and ethnic groups have been identified to be at increased risk populations during the coronavirus disease 2019 (COVID-19) pandemic. The "Other" category is inclusive of "American Indian or Alaskan Native," "Native Hawaiian or Other Pacific Islander," or "Other," which is a selectable category for some included hospital systems.

[‡] High-risk SVI is the top quartile of SVI values across the cohort.

[§] Data are missing for 25 women (one in the positive SARS-CoV-2 infection group and 24 in the negative SARS-CoV-2 test group).

observed here in baseline characteristics between those considered positive compared with negative for SARS-CoV-2 infection have been similarly described in the existing literature.[32,34,35]

We did not find any meaningful differences in standardized differences in adverse pregnancy outcomes between women classified as positive compared with negative for SARS-CoV-2 infection, which differs from prior studies. However, it is important to note that our study was able to identify women with SARS-CoV-2 infection based mainly on laboratory testing and compare them with women confirmed negative for SARS-CoV-2 infection. This is a unique study strength because comparisons based solely on the presence or absence of a COVID-19 diagnosis code bias data with the inclusion of women with SARS-CoV-2 infection who are more likely to be symptomatic or exhibit more severe COVID-19 illness. A U.S. study[14] using the Premier Healthcare database included 406,446 women hospitalized for childbirth during the COVID-19 pandemic, of whom 6,380 (1.6%) had a COVID-19 ICD-10-CM billing code. In their study, women with a COVID-19 diagnosis code had significantly higher risks of preeclampsia and preterm birth compared with those without a COVID-19

Table 4. Neonatal and Adverse Pregnancy Outcomes Among Women With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Testing

	SARS-CoV-2 Infection Status		
Outcome	Positive (n=7,432)	Negative (n=100,635)	Standardized Difference
Preterm birth*	631 (8.5)	7,669 (7.6)	0.032
Stillbirth	26 (0.4)	366 (0.4)	−0.002
Birth weight category			
SGA	478 (6.4)	6,528 (6.5)	−0.002
AGA	6,383 (85.9)	86,337 (85.8)	0.003
LGA	571 (7.7)	7,770 (7.7)	−0.001
HDP	1,213 (16.3)	15,914 (15.8)	0.014
Placental abruption	35 (0.5)	428 (0.4)	0.007
Cesarean birth	2,320 (31.2)	29,593 (29.4)	0.039
PPH	253 (3.4)	3,094 (3.1)	0.019

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age; HDP, hypertensive disorders of pregnancy; PPH, postpartum hemorrhage.
Data are n (%) unless otherwise specified.
* Preterm birth is defined as birth before 37 weeks of gestation.

diagnosis code, but the study was limited by reliance on diagnosis codes to classify COVID-19 status and inability to distinguish between untested women and those testing negative. Similarly, the INTERCOVID multinational cohort study[36] found that women with a COVID-19 diagnosis were at higher risk for preeclampsia and eclampsia, severe infections, intensive care unit admission, maternal mortality, preterm birth, and severe perinatal morbidity compared with unmatched, consecutive women without a COVID-19 diagnosis. In this study, however, women were considered positive for COVID-19 based on multiple criteria (varying laboratory tests, radiologic findings, or predefined symptoms), whereas those considered not to have COVID-19 were simply women who did not meet the aforementioned criteria, not those who were known to be tested with a negative result.

Table 5. Mixed Effects Logistic Regression Models to Evaluate the Association Between Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Positivity and Pregnancy Outcomes

Outcome	Crude OR (95% CI)	Adjusted OR (95% CI)*
Preterm birth[†]	1.12 (1.01–1.26)	1.11 (0.98–1.25)
Cesarean birth	1.09 (1.02–1.16)	1.06 (0.99–1.13)

OR, odds ratio.
* Adjusted for maternal age, race and ethnicity, insurance type, high-risk Social Vulnerability Index, obesity, chronic hypertension, pregestational diabetes, heart disease, urban area, and hospital system as a random intercept.
[†] Preterm birth is defined as birth before 37 weeks of gestation.

In our cohort, among women positive for SARS-CoV-2 infection, the overwhelming majority were tested during their third trimester of pregnancy. In part, this finding could result from the fact that the cohort included only women who delivered during the 10-month study period, reducing the number of women who could have been both tested early in their pregnancy and delivered during the study period. Though we found that women who tested positive for SARS-CoV-2 infection during the third trimester of pregnancy were more likely to experience preterm birth, given the aforementioned limitation, this finding should be interpreted with caution and data are presented to generate hypotheses and drive further research.

Strengths of this study include the large number of pregnant women and diversity of U.S. hospitals included in the analytic cohort. The size of our cohort enabled us to examine pregnant women who delivered before and during the COVID-19 pandemic as well as the SARS-CoV-2 testing status of all individuals included in the pandemic epoch. This is unique to our study; prior studies have been limited by use of only the presence or absence of diagnosis codes for COVID-19 infection[14,36] or small numbers of confirmed tested women. Additionally, our data were obtained from 465 hospitals across all four U.S. Census Bureau regions. This is an important strength because SARS-CoV-2 cases have fluctuated significantly over time, with migratory geographical hotspots. In addition, we were able to include any SARS-CoV-2 testing results during the span of a pregnancy. This is valuable because certain outcomes (eg, preterm birth, hypertensive disorders of pregnancy, birth weight)

would have been difficult to evaluate if SARS-CoV-2 infection status was determined only at the time of delivery hospitalization, given inadequate latency between exposure and outcome. We recognize that outpatient SARS-CoV-2 testing may have been more variable, and testing earlier in a pregnancy may have been more likely in women who were symptomatic or had suspected or known exposures.

Our study has limitations. First, we could not distinguish between asymptomatic and symptomatic SARS-CoV-2 infection nor severity of disease, which has been shown to have differential effects on pregnancy outcomes.[37] Given the significant variability in how these data are reported (symptoms, clinical examination findings, and radiographic imaging results) and captured across health systems, these data could not be consistently abstracted from Cosmos. Second, positive SARS-CoV-2 infections may have been missed due to testing availability and testing practices, which likely varied across hospitals and over time. Patients who were tested for SARS-CoV-2 infection before their delivery hospitalizations also may have been missed if they were tested at a non-Epic facility or site that does not participate in Cosmos. Third, the gestational age at birth to determine preterm birth was based on the delivery date documented by the obstetrician, though there may have been deviations in accuracy based on the method used to determine gestational age for each included patient. Further, we were unable to determine whether a preterm birth was spontaneous or medically indicated; therefore, we cannot exclude the possibility that, although the overall preterm birth rate was not significantly different, indications for preterm births may have differed related to SARS-CoV-2 infection status or health care delivery and utilization. Encouragingly, however, a previous study did not show differences in preterm birth even when stratified by preterm birth phenotype.[6] Fourth, we did not assess early pregnancy outcomes such as miscarriage or pregnancy loss due to the inability to accurately ascertain these outcomes using EHR data and our decision to exclude women delivering before 24 weeks of gestation. Last, some of the outcomes examined are still rare occurrences (eg, stillbirth and placental abruption), and we were likely underpowered to adequately assess these outcomes despite our very large sample size.

In conclusion, in a large, geographically diverse U.S. cohort of pregnant women in which nearly half of women who delivered during the COVID-19 pandemic had evidence of SARS-CoV-2 testing, we found no meaningful differences in adverse pregnancy outcomes between those who delivered in the prepandemic and COVID-19 pandemic epochs. Pregnant women with evidence of SARS-CoV-2 infection had similar outcomes to those without evidence of viral infection. It is possible that COVID-19, disruption of health care delivery and utilization, or other unintended consequences may be offsetting one another with regard to pregnancy outcomes, or that symptomatic disease, severity of disease, or timing of disease during pregnancy may be more important prognostic factors.

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