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# The impact of trimester of COVID-19 infection on pregnancy outcomes after recovery

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**Abstract**

**Objectives:** Many physiological adaptations occur during pregnancy. It is not currently known how timing of COVID-19 infection impacts pregnancy. We hypothesize that maternal and neonatal outcomes are different if COVID-19 infection occurs in different trimesters of pregnancy.

**Methods:** This retrospective cohort study was conducted from 3/2020 to 6/2022. Pregnant patients with a positive COVID-19 infection more than 10 days before delivery (COVID-recovered) were identified and grouped by trimester of infection. Demographics and maternal, obstetric, and neonatal outcomes were analyzed. ANOVA, Wilcoxon rank-sum test, Pearson's chi-squared test, and Fisher's exact test were used to compare continuous and categorical data.

**Results:** A total of 298 COVID-recovered pregnant patients were identified. Of those, 48 (16 %) were infected in the 1st trimester, 123 (41 %) in the 2nd, and 127 (43 %) in the 3rd. There were no significant demographic differences between the study groups. Vaccination status was similar. Hospital admission rate and the need for oxygen therapy while infected were significantly higher in patients with 2nd or 3rd trimester infection (18 % & 20 % vs. 2 % and 13 % & 14 % vs. 0 %, respectively). Rates of preterm birth (PTB) and extreme PTB were higher in the 1st trimester infection group. Infants born to mothers infected in the 2nd trimester had more neonatal sepsis workups (22 % vs. 12 % & 7 %). Other outcomes were similar between groups.

**Conclusions:** First trimester COVID-recovered patients were more likely to have a preterm birth despite having lower rates of hospital admission and oxygen supplementation while infected than patients who recovered from a 2nd or 3rd trimester infection.

**Keywords:** COVID-19; maternal outcomes; neonatal outcomes; pandemic; trimester.

## Introduction

The COVID-19 outbreak was declared a pandemic by the World Health Organization on March 11, 2020 [1]. Since then, there have been over 87 million cases with over one million deaths in the United States alone [2]. Studies have shown that COVID-19 tends to be more severe in pregnant compared to non-pregnant patients [3]. During pregnancy, various physiological immune and respiratory adaptations could increase the susceptibility of patients to infection and lead to worsening outcomes [4]. These changes include increased oxygen demand, reduced functional residual capacity, downregulation of adaptive immune responses, and increased edema and hyperemia of the upper respiratory tract mucous membranes making them prone to upper respiratory tract infection [5, 6]. In addition to worse maternal outcomes, recent studies have found worsened obstetrical and neonatal outcomes in pregnant patients with COVID-19 [7].

Studies on other viral infections in pregnancy have shown that the effect of infection on outcomes depends on the timing of exposure to the virus. For instance, studies have shown that influenza infection in the first trimester can cause increased neonatal mortality. By contrast, influenza infection in the third trimester can result in an increased preterm birth rate [8]. Since it is known that SARS-CoV-2 mimics the influenza virus regarding transmission modes, clinical features, and related immune responses [9], we expected different outcomes based on the timing of infection with the SARS-CoV-2 virus.

It is not currently known how the timing of COVID-19 infection impacts pregnancy. Therefore, we aimed to study if maternal and neonatal outcomes were different based on timing of infection in the pregnancy. We hypothesize that maternal and neonatal outcomes are different if COVID-19 infection occurs in different trimesters of pregnancy.

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## Methods

This retrospective cohort study was conducted at a single major university health system in the State of Maryland between March 2020 and June 2022. IRB approval was obtained (IRB# HP-00091254). First, we conducted a literature review using the terms "SARS-CoV-2", "COVID-19", "pregnancy", and "trimester" on PubMed. Next, pregnant patients at any gestational age with SARS-CoV-2 positive status were identified. We only included those with a positive SARS-CoV-2 status more than 10 days before delivery (i.e., COVID-recovered, per definition by the Centers for Disease Control [CDC] (2), at the time of delivery) and divided them into three groups based on the trimester during which the infection had occurred. We did not include the patients who were found to have COVID-19 at the time of delivery.

Electronic medical records were reviewed and the following data were extracted: demographic information (age, gestational age at infection with SARS-CoV-2 virus, race, body mass index [BMI], parity, medical history, social history, and vaccination status), maternal outcomes (need for admission to the hospital due to COVID 19, need for intensive care unit admission, need for intubation, need for oxygen supplementation, gestational diabetes, hypertensive disorders of pregnancy, preterm premature rupture of membranes, preterm labor, gestational age at delivery, mode of delivery, development of chorioamnionitis or post-partum hemorrhage, need for blood transfusion), and neonatal/fetal outcomes (neonatal sex, birth weight, Apgar scores at 1 and 5 min, umbilical artery cord pH, need for neonatal intensive care unit admission, need for sepsis workup, positive neonatal SARS-CoV-2 PCR, neonatal death, intrauterine fetal demise, spontaneous abortion, and fetal growth restriction).

Stata 16 [10] and MedCalc version 19.5.1 were used for data analysis. ANOVA, Wilcoxon rank-sum test, Pearson's chi-squared test, and Fisher's exact test were used to compare continuous and categorical data. To account for multiple comparisons, a significant p-value was considered to be significant when it was equal or less than 0.01.

## Results

During the study period, 731 pregnant patients with positive SARS-CoV-2 test results were identified. Two hundred ninety-eight (41 %) patients were COVID-recovered at the time of delivery. Of those, 48 (16 %) were infected in the 1st trimester, 123 (41 %) in the 2nd trimester, and 127 (43 %) in the 3rd trimester. The demographic data of these three groups are presented in Table 1. The three groups were similar demographically, and vaccination status was not statistically different between the groups (14.6 % vs. 5.7 % vs. 8 %, p=0.17).

The hospital admission rate was significantly higher in pregnant patients infected in the 2nd and 3rd trimesters compared to those infected in the 1st trimester (18 and 20 % vs. 2 %, p=0.005 and p=0.003). Similarly, 2nd and 3rd trimester COVID-infected pregnant patients were more likely to require oxygen supplementation than those infected in the 1st trimester (13% and 13.4 % vs. 0 %, p=0.007 and p=0.004). The rates of intubation, admission to the intensive care unit, and vasopressor need were not statistically different between the groups (Table 2). Rates of preterm birth <37 weeks (33 % vs. 19 % vs. 12 %, p=0.006) and extreme preterm birth <28 weeks (19 % vs. 5 %, p<0.001) were higher in the 1st trimester infection group. Otherwise, obstetrical outcomes were similar, including rates of cesarean birth, intra-amniotic infection, postpartum hemorrhage, blood transfusion requirement, and surgical site infection (Table 2). In addition, the rates of intrauterine fetal demise and fetal growth restriction were not different between the three groups. The spontaneous abortion rate for patients infected in the first trimester was 12.5 %, similar to the rate of miscarriage in the general population (Table 2).

Infants born to mothers infected in the 2nd trimester were more likely to have neonatal sepsis workups compared to those infected in the 1st and 3rd trimesters (22% vs. 12 and 7 %, p=0.31 and p=0.004). There were no significant differences in other neonatal outcomes between the three groups, including birthweight, Apgar scores, umbilical artery cord pH, admission to the neonatal intensive care unit, and neonatal death (Table 3). None of the newborns in our study groups had a positive SARS-CoV-2 test in their immediate postnatal course.

## Discussion

In this study, we aimed to examine the impact of gestational age at infection with the SARS-CoV-2 virus on maternal, obstetrical, and neonatal outcomes. We found that outcomes differed depending on the trimester of pregnancy during which the infection occurred. Patients with a first-trimester COVID-19 infection were less likely to have severe disease requiring hospital admission and oxygen supplementation compared to patients with a COVID-19 later in pregnancy. On the other hand, we found that patients who recovered from a first-trimester COVID-19 infection were more likely to have a preterm (<37 weeks) or an extremely preterm (<28 weeks) birth compared to patients who recovered from a 2nd or 3rd-trimester infection. These findings suggest that the physiological changes that occur as pregnancy progresses can lead to a worse clinical course if COVID-19 occurs at a later gestational age; however, infection with COVID-19 earlier in the pregnancy may lead to physiological changes that predispose to preterm delivery.

Although many studies have looked at obstetrical and neonatal outcomes of pregnant patients affected by COVID-19, very few have focused on stratifying these outcomes according to the gestational age at which the SARS-CoV-2 infection occurred. A study by Badr et al. in 2020 showed that patients with infection after 20 weeks of

**Table 1:** Demographics by trimester of infection.

| Characteristics | 1st tri n=48 Median [IQR], n (%) | 2nd tri n=123 Median [IQR], n (%) | 3rd tri n=127 Median [IQR], n (%) | p-Value |
|---|---|---|---|---|
| Age | 28.6 [23.05–32.55] | 28.6 [24.6–34.3] | 28.7 [24.8–33.8] | 0.63 |
| Race | | | | |
| Black | 23 (56.1 %) | 56 (55.4 %) | 61 (59.8 %) | 0.93 |
| White | 16 (39.0 %) | 41 (40.6 %) | 35 (34.3 %) | |
| Other | 2 (4.8 %) | 4 (4.0 %) | 6 (5.8 %) | |
| Hispanic | 7 (14.6 %) | 24 (19.5 %) | 26 (20.5 %) | 0.68 |
| BMI | 29.1 [24.3–34.75] | 30.3 [27.1–37.35] | 31.15 [27–38.3] | 0.13 |
| Parity | 1 [0–1] | 1 [0–2] | 1 [0–2] | 0.07 |
| No PMH | 14 (29.2 %) | 51 (41.5 %) | 47 (37 %) | 0.32 |
| Asthma | 11 (22.9 %) | 17 (13.8 %) | 19 (15 %) | 0.32 |
| Lung diseases | 0 (0 %) | 0 (0 %) | 0 (0 %) | |
| Chronic HTN | 5 (10.4 %) | 17 (5.7 %) | 10 (8 %) | 0.32 |
| Cardiac disease | 3 (6.3 %) | 3 (2.4 %) | 4 (3.1 %) | 0.47 |
| Chronic kidney disease | 0 (0 %) | 0 (0 %) | 0 (0 %) | |
| Diabetes mellitus | 1 (2 %) | 7 (5.7 %) | 2 (1.5 %) | 0.19 |
| Smoking | 4 (8.3 %) | 10 (8.1 %) | 3 (2.4 %) | 0.08 |
| Alcohol abuse | 0 (0 %) | 0 (0 %) | 0 (0 %) | |
| Illicit drug use | 3 (6.3 %) | 15 (12.2 %) | 13 (10 %) | 0.59 |
| Received at least 1 dose COVID vaccine | 7 (14.6 %) | 7 (5.7 %) | 10 (8 %) | 0.17 |

BMI, body mass index; PMH, past medical history; HTN, hypertension; tri, trimester; IQR, interquartile range.

**Table 2:** Maternal characteristics and obstetric outcomes by trimester of infection.

| | Infection & hospitalization outcomes | | | |
|---|---|---|---|---|
| **Characteristics** | **1st tri n=48 Median [IQR], n (%)** | **2nd tri n=123 Median [IQR], n (%)** | **3rd tri n=127 Median [IQR], n (%)** | **p-Value** |
| Vaccinated | 7 (14.6 %) | 7 (5.7 %) | 10 (7.9 %) | 0.17 |
| Admission | 1 (2.1 %) | 22 (18.0 %) | 24 (19.5 %) | **0.006** |
| Intubation | 0 (0.0 %) | 5 (4.1 %) | 2 (1.6 %) | 0.33 |
| Oxygen supplementation | 0 (0.0 %) | 16 (13.0 %) | 17 (13.4 %) | **0.01** |
| ICU admission | 0 (0.0 %) | 6 (4.9 %) | 8 (6.3 %) | 0.22 |
| Vasopressors | 0 (0.0 %) | 4 (3.3 %) | 2 (1.6 %) | 0.55 |
| **Obstetric outcomes** | | | | |
| Gestational age (delivery) | 267.5 [240–276.5] | 273 [260–280] | 273 [268–278] | 0.018 |
| Mode of delivery | | | | |
| Vaginal delivery | 31 (64.6 %) | 81 (65.9 %) | 86 (67.7 %) | 0.58 |
| Cesarean section | 10 (20.8 %) | 40 (32.5 %) | 40 (31.5 %) | |
| Intraamniotic infection | 1 (2.1 %) | 4 (3.3 %) | 2 (1.6 %) | 0.78 |
| Postpartum hemorrhage | 1 (2.1 %) | 3 (2.4 %) | 7 (5.5 %) | 0.46 |
| Blood transfusion | 0 (0.0 %) | 0 (0.0 %) | 4 (3.1 %) | 0.13 |
| Surgical site infection | 1 (2.1 %) | 0 (0.0 %) | 0 (0.0 %) | 0.16 |
| Spontaneous abortion | 6 (12.5 %) | N/A | N/A | |
| Fetal growth restriction | 6.7 % | 2.6 % | 3.5 % | 0.63 |
| Intrauterine fetal demise | 1 (2.1 %) | 1 (0.8 %) | 0 (0 %) | |
| **Preterm birth (PTB) rates** | | | | |
| PTB<37 weeks | 16 (33.3 %) | 23 (18.7 %) | 15 (11.8 %) | **0.006** |
| PTB<34 weeks | 11 (22.9 %) | 15 (12.2 %) | 1 (0.8 %) | **<0.001** |
| PTB<28 weeks | 9 (18.8 %) | 6 (4.9 %) | N/A | **<0.001** |

ICU, intensive care unit; PTB, preterm birth; tri, trimester; IQR, interquartile range. Bold values are considered to be significant (p<0.01).

**Table 3:** Neonatal outcomes by trimester of infection.

| Neonatal outcomes by trimester of infection | | | | |
|---|---|---|---|---|
| **Characteristics** | **1st tri n=48 Median [IQR], n (%)** | **2nd tri n=123 Median [IQR], n (%)** | **3rd tri n=127 Median [IQR], n (%)** | **p-Value** |
| Female | 21 (43.8 %) | 55 (44.7 %) | 62 (48.8 %) | 0.74 |
| Birthweight | 3200 [2570–3440] | 3215 [2695–3470] | 3242.5 [2865–3570] | 0.33 |
| APGAR (1 min) | 8 (8–9) | 8 (8–9) | 8 (8–9) | 0.6 |
| APGAR (5 min) | 9 (9–9) | 9 (9–9) | 9 (9–9) | 0.27 |
| Arterial cord pH | 7.24 [7.2–7.28] | 7.213 [7.18–7.29] | 7.2515 [7.19–7.31] | 0.63 |
| NICU admission | 6 (18.8 %) | 22 (21.6 %) | 16 (14.2 %) | 0.35 |
| Sepsis evaluation | 4 (12.1 %) | 21 (21.6 %) | 8 (7.1 %) | **0.008** |
| SARS-CoV-2 positive | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | N/A |
| Neonatal death | 0 (0.0 %) | 1 (0.8 %) | 0 (0.0 %) | 0.57 |

NICU, neonatal intensive care unit; tri, trimester; IQR, interquartile range. Bold value is considered to be significant ($p<0.01$).

gestation had a significantly increased risk for intensive care unit admission, endotracheal intubation, hospitalization for disease-related symptoms, and need for oxygen therapy [11]. Our results were similar in that patients with first trimester COVID-19 were less likely to require hospitalization and oxygen supplementation. However, in our study, the rate of intensive care unit admission and endotracheal intubation was not different between the three groups. This could be explained by the improved understanding of the disease and the improved management techniques in pregnancy at the time of our study compared to 2020. Another explanation could be the difference in various strains' virulence and their subsequent outcomes between that study and ours.

Another retrospective cohort study showed a statistically significant increase in a composite of adverse maternal outcomes and a composite of neonatal outcomes if infection occurred at >20 weeks' gestation and >26 weeks' gestation, respectively [12]. The composite neonatal outcomes included low birth weight, neonatal intensive care unit admission, low Apgar scores at 5 min of life, respiratory distress syndrome, and neonatal death. However, the timing of infection did not seem to affect neonatal outcomes significantly in our study groups. Also, third-trimester exposure did not result in increased rates of SARS-CoV-2 positive test results for the neonates in our study cohort. This is consistent with an NIH-funded study that showed that SARS-CoV-2 infections during the third trimester are unlikely to pass through the placental to the fetus [13]. In that study, patients who were positive for SARS-CoV-2 had detectable levels of the virus in respiratory fluids, but no virus was detected in the maternal bloodstream or placenta.

Previous studies have shown that preterm delivery rates are increased in pregnant patients with COVID-19 compared to pregnant patients without COVID-19 [14, 15]; however, there are not many studies that looked at this association by the timing of infection during pregnancy. For example, a study by Fallach et al. used logistic regression to compare the odds of preterm birth in patients based on whether the infection happened in the first or the third trimester [16]. The study found that SARS-CoV-2 infection was associated with an increased risk of preterm birth among patients infected during the third trimester. This is in contrast with our study which showed that infection early in the pregnancy was more likely to result in both preterm and extreme preterm birth. One explanation could be that the study by Fallach et al. included all pregnant patients with a positive SARS-CoV-2 test. In contrast, we only included those who recovered from COVID-19 at the delivery time. Also, their study was conducted before July 2021 and, therefore, before the emergence of Delta and Omicron variants. Furthermore, due to the limited understanding of the disease process and how to manage it at the time of Fallach's study, clinicians may have been more inclined to deliver COVID-19-infected patients nearing the end of their pregnancy.

It is important to note that all of the patients in our study who required ICU admission received IV dexamethasone for 10 days as part of our ICU protocol for patients with severe COVID-19 illness: Dexamethasone 40 mg IV twice a day for 48 h (fetal lung maturity dose) followed by dexamethasone 80 mg twice a day for eight days IV as suggested by the World Association of Perinatal Medicine and the Perinatal Medicine Foundation [17].

A study by D'Antonio et al. showed that patient demographics, such as advanced maternal age could be an independent risk factor for severe COVID-19 illness [18]. Demographic differences between the three study groups were not statistically significant in our study population. The

focus of our study was to evaluate the role of the trimester of infection, specifically on maternal, neonatal, and obstetrical outcomes. Perhaps in future studies, we could incorporate the roles of specific demographic risk factors such as maternal age, and evaluate if their effects change based on the trimester of infection as well.

To our knowledge, our study is one of the few to look at the relationship between gestational age at infection with SARS-CoV-2 and pregnancy outcomes. Furthermore, we had a relatively large number of pregnant patients with COVID-19 in our study, as our health system is one of the two major health systems in the State of Maryland and one of its hospitals serves as a state referral center for COVID-19 in pregnancy. Another strength of this study was that we focused on patients who were COVID-recovered at the time of delivery, meaning that their SARS-CoV-2 positive result was more than 10 days from the time of delivery. This allowed excluding patients who were incidentally found to have COVID-19 at the time of delivery and whose outcomes were unlikely to be affected by the SARS-CoV-2 infection. Finally, our cohort included patients from a diverse racial background, increasing our result generalizability.

Our study has some limitations. We did not stratify the results by variant types since we did not have laboratory confirmation on which variant was responsible for the positive SARS-CoV-2 test. Furthermore, although all our patients were tested for SARS-CoV-2 at the time of hospitalization for any medical reason or at the time of presentation for symptoms, we have likely missed some pregnant patients who were infected with COVID-19 but did not have a positive SARS-CoV-2 test result either because they did not present for testing or because of false negative results.

## Conclusions

The timing of infection with SARS-CoV-2 plays an important role in COVID-19 during pregnancy. Patients infected early in pregnancy seem to have a less severe disease course, however, they have an increased risk for preterm delivery. Further studies are needed to explore the potential pathophysiology behind this finding. Also, other studies should aim to confirm if the outcomes of this study could be replicated for different variants of SARS-CoV-2.

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**Competing interests:** Authors state no conflict of interest.

**Informed consent:** Not applicable.

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