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Placental pathological findings in coronavirus disease 2019: Perinatal outcomes

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ABSTRACT

Introduction: Placental alterations caused by severe acute respiratory coronavirus-2 (SARS-CoV-2) infection have already been described, but most studies used small sample groups and the difference according to the severity of the disease has not been verified. Our objective was to describe placental alterations in patients with coronavirus disease 2019 (COVID-19) and analyze the association of pathological placental findings with the clinical parameters of COVID-19 and perinatal results.

Methods: This was a nested study within a prospective cohort study involving 109 symptomatic pregnant women with COVID-19. The prevalence of observed placental alterations was described, and the associations of pathological findings with the clinical parameters of COVID-19 severity and with perinatal outcomes were assessed.

Results: The frequency of types of placental features was poor maternal vascular perfusion in 45% of cases, poor fetal vascular perfusion in 33.9%, hematogenous origin infection in 32.1%, and morphological changes corresponding to ascending infection in 21.1%. Hematogenous infection differed significantly according to COVID-19 severity ($p = 0.008$), with a prevalence ratio (PR) of 1.74 (95% confidence interval, 1.02–2.98) in the moderate COVID-19 group compared to the mild COVID-19 group. Among the perinatal outcomes, there was an unexpected inverse association between prematurity and placental infection of hematogenous origin, with lower rates of prematurity among cases with inflammation of hematogenous origin ($p = 0.029$).

Discussion: Moderate SARS-Cov-2 infection presented a higher prevalence of placental pathological findings. There was no association of placental findings with adverse perinatal outcomes.

1. Introduction

Severe acute respiratory coronavirus-2 (SARS-CoV-2) infection, which primarily affects the airways, can manifest asymptomatically or evolve into severe forms such as pneumonia, thromboembolic events, and death [1]. Pregnant women do not appear to have a higher risk of viral infection; however, when infected, they are more vulnerable to unfavorable outcomes, such as a greater need for intensive care unit (ICU) hospitalization, mechanical ventilation and a higher risk of death compared to the general population, especially in middle- and low-income countries [2,3]. In addition, related adverse outcomes, such as higher rates of iatrogenic prematurity, fetal distress, spontaneous abortion, and fetal death associated with SARS-CoV-2 infection, have been reported [4,5].

The placenta is an organ with immunological capabilities, functioning as a shield against intrauterine and fetal infections due to the association of innate and acquired immunity [6,7]. Viral infections usually occur hematogenously with a maternal immunohistological response manifested by neutrophilic invasion into the intervillous space and may reach the amniotic fluid, as well as the local response of innate

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immunity, and may exhibit different inflammatory levels and types of response [8]. With new types of viral infections, it is necessary to understand placental alterations and impaired placental function related to the specific infection.

Therefore, despite the recent appearance of SARS-CoV-2, some studies have already described placental alterations in coronavirus disease 2019 (COVID-19), however, with small sample groups [5,9,10]. The alterations most frequently associated with COVID-19 were related to poor maternal and fetal perfusion, in addition to inflammatory alterations [11,12]. However, to date, we have found only one case report presenting unfavorable perinatal results associated with the histopathological finding of massive fibrin deposition and necrosis of the syncytiotrophoblast layer of the villi [13]. No studies assessing placental alterations with the severity of COVID-19 in symptomatic patients were found or studies investigating the association of placental alterations in COVID-19 with perinatal outcomes. Therefore, this study aimed to describe placental alterations in a cohort of patients with COVID-19 and to analyze the association of placental pathological findings with the clinical parameters of COVID-19 and perinatal results.

2. Methods

This was a nested within a prospective cohort study involving pregnant women with COVID 19 conducted in the Hospitals of the University of São Paulo (Department of Obstetrics and Gynecology—Hospital das Clínicas and University Hospital of the Faculty of Medicine). The study was approved by the research ethics committee of the Institution (CAAE: 30270820.3.0000.0068). An informed consent form was obtained from all participants before entry in the study.

Cases of pregnant women with single fetuses diagnosed with COVID-19, symptomatic, admitted in one of the Hospitals from April 12, 2020, to March 26, 2021, and who had a pathological evaluation of the placenta were selected from the database. The diagnosis of COVID-19 was considered positive in the presence of swab positive for SARS-CoV-2 or positive serology for SARS-CoV-2 with associated COVID-19 symptoms, such as fever, cough, odynophagia, myalgia, asthenia, coryza, diarrhea, anosmia, dysgeusia, dyspnea, headache, and fatigue [2,14].

Placental findings were compared with clinical parameters of the severity of COVID-19, and the cases were divided into three groups according to the severity of the disease: mild, women with no symptoms or when there was no need for ventilatory support; moderate, symptomatic women with need for hospitalization (SpO2 <94% and/or respiratory rate >24 breaths per minute) and in the hospital admission with the need for supplemental oxygen delivered by a simple catheter and severe was defined as a hospital admission with the need for admission in the ICU (i.e., supplemental oxygen delivered in forms other than simple catheter [e.g., venturi mask] and/or organ involvement), using an adapted version of the classification proposed by the Ministry of Health of Brazil [15,16]. The evaluated obstetric parameters were: oligohydramnios (defined as amniotic fluid index <5), preeclampsia, and gestational diabetes.

Adverse perinatal outcomes evaluated were the occurrence of prematurity, presence of fetal growth restriction (birth weight < P10), fetal distress (defined as abnormal biophysical profile), intrauterine death, APGAR <7 at the 5th min, and the need for a neonatal intensive care unit [4,5,17]. Cases of fetal malformation were excluded from the analysis of neonatal outcomes.

2.1. Placental analysis

A total of 109 placentas were analyzed. After expulsion, the placenta was placed in 10% buffered formalin solution, fixed for 24 h, and analyzed. The macroscopic examination of the placenta consisted in measuring the length and average thickness of the cord and three placental disc measurements. The weight of the placenta was measured after the removal of the membranes and umbilical cord. A roll of extraplacental membranes, sections of the umbilical cord, and a minimum of eight sections containing the full thickness of normal-appearing placenta parenchyma were presented for histological analysis. Sections underwent routine processing, embedding, sectioning at 4μ and staining with H&E.Histologic examination was performed by two perinatal pathologist experts (R.S performed 88 analysis and A.B·S perfomed 21) with extensive experience in the anatomopathological analysis of normal and altered placentas.

Microscopic alterations were divided into 4 large groups: maternal vascular malperfusion, fetal vascular malperfusion, hematogenous and ascending infection, in addition to a group called “other lesions”, that subchorionic fibrin deposition, fibrinoid necrosis of the villous trophoblast, calcification of the basal membrane of the stem villi, chorionic meconium depots, peripheral capillary proliferation of the stem villi, chorangiosis, hypertrophy of the medial tunica of placental arteries and intraplacental hematomas [18]. For chorangiosis to be characterized, ten villi are required, each with ten or more vascular channels in ten or more noninfarcted and nonischemic zones of at least three different placental areas [19].

Maternal vascular malperfusion of the placental bed also included gross findings such as placental hypoplasia, villous infarction, and retroplacental hematoma or hemorrhage. Microscopic findings included abnormalities in villous development, with distal villous hypoplasia and accelerated villous maturation, perivillous fibrin, and decidual arteriopathy. Furthermore, microscopic findings of fetal vascular malperfusion included thrombotic occlusion of chorionic or stem villous vessels, with complete obstruction to the villi downstream, partially obstructed umbilical blood flow with venous ectasia, intramural fibrin deposition in large vessels, foci of avascular or karyorrhectic villi, and stem vessel obliteration with marked thickening of the vessel wall and resultant obliteration of the vascular lumen [20].

Signs of ascending intrauterine infection were defined as inflammation of the subchorionic space, involving the chorion and amnion with or without omphalitis, characterized by umbilical phlebitis or arteritis.

When evaluating placental alterations, the same placenta could have different types of microscopic alterations, classified into one or more of the large groups. Moreover, if a placenta presented more than one type of microscopic alteration in the same group, it was counted as a single alteration in the respective group that represented it.

2.2. Statistical analysis

Descriptive analysis of the data was performed using absolute (n) and relative frequencies (%), measures of central tendency (mean and median) and dispersion (standard deviation and interquartile intervals). Categorical variables were evaluated using the chi-square association test or Fischer and linear-by-linear exact test, applied when necessary. In addition, univariate Poisson regression analysis with robust variance was applied to estimate the prevalence ratios (PR) and their 95% confidence intervals (CI). The Kruskal−Wallis test and Dunnett’s post hoc test were applied to compare the COVID-19 severity groups. A statistical significance of 5% ($p \leq 0.05$) was set. Data were analyzed using the Statistics Package for Social Sciences (SPSS) version 20.0 for Windows.

3. Results

Between April 12, 2020, and March 21, 2021, 109 placentas of patients symptomatic with COVID-19 who gave birth in the two hospitals were analyzed. The mean age of the patients was 30.5 years and the most common gestational comorbidity was gestational diabetes mellitus, present in 19.4%. RT-PCR was used to diagnose COVID-19 in 83.5% of the cases. With reference to the delivery route, a cesarean section was performed in 74.8% of the patients. Excluding malformed fetuses, the average birth weight was 3065 g (2130–3430 g). The complete details of

the maternal and neonatal characteristics are presented in Table 1.

Regarding placental findings, alterations secondary to maternal vascular malperfusion were present in 45% of cases and fetal vascular malperfusion was observed in 33.9% of the samples; inflammation of hematogenous origin was observed in 32.1% of cases and alterations corresponding to ascending infection in 21.1%. Other findings were observed in 56% of the placentas. In our cohort, 68 pregnant women were in the mild group, 13 in the moderate group, and 28 in the severe group. We showed 4 histological micrographs of multiple placental findings observed in our cohort grouped into 2 figures (Figs. 1 and 2). Table 2 presents the association between placental diagnosis and the severity of infection with SARS-CoV-2. We can notice the highest frequency of placental alterations in the group with moderate COVID-19, and we can also observe that the inflammation of hematogenous origin was different between the mild, moderate, and severe groups ($p = 0.008$). Moreover, patients with moderate form presented an approximately two-fold risk of hematogenous inflammation compared with patients in the mild group (PR, 1.74; 95% CI, 1.02–2.98). Others groups of placental features were not associated with COVID-19 severity. More details of the placental features associated with COVID-19 severity are shown in Supplementary Table 1.

Table 3 presents the occurrence of perinatal outcomes according to the presence of placental alterations. An interesting result was that in patients without hematogenous inflammation, 43.9% had prematurity as an outcome, while the prematurity rate was lower in those who had this inflammation, 22.2% ($p = 0.029$). The other groups of placental alterations did not show differences in relation to neonatal outcomes. Supplementary Table 2 shows details of placental features and neonatal outcomes.s.

Regarding the time interval between infection and delivery, this interval was longer (74 days) in patients who had villitis (n = 9) than in those who did not have the finding. Furthermore, the interval between diagnosis and delivery was 36.5 days (6.25–103.5) in the mild group, 42 days (21–91) in the moderate group, and 12 days (7–18.25) in the severe group, with significant differences between the mild and severe groups ($p < 0.001$).

Table 1
Demographic, clinical, obstetric, and neonatal characteristics of the sample (N = 109).

	Median (interquartil)/n (%[a])
Maternal Age[a], years	30.5 ± 6.9
BMI	31.4; (27.9–36.7)
Tabagism	8 (7.4)
Parity	
Nulliparous	33 (30.3)
Multiparous	76 (69.7)
Previous Comorbidities	
Hypertension	20 (18.3)
DM type 1/2	5 (4.6)
Gestacional Comorbidities	
Preeclampsia	11 (10.2)
GDM	21 (19.4)
Maternal data	
Diagnosis by PCR	91 (83.5)
Diagnosis by Sorology	18 (16.5)
GA at diagnosis	31 (25–34,7)
Time between diagnosis and delivery in days	19 (7–90)
COVID mild	68 (62.4)
COVID moderate	13 (11.9)
COVID severe	28 (25.7)
Maternal death	5 (4.6)
Delivery data	
Cesarean section	77 (74.8)
Gestational age	38 (34.8–39.57)
Oligohydramnios	11 (10.8)
Perinatal data* **	
Fetal death	2 (1.9)
Prematurity	37 (36.3)
Birth weight	3065 (2130–3430)
Fetal growth restriction	7 (6.9)
Apgar <7 at 5 min	10 (9.9)
Admission to NICU	41 (40.6)
Neonatal death	1 (1)

BMI, body mass index; DM, diabetes mellitus; GDM, gestational diabetes mellitus; PCR, polymerase chain reaction; NICU, neonatal intensive care unit.
[a] Mean ± **SD** excluding six cases of malformation.

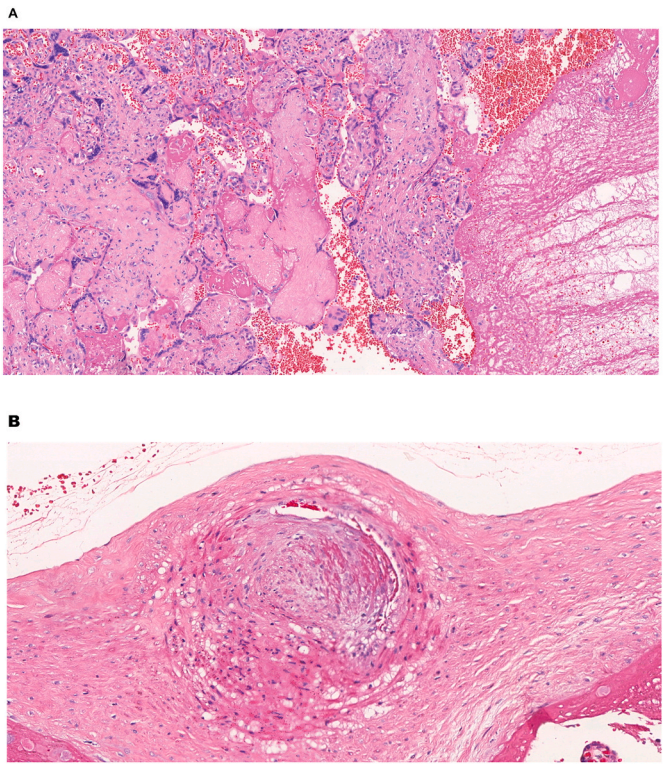

Fig. 1. A. Large focus of avascular villi, a focus of chronic villitis and intervillous thrombosis (hematoxilyn-eosin, original magnification 10×). B. Thrombosis of a chorionic artery with intramural fibrin deposition (hematoxilyn-eosin, original magnification 10×).

The association between neonatal outcomes and severity of COVID-19 can be assessed in Supplementary Table 3. Pregnant women in the severe group had a PR of 3.23 (95% CI, 1.19–8.76) of having a premature newborn compared to those in the moderate group.

4. Discussion

4.1. Main findings of the study

The main finding of the present study is the highest frequency of placental alterations in the group with moderate COVID-19. A possible explanation for this finding is that patients with moderate severity have a lower need for immediate resolution of pregnancy and, therefore, have a longer exposure time to systemic inflammatory involvement of COVID-19, leading to a greater number of typical and/or nonspecific pathological alterations of the infection. This assumption is corroborated by the longer interval between disease and delivery in the moderate group, observed in our data and the finding of villitis, which is a typical placental finding in COVID-19 [12].

Villitis is a common pathological finding and generally without perinatal clinical repercussions; however, if greater placental involvement occurs, the greater the chance of association with unfavorable perinatal outcomes [21]. The lower rate of placental alterations in the group of patients with mild disease may be justified because these patients did not significantly suffer the inflammatory effects of the disease to the point of manifesting placental alterations.

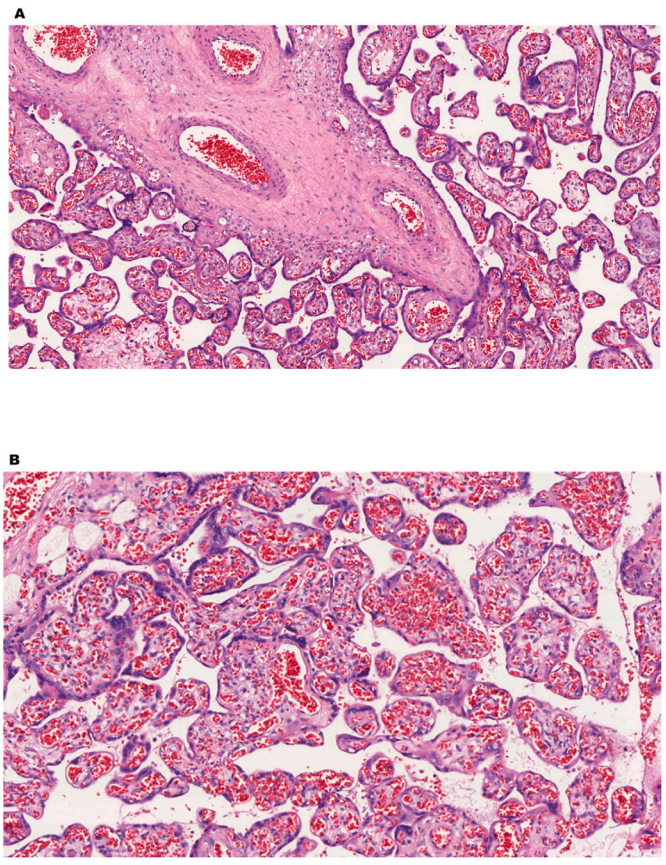

Fig. 2. A. Peripheral capillary proliferation of stem villi (hematoxilyn-eosin, original magnification 10×). B. Chorangiosis, with more then ten vessels in terminal villi (hematoxilyn-eosin, original magnification 10×).

Table 2
Placental diagnosis associated with coronavirus disease 2019 severity (n = 109).

Features	COVID-19				
	Mild N = 68	Moderate N = 13	Severe N = 28	Total N = 109	
	N (%)	N (%)	N (%)	N (%)	p
Inflammation (hematogenous)	24 (35.3)	8 (61.5)	6 (21.4)	38 (34.9)	0.0041[a]
Maternal vascular malperfusion	30 (44.1)	5 (38.51)	14 (50)	49 (45)	0.7402[b]
Fetal vascular malperfusion	25 (36.8)	6 (46.2)	6 (21.4)	37 (33.9)	0.1971[a]
Ascending intrauterine infection	15 (22.1)	4 (30.8)	4 (14.3)	23 (21.1)	0.4511[a]
Others	41 (60.3)	9 (69.2)	11 (39.3)	61 (56.0)	0.0962[b]

[a] Fisher-test.
[b] Linear by linear association.

4.2. Comparison with previous studies

Shanes et al. [9] were the first to publish a series of cases with analyses of the placentas of patients affected by COVID-19, highlighting diseases compatible with maternal vascular malperfusion, especially decidual arteriopathy, which were significantly more prevalent among those affected by the disease compared to the control group. Other authors [22,23] corroborated these findings by showing others placental features compatible with maternal vascular malperfusion (decidual arteriopathy, subchorionic thrombus, perivillous fibrin deposition, and villous agglutination) as more prevalent in the population with COVID-19. In the other hand, other studies [24–26] were unable to reproduce these findings and also did not show a significant difference between cases with COVID-19 compared to controls regarding maternal vascular malperfusion. In the present study we also observed maternal vascular malperfusion in patients with COVID-19 and the most frequent finding was villous infarction which was also previously described [9,10,12,22,24,27]. We did not compare our data with a control group, however no statistical difference in the pathological findings was noticed between groups of mild, moderate and severe disease. The differences between studies could be explained by the various pathological changes compatible with maternal vascular malperfusion and the lack of padronization of the anatomopathological descriptions.

Regarding the finding of fetal vascular malperfusion, several studies [12,23,28] have shown a higher prevalence of typical alterations in this group of patients with COVID-19 compared to the control group. In our analyses, although no comparison was made with the control group, no significant differences were observed in the frequency of fetal vascular malperfusion in relation to the severity of the disease, although the mild disease group showed a lower frequency of this placental alteration.

Previous studies evaluating placental alterations compatible with inflammation of hematogenous origin also describe an important heterogeneity of the data [11,12,22,29–31]. Although villitis was significantly more common in the study of Patberg [12], other studies [11,29–31] did not report the same result. In our data, more than one-third (34.9%) of the placentas presented changes typical of an inflammatory response, more common in moderate cases (p = 0.041).

The diagnosis of hematogenous inflammation was significantly more frequent in patients with longer time between COVID-19 diagnosis and delivery (p = 0.01); this finding may be due to a extended period of local immune response to the virus that spreads hematogenously [32,33]. Patberg [12] postulates that a high placental viral load increases the possibility of a placental inflammatory response, resulting in placental injury. In addition, this way of dissemination of the infection may justifies the low prevalence of acute placental injury, mainly represented by the finding of chorioamnionitis, since they are mainly due to ascending infection (microorganisms of the vaginal flora) [8], which is consistent with other studies [34,35].

Another characteristic of COVID-19 infection is the predisposition to a state of hypercoagulability and thromboembolic events, which may also manifest through maternal and fetal placental alterations. However, in our cohort, no association was observed, which may be explained by the appropriate clinical management of patients infected with SARS-CoV-2, focusing on prophylaxis of thromboembolic events. This is corroborated by the fact that when these pathological changes are present in abundance, there is a greater association with fetal death, fetal growth restriction, and preterm birth [12,28] which were not observed in our cohort.

Regarding the perinatal outcomes and placental findings, we observed only an inverse association between prematurity and hematogenous inflammation in the placenta, which may be due to higher rates of prematurity in the severe group where the delivery occurred in a shorter infection time of the disease. Hosier et al. [36] postulate that placental immune activation can act as a barrier to inflammatory and infectious damage (facilitators of vertical transmission), which, ultimately, would be a protective factor for unfavorable perinatal outcomes. In respect of fetal and neonatal mortality due to COVID-19 infection, we had low rate of unfavorable neonatal outcomes, which is consistent with Di Toro et al. [37], that in a recent systematic review with meta-analysis, also suggested that the risks of fetal and neonatal mortality due to COVID-19 infection are extremely low.

The strengths of this study were that we have a cohort with a significant number of analyzed placentas according to the severity of COVID-19 and also we could compare the placental pathological findings with the perinatal outcomes. The limitation of this study is the absence of a control group or negative SARS-CoV-2, which would

Table 3
Association between placental features and perinatal outcomes.

Perinatal outcomes	MVM		FVM		Hematogenous infection		Ascending infection		Others	
	No N = 56	Yes N = 46	No N = 65	Yes N = 37	No N = 66	Yes N = 36	No N = 81	Yes N = 21	No N = 45	Yes N = 57
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Prematurity (n = 102)	18 (32.1)	19 (41.3)	24 (36.9)	13 (35.1)	29 (43.9)	8 (22.2)[a]	31 (38.3)	6 (28.6)	17 (37.8)	20 (35.1)
FD (n = 101)	16 (28.6)	13 (28.9)	20 (31.2)	9 (24.3)	17 (26.2)	12 (33.3)	25 (31.2)	4 (19)	13 (29.5)	16 (28.1)
Fetal death (n=103)	0	2 (4.3)	2 (3)	0	1 (1.5)	1 (2.7)	1 (1.2)	1 (4.5)	2 (4.3)	0
APGAR (n = 101)	7 (12.5)	3 (6.7)	6 (9.4)	4 (10.8)	7 (10.8)	3 (8.3)	9 (11.2)	1 (4.8)	5 (11.4)	5 (8.8)
P < P10 (N = 102)	4 (7.1)	3 (6.5)	5 (7.7)	2 (5.4)	5 (7.6)	2 (5.6)	6 (7.4)	1(4.8)	6 (13.3)	1 (1.8)[b]
NICU (N = 101)	21 (37.5)	20 (44.4)	28 (43.8)	13 (35.1)	31 (47.7)	10 (27.8)	32 (40)	9 (42.9)	19 (43.2)	22 (38.6)

MVM, maternal vascular malperfusion; FVM, fetal vascular malperfusion; FD, fetal distress; NICU, neonatal intensive care unit.
[a] Chi-square test, p = 0.029.
[b] Fisher test, p = 0.043; * excludes six cases of malformation.

minimize bias in the analysis of placental alterations and allow discrimination of cases that occur secondarily to COVID-19.

5. Conclusion

The highest frequency of placental changes was observed in moderate cases of SARS-CoV-2 infection. No association was observed between placental findings and unfavorable perinatal outcomes.

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Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.placenta.2022.08.006.

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