

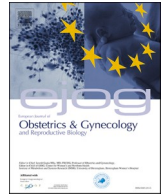


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Full length article

## Impact of asymptomatic and mild COVID-19 infection on fetal growth during pregnancy

Kavita Narang<sup>a,\*</sup>, Megan Miller<sup>b</sup>, Charisse Trinidad<sup>a</sup>, Myra Wick<sup>b</sup>, Regan Theiler<sup>b</sup>, Amy L. Weaver<sup>c</sup>, Ramila A. Mehta<sup>c</sup>, Mauro Schenone<sup>a</sup>

<sup>a</sup> Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, United States

<sup>b</sup> Department of Obstetrics and Gynecology, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, United States

<sup>c</sup> Division of Clinical Trials and Biostatistics, Department of Quantitative Health Sciences, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN, 55905, United States



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### ABSTRACT

**Background:** During pregnancy, certain viral infections are known to significantly affect fetal development. Data regarding the impact of COVID-19 viral infection in pregnancy, specifically in asymptomatic or mild cases, remains limited. This presents a challenge in providing prenatal counseling and antepartum surveillance in pregnancies complicated by COVID-19 infection. Placenta studies have demonstrated that vascular malperfusion patterns attributed to COVID-19 appear to depend on the timing of infection. Given these placental changes, we aim to evaluate the impact of COVID-19 on fetal growth in pregnant patients with asymptomatic or mild disease, stratified by trimester of infection. We hypothesize that COVID-19 infection, especially early in pregnancy, increases the risk of fetal growth restriction (FGR).

#### Study design.

This is a single institution, retrospective cohort study of patients ages 16–55 years old with a singleton delivery between December 10, 2020, and April 19, 2021 who had not received a COVID-19 vaccination prior to delivery. COVID-19 infection during pregnancy was defined as a positive SARS-CoV-2 RT-PCR test. FGR was defined as an estimated fetal weight less than the 10th percentile for gestational age or abdominal circumference less than the 10th percentile for gestational age. Maternal and fetal characteristics, including FGR, were compared between women with versus without COVID-19 infection during pregnancy.

**Results:** Among 1971 women with a singleton delivery, 208 (10.6 %) had a prior asymptomatic or mild COVID-19 infection during pregnancy. With the exception in the median prenatal BMI being significantly higher in the COVID-19 group (median, 27.5 vs 26.3,  $p = 0.04$ ), there were no significant differences in demographics, baseline maternal comorbidities or gestational age between those with versus without COVID-19 infection during pregnancy, or in the proportion of their offspring with FGR (3.4 % (7/208) vs 4.8 % (84/1763),  $p = 0.36$ ). When the 208 women were stratified by the timing of their COVID-19 infection, the proportion with an offspring with FGR was 8.7 % (2/23), 1.2 % (1/84), and 4.0 % (4/101), for those first diagnosed with COVID-19 during the 1st, 2nd, and 3rd trimesters, respectively ( $p = 0.72$  Cochran-Armitage test for trend).

**Conclusion:** Asymptomatic or mild COVID-19 infection in pregnancy, regardless of timing of infection, does not appear to be associated with FGR. Routine serial fetal growth assessment may not be warranted solely for history of COVID-19 infection.

**Abbreviations:** COVID-19, Coronavirus disease 2019; EFW, Estimated fetal weight; FGR, Fetal growth restriction; FIGO, International Federation of Gynecology and Obstetrics; SMFM, Society of Maternal Fetal Medicine.

\* Corresponding author.

E-mail address: [Kavita.narang@outlook.com](mailto:Kavita.narang@outlook.com) (K. Narang).

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## Introduction

The SARS-CoV-2 virus outbreak began in December 2019 and the World Health Organization (WHO) declared its global pandemic in March of 2020 [1]. This strain of the coronavirus results in COVID-19 infection; a term we have become too familiar with over the past few years. Since then, we have experienced its lethality and varying impact on various patient populations. Pregnant patients remain at high risk for SARS-CoV-2 infection due to several physiologic changes [2]. The Society of Maternal Fetal Medicine (SMFM) classifies COVID-19 disease severity in pregnancy, as asymptomatic, mild, moderate, severe, critical, or refractory hypoxemia [3]. Asymptomatic disease is defined as a positive SARS-CoV-2 PCR test result with no symptoms, mild disease is defined as flu-like symptoms such as fever, cough, myalgias, and anosmia without dyspnea, shortness of breath or abnormal chest imaging; moderate disease is defined by evidence of lower respiratory tract disease with clinical assessment (dyspnea, pneumonia on imaging, abnormal blood gas. results, refractory fever of 39.0 °C/102.2 °F or greater not alleviated with acetaminophen), severe disease is defined by a respiratory rate greater than 30 breaths per minute (bpm) and hypoxia with oxygen saturation <94 %, critical disease is defined as multi-organ failure or dysfunction, shock, or respiratory failure requiring mechanical ventilation or high-flow nasal cannula, and refractory hypoxemia is defined as persistent, inadequate oxygenation and/or ventilation despite substantial and appropriate measures to optimize it, and represents a further escalation of severity on the spectrum of disease [3].

Despite the increasing number of published studies, there are insufficient data to draw conclusions on the impact of severity of maternal infection on fetal growth. This creates challenges when constructing evidence-based guidelines for appropriate prenatal care in those who are infected. Placental studies have demonstrated that vascular malperfusion patterns attributed to COVID-19 can occur and appear to depend on the timing of infection [4]. Placental vasculopathy and uteroplacental insufficiency can have direct consequences on fetal growth.

Use of ultrasound to measure fetal biometry as part of assessment of fetal growth is routine for several underlying maternal conditions that may impact fetal wellbeing [5,6]. However, these additional assessments do not come without added maternal psychosocial impact, healthcare costs and unnecessary early intervention to the fetus. Out of caution for fetal well-being, while quality data remains inadequate, our institutional guidelines currently recommend serial fetal growth ultrasounds for every pregnant patient that has a diagnosis of COVID-19 infection during pregnancy, regardless of severity and trimester of acquired infection. We aim to evaluate the impact of COVID-19 on fetal growth in pregnant patients with asymptomatic or mild disease, stratified by trimester of infection. We hypothesize that COVID-19 infection, especially early in pregnancy, increases the risk of fetal growth restriction (FGR).

## Methods

This is a single institution, retrospective cohort study of patients ages 16 to 55 years old with a singleton pregnancy, who delivered at Mayo Clinic Health System between December 10, 2020, and April 19, 2021, at the time when all people aged 16 and older were eligible for the COVID-19 vaccine. Patients with a singleton pregnancy with asymptomatic or mild COVID-19 infection were included. Patients who delivered at a Minnesota facility who opted out of use of their medical records for research were excluded from the study. In addition, patients who were diagnosed with FGR in the setting of a known fetal anomaly, and all patients who received the COVID-19 vaccination prior to delivery were excluded to avoid any unknown confounding effect on fetal growth. The study was approved by the Mayo Clinic International Review Board.

The data abstraction included maternal factors of age at delivery,

prenatal body mass index (BMI), gravidity, parity, race and ethnicity, and presence of the following pre-gestational comorbidities: asthma, tobacco use, pregestational diabetes, and chronic hypertension. The data collection also included gestational age at time of delivery, presence of FGR and gestational age at diagnosis of FGR, with FGR defined as an estimated fetal weight (EFW) of less than the 10th percentile for gestational age or abdominal circumference (AC) less than the 10th percentile for gestational age [7], using the Hadlock growth curve.

COVID-19 infection during pregnancy was defined as a positive SARS-CoV-2 RT-PCR test documented in the medical records between the dates of conception and delivery and was stratified into trimesters as follows: first trimester (2 to 13 6/7 weeks gestation, second trimester (14 0/7 to 27 6/7 weeks gestation), and third trimester ( $\geq 28$  0/7 weeks gestation).

Asymptomatic and mild infection were defined in accordance with SMFM guidelines, where asymptomatic patients were those with a positive SARS-CoV-2 PCR test result with no symptoms, mild disease included those with a positive SARS-Cov-2 test result with flu-like symptoms such as fever, cough, myalgias, and anosmia without dyspnea, shortness of breath or abnormal chest imaging [7]. Both groups of patients were primarily managed outpatient and did not require supplemental oxygen or inpatient level care. Patients were not treated with monoclonal antibodies, as these data preceded FDA guidelines to expand monoclonal antibody treatment to pregnant women with mild to moderate COVID-19 symptoms.

Data are summarized using standard descriptive statistics. Comparisons between women with versus without a COVID-19 infection during pregnancy were evaluated using the two-sample *t*-test for age, the Wilcoxon rank sum test for prenatal BMI and the ordinal GA categories, and the chi-square test for categorical variables. Among the women with a COVID-19 infection during pregnancy, the proportion with an offspring with FGR was compared according to the trimester first diagnosed with COVID-19 using the Cochran-Armitage test for trend. All calculated *p*-values were two-sided and *p*-values <0.05 were considered statistically significant. Analyses were performed using the SAS version 9.4 (SAS Institute, Inc.; Cary, NC).

## Results

Among 1971 patients with a singleton delivery, 208 (10.6 %) had a prior asymptomatic or mild COVID-19 infection during pregnancy, including 23 (11.1 %), 84 (40.4 %) and 101 (48.6 %) during the 1st, 2nd, and 3rd trimesters respectively. There were no statistically significant differences in demographics and baseline maternal comorbidities between those with versus without COVID-19 infection during pregnancy, with the exception that the median prenatal BMI was significantly higher in the group with COVID-19 infection during pregnancy (median, 27.5 vs 26.3, *p* = 0.04, Table 1). Pregnancy was dated by the last menstrual period consistent with first trimester ultrasound, or by first or second trimester ultrasound, in all patients.

There was no significant difference in the rate of FGR in patients with and without COVID-19, (3.4 % (7/208) vs 4.8 % (84/1763), *p* = 0.36 (95 % CI for difference of 1.4 %: -1.2 to 4.0 %). When the 208 women were stratified by the timing of their COVID-19 infection, the proportion with an offspring with FGR was 8.7 % (2/23), 1.2 % (1/84), and 4.0 % (4/101), for those first diagnosed with COVID-19 during the 1st, 2nd, and 3rd trimesters, respectively (*p* = 0.19 chi-square test; *p* = 0.72 Cochran-Armitage test for trend). The umbilical artery doppler studies were normal in all 7 cases of FGR. FGR was diagnosed prior to 37 weeks for 6/7 (85.7 %) in the COVID infection group, and in those without a COVID infection, 44/84 (52.4 %) was diagnosed prior to 37 6/7 weeks; this is likely attributed to the earlier discovery of FGR in the COVID group, as they undergo serial fetal growth assessments. There was no significant difference in the gestational age at delivery between the two groups (*p* = 0.56); in particular, the proportion of women with a term delivery was 95.7 % (199/208) among those with COVID-19 infection

**Table 1**  
Maternal and fetal characteristics at diagnosis and delivery.

Characteristic	COVID-19 infection during pregnancy		P-value†
	No (N = 1763)	Yes (N = 208)	
<b>Maternal Age at Delivery (years), Mean (SD)</b>	30.1 (5.1)	29.5 (5.3)	0.08
<b>Parity, n (%)</b>			0.27
Nulliparous	662 (37.5 %)	70 (33.7 %)	
Multiparous	1101 (62.5 %)	138 (66.3 %)	
<b>Race, n (%)</b>			0.32
Asian	82/1638 (5.0 %)	12/187 (6.4 %)	
Black or African American	89/1638 (5.4 %)	12/187 (6.4 %)	
White	1467/1638 (89.6 %)	163/187 (87.2 %)	
<b>Ethnicity, n (%)</b>			0.05
Hispanic or Latino	148/1724 (8.6 %)	27/206 (13.1 %)	
Not Hispanic or Latino	1576/1724 (91.4 %)	179/206 (86.9 %)	
<b>Comorbidities</b>			
Asthma	195 (11.1 %)	24 (11.5 %)	0.84
Current smoker	178 (10.1 %)	16 (7.7 %)	0.27
Pre-gestational Diabetes	11 (0.6 %)	1 (0.5 %)	0.80
Pre-gestational Hypertension	62 (3.5 %)	6 (2.9 %)	0.64
<b>Prenatal BMI (kg/m<sup>2</sup>), Mean (SD)</b>	26.3 (22.8, 32.0)	27.5 (23.4, 33.0)	0.04
<b>Presence of FGR, n (%)</b>	84 (4.8 %)	7 (3.4 %)	0.36
<b>GA at FGR Diagnosis, n (%)</b>			–
37+	40/84 (47.6 %)	1/7 (14.2 %)	
32–36 6/7	25/84 (29.8 %)	4/7 (57.1 %)	
24–31 6/7	16/84 (19.0 %)	2/7 (28.5 %)	
<24	3 /84 (3.6 %)	0/7 (0.0 %)	
<b>GA at COVID Diagnosis, n (%)</b>			–
28+		101 (48.6 %)	
14–27 6/7		84 (40.4 %)	
<14		23 (11.1 %)	
<b>GA at Delivery (weeks), n (%)</b>			0.56
37+	1618 (91.8 %)	199 (95.7 %)	
32–36 6/7	121 (6.7 %)	9 (4.3 %)	
24–31 6/7	21 (1.2 %)	0	
<24	3 (0.2 %)	0	

Abbreviations; BMI: Body mass index, COVID-19: Coronavirus 19, GA: gestational age, FGR: fetal growth restriction, SD: standard deviation.

†Comparisons between the two groups were evaluated using the two-sample t-test for age, the Wilcoxon rank sum test for prenatal BMI and the ordinal GA categories, and the chi-square test for categorical variables.

during pregnancy and 91.8 % (1618/1763) among those without COVID-19 infection during pregnancy.

## Discussion

### Principal findings

The declaration of the COVID-19 pandemic led to our institutional development of a COVID-19 task force to appropriately triage patients and guide management for patients with a SARS-CoV2 positive test. A pregnancy-specific task force was also developed to draft evidence-based guidelines and update recommendations as knowledge surrounding the disease and its implications on pregnancy outcomes

emerged.

One pregnancy complication of interest, FGR, affects 5–10 % of pregnancies. While there are many causes of FGR, it is well-established that both insufficient umbilical cord blood flow, and suboptimal uteroplacental perfusion contribute as both early and late onset FGR [8]. Other infectious diseases and states of chronic hypoxia have been implicated as causes of FGR. This raises concern that complications due to COVID-19 infection during pregnancy may also be associated with FGR. Our study evaluating the association between FGR and asymptomatic to mild COVID-19 infection in unvaccinated pregnant patients found no statistically significant increased risk of FGR among those with COVID-19 infection during pregnancy.

### Results- in the context of what is known

Maternal viral infections during pregnancy are associated with many fetal complications including FGR [9]. An international multicenter retrospective cohort study by Badr et al. [10] investigated pregnancy outcomes in COVID-19 infection and reported increased composite adverse obstetric outcomes in second trimester infections, and adverse neonatal outcomes associated with third trimester infections. While data remains insufficient regarding pregnancy complications associated with COVID-19 infection, there does not appear to be a significant increase in FGR. Three systematic reviews focusing on this complication report low rates of FGR, ranging from 0 % to 9% [11,12]. A large meta-analysis and systematic review by Di Mascio et al. [2], which evaluated the impact of COVID-19 infections during pregnancy, reported no increased risk of FGR using pooled proportions from 10 studies. This study included patients affected by varying COVID-19 infection severity. However, the findings are still consistent with our study findings, which found no association with FGR in patients with asymptomatic to mild COVID-19 infection.

Currently, perinatal outcomes for COVID-19 infection remain limited and organizations are establishing recommendations for antenatal surveillance. International Federation of Gynecology and Obstetrics (FIGO), SMFM and other institutions recommend considering interval growth ultrasounds to assess risk of FGR until more data are available [13–17]. Close fetal monitoring is most strongly endorsed in cases of severe infection, infection early in pregnancy or in women suffering chronic hypoxia, given the pathophysiology of FGR and placental hypoperfusion. The lack of absolute data has prompted our institution to continue fetal growth surveillance in all patients with the COVID-19 infection, regardless of severity and trimester of infection [10].

### Clinical implications

Increased antenatal testing has several clinical implications including increased distribution of resources, maternal anxiety, and potential for early fetal intervention. Organizational guidelines recommending fetal growth surveillance in pregnancies complicated by COVID-19 infection may strain healthcare systems with additional outpatient visits and specialty care, especially in communities with poor access to prenatal care and resources. Over the past several years, United States hospitals have been closing obstetric units, predominantly in rural and non-Hispanic Black resident communities [18]. In one study evaluating accessibility of obstetric care within 30 min among rural patients, 61.6 % of patients had access to an obstetric care facility and only 23.4 % of patients had access to a level III facility with maternal-fetal medicine or care for serious illness [19]. Due to the COVID-19 pandemic, additional workforce shortages have emerged and promoted the adoption of telemedicine. An increase in outpatient prenatal care and ultrasound assessments will not only be more costly and time consuming to patients, but also require more obstetrics specialists and ultrasonographers.

Additionally, there is evidence that increased prenatal testing are associated with maternal distress. The pregnant population is already at

risk for anxiety and depression and routinely screened throughout the antepartum and postpartum periods. Women with equivocal findings and frequent evaluation had significantly higher state anxiety due to the diagnostic uncertainty [20]. Therefore, pregnancy complicated by COVID-19 infection, which requires additional fetal monitoring, may experience an increase in psychiatric symptoms and it is important to avoid unnecessary screening ultrasounds [16].

Finally, additional fetal surveillance increases the likelihood of early intervention and delivery for fetal indications due to false positive findings. This is in efforts to reduce perinatal morbidity and mortality until more data are available. However, our institutional retrospective study and several systematic reviews previously discussed suggest COVID-19 infection during pregnancy is not associated with FGR. As obstetrics organizations continue to investigate pregnancy outcomes of COVID-19, it is important to reassess the recommendation for fetal growth surveillance given the high prevalence of COVID-19 infection and potential burden on the healthcare system.

#### Research implications

Pregnancies complicated by COVID-19 infection will become more common as COVID-19 variants emerge, some strains increasingly infectious. Next steps for research will include risk stratification based on virus strain, severity of disease, maternal co-morbidities, and timing of infection to tailor guidelines. As the population data of COVID-19 infection in pregnancy become more robust with pregnancy outcomes, there will be larger sample sizes to make evidence-based guidelines. While our study focused on FGR, investigation of perinatal outcomes including low birth weight, neonatal intensive care unit admission and intraventricular hemorrhage will also characterize impact of COVID-19 infection during pregnancy. Additional data will guide recommendations of antenatal testing and serial growth ultrasounds in pregnancy.

#### Strengths and limitations

This study included a cohort of patients that had asymptomatic to mild cases of COVID-19, reflecting the severity of infections seen among most of the pregnant population. Patients underwent serial growth ultrasounds, consistent with current SMFM and FIGO guidelines. Our institution was fortunate to have the capability of testing asymptomatic patients during a pandemic where many geographic regions had limited testing supplies. This included testing prior admission, whether it was for planned surgical case, induction of labor, spontaneous labor or planned floor admission. Additionally, our institution has a robust ultrasound department with the ability to accommodate serial growth scans for a large patient population. While our study had many patients with COVID-19 infection detected in the second and third trimester, data collection was initiated early in the pandemic with a small proportion of patients infected during the first trimester and prior to the emergence of the delta variant, which is associated with more perinatal complications, such as stillbirth.

However, this data is limited in the fact it is a retrospective cohort at one institution and relies on electronic medical record documentation. Our facility resides in an urban setting with a predominantly white population and may not be generalizable across United States health systems, especially in centers with limited prenatal care or ultrasound capabilities. The cohort was relatively small given the timeline focused on COVID-19 infection prior to vaccination eligibility to the general population and evaluates the outcomes associated with one variant of SARS-CoV-2. Now that there are different variants and subvariants, results may not be generalizable to the clinical courses of future variants.

It is important to comment that while FGR is strongly associated with perinatal mortality, it is generally uncommon in pregnancy [8]. As a result, a small number of pregnancies complicated by FGR were identified. Finally, our study does not assess severe cases of COVID-19 infection, which likely have increased perinatal complications. New

variants of COVID-19 have also emerged since the completion of data collection for this study, and thus are not included in the analyses.

#### Conclusion

Asymptomatic and mild COVID-19 infection in pregnancy, regardless of timing of infection, does not appear to be associated with FGR. Routine serial fetal growth assessment may not be warranted solely based on history of COVID-19 infection during pregnancy. Further investigation is necessary to stratify risk among maternal COVID-19 infection and delineate which patients benefit from antenatal testing in improve perinatal morbidity and mortality.

#### Financial support

None.

#### Patient consent

Patient consent is not required because no personal information or details are included.

#### Presentation

This study was presented as a virtual poster presentation at the Society for Maternal Fetal Medicine, 42nd Annual Meeting, in February 2022

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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