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Research Article

Placental Histopathological Alterations in COVID-19 Infected Pregnancies

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Abstract

Aim: The ongoing global COVID-19 pandemic, caused by the SARS-CoV-2 virus, has generated significant apprehensions in maternal-fetal medicine. Initially considered to affect the respiratory system primarily, recent findings have indicated that the pandemic has far-reaching implications for various physiological functions, particularly in pregnant individuals. This study focused on examining the influence of COVID-19 on placental histopathology in pregnant women infected with SARS-CoV-2.

Material and Methods: We conducted a comparative study involving two groups of pregnant women with similar demographic characteristics: a group testing positive for COVID-19 (n=31) and a control group of COVID-19-negative pregnant women (n=31). After delivery, placental tissues were collected and subjected to comprehensive histopathological examination to determine any potential alterations in the placenta induced by SARS-CoV-2 infection.

Results: Our study revealed substantial histopathological alterations in pregnant women with COVID-19 placentas. Notably, the COVID-19 group displayed a higher incidence of cesarean deliveries, possibly due to concerns related to maternal-fetal transmission and respiratory complications. Furthermore, neonates born to mothers in the COVID-19 group had significantly lower birth weights. Several placental histopathological changes, including villous fibrin deposits, thrombosis, intervillous hemorrhage, agglutination, avascular fibrotic villi, and syncytial knots, were markedly increased in the COVID-19 group, indicating compromised fetal blood circulation. Although not statistically significant, trends toward elevated villous infarction, fetal vascular malperfusion, and chorioamnionitis were observed.

Conclusion: Our study underscores the potential risks associated with COVID-19 on placental health, maternal well-being, and neonatal outcomes. We must understand the underlying physiological mechanisms behind these pathological changes to provide optimal maternal-fetal care during this ongoing crisis. Comprehensive and multicentric studies are urgently required to confirm and expand our findings.

Keywords: COVID-19, Placental histopathological changes, pregnancy

INTRODUCTION

The emergence of COVID-19, which is linked to the SARS-CoV-2 virus, has caused many public health complications worldwide (1,2). Although it is primarily viewed as a disease affecting the respiratory system, mounting data indicate that its scope is broader, extends to various physiological functions, and notably has repercussions on pregnant individuals (3-5).

Pregnant individuals have been identified as a group requiring special attention in the context of COVID-19 owing to the immediate and potential long-term health considerations for both the mother and the unborn child (6-8).

The placenta is a vital organ during gestation that enables the exchange of essential nutrients and oxygen between the mother and the fetus. Its function is paramount for a successful pregnancy (9,10). Initial studies have pointed toward the susceptibility of the placenta to SARS-CoV-2 due to the presence of ACE-2 receptors on placental cells (11,12). Nevertheless, the exact histological changes occurring in the placenta due to COVID-19 and their impact on fetal health still need to be clearly defined (13).

CITATION

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Given the limited breadth of research focusing on this crucial aspect of maternal and fetal health, our study scrutinized the available scientific literature regarding the histopathological effects of SARS-CoV-2 on the placenta. Therefore, we aim to shed light on this critical area. Our study also provides the groundwork for future research. Future work could lead to better treatment strategies for managing COVID-19 during pregnancy.

MATERIAL AND METHOD

This study involved two groups of pregnant women. The test group comprised 31 women who were COVID-19-positive, as confirmed by PCR tests, but had no chronic diseases. The patients were hospitalized and treated according to standard protocols based on their symptoms and disease severity. Treatments included oxygen support through a nasal cannula, antiretroviral drugs lopinavir/ritonavir (400 mg twice daily for seven days), and hydroxychloroquine (200 mg once daily) when necessary. Prophylactic low-molecular-weight heparin (LMWH) was administered to all COVID-19-positive patients throughout their hospitalization and postpartum period. Antibiotics such as ampicillin or cephalosporins were administered as required.

The control group consisted of 31 pregnant women who were COVID-19-negative, as confirmed by PCR tests and had no chronic diseases or COVID-19 symptoms.

Placentas from both groups were collected immediately post-delivery and underwent routine gross examinations. Tissue specimens were fixed in formalin for 48 h and processed for histological analysis. These were embedded in paraffin, sectioned at 5 microns, and stained with hematoxylin and eosin.

An experienced pathologist evaluated the slides for chorioamnionitis, maternal vascular malperfusion, and fetal malperfusion based on the Amsterdam criteria (13). Definitions for these conditions were as follows:

Chorioamnionitis was identified by neutrophil infiltration into the chorion and amnion.

Maternal vascular malperfusion was marked by lesions such as fibrinoid necrosis, intervillous thrombi and infarcts.

Fetal vascular malperfusion was characterized by chorangioma, villous fibrosis, or villous edema.

Neither the mothers nor the infants were subjected to COVID-19 testing of their placental tissue; only RT-PCR was used for diagnosis.

This study was approved by our institution's Clinical Research Ethics Committee (approval number KAEK/2020.06.66) and the Ministry of Health. All the participants provided written informed consent.

RESULTS

The characteristics of mothers in both the control and COVID-19 groups are outlined in Table 1. The control and COVID-19 groups comprised 31 participants of comparable ages. There were no marked statistical differences in variables like gravidity, parity, history of miscarriage, smoking habits, and BMI between the control and COVID-19 groups ($p>0.05$).

Details of the COVID-19-positive cases are summarized in Table 2. This table shows variables such as gestational age at diagnosis and delivery, severity of the disease, and treatment modalities. Table 3 indicates no statistically significant difference in gestational age at delivery between the two groups ($p=0.096$). Notably, all deliveries in the COVID-19 group were by cesarean section, in contrast to 71% of deliveries in the control group ($p=0.001$). The reasons for cesarean deliveries were multifaceted and included previous cesarean sections and COVID-19-related indications ($p=0.009$).

Regarding neonatal outcomes, the mean newborn weight was 3158±188 g in the control group and 2940±149 g in the COVID-19 group, which was statistically significant ($p=0.037$). No significant difference was observed in the neonatal intensive care unit (NICU) admissions rate between the two groups ($p=0.215$). One fetal death occurred in each group, accounting for a rate of 3.2%, which was not statistically significant.

Although pharmacological treatment was administered in a few cases, most patients did not receive specific drug therapies. Oxygen therapy was primarily administered through a nasal cannula when required. One maternal death occurred 26 days after delivery.

Table 1. Maternal characteristics of the study groups.

	Controls (n=31)	COVID-19 (n=31)	Significance
Age (years)	29.1±5.6	31.4±5.6	0.109
Gravidity	3.0 (1-6)	3.0 (1-9)	0.317
Parity	1.0 (0-4)	2.0 (0-4)	0.273
Miscarriage	0 (0-3)	0 (0-3)	0.361
Smoking	9 (29%)	11 (35%)	0.587
Body mass index (kg/m^2)	23 (20-40)	21 (20-37)	0.312

Continuous variables are represented by the mean value and the standard deviation (SD), derived using descriptive statistics. On the other hand, categorical variables are displayed as frequencies, calculated using frequency distribution, with their corresponding percentages enclosed in parentheses.

Table 2. COVID-19 positive cases features

Features	Values
Gestational age at infection diagnosis (wks)	36 (24-39)
Gestational age at delivery (wks)	38 (26-41)
Severity of the disease	
Mild	29 (93.5%)
Moderate	1 (3.2%)
Severe	1 (3.2%)
Pharmacologic therapy	
None	26 (83.9%)
Lopinavir/Ritonavir	1 (3.2%)
Hydroxychloroquine	4 (12.9%)
Oxygen therapy	
None	24 (77.4%)
Nasal cannulae	7 (22.6%)
Maternal death	1 (3.2%)

Continuous variables are represented by the mean value and the standard deviation (SD), derived using descriptive statistics. On the other hand, categorical variables are displayed as frequencies, calculated using frequency distribution, with their corresponding percentages enclosed in parentheses.

Table 3. Perinatal Outcomes of the study groups.

	Controls (n=31)	COVID-19 (n=31)	Significance
Gestational age at delivery (wks)	38 (26-41)	38 (26-41)	0.096
Delivery mode			
Vaginal delivery	22 (71%)		0.001
Cesarean section	9 (29%)	31 (100%)	
Indications for cesarean section			
Prior cesarean section	17 (68%)	21 (67.7%)	0.009
COVID-19	0	7 (22.6%)	
Non-reassuring fetal status	8 (32%)	2 (6.5%)	
Preeclampsia	0	1 (3.2%)	
Newborn weight (g)	3158±188	2940±149	0.037
NICU admission	6 (19.4)	10 (33.4%)	0.215

Table 4. Placental histopathologic findings of study groups.

Histopathological findings	Controls (n=31)	COVID-19 (n=31)	Significance
Villous infarction	14 (45.2%)	18 (58.1%)	0.31
Fetal Vascular Malperfusion (Chorangiosis)	30 (96.8%)	31 (100%)	0.31
Chorioamnionitis	3 (9.7%)	6 (19.4%)	0.28
Villitis	6 (19.4%)	10 (32.3%)	0.25
Villous fibrin deposits	9 (29%)	27 (87.1)	0.001
Villous thrombus	14 (45.2%)	31 (100%)	0.001
Intervillous hemorrhage	15 (48.4%)	31 (100%)	0.001
Villous agglutination	10 (32.3%)	25 (80.6%)	0.001
Avascular fibrotic villi	7 (22.6%)	17 (54.8%)	0.009
Increased syncytial knots	7 (23.3%)	27 (87.1%)	0.001

The chi-square test was utilized to evaluate the statistical differences indicated in this table. The 'Significance' values are representative of the differences in each histopathological finding between the control and COVID-19 groups. A p-value of <0.05 is considered to be statistically significant.

As illustrated in Table 4, significant increases in specific placental histopathological changes were identified in the COVID-19 group. These included villous fibrin deposits, thrombosis, intervillous hemorrhage, agglutination, avascular fibrotic villi, and syncytial knots ($p<0.05$). Increases in villous infarction, fetal vascular malperfusion, and chorioamnionitis were also noted, but these were not statistically significant.

DISCUSSION

The global reach and complexity of the COVID-19 crisis have made it essential to examine its effects on specific high-risk groups, among which pregnant women stand out. This study contributes to the scant but growing body of literature on placental histopathological changes in SARS-CoV-2-infected pregnancies.

Our study was particularly strengthened by the comparable maternal characteristics between the control and COVID-19-positive groups, enabling a more accurate interpretation of the direct impact of the virus on pregnancy outcomes. Notably, there was a disproportionately high rate of cesarean sections in the COVID-19-positive group. This finding suggests that the pandemic could influence obstetric care decisions, potentially due to maternal-fetal transmission concerns or respiratory complications.

Histologically, the dominant feature in our COVID-19-affected cohort was cholangitis, a finding associated with compromised fetal blood circulation. Previous studies, including those by Umar et al., Shanes et al., and Bobei et al., resonate with our observations, indicating heightened maternal vascular malperfusion, fetal vascular thrombosis, and increased inflammation (14-16). The clinical relevance of these placental changes, seen in the increased risk of adverse outcomes, such as preterm birth and fetal distress, cannot be overstated.

Acknowledging that our findings do not align universally with the broader scientific discourse is essential. A recent multicenter case-control study found no discernible differences in placental histology between COVID-19-positive and -negative groups (17). These inconsistencies necessitate further research to untangle the true extent of COVID-19's impact on pregnancy and fetal outcomes.

While our study offers crucial insights, its limitations are nontrivial. The limited sample size, geographic specificity, and potential methodological constraints suggest that caution should be exercised when generalizing these findings. Future research should strive for a more expansive and multicentric approach to corroborate or challenge our results.

CONCLUSION

In summary, our research, alongside existing studies, signifies the latent risks of COVID-19 on placental health and, by extension, maternal and neonatal well-being (13,14,18,19). The pathologies we identified could be the mechanisms that contribute to adverse pregnancy outcomes, including reduced neonatal weight. This situation necessitates vigilant monitoring and tailored medical interventions for pregnant women with SARS-CoV-2 infection. Further studies are urgently needed to decode the physiological mechanisms behind these pathological changes, paving the way for optimized maternal-fetal care during this ongoing crisis.

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Conflict of Interest: *The authors declare that they have no competing interest.*

Ethical approval: This study was approved by our institution's Clinical Research Ethics Committee (approval number KAEK/2020.06.66) and the Ministry of Health.

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