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An Analysis of Preterm Birth Related to SARS-COV-2 Infection by Race

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ABSTRACT

Research investigating the association between pregnant women with COVID-19 infection and adverse birth outcomes, including preterm birth, having been contradicting. Individual differences between study populations, e.g., racial composition, may explain some of these inconsistencies. The aim of the present study is to determine if the association between SARS-CoV-2 infection and pre-term birth varies according to race.

A cross-sectional study was conducted using data from the Vizient Clinical Data Base/Research Manager (CDB/RM). The study participants were women who gave birth in one of the Vizient facilities between March 2020 and January 2021. A positive COVID-19 test status was the primary exposure with preterm birth (<37 weeks) being the primary outcome of interest. Logistic regression was used to estimate the association between COVID-19 and preterm birth adjusted for demographic and clinical characteristics, stratified by race.

There were 641,598 deliveries in the study population of which 12,035 (1.9%) were to women who had ever tested positive for SARS-CoV-2. The results suggested among those who were Black, Hispanic, or of other racial/ethnic group there was an increased odds ratio for the association between COVID-19 and preterm birth.

Current results suggest that COVID-19 is independently associated with pre-term birth in most racial and ethnic groups. The odds for some poor pregnancy outcomes also seem to be

higher among those who were COVID-19 positive. Future studies that explore the effects of COVID-19 on pregnancy outcomes should consider accounting for possible racial and ethnic variation.

Keywords: Preterm birth, COVID-19, SARS-CoV-2, Race

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INTRODUCTION

COVID-19 is the clinical disease caused by the SARS-CoV-2 virus. While all populations are at risk of SARS CoV-2, pregnant women are thought to be at increased risk of contracting the disease due to physiological respiratory and non-respiratory changes during pregnancy, including decreased lung volume, airway edema, increased oxygen consumption and altered cell immunity[1]. Similar to observations during the H1N1 pandemic[2], research suggests that adverse pregnancy outcomes, such as preterm birth, low birth weight, pre-eclampsia, and cesarean delivery, may be increased in women with SARS CoV-2 during pregnancy[3,4]. The importance of understanding the role of a viral infection during pregnancy, though not new, has grown substantially during the current COVID-19 pandemic[5].

Studies evaluating the association between SARS-CoV-2 infection and birth outcomes have compared either pre- and post-COVID-19 time periods or contemporaneous groups of COVID-19 positive and negative pregnant women. The former studies have not differentiated between COVID positive and negative women. The number of studies comparing birth outcomes among contemporaneous groups of COVID-19 positive and negative women has evolved from small, single center studies[6] to the largest study to date that includes nearly 900,000 women from almost 500 academic medical centers[7]. With respect to preterm birth, the results from these studies have been mixed with some studies reporting positive associations[7,8,9,10,11] and others reporting no association[3,12,13,14]. These studies have not been without limitations including limited sample size and a lack of geographic variability.

The risk of death is 70% higher in pregnant women with COVID-19 than in non-pregnant women[1]. In a study of 706 women with a COVID-19 diagnosis, the relative risk for preterm birth and fetal distress were elevated by 60% and 70%, respectively[15.] Similarly, women with symptomatic COVID-19 were more nearly four times as likely to give birth before 32 weeks' gestation and nearly twice as likely before 37 weeks' gestation[1]. Further, the risk of SARS-CoV-2 infection and certain infection-related outcomes including mortality are higher among minority groups[16,17]. Chinn et al. reported that pregnant women with COVID-19 were more likely to be Hispanic 43.1% or Black 22.3% and that women with COVID-19 were more likely to have a preterm birth (16.4%) compared to those without COVID-19 (11. 5%)[7].

To date, no study has stratified the association of SARS-CoV-2 infection and preterm birth by race. If racial differences exist, this may explain, in part, the heterogeneous findings among the prior studies that have included study populations with differing racial and ethnic compositions. To explore this issue further, the present study aims to determine whether the association between SARS-CoV-2 infection and pre-term birth varies according to race.

MATERIALS AND METHODS

Study Design and Data

A retrospective cross-sectional study was conducted using hospital discharge reports from Vizient Clinical Data Base/ Research Manager (CDB/RM). The Vizient database is sourced by a collection of academic medical centers across the United States[18]. This grouping of medical centers aims to improve institutional, clinical, operational, and financial performance across health systems. In efforts to maintain quality comparisons, Vizient creates a hospital discharge dataset, which includes all information regarding hospital discharge for which the medical centers contribute data. This dataset includes all aspects of standard discharge dataset (i.e., patient

demographics, discharge diagnoses, procedures and outcomes). All data used in this study was de-identified by Vizient to conform with the requirements of HIPAA. The study received approval from the Institutional Review Board of the University of Alabama at Birmingham.

Study Participants

Women who gave birth in one of the Vizient academic medical centers between March 2020 and January 2021 were identified using ICD-10 code Z37. X.

Variable Definitions

The primary exposure of interest was SARS-CoV-2 infection at any point in time prior to delivery, defined by the encounter having a billed diagnosis of ICD-10 code U07.1. Demographic characteristics were also obtained such as age and race/ethnicity. Race/ethnicity were self-reported variables and included in the analysis based on the Vizient classification. These categories were Asian, Black, Hispanic, White, Other and Unknown. Maternal comorbidities including gestational diabetes (ICD-10:024), pre-eclampsia (ICD-10:014), gestational hypertension (ICD-10: O13), and obesity (ICD-10: E66) were all obtained from each woman's billing diagnosis record. Gestational age (GA) of the neonate at the time of delivery was derived from the ICD-10 diagnosis codes Z3A.0 (GA <10 weeks) to Z3A.4 (GA ≥40 weeks).

Primary Outcomes

The primary outcome of interest was preterm birth (<37 weeks of pregnancy), which was identified using ICD-10 code O60.1X.

Statistical analysis

Demographic and clinical characteristics were compared between COVID-19 positive and COVID-19 negative women using chi-square tests for categorical variables and t-tests for continuous variables. Additionally, characteristics and COVID-19 status were further stratified by

race. Logistic regression was used to estimate the crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the association between COVID-19 and pre-term pregnancy stratified by race. Age, preeclampsia, hypertension, gestational hypertension, gestational age, and obesity were included within the adjusted model. A race-stratified analysis was conducted to determine if quantitative effect modification exists in the association between COVID-19 status and preterm birth status. Statistical significance was set at $p<0.05$. All analyses were conducted using SAS, Version 9.4 (SAS institute, Cary, NC).

RESULTS

The study population consisted of 641,598 deliveries, of which 12,035 (1.9%) were to women who had ever tested positive for COVID-19 and 629,563 (98.1%) were among those who were COVID-19 negative. The mean age at admission for those that tested positive for COVID-19 was younger than that of those who tested negative (28.5±6.2 vs 29.8±5.8 years, respectively; $p <0.0001$) (Table 1). Of those that tested

positive for COVID-19, 24.3% were White, 42.5% were Hispanic, and 19.4% were Black ($p <0.0001$). A higher proportion of women who tested positive for COVID-19 experienced preeclampsia compared to those who did not test positive (10.1% vs 6.9% respectively, $p<0.0001$). Gestational hypertension was more prevalent among women who tested negative for COVID-19 compared to those that tested positive (8.1% vs 7.2%; $p <0.0001$). Conversely, gestational diabetes was more prevalent among women who tested positive for COVID-19 compared to those that tested negative, (2.4% vs. 1.9%, respectively; $p <0.0001$). Mean gestational age was lower for those who tested positive than those who tested negative (37.8 vs

38.2 weeks respectively; p <0.0001). The prevalence of obesity was 16.4% among those who tested positive for COVID-19 compared to 13.4% among those who tested negative (p <0.0001).

With the exception of Asian race, among each racial group, the COVID-19 positive women had a higher prevalence of preeclampsia (p <0.05, Table 2). Despite some significant differences among some groups, perhaps owing to the large sample size, the prevalence of gestational diabetes and gestational hypertension was approximately equivalent between COVID-19 positive and negative women within each racial group. The prevalence of obesity was higher among positive COVID-19 women compared to those who tested negative, significantly so for all racial/ethnic groups except Black and Hispanic (p <0.05). Among each racial/ethnic group, the gestational age was significantly younger for COVID-19 positive women compared to those who tested negative (p<0.0001). Similarly, COVID-19 positive women were significantly younger than those who tested negative regardless of racial group (p<0.0001) (Table 2).

For each of the racial/ethnic groups, the risk of preterm birth was higher among the COVID-19 positive compared to negative patients (p<0.0001). The adjusted regression model showed those who were Black (OR 1.2, 95%CI 1.01-1.43), Hispanic (OR 1.22, 95%CI 1.07-1.40), or of other (OR 1.44, 95%CI 1.08-1.92) racial/ethnic group showed a positive association between COVID-19 and preterm birth after adjusting for possible confounders (Table 3). The association was not significant among those of Asian, White or unknown decent.

DISCUSSION

The results of the current study indicate that the risk of preterm birth is greater among the COVID-19 positive patients compared to the negative patients. With the exception of whites, this positive association was consistent among each racial/ethnic category, though not always significantly so. The overall positive association is consistent with the results of other studies

reporting as high as a four-fold increased odds of preterm birth for COVID-positive women[7,8,9,10]. Woodworth et al. reported that 31.3% of births to RT-PCR positive women were moderate to very preterm compared to 5.6% of births to negative RT-PCR negative women[19]. A similar trend was found where 13.8% of deliveries within the infected cohort occurred at less than 37 weeks compared to 6.7% of deliveries in the uninfected cohort [20]. From a large, population-based study from Wuhan, China, women with confirmed SARS-CoV-2 infection experienced a statistically significant four-fold increased odds of preterm birth compared to those who do not have COVID-19[9]. While not statistically significant, Jafari, et al. determined that COVID-19 positive pregnant women were at 2.5 times greater odds of having a preterm birth compared to pregnant women without COVID-19[10]. In an adjusted analysis, severe COVID-19 was associated with a significantly increased risk of preterm birth (aRR 3.53, $p<0.001$)[11].

It is important to note that not all studies have reported a positive association between COVID-19 and preterm birth. Janevic, et al. found no evidence that COVID-19 increased the racial/ethnic health disparities in regard to preterm birth in New York City [21]. While this is significant, it only accounts for those that gave birth within the cohort and may not be representative of the total population. When interpreting these results against others, it is important to be cognizant of other factors that may impact the direction of the results. A local decrease in preterm birth was reported using the same justification. However, further study on the nature of preterm birth, spontaneous versus indicated, is a topic worthy of further investigation[22,23]. While not included in the present data, it could be suggestive of the viral impact on preterm births for those who have had tested positive for COVID-19.

Despite the growing body of research on pregnancy outcomes among pregnant women with COVID-19, none have evaluated whether race/ethnicity has a modifying role. The current results revealed elevated odds ratios amongst some but not all racial groups; additionally, though

only some of the associations were significant, the odds ratios were of similar magnitude, suggesting effect modification may not exist. Despite this, we are confident that it is not solely pregnancy status with a positive test or the effect of additional risk factors for pre-term birth such as pre-eclampsia, but the additional independent impact that race plays in susceptibility to SARS-CoV-2. This notion is supported by similar findings where SARS-CoV-2 positivity was most common among Hispanic women (91% positive vs 73% negative; $p<0.0001$) in a cohort of maternal and neonatal outcomes[4]. Among COIVD-19 positive pregnant women studied by Ellington et al., 46.2% were Hispanic, 23.0% were Non-Hispanic White and 22.1% were Non-Hispanic Black. This was compared to 38.1%, 29.4%, 25.4%, and 3.2%, respectively, among non- pregnant women[24]. A similar trend was found where the majority of COVID-19 positive pregnant women were Hispanic (42.5%) and Black/ African American (26.5%)[25].

Previously, it had been identified that Pacific Islander, Latino, Indigenous and Black Americans all have a COVID-19 death rate of at least double that of White and Asian Americans, who specifically experience the lowest age-adjusted rates[26]. When analyzing demographic characteristics, Perez, et al. found that the only variable that yielded significant differences was ethnicity, specifically Latin American women being more represented in the infected cohort compared to the uninfected[20]. Interestingly, in our study almost half of our COVID-19 positive population was Hispanic. Among a large population of New York residents, it was found that racial/ethnic minority populations had a greater likelihood of COVID-19 diagnosis, hospitalization, and death, compared to white non- Hispanic adults[27]. In another study, it was reported that Non-Hispanic Black and Hispanic women were disproportionally represented [20]. While poor maternal morbidity, mortality and birth outcomes already exist for these races, the increased incidence of COVID-19 cases among these races might further widen these disparities[28]. Metz, et al. reported that more Hispanic's and Non-Hispanic Black individuals were

identified as “critical-severe cases”. Consequently, the critical-severe cases also had a highly elevated risk of preterm birth compared to those identified as moderate-mild cases[11]. While there are currently few studies to support this, we are confident that the findings in the present study are substantial in terms of the association between race, COVID-19 and pregnancy outcome, given what is known thus far regarding SARS-CoV-2 and its effect on the human body.

The results of the present study, and those supporting it, further highlight the importance of vaccinations. While there are still many aspects of this virus that have yet to be discovered, there are aspects that we can assume to be valid. It has been understood that: (1) those in an immunocompromised state are at higher risk of contracting the disease[29], (2) that racial disparities in health have persisted throughout these times[4,30], and (3) it has also been indicated that those who choose not to protect themselves from this virus are at increased risk of contracting the disease. The CDC has urged those pregnant, thinking about becoming pregnant and those nursing to get vaccinated to protect themselves and their offspring, while indicating it is safe for this population[31]. Despite their guidance, there is still hesitancy among this population. According to research from UT Medical Center, hospitalization for pregnant women has increased from 10% to 15% during the study period[32]. It is our hope that the results of the present study, and those that may follow, continue to inform the public, specifically the pregnant population, about the risks of infection and how to best protect themselves through proper vaccination.

While the present data did not include a “Non-White Hispanic”, “Hispanic/Latino” race category, it may be possible that those individuals were included in the “Unknown” category, thus explaining the large difference in COVID-19 positive cases for that group. It was not possible to determine whether the preterm births were spontaneous or indicated. Thus, it is not possible to determine whether the presence of the disease causes spontaneous preterm birth or

whether the presence of the disease and its symptoms leads to the induction of preterm labor, in order to protect the mother and child. The status of COVID-19 vaccination status of women was unknown and thus its effects on disease severity and pregnancy is unknown. However unlikely, it may be possible that some COVID-19 positive women were vaccinated. It is also possible that this may not be a representative sample as the SARS-CoV-2 testing modalities may not have been consistent across each contributing hospital, it is also unclear whether this would be differential by race. There may also be known and unknown factors that were not accounted for in this analysis. This study also did not have data on potential confounders.

CONCLUSION

This study investigated the adverse impact of SARS-CoV-2 infection has on pregnancy outcomes, specifically preterm birth. The results indicated that those with COVID-19 were more likely to have a preterm birth, with the exception of whites. Given the possible severity of the disease and its continued prevalence in our society, this study further highlights the risks of infection as well as the importance of proper vaccination for expecting mothers of all races.

Table 1. Demographic and Clinical Characteristics of Women Experiencing Childbirth by COVID-19 Status

Characteristic	COVID-19 Negative n= 629,563 (98.1%)	COVID-19 Positive n= 12,035 (1.9%)	P-value
Age (years), mean ± sd	29.8± 5.8	28.5 ± 6.2	<0.0001
Race, N (%)			<0.0001
White	320745 (50.9)	2929 (24.3)	
Black	107621 (17.1)	2330 (19.4)	
Hispanic	114895 (18.3)	5109 (42.5)	
Asian	36658 (5.8)	396 (3.3)	
Other	35622 (5.7)	981 (8.2)	
Unknown	14022 (2.2)	290 (2.4)	
Preeclampsia, N (%)	43785 (6.9)	1211 (10.1)	<0.0001
Gestational hypertension, N (%)	51161 (8.1)	862 (7.2)	<0.0001
Gestational diabetes, N (%)	11960 (1.9)	294 (2.4)	<0.0001
Gestational age (weeks), mean ± sd	38.2 ± 2.8	37.8 ± 3.2	<0.0001
Obesity, N (%)	84516 (13.4)	1978 (16.4)	<0.0001

Table 2. Demographic and Clinical Characteristics by Race and COVID-19 Status

	White		**Hispanic**		**Black**		**Asian**		**Other**		**Unknown**	
COVID-19 Status	+ **2929 (24.3)**	- **320745 (50.9)**	+ **5109 (42.5)**	- **114895 (18.3)**	+ **2330 (19.4)**	- **107621 (17.1)**	+ **396 (3.3)**	- **36658 (5.8)**	+ **981 (8.2)**	- **35622 (5.7)**	+ **290 (2.4)**	- **14022 (2.2)**
Preeclampsia N (%)	222 (7.6) *	19456 (6.1)	555 (10.9) *	8876 (7.7)	281 (12.1) *	10145 (9.4)	13 (3.3)	1681 (4.6)	109 (11.1) *	2628 (7.4)	31 (10.7) *	999 (7.1)
Gestational diabetes N (%)	44 (1.5)	4549 (1.4)	138 (2.7)	2849 (2.5)	61 (2.6)	2744 (2.6)	9 (2.3)	779 (2.1)	36 (3.7) *	815 (2.3)	6 (2.1)	224 (1.6)
Gestational hypertension N (%)	196 (6.7) *	27172 (8.5)	314 (6.2) *	7961 (6.9)	245 (10.5)	10920 (10.2)	17 (4.3)	1582 (4.3)	71 (7.2)	2521 (7.1)	19 (6.6)	1005 (7.2)
Obesity N (%)	401 (13.7) *	35737 (11.1)	885 (17.3)	19739 (17.2)	475 (20.4)	21576 (20.1)	32 (8.1) *	1634 (4.5)	146 (14.9) *	4459 (12.5)	39 (13.5) *	1371 (9.8)
Gestational age (Weeks) Mean ± **sd**	37.9 ± 3.1 *	38.3 ± 2.6	37.8 ± 3.2 *	38.2 ± 2.7	37.4 ± 3.6 *	37.6 ± 3.4	37.9 ±2.8 *	38.4 ± 2.3	37.8 ± 2.9 *	38.1 ± 2.9	37.8 ± 3.00 *	38.2 ± 3.0
Age at admission (Years) Mean ± **sd**	29.5 ± 5.8 *	30.5 ± 5.4	27.8 ± 6.4 *	28.5 ± 6.2	27.9 ± 6.2 *	28.4 ± 6.1	30.8 ± 5.2 *	32.4 ± 4.8	29.1 ± 6.4 *	29.9 ± 5.9	30.0 ± 6.3 *	30.6 ± 5.8

* P<0.05.

Table 3. Risk of Preterm Birth According to COVID-19 Status Stratified by Race and Associated Odds Ratios and 95% Confidence Intervals

	White		**Hispanic**		**Black**		**Asian**		**Other**		**Unknown**	
COVID-19 Status	+ **2929 (24.3)**	- **320745 (50.9)**	+ **5109 (42.5)**	- **114895 (18.3)**	+ **2330 (19.4)**	- **107621 (17.1)**	+ **396 (3.3)**	- **36658 (5.8)**	+ **981 (8.2)**	- **35622 (5.7)**	+ **290 (2.4)**	- **14022 (2.2)**
Preterm Birth <37 weeks N (%)	117 (4.0) **	10861 (3.4)	321 (6.3) **	5140 (4.5)	171 (7.3) **	6416 (5.9)	18 (4.6) **	1120 (3.1)	63 (6.4) **	1483 (4.2)	21 (7.2) **	592 (4.2)
Crude Odds Ratio 95% CI	1.19 (0.99, 1.43)		1.43 (1.27, 1.61)		1.25 (1.07, 1.46)		1.51 (0.94, 2.43)		1.58 (1.22, 2.05)		1.77 (1.13, 2.78)	
Adjusted Odds Ratio 95% CI*	0.96 (0.78, 1.19)		1.22 (1.07, 1.40)		1.20 (1.01, 1.43)		1.11 (0.65, 1.91)		1.44 (1.08, 1.92)		1.56 (0.95, 2.57)	

*Adjusted for age, preeclampsia, gestational diabetes, gestational hypertension, obesity, and gestational age.
**p <0.05

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APPENDIX

IRB APPROVAL

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Institutional Review Board for Human Use

470 Administration Building
701 20th Street South
Birmingham, AL 35294-0104
205.934.3789 | Fax 205.934.1301 |
irb@uab.edu

NHSR DETERMINATION

TO: McGwin, Gerald

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)
IORG Registration # IRB00012550 (IRB 03)

DATE: 05-Aug-2021

RE: IRB-300007725
Adverse Pregnancy Outcomes Associated with COVID-19

The Office of the IRB has reviewed your Application for Not Human Subjects Research Designation for the above referenced project.

The reviewer has determined this project is not subject to FDA regulations and is not Human Subjects Research. Note that any changes to the project should be resubmitted to the Office of the IRB for determination.

if you have questions or concerns, please contact the Office of the IRB at 205-934-3789.