Placental lesions and SARS-Cov-2 infection: Diffuse placenta damage associated to poor fetal outcome

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ABSTRACT

Introduction: Pregnant women with covid-19 are more likely to experience preterm birth. The virus seems to be associated with a wide range of placental lesions, none of them specific.

Method: We collected cases of Covid-19 maternal infection during pregnancy associated with poor pregnancy outcomes, for which we received the placenta. We studied clinical data and described pathological findings of placenta and post-mortem examination of fetuses. We performed an immunohistochemical study and RT-PCR of SARS-Cov-2 on placenta samples.

Results: We report 5 cases of poor fetal outcome, 3 fetal deaths and 2 extreme premature neonates, one with growth restriction, without clinical and biological sign of SARS-Cov-2 infection. All placenta presented massive perivillous fibrin deposition and large intervillous thrombi associated with strong SARS-Cov-2 expression in trophoblast and SARS-CoV-2 PCR positivity in amniotic fluid or on placenta samples. Chronic histiocytic intervillositis was present in 4/5 cases. Placental ultrasound was abnormal and the sFLT1-PIGF ratio was increased in one case. Timing between mothers' infection and the poor fetal outcome was ≤10 days in 4 cases. The massive placental damage are directly induced by the virus whose receptors are expressed on trophoblast, leading to trophoblast necrosis and massive inflammation in villous chamber, in a similar way it occurs in diffuse alveolar damage in adults infected by SARS-Cov-2.

Discussion: SARS-Cov-2 can be associated to a rare set of placental lesions which can lead to fetal demise, preterm birth, or growth restriction. Stronger surveillance of mothers infected by SARS-Cov-2 is required.

1. Introduction

Since late 2019, SARS-Cov-2 has been circulating all over the world infecting more than 70 million people and causing more than 2 million deaths [1]. Since the beginning of the pandemic, some authors tried to assess the transplacental transmission of the virus and its effects on both pregnancy and fetus [2,3]. It is now known that SARS-Cov-2 requires 2 receptors to infect a cell: the ACE2 and the TMPRSS2. Both are expressed in the syncytiotrophoblast. According to some authors, the low co-expression profile of those two receptors in the placenta probably explain the low risk of vertical transmission of SARS-CoV-2 from mother to fetus during pregnancy [4]. However the potential adverse effects of the virus on maternal and perinatal outcomes are of concern [5]. Indeed, pregnant women with covid-19 are at increased risk of admission to an intensive care unit and are more likely to experience preterm birth [6]. There are growing arguments for an increased risk of fetal death (2) and hypertensive complications of pregnancy [7]. Intra-uterine growth restriction (IUGR) seems to be three times more frequent than in COVID

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negative patients [5]. Furthermore there is an increased risk of abnormalities in fetal oxygenation that could induce cardiac and neurological disorders in fetus and neonates, including in patients without particular risk factors for COVID19 [8]. For these reasons, the International Society of Ultrasound in Obstetrics & Gynecology recommends monitoring the fetuses of infected mothers closely [9]. These anomalies could be explained by placental damage. Regarding placental lesions in SARS-Cov-2 infection, some authors found no significant placental histopathological changes [10] whereas other reported various lesions such as villositis, chorangiosis, chorioamniotis, fetal vascular malperfusion or fetal vascular thrombosis [11,12], villous edema and retroplacental hematoma [13] as well as massive fibrin deposition along with chronic histiocytic intervillositis [14,15]. None of them seem to be specific of SARS-Cov-2 infection [6]. However, some authors noticed that placentas from SARS-CoV-2-positive women significantly harbor more villous agglutination and subchorionic thrombi than placentas from SARS-CoV-2-negative women. Fetal deaths issued from Covid 19 infected mothers have been reported in a few isolated cases to date [14,16–18] and some authors suggested a link with placental lesions. We report here 5 cases of massive placental damage due to SARS-Cov-2 infection, harboring all similar pathological findings, which rapidly led to 3 fetal deaths and 2 extreme premature births requiring intensive care unit hospitalization. We clearly attribute this poor fetal outcome to this massive placental damage. We aim to alert clinicians of potential poor outcomes of SARS-cov-2 maternal infection during pregnancy and to better understand the pathophysiology of this infection.

2. Materials and method

In this study, from March 2020 to March 2021, we collected all cases of Covid-19 maternal infection during pregnancy associated with poor pregnancy outcomes including fetal death (FD) and prematurity, for which we received the placenta.

We assessed clinical and biological data of mothers and pregnancies: maternal age, ethnicity, past medical history, presence of predisposing factor of severe COVID-19 (hypertension, gestational diabetes, thrombophilia, auto-immune and thyroid disorders, smoking, drug and alcohol consumption and obesity or high Body Mass Index (BMI), prenatal ultrasounds findings, delivery mode, term of pregnancy, delay between maternal COVID-19 with PCR positivity from nasopharyngeal swab and adverse fetal outcome, and clinical signs which led to perform nasopharyngeal tests.

Data from postmortem examination and neonates' outcome were also collected.

Macroscopic and microscopic features of placentas were described. Placental sampling, gross and microscopic examinations were performed according to the Amsterdam Consensus statement [19]. Samples of placenta were fixed in 4% buffered formalin and paraffin embedded (FFPE) and stained with Hematoxylin Eosin Saffron (HES). An immunohistochemical study was performed on FFPE placenta tissue with VENTANA™ OptiView DAB automat using the Bond Polymer Refine Detection kit (Leica™ DS9800) with the following antibodies: CD68 (Dako PG-M1, 1:200), CD3 (Dako F7.2.38, 1:50), CD4 (Ventana™, 1F6, prediluated), CD15 (LeuM1, Becton Dicikinson), CD8 (Dako, C8/144 B, 1:50), SARS-CoV-2 (Diagomics, rabbit pAB, 2019-nCoV N Protein, 1:2400). Negative controls for SARS-CoV-2 immunohistochemistry were performed on SARS-CoV-2 negative placental specimen with similar pre-analytic conditions.

RNA extraction from nasopharyngeal RT-PCR swabs, placentas and amniotic fluid was realized using MagNA Pure 24 from ROCHE Diagnostics™, according to GISAID database of January 2020, primers and probes (nCoV_IP2 and nCoV_IP4) were designed to target the RdRp gene spanning nt 12,621–12727 and 14,010–14116 (positions according to SARS-CoV, NC_004718). The same block of FFPE placenta was used to perform the Sars-Cov2 PCR and the immunostaining.

3. Results

From March 2020 to March 2021, 5 out of 82 placentas of Covid-19 infected mothers during pregnancy were associated with an adverse pregnancy outcome (3 FD and 2 extreme preterm births). One case occurred during the first French lockdown and 4 during the second one. All results are summarized in Table 1.

3.1. Clinical and biological data of mothers and pregnancies

Mean age of mothers was 36,4-year-old (26–43 years old). All were Caucasians and had no peculiar past medical history, except one who had a gastric bypass surgery for obesity (case 5). Three were primiparous. Regarding obstetrical history, one had a background of genital herpes (case 1) which was absent at the time of the delivery, and one had 3 previous unexplained first trimester miscarriage (case 5). No mother presented with predisposing factor of severe COVID-19, except case 5 who still had a high BMI despite gastric bypass surgery.

Prenatal US findings: second trimester prenatal US suggested fetal growth restriction in case 5 and were normal in other cases. Furthermore, an abnormal heterogeneous aspect of the placenta was noted in case 5 at 26 GW placenta with coexistence of hypo and hyperechoic areas, suggestive of infarction and calcification respectively. (Figs. .1 A and 1 B). This lead to test sFlt-1/PlGF which was increased (116 pg/mL). None of the five mothers presented with preeclampsia or HELLP syndrome. Coagulation tests were normal and Factor V Leiden mutation has been investigated in one patient (case number 1) and was negative.

Delivery mode and term of pregnancy: a C-section was performed in cases 1 and 5, at 26 + 5 GW because of fetal heart rate anomalies in case 1 and pathologic Doppler ultrasound of fetal vessels in case 5. Intrauterine fetal demises were observed in the 3 other cases and led to vaginal delivery at 34 W G, 30 W G, and 22 W G (case 2, 3 and 4 respectively). Parents gave their consents for post-mortem examination.

Delay between maternal nasopharyngeal swab PCR positivity and adverse fetal outcome or premature delivery was ≤10 days in 4 cases out of 5.

Fever was the only clinical sign which led to perform nasopharyngeal tests in mothers 1, 2, 3. Mother 4 presented also with ageusia, and mother 5 with fever, myalgia and rhinopharyngitis.

3.2. Neonates' outcome

The 2 cases born prematurely by C-section were admitted and followed in a level III Neonatal Intensive Care Unit (NICU) for 3 months. They presented neither fever nor sign suggestive of infection. Nasopharyngeal swabs for SARS-CoV-2 RT-PCR performed at admission were negative in case 1 and was not performed in case 5. Apgar scores were 2-3-6-8 and 7-9-10-10 at 1, 3, 5 and 10 min, respectively. Both received basic cares of premature neonates including support for thermal, respiratory and nutrition. Both are now doing well with normal physical exam and normal development, after respectively 11 and 3 months of follow-up since NICU discharge.

3.3. Post-mortem examination

An autopsy was performed in the 3 fetal demises (cases 2, 3 and 4), 2 males and 1 female, and revealed neither gross nor microscopic abnormality, especially no IUGR, no sign suggestive of diabetes, no thrombosis, no malformation, no signs of vertically transmitted infection. We only noticed signs suggestive of chronic hypoxemia with lymphoid depletion in thymus and spleen in case 2.

3.4. Placenta findings

All 5 placentas had the same macroscopic features (Fig. 1C and D) with whitish mottled net-like appearance involving at least 80% of

Table 1
Summary of our fives cases and comparison with similar cases.

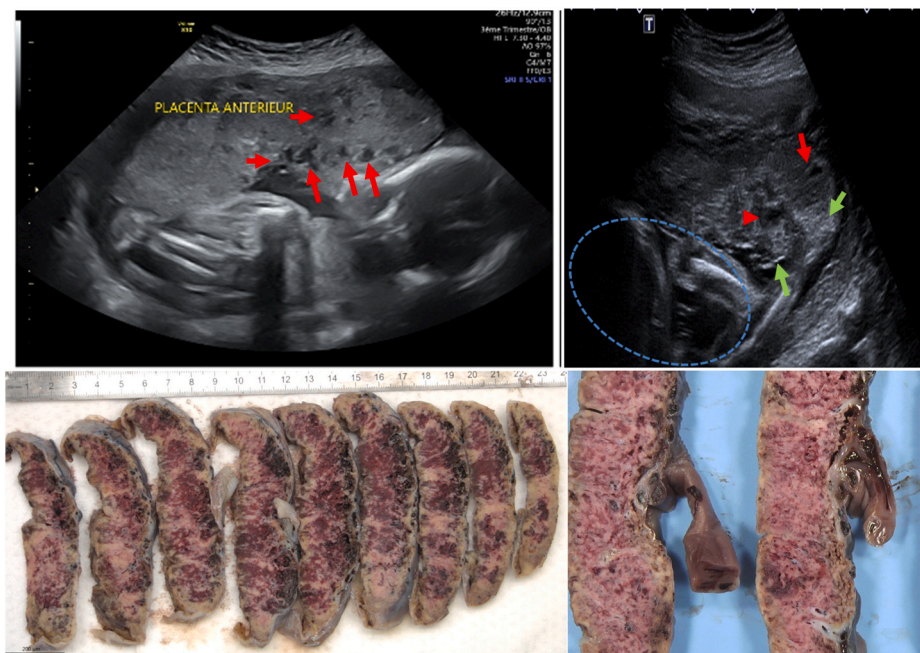|	1st case	2nd case	3rd case	4th case	5th case	Richtmann et al. (1st case) [16]	Richtmann et al. (2nd case) [16]	Pulinx et al. [17]	Schwartz et al. [18]	Hosier et al. [14]
Date of SARS-Cov-2 infection	April 2020	September 2020	November 2020	December 2020	December 2020	NC	NC	NC	NC	March 2020
Maternal age	35	26	33	30	43	32	35	32	32	35
Mother BMI (beginning at of the pregnancy)	19,6	20.1	21	20.3	26.8	30.5	25.7	NC	NC	NC
Ethnicity	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	NC	NC	Asian American
Obstetrical background	G2P1	G1P0	G2P1	G1P0	G11P8	G1P0	G2P1	G2P1	NC	G3P1
Other background	Genital Herpes	None	None	None	Bypass surgery	None	None	NC	NC	None
Risk factors	None	None	None	None	Smoking (10 cigarettes a day before pregnancy)	None	None	Diabetes mellitus	NC	Psoriasis (without current symptoms) Gestational hypertension
Pregnancy follow up	Normal	Normal	Normal	Normal	IUGR at 26 GW	Normal	Normal	Normal	Normal	Normal
Clinical signs leading to SARS-Cov-2 RT-PCR	Fever	Fever	Fever	Ageusia and fever	Fever	Rhinorrhea, myalgia and fever	Fever, dry cough	Rhinitis and fever	None	Fever, cough, myalgia, nausea, anorexia, diarrhea
Delay between COVID PCR swab and onset of the Poor outcome	COVID day 6	COVID day 10	COVID day 10	COVID day 4	COVID day 28	COVID day 4	COVID day 6	COVID day 15	Unknown	COVID day 10
Delivery mode	C-section	Natural	Natural	Natural	C-section	Natural	Natural	Natural	NC	Dilatation and evacuation (Under general anesthesia)
Term (weeks)	26 + 5	34 + 5	30	22 + 4	26 + 5	28	21	24	39	22
Sex	Female	Female	Male	Male	Female	Female	Male	NC	Male	Unknown
Fetal weight (g)	680	2410	1210	465	630	1070	329	NC	NC	485
Fetal outcome	Neonatal intensive unit care	Fetal death	Fetal Death	Fetal death	Neonatal intensive care unit	Fetal death	Fetal death	Fetal death	Fetal death	Termination of pregnancy (Severe Pre-eclampsia)
Autopsy results	Not concerned	No abnormality	No abnormality	No abnormality	Not concerned	NP	No abnormality	NP	NP	No abnormality
Placental weight (g)	187 ($<$10th p$^+$)	346 ($<$10thp$^+$)	255 ($<$10th$^+$)	105 ($<$10thp$^+$)	196 ($<$10th p$^+$)	NC	NC	NC	NC	NC
Ratio of fetal-placental weight ratio percentiles	3.63 (25-50thp$^+$)	6.96 (50-75thp$^+$)	4.74 (25-50thp$^+$)	4.42 ($>$95thp$^+$)	3.21 (10-25thp$^+$)	NC	NC	NC	NC	NC
Placental histology	CHI MPFD LIT	CHI MPFD LIT	CHI MPFD LIT	CHI MPFD LIT	Focal CHI MPFD	CHI MPFD VUE	CHI MPFD	CHI MPFD	CHI MPFD	CHI MPFD
SARS-Cov-2 RT-PCR on placenta (CT)	23	+ (38.7)	+ (27.59)	–	+ (30.5)	+ (NC)	NP	33	+ (NC)	+ (NC)
SARS-Cov-2 immunostaining	+	+	+	+	+	NP	NP	+	+	+

Fig. 1. Prenatal ultrasounds and gross features of placenta (case 5): A: prenatal ultrasounds at 26 GW: hypoechoic lacunae (red arrows)

B: prenatal ultrasounds at 26 GW: coexistence of hyperechoic lesion (green arrows) and hypoechoic lesion (red arrows) suggestive of calcification and infarction respectively. Blue circle: Fetus

C: gross features on cut sections after formalin fixation: whitish mottled net-like appearance involving at least 80% of parenchyma suggestive of massive fibrin deposition

D: gross features on cut sections after formalin fixation: same anomalies on higher magnification.

parenchyma suggestive of massive fibrin deposition.

On microscopic examination, all placentas presented (Fig. 2) massive perivillous fibrin deposition (MPFD) and numerous large intervillous thrombi (LIT). Among areas of MPFD, trophoblast was necrotic and sometimes replaced by neutrophils or infiltrated by histiocytes and/or lymphocytes. Severe chronic histiocytic intervillositis (CHI) was also observed in all cases except one (case 5), which was the one with the largest delay between SarsCov2 infection and the poor outcome. The
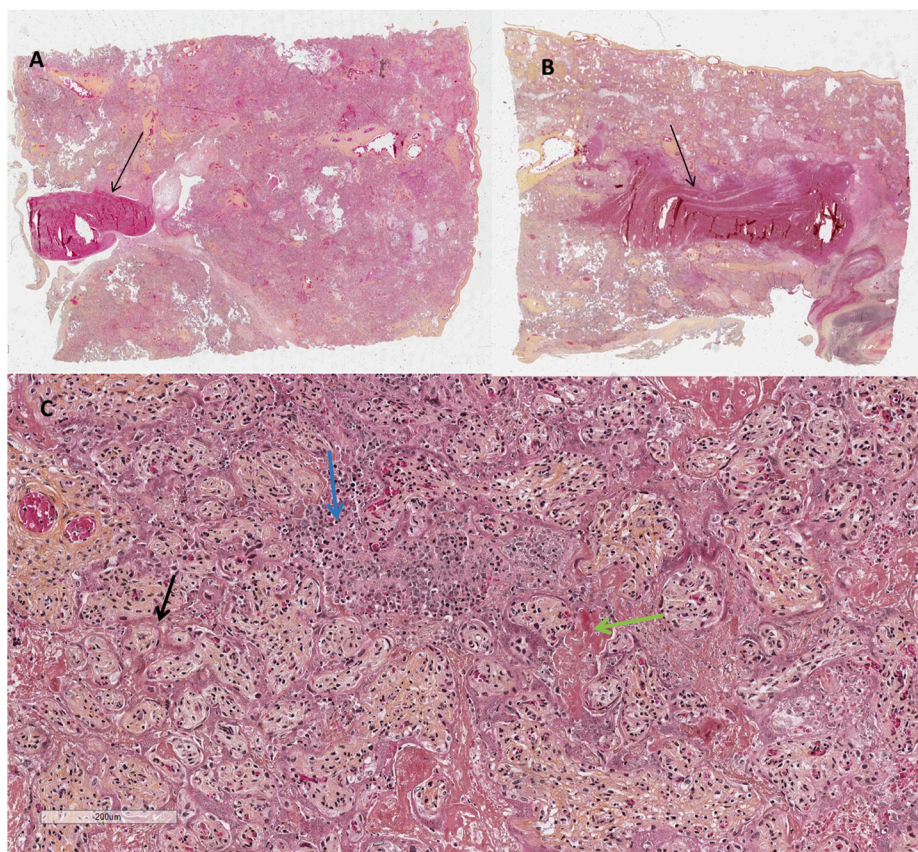

Fig. 2. Microscopic features of the placenta on HES (Hematoxylin Eosin Saffron)

A & B: x 5: 2 different cut sections showing large intervillous thrombi (black arrows)

C: x 200: MPFD with trophoblast necrosis (black arrow), fibrin deposits (green arrow) along with CHI (blue arrow).

large intervillous thrombi were disseminated throughout all the placental parenchyma and were not only confined to the basal plate. The features were not those of infarction-hematoma or rounded intra-placental hematoma [20–22]. Furthermore there was no lesion suggestive of maternal vascular malperfusion such as infarct or decidual vasculopathy. We did not observe other lesions such as villositis, chorangiosis, chorioamniotis, or features suggestive of fetal vascular malperfusion.

Immunohistochemistry (Fig. 3) showed that severe chronic histiocytic intervillositis was mainly composed of CD68$^+$ macrophages along with lymphocytes T CD3$^+$ CD8$^+$. Neutrophils in areas of trophoblast necrosis expressed CD15. SARS-Cov-2 was diffusely expressed in trophoblast of all placentas (Fig. 4).

SARS-Cov-2 RT-PCR from FFPE placenta samples was positive for case 1, 2, 3 and was negative for case 4. In case 5, RT-PCR was positive on both amniotic fluid and placenta sample.

3.5. Comment

3.5.1. Principal findings

We report 5 cases of poor fetal outcomes due to SARS-Cov-2 maternal infection during pregnancy leading to 3 fetal deaths and 2 extreme premature neonates who required NICU hospitalization. All cases have in common MPFD with LIT and strong SARS-Cov-2 expression in trophoblast. MPFD and LIT corresponded respectively to hypo and hyperechoic areas seen on prenatal US in case 5 at 26 GW. MPFD was associated with CHI in 4 cases out of 5. These placental lesions, especially MPFD and CHI, explain the poor fetal outcome as oxygen and nutriments exchange between mother and fetus are highly compromised, leading in turn to IUGR or FD.

3.5.2. Results

MPFD is a classical cause of fetal demises. The fundamental pathogenesis of this lesion remains unknown. Different hypotheses have been suggested: trophoblast anomaly, blood stasis in intervillous space or inflammatory cause [23]. Indeed, MPFD has been reported in Coxsackie virus, CMV and syphilis infections during pregnancy [24–27]. Occasionally this disorder overlaps with maternal floor infarction. Focal PFD is reported in diabetes but no mother presented with diabetes in our series [23].

Numerous and large intervillous thrombi (LIT) were also present in 4 cases out of 5 in our series. LIT may develop in case of maternal thrombophilia or pre-eclampsia [23], which was not present in our series. According to Mendoza et al. numerous LIT can be related to a pre-eclampsia-like syndrome [28]. Indeed, Mendoza et al. reported pre-eclampsia-like syndrome in women with severe COVID19 pneumonia [28], with an increased sFlt1/PIGF ratio before the clinical onset of preeclampsia in 1 out of 42 mothers included in their series [28,29]. In our series, we only assessed sFlt1/PIGF ratio in one case which was >85 pg/mL, threshold beyond which the positive predictive value at admission for indicated delivery within 2 weeks is 91%[30]. As the mother did no present clinical signs of PE, increased sFLT1/PIGF ratio associated with placental US anomalies could be a way of foreseeing PE-like syndrome among COVID-19 pregnancies.

The increased sFLT1/PIGF ratio could be explained by trophoblast infected cells inducing cell apoptosis, thus in turn leading to massive release of anti-angiogenic factors.

Chronic histiocytic intervillositis (CHI) is a rare idiopathic inflammatory lesion distinct from villitis of unknown origin (VUE) and associated lesions. It is characterized by maternal histiocytic infiltrate in the intervillous space without villitis. CHI is usually highly suggestive of an immunological conflict between mother and fetus [23]. However CHI can be observed in some infections such as Chagas' disease, malaria and cytomegalovirus [31–33]. Like MPFD, chronic histiocytic intervillositis is strongly associated with miscarriage, IUGR, preterm birth, and early intrauterine fetal demise. It has the highest recurrence rate of any placental lesion, sometimes affecting 10 or more consecutive pregnancies [12,13]. Interestingly, the only case without CHI in our series was the one with the largest delay (28 days) between infection and the poor outcome. Inflammatory elements might have been present in the intervillous space at the beginning of the infection of this case and then might have disappeared. This case is also the only one with IUGR. In the other cases of our series, the delay between infection and poor outcome might have been too short to allow IUGR to settle.

Twelve cases with MPFD/CIH dyad and Sars-cov2 infection during pregnancy have been reported in the literature, 8 of whom during the third trimester and 3 during the second one. Five cases out of 12 were associated with fetal demises (included in our table), including 1 termination of pregnancy at 22 GW for severe PE [3,14,16–18,34–36].

Compared to our cases, predisposing factors for severe COVID 19 were present in 5/12 (3 BMI>25, 1 diabetes mellitus, 1 gestational hypertension), corresponding to the 5 cases with fetal demises. Four newborns were preterm and three of them were SARS-Cov-2 positive. One presented with neurological signs at physical examination and MRI [3,14,18,37].

We also report the 4th case in literature [3,16,38] of SARS-Cov-2 positive amniotic fluid. However, RT-PCR performed from placenta was negative, whereas SARS-Cov-2 was strongly expressed in trophoblast on immunohistochemistry. This mismatch could be explained by a false negative. SARS-Cov-2 mother-to-child transmission can be secondary to amniotic fluid inhalation [39]. However, we did not find any sign of mother to fetus infection on post-mortem examination in our case with RT-PCR amniotic fluid positivity. Microscopic examination of the fetus was normal without any neutrophils in lungs as reported in one case of FD by Richtmann et al. [16]. It is interesting to note that ACE-2 receptors are not expressed in fetal lungs whereas they are in adults [4, 40].

3.6. Clinical implications

Finding such lesions on placental gross and microscopic examination should suggest the diagnosis of SARS-Cov-2 infection during pregnancy when COVID-19 has not been previously diagnosed. MPFD and LIT could be evoked on prenatal ultrasounds and this should alert clinicians
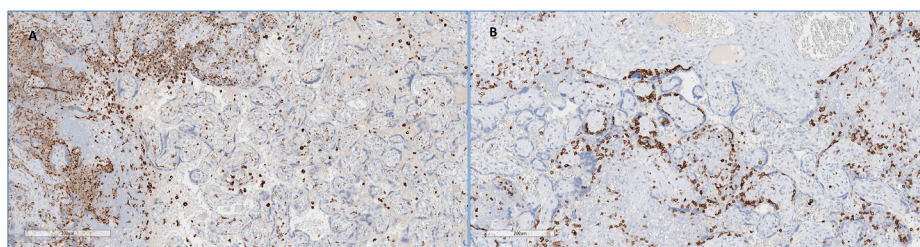

Fig. 3. Immunohistochemical study
A: CD68 antibody x 80: numerous histiocytes in the intervillous chamber
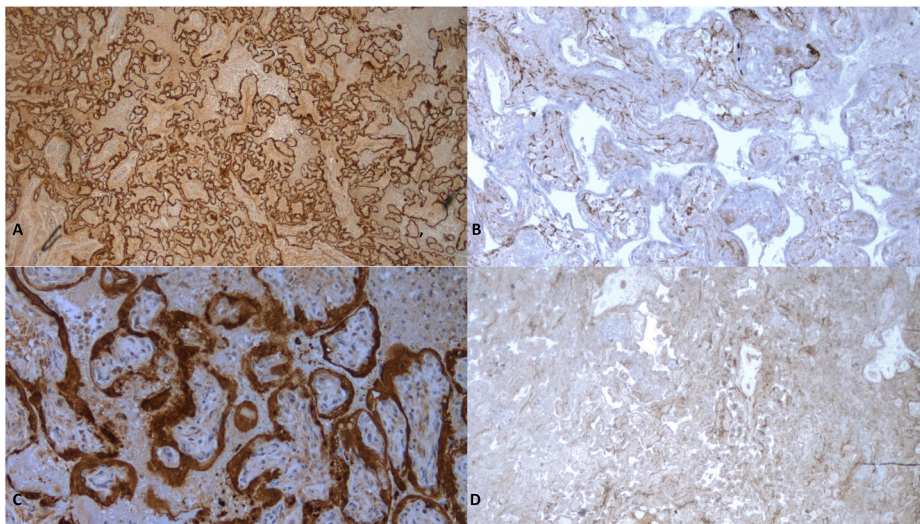B: CD3 antibody x 80: numerous lymphocytes inside or adjacent to the trophoblast.

Fig. 4. Immunohistochemical study of Sars-Cov2 on placenta

A: case 2 (34+5 GW) x 25: diffuse and strong expression on trophoblast

B: negative control x 25: placenta from annon-infected mother at 34 GW: no expression on trophoblast

C: case 4 × 200 (22 +4 GW): diffuse and strong expression on trophoblast

D: negative control x 200: placenta from a non-infected mother at 22 GW: no expression on trophoblast.

in order they harder follow the pregnancy, look for IUGR as well as an increased sFlt1/PLG1 ratio suggestive of PE [29] and eventually process to premature delivery, especially as COVID-19 is an insidious disease and as poor outcome can happen in a short lapse of time.

3.7. Research implications

As we did not find any sign of mother to fetus infection on postmortem examination as well as in the 2 premature neonates, the poor fetal outcome cannot be explained by the virus transmissibility to the fetus but rather by the massive placental damage.

Severe lung lesions with diffuse alveolar damage observed in infected adults are mainly caused by the cytokine storm and the exaggerate immune response [41]. The diffuse placental damage might be rather a consequence of the exaggerate mother inflammation (CHI) in the placenta than a consequence of the virus itself, just as it happens in lungs. Inflammatory elements involved in diffuse alveolar damage are the same we observed in intervillous spaces: $CD68^+$ macrophages along with lymphocytes T $CD3^+$ $CD8^+$. Inflammation could lead in turn to perivillous deposition and villous necrosis, in parallelism with the fibrin deposition along the alveolar spaces. Trophoblastic necrosis could be either a direct cause of the virus or a consequence of the inflammation surrounding the trophoblast in reaction of the virus infection.

SARS-Cov-2 infection is also known to cause severe thrombosis [42] that might be explained by Tissue Factor activation by the virus itself. This could explain LIT as well as some cases of maternal vascular malperfusion observed in previous reports of maternal Covid 19 infection during pregnancy [2,14,15].

3.8. Strengths and limitations

Numerous pregnant women were infected by SARS-Cov-2 during the pandemic, but only a small fraction ended up in maternal or NICU hospitalization or fetal demise [43]. According to the literature and to our cases, this poor fetal outcome is linked to massive placental damage with MPFD, LIT and CHI. This massive placental damage could be compared to the one that occurs in lungs. In adult's severe form of COVID-19, there is some evidence of disturbed interferon profile in severe inflammatory reaction to SARS-Cov-2 [44]. Unfortunately, interferon profile was not realized in our series as it requires special blood sample conditioning which was not available at time of delivery. We could also not eliminate the role of mutants could have played in the poor prognosis of our cases, as mutations strengthened SARS-CoV-2 transmissibility and mortality [45].

4. Conclusions

We reported 5 cases of massive placental damages due to SARS-Cov-2 infection during pregnancy which led to 3 fetal deaths and 2 extreme premature births requiring NICU hospitalization. The poor outcome is explained by diffuse placental damage due to SARS-Cov-2 infection without transmission of the virus to the fetuses and neonates. The massive placental damage with MPFD, CHI and LIT are directly induced by placental infection by the virus whose receptors are expressed on trophoblast leading to inflammatory reaction in the villous chamber. This leads to trophoblast necrosis, massive fibrin deposition, and decreased exchange between mother and fetus in a short lapse of time. As some mothers did not present predisposing factor of severe COVID-19 or severe clinical sign of COVID-19, these findings should alert clinicians and entail them to look for IUGR and placental lesions on prenatal US and test sFlt1/PlGF ratio to predict possible pre-eclampsia-like syndrome.

Ethics declaration

Written informed consent was obtained from the woman for the publication of this report. According to French regulation, institutional review board (IRB) approval is not required for case reports, if patients' written consent is obtained. The case study was performed in agreement with principles of the Declaration of Helsinki and CARE guidelines [46].

Conflict of interest statement

Amine BOUACHBA, Fabienne ALLIAS, Beatrice NADAUD, Alexis TRECOURT and Sophie COLLARDEAU-FRACHON declare no conflict of interest.

Jerome MASSARDIER, Benoit DE LA FOURNIERE and Cyril HUIS-SOUD declare no conflict of interest.

Yahia MEKKI and Maude BOUSCAMBERT DUCHAMP declare no conflict of interest.

Declaration of competing interest

None.

Acknowledgements

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