ISSN: 3065-7628

Research Article

Journal of Future Medicine and Healthcare Innovation

The Comparison of Placental Findings and Pregnancy Outcomes Before and During COVID-19 Pandemic

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Submitted: 2024, Dec 23; **Accepted:** 2025, Jan 28; **Published:** 2025, Feb 07

Citation: How, H. Y., Turnquest-Wells, M., Daniels, M., Waldon, C. L. (2025). The Comparison of Placental Findings and Pregnancy Outcomes Before and During COVID-19 Pandemic. *J Future Med Healthcare Innovation, 3*(1), 01-06.

Abstract

Background: *During the SARS-CoV-2 pandemic, pregnancy outcomes remain in question with relationship to individuals who tested positive for COVID-19. There is a plethora of evidence that pregnant people who become infected with the SARS-CoV-2 virus may be at increased risk for perinatal loss. These losses are believed to be due to the destruction of the placenta, which then deprives the fetus of oxygen.*

Objective: *This study aimed to compare placental findings and fetal outcomes between two 18-month periods, pre-COVID-19, and COVID-19, and to determine if there was an increase in abnormal placental findings and fetal complications during the COVID-19 period. The study hypothesized that pregnant individuals with COVID-19 positivity would have a higher risk of intrauterine fetal demise and FGR due to placental injury caused by the virus.*

Study Design: *The placental findings and fetal outcomes of 34,102 deliveries were retrospectively compared between two equal seasonal 18-month timeframes. The COVID-19 period was April 1, 2020, to September 30, 2021. The pre-COVID-19 period was April 1, 2018, to September 30, 2019, with a wash-out period of October 1, 2019, to March 31, 2020. Chi-squared statistical tests with odds ratios and 95% confidence intervals were used to contrast three placental findings and two fetal outcomes.*

Results: *The study found a significant increase in chorangiosis, chorioamnionitis, villitis, and FGR during the COVID-19 period compared to the pre-COVID-19 period. Additionally, there was a higher incidence of chorangiosis, chorioamnionitis, villitis, and marginally higher FGR in placentae from mothers with a history of COVID-19 infection compared to those without a positive test. There was no significant increase in intrauterine fetal demise among COVID-19-positive mothers.*

Conclusion: *The study concludes that antenatal testing is not warranted solely for positive COVID-19 infection without other comorbidities present because there was no significant increase in intrauterine fetal demise. However, the study found a rise in FGR among pregnant individuals with a positive COVID-19 test. We agree with the Society for Maternal-Fetal Medicine's recommendations that a repeat fetal growth ultrasound should be conducted four weeks after a positive COVID-19 test. We acknowledge that chorangiosis can occur due to other maternal comorbidities. In the absence of data regarding maternal demographics, we cannot conclude whether chorangiosis occurred due to COVID-19 or other conditions.*

"When you believe in things that you don't understand, then you suffer. Superstition ain't the way!" Stevie Wonder, 1972.

1. Introduction

The impact of COVID-19 on pregnancy outcomes is a topic of ongoing research. Pregnant individuals who contract the virus may be at an increased risk of perinatal loss due to the destruction of the placenta, resulting in fetal hypoxia. SARS-CoV-2 placentitis, characterized by histiocytic intervillositis, perivillous fibrin deposition, and trophoblast necrosis, has been identified as a significant pathological finding associated with intrauterine fetal demise and neonatal deaths [1, 2]. Other abnormal placental findings reported with COVID-19 include chorangiosis, chorioamnionitis, and villitis [1, 2].

Chorangiosis, a vascular change in the terminal chorionic villi, is associated with fetal growth restriction (FGR), diabetes, and hypertensive disorders of pregnancy (Figure 1) [3]. Chorioamnionitis is inflammation of the fetal membranes, while villitis is inflammation of the chorionic villi surface of the placenta. Villitis may also be seen with maternal infection from cytomegalovirus, herpes, and varicella (Figure 2, 3) [4, 5].

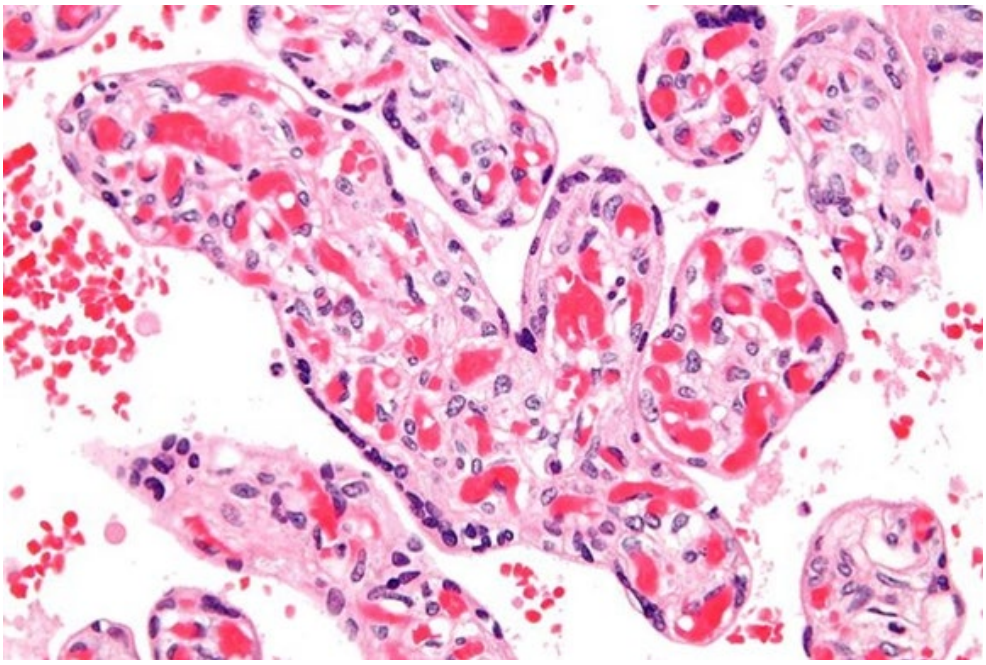

Figure 1: Chorangiosis- the Proliferation of Fetal Vessels (>10 capillaries in 10 terminal villi of at least 10 low power fields)

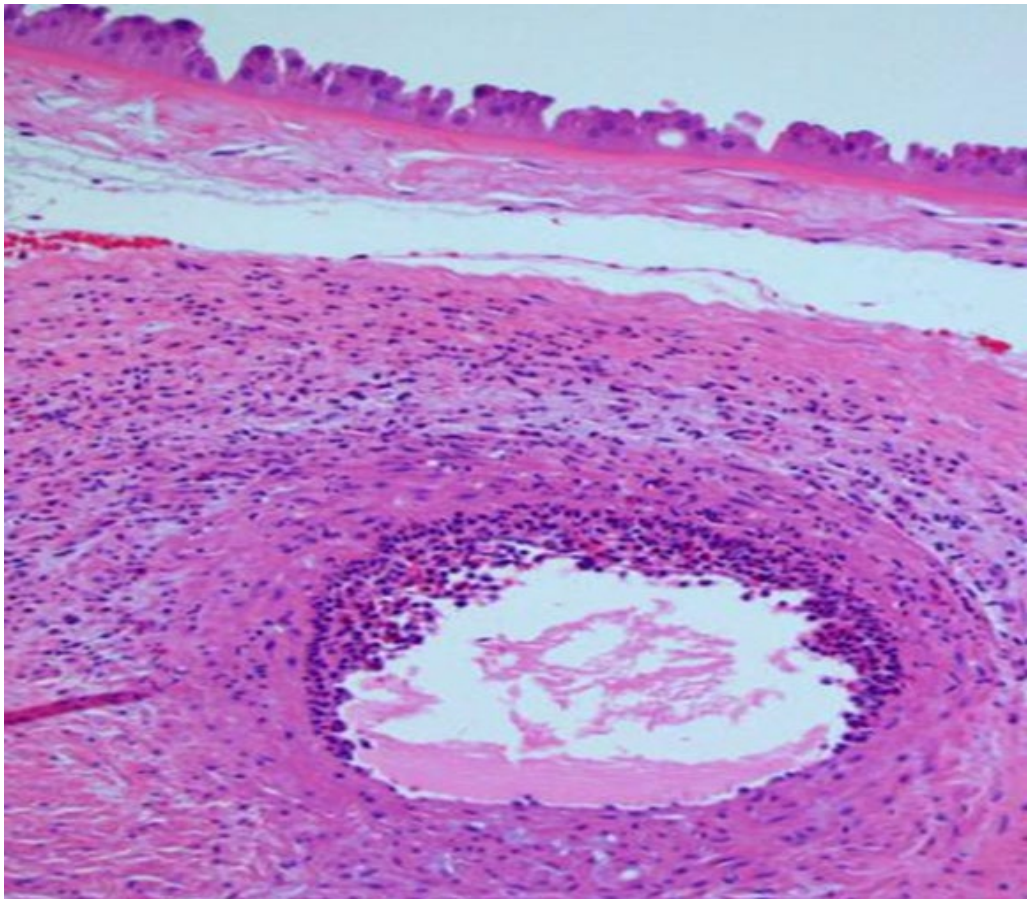

Figure 2: Chorioamnionitis- Inflammation of the Fetal Membranes

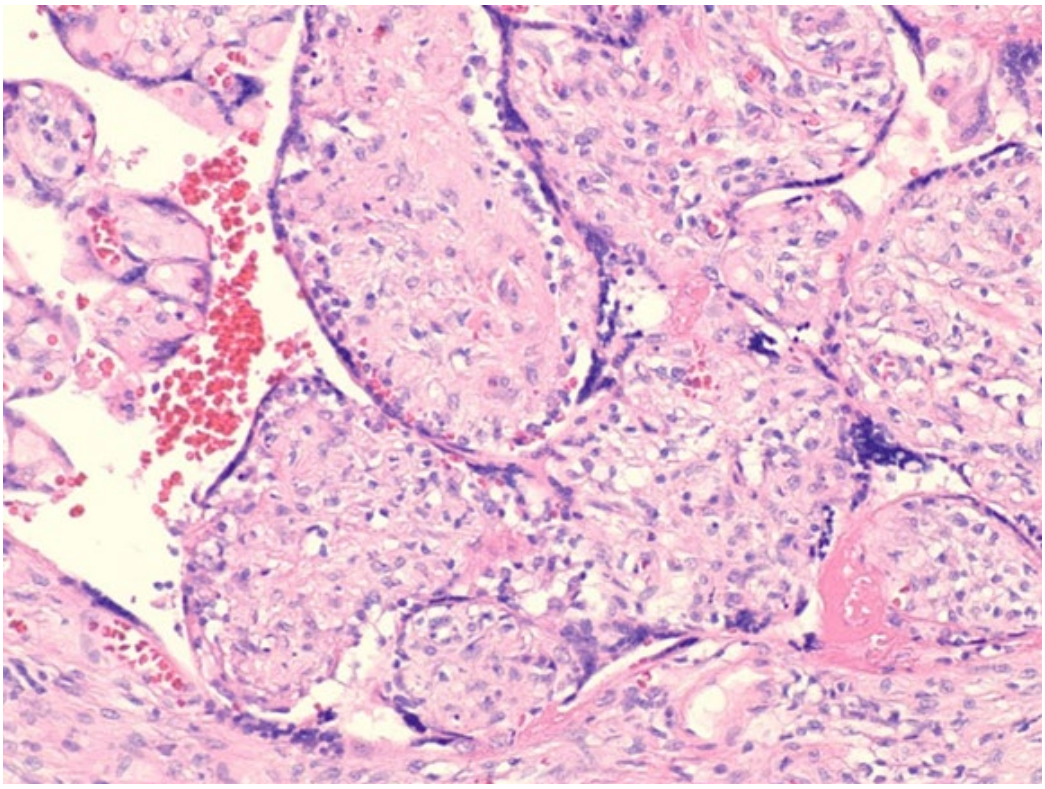

Figure 3: Villitis- Inflammation of the Chorionic Villi on the Surface of the Placenta

Studies have reported a higher incidence of fetal death and FGR associated with COVID-19, and anecdotal evidence suggests an increase in chorangiosis during the pandemic. We hypothesize that pathology reports throughout the COVID-19 period would show significantly increased abnormal placental findings and an increased risk of intrauterine fetal demise FGR in those with COVID-19 positivity.

2. Materials and Methods

To evaluate our hypothesis, we retrospectively compared the placental findings and fetal outcomes during the pre-COVID-19 and COVID-19 periods, each consisting of equal 18-month timeframes. Universal testing for COVID-19 began within our hospital system on April 1, 2020. This date was used as the beginning of the COVID-19 period (April 1, 2020, - September 30, 2021). The pre-COVID-19 period utilizes the same 18-month seasonal timeframe (April 1, 2018, - September 30, 2019). Before the first publicized variant (Alpha) of COVID-19, differences in COVID-19 were identified by strains. Most of the U.S. cases of COVID-19 from February 2020 through November 2020 were identified as the GH strain. Once Alpha was identified as the first variant in November 2020 the variant was responsible for 66% of U.S. cases. The Delta variant was the next variant that was held responsible for the majority of cases of COVID-19 in the U.S. beginning in April 2021 through September 2021. These are the strains and variants found in the U.S. during our study period [6].

Pediatric-Perinatal Pathology Associates examine all placentae on a routine basis within the hospital system. Maternal and fetal diagnoses were provided on the pathology requisition. Chi-squared statistical tests along with odds ratios and their 95% confidence intervals contrasted three placental findings (*chorangiosis, chorioamnionitis, villitis*) and two fetal outcomes (*intrauterine fetal demise and FGR*). These were analyzed between equal seasonal times, as previously defined, and a sub-analysis for the COVID-19 period based on the maternal COVID-19 status during pregnancy. In this study, intrauterine fetal demise was defined as fetal death at any gestational age. FGR is defined as an estimated fetal weight less than the 10th percentile for gestational age.

3. Results

We analyzed 34,102 placentae, of which 12,432 (36%) were from the pre-COVID-19 period, and 21,679 (64%) were from the COVID-19 period. Among the placentae from the COVID-19 period, 1,434 (7%) were from women who tested positive for COVID-19 during their pregnancy.

During the COVID-19 period, there was a significant increase in the presence of chorangiosis (OR 1.25; 95% CI 1.16-1.34, $p < .001$), chorioamnionitis (OR 1.59; 95% CI 1.52-1.66, $p < .001$), and villitis (OR 1.1; 95% CI 1.02-1.19, $p= .019$) when compared to the matched prior period. Regarding fetal outcomes, there was a significant increase in FGR (OR 1.13; 95% CI 1.04-1.23, $p = .002$) but only a slight increase in intrauterine fetal demise (OR 1.09; 95% CI 0.93-1.27, $p= .299$) (Table 1).

COVID-19 Period						
	Overall	No	Yes			
Characteristics	**N=34,102**	**N=12,432**	**N=21,670**	**OR**	**95% CI**	**95% CI**
Chorangiosis	3591 (10.5%)	1151 (9.3%)	2444 (11.3%)	1.25	(1.16-1.34)	<.001
Chorioamnionitis	15,466 (45.5%)	4,763 (38.3%)	10,761 (49.6%)	1.59	(1.52-1.66)	<.001
Villitis	2867 (8.4%)	990 (8.0%)	1886 (8.7%)	1.10	(1.02-1.19)	.019
FGR	2887 (8.5%)	977 (7.9%)	1910 (8.8%)	1.13	(1.04-1.23)	.002
Intrauterine fetal demise	746 (2.2%)	258 (2.1%)	488 (2.3%)	1.09	(0.93-1.27)	.299

Table 1: Comparison Between Two Equally Seasonal 18-Month Timeframes

There were significantly more chorangiosis (11.3% vs. 9.3%, OR=1.25 (1.16-1.34), p<.001), more chorioamnionitis (49.6% vs 38.3%, OR=1.59 (1.52-1.66), p<.001), more villitis (8.7% vs. 8.0%, OR=1.10 (1.02-1.19), p=.019), and more fetal growth restriction (8.8% vs 7.9%, OR=1.13 (1.04-1.23), p=.002) during the COVID-19 period when compared to the matched prior period. There was a slight increase in the risk of intrauterine fetal demise (2.3% vs 2.1%, OR=1.09 (0.93-1.27), p=.299).

In women who tested positive for COVID-19, their placentae had significantly more chorangiosis (OR 1.40; 95% CI 1.20-1.63, p< .001), chorioamnionitis (OR 1.51; 95% CI 1.36-1.69, p< .001), and villitis (OR 1.49; 95% CI 1.26-1.77, p< .001) when compared to women without COVID-19. In addition, the risk of FGR was slightly increased (19%) in women who tested positive for COVID-19 (OR 1.19; 95% CI 0.99-1.42, p= .06). It is important to note that women with COVID-19 had a 37% less chance of experiencing an intrauterine fetal demise (Table 2).

COVID-19 +						
	Overall	No	Yes			
Characteristics	**N=21,679**	**N=20,245**	**N=1,434**	**OR**	**95% CI**	**P-value**
Chorangiosis	2444 (11.3%)	2232 (11.0%)	212 (14.8%)	1.40	(1.20-1.63)	<.001
Chorioamnionitis	10761 (49.6%)	9912 (49.0%)	849 (59.2%)	1.51	(1.36-1.69)	<.001
Villitis	1886 (8.7%)	1712 (8.5%)	174 (12.1%)	1.49	(1.26-1.77)	<.001
FGR	1910 (8.8%)	1764 (8.7%)	146 (10.2%)	1.19	(0.99-1.42)	.060
Intrauterine fetal demise	488 (2.3%)	467 (2.3%)	21 (1.5%)	0.63	(0.38-0.98)	.042

Table 2: Comparison of Positive and Negative Test Results During the COVID-19 Period

There were significantly more chorangiosis (14.8% vs. 11.0%, OR=1.40 (1.20-1.63), p<.001), chorioamnionitis (59.2% vs. 49.0%, OR=1.51 (1.36-1.69), p<.001), villitis (12.1% vs 8.5%, OR=1.49 (1.26-1.77), p<.001), and marginally more FGR (10.2% vs. 8.7%, OR=1.19 (0.99-1.42), p=.060) in placentae from mothers with a history of COVID-19 infection compared to those without a positive test. However, COVID-19 positive mothers had less intrauterine fetal demise (1.5% vs. 2.3%, OR=0.63 (0.38-0.98), p=.042).

Overall, our findings suggest that the COVID-19 period was associated with an increased incidence of specific placental findings and FGR, particularly in women who tested positive for COVID-19 during pregnancy.

3.1. Principal Findings

In this study, we compared the pathological findings observed in the placentae of women delivering during pre-COVID-19 and COVID-19 periods. We found that there was a statistically significant increase in placental abnormalities and FGR during the COVID-19 period. We found a slight but insignificant increase in intrauterine fetal demise during the COVID-19 period; however, the sub-analysis showed that this increase was not due to COVID-19 because more intrauterine fetal demise occurred in women who did not have COVID-19.

4. Discussion

In contrast to our findings, Narang et al published outcomes of 208 patients with positive COVID-19. They found that women with

asymptomatic or mild COVID-19 during pregnancy, regardless of the timing of infection, were not associated with FGR [7]. It is plausible that the rate of FGR was not increased because patients with severe illness were not included in this study. In addition, the sample size was small; therefore, they may not have had enough power to detect possible differences. Although our study does not stratify by the severity of COVID-19, placentae would have been examined from all patients including those with severe illness.

Obata et al, in a retrospective study of infants admitted to the neonatal intensive care unit (NICU), found that there was no difference in FGR among those infants born during the pre-pandemic versus those during the pandemic period. This study included only infants admitted to the NICU or the Growth Care Unit, resulting in a small sample size (156 patients) and based on only a 5-month duration [8]. Our study included larger sample size, longer study periods, and involved all placentae not only those of NICU admissions.

A large population-based cohort study by Ferrara et al included 43,886 pregnant individuals, of which 1,332 (3%) were COVID-19 positive. The findings reported no increased rate in small for gestational age (SGA) and intrauterine fetal demise. This study references a large population size but only 3% of the population was COVID-19 positive [9]. With a comparable sample size, our study showed a 7% positivity rate during the COVID-19 period which could account for the difference in the prevalence of FGR in our study.

Khalil et al compared a four-month period of different seasonality in London, COVID-19 period (February 1, 2020, - June 14, 2020). Within this study, they compared the data against a pre-pandemic era (October 1, 2019, - January 31, 2020). They found an increase in intrauterine fetal demise among women who delivered during the COVID-19 period, however; similar to our findings the increase was not due to COVID-19 in the mother. They postulate, and we agree, that the increase in intrauterine fetal demise could have been due to reduced clinic hours or patients failing to go to the hospital when indicated for fear of contracting COVID-19 [10].

4.1. Clinical Implications

This study hypothesized that pathology reports throughout the COVID-19 period would show significantly increased abnormal placental findings such as chorangiosis, chorioamnionitis, and villitis. We also estimated that the risk of IUFD and FGR would be higher in those with COVID-19 positivity during pregnancy.

4.2. Research Implications

Within our limitations, we note that maternal and fetal demographics were not obtained. Future research including demographics, the severity of COVID-19, and the timing interval between positive tests to delivery would determine if the placental findings and pregnancy outcomes were related directly to COVID-19 or other comorbidities during the pregnancy.

4.3. Strengths and Limitations

This study had numerous strengths, including a large number of placental samples during the COVID-19 period, longer periods with comparable durations (18 months), and seasonal variations including two springs, two summers, one fall, and one winter. Finally, we included all pregnant individuals with different stages of COVID-19 severity and all neonates regardless of the intensity of care.

There are several limitations to this study. We do not have information regarding the gestational age, maternal or fetal demographics, the severity of COVID-19, or the interval from the date of a positive COVID-19 test until delivery.

5. Conclusion

This study noted an increase in chorangiosis during the COVID-19 period, yet we recognize that chorangiosis can be seen with other conditions such as diabetes and hypertensive disorders of pregnancy. Since we do not have information on maternal demographics, we cannot conclude if chorangiosis occurred due to COVID-19 or in relation to other maternal comorbidities.

This study found an increase in FGR among pregnant women who tested positive for COVID-19 during pregnancy. Given these findings, we agree with the recommendations from the Society for Maternal-Fetal Medicine that a repeat fetal growth ultrasound should be done four weeks after a positive COVID-19 test [11].

Our study also showed a slight increase in intrauterine fetal demise between the two periods; however, the increase was not due to COVID-19 because the majority of the intrauterine fetal demise occurred in women who were COVID-19-negative. Since there was no significant increase in intrauterine fetal demise, we can conclude that antenatal testing is not warranted solely for positive COVID-19 in the absence of other comorbidities such as diabetes, hypertension, and FGR.

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