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Impact of COVID-19 disease on placental histopathology. PLAXAVID study

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Summary. Background. The impact of COVID-19 on pregnancy has been analyzed suggesting an increased risk of placental lesions that might lead to maternal and neonatal complications. However, the current published evidence is not conclusive because contradictory results.

Methods. PLAXAVID is an observational, retrospective, histopathological, single-center study that aimed to evaluate the prevalence of vascular and inflammatory lesions in placental and umbilical cord samples of one hundred women infected by SARS-CoV-2 during pregnancy.

Results. The histopathological analysis showed that in most of the placentas (77.8%) there were signs of maternal vascular malperfusion (MVM; primary endpoint). The most common MVM features were an accelerated villous maturation (37.4%), central villous infarcts (33.3%), and villous agglutination (46.5%). Fetal vascular malperfusion (FVM) was identified in 57.6% of samples, and the most frequent features were hyalinized avascular villi (38.4%), fetal vascular thrombi (20.2%) and umbilical cord at risk of partial obstruction (14.1%). Acute and chronic inflammatory pathology were noticed in 22.2% and 49.5% of placentas, respectively. No significant correlations were found between MVM presence and the time, duration, and severity of infection, nor with the duration of pregnancy. However, in critically ill patients, the pregnancy duration (p=0.008), newborn weight (p=0.003), and APGAR test scores (p<0.001) were significantly lower. The same trend was observed considering the presence of infection at the time of delivery and in preterm births.

Conclusion. A very high percentage of placentas with vascular and/or inflammatory lesions was found in the analyzed cohort. Therefore, PLAXAVID study results supported that COVID-19 should be considered a risk factor during gestation and requires close monitoring of pregnancy.

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Key words: COVID-19, SARS-CoV-2, pregnancy, placenta, maternal vascular malperfusion, fetal vascular malperfusion, thrombus

Introduction

COVID-19 is a novel infectious disease caused by the SARS-CoV-2 virus (Hui et al., 2020). The first cases were reported in Wuhan (China) at the end of 2019, and within a few months, the number rapidly increased and spread worldwide. In March 2020, World Health Organization (WHO) declared COVID-19 a global pandemic due to the increasing number of patients and deaths (Cucinotta and Vanelli, 2020). Symptoms caused by SARS-CoV-2 infection are heterogeneous, affecting respiratory, musculoskeletal, gastrointestinal, and neurological systems (Li et al., 2021; Tsai et al., 2021; World Health Organization, 2022a). While most patients have mild or no symptoms, others experience a varied range of symptoms with different severity degrees (Wu and McGoogan, 2020; Kim et al., 2021). Although the underlying pathophysiology is not fully understood, it is known that severe systemic inflammatory response and thrombotic complications are clinical manifestations associated with COVID-19 disease, especially in hospitalized severe cases (Connors and Levy, 2020; Helms et al., 2020; Klok et al., 2020).

Pregnancy predisposes women to be in a pro-coagulant state, which can contribute to the occurrence of gestational vascular complications and increase the risk of venous thromboembolism (VTE). Alterations in the vascularization of the placenta/umbilical cord may translate into a predisposition to thrombosis in COVID-

Abbreviations. FVM, fetal vascular malperfusion; GCP, good clinical practice; HAV, hyalinized avascular villi; IHC, immunohistochemistry; IQR, interquartile range; ISH, *in-situ* hybridization; IUGR, intrauterine growth retardation; LMWH, low-molecular-weight heparin; MVM, maternal vascular malperfusion; SD, standard deviation; VSK, villous stromal-vascular karyorrhexis; VTE, venous thromboembolism; WHO, World Health Organization

19 positive patients during pregnancy. Furthermore, the expression of angiotensin-converting enzyme 2 (ACE2), the main receptor for SARS-CoV-2, in human placentas indicates that this organ may be susceptible to viral infection (Azinheira Nobrega Cruz et al., 2021). Additionally, ACE2 has a role in maternal hemodynamic adaptations and during placentation. Since the receptor is depleted after SARS-CoV-2 binding, the infection could be responsible for vascular alterations in the placenta (Azinheira Nobrega Cruz et al., 2021). Nonetheless, vertical viral transmission is still under investigation. Firstly, it should be considered that virus entry and replication require additional molecules to be co-expressed along with ACE2. Additionally, the levels and distribution of the receptor, as well as whether they can change during pregnancy, are not fully stated (Resta et al., 2022). For this reason, the impact of the SARS-CoV-2 infection on pregnant women has been a big concern for clinicians and patients since the pandemic outbreak.

An increasing number of studies evaluating histopathological lesions, especially inflammatory and vascular alterations in placentas as well as maternal, obstetric, and neonatal outcomes after infection have been performed. However, the currently available evidence is controversial and not conclusive (Di Girolamo et al., 2021; Resta et al., 2021; Suhren et al., 2022). Placental lesions might lead to maternal and neonatal complications. Maternal vascular malperfusion (MVM) and fetal vascular malperfusion (FVM) are placental injury patterns related to abnormal vascular perfusion that lead to pathological changes and adverse pregnancy outcomes (Redline and Ravishankar, 2018; Wong et al., 2021). An increased risk of these vascular lesions has been reported in the placentas of women infected by SARS-CoV-2 (Shanes et al., 2020; Smithgall et al., 2020; Di Girolamo et al., 2021; Patberg et al., 2021; Resta et al., 2021). However, other published data have not identified differences between the placentas of infected, and non-infected women (Gulersen et al., 2020; Blasco Santana et al., 2021; Levitan et al., 2021; Tasca et al., 2021; Suhren et al., 2022).

COVID-19 disease increased severe maternal morbidity and mortality. Also, it was linked with newborn complications in a prospective, observational, and multinational cohort study (Villar et al., 2021). Moreover, SARS-CoV-2 infection at the time of birth was related to higher rates of fetal death, preterm birth, preeclampsia, and emergency cesarean delivery in a population-based cohort study in England (Gurol-Urganci et al., 2021). Thus, although pregnant women might not be at higher risk for SARS-CoV-2 infection, they may be a vulnerable population due to the influence of COVID-19 disease in maternal and neonatal outcomes (Kotlar et al., 2021; Wang et al., 2022; World Health Organization, 2022b). Therefore, generating more evidence regarding the effects of SARS-CoV-2 during pregnancy is necessary to unveil the potential risks and provide adequate management to patients.

The objective of the present study was to evaluate the prevalence of histopathological lesions in placental and umbilical cord samples of women infected by SARS-CoV-2 during pregnancy. In particular, MVM signs and other alterations, such as FVM and acute or chronic inflammatory pathology, were analyzed. Furthermore, the relationship between these lesions and clinical parameters, pregnancy outcomes, or newborn-related problems were analyzed.

Materials and methods

Study design

An observational, retrospective, histopathological, single-center study was carried out in placenta and umbilical cord samples from women infected with SARS-CoV-2 during pregnancy between March 2020 - April 2021.

Placenta and umbilical cord samples were obtained from women with SARS-CoV-2 infection during pregnancy who were included in the Gesta-COVID19 study at the Vall d'Hebron Hospital in Spain and were stored in the Pathological Anatomy archive (Suy et al., 2021). The samples were sent to the Anatomo-pathological Center in Madrid (Spain) to conduct the histopathological analysis.

Certain patient data were collected from the Gesta-COVID19 registry database. Data were also collected from the macroscopic analysis of the placenta and umbilical cord carried out at the Vall d'Hebron University Hospital. The Gesta-COVID19 study is a Spanish epidemiological registry of pregnant women with SARS-CoV-2 infection in which biological samples are collected from the mother and the newborn, to study the presence of SARS-CoV-2 and conduct related research with COVID-19.

The Ethics Committee approved the PLAXAVID study of the Vall d'Hebron University Hospital (Barcelona, Spain) (CEIm-VHIR). All the procedures were in accordance with the ethical principles of the Declaration of Helsinki, following good clinical practice (GCP) and ICH guidelines. Written consent was obtained from all women participating in the study.

Endpoints and variables

The primary endpoint was to assess the percentage of placentas with Maternal Vascular Malperfusion (MVM) signs. The secondary endpoints were to determine the percentage of placentas with: 1) any feature of MVM and/or villous agglutination (focal or diffuse accelerated villous maturation; central or peripheral villous infarcts; central or peripheral retroplacental hemorrhage/hematoma; decidual arteriopathy; and focal or extensive villous agglutination); 2) signs of Fetal Vascular Malperfusion (FVM); 3) any feature of FVM (umbilical cord at risk for partial/intermittent complete obstruction; foci of villous stromal-vascular karyorrhexis [VSK] or foci of

hyalinized avascular villi [HAV] affecting 2-4, 5-10 or >10 villi; early, subacute or late fibrin intramural accumulation and fetal vascular thrombi in large fetal vessels; and obliteration of the chorionic vessels); 4) evidence of acute inflammatory pathology (early acute subchorionitis, acute and necrotizing chorioamnionitis, umbilical phlebitis or chorionic vasculitis, umbilical arteritis, and necrotizing funisitis); 5) evidence of chronic inflammatory pathology (such as chronic chorioamnionitis, chronic histiocytic intervillositis, chronic lymphocytic or lymphoplasmacytic deciduitis, and chronic low- or high-grade villositis); 6) other histopathological alterations (increased levels of nucleated erythrocytes, adherent basal plate myometrial fibers, villous edema, and intervillous thrombosis among others); and 7) higher or lower weight for the gestational age. Other secondary endpoints were determining pregnancy features (such as pregnancy duration, abortion number, and premature delivery), neonates' characteristics (newborn weight, Apgar test result), and umbilical pH at the time of birth.

Statistical analysis

A descriptive analysis of variables was performed. Continuous variables were expressed as mean, standard deviation (SD), median, 25% and 75% percentiles (Q1 and Q3), and minimum and maximum values. Categorical variables were expressed as frequencies and percentages. Five categorical variables were defined to perform subgroup analysis. Defined subgroups were time (pregnancy trimester) of infection, duration, and severity at the time of the diagnosis of SARS-CoV-2 infection, the presence and severity at the time of delivery, and pregnancy duration. Correlation between variables was assessed using chi-square or Fisher's exact test for categorical variables and using parametric (T-test or ANOVA) or non-parametric tests (Wilcoxon or Kruskal-Wallis) for continuous ones. All statistical analyses were performed using SAS® statistical software, version 9.4.

Results

Study population

A total of 100 women were included in the study after excluding one by confirming a negative diagnosis of COVID-19 (Fig. 1). From those, 100 umbilical cords and 99 placental samples were valid for the analysis. The mean age of pregnant women was 31.7 years (SD: 6.5), most of them were Caucasian or Latin-American (46.9% or 39.8%, respectively), 15% had at least one comorbidity, and 3% were smokers (Demographic and clinical characteristics of the women are presented in Table 1).

Data related to SARS-CoV-2 infection is presented in Table 2. At the time of infection diagnosis, most women were in the third trimester of pregnancy (69.0%) with a mean gestational age of 30.8 weeks (median time from diagnosis to delivery 47 days, interquartile range [IQR]: 8,101). The majority were asymptomatic (24.0%) or had mild or moderate symptoms (39.0% and 23.0%, respectively). The mean time from COVID-19 diagnosis to delivery was 60.7 days (SD: 56.2), with a median of 47 days (Q1, Q3: 8, 101 days). One-third of the women (33.0%) were PCR-positive for COVID-19 at the time of delivery, most of them were asymptomatic (15.0%), and

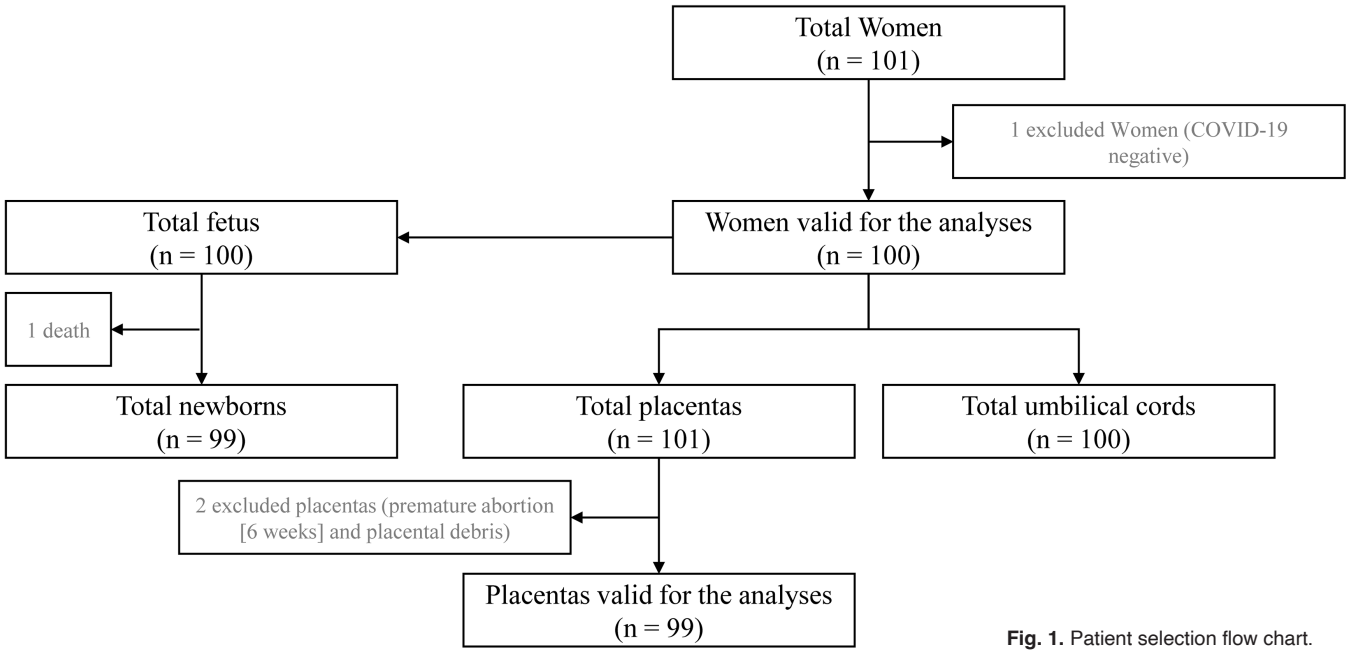


Fig. 1. Patient selection flow chart.

Table 1. Demographic and clinical characteristics of the women included in the analysis, delivery characteristics and pregnancy complications.

Variable	Total women (n=100)
Age (years)	
Mean (SD)	31.7 (6.5)
Median (Q1, Q3)	32.0 (26.0, 37.0)
Min, Max	20, 51
Weight (Kg)	
Mean (SD)	71.1 (15.6)
Median (Q1, Q3)	68.5 (60.0, 77.0)
Min, Max	47, 128
Height (cm)	
Mean (SD)	161.2 (6.5)
Median (Q1, Q3)	161.0 (157.0, 166.0)
Min, Max	140, 172
BMI (Kg/m^2)	
Mean (SD)	27.4 (6.2)
Median (Q1, Q3)	26.1 (22.4, 30.5)
Min, Max	17, 48
Ethnicity, n (%)	100 (100.0%)
Caucasian	46 (46.0%)
Latin-American	39 (39.0%)
Asian	10 (10.0%)
African	3 (3.0%)
Non-reported	2 (2.0%)
Comorbidities, n (%)	15 (15.0%)
Hypertension	4 (4.0%)
Autoimmune disease (hypothyroidism)	3 (3.0%)
Acquired cardiopathy	1 (1.0%)
Cancer	2 (2.0%)
Psychiatric disease	2 (2.0%)
Smoker, n (%)	3 (3.0%)
Gestational age at the time of delivery (weeks)	
Mean (SD)	38.9 (4.0)
Median (Q1, Q3)	39.5 (38.4, 40.6)
Min, Max	6.0, 42.3
Type of delivery, n (%)	99* (100.0)
Spontaneous	43 (43.4)
Programmed	56 (56.6)
Types of birth, n (%)	99* (100.0)
Vaginal birth	63 (63.6)
Scheduled cesarean	25 (25.3)
Urgent cesarean	11 (11.1)
Complications during the gestational period, n (%)**	25 (25.0)
Abortion <14 weeks	1 (1.0)
TPL requiring admission	2 (2.0)
Tocolysis	1 (1.0)
PROM	7 (7.0)
Gestational age, Mean (SD)	28.7 (10.4)
Median (Q1, Q3)	32.0 (28.0,35.0)
Min, Max	6.0, 35.0
Preeclampsia	6 (6.0)
Gestational hypertension	1(1.0)
Gestational diabetes	4 (4.0)
Corticoids for fetal maturation	8 (8.0)
IUGR	6 (6.0)
Alterations in Doppler	4 (4.0)
Gestational age, Mean (SD)	31.9 (3.3)
Median (Q1, Q3)	32.9 (29.9, 33.9)
Min, Max	27.1, 34.7
Fetus malformation	4 (4.0)

BMI: body mass index; IUGR: intrauterine growth retardation; PROM: Premature rupture of membranes; Q: quartile; SD: standard deviation; TPL: Threatened preterm labor. *One of the patients suffered a premature abortion (<6 weeks); **The same patient might have presented more than one complication.

only 5% were critically ill. The duration of the SARS-CoV-2 infection was determined only in 87 women. In most of them, the infection lasted less than 2 weeks (14 days; 48.3%) or between 2 and 4 weeks (15-28 days; 35.6%). Oxygen therapy (36.0%), antivirals (33.0%), antibiotics (31.0%), and chloroquine/hydroxychloroquine (35.0%) were the most used treatments in SARS-CoV-2 infection. More than half of the patients (53%) received anticoagulant or antiplatelet therapy with Low-molecular-weight heparin (LMWH) in the course of SARS-CoV-2 infection. The mean number of days of treatment since diagnosis was 19.7 (SD: 35.2), and 32.0% (n=32) were on LMWH treatment during delivery.

Regarding obstetrical history, 41.0% (n=41) were primiparous women, 38.0% (n=38) and 21.0% (n=21) had one or two or more previous deliveries, respectively,

Table 2. SARS-CoV-2 infection characteristics.

Variable	n (%)
Time of infection	
1st trimester	6 (6.0%)
2nd trimester	25 (25.0%)
3rd trimester	69 (69.0%)
Disease severity at the time of diagnosis	
Asymptomatic	24 (24.0%)
Mild	39 (39.0%)
Moderate	23 (23.0%)
Severe	4 (4.0%)
Critical	10 (10.0%)
Infection at the time of delivery & severity	
Asymptomatic	15 (15.0%)
Mild	4 (4.0%)
Moderate	9 (9.0%)
Critical	5 (5.0%)
Cured	67 (67.0%)
Duration of infection[1]	
Less than 2 weeks (14 days)	42 (48.3%)
2 to 4 weeks (15-28 days)	31 (35.6%)[1]
More than 4 weeks (>29 days)	14 (16.1%)[1]
Infection treatments	
Oxygen therapy	36 (36.0%)
Antivirals[2,3]	33 (33.0%)
Lopinavir/Ritonavir	32 (32.0%)
Remdesivir	2 (2.0%)
Antibiotics[4]	31 (31.0%)
Amoxicillin-clavulanic acid	1 (1.0%)
Azithromycin	26 (26.0%)
Ceftriaxone	9 (9.0%)
Corticoids	5 (5.0%)
Prednisone	1 (1.0%)
Chloroquine/Hydroxychloroquine	35 (35.0%)
Interferons	1 (1.0%)
Others	9 (9.0%)

[1]Percentage concerning the number of patients with follow-up for the infection or a negative PCR result (n=87; missing patients n=13); [2]Patients might have taken more than one antiviral; [3]No case of umifenovir or favipiravir treatment; [4]Patient might have taken? more than one antibiotic.

and 91.0% (n=91) of women had a term pregnancy. One of the included women had a monochorionic twin pregnancy. The mean gestational age was 38.9 weeks (SD: 4.0), and labor was induced in 56.6% (n=56). Among them, the induction was due to COVID-19 complications in 4.0% (n=4). During the gestational period, 25.0% (n=25) women presented complications, 6.0% (n=6) had a preeclampsia diagnosis, 4.0% (n=4) gestational diabetes and 1.0% (n=1) gestational hypertension (Table 1). Four fetuses presented fetal malformations, six had intrauterine growth retardation (IUGR), and fetal maturation was stimulated by corticosteroids in eight women.

Newborn's mean weight was 3.19 kg (SD: 0.6) and 44.4% (n=44) were male. Positive COVID-19 diagnosis was confirmed by PCR only in one of the 97 newborns tested. Neonatal assessments of umbilical pH and APGAR test (one and five minutes after birth) were summarized in Table 3.

Placenta and umbilical cord macroscopic data

Placental macroscopic characteristics are presented in Table 4. Sixty-five hematomas were detected in 46 (46.5%) placentas. In most of them, there was only one hematoma (n=32; 32.3%) and had a subchorionic (n=33; 50.8%) or intraparenchymal (n=27; 41.5%), location. Thirty-nine placentas (39.8%) presented lesions suggestive of infarcts. Most of them (n=32; 32.7%) presented only one lesion and had a central location (n=45; 86.5%). Additional lesions were identified in 79 placentas, particularly, color alterations (n=77; 77.8%).

Umbilical cord samples had a mean diameter of 1.1 cm (SD=0.2), but the full length of umbilical cords could not be assessed, as only cord fragments were available. The cord insertion was eccentric or peripheral (n=49; 50.0%), central (n=35; 35.7%), or marginal (n=14; 14.3%). Anomalous insertions (velamentous or bifurcated) were not identified. Ninety-five (97.9%) cords had three vessels, and only two cords (2.1%) had two vessels. No knots, hyperspiralization, or stenosis were found.

Table 3. Apgar determinations (1 and 5 minutes), arterial and venous pH of newborns.

Variable	Total newborns (n=99)
Apgar 1'	
Mean (SD)	8.61 (1.39)
Median (Q1, Q3)	9.0 (9.0, 9.0)
Min, Max	3.0, 10.0
Apgar 5'	
Mean (SD)	9.74 (0.95)
Median (Q1, Q3)	10.0 (10.0, 10.0)
Min, Max	5.0, 10.0
Arterial pH (umbilical cord)	
Mean (SD)	7.22 (0.09)
Median (Q1, Q3)	7.23 (7.17, 7.29)
Min, Max	6.9, 7.4
Venous pH (umbilical cord)	
Mean (SD)	7.29 (0.07)
Median (Q1, Q3)	7.3 (7.26, 7.34)
Min, Max	7.1, 7.4

Q: quartile; SD: standard deviation.

Table 4. Placental macroscopic characteristics.

Characteristic	Total placentas (n=99)
Percentile weight1	
Mean (SD)	32.8 (26.0)
Median (Q1, Q3)	25.0 (10.0, 55.0)
Min, Max	3, 93
Weight without membranes (g)[1]	
Mean (SD)	429.6 (94.5)
Median (Q1, Q3)	426.4 (381.1, 486.9)
Min, Max	137, 691
Larger diameter/length (cm)	
Mean (SD)	17.9 (2.4)
Median (Q1, Q3)	17.0 (16.0, 19.0)
Min, Max	13, 27
Smaller diameter/width (cm)	
Mean (SD)	14.9 (2.1)
Median (Q1, Q3)	15.0 (14.0, 16.0)
Min, Max	8, 22
Chorionic plate surface (cm^2)	
Mean (SD)	269.8 (65.5)
Median (Q1, Q3)	256.0 (236.3, 292.5)
Min, Max	117, 572
Disc thickness (cm2)	
Mean (SD)	2.6 (0.7)
Median (Q1, Q3)	2.5 (2.0, 3.0)
Min, Max	2, 5
Placentas with hematomas/hemorrhage, n (%)	46 (46.5%)
One hematoma/hemorrhage	32 (32.3%)
Two hematomas/hemorrhages	10 (10.1%)
Three hematomas/hemorrhages	3 (3.0%)
Four hematomas/hemorrhages	1 (1.0%)
Total hematomas/hemorrhages, n (%)	65 (100.0%)
Subchorionic	33 (50.8%)
Intraparenchymal	27 (41.5%)
Retroplacental and subamniotic	2 (3.1%)
Marginal	1 (1.5%)
Size of hematoma/hemorrhage (cm), mean (SD)	1.9 (2.1)
Placentas with lesions suggestive of infarction, n (%)	39 (39.8%)
One lesion	32 (32.7%)
Two lesions	4 (4.1%)
Four lesions	3 (3.1%)
Total infarction lesions, n (%)	52 (100.0%)
Central location	45 (86.5%)
Marginal location	7 (13.5%)
Size of lesions (cm), mean (SD)	1.7 (2.0)
Placentas with additional lesions, n (%)	79 (79.8%)
Color alteration	77 (77.8%)
Thrombosis of chorionic vessels	11 (11.1%)
Thickened membranes	2 (2.0%)

Q: quartile; SD: standard deviation. [1]The weight data correspond to placentas proportion, thereby data are not comparable with whole placentas.

Primary and secondary endpoints

Primary endpoint

Regarding the primary endpoint, 77.8% (n=77) of the placental samples presented some MVM characteristic (Figs. 2A, 3).

Secondary endpoints

Among identified MVM characteristics, the most common were accelerated villous maturation (37.4%, n=37), central villous infarcts (33.3%, n=33), and villous agglutination (46.5%, n=46). Accelerated villous maturation was focalized in 18 (18.2%) samples and diffused in 19 (19.2%). Villous agglutination was focalized and extensively localized in 33 (33.3%) and 13 (13.1%) cases, respectively. Features of FVM were determined in 57.6% (n=57) of samples, and HAV (38.4%, n=38), fetal vascular thrombi (20.2%, n=20), and risk of umbilical cord partial obstruction (14.1%, n=14; Fig. 2B) were the more frequent. Among the placentas with HAV, 18 (18.2%) had 2-4 affected villi, 9 (9.1%) had 5-10 affected villi, and 11 (11.1%) had more than 10 affected villi. Only five placentas had VSK with 2-4 villi affected (Fig. 4).

Acute inflammatory pathology was also noticed in 22.2% (n=22) of analyzed placentas, 16.2% (n=16) with acute chorioamnionitis, 13.1% (n=13) with early acute subchorionitis, 9.1% (n=9) with umbilical phlebitis or chorionic vasculitis, and 5.1% (n=5) with umbilical arteritis (Fig. 2C). No cases of necrotizing chorioamnionitis or necrotizing funisitis were detected. Regarding chronic inflammatory pathology, it was present in half (49.5%, n=49) of the samples (Figs. 2D, 5). All analyzed placental samples present some histopathological alteration (Table 5, Fig. 6). Most placentas (38.4%) had 10-15% of global fibrin (Fig. 7).

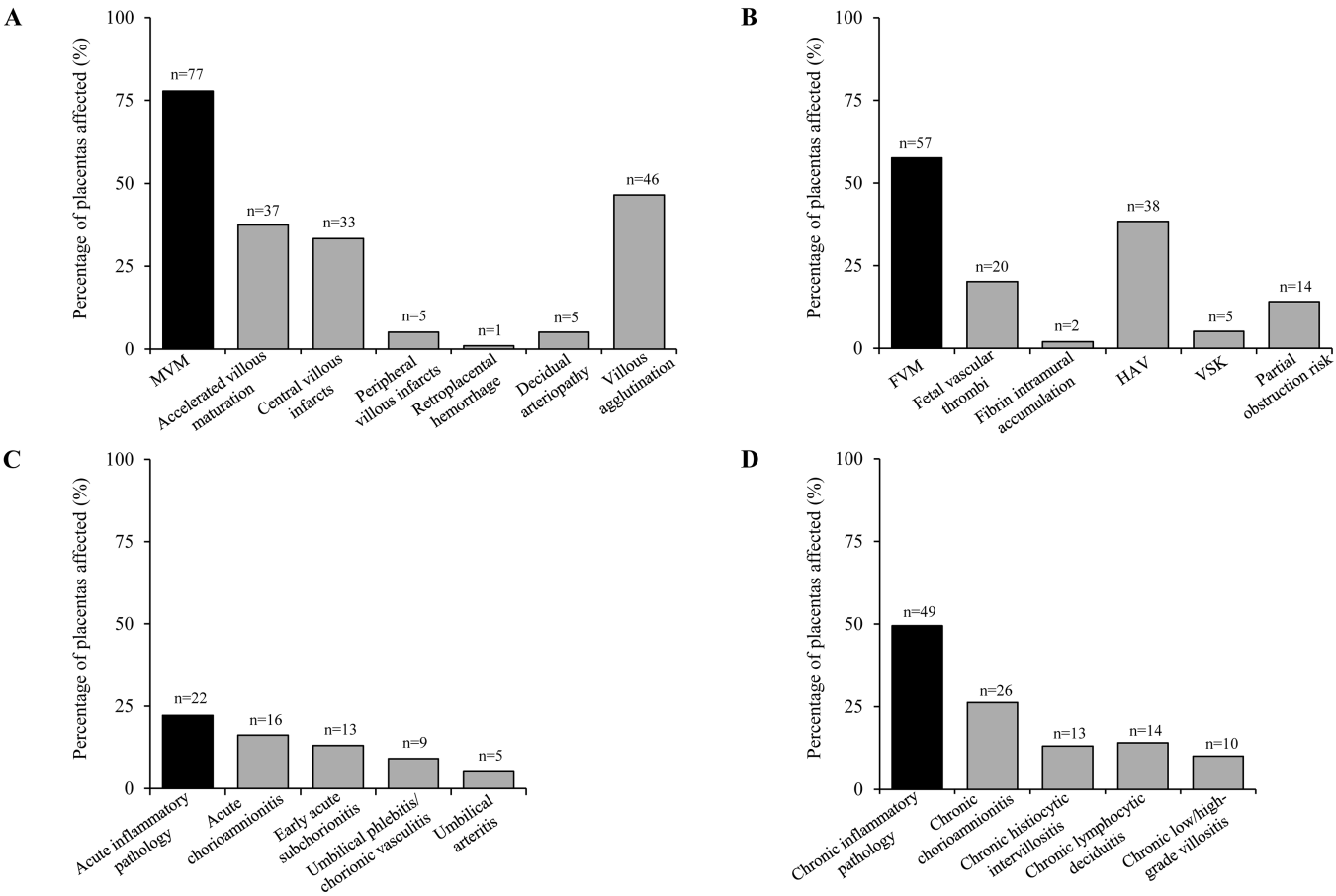


Fig. 2. Percentage of placental samples with characteristics of MVM **(A)**, FVM **(B)**, acute inflammatory pathology **(C)** or chronic inflammatory pathology **(D)**. The same placenta might have more than one alteration. All the percentages have been calculated in terms of the total number of placental samples. FVM, fetal vascular malperfusion; HAV, hyalinized avascular villi; MVM, maternal vascular malperfusion; VSK, villous stromal-vascular karyorrhexis.

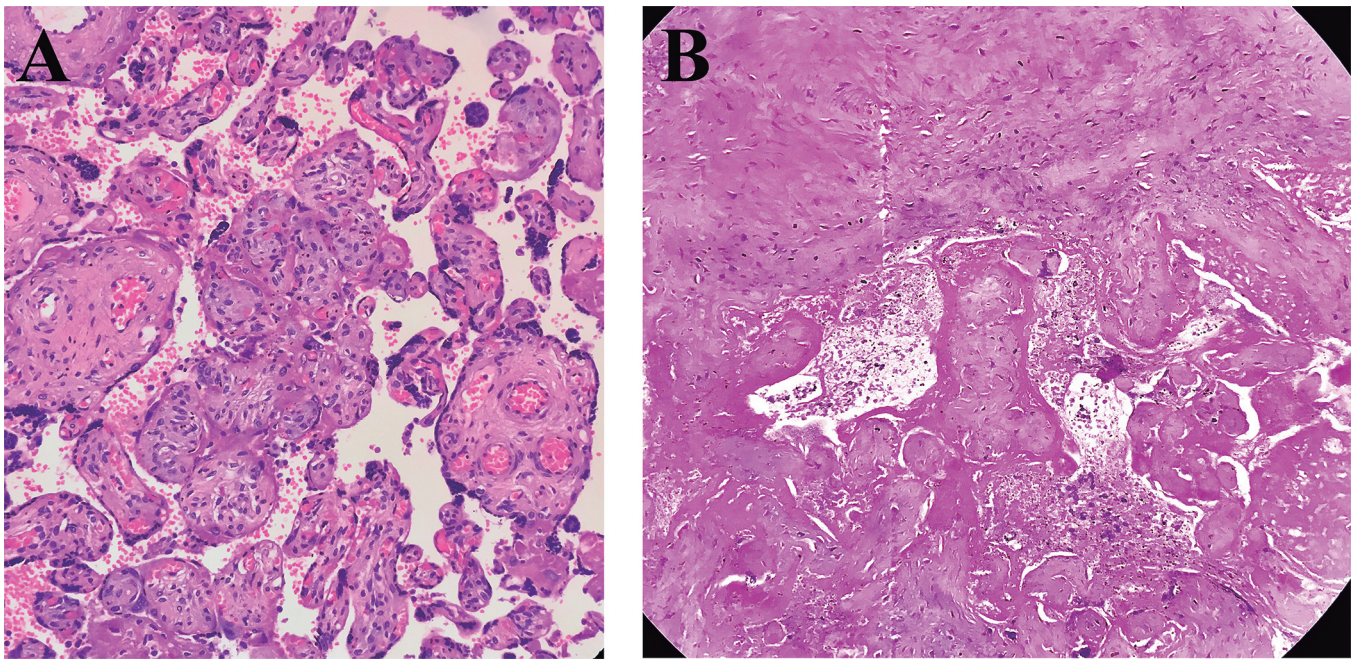


Fig. 3. Representative histological sections showing MVM lesions: villus agglutination **(A)** and central villous infarct **(B)**. Hematoxylin-eosin stain. x 200.

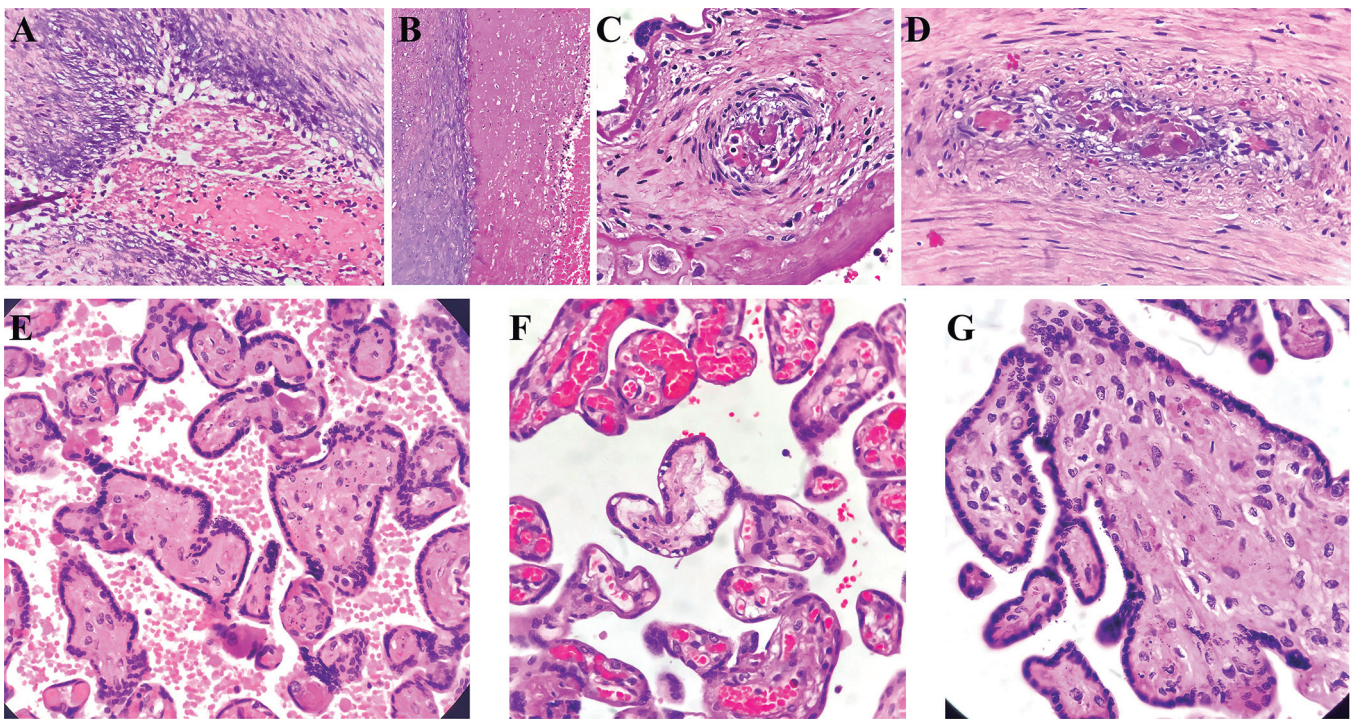


Fig. 4. Representative histological sections showing FVM lesions: vascular thrombus in a large fetal vessel **(A, B)**; vascular thrombus in a small vessel **(C, D)**, HAV foci **(E, F)**, VSK foci **(G)**. Hematoxylin-eosin stain. x 400.

Subgroup analysis of variables

Five clinical subgroups were defined to better assess the influence of COVID-19 clinical characteristics over PLAXAVID study endpoints. The following subgroups were already defined in the study protocol: time (pregnancy trimester), duration and severity of COVID-19 disease at the time of the diagnosis of SARS-CoV-2 infection, the presence and severity of COVID-19 at the time of delivery, and pregnancy duration. The correlation between the histopathological features and these five clinical variables was evaluated. Most of the affected placentas by MVM were from women infected in the third trimester of pregnancy (70.1%, n=54), with a duration lower than two weeks (47.8%, n=32), mild symptoms at the time of diagnosis (39.0%, n=30), cured at the time of delivery (68.8%, n=53), and had a term birth (89.6%, n=69; Fig. 8). There was no statistically significant correlation between any clinical variables with the presence of MVM characteristics in placental samples (Fisher's exact test, $p>0.1$ in all cases; Table 6). However, statistically, significant differences were observed when MVM characteristics were individually analyzed. The presence of central villous infarcts ($p=0.03$) and retroplacental hemorrhage correlated with the time of SARS-CoV-2 infection ($p=0.04$; Table 7). Also, the decidual arteriopathy correlated with the presence and severity of SARS-Cov-2 infection at the time of delivery ($p=0.04$; Table 7).

Significant correlations between the existence of

Table 5. Histopathological alteration in placental samples.

Histopathological alteration*	Total placentas (n=99)
Villous edema	1 (1.0%)
Amnion nodosum	2 (2.0%)
Chorangioma – Membranes with microcysts	1 (1.0%)
Chorangiosis	26 (26.3%)
Intense Chorangiosis	2 (2.0%)
Mild chorangiosis	1 (1.0%)
Mild chorangiosis – Cord blood extravasation	1 (1.0%)
Mild chorangiosis – Extravillous trophoblast cyst – Macrophages with meconium in the membranes	1 (1.0%)
Chorangiosis – Histiocytes with meconium on membrane surface	1 (1.0%)
Chorangiosis – Chorionic membrane with microcysts	6 (6.1%)
Chorangiosis – Membranes with microcysts	1 (1.0%)
Chorangiosis – Decidual plaque in membranes	1 (1.0%)
Corangiosis – Extravillous cytotrophoblast cyst	1 (1.0%)
Chorionic membrane with microcysts – Macrophages with meconium in membrane	1 (1.0%)
Chorionic membrane with microcysts	9 (9.1%)
Chorionic membrane with microcysts – Cord vascular dilatations	1 (1.0%)
Chorionic membrane with microcysts – Lamellar necrosis in membranes	1 (1.0%)
Chorionic membrane with microcysts – Eosinophilic chorionic vasculitis	1 (1.0%)
Lamellar necrosis of membranes	1 (1.0%)
Lamellar necrosis of membranes – Chorangiosis	1 (1.0%)
Decidual lamellar necrosis	1 (1.0%)
Decidual lamellar necrosis – Membrane with microcysts	1 (1.0%)

*Each placental sample could present more than one histopathological alteration.

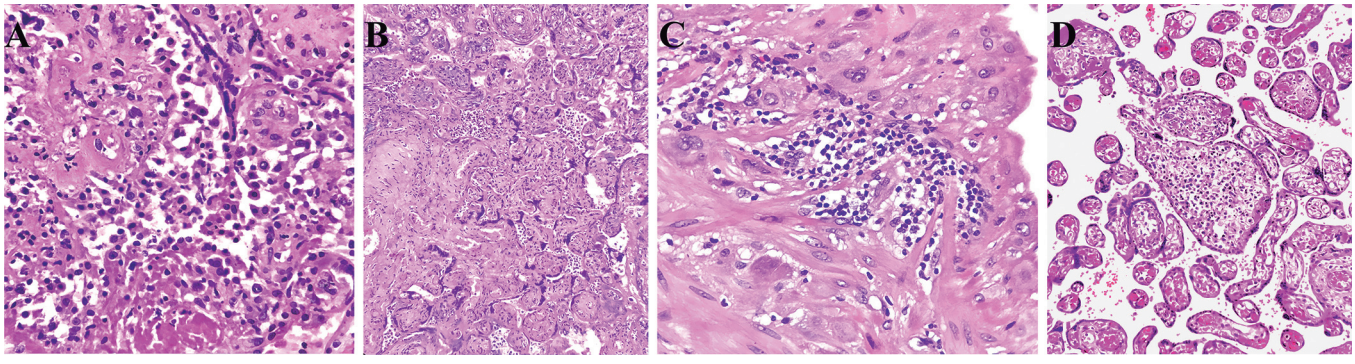


Fig. 5. Representative histological sections showing chronic inflammatory lesions: chronic histiocytic intervillositis **(A)** and **(B)**; chronic deciduitis **(C)**; and chronic villositis **(D)**. Hematoxylin-eosin stain. A, D, x 260; B, x 100; C, x 200.

other histopathological features and defined clinical variables were also identified. The presence of thrombi in large fetal vessels correlates with the time of infection (p<0.001) and with the presence and severity of the infection at the time of delivery (p=0.003; Table 7). Similarly, there was a correlation between HAV and the presence and severity of SARS-CoV-2 infection at the time of delivery (p=0.01); between the incidence of chronic lymphocytic deciduitis and the time of infection (p=0.048); and between fibrin accumulation and SARS-CoV-2 infection duration (p=0.006).

Critically ill patients due to SARS-CoV-2 infection had a significantly shorter duration of pregnancy (p=0.008), the newborns had a lower weight (p=0.003) and lower APGAR test scores at one and five minutes (p<0.001 for both; Table 8). The trend is the same considering the presence of SARS-CoV-2 infection at the time of delivery and in the case of preterm births. No statistical differences were observed regarding the time and duration of infection (Table 8).

Discussion

PLAXAVID study is the first case series report that evaluates the histopathological characteristics of the placenta and umbilical cord samples of women infected by SARS-CoV-2 in Spain. We found histopathological alterations in a significant proportion of the samples, especially signs of MVM, FVM, and chronic inflammatory pathology.

The prevalence of vascular alterations found in our study is remarkably greater than that reported in other case series of pregnant women without COVID-19. Romero et al. (2018) performed a retrospective analysis of placental samples from 944 women who delivered at term without complications and identified that 78% of placentas had histopathological alterations consistent with inflammatory or vascular lesions. They found MVM and FVM lesions in 35.7% and 19.7% of samples, respectively. These figures are about half the observed number in our cohort (77.8% and 57.6%, respectively). Similarly, a higher percentage of chronic inflammatory lesions has been observed in our study (49.5% vs. 29.9%), but the proportion of acute inflammatory lesions is lower than the one published by Romero et al. (22.2% vs. 42.3%). This difference could be explained due to the different racial representation in both cohorts. Indeed, in the Romero et al., authors observed a statistical association between acute inflammatory pathology and

Table 6. Total placentas samples and placentas with maternal vascular malperfusion (MVM) were distributed according to clinical variables.

Variable	Total placentas (n=99)	Placentas with MVM (n=77)	p (Fisher's exact test)
Time of infection, n (%)			
1st trimester	5 (5.1)	3 (3.9)	0.578
2nd trimester	25 (25.2)	20 (26.0)	
3rd trimester	69 (69.7)	54 (70.1)	
Duration of infection1, n (%)			
Less than 2 weeks (14 days)	42 (48.8)	32 (47.8)	0.347
2 to 4 weeks (15-28 days)	29 (33.7)	22 (32.8)	
More than 4 weeks (>29 days)	15 (17.4)	13 (19.4)	
Disease severity at the diagnosis, n (%)			
Asymptomatic	24 (24.2)	16 (20.8)	0.237
Mild	38 (38.4)	30 (39.0)	
Moderate	23 (23.2)	20 (26.0)	
Severe	4 (4.1)	2 (2.6)	
Critical	10 (10.1)	9 (11.7)	
Infection & severity at the delivery, n (%)			
Asymptomatic	15 (15.2)	8 (10.4)	0.128
Mild	4 (4.0)	3 (3.9)	
Moderate	9 (9.1)	8 (10.4)	
Critical	5 (5.0)	5 (6.5)	
Healed	66 (66.7)	53 (68.8)	
Duration of pregnancy, n (%)			
Preterm birth	9 (9.1)	8 (10.4)	0.193
Term birth	90 (90.9)	69 (89.6)	

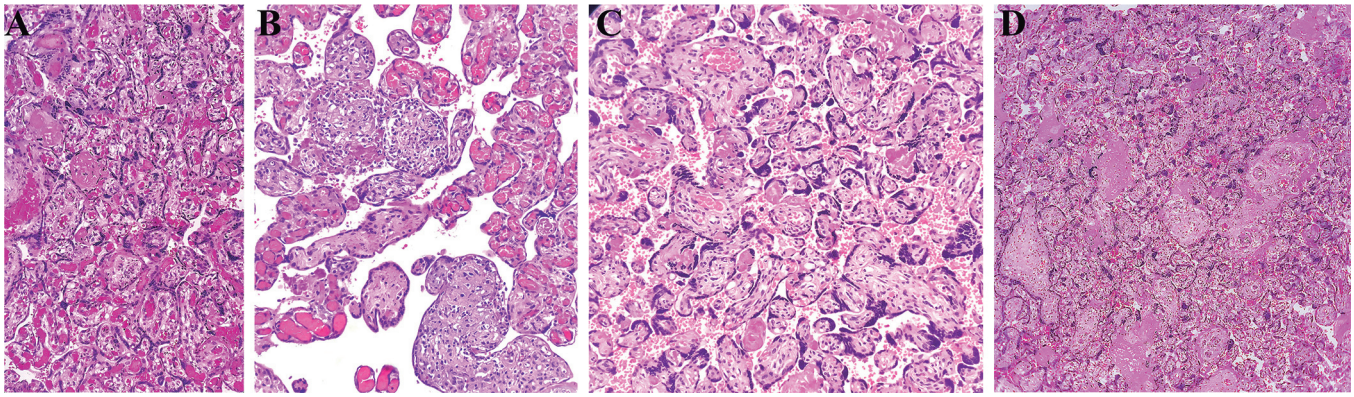


Fig. 6. Representative histological sections showing other histopathological lesions: Villi with large chorangiosis **(A)**; chronic villitis adjacent to cilli with chorangiosis, HAV foci, and intervillous fibrin **(B)**; increased syncytial nodes in villi **(C)**; and increased intervillous fibrin **(D)**. Hematoxylin-eosin stain. A, C, x 200; B, x 150; D, x 100.

African American ethnicity, represented by 82.4% of the cohort. Our case series included a much lower proportion of African women (3%), which may explain the observed difference.

Pregnancy has been reported to be an independent risk factor for adverse outcomes in women with SARS-CoV-2 infection with a suggested increased risk of placental lesions (Di Girolamo et al., 2021). However,

Table 7. Secondary endpoints related to histopathological features are distributed according to defined clinical variables.

	Time of infection				Duration of infection				Duration of pregnancy		
	1st Trimester	2nd Trimester	3rd Trimester	*p*	<2 weeks	2-4 weeks	>4 weeks	*p*	Preterm birth	Term birth	*p*
MVM, n (%)	3 (3.9)	20 (26.0)	54 (70.1)	>0.05	32 (47.8)	22 (32.8)	13 (19.4)	>0.05	8 (10.4)	69 (89.6)	>0.05
Accelerated villous maturation	2 (5.4)	7 (18.9)	28 (75.7)	>0.05	14 (45.2)	10 (32.3)	7 (22.6)	>0.05	5 (26.3)	14 (73.7)	>0.05
Central villous infarcts	1 (3.0)	4 (12.1)	28 (84.8)	0.029*	17 (56.7)	6 (20.0)	7 (23.3)	>0.05	2 (6.1)	31 (93.9)	>0.05
Peripheral villous infarcts		1 (20.0)	4 (80.0)	>0.05	2 (40.0)	1 (20.0)	2 (40.0)	>0.05		5 (100.0)	>0.05
Retroplacental hemorrhage/hematoma	1 (100.0)			0.039*			1 (100.0)	>0.05	1 (100.0)		>0.05
Decidual arteriopathy	1 (20.0)	2 (40.0)	2 (40.0)	>0.05	1 (20.0)	2 (40.0)	2 (40.0)	>0.05	1 (20.0)	4 (80.0)	>0.05
Villous agglutination	1 (2.2)	13 (28.3)	32 (69.6)	>0.05	21 (52.5)	11 (27.5)	8 (20.0)	>0.05	5 (10.9)	41 (89.1)	>0.05
FVM, n(%)	4 (7.0)	12 (21.1)	41 (71.9)	>0.05	26 (52.0)	17 (34.0)	7 (14.0)	>0.05	7 (12.3)	50 (87.7)	>0.05
Umbilical cord at risk for partial obstruction		3 (21.4)	11(78.6)	>0.05	6 (66.7)	2 (22.2)	1 (11.1)	>0.05	2 (14.3)	12 (85.7)	>0.05
Fibrin intramural accumulation		1 (50.0)	1 (50.0)	>0.05	2 (100.0)			0.006*		2 (100.0)	>0.05
Vascular thrombi	4 (20.0)	7 (35.0)	9 (45.0)	>0.05	7 (36.8)	9 (47.4)	3 (15.8)	>0.05	2 (10.0)	18 (90.0)	>0.05
VSK		3 (60.0)	2 (40.0)	>0.05	3 (60.0)	2 (40.0)		>0.05	5 (100.0)		>0.05
HAV		8 (21.1)	30 (78.9)	>0.05	17 (51.5)	12 (36.4)	4 (12.1)	>0.05	34 (89.5)	4 (10.5)	>0.05
Acute inflammatory pathology, n(%)	1 (4.5)	5 (22.7)	16 (72.7)	>0.05	8 (38.1)	9 (42.9)	4 (19.0)	>0.05		22 (100.0)	>0.05
Early acute subchorionitis		4 (30.8)	9 (69.2)	>0.05	5 (41.7)	6 (50.0)	1 (8.3)	>0.05		13 (100.0)	>0.05
Acute corioamnionitis	1 (6.3)	2 (12.5)	13 (81.3)	>0.05	5 (33.3)	7 (46.7)	3 (20.0)	>0.05		16 (100.0)	>0.05
Umbilical phlebitis or chorionic vasculitis		1 (11.1)	8 (88.9)	>0.05	3 (33.3)	3 (33.3)	3 (33.3)	>0.05		9 (100.0)	>0.05
Umbilical arteritis			5 (100.0)	>0.05	1 (25.0)	1 (25.0)	2 (50.0)	>0.05		5 (100.0)	>0.05
Chronic inflammatory pathology, n(%)	3 (6.1)	13 (26.5)	33 (67.3)	>0.05	18 (42.9)	18 (42.9)	6 (14.3)	>0.05	4 (8.2)	45 (91.8)	>0.05
Chronic chorioamnionitis	2 (7.7)	7 (26.9)	17 (65.4)	>0.05	13 (56.5)	8 (34.8)	2 (8.7)	>0.05	1 (3.8)	225 (96.2)	>0.05
Chronic histocytic	1 (7.7)	3 (23.1)	9 (69.2)	>0.05	4 (33.3)	6 (50.0)	2 (16.7)	>0.05	2 (15.4)	11 (84.6)	>0.05
Chronic lymphocytic/lymphoplasmacytic deciduitis	1 (7.1)	7 (50.0)	6 (42.9)	0.048*	5 (38.5)	7 (53.8)	1 (7.7)	>0.05	1 (7.1)	13 (92.9)	>0.05
Chronic low-grade villositis		3 (30.0)	7 (70.0)	>0.05	3 (37.5)	2 (25.0)	3 (37.5)	>0.05		10 (100.0)	>0.05
Chronic high-grade villositis	1 (11.1)	4 (44.4)	4 (44.4)	>0.05	2 (25.0)	5 (62.5)	1 (12.5)	>0.05	1 (11.1)	8 (88.9)	>0.05

	Severity at the time of diagnosis						Diagnosis & Severity at the time of delivery					
	Asymp.	Mild	Moderate	Severe	Critical	*p*	Asymp.	Mild	Moderate	Critical	Healed	*p*
MVM, n(%)	16 (20.8)	30 (39.0)	20 (26.0)	2 (2.6)	9 (11.7)	>0.05	8 (10.4)	3 (3.9)	8 (10.4)	5 (6.5)	53 (68.8)	>0.05
Accelerated villous maturation	8 (21.6)	16 (43.2)	7 (18.9)	1 (2.7)	5 (13.5)	>0.05	4 (10.8)	1 (2.7)	5 (13.5)	4 (10.8)	23 (62.2)	>0.05
Central villous infarcts	9 (27.3)	11 (33.3)	10 (30.3)	1 (3.0)	2 (6.1)	>0.05	5 (15.2)	1 (3.0)	3 (9.1)	1 (3.0)	23 (69.7)	>0.05
Peripheral villous infarcts		2 (40.0)	3 (60.0)			>0.05		1 (20.0)	3 (9.1)		3 (60.0)	>0.05
Retroplacental hemorrhage/hematoma		1 (100.0)				>0.05					1 (100.0)	>0.05
Decidual arteriopathy		5 (100.0)				>0.05		2 (40.0)			3 (60.0)	0.042*
Villous agglutination	9 (19.6)	17 (37.0)	12 (26.1)	2 (4.3)	6 (13.0)	>0.05	4 (8.7)	2 (4.3)	6 (13.0)	3 (6.5)	31.6 (67.4)	>0.05
FVM, n(%)	15 (26.3)	20 (35.1)	12 (21.1)	2 (3.5)		>0.05	9 (15.8)	3 (5.3)	5 (8.8)	5 (8.8)	35 (61.4)	>0.05
Umbilical cord at risk for partial obstruction	5 (35.7)	2 (14.3)	4 (28.6)	1 (7.1)		>0.05	4 (28.6)		2 (14.3)	1 (7.1)	7 (50.0)	>0.05
Fibrin intramural accumulation			1 (50.0)			>0.05					2 (100.0)	>0.05
Vascular thrombi	5 (25.0)	9 (45.0)	4 (20.0)	1 (5.0)		>0.05	1 (5.0)				19 (95.0)	>0.05
VSK	1 (20.0)	2 (40.0)	1 (20.0)	1 (20.0)		>0.05	1 (20.0)				4 (80.0)	>0.05
HAV	8 (21.1)	12 (31.6)	9 (23.7)	2 (5.3)		>0.05	6 (15.8)	3 (7.9)	4 (10.5)	5 (13.2)	20 (52.6)	>0.05
Acute inflammatory pathology, n(%)	5 (22.7)	15 (54.5)	5 (22.7)			>0.05	3 (13.6)		1 (4.5)		18 (81.8)	>0.05
Early acute subchorionitis	3 (23.1)	8 (61.5)	2 (15.4)			>0.05	1 (7.7)				12 (92.3)	>0.05
Acute corioamnionitis	3 (18.8)	9 (56.3)	4 (25.0)			>0.05	1 (6.3)		1 (6.3)		14 (87.5)	>0.05
Umbilical phlebitis or chorionic vasculitis	1 (11.1)	5 (55.6)	3 (33.3)			>0.05	1 (11.1)				8 (88.9)	>0.05
Umbilical arteritis		4 (80.0)	1 (20.0)			>0.05					5 (100.0)	>0.05
Chronic inflammatory pathology, n(%)	11 (22.4)	18 (36.7)	11 (22.4)	2 (4.1)	7 (14.3)	>0.05	5 (10.2)	3 (6.1)	4 (8.2)	3 (6.1)	34 (69.4)	>0.05
Chronic chorioamnionitis	5 (19.2)	11 (42.3)	5 (19.2)	2 (7.7)	3 (11.5)	>0.05	2 (7.7)	2 (7.7)	1 (3.8)	1 (3.8)	20 (76.9)	>0.05
Chronic histocytic	5 (38.5)	5 (38.5)	2 (15.4)		1 (7.7)	>0.05	1 (7.7)	1 (7.7)	1 (7.7)		10 (76.9)	>0.05
Chronic lymphocytic/lymphoplasmacytic deciduitis	2 (14.3)	5 (35.7)	5 (35.7)	1 (7.1)	1 (7.1)	>0.05			1 (7.1)	1 (7.1)	12 (85.7)	>0.05
Chronic low-grade villositis	1 (10.0)	2 (20.0)	4 (40.0)	1 (10.0)	2 (20.0)	>0.05	1 (10.0)		2 (20.0)	1 (10.0)	6 (60.0)	>0.05
Chronic high-grade villositis	3 (33.3)	4 (44.4)	2 (22.2)			>0.05	1 (11.1)	1 (11.1)			7 (77.8)	>0.05

FVM: fetal vascular malperfusion; HAV: hyalinized avascular villi; MVM: maternal vascular malperfusion; Q: quartile; SD: standard deviation; VSK: villous stromal-vascular karyorrhexis. *Statistically significant according to Fisher's exact test.

the reported frequencies of these histopathological alterations vary across the studies (Gulersen et al., 2020; Shanes et al., 2020; Smithgall et al., 2020; Blasco Santana et al., 2021; Di Girolamo et al., 2021; Levitan et al., 2021; Patberg et al., 2021; Resta et al., 2021; Tasca et al., 2021; Suhren et al., 2022). Significant rates of MVM and FVM (30.7% and 27.1%, respectively) were reported in a systematic review and meta-analysis including 56 studies and 1,008 pregnancies, suggesting placental hypoperfusion and inflammation according to our results (Di Girolamo et al., 2021). However, a case-control study identified a significantly higher prevalence of FVM (21.1% vs. 4.2%; $p<0.001$) but not of MVM (54.3% vs. 43.7% $p=0.19$) in SARS-CoV-2 infected women, although significant differences in decidual arteriopathy frequency (40.9% vs. 1.4% $p<0.001$), an MVM characteristic, were also reported (Resta et al., 2021). Patberg et al. (2021) compared the placental histopathologic findings in positive COVID-19 women (regardless of symptomatology), who delivered at term with non-infected women. Similar to our results, infected women were more likely to have signs of FVM, in particular, HAV (32.5% vs. 3.6%; p<0.001). These differences were observed even when asymptomatic women were individually analyzed. Smithgall et al. (2020) also identified signs of MVM (41.2% showed

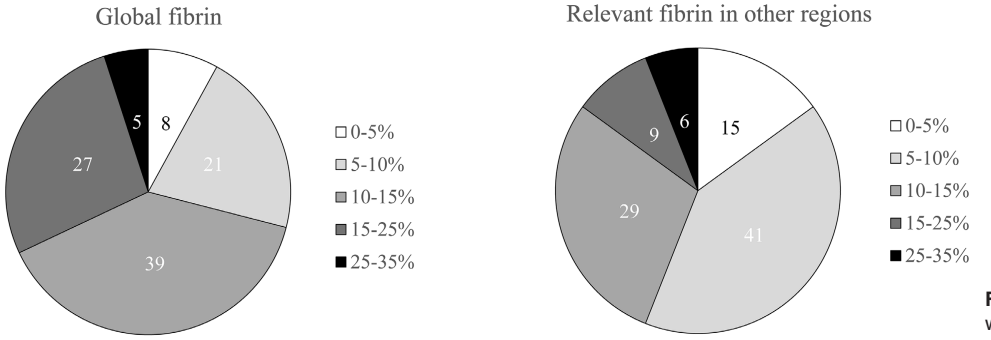
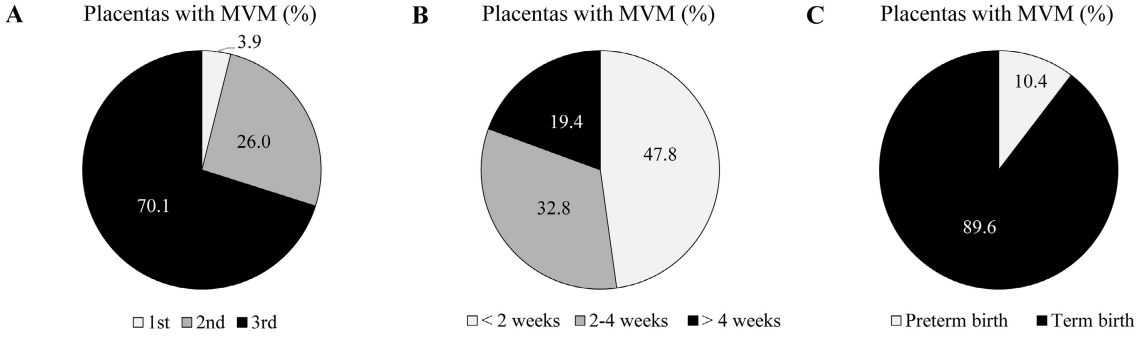


Fig. 7. Percentage of placental samples with fibrin deposits.



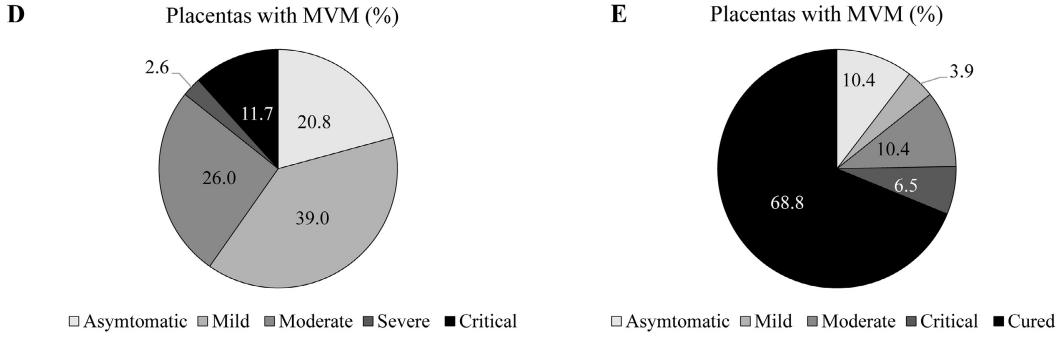


Fig. 8. Percentages of placental samples with characteristics of MVM according to subgroup populations: time of SARS-CoV-2 infection **(A)**, duration of SARS-CoV-2 infection **(B)**, pregnancy duration **(C)**, the severity of SARS-CoV-2 infection **(D)**, presence and severity of SARS-CoV-2 infection **(E)**. Percentages have been calculated in terms of the total number of placental samples affected by MVM (n=77).

villous agglutination) and FVM (17.7% had subchorionic thrombus) in third-trimester placentas of SARS-CoV-2 infected women, but the use of in-situ hybridization (ISH) and immunohistochemistry (IHC) provided no evidence of direct viral involvement or vertical transmission. In the PLAXAVID study, the direct viral involvement cannot be determined since SARS-CoV-2 PCR was not performed in placental tissue. Therefore, whether the observed lesions are a consequence of the placental virus infection or secondary to maternal systemic infection cannot be concluded. Shanes et al. (2020) identified third-trimester placentas presented MVM features compared to historical controls (non-infected), especially abnormal or injured maternal vessels, and intervillous thrombi. However, rates of acute and chronic inflammation did not increase. In contrast, the present study also reported higher rates of chronic than acute inflammatory pathology (49.5% vs. 22.2%). Similarly, the Di Girolamo et al. (2021) systematic review also identified a significant number of placentas with these features but in a similar proportion (22.7% and 25.7% of cases present acute and chronic inflammatory pathology, respectively). Differences between the studies regarding rates of acute and chronic inflammation could be due to the different size samples, much lower in Shanes et al. study.

Controversial results obtained from studies comparing infected and non-infected women's pregnancy outcomes may be a consequence of the limited sample size, heterogeneous inclusion criteria and outcome assessments, or selected control group characteristics. It should be noted that some studies use historical controls in which placental samples frequently referred for the histological study came from pregnancies with obstetric problems (Gulersen et al.,

Table 8. Secondary endpoints related to the newborn distributed according to defined clinical variables.

	Time of infection			Duration of infection			Duration of pregnancy	
	1st Trimester	2nd Trimester	3rd Trimester	<2 weeks	2-4 weeks	>4 weeks	Preterm birth	Term birth
Pregnancy duration (weeks) n=5		n=26	n=68	n=42	n=29	n=15	n=9	n=90
Mean (SD)	38.49 (2.93)	38.78 (2.54)	39.36 (1.91)	39.40 (1.68)	39.20 (2.13)	38.81 (3.65)	34.02 (3.14)	39.62 (1.27)
Median (Q1, Q3)	39.57 (38.71, 39.86)	38.86 (38.14, 40.43)	39.86 (38.57, 40.71)	39.50 (38.43, 41.00)	39.71 (38.71, 40.43)	40.14 (39.29, 40.57)	35.36 (31.79, 36.29)	39.86 (38.71, 40.71)
Min, max	33.40, 40.90	28.40, 41.60	30.10, 41.60	35.10, 41.60	30.10, 41.40	28.40, 41.60	28.40, 36.90	37.00, 41.60
p-value		0.422			0.821		<0.001*	
Newborn weight	n=5	n=26	n=68	n=42	n=29	n=15	n=9	n=90
Mean (SD)	3.13 (1.01)	3.00 (0.75)	3.26 (0.55	3.23 (0.53)	3.32 (0.57)	2.88 (0.98)	1.95 (0.85)	3.31 (0.46)
Median (Q1, Q3)	3.51 (3.16, 3.56)	(2.66, 3.52)	3.31 (3.07, 3.58)	3.28 (2.90, 3.57)	3.46 (3.05, 3.66)	3.19 (2.31, 3.55)	1.52 (1.40, 2.66)	3.29 (3.08, 3.60)
Min, max	1.40, 4.01	1.00, 3.95	1.47, 4.46	1.52, 4.43	1.47, 4.26	1.00, 3.95	1.00, 3.34	2.31, 4.46
p-value		0.200			<0.001*		0.001*	
APGAR 1' test	n=5	n=26	n=68	n=42	n=29	n=15	n=9	n=90
Mean (SD)	9.00 (0.0)	8.54 (1.65)	8.60 (1.34)	8.83 (0.85)	8.62 (1.42)	8.20 (2.11)	7.00 (3.00)	8.77 (1.02)
Median (Q1, Q3)	9.00 (9.00, 9.00)	9.00 (9.00, 9.00)	9.00 (9.00, 9.00)	9.00 (9.00, 9.00)	9.00 (9.00, 9.00)	9.00 (9.00, 9.00)	9.00 (3.00, 9.00)	9.00 (9.00, 9.00)
Min, max	9.00, 9.00	3.00, 10.00	3.00, 9.00	4.00, 10.00	3.00, 9.00	3.00, 9.00	3.00, 9.00	4.00, 10.00
p-value		0.827			0.577		0.005*	
APGAR 5' test	n=5	n=26	n=68	n=42	n=29	n=15	n=9	n=90
Mean (SD)	10.00 (0.00)	9.62 (1.36)	9.76 (0.79)	9.90 (0.43)	9.79 (0.82)	9.33 (1.76)	8.44 (2.35)	9.87 (0.56)
Median (Q1, Q3)	10.00 (10.00, 10.00)	10.00 (10.00, 10.00)	10.00 (10.00, 10.00)	10.00 (10.00, 10.00)	10.00 (10.00, 10.00)	10.00 (10.00, 10.00)	10.00 (6.00, 10.00)	10.00 (10.00, 10.00)
Min, max	10.00, 10.00	5.00, 10.00	6.00, 10.00	8.00, 10.00	6.00, 10.00	5.00, 10.00	5.00, 10.00	7.00, 10.00
p-value		0.793			0.479		0.002*	
Arterial pH	n=5	n=25	n=53	n=37	n=23	n=12	n=8	n=75
Mean (SD)	7.25 (0.06)	7.24 (0.08)	7.21 (0.10)	7.21 (0.09)	7.21 (0.11)	7.22 (0.09)	7.24 (0.07)	7.22 (0.10)
Median (Q1, Q3)	7.23 (7.23, 7.29)	7.22 (7.17, 7.31)	7.22 (7.16, 7.27)	7.22 (7.14, 7.27)	7.23 (7.16, 7.29)	7.21 (7.18, 7.30)	7.24 (7.19, 7.29)	7.22 (7.17, 7.29)
Min, max	7.20, 7.30	7.10, 7.40	6.90, 7.40	7.00, 7.30	6.90, 7.40	7.10, 7.40	7.1, 7.3	6.9, 7.4
p-value		0.555			0.896		0.621	
Venous pH	n=4	n=24	n=50	n=37	n=21	n=11	n=7	n=71
Mean (SD)	7.26 (0.04)	7.31 (0.06)	7.28 (0.07)	7.29 (0.07)	7.28 (0.07)	7.27 (0.08)	7.30 (0.04)	7.29 (0.07)
Median (Q1, Q3)	7.24 (7.24, 7.28)	7.32 (7.27, 7.35)	7.30 (7.27, 7.32)	7.31 (7.27, 7.34)	7.28 (7.24, 7.33)	7.31 (7.23, 7.32)	7.32 (7.27, 7.34)	7.30 (7.24, 7.34)
Min, max	7.20, 7.30	7.20, 7.40	7.10, 7.40	7.10, 7.40	7.10, 7.40	7.10, 7.30	7.2, 7.4	7.1, 7.4
p-value		0.102			0.574		0.611	

2020). Most of these studies did not assess the observed histological lesions according to different clinical parameters such as is considered in the PLAXAVID study (e. g. duration of the COVID disease, time of infection in pregnancy, or severity of the condition at delivery).

Furthermore, the PLAXAVID study has found some specific correlations between vascular, inflammatory lesions and SARS-CoV-2 infection characteristics. Although no studies specifically analyzed the impact of COVID-19 infection characteristics in placental histopathology, some published data have pointed out that the timing of infection concerning delivery may alter placental pathology, increasing the risk of thromboembolic events affecting fetal health. In addition to a higher proportion of FVM among women infected by SARS-Cov-2, Glynn et al. (2022) reported a relationship between the time of infection and the occurrence of FVM. These lesions were found in higher proportion when the infection was proximate (less than 14 days) to delivery. Another study performed on pregnant women with mild or no symptoms of COVID-19 also identified placental injury at a microscopic level (Jaiswal et al., 2021). Nonetheless, this injury did not lead to poor outcomes. Along the same line, a cohort study suggested that maternal COVID-19 symptoms did not predict the severity of placental injuries (Husen et al., 2021). Therefore, further studies are needed to identify the relationships between the SARS-CoV-2 infection characteristics and placental lesions. It is also important to emphasize the necessary monitoring of women infected during pregnancy.

Table 8. (Continuation).

	Severity at the time of diagnosis					Diagnosis and Severity at the time of delivery				
	Asymp.	Mild	Moderate	Severe	Critical	Asymp.	Mild	Moderate	Critical	Healed
Pregnancy duration (weeks)	n=23	n=38	n=23	n=4	n=11	n=15	n=4	n=9	n=6	n=65
Mean (SD)	39.68 (1.77)	39.51 (1.72)	39.35 (1.25)	38.11 (1.13)	36.63 (4.02)	39.57 (1.83)	39.43 (2.50)	39.29 (1.15)	34.34 (4.70)	39.41 (1.56)
Median (Q1, Q3)	40.21 (39.07, 41.07)	39.93 (38.71, 40.71)	39.57 (38.43, 40.57)	38.07 (37.14, 39.07)	38.07 (36.71, 38.86)	40.14 (38.86, 41.14)	40.14 (37.79, 41.07)	39.29 (38.57, 40.00)	36.71 (30.14, 37.86)	39.71 (38.57, 40.57)
Min, max	35.10, 41.40	33.40, 41.60	37.00, 41.40	37.00, 39.30	28.40, 40.60	35.10, 41.40	35.90, 41.60	37.70, 41.40	28.40, 38.60	33.40, 41.60
p-value			0.008*					0.032*		
Newborn weight	n=23	n=38	n=23	n=4	n=11	n=15	n=4	n=9	n=6	n=65
Mean (SD)	3.24 (0.51)	3.30 (0.52)	3.27 (0.59)	3.21 (0.43)	2.48 (0.96)	3.22 (0.36)	3.32 (0.63)	3.45 (0.57)	1.96 (0.95)	3.25 (0.55)
Median (Q1, Q3)	3.34 (3.13, 3.46)	3.29 (3.10, 3.66)	3.30 (2.90, 3.61)	3.22 (2.93, 3.48)	2.66 (1.47, 3.25)	3.28 (2.85, 3.41)	3.43 (2.89, 3.75)	3.22 (3.08, 3.85)	1.90 (1.00, 2.72)	3.28 (3.01, 3.60)
Min, max	1.52, 4.06	1.40, 4.26	2.31, 4.46	2.67, 3.71	1.00, 3.68	2.66, 4.06	2.47, 3.95	2.63, 4.46	1.00, 3.25	1.40, 4.43
p-value			0.003*					<0.001*		
APGAR 1' test	n=23	n=38	n=23	n=4	n=11	n=15	n=4	n=9	n=6	n=65
Mean (SD)	8.78 (1.04)	8.89 (0.83)	8.91 (0.42)	9.00 (0.00)	6.45 (2.81)	8.67 (1.29)	9.00 (0.00)	9.00 (0.00)	4.50 (2.35)	8.89 (0.69)
Median (Q1, Q3)	9.00 (9.00, 9.00)	9.00 (9.00, 9.00)	9.00 (9.00, 9.00)	9.00 (9.00, 9.00)	8.00 (3.00, 9.00)	9.00 (9.00, 9.00)	9.00 (9.00, 9.00)	9.00 (9.00, 9.00)	3.50 (3.00, 5.00)	9.00 (9.00, 9.00)
Min, max	4.0, 9.0	4.0, 10.0	7.0, 9.0	9.0, 9.0	3.0, 9.0	4.0, 9.0	9.0, 9.0	9.0, 9.0	3.0, 9.0	4.0, 10.0
p-value			<0.001*					<0.001*		
APGAR 5' test	n=23	n=38	n=23	n=4	n=11	n=15	n=4	n=9	n=6	n=65
Mean (SD)	9.91 (0.42)	9.95 (0.32)	9.91 (0.42)	10.00 (0.00)	8.18 (2.18)	9.87 (0.52)	10.00 (0.00)	10.00 (0.00)	6.67 (1.86)	9.94 (0.35)
Median (Q1, Q3)	10.00 (10.00, 10.00)	10.00 (10.00, 10.00)	10.00 (10.00, 10.00)	10.00 (10.00, 10.00)	10.00 (6.00, 10.00)	10.00 (10.00, 10.00)	10.00 (10.00, 10.00)	10.00 (10.00, 10.00)	6.50 (5.00, 7.00)	10.00 (10.00, 10.00)
Min, max	8.0, 10.0	8.0, 10.0	8.0, 10.0	10.0, 10.0	5.0, 10.0	8.0, 10.0	10.0, 10.0	10.0, 10.0	5.0, 10.0	8.0, 10.0
p-value			< 0.001*					<0.001*		
Arterial pH	n=19	n=34	n=19	n=3	n=8	n=12	n=4	n=4	n=4	n=59
Mean (SD)	7.23 (0.08)	7.21 (0.09)	7.22 (0.10)	7.24 (0.05)	7.22 (0.14)	7.24 (0.08)	7.28 (0.07)	7.29 (0.05)	7.25 (0.08)	7.20 (0.10)
Median (Q1, Q3)	7.24 (7.17, 7.28)	7.21 (7.17, 7.27)	7.22 (7.14, 7.31)	7.21 (7.21, 7.30)	7.26 (7.18, 7.33)	7.26 (7.23, 7.28)	7.28 (7.22, 7.34)	7.31 (7.26, 7.33)	7.26 (7.19, 7.30)	7.21 (7.14, 7.27)
Min, max	7.0, 7.4	7.0, 7.4	7.0, 7.3	7.2, 7.3	6.9, 7.4	7.0, 7.4	7.2, 7.4	7.2, 7.3	7.1, 7.3	6.9, 7.4
p-value			0.904					0.087		
Venous pH	n=19	n=34	n=15	n=3	n=7	n=11	n=4	n=2	n=3	n=58
Mean (SD)	7.28 (0.06)	7.29 (0.07)	7.28 (0.07)	7.32 (0.07)	7.28 (0.08)	7.29 (0.07)	7.33 (0.04)	7.30 (0.08)	7.31 (0.03)	7.28 (0.07)
Median (Q1, Q3)	7.30 (7.27, 7.32)	7.31 (7.26, 7.34)	7.28 (7.23, 7.34)	7.36 (7.24, 7.37)	7.28 (7.26, 7.34)	7.30 (7.27, 7.33)	7.34 (7.30, 7.37)	7.30 (7.24, 7.35)	7.32 (7.28, 7.34)	7.30 (7.24, 7.33)
Min, max	7.1, 7.4	7.1, 7.4	7.1, 7.4	7.2, 7.4	7.1, 7.4	7.1, 7.4	7.3, 7.4	7.2, 7.4	7.3, 7.3	7.1, 7.4
p-value			0.706					0.565		

FVM: fetal vascular malperfusion; HAV: hyalinized avascular villi; MVM: maternal vascular malperfusion; Q: quartile; SD: standard deviation; VSK: villous stromal-vascular karyorrhexis. *Statistically significant according to Fisher's exact test.

Clinical implications of placental vascular alterations on neonatal and pregnancy outcomes are not fully known. MVM has been associated with preterm birth, fetal growth restriction and fetal death (Shanes et al., 2020; Wong et al., 2021) and FVM has been related to fetal growth restriction, fetal CNS injury, and stillbirth (Redline and Ravishankar, 2018). The results obtained in the analysis of neonatal characteristics according to the defined subgroups have shown that the severity of COVID-19 disease and its presence at the time of delivery has a significant impact on neonatal characteristics, especially in newborn weight and APGAR test. Only one neonate was COVID-19 positive after PCR testing, confirming vertical transmission of the virus is uncommon (Jeganathan and Paul, 2022). Regarding the duration of pregnancy, preterm birth seems to be related to COVID-19 severity. The literature is not clear regarding the effect of SARS-CoV-2 infection on pregnancy duration. Indeed, a systematic review showed a reduction in preterm birth since the pandemic outbreak, although this reduction was only noted in single-center studies, which may indicate a referral bias (Yang et al., 2022).

The main strength of PLAXAVID study is that it contributes to generating clinical evidence about COVID-19 as a risk factor for poor obstetric outcomes, and its observations are aligned with recent Spanish recommendations of Thromboembolism Prophylaxis in Pregnancy and Puerperium and COVID-19 (SETH, 2022). This guideline highlights the relevance of considering COVID-19 in pregnant women as an important risk factor for thrombosis, which along with the PLAXAVID study results (high rates of MVM) reinforces the need of considering thromboprophylaxis (mainly with Low-molecular-weight heparins (LMWH) during pregnancy in these patients. Moreover, samples collected at referral centers for pregnant women with COVID-19 will allow the analysis of the virus behavior in pregnancy and postpartum in a representative cohort of the Spanish population. The descriptive analysis of samples from the Gesta-COVID19 results presented here can contribute to increasing knowledge of the COVID-19 impact on placental histopathology and, therefore, identify the potential risks to maternal and neonatal outcomes.

However, the study is not without limitations. The lack of a control group limits the interpretation of the obtained results which should be only descriptively interpreted. Nonetheless, the study sample size is larger than other studies and COVID-19 cases during the second and third trimesters are high. Thus, our findings can complement the evidence reported by other case series. Furthermore, COVID-19 vertical transmission cannot be determined since no PCR on placental samples was performed. However, observed placental lesions may be an argument in favor of the risk of vertical transmission of the infection. Moreover, it should be considered that samples and clinical data were obtained during the first months of the pandemic, before the protocolization of COVID-19 diagnosis. Nor were indicated treatments established or standardized and depended on medical criteria. On the other hand, the precise placental weight, which might be a good indicator of MVM severity, had to be eliminated for the analysis because placental samples were not uniformly collected. Nonetheless, in general, identified cases of MVM corresponded to those usually considered at low severity, considering that cases with a weight under the 3rd percentile were few despite their non-uniform collection.

Conclusions

PLAXAVID study reports a high percentage of inflammatory and vascular alterations in analyzed samples, especially signs of MVM, FVM, and chronic inflammatory pathology. The most prevalent histopathological features were lesions suggestive of infarcts, HAV foci, and placental thrombi that indicate placental oxygenation alteration. Moreover, the presence of ischemic and thrombotic placental lesions reported in the study, supports the need of considering thromboprophylaxis use with Low-Molecular-Weight Heparins during pregnancy in those women infected by SARS-CoV-2. Samples included in this first case series report are for women infected during the pandemic's first months. Therefore, data corresponds to the first wave of the COVID-19 pandemic in Spain, when the infection was more lethal and aggressive. PLAXAVID study, thus, contributes to generating clinical evidence about the effect of SARS-CoV-2 infection in placental histopathology and underpins that COVID-19 is a risk factor for a poor obstetrical outcome sustaining the need for close monitoring of pregnant women and fetuses.

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