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COMPARISON OF HISTOPATHOLOGICAL FINDINGS IN PLACENTAS FROM PARTURIENTS INFECTED OR NOT BY SARS-CoV-2

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ABSTRACT

Objectives: It is not clear whether COVID-19 has any effect on the placenta or even impacts pregnancy outcomes. The aim was to compare the histomorphological characteristics of placentas from parturients with positive and negative PCR for SARS-CoV-2. **Methods:** Cross-sectional study from May 2021 to March 2022 where histopathological analysis of placentas from women who underwent PCR for the diagnosis of COVID-19, were performed using the Hematoxylin/Eosin staining method. **Results:** The sample consisted of placentas from thirty parturients, among which ten had been diagnosed with COVID-19 confirmed by PCR (33.3%). Results revealed higher levels of congestion, chronic focal villitis and acute funisitis in placentas from parturients diagnosed with COVID-19. Negative parturients had a higher percentage of intervillous hemorrhage with thrombus formation, dystrophic calcification, placental infarction, and capsular acute deciduitis. **Conclusion:** No unusual placental histopathological pattern was found among women with positive PCR for SARS-CoV-2. Observational studies with larger samples are warranted.

Keywords: placenta pathology; vascular calcification; perinatology.

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INTRODUCTION

The impact of coronavirus disease 2019 (COVID-19) on pregnancy outcomes and its effects on the placental unit is not clearly established. Evidence of the systemic inflammatory response caused by COVID-19 demonstrates a greater state of hypercoagulability and formation of microthrombi in several organs (Connors et al. 2020, Rapkiewicz et al 2020), in addition to vascular lesions and thrombosis in placentas of infected women (Sharps et al. 2020).

Placental changes have been demonstrated in maternal COVID-19 infection. Histomorphological analysis of placentas from PCR-positive women showed poor maternal vascular perfusion and a greater number of syncytial knots when compared to the control group, which is indicative of preplacental hypoxia (Khong et al. 2016, Beyerstedt et al. 2021, Rad et al 2021). Increased focal perivillous fibrin deposition, villous clumping, and microcalcifications have also been reported (Shchegolev et al. 2021, Gao et al. 2021, Singh et al. 2021, Jamieson et al. 2022).

A case-based retrospective analysis of women infected with SARS-CoV-2 has identified chronic histiocytic intervillitis (CHI) and trophoblastic necrosis in all placentas analyzed (Schwartz et al. 2021). However, in women without the infection, a frequency of < 10% of CHI, a massive fibrin deposition, and chronic deciduitis have been evidenced (Feist et al. 2015). Moreover, acute chorioamnionitis has been reported at a frequency of 10 to 20% (Kim et al. 2015, Czikk et al. 2011).

It has not yet been possible to trace a placental histopathological pattern in women with COVID-19 (Rad et al. 2016, Rebutini et al. 2021, Wong et al. 2021, Suhren et al. 2022). A recent meta-analysis concluded that signs of poor perfusion as well as placental changes were non-specific for SARS-CoV-2 infection (Suhren et al. 2022). On the other hand, a structured review that evaluated 150 placentas of pregnant women in the third gestational trimester previously diagnosed with COVID-19 reported a variety of histopathological abnormalities, including maternal vascular malperfusion (MVM), fetal vascular malperfusion (FVM), and signs of inflammation. However, in the majority of the studies included in this review, the severity of lesions was not compared between women with and without COVID-19 (Sharps et al. 2020).

Therefore, there is still considerable uncertainty regarding the association between abnormal placental histomorphological features and COVID-19. Understanding placental pathology in COVID-19 infection is important to define the disease trajectory, as well as the potential risks for the mother and the resulting complications for the fetus in utero (Linehan et al. 2021). The aim of this study was to compare the histomorphological characteristics of placentas from PCR-positive parturients for SARS-CoV-2 with those from PCR-negative results.

MATERIALS AND METHODS

A cross-sectional study with histopathological analysis was performed on placentas of parturient women aged 18 or older, with positive or negative PCR for SARS-CoV-2. The sample collection was made between the months of May 2021 and March 2022, in a university hospital in the northeast region of Brazil and further analyzed by the Laboratory of Pathological Anatomy from the same university. The study was approved by the institutional ethics committee under the protocol number 44624921.5.0000.5292.

Placentas of parturients who underwent PCR testing for the diagnosis of COVID-19, with active infection or not and with deliveries in the second and third trimesters of pregnancy, were included in this study. Placentas from abortions were excluded. After signing the Free and Informed Consent Term, the pregnant women underwent an interview to collect data, such as vaccination against Coronavirus, obstetric data and the existence of comorbidities.

Placentas were fixed in 10% buffered formalin for at least 48 hours. After fixation of the placental tissue, the extraplacental membranes and the umbilical cord were sectioned into fragments with thickness of 4 to 5 mm and processed for 18 hours in an automatic tissue processor using a Leica ASP 300S equipment (Nussloch, Germany). After inclusion of the fragments and preparation of the blocks, the histological sections were obtained using a Leica RM 2125 RTS microtome (Nussloch, Germany), with a thickness of 3 micrometers. The samples were stained by the Hematoxylin/Eosin technique using an automatic dye Leica ST5020 (Nussloch, Germany) and later analyzed under an optical microscope CX40

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(Olympus, Tokyo, Japan).

Umbilical cord, membranes and placental disc samples were obtained using the criteria established by the Amsterdam Consensus Group protocol (Khong et al. 2016) which included 01 extraplacental membrane roll section; 03 cross-sections of the umbilical cord, 01 cross-section from the distal end excluding the area of cord clamping, 01 from the proximal end and sections of 2.0 to 3.0 cm from its insertion, as well as 01 from the middle portion. From the placental disc, 03 to 04 fragments of the total placenta thickness from areas of normal appearance were obtained, which were chosen randomly in the central two thirds of the disc. In addition, a section of 01 fragment containing the total thickness of the area corresponding to the insertion of the umbilical cord was obtained. Representative fragment of any macroscopically identified lesion, regardless of location, was also included. When the total thickness of the fragment exceeded the length of the cassette, the sample was divided into 02 portions and placed in separate cassettes. The reports were performed by a single pathologist with years of experience in the area, in addition to being a university professor and co-author of this study.

Statistical analyzes were performed using SPSS (Statistical Package for the Social Sciences, Chicago, USA), version 25.0. The Shapiro-Wilk normality test was applied to verify adherence to the normal distribution. Descriptive analysis was performed using mean and standard deviation (Mean ± SD), as well as absolute and relative frequencies. Student's t test for independent samples was applied to assess differences in the placental weight between the two analyzed groups. The homogeneity of variances was verified using the Levene test. Fisher's exact test was used to analyze the association between variables of a categorical nature. The significance level of 5% was used for all analyzes.

RESULTS

Placentas of thirty parturients were included in this study. Among them, ten had COVID-19, which was confirmed by PCR test (33.3%), twenty had at least one comorbidity (66.7%) and three were diagnosed with syphilis through the rapid test performed at the time of childbirth (10%). The median age of parturients was 24 years old (20-32). Most had vaginal delivery (70%) and gestational age at delivery greater than 37 weeks (70%) (Table 1). Only one admitted to using crack and none reported smoking cigarettes or drinking alcohol.

Table 1. Sample characterization of participants.

Variables	Total
PCR, n (%)	30 (100.0)
Positive	10 (33.3)
Negative	20 (66.7)
HIV, n (%)	30 (100.0)
Positive	0 (0.0)
Negative	30 (100.0)
Syphilis, n (%)	30 (100.0)
Positive	3 (10.0)
Negative	27 (90.0)
Gestational age, n (%)	30 (100.0)
≤ 37 weeks	9 (30.0)
> 37 weeks	21 (70.0)
Type of delivery, n (%)	30 (100.0)
Vaginal	21 (70.0)
Cesarean	9 (30.0)
Comorbidities, n (%)	20 (66.7)
Diabetes, n (%)	10 (33.3)
Hypertension, n (%)	8 (26.7)
Other comorbidities, n (%)	5 (16.7)

Data are expressed in absolute (n) and relative (%) frequency. Abbreviations: n-number, PCR-polymerase chain reaction.

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The mean weight, in grams, of the placentas of infected women was greater (441.13 ± 119.92) than that of non-infected ones (437.02 ± 132.48), although without statistical significance (p = 0.933). Most of the histopathological changes had a similar distribution between the two groups, as shown in Table 2.

Table 2. Findings of the histopathological analysis of placentas as well as comorbidities of parturients with positive and negative PCR for COVID-19

Histopathological findings	PCR		P value	Total
	Positive	Negative		
Intervillous hemorrhage with thrombus formation, n (%)	3 (30,0)	8 (40,0)	0,702	11 (36,7)
Subchorial hemorrhage with thrombus formation, n (%)	1 (10,0)	3 (15,0)	1,000	4 (13,3)
Syncytial Knot Formation, n (%)	6 (60,0)	13 (65,0)	0,461	19 (63,3)
Congestion, n (%)	6 (60,0)	10 (50,0)	0,709	16 (53,3)
Villous fibrin < 30%, n (%)	10 (100,0)	18 (90,0)	0,540	28 (93,3)
Dystrophic Calcification, n (%)	6 (60,0)	16 (80,0)	0,384	22 (73,3)
Placental Infarction Except Marginal, n (%)	0 (0,0)	6 (30,0)	0,074	6 (20,0)
Delayed villous maturation and increased Hofbauer cells, n (%)	1 (10,0)	7 (35,0)	0,210	8 (26,7)
Chronic Focal Villitis, n (%)	1 (10,0)	1 (5,0)	1,000	2 (6,7)
Intervillositis, n (%)	0 (0,0)	1 (5,0)	1,00	1 (3,3)
Chronic Basal Deciduitis, n (%)	1 (10,0)	3 (15,0)	1,000	4 (13,3)
Capsular Acute Deciduitis, n (%)	4 (40,0)	10 (50,0)	0,709	14 (46,7)
Chronic Capsular Deciduitis, n (%)	2 (20,0)	3 (15,0)	1,000	5 (16,7)
Chorioamnionitis, n (%)	1 (10,0)	3 (15,0)	1,000	4 (13,3)
Acute Funisitis, n (%)	2 (20,0)	2 (10,0)	0,584	4 (13,3)
Comorbidities, n (%)	8 (80,0)	12 (60,0)	0,273	20 (60,7)
Diabetes, n (%)	5 (50,0)	5 (25,0)	0,171	10 (33,3)
Hypertension, n (%)	3 (30,0)	5 (25,0)	0,770	8 (26,7)
Other comorbidities, n (%)	1 (10,0)	4 (20,0)	0,640	5 (16,7)

Data are expressed in absolute (n) and relative (%) frequency, considering the lines. [a] Significance of the difference between the groups by Fisher's exact test.

Six out of ten patients with reactive PCR expressed congestion and six expressed syncytial knot formation in their placentas (60%). Syncytial knot and congestion were present in 65% and 50%, respectively, of the placentas from the control group. Analysis of placentas from parturients who had been diagnosed with COVID-19 revealed that six had dystrophic calcification. Among them, three (50%) expressed the mild form, whereas in the placentas of women without infection, the mild form was observed in 37.5%. On the other hand, in the placentas of the PCR negative group, a higher percentage of the moderate form of dystrophic calcification was observed, but with no significant difference (p=0.655). There was no significant difference in the comorbidities diagnosed in the two groups (p=0.273).

Figure 1 shows the macroscopic aspect of the placenta from a parturient with positive PCR for SARS-CoV-2, while the photomicrographs show the presence of syncytial knots, vascular/intervillous space congestion and calcification of the placental tissue of different analyzed cases.

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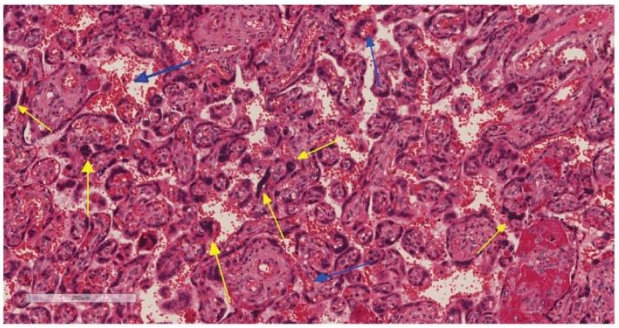
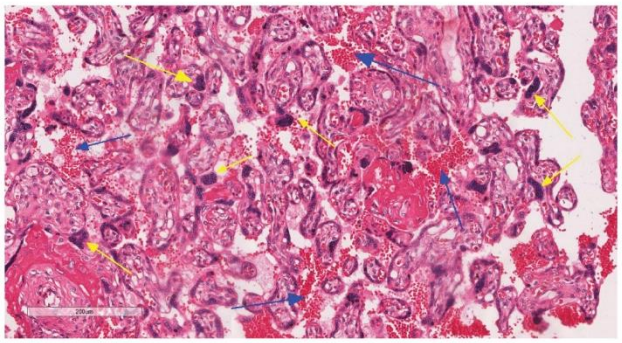
Figure 1. Macroscopic picture of a placenta and histological placental sections of parturient infected with SARS-CoV-2.

A Macroscopic photo of a placenta.

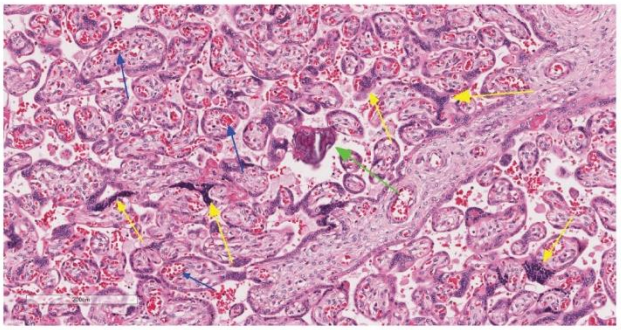
B H&E stained photomicrograph of placental parenchyma showing congestion.



C H&E stained photomicrograph of placental parenchyma showing syncytial knot formation.



D H&E stained photomicrograph of placental parenchyma showing congestion, syncytial knot and calcification.



A- Macroscopic aspect of a placenta showing the chorionic plate and the umbilical cord. B- Photomicrograph of placental parenchyma stained with hematoxylin and eosin (H&E) showing areas of congestion (blue arrows) and syncytial knot formation (yellow arrows) with original magnification of 10x (200um). C- H&E-stained photomicrograph congestion (blue arrows) and of syncytial knot formation (yellow arrows) at 10x (200um) magnification. D- Photomicrograph stained with H&E showing areas of congestion (blue arrows), syncytial knot (yellow arrows) and calcification (green arrow) at 10x (200um) magnification.

DISCUSSION

In this study, the placentas of parturients diagnosed with COVID-19 did not show a different placental histopathological pattern. However, the results revealed higher levels of congestion, chronic focal villitis and acute funisitis in placentas from parturients diagnosed with COVID-19. PCR-negative parturients for SARS-CoV-2 had a higher percentage of intervillous hemorrhage in their placentas with thrombus formation, dystrophic calcification, placental non marginal infarction, and capsular acute deciduitis.

The inflammatory disorders (villitis and funisitis) in parturients with COVID-19 may be due to the occurrence of cytokine storms as a result of the infection, especially in severe cases of the disease. These events cause inflammatory disorders that lead to damage in the epithelium and alter the coagulation cascade, which result in a state of hypercoagulability and generalized inflammation (Lokken et al. 2020, Thompson et al. 2020).

Acute hypoxia also appears to be associated with acute funisitis. Baergen et al. (2020) report a case, in which the patient had pneumonia and acute hypoxia, associated with acute chorioamnionitis and acute funisitis (Baergen et al. 2020). However, the small number of placentas from parturients with positive PCR may have contributed to the lack of significant differences in all histopathological findings between the groups.

The presence of inflammatory lesions in the placentas of uninfected pregnant women seems to be due to the comorbidities associated with the participants of this group, such as diabetes and others that can also generate a state of hyperinflammation with repercussions in the placenta (Carrasco-Wong et al. 2020, Stanek et al. 2018). Additionally, the detection of placental infarction (6 out of 20), excluding those of marginal location and consequently the areas of denaturation (7 out of 20), was higher in the placentas of uninfected parturients, but with no significant difference between the groups. Interestingly, these findings are related to other clinical conditions, such as hypertension, which seems to be due to some alterations such as infarcts, increased syncytial knots, hypovascularity of the villi, cytotrophoblastic proliferation, thickening of the trophoblastic basement membrane, obliterative enlarged endothelial cells in the fetal capillaries and atherosis of the spiral arteries in the placental bed (Pietro et al. 2021, Weiner et al. 2018, Chhatwal et al. 2018, Soma et al. 1982, Khong et al. 2016). Therefore, it seems that multiple etiologies may influence the emergence of these nonspecific findings, which are commonly found in parturients not necessarily affected by COVID-19 (Parks et al. 2017, Franco et al. 2011, Ditisheim et al. 2020).

Most of the placentas investigated showed increased syncytial knots, congestion and perivillous fibrinoid deposition. These signs corroborate a state of MVM of the placental bed (Sharps et al. 2020), characterized by a pattern of placental injury related to abnormal uterine perfusion that causes the pathological changes found in our study. Evidence has shown that such histopathological findings attributed to MVM and FVM are associated with the placentas of pregnant women diagnosed with COVID-19 (Wong et al. 2021, Baergen et al. 2020, Shanes et al. 2020, Hecht et al. 2020, Hosier et al. 2020, Menter et al. 2021, Husen et al. 2021). Previously published meta-analysis showed that in placentas of women infected with the coronavirus, histopathological changes are associated with inflammatory reaction and hypoperfusion (Di Girolamo et al. 2021). In our study, these histopathological alterations were not markedly found in the infected group, which may have been caused by the high prevalence of comorbidities, such as hypertension and diabetes, in the two groups studied (Wong et al. 2021).

These changes, however, are not unique to the placentas of women with COVID-19, as evidenced by other studies (Hecht et al. 2020, Zhang et al. 2020, Schwartz et al. 2020, de Noronha et al, 2018). Meta-analysis published by Suhren et al. (2022) revealed that the pattern of placentas from women with COVID-19 is based on nonspecific and non-pathognomonic findings, in which the main variations in placental histopathology are associated with the maternal-fetal hypoxia caused by a pulmonary condition with severe hypoxia, especially in the most severe cases of COVID-19 infection. Sharps et al. (2020) revealed a difficulty in finding specific placental lesions in women with SARS-CoV-2 infection, highlighting the absence of a control group as a limitation of their study. Likewise, He et al. (2022) concluded that placentas from SARS-CoV-2-positive women do not demonstrate a specific pathological pattern.

However, an association between the histopathological changes of placental hypoxia and the acute or chronic involvement of COVID-19 cannot be ruled out. In chronic conditions, a notable change is the appearance of trophoblastic hyperplasia with formation of syncytial knots in the placenta, whereas in acute conditions, congestion is more frequently observed (Stanek et al. 2013). Thus, the combination of these two findings seems to indicate the presence of concomitant acute and chronic hypoxia in pregnant women infected with SARS-CoV-2 (Giordano et al. 2021). In our study, four placentas in the PCR-positive group (40%) presented a condition of chronic hypoxia with exacerbation at the time of delivery.

In the placentas analyzed in this study, findings related to chronic inflammation, such as chronic focal villitis, chronic capsular deciduitis and dystrophic calcification were identified. These inflammation processes also occur in other infections by RNA-type viruses, such as Zika virus, cytomegalovirus and dengue virus (Wong et al. 2021). Such inflammatory responses

may be caused by the release of a large number of pro-inflammatory cytokines, leading to an exacerbated immune response in the maternal organism and to histopathological abnormalities in the placentas of pregnant women infected by these viruses (Shanes et al. 2020, Hecht et al. 2020, Zhang et al. 2020, Schwartz et al 2020, Stanek et al. 2013, Giordano et al. 2021).

Furthermore, no active inflammatory processes with necrosis were identified in any of the placentas in the PCR-positive group. Calcifications were already well established in the tissues and were not significant in terms of extent, or intensity and could be associated with the placental aging degeneration process itself. Studies indicate that calcification can be found, with wide interplacental variations, even in healthy pregnancies, with a tendency to increase as the pregnancy progresses to term. (Anthis et al. 2019, Moran et al. 2015).

The limitations of this study include the low number of placentas analyzed and the cross-sectional nature of the study, which may have underestimated the appearance of some findings, resulting in the lack of a significant difference between the groups and therefore, preventing the causal association of the histopathological aspects with the viral infection. Furthermore, it was not possible to classify parturients diagnosed with COVID-19 according to the severity of the disease, as some previous studies have shown that the greater the severity, the greater the possibility of detecting more severe placental changes. Furthermore, we were not able to identify the presence of SARS-CoV-2 by PCR in the placentas analyzed in this study, nor classify the variants by genetic sequencing, much less quantify the viral load in the infected ones. Finally, there was no control for biases such as the presence of comorbidities associated with inflammatory and congestive placental changes, such as hypertension and diabetes, which may have contributed to the histopathological findings in the analyzed placentas. The concomitant presence of COVID-19 and other comorbidities prevents us from stating that in the placentas of parturients with COVID-19 and these comorbidities the histopathological findings were caused by the virus only. However, this study shows the possibility of viral infection causing placental changes capable of complicating pregnancy. In addition, this study involves parturients from Latin America, where studies comparing histopathological findings due to COVID-19 infection are rare.

CONCLUSION

Although there is no predominant histopathological pattern associated with placentas from parturients infected with SARS-CoV-2, the comparison of the histopathological analysis of placentas from infected parturients with those of uninfected ones, revealed a higher percentage of congestion, focal chronic villitis and acute funisitis in the group with COVID-19 infection. Parturients tested negative for SARS-CoV-2 had a higher percentage of intervillous hemorrhage with thrombus formation, dystrophic calcification, delayed villous maturation of Hofbauer cells and capsular acute deciduitis on their placentas.

However, the small sample size in this cross-sectional study and the high prevalence of comorbidities in both groups probably influenced the results. Observational studies with larger samples and bias control are essential to demonstrate whether those placental changes are caused directly by the virus itself or as a consequence of the outcome of maternal health triggered by SARS-CoV-2.

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