The association between parental SARS-CoV-2 infection in pregnancy and fetal growth restriction

Abstract

Objectives: Although the relationship between maternal viral infections and fetal growth restriction (FGR) is well established, the association between SARS-CoV-2 infection in pregnancy and FGR remains unclear. We investigated the association between SARS-CoV-2 infection in pregnancy and FGR at a single county hospital.

Methods: We performed a prospective cohort study with cohorts matched by gestational age and month of SARS-CoV-2 PCR testing between April 2020 and July 2022. Individuals were included if they had a SARS-CoV-2 PCR testing up to 32 weeks of gestation and had a third trimester ultrasound. Primary outcome was a diagnosis of FGR, while secondary outcomes were rates of preeclampsia, small for gestational age (SGA) and birthweight. Univariate analyses, chi-square test and logistic regression were used for analysis.

Results: Our cohorts constituted of 102 pregnant individuals with a positive SARS-CoV-2 PCR test result and 103 pregnant individuals with a negative SARS-CoV-2 PCR test result in pregnancy. FGR rates were 17.8 % and 19.42 % among positive and negative SARS-CoV-2 cohorts respectively. While a statistical difference in preeclampsia rates was noted (34.31 % vs. 21.36 %, p=0.038) between cohorts, odds of getting preeclampsia based on SARS-CoV-2 test result was not significant (aOR 1.01, CI=0.97–1.01, p=0.75). No statistical difference was noted in demographics, FGR and SGA rates, and birthweight.

Conclusions: Our findings suggest no association between SARS-CoV-2 infection in pregnancy and FGR at a single institution. Our results validate emerging data that additional fetal growth ultrasonographic assessment is not indicated solely based on SARS-CoV-2 infection status.

Keywords: maternal SARS-CoV-2 infection; pregnancy; fetal growth restriction; small for gestational age; birthweight

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been shown to increase the risk of multiple adverse perinatal outcomes in the pregnant population [1]. Some parental viral infections, such as cytomegalovirus (CMV) or Zika virus, have been strongly associated with a diagnosis of fetal growth restriction (FGR) [2, 3] during pregnancy, as viral infections at the maternal-fetal interface have been shown to affect or alter placental function, which then in turn may lead to fetal growth restriction [3]. However, the data on other coronavirus spectrum infections such as SARS as well as SARS-CoV-2 has been more mixed [4]. While a meta-analysis in placental histopathologic abnormalities seen in SARS-CoV-2 infection showed that there is evidence of intervillous thrombi, placental inflammation and signs of maternal vascular malperfusion [5, 6], all of which are markers of placental damage, the results from at least one large, prospective meta-analysis indicated that parental SARS-CoV-2 infection during pregnancy did not increase the risk of FGR or Small for Gestational Age (SGA) [7]. In a prospective case control study conducted by Rizzo et al, findings demonstrated no effect of SARS-CoV-2 infection on fetal growth, growth velocity and fetal hemodynamics [8]. Also, SARS-CoV-2 infection doesn’t appear to affect fetal brain biometry and cortical development after maternal infection [9].

Given the novelty of the SARS-COV-2 virus and the lack of knowledge of its natural history, initial clinical guidelines for obstetric providers included consideration for interval growth assessments [10], as a diagnosis of FGR has been associated with multiple adverse outcomes including intrauterine demise, neonatal morbidity and neonatal death [11]. However, as the pandemic continued, while evidence from several large trials showed a clear association between
SARS-CoV-2 infection and stillbirth [12], there was limited data on the association between SARS-CoV-2 infection during pregnancy and a subsequent diagnosis of FGR, making it difficult for clinicians to know whether increased surveillance was warranted and/or effective in this patient population.

The objective of our study was to evaluate the association between SARS-CoV-2 infection in pregnancy and FGR in a high-risk obstetric cohort at a single institution in Atlanta, Georgia. While excluding patients without ultrasound data significantly limited our cohort numbers, we purposefully limited our analysis to only those patients who had received a third trimester ultrasound after their positive SARS-CoV-2 result in order to ensure that the exposure of SARS-CoV-2 infection predated the outcome, i.e. the diagnosis of FGR. While other studies have shown the association of SARS-CoV-2 and SGA, the goal in this study was to more thoroughly investigate the diagnosis of FGR, a diagnosis which, unlike the postnatal diagnosis of SGA, significantly impacts pregnancy management [13]. Therefore, this study was designed to more closely investigate the association between SARS-CoV-2 and FGR, and therefore inform best clinical practices for prenatal management of patients affected by SARS-CoV-2 during pregnancy.

**Methods**

This study was a matched controlled, prospective cohort study conducted among admitted pregnant individuals who delivered at Grady Memorial Hospital in Atlanta, Georgia from April 2020 to July 2022. During this time, our institution adopted universal SARS-CoV-2 testing, so all patients admitted to labor and delivery were tested for SARS-CoV-2; all suspected infections were confirmed by a positive nasopharyngeal reverse transcription (RT) PCR swab result. The individuals in the SARS-CoV-2 negative cohort were matched based on the months of SARS-CoV-2 PCR testing and gestational age at the time the SARS-CoV-2 swab was performed. The gestational age was established by certain LMP confirmed by standard sonographic biometric measurements.

Patients who had SARS-CoV-2 PCR testing from early pregnancy up to 32 weeks of gestational age at the time of testing as either part of universal for SARS-CoV-2 at admission to labor and delivery for any obstetrical indications or suspected SARS-CoV-2 infection were included in the analyses. The threshold of 32 weeks of gestational age at the time of testing was determined based on the observation that the majority of patients beyond this gestational age were undergoing SARS-CoV-2 PCR testing and didn’t have a third trimester ultrasound to assess fetal growth. Therefore, we couldn’t correlate if SARS-CoV-2 infection preceding ultrasound growth examination was associated with fetal growth restriction.

In the SARS-CoV-2 positive cohort, patients had to have a positive SARS-CoV-2 PCR result documented in their chart, and had to have a singleton, non-anomalous pregnancy and had at least one third trimester (>27 weeks of gestation) ultrasound during their pregnancy at least 8 days after PCR testing.

Patients in the SARS-CoV-2 negative cohort were included if they had at least one third trimester ultrasound after a negative SARS-CoV-2 PCR test during pregnancy. Individuals were excluded from both cohorts if the pregnancy was a multi-gestation pregnancy, or if the pregnancy resulted in intra-uterine fetal demise (IUD). Data was initially abstracted using the Grady Obstetric and Gynecological Outcomes (GOGO) database using ICD-10 codes, a method which use has been previously validated by our institution [14]. From there, the authors obtained more detailed information on maternal demographics including age, race, BMI, and medical co-morbidities including chronic hypertension (cHTN), ultrasonographic data from growth assessment, obstetrical, and neonatal outcomes was obtained via abstraction from the medical chart. Data on the presence of symptomology or COVID-19 vaccination status at the time of SARS-CoV-2 PCR testing was not available for analysis.

The primary outcome of the study was the rate of FGR in each cohort, defined by an estimated fetal weight (EFW) <10 % or a fetal abdominal circumference (AC) <10 % at time of ultrasound as per defined by American College of Obstetrics and Gynecology (ACOG) guidelines [11]. Secondary outcomes included rate of preeclampsia, gestational diabetes (GDM), and small for gestational age (SGA) at time of birth. Preeclampsia was diagnosed using the classical criteria as defined ACOG guidelines [15].

Univariate analyses, chi-square tests and logistic regression were performed. Categorical variables were described by percentages. Rates were compared using Chi-square test. Regression model was adjusted for potential confounders including pre-existing medical problems including cHTN, smoking and BMI. A p-value<0.05 was considered statistically significant. Data was analyzed using STATA version 14.0 (College Station, Texas). This research study received Emory University School of Medicine Institutional Review Board and Grady Memorial Hospital Research Oversight Committee approval.

**Results**

Using an internal electronic medical record database (GOGO database), we initially identified a total of 844 pregnant individuals who underwent SARS-CoV-2 PCR testing between April 2020 and July 2022. Of these 844 pregnant patients, a total of 205 pregnant individuals met all of the inclusion criteria, including having had a third trimester ultrasound during the pregnancy at least 8 days (range: 8–163 days) after PCR testing and had SARS-CoV-2 PCR testing before 32 weeks of gestation (Figure 1).

Of these 205 individuals, 102 individuals had a positive SARS-CoV-2 PCR test and 103 individuals had a negative SARS-CoV-2 PCR test. Overall, individuals in both cohorts self-identified as of Black race (78.4 % vs. 83.5 %, respectively), had Medicaid insurance (87.2 % vs. 82.52 %, respectively) and were classified as single (77.4 % vs. 76.7, respectively) (Table 1). Similarly, there was not a significant difference in the maternal age, 1st trimester BMI, mean gestational age at time of SARS-CoV-2 testing, or at delivery between the two cohorts.
There was not a significant difference the rate of FGR between the two cohorts (17.8% in the positive cohort vs. 19.4% in the negative cohort, p=0.77) (Table 2). Similarly, there was no difference in the rates of obesity, cHTN, GDM, pre-pregnancy diabetes, and SGA among the groups (Table 2). While a statistical difference in the rate of preeclampsia was noted between the two groups (34.31% in the positive cohort vs. 21.36% in the negative cohort, p=0.038), this did not remain significant after adjusting for confounders such a history of cHTN and BMI (aOR 1.01, CI=0.97–1.01, p=0.75).

### Discussion

In this prospective cohort study, we aimed to investigate the association between parental SARS-CoV-2 infection and FGR at a single institution during the peak of the COVID 19 pandemic. The population served by our institution is a high-risk population, as multiple studies have shown patients who self-identify as Black or Hispanic and have Medicaid have been more adversely affected by the pandemic [16, 17]. However, even in our high-risk patient population, there was no difference in FGR rates, as well as in rates of SGA and preeclampsia, even after ensuring that the ultrasound occurred after the SARS-CoV-2 infection. These results agree with other retrospective and prospective studies [8, 18] as well as recent large data meta-analysis [7], as all have shown there appears to be no association between SARS-CoV-2 infection and a diagnosis of FGR, regardless of the timing of SARS-CoV-2 infection.

The results of our study help inform some of the uncertainty regarding clinical guidelines for fetal growth assessment for pregnant individuals affected by SARS-CoV-2 infection during pregnancy. Since 2020, there has been heterogeneity among national and international clinical practice guidelines regarding ultrasound recommendation after SARS-CoV-2 infection [6]. Although the Society of Maternal Fetal Medicine (SMFM) proposed guidelines that included consideration for interval fetal growth for...
pregnant individuals with SARS-CoV-2 infection [10], the guidelines on ultrasound follow up after infection remained unclear. Our findings further support that additional growth assessment with ultrasound for pregnant individuals with SARS-CoV-2 infection solely due to infection is not necessary [18].

Our study contains several strengths and limitations. One of the strengths of our study is that our institutional database provided us with a large sample of pregnant persons with documented SARS-CoV-2 PCR testing. In addition, we were able to carefully validate all ultrasound data by having access to ultrasound measurements from the individual's medical charts and verify the timing of the ultrasounds, a level of detail not often available in large meta-analysis or cohort studies. The cohorts were also matched for gestational age and time of testing which further strengthens the study. This matching ensured a balanced representation of the risk for pregnancy outcomes across different gestational ages and SARS-CoV-2 infection time periods in both groups.

Our study also had several limitations. When adjusting for confounders, we were limited to using the first trimester BMI as a surrogate for pre-pregnancy BMI, and we were not able to identify those who were symptomatic vs. asymptomatic when they tested positive for SARS-CoV-2, and so our study is not able to comment on the relationship between FGR and the severity of disease. Additionally, it is possible that the patients in our negative cohort may have had a SARS-CoV-2 infection at some point during pregnancy, and either did to present to care and/or presented to another institution at that time, and so that may have impacted our results. Additionally, the indications for a third trimester interval growth ultrasound in our cohorts varied, and even in the SARS-CoV-2 cohort, the ultrasound was not always solely for maternal SARS-CoV-2 infection, and so there may be other confounders driving these results. It’s also possible that the exclusion of patients beyond 32 weeks of gestation could have contributed to selection bias.

Finally, these data represent a single institution, and may not apply to a more general obstetric population; however, given our patients represent the demographics associated with the highest rates of poor perinatal outcomes after SARS-CoV-2 infection, this may be a strength.

Conclusions

In conclusion, our findings suggest that parental SARS-CoV-2 infection is not associated with a diagnosis of FGR, and that routine fetal growth surveillance via ultrasound solely for that indication may be unnecessary. Further studies are needed to understand the impact the SARS-CoV-2 infection has on fetal wellbeing, so that more appropriate surveillance measures are identified.

Research ethics: This study was approved by the Institutional Review Board by Emory University School of Medicine under protocol MOD001-STUDY00002743.

Informed consent: Not applicable.

Author contributions: Each author participated actively in drafting the manuscript, editing and approving final, revised submitted version. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: The authors state no conflict of interest.

Research funding: None declared.

Data availability: The raw data can be obtained on request from the corresponding author.

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