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Original contribution

# Severe placental lesions due to maternal SARS-CoV-2 infection associated to intrauterine fetal death<sup>☆</sup>



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**Summary** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can cause severe placental lesions leading rapidly to intrauterine fetal death (IUFD). From August 2020 to September 2021, in the pathology department of Toulouse Oncopole, we analyzed 50 placentas from COVID-19-positive unvaccinated mothers.

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## COVID-19 placental lesions

The purpose of our study is to describe the clinicopathological characteristics of these placental damages and to understand the pathophysiology.

Ten of them (20%) showed placental lesions with positive immunohistochemistry for SARS-CoV-2 in villous trophoblasts. In five cases (10%), we observed massive placental damage associating trophoblastic necrosis, fibrinous deposits, intervillitis, as well as extensive hemorrhagic changes due to SARS-CoV-2 infection probably responsible of IUFD by functional placental insufficiency. In five other cases, we found similar placental lesions but with a focal distribution that did not lead to IUFD but live birth.

These lesions are independent of maternal clinical severity of COVID-19 infection because they occur despite mild maternal symptoms and are therefore difficult to predict. In our cases, they occurred 1–3 weeks after positive SARS-CoV-2 maternal real-time polymerase chain reaction testing and were observed in the 2nd and 3rd trimesters of pregnancies. When these lesions are focal, they do not lead to IUFD and can be involved in intrauterine growth restriction.

Our findings, together with recent observations, suggest that future pregnancy guidance should include stricter pandemic precautions such as screening for a wider array of COVID-19 symptoms, enhanced ultrasound monitoring, as well as newborn medical surveillance.

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## 1. Introduction

Vertical transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and pregnancy complications induction are serious concerns for pregnant individuals with COVID-19. Based on early RNA detection of SARS-CoV-2 after birth, vertical transmission's incidence of SARS-CoV-2 has been estimated to occur in around 2–3% of neonates [1,2]. The short- and long-term consequences of this infection on the newborn are still poorly understood. However, even if a neonate tests negative for SARS-CoV-2, different abnormal placental findings have been reported in cases of COVID-19–positive mothers [3]. Since the beginning of the pandemic, many nonspecific placental lesions have been described, including fetal and maternal vascular malperfusion, or chorioamnionitis, all negative in immunohistochemistry with the anti–SARS-CoV-2 antibody [4]. On the other hand, lesions characterized by trophoblastic necrosis, fibrinous deposits, and intervillitis are more suggestive of viral involvement and can lead to IUFD [5].

The purpose of our study is to describe the clinicopathological characteristics of placental damages associated with SARS-CoV-2 maternal infection in 50 placentas from COVID-19–positive unvaccinated mothers and to understand the pathophysiology. Histopathological findings are heterogeneous. Among positive SARS-CoV-2 placentas, specific histological findings are extremely variable in intensity from diffuse placental hemorrhagic lesions to focal perivillous fibrin deposition lesions possibly sequelar. In 10% of cases, lesions are diffuse and associated to an increase of IUFD in the 2nd and 3rd trimester of pregnancy.

## 2. Materials and methods

From August 2020 to September 2021, in the pathology department of Toulouse Oncopole (attached to the biggest maternity unit in Occitania [south of France] with more than 5000 births a year), we analyzed fifty placentas from COVID-19–positive unvaccinated mothers. Forty of them were normal or nonspecific at histological examination, whereas 10 of them showed particular abnormal histological signs reported here.

### 2.1. Immunohistochemistry

Automated classical immunohistochemical (IHC) stains were performed using the Benchmark ULTRA (Roche, Ventana Medical Systems, Innovation Park Drive Tucson, Arizona 85755, USA) on formalin-fixed and paraffin-embedded (FFPE) tissue sections (3  $\mu$ m). After dewaxing, tissue slides were heat pretreated using a CC1 (pH8) buffer (05424569001, Roche) for 64 min at 98 °C. The slides were blocked for endogenous peroxidase activity and incubated with primary anti–2019-nCoV Spike rabbit polyclonal (A20022, ABclonal, Diagomics, Blagnac, France) (1/100 in Envision FLEX antibody diluent, K800621-2, Agilent, Santa Clara, CA 95051, USA) and anti–SARS-CoV-2 nucleocapsid mouse monoclonal (Ready to Use, clone BSB-134, BioSB, Diagomics, Blagnac, France) antibodies for 64 and 92 min, respectively. Targets were then visualized using the OptiView DAB detection kit (06396500001, Roche). The tissue slides were counterstained using hematoxylin (05277965001, Roche) for 8 min followed by postcoloration using Bluing

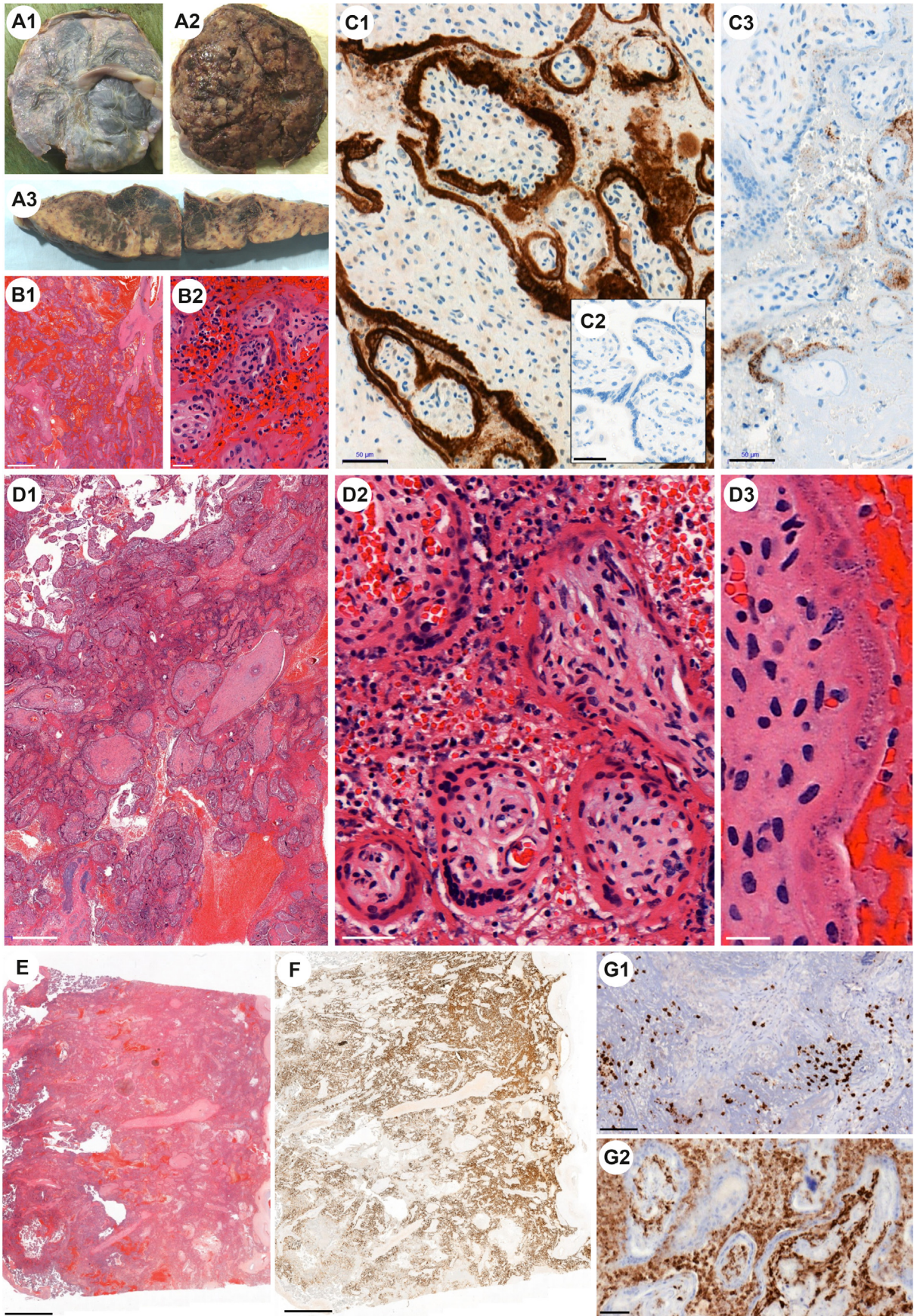
**Table 1** Pregnancy outcome and maternal and placental characteristics.

Cases	Age of onset of maternal symptoms (WoG)	Term of delivery (WoG)	Time between maternal symptoms and delivery (days)	Pregnancy outcome	Maternal symptoms	Fetal weight (g)	Fetal weight (percentile)	Histological placental lesions
1	32	34 + 1	15	IUFD	Influenza-like illness + hyperthermia	1640	3-5th	Diffuse TN + intervillitis + PFD + IH
2	21	23	14	IUFD	Influenza-like illness	585	<3rd	Diffuse TN + intervillitis + PFD + IH
3	18 + 4	19 + 4	7	IUFD	Influenza-like illness	240	<3rd	Diffuse TN + intervillitis + PFD + IH
4	19 + 3	21	11	IUFD	Hyperthermia	380	10-25th	Diffuse TN + intervillitis + PFD + IH
5	34	36 + 6	20	IUFD	Influenza-like illness	2990	50th	Diffuse TN + intervillitis + PFD + IH
6	unknown	38 + 5	unknown	Cesarean section for bradycardia and preeclampsia live newborn	Hyperthermia	2440	<5th	Focal TN + intervillitis + PFD
7	30	33	21	Cesarean section live newborn	Influenza-like illness	1940	20-50th	Focal TN + intervillitis + PFD
8	33	33	0	Cesarean section live newborn	Influenza-like illness	1730	30th	Focal TN + intervillitis + PFD
9	35	37 + 3	18	Cesarean section live newborn	Asymptomatic	2465	10-25th	Focal TN + intervillitis + PFD
10	35 + 4	40 + 4	35	Vaginal delivery live newborn	Hyperthermia	2860	5-10th	Focal TN + intervillitis + PFD
11	32	39	49	Vaginal delivery live newborn	Influenza-like illness	2550	3-5th	MVM
12	25	36 + 5	82	Vaginal delivery live newborn	Hypoxemic pneumonia	4250	95th	Normal
13	31	32	7	Cesarean section live newborn	Hypoxemic pneumonia	1800	70th	Normal
14	32	33	7	Cesarean section live newborn	Influenza-like illness	1700	30th	Normal
15	31 + 3	37	45	Cesarean section live newborn	Asymptomatic	3100	>75th	Normal
16	30	30 + 5	5	Cesarean section live newborn	Hypoxemic pneumonia	1600	>50th	MVM
17	39	41	14	Vaginal delivery live newborn	Asymptomatic	4210	>95th	MVM
18	35	39 + 4	32	Vaginal delivery live newborn	Asymptomatic	3350	>95th	Normal
19	38 + 2	39 + 2	7	Cesarean section live newborn	Unknown	2890	25th	Normal
20	29 + 2	30	5	Cesarean section live newborn	Hypoxemic pneumonia	1620	>75th	Chorangiosis
21	28	28 + 2	2	Cesarean section live newborn	Hypoxemic pneumonia	1100	>50th	Chorangiosis

22	37	39 + 1	15	Vaginal delivery live newborn	Unknown	2250	<3rd	MVM
23	35	38 + 1	22	Vaginal delivery live newborn	Hypoxemic pneumonia	3350	>75th	Normal
24	33 + 2	34 + 1	6	Cesarean section live newborn	Hypoxemic pneumonia	1935	>25th	MVM
25	13	40 + 6	195	Vaginal delivery live newborn	Influenza-like illness	2680	<3rd	MVM
26	34 + 2	41 + 5	46	Vaginal delivery live newborn	Hypoxemic pneumonia	3300	25th	Normal
27	28	33 + 3	38	Vaginal delivery live newborn	Unknown	2130	>75th	MVM
28	25	40 + 4	109	Vaginal delivery live newborn	Influenza-like illness	3730	59th	Normal
29	34 + 3	39 + 4	36	Vaginal delivery live newborn	Unknown	3120	>25th	MVM
30	26	38 + 2	86	Vaginal delivery live newborn	Unknown	2990	47th	Normal
31	31 + 4	32 + 6	9	Vaginal delivery live newborn	Hypoxemic pneumonia	1505	25th	FVM
32	Unknown	29	Unknown	Vaginal delivery live newborn	Unknown	1230	>50th	Chorioamnionitis
33	34 + 5	34 + 6	1	Cesarean section live newborn	Asymptomatic	2350	>25th	MVM
34	17	18 + 5	12	Twins pregnancy: miscarriage	Unknown	120 and 240	10th and >50th	Chorioamnionitis
35	36	39	21	Vaginal delivery live newborn	Asymptomatic	3840	>95th	Normal
36	21	38	119	Vaginal delivery live newborn	Influenza-like illness	3715	>95th	MVM
37	32	39	49	Vaginal delivery live newborn	Influenza-like illness	3440	>50th	Normal
38	33 + 1	41	55	Vaginal delivery live newborn	Unknown	4200	90th	MVM + chorioamnionitis
39	31	37	42	Vaginal delivery live newborn	Unknown	3390	>75th	Normal
40	4	41	259	Vaginal delivery live newborn	Influenza-like illness	Unknown	x	Normal
41	10	39 + 6	209	Vaginal delivery live newborn	Unknown	3090	20th	Focal intervillitis
42	28	39	77	Vaginal delivery live newborn	Influenza-like illness	3470	47th	Chorioamnionitis
43	4	39	245	Vaginal delivery live newborn	Unknown	3600	75th	Normal
44	34 + 3	39 + 4	36	Vaginal delivery live newborn	Unknown	3120	25th	MVM
45	18 + 5	28 + 5	70	Vaginal delivery live newborn	Unknown	1030 and 1220	25th and 50th	MVM
46	34	40 + 4	46	Vaginal delivery live newborn	Unknown	3470	60th	Chorioamnionitis
47	32	40 + 2	58	Vaginal delivery live newborn	Unknown	Unknwon	X	MVM + chorioamnionitis
48	13	23 + 3	73	Miscarriage	430	NA	X	MVM + chorioamnionitis
49	20 + 3	40 + 3	143	Vaginal delivery live newborn	Unknown	3260	40th	MVM + chorioamnionitis
50	24	39 + 5	110	Vaginal delivery live newborn	Unknown	3260	25th	MVM

Abbreviations: IUFD, intrauterine fetal death; TN, trophoblastic necrosis; PFD, perivillous fibrin deposition; IH, intervillous hemorrhage; MVM, maternal vascular malperfusion; FVM, fetal vascular malperfusion.







reagent for 4 min at room temperature (05266769001, Roche). The slides were then dehydrated (ethanol and xylene) and mounted using xylene-based mounting (TissueTek Prisma®, Sakura Finetek Europe B.V., The Netherlands).

## 2.2. SARS-CoV-2 real-time polymerase chain reaction

SARS-CoV-2 genomic RNA was detected on the specimen taken by nasopharyngeal swabs by Hologic Aptima SARS-CoV-2 transcription-mediated amplification on the Panther instrument as recommended by the manufacturer. For SARS-CoV-2 genomic RNA detection on placenta, samples were crushed and nucleic acids extracted using MagNA Pure 96 small volume protocol (Roche Diagnostics). The targets were localized on the RNA-dependent polymerase gene (IP2 and IP4, Institut Pasteur, Paris, France). Amplification and real-time detection were performed using qScript XLT 1-step RT-qPCR ToughMix (Quantabio, VWR International SAS, France) on Light Cycler 480 (Roche Diagnostics).

## 3. Results

In our study, 40 of the 50 placentas analyzed showed histological findings either normal ( $n = 16/40$ , 40%) or with various nonspecific lesions as previously described in the literature [4,6,7] such as fetal vascular malperfusion ( $n = 1/40$ ) and maternal vascular malperfusion ( $n = 17/40$ , 42,5%), chorioamnionitis ( $n = 8/40$ , 20%), or focal intervillitis ( $n = 1/40$ ) (Table 1) according to the Amsterdam Placental Consensus classification [8]. All these cases were negative with anti-SARS-CoV-2 antibody and real-time polymerase chain reaction (RT-PCR) in the placenta. Thirty-eight of them were associated with live births; the two other cases were late miscarriages, one associated with a monochorial diamniotic twin pregnancy with transfused transfusion syndrome and one in a context of septate uterus with a history of multiple miscarriages.

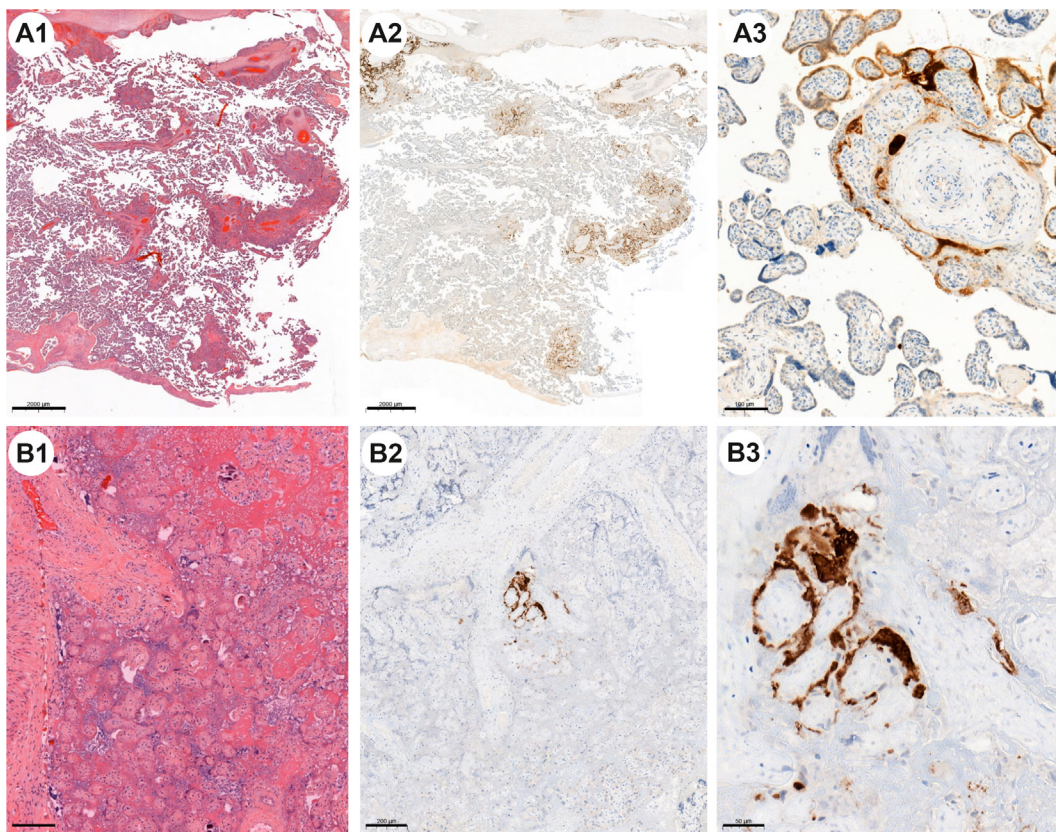
Among the 10 cases with significant placental lesions, five were associated with IUFD, whereas the other five were associated with live birth.

Five of the ten patients (Cases n°1–5) were hospitalized in our department for IUFD discovered between 19 weeks of gestation (WoG) and 36 + 6 WoG. None of them had a medical history. The pregnancy was marked by maternal COVID-19 infection between 18 + 4 WoG and 34 WoG, therefore between 1 and 3 weeks before IUFD occurred. Maternal symptoms were unspecific and mild, mainly hyperthermia (detailed in Table 1). Interestingly, three of them were tested for SARS-CoV-2 by nasopharyngeal swabs not because of symptoms suggestive of COVID but because they were considered contact cases. All five patients presented in our emergency unit for decreased fetal movements. Ultrasound examination discovered IUFD with a variable estimated fetal weight from <3rd percentile to 50th percentile. The standard IUFD examinations (CGH array, CMV, and Parvovirus B19 research in amniotic fluid, as well as maternal autoimmune tests excluding other causes of IUFD) were negative in the five cases. Placental bacteriology came back negative as well. All five placentas weighed within 10th-25th percentile for reference ranges. Cross-placental examination revealed unusual diffuse macroscopic lesions, characterized by several intraplacental and subchorial hematoma, dissociating the placenta tissue (Fig. 1, A3). These lesions involved at least 80% of the parenchyma.

Histologically, lesions were characterized by massive hemorrhagic inundation of intervillous space and extensive villous trophoblastic necrosis (Fig. 1, B1, D1-2, E). Surrounding the villi, chronic intervillitis and fibrin deposits were present (Fig. 1, B2, E2). Polymorphonuclears were observed, owing to hemorrhagic lesions. At high magnification, villous trophoblasts showed signs of cellular injury including karyorrhexis, fragmentation of trophoblast nuclei, and clearing of cytoplasm (Fig. 1, D3). Neither intravillous inflammation nor vascular thrombosis in villous capillaries was detected.

Viral immunostaining with SARS-CoV-2 antibodies (anti-SARS-CoV-2 nucleocapsid antibody and anti-SARS-CoV-2-spike antibody) was positive in syncytiotrophoblasts, cytotrophoblasts, but not endothelial cells (Fig. 1, C1-3, F). Intense positive cytoplasmic staining was

**Fig. 1 Case n°1:** No significant macroscopic placental lesions on the chorionic **A1** and basal **A2** plates. **A3** Unusual diffuse macroscopic lesions, characterized by several intraplacental and subchorial hematoma, dissociating the placental tissue. **B1** Diffuse intervillous hemorrhagic lesions associated with extensive trophoblast necrosis and chronic intervillitis. Hematoxylin and eosin (H&E) staining. **B2** Trophoblast necrosis and chronic intervillitis. H&E. **C1** Brown staining at the periphery of the chorionic villi represents trophoblast infection identified by immunohistochemistry (IHC) using SARS-CoV-2 nucleocapsid protein antibody. Few inflammatory cells in the intervillous space show also positive staining. **C2** Negative control (patient COVID + with no placental lesion), IHC with anti-SARS-CoV-2 nucleocapsid antibody show no positivity. **C3** IHC with anti-SARS-CoV-2-spike antibody show patchy granular cytoplasmic staining. **Case n°2:** Both **D1** (H&E) and **D2** (H&E) show massive hemorrhagic inundation of intervillous space and extensive villous trophoblast necrosis. Surrounding the villi, chronic histiocytic intervillitis and fibrin deposits are observed as well as several polynuclear. **D3** (H&E) Villous trophoblast shows signs of cellular injury including karyorrhexis, fragmentation of trophoblast nuclei, and clearing of the cytoplasm. **Case n°3:** **E** Microscopic aspects comparable to cases 1 and 2 (H&E). **F** IHC with anti-SARS-CoV-2 nucleocapsid antibody is highly positive in necrosis trophoblast. Intervillous inflammatory infiltrate **G1** with both T lymphocytes (IHC with CD3 antibody) and **G2** monocytic cells (IHC with CD68 antibody).



**Fig. 2** Case n°9: **A1** (H&E) multifocal lesions occupying less than 30% of the placental parenchyma. **A2** and **A3** IHC with anti-SARS-CoV-2 nucleocapsid antibody is highly positive. Some areas show strong diffuse staining of the trophoblast (facing necrosis trophoblast) contrasting with negative nonaffected villi (facing preserved trophoblast). Case n°10: **B1** (H&E) massive perivillous fibrin deposition with villous infarctions and without significant inflammatory infiltrate. **B2** and **B3** IHC with anti-SARS-CoV-2 nucleocapsid antibody. Note residual and focal immunostaining on this more fibrinous lesion.

observed in villous trophoblasts with anti-SARS-CoV-2 nucleocapsid (N) antibody (Fig. 1, C1, F). Immunostaining with anti-SARS-CoV-2-spike (S) antibody showed granular cytoplasmic staining (Fig. 1, C3). Detection of SARS-CoV-2 RNA in placenta confirmed these results with low cycle threshold (Ct < 20) in favor of high levels of genomic SARS-CoV-2 RNA.

Associated chronic intervillous inflammatory infiltrate was characterized by abundant presence of T lymphocytes (CD3 +, with no predominance of neither CD4+ nor CD8+ T-cell subsets) and CD68+ monocytic cells. Few mononuclear cells circulating in maternal vascular space also showed strong positivity with anti-SARS-CoV-2 nucleocapsid (N) antibody.

Among these five cases, two fetuses were autopsied and none had visceral malformation, nor visceral (lung, kidney, heart) positive SARS-CoV-2 immunostaining.

The five other cases (cases n°6–10) showed similar lesions associating trophoblastic necrosis, fibrinoid deposits, and intervillitis but focally located with less than 30% of the parenchyma involved (Fig. 2, A1). Immunostaining with anti-SARS-CoV-2 nucleocapsid (N) antibody showed positive cytoplasmic staining only located in pathological villous trophoblasts (Fig. 2, A2, A3). Likewise, the

lymphohistiocytic infiltrate demonstrated by anti-CD3 and CD68 antibodies was limited to the lesion areas.

One case (n°10) was particularly interesting because placental histological examination showed pathological foci characterized by perivillous fibrin deposition surrounding necrotic villi. These lesions were less inflammatory with more fibrin deposits, in the process of organization. Immunohistochemical anti-SARS-CoV-2 staining was not diffusely detected in trophoblasts as observed in other cases, but was only very focally present (Fig. 2, B1, B2, B3). Clinically, the time from maternal infection to childbirth was more than 2 months.

## 4. Discussion

### 4.1. Placenta's pathological lesions

In cases of maternal SARS-CoV-2 infection, most of the placental histopathological lesions largely reported were nonspecific such as fetal vascular malperfusion, maternal vascular malperfusion, chorangiosis, chorioamnionitis, and villitis [4,6,7]. Indeed 40 of the 50 placentas analyzed in our study (80%) showed histological findings either normal



or with various nonspecific lesions as previously described in the literature, and all these cases were negative with anti-SARS-CoV-2 antibody and RT-PCR.

However, 10 of the 50 placentas analyzed showed specific placental lesions directly linked to SARS-CoV-2 infection because all were positive with anti-SARS-CoV-2 antibody and SARS-CoV-2 RT-PCR. Depending on their intensity, these lesions had variable consequences on pregnancy outcome ranging from intrauterine growth restriction (IUGR) to IUFD by functional placental insufficiency.

#### 4.1.1. Placental damages linked to SARS-CoV-2 infection associated to IUFD

In five cases (cases n°1–5), placental damage was diffuse, involving at least 80% of parenchyma. Lesions were characterized by unusual massive hemorrhagic inundation of intervillous space and extensive villous trophoblastic necrosis associated with chronic intervillitis and fibrin deposits. Placental lesions observed in our cases were in agreement with the few IUFD cases described in literature but were additionally characterized by multiple intraplacental hemorrhagic lesions associated with extensive trophoblastic necrosis and chronic intervillitis [5,9,10]. The trophoblastic necrosis showed disappearance of trophoblastic cytoplasmic membranes, enlarged nuclei often vesicular with diffuse fine chromatin, or fragmentation of trophoblast nuclei possibly suggestive of viral toxicity of SARS-CoV-2 infection (Fig. 1, D3). This was supported by immunohistochemical studies showing positivity of villous trophoblast with SARS-CoV-2 antibodies. Otherwise, decidual arteriopathy was not seen but rather hemorrhagic changes dissociating the decidua, which is in agreement with literature [11]. Unlike other authors, we did not find fetal vascular thrombi [12].

The fact that these lesions were unusually intense and largely diffuse, both inflammatory and hemorrhagic, seems sufficient to explain functional placental insufficiency and its involvement in the fetal death due to placental destruction, especially because the IUFD assessment was negative.

On the clinical level, these lesions were observed between the 7th day and the 20th day after maternal infection occurred which is in agreement with the observation in the literature [11].

It is interesting to point out that hemorrhagic changes were especially marked in the diffuse placental damage associated to poor fetal outcome. These hematomas because of their intensity are unusual and cannot be explained by caesarian section.

Interestingly, Flores et al. analyzed the impact of COVID-19 infection on placental endothelium, by analyzing expression of von Willebrand factor (vWf), claudin-5, and vascular endothelial cadherin (VEC) in placentas of women with severe COVID-19 [13]. Their results showed an increase in the expression of vWf, suggesting the existence of a vascular thrombotic condition, and a decreased expression

of both claudin-5 and VEC. Thus, enhanced vessel permeability is possibly responsible for a possible breach in the maternal–fetal interface leading to hemorrhages in the decidua and the intervillous space.

In the setting of adults SARS-CoV-2 infections, hemorrhagic lesions affecting other different organs have also been described such as hemorrhagic colitis [14], hemorrhagic pericardial effusion with tamponade [15], and hemorrhagic encephalopathy related to blood–brain barrier breakdown [16,17]. Some authors have suggested that these lesions are the result of a cytokine storm syndrome responsible for widespread microvascular injury [18].

#### 4.1.2. Focal lesions linked to SARS-CoV-2 infection

In five other cases (cases n°6–10), lesions were focal or plurifocal mainly associated with IUGR and involved less than 30% of the parenchyma. On microscopic examination, several focal lesions were observed, still characterized by trophoblastic necrosis, chronic histiocytic intervillitis, and perivillous fibrin deposition, contrasting with nonlesional areas. Hemorrhagic changes were absent or rare.

Immunohistochemistry with anti-SARS-CoV-2 antibody was in agreement with the histological aspect and showed diffuse trophoblastic positivity in the lesion foci, whereas no positivity was noted elsewhere.

Interestingly, in case 10, the time from maternal infection to childbirth was more than 2 months, which is much longer than the 3 weeks observed in IUFD cases. This could suggest that lesions induced by SARS-CoV-2 infection evolve over time with only focal or even negative immunostaining for SARS-CoV-2, making the histological diagnosis of SARS-CoV-2 infection difficult.

#### 4.2. SARS-CoV-2 vertical transmission

Among placentas and neonates tested for SARS-CoV-2 infection, a minority of neonates (2–3%) and placental samples (around 20%) tested positive for SARS-CoV-2 infection from the infected mother. This is what we have as well in our study because 10 of the 50 placentas tested positive for SARS-CoV-2 (20%) [19].

On reminder, SARS-CoV-2 infects tissues via its receptor angiotensin-converting enzyme 2 (ACE2), and its entry into cells requires spike protein cleavage by the serine protease TMPRSS2. ACE2 is highly expressed in maternal–fetal interface cells, such as syncytiotrophoblasts and cytotrophoblasts from 7 weeks onward and across gestation with similar intensity and distribution of ACE2 staining [20,21]. It is believed that high cellular coexpression of ACE2 (allowing virus attachment in cells) and TMPRSS2 (allowing virus penetration in cells) is required for viral transmission [22]. However, this rare coexpression in placenta could explain the high heterogeneity of placental lesions and thus variable and low occurrence of SARS-CoV-2 transplacental infection [13], as we expose it in case n°10 where lesions were highly heterogeneous (Fig. 1, D).

Schwartz et al. summarized the spectrum of pathology findings from pregnant women with COVID-19 based on the infection status of their infants. Authors concluded that co-occurrence of chronic histiocytic intervillitis and trophoblastic necrosis appears to be a risk factor for placental infection with SARS-CoV-2 as well as for maternal–fetal viral transmission and suggest a potential mechanism by which the coronavirus can breach the maternal–fetal interface [5]. However, the intensity and acute onset of the placental lesions could explain the rare positive fetal cases described to date because the death occurs rapidly by placental functional insufficiency before a possible fetal viral diffusion.

### 4.3. Correlation between severity of maternal signs and placental damage

In our study, placental lesions did not appear to be correlated with maternal infection severity. Indeed, third trimester's pregnant women placentas received in our laboratory showed subnormal placental examination while they presented severe symptoms with respiratory distress requiring emergency fetal extraction. On the other hand, second trimester's or third trimester's maternal infections have been reported several times with IUFD despite mild maternal COVID-19 symptoms [12,23–26]. This makes clinical monitoring difficult and raises the question of ultrasound monitoring. Retrospectively, we did not find any ultrasound finding in the five cases with IUFD and suggest a possible rapid and fulminant onset of placental damage within a period of 1–3 weeks.

## 5. Conclusion

SARS-CoV-2 infection can cause severe placental lesions associating chronic inflammation with trophoblastic necrosis and massive hemorrhage leading rapidly to placental destruction and IUFD as observed in our laboratory. These lesions are independent of maternal symptoms because they occur despite mild maternal symptoms and are therefore difficult to predict. In our cases, they occurred 1–3 weeks after positive SARS-CoV-2 maternal RT-PCR testing and were observed in the 2nd and 3rd trimesters of pregnancy. IUFD associated to SARS-CoV-2 placental lesions is not so rare because in our study they occurred in 5 of 50 cases (10%). These lesions can also appear focally in the placenta and lead to live birth with sometimes IUGR. The discovery of such lesions in the placenta should initiate a medical monitoring of the newborns for which the long-term effects are not known to date. Moreover, focal SARS-CoV-2 lesions seem to evolve over time with more fibrin deposits, becoming difficult to diagnose because SARS-CoV-2 immunostaining could become negative. This study highlights the need for systematic placental and fetal gross and microscopic evaluation, which can help elucidate the pathophysiology of COVID-19.

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