COVID-19 in Pregnancy with Findings of Reduced Head Circumference: A Retrospective Cohort Study

Kristen Lee MORIARTY[1], Kelsey MANFREDI[1], Pascale CARREL[1], Emma KRYZANSKI[1], David A. Schwartz[2], Lucas GODOY[1], Chia-ling Kuo[1], and Andrea Shields[1]

[1]UConn Health
[2]Augusta University Medical College of Georgia

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Abstract

Objective: We investigated the relationship between trimester-specific SARS-CoV-2 infection and newborn growth metrics. We hypothesize that COVID-19 may result in disproportion between neonatal head measurements and weight without increasing the risk of SGA, and that this relationship may be associated with timing of COVID-19 exposure in pregnancy. **Design:** Retrospective cohort **Setting:** Northeast USA academic tertiary hospital **Population of sample:** COVID-19-infected (n=140) and COVID-19-uninfected (n=136) patients **Methods:** Inclusion criteria: a) singleton birth between April 28, 2020, and December 31, 2022; and b) maternal COVID-19 infection diagnosed via PCR. Exclusion criteria: $<$ 12 years of age, major fetal anomalies, and fetal loss $<$ 15 weeks. **Main Outcomes Measures:** Outcomes were a comparison of newborn growth measurements (length, weight, and head circumference (HC) at birth), Ponderal Index (PI), and development of SGA between SARS-CoV-2-infected and uninfected patients. Maternal and neonatal characteristics were descriptively summarized, and multivariate analyses and linear regression models were performed. **Results:** Baseline maternal demographics did not significantly differ among the uninfected and infected cohorts. Compared to the uninfected cohort, COVID-19 diagnosed in the third trimester was associated with a lower neonatal HC compared to newborns of uninfected patients (β=-0.38 [0.38 SD lower], 95% CI -0.65 to -0.10, p=0.024). There was no significant difference among the cohorts for birth length, weight, or diagnosis of small for gestational age. **Conclusion:** We found that COVID-19 infection in the third trimester was associated with a lower neonatal head circumference without associated SGA. The cause underlying this association is unknown. Further research to determine the risk of neurotropic fetal infection by SARS-CoV-2, like ZIKA's effect on the fetal immune system leading to microcephaly, is urgently needed.

COVID-19 in Pregnancy with Findings of Reduced Head Circumference: A Retrospective Cohort Study

Dr. Kristen Lee MORIARTY M.D.[1], Dr. Kelsey MANFREDI M.D.[1], Ms. Pascale CARREL, B.A.[1], Emma KRYZANSKI B.S.[1], Dr. David Alan SCHWARTZ, M.D., M.S.Hyg.[2]., Mr. Lucas GODOY M.S.[3], Dr. Chia-Ling KUO, Ph.D.[3], Dr. Andrea SHIELDS M.D., M.S.[1]

[1] Department of Obstetrics & Gynecology, University of Connecticut Health School of Medicine

[2] Perinatal Pathology Consulting, Atlanta, Georgia

[3] Department of Statistics, University of Connecticut School of Medicine

Corresponding Author:

Kristen Lee Moriarty, M.D.

UCONN Health, Department of Obstetrics and Gynecology

263 Farmington Ave, Farmington, CT 06030

Email: kmoriarty@uchc.edu, Cell (610)-202-0501

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Design: Retrospective cohort

Setting: Northeast USA academic tertiary hospital

Population of sample: COVID-19-infected (n=140) and COVID-19-uninfected (n=136) patients

Methods: Inclusion criteria: a) singleton birth between April 28, 2020, and December 31, 2022; and b) maternal COVID-19 infection diagnosed via PCR. Exclusion criteria: $<$ 12 years of age, major fetal anomalies, and fetal loss $<$ 15 weeks.

Main Outcomes Measures: Outcomes were a comparison of newborn growth measurements (length, weight, and head circumference (HC) at birth), Ponderal Index (PI), and development of SGA between SARS-CoV-2-infected and uninfected patients. Maternal and neonatal characteristics were descriptively summarized, and multivariate analyses and linear regression models were performed.

Results: Baseline maternal demographics did not significantly differ among the uninfected and infected cohorts. Compared to the uninfected cohort, COVID-19 diagnosed in the third trimester was associated with a lower neonatal HC compared to newborns of uninfected patients (β=-0.38 [0.38 SD lower], 95% CI -0.65 to -0.10, p=0.024). There was no significant difference among the cohorts for birth length, weight, or diagnosis of small for gestational age.

Conclusion: We found that COVID-19 infection in the third trimester was associated with a lower neonatal head circumference without associated SGA. The cause underlying this association is unknown. Further research to determine the risk of neurotropic fetal infection by SARS-CoV-2, like ZIKA's effect on the fetal immune system leading to microcephaly, is urgently needed.

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Introduction:

Coronavirus disease 2019 (COVID-19) has been linked to multiple adverse pregnancy outcomes (APOs) for both the mother and fetus, including preterm delivery, miscarriage, stillbirth, pre-eclampsia-like syndrome, and abnormal fetal growth and development.(1-5) These APOs result in a greater need for neonatal intensive care unit (NICU) admissions, comorbidities of asphyxia-related complications, hyperbilirubinemia, and increased perinatal mortality. Recent data demonstrate that patients infected with the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) can develop a placental infection, termed SARS-CoV-2 placentitis, that causes an average of 77% placental destruction and consequent placental insufficiency among stillbirths and early neonatal deaths.(6, 7) However, the literature is inconsistent on the impact of SARS-CoV-2 infection during pregnancy and growth of the fetus.(1, 5, 8-11)

Some viral agents have been reported to cause fetal growth and development abnormalities. Among these, cytomegalovirus is the most common viral cause of fetal growth restriction (FGR)(12), but other viruses, including Zika virus (ZKV)(13), rubella virus(14), and varicella-zoster virus(15), have been associated with abnormal fetal growth and development. Specially, Zika virus has been associated with the diagnosis of disproportionate microcephaly without associated small for gestational age (SGA).(13, 16-19) Fetal head

circumference (HC) enlarges by approximately 1 mm/day between 26 weeks of gestation and 32 weeks and about 0.7 mm/day between 32 and 40 weeks.(20) Given the importance of fetal neurodevelopment, early recognition and knowledge of specific viruses that cause neurotropic fetal infections are paramount. Because the SARS-CoV-2 pandemic did not start until 2020, there is limited data on the effects of COVID-19 during pregnancy and newborn growth measurements, specifically head measurements of the newborn in the absence of SGA. The primary objective was to investigate the relationship between trimester-specific SARS-CoV-2 infection and newborn growth metrics. We hypothesize that COVID-19 may result in disproportion between neonatal head measurements and weight without increasing the risk of SGA, and that this relationship may be associated with timing of COVID-19 exposure in pregnancy.

Materials and Methods:

We performed a retrospective chart review at an academic tertiary hospital in the Northeast region of the United States. Our study received approval from our hospital's institutional review board (IRB #23X-086-2) and met all ethical standards. Medical records were obtained from the electronic medical record system (EMR). The inclusion criteria included a) singleton pregnancy; b) birth occurring at our institution between April 28, 2020, and December 31, 2022; and c) maternal COVID-19 infection diagnosed via PCR. Exclusion criteria included $<$ 12 years of age, major fetal anomalies, and fetal loss $<$ 15 weeks. All patients in the study had a first or second trimester ultrasound that was used to establish or confirm their estimated due date.

We performed an Epic query to collect data on all births. A total of 2642 patients were initially generated from an Epic query of pregnant patients with prenatal care between February 2020 – August 2022. We randomly selected 276 pregnant patients from this Epic query. These women were split between two groups: 136 patients in the COVID negative group and 140 in the COVID-19-infected group. Study data were collected using Research Electronic Data Capture (REDCap), a secure, web-based application designed to support data capture for research studies.(21, 22) A core outcome set was not used in the initial study design. Baseline maternal demographics included maternal age at delivery, gravidity and parity, recreational drug use, pre-pregnancy BMI (body mass index), pre-existing maternal medical conditions; gestational age, weight and percentile at anatomy scan (to account for constitutional differences in fetal growth during pregnancy); gestational age at delivery, mode of delivery, indication(s) for delivery, COVID-19 vaccination status, gestational age and symptoms at time of COVID 19 diagnosis, hospitalization at the time of COVID-19 diagnosis, and receipt of treatment for COVID-19. Outcomes data collected included growth measurements (length, weight, and HC at birth), gender of the neonate, Apgar scores at delivery, and NICU admission. Outcomes consisted of collecting and comparing newborn growth measurements (length, weight, and head circumference (HC) at birth), PI and SGA between COVID-19-exposed and non-exposed pregnancies. The definition of SGA is a newborn whose birthweight $< 10^{\text{th}}$percentile for gestational age and gender as defined by the Society of Maternal Fetal Medicine.(23) Growth percentile at birth was assigned based on the 2013 Fenton Preterm Growth Chart,(24) which considers weight, length, and HC adjusted for gender and gestational age at birth. The PI, a calculated metric of body proportionality that factors the relationships between weight and length, was determined for every neonate to distinguish between symmetric versus asymmetric growth restriction. The PI formula is [birth weight (in g) x 100] $\div$ [birth length (in cm)^3]. A PI less than the 10^{th} percentile (adjusted for gestational age) is diagnostic of asymmetric growth restriction, and a PI of less than the 3rd percentile indicates severe fetal wasting. Other neonatal outcomes collected included APGAR scores and admission to NICU. Maternal and neonatal characteristics were descriptively summarized, and multivariate analyses and linear regression models were performed.

Maternal and neonatal characteristics and infant growth outcomes were descriptively summarized overall and by COVID-19 infection status and timing of maternal infection diagnosis. Pregnant women infected with COVID-19 were grouped by time of diagnosis and compared to COVID-19 uninfected women. Kruskal-Wallis test was used to compare the infected and uninfected cohorts for continuous and ordinal variables and a Fisher's exact test was used to analyze categorical variables. Significant associations with the cohorts ($p<0.05$) were jointly examined in a multiple linear regression model. The adjusted mean differences comparing the

COVID-19-infected cohorts to the uninfected cohort were reported, including the 95% confidence intervals and p-values. P-values less than 5% were considered statistically significant. All the statistical tests were two-sided, and the statistical analyses were performed in R version 4.2.2.

Results:

The maternal baseline demographic data for the entire study population, including both COVID-19-infected (n=140) and COVID-19-uninfected (n=136) patients, is represented in Table 1. Twenty-seven percent (n=74) of the population self-identified as Hispanic, and 72% (n=199) self-identified as non-Hispanic. Forty-four percent (n=122) self-identified as White, 22% (n=60) as African American, and 23% (n=64) as "other." The "other" category encompasses Native Hawaiian or Pacific Islander, unknown race, or patient-reported "other," which may include multiple racial identities. The mean pre-pregnancy BMI was 29.01 ± SD 7.52, and the mean maternal age at delivery was 30.41 years ± SD 5.26. Twenty-five percent (n=49) of patients had a hypertensive disorder of pregnancy; 6% (n=17) had chronic hypertension, 10% (n=27) had gestational hypertension, 4% (n=10) had pre-eclampsia with severe features, 2% (n=5) had pre-eclampsia without severe features, and 3% (n=8) had superimposed pre-eclampsia with severe features. Thirteen percent (n=22) of patients had diabetes; one patient had type 1 diabetes, 3% (n=8) had type 2 diabetes, 5% (n=14) had GDMA1 (diet-controlled gestational diabetes), and 5% (n=13) had GDMA2 (gestational diabetes treated with medication). Very few patients reported drug use of any kind, with the highest percentage (9%, n=26) reporting cannabis use. Three percent of patients (n=7) had a history of prior FGR. Sixty-six percent (n=181) of infants were born via vaginal delivery, 33% (n=90) via cesarean delivery, and 2% (n=5) via vaginal birth after cesarean delivery. There was no significant difference in the mode of delivery (p=0.413) or gestational age at delivery (p=0.199) among maternal COVID-19-infected and -uninfected groups.

Table 1 further stratifies maternal demographic data by trimester-specific timing of infection with COVID-19: COVID diagnosis before 13 weeks (first trimester), between 13 and 28 weeks (second trimester), and between 28 and 42 weeks (third trimester). There was a trend toward a history of pregnancy induced hypertension for patients with a diagnosis of COVID-19 in the third trimester (p=0.074). Otherwise, maternal baseline demographics were similar between cohorts.

Table 2 shows newborn outcome data, including infants born to COVID-19-infected (n=140) and COVID-19-uninfected (n=136) patients. All infants were singleton gestations. Infants were evenly distributed by gender, 49% female (n=135) and 51% male (n=141). Thirteen percent (n=37) of infants were admitted to the NICU. The mean birth percentile growth measurements reported in the Z score are summarized for the total population with weight -0.16 ± SD 0.88, HC -0.17 ± SD 0.98, length 0.19 ± SD 1.08. The median PI was 2.54 (range 1.62 to 3.37). Note, a normal PI for a newborn varies between 2.2 and 3.0 depending on gestational age. Eight percent (n=21) had a diagnosis of SGA, and 13% (n=35) had a diagnosis of FGR.

Table 2 also stratifies infant demographic data by timing of maternal COVID-19 diagnosis: diagnosis before 13 weeks (first trimester), between 13 and 28 weeks (second trimester), and between 28 and 42 weeks (third trimester). The COVID-19 groups were significantly associated with lower infant HC percentile (in z scores) in the third trimester (p=0.010). Newborns from patients affected with COVID-19 between 28 and 42 weeks had a significantly lower mean HC compared to newborns from COVID-19 uninfected patients (β=-0.49 ± 0.92, p=0.010). There was no statistical significance for mean PI (p=0.417), birth weight (p=.431), or birth length (p=.577). Neither a diagnosis of SGA (p=0.878) nor FGR (p=0.496) were statistically significant between groups. There was a trend toward a higher prevalence of female compared to male infants that were affected with COVID-19 in the third trimester compared to the first and second, although not statistically significant (p=0.092). Additionally, the gestational age at anatomy scan differed between the trimester of COVID-19 diagnosis with infants in the third trimester with maternal infection with COVID-19 having slightly increased gestational age at anatomy scans compared to the other cohorts (p=0.043).

Significant associations between the COVID groups and growth outcomes were further examined in multivariate analyses as shown in Table 3. Linear regression models were fitted for the growth outcomes comparing COVID moms by diagnosis time to non-COVID moms adjusting for covariates that were selected for signi-

ficant associations with COVID groups at 10% significance level. In the multivariate analysis, adjusting for gestational age at diagnosis, gestational age at anatomy scan, was no longer statistically significant (p=0.3). However, infant head HC remained significantly lower comparing COVID patients diagnosed in the third trimester to non-infected patients (p=0.023).

1. **Comment:**
2. **Main Findings** – Our study found that COVID-19 diagnosed in the third trimester had a significant association with newborn growth measurements, specifically the development of a small HC. Although our study did not show an abnormal PI in COVID-19 affected patients, the calculation of the PI does not factor in head circumference, only length and weight into the computation and may limit its application to determine asymmetric growth issues in pregnancies affected by COVID-19. Our study did not show an association of maternal COVID-19 with the development of SGA.
3. **Strength and Limitations -** Based on the retrospective data collection, we did not have data on parental head circumference, which can strongly influence neonatal head circumference. It has been reported that 50% of head size variation in newborns is familial, so adjusting for parental head size is essential.(25) Moreover, we did not examine long-term neurodevelopmental outcomes of the newborns. The neurotropic impact of the SARS-CoV-2 virus beyond a newborn head circumference is critical to understand. Additionally, we did not examine specific SARS-CoV-2 variants in the cases. Different virus variants may have varying impacts on maternal and fetal health. We also did not examine placental pathology as it was not reported in all cases; COVID-19 has resulted in placental tissue destruction and insufficiency, an essential cause of growth restriction.[30] Understanding the effects of COVID-19 on placental tissue, especially tissue destruction and insufficiency, could provide insights into the mechanisms behind growth restriction and further our understanding of the maternal-fetal impact of the virus. Although our baseline maternal and infant baseline demographic data showed minimal differences between cohorts, differences between groups may be appreciated with larger sample sizes. Gestational age at anatomy scan differed between cohorts, however, there was no difference between estimated fetal weight or the percentile at the anatomy scan. In our practice, almost all patients have EDD established by first trimester ultrasound.
4. **Interpretation:** Inconsistent studies have shown a link to COVID-19 and altered fetal development with formation of FGR and or SGA. However, little is known about COVID-19 and potential for altered fetal head development and potential for microcephaly. Steiner et al. demonstrated that infants born to women requiring hospitalization for COVID-19 had lower birth weight (p<0.01), shorter birth length (p=0.02), and smaller HC (p=0.03) than did infants born to COVID-19-infected women who did not require hospitalization.(26) Additionally, The INTERCOVID Multinational Cohort Study by Giuliani et al.[13]demonstrated that patients diagnosed with COVID-19 were more likely to deliver infants with lower birth weight (P<0.001), length (P<0.01), and HC (P<0.01) than uninfected patients. Farrell et al.[11] found that the trimester in which a pregnant patients contracted COVID-19 had no significant effects on the birth weight, customized birth weight percentiles, or prevalence of SGA among newborns. However, infants born to patients having symptomatic COVID-19 infection had significantly lower mean birth weight and median birth weight percentiles than did infants born to infected women who were asymptomatic.[11] They also found a higher prevalence of SGA among patients infected with COVID-19 than in previous studies, with one possible explanation being vertical transmission of COVID-19 from mother to fetus irrespective of gestational age at diagnosis.[11] A longitudinal cohort study by Ockene et al.[12] found that fetuses exposed to COVID-19 *in utero* had a lower BMI after delivery than unexposed fetuses, even after adjusting for gestational age and other potential confounders. Infants born to COVID-19-infected patients also had a more rapid increase in BMI in their first 12 months of life, with the steepest rate of rise in infants born to patients with the most severe infection. Differences in body length between infants exposed and unexposed to COVID-19 were not statistically significant.(27) Fetal head growth in the third trimester contributes substantially to the final head circumference at birth. Disruption of the fetal HC growth has been associated with neurodevelopmental abnormalities, as has been seen with other viral infections.(13, 16-18) Specifically, Zika virus, a flavivirus, has received great attention due to its association with microcephaly.(13, 16-

18) A systemic review by Antoniou et al. analyzed 15 articles and found an incidence rate of 15% of pregnancies affected with Zika. Zika virus cases were first documented in 2015 when providers in Brazil noted an increase in fetuses born with microcephaly. The definition of microcephaly is challenging and not formally explicit, but most studies agree that the diagnosis can be made if the mean head circumference is two standard deviations below the mean for gestational age. Microcephaly can arise from viral infection and insufficient neural stem cell development and eventual neuronal cell death.(17, 28) Our study sheds an association with COVID-19 and concern for smaller HC if diagnosed with COVID in the third trimester independent of the diagnosis of SGA and or a ponderal index <10%. Since fetal head circumference dramatically increases in the third trimester, it is concerning that our study finds COVID-19 diagnosis in the third trimester is associated with smaller head circumference. Future studies should aim to expand the data collection to include parental head circumference, gathering data on neurodevelopmental outcomes between groups, and examining the influence of specific viral variants on fetal growth and other outcomes. Rigorous prospective studies exploring the neurotropic impact of COVID-19 in pregnancy may contribute to a more comprehensive understanding of the relationship and mechanism between maternal COVID-19 infection and fetal neurodevelopment. Our pilot study finding of an association between smaller fetal HC and maternal COVID-19 infection in the third trimester is important. This information highlights the need for further research to delve deeper into the relationship between COVID-19 during pregnancy and its neurotropic impact on fetal head growth and long-term neurodevelopmental outcomes, particularly with third trimester exposure. Continued research in these areas will contribute to a more comprehensive understanding of how maternal COVID-19 infection affects fetal and neonatal neurodevelopment and growth, enabling better care and management for pregnant individuals and newborns.

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