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Review

SARS-CoV-2 placentitis: An uncommon complication of maternal COVID-19

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ABSTRACT

We present a case of third trimester pregnancy complicated by SARS-CoV-2 infection and subsequent reduced fetal movements, resulting in emergency Caesarean delivery with demonstrable placental SARS-CoV-2 placentitis.

We show through illustration of this case and literature review that SARS-Co-V-2 placentitis is an uncommon but readily recognisable complication of maternal SARS-CoV-2 infection that may be a marker of potential vertical transmission and that may have the capacity to cause fetal compromise through a direct injurious effect on the placenta.

1. Introduction

As global cases of the novel coronavirus SARS-CoV-2 approach 85 million cases and 2 million deaths, our knowledge of this disease is increasing as is the acceptance that the far-reaching restrictions and waves of infection will be recurrent for the foreseeable future [1].

The majority of pregnant patients infected with SARS-CoV-2 have had a mild illness and their babies have also been well [2,3]. There have also however been reports of serious maternal illness, maternal death, intrauterine death and preterm birth [2–5], but with no clear correlation between illness severity and pregnancy sequelae. Overall, the cumulative incidence of COVID-19 in the estimated Irish pregnant population was low at 173 per 100,000 women [6]. Complete data on pregnant women requiring hospitalisation in Ireland are not yet available, and subject to change given the recent resurgence in cases.

The UKOSS prospective cohort study offers better insight into the outcomes among pregnant women in a proximate island population, reporting an estimated incidence of hospital admission of 4.9 pregnant women per 1000 maternities (95% confidence interval 4.5 to 5.4).(2) Additionally, 10% (41/424) of women admitted to hospital with a SARS-CoV-2 infection required respiratory support [2]. The maternal death rate was low at 1% [2]. The initial WHO report in China suggested an 8% rate of serious illness and 1% critical illness rate [7]. UKOSS recognised the disproportionate representation of women of black and other ethnicities (233/427; 54.5%) and overweight or obese women (281/427; 65%) among those admitted [2]. This was confirmed in an international systematic review [8]. Pregnancy, in particular of over 20 weeks' gestation [4], increases the risk of admission to intensive care and invasive ventilation in comparison to non-pregnant controls [8]. These risks are further amplified in those countries where women do not have equitable access to healthcare and intensive care, demonstrated by the high level of maternal deaths in Brazil [9]. As many countries are still in the grips of the pandemic, further data are awaited to determine the true effect of this disease on maternal morbidity and mortality and authenticate the international variances.

The majority of neonatal outcomes are reassuring and are congruent with the asymptomatic or mild disease course seen in most mothers, with no increased rate of neonatal death or stillbirth demonstrated to date [8]. Studies have demonstrated some correlation with SARS-Cov-2 infection and pregnancy loss [10–12]. However, the consequences of severe COVID-19 in early pregnancy on fetal outcomes are unclear. Larger cohort studies will be required to verify these correlations or any association with placenta associated pathologies such as intra-uterine growth restriction or pre-eclampsia. Vertical transmission appears to be uncommon, regardless of mode of delivery or feeding method, but is recognised [3,13]. Furthermore, there is a question as to how this is best identified, as the strength of IgM antibodies and IL-6 levels as confirmation of infection in the neonate has been contested [14].

Placental pathological reports in mothers with SARS-CoV-2 infection are emerging, most recently appraised by Sharps et al. [15], but no

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consensus has transpired as to the placental features of this viral infection. Understanding placental pathology in COVID-19 infection is important to defining disease trajectory and potential risks for the mother, potential complications for the fetus in utero (through possible placental injury) and the potential for vertical transmission. These will inform appropriate management and delivery decisions regarding SARS-CoV-2 infections in pregnancy.

We present a case of mild SARS-CoV-2 disease in a woman in the third trimester of pregnancy who developed an abnormal cardiotocograph necessitating delivery. On review and consideration of the available literature, we believe the subsequent placental histology findings represent SARS-CoV-2 placentitis.

2. Methods

A pregnant woman with COVID-19 was evaluated in Cork University Maternity Hospital on May 26, 2020. Information was obtained from the patient's medical electronic records. Informed written consent was obtained prior to submission.

Following delivery of the placenta the whole placenta was placed directly in 10% buffered formalin for fixation at room temperature. It was then transported to the pathology laboratory at Cork University Hospital for pathological examination. The placenta was fixed for >72 h, prior to sampling, to minimise the potential risk of infection. Because of the unusual gross appearance of the placenta extra sections were taken over and above our standard sampling regime. Two full thickness membrane rolls (including amnion, chorion and decidua), 4 cord sections (at intervals along the cord to include fetal and placenta ends) and 7 parenchymal sections were taken. Parenchymal sections were full thickness from fetal to maternal surfaces and were targeted to provide representative samples that would be reflective of the gross appearances. Diagnostic samples were paraffin embedded. Staining methods performed on 3 μm thick sections were: Harris haematoxylin and eosin for routine morphology evaluation and a Martius, Scarlet and Blue (MSB) to identify fibrin. Immunohistochemistry was performed on 3 μm thick sections using a Ventana BenchMark Ultra with a Ventana Optiview DAB IHC Detection Kit with Ventana Bluing reagent as a counter stain. Heat pre-treatment was performed using Ultra Cell Conditioning Solution (Ultra CC1) and Cell Conditioning Solution (Ultra CC2) depending on the monoclonal antibodies tested: CD 68 (BOND, RTU, 514H12), CD3 (Ventana, RTU, 2GV6), CD20 (Ventana, RTU, L26), CD138 (CellMarque, RTU B-A38), Sars-CoV-2 (Covid-19) Spike Antibody (GeneTex, 1A9, 1:200). Negative controls for SARS-CoV-2 immunohistochemistry were four recent routine placental specimens. A fifth normal third trimester placenta provided control images for Fig. 2. Images were taken using a Leica DM3000 microscope with a Leica DFC495 camera and personal computer running Leica Application Suite 4.1 software.

3. Results

A 26-year-old woman of Polish nationality booked in our hospital at 12 weeks' gestation in her second pregnancy. She had a previous miscarriage at 6 weeks' gestation. Her Body Mass Index (BMI) was 24, and apart from stable hypothyroidism, had no significant medical or surgical history. Her pregnancy course was uncomplicated, and she attended midwifery-led antenatal clinics.

At 36 weeks' gestation, she screened positive for SARS-CoV-2, following an outbreak at her husband's workplace. She presented to our hospital five days after the confirmed positive test result feeling unwell and with reduced fetal movements. On assessment, she reported a fever of 38.7 °C recorded at home, rigors, dry cough, generalised abdominal pain and headaches. Observations demonstrated a tachycardia of 120bpm, respiratory rate 24pm, blood pressure 111/69 and SpO2 of 100% on room air. Her temperature 50 min after arrival was 38.4 °C (tympanic). Blood gas and white cell count were normal. C-reactive protein was 50, renal and liver function tests also normal. Fetal assessment was reassuring with a normal cardiotocograph (CTG), biophysical profile and liquor volume. A chest x-ray was normal. She was assessed in the adjoining general medical hospital and determined to be suitable for discharge home by the Respiratory Consultant.

The patient represented five days later with reduced fetal movements for several hours. She was feeling physically well and vital signs were normal. She was assessed by the Consultant on-call and the CTG was within normal limits. Departmental ultrasound was reported as normal, demonstrating a normally grown fetus, an amniotic fluid index of 15 and normal fetal movements.

However, the mother still reported reduced movements and subsequent CTG showed a wandering baseline with reduced variability and few accelerations. She was admitted to an isolation room in the hospital's COVID ward, where electronic fetal monitoring system (FETAlink) allowed for remote monitoring. The CTG began to demonstrate a baseline of 120bpm with shallow late decelerations to 90bpm for over 120 s with reduced variability that was questionably sinusoidal. On review of the clinical scenario, in conjunction with reduced fetal movements and non-reassuring CTG, the decision was made for a caesarean section (category 2).

Surgery was carried out in a specially designated theatre with the appropriate personal protective equipment. The Caesarean was uncomplicated, and a baby girl was delivered weighing 2.8 kgs. She underwent Delayed Cord Clamping for 50 s. Her heart rate (HR) was 80bpm on examination at the resuscitaire. She received positive pressure ventilation (PPV) x 1 min with oral and nasal suction. At 2 min 50 s of life, HR was over 100 and so FiO2 was weaned to 60% and baby cried at 3 min 20 s. The APGAR scores were 4 and 8 at one and 5 min of life, respectively. The neonatal care plan was that the baby would remain with the mother in an isolation room on the designated COVID-19 ward to facilitate breast-feeding, accommodated in an incubator instead of the standard cot. As per hospital protocol, the baby was not swabbed for SARS-CoV-2 and was for four-hourly observations on the ward. The placenta was sent for pathological examination.

The maternal naso-pharyngeal swab for SARS-CoV-2 remained positive on day three of admission (day 14 since first positive swab). The mother's recovery was generally uneventful, except for the development of a wound haematoma, which subsequently required a blood transfusion. Clinically well, both mother and baby went home on day eight.

3.1. Placental pathology

The placenta weighted 517 g at 37 weeks gestation (between the 50th and 75th percentiles) and had a marginal cord insertion, 1 cm from the disc edge. Fetal and maternal surfaces were unremarkable. The cut surface had lace-like pattern of cream nodules and streaks running through the parenchyma (Fig. 1). This process resembled perivillous fibrinoid deposition and involved 25% of the placental parenchyma. On microscopic assessment these areas were composed of clumped villi with loss of intervillous space (Fig. 2a). There was a patchy inflammatory infiltrate in these regions that was predominantly composed of CD68 positive macrophages with much smaller numbers of CD3 positive T-lymphocytes and CD20-positive B-lymphocytes (Fig. 3). Plasma cells (CD138 positive) were inconspicuous. The inflammatory infiltrate appeared focused on the villous surfaces and was associated with conspicuous villous trophoblast necrosis. Necrotic trophoblast debris was present in the intervillous space with relatively little deposition of fibrin (Fig. 1b). The inflammatory infiltrate did not appear to invade the stroma of the involved villi and so was predominantly a histiocytic intervillositis. Immunohistochemistry for SARS-CoV-2 showed extensive, strong positive staining in trophoblast of the involved areas (Fig. 3c).

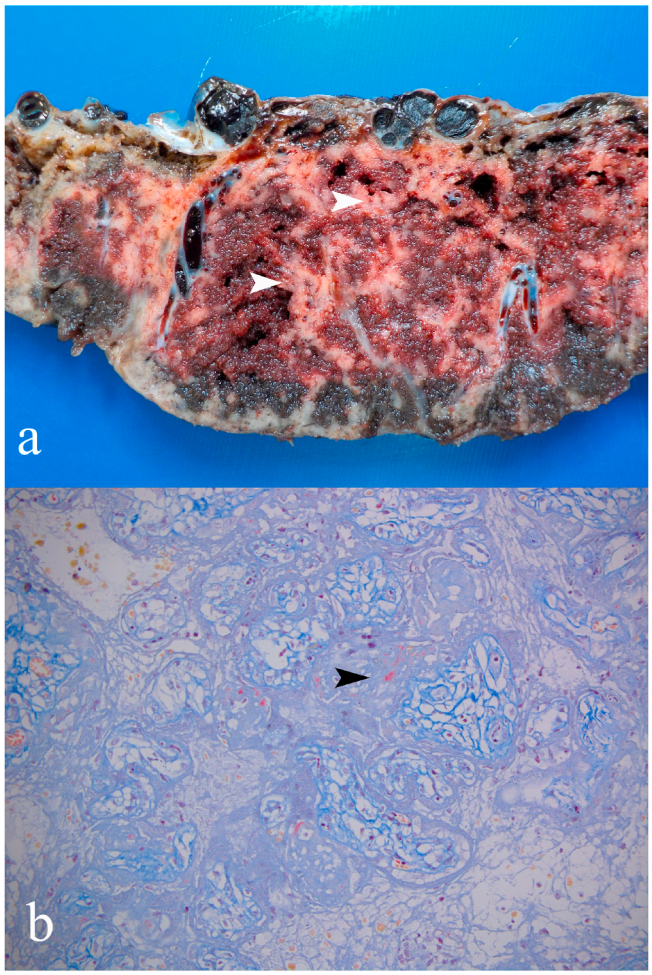

Fig. 1. Gross appearance:a) The gross appearance of the cut surface of the placenta shows pale nodules and streaks (white arrowheads) resembling massive perivillous fibrinoid deposition with involvement of a significant volume of placental parenchyma. b) Although the gross appearance suggests fibrin deposition, an MSB stain (200x) shows only focal fibrin deposition (orange/red), at the arrowhead tip, in what would have been the pale areas grossly.

4. Discussion

We present a case of third trimester pregnancy complicated by SARS-CoV-2 infection and subsequent reduced fetal movements, resulting in emergency Caesarean delivery with demonstrable placental SARS-CoV-2 placentitis.

There have been a number of cases series and case reports published describing the placental pathology findings from pregnant mothers with COVID-19. Chen et al. described three cases in which there were no specific placental pathological features of infection; all three placentas showed fibrin deposition and local increases in syncytial knots [16]. One case showed a chorangioma and another, a massive placental infarct [16]. They reported no villitis or chorioamnionitis [16]. Xiong et al. reported a single case with no evidence of placental inflammation and negative placental immunohistochemistry for SARS-CoV2 [17]. Hsu et al. also reported a single case with focal lymphohistiocytic inflammation in keeping with chronic villitis, hypertrophic arteriolopathy and islands of extravillous trophoblast [18]. Immunohistochemistry for SARS-CoV-2 was reported as positive but only rarely in trophoblast [18], in contrast to other reports of positive staining reviewed below. Ferraiolo et al. reported a single case with no evidence of inflammation but with a single ischaemic area, delayed villous maturation, deposition of fibrin and intervillous haemorrhages [19]. Baergen and Heller described the placental pathology in 20 cases of maternal COVID-19 [20]. The most common lesions seen related to fetal vascular malperfusion (9 cases); 5 cases showed lesions of maternal vascular malperfusion [20]. It is assumed that the 5 cases reported by Mulvey et al. are incorporated in the larger report by Baegen and Heller from the same institution [20, 21]. Cribiù et al. reported placentas from 9 patients [22]. Maternal vascular malperfusion was seen in 2 cases; delayed villous maturation in 5 cases and perivillous fibrin deposits in 8 cases [22]. Smithgall et al. described 51 cases and reported that villous agglutination and subchorionic intervillous thrombi were statistically more common in COVID-19 cases [23]. Placental in-situ hybridisation and immunohistochemistry for SARS-CoV-2 was negative in all tested cases [23]. Hecht et al. reported no characteristic histopathology in 19 cases, although in two cases SARS-CoV-2 RNA was identified in syncytiotrophoblast and cytotrophoblast [24]. They had one case of histiocytic intervillositis but this was not one of their cases with documented virus in the placenta [24]. In 16 cases reported by Shanes et al., cases were more likely than controls to show lesions of maternal vascular malperfusion, particularly abnormal or injured maternal vessels [25]. Chorangiosis was also increased [25]. Acute and chronic inflammation was not more common [25]. Richtmann et al. reported 5 cases of maternal COVID-19, all associated with fetal deaths [11]. Acute chorioamnionitis was present in all 5 cases [11]. They also reported increased intervillous fibrin in 2 cases associated with mixed intervillitis and villitis with intense neutrophil and lymphocyte infiltration [11]. We note that in one of their figures, (Fig. 2B), a component of a histiocytic intervillositis appears to be present [11]. The case report of Baud et al. also describes a pregnancy loss in a mother with COVID-19 [10]. Placental pathology in this case describes a mixed inflammatory infiltrate in the subchorionic space, intervillous fibrin deposition and funisitis [10]. A case report by Kuhrt et al. described a case of placental abruption in MCDA twins in which the placenta showed accelerated villous maturation [26].

From the above reports, no consistent characteristic pathological findings emerge although some association with lesions of maternal and fetal vascular malperfusion were present. It is notable that in these studies there was no definitive demonstration of virus within the placentas, except for two of the 19 cases reported by Hecht et al. [24] Given this fact, any associations with pathologies not readily attributable to SARS-CoV-2 need to be interpreted with caution and are at most is indirect. Many of the placental pathologies described above are not uncommon in routine placental diagnostic practice (pre-COVID-19). Further studies are required to evaluate any potential associations identified in these published series, ideally with blinding to COVID-19 status to eliminate potential bias.

However, the following reports appear to identify a more specific lesion of direct placental involvement in COVID-19 infection. In the case series of Patanè et al., two of the 22 neonates born from COVID-19 mothers had positive nasopharyngeal swabs for SARS-CoV-2 [27]. Both of the placentas in these cases showed a chronic histiocytic intervillositis which was associated with macrophages in the intervillous and villous space [27]. Notably in both cases viral spike antigens were also identified in villous syncytiotrophoblast by in-situ hybridisation [27]. Placental examinations in the remaining 20 cases showed no specific alterations [27]. Zhang et al. reported 74 placentas and performed in-situ hybridisation for SARS-CoV-2 on 53 cases [28]. No histopathological features specific to COVID-19 were reported to have been identified but two cases were positive for SARS-CoV-2 by in-situ hybridisation [28]. In one of these two cases the positivity by in-situ hybridisation was described in syncytiotrophoblast, where it was associated with infarcts with increased maternal macrophages and thrombosis [28]. The neonate in this case had a positive nasopharyngeal swab for SARS-CoV-2 [28]. In our opinion however, their figure of such an infarct (Fig. 3) shows a histiocytic intervillositis with associated syncytiotrophoblast injury and villous clumping [28], akin to the findings described by Patanè et al. Their second positive case had staining only in decidual glands with a negative neonatal swab [28]. Other case reports

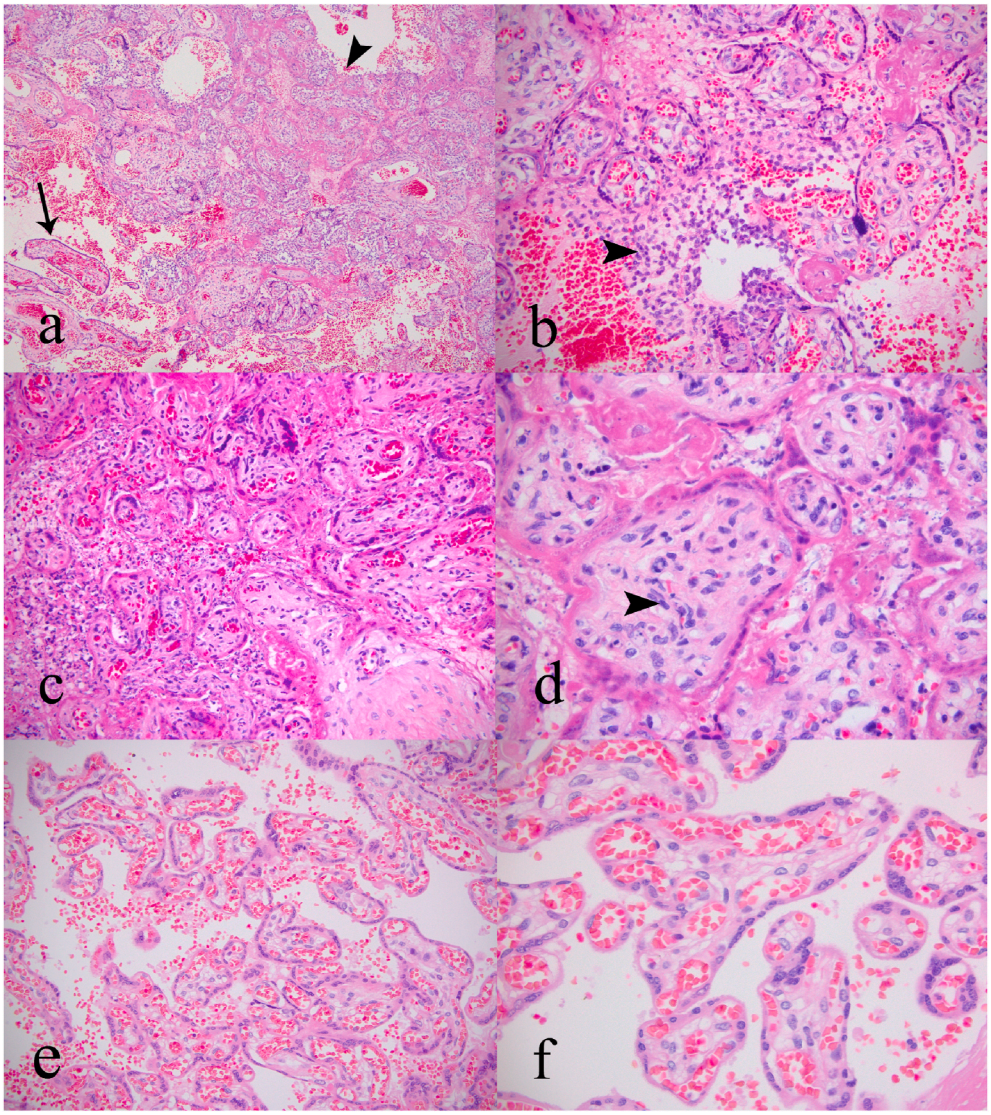

Fig. 2. H/E appearances:a) On low power (50x) there is conspicuous clumping and adherence of villi with obliteration of the intervillous space in involved areas (arrowhead). This contrasts with the non-clumped areas (arrow). b) There is a conspicuous intervillositis, with inflammatory cells in the intervillous space (arrowhead, 200x). c) In the clumped areas the intervillous space is filled with eosinophilic material and cellular debris as a result of trophoblast necrosis (200x). d) A higher power view (400x) shows sparing of the villous stroma (arrowhead) but obvious trophoblast necrosis and debris accumulation in the intervillous space. e) A normal term placenta at 200x, for comparison with panel 2c, shows preservation of the intervillous space and separated villi. f) A normal term placenta at 400x, for comparison with panel 2 d, shows normal villi with intact trophoblast and a clean intervillous space.

also describe a histiocytic intervillositis in maternal COVID-19. Vivanti et al. describe transplacental transmission of SARS-CoV-2 [13]. The placenta in this case showed diffuse perivillous fibrin deposition with infarction and acute and chronic intervillositis; there was positivity in villous trophoblast for SARS-CoV-2 N-protein by immunohistochemistry [13]. Hosier et al. report a patient with COVID-19 and severe pre-eclampsia and abruption necessitating pregnancy termination in the maternal interest [29]. This placenta had a marginal haematoma with focal placental infarct in keeping with the clinical impression of abruption [29]. It also showed diffuse perivillous fibrin deposition and an inflammatory infiltrate composed of macrophages and T-lymphocytes [29]. Immunohistochemistry for the SARS-CoV-2 spike protein was positive [29]. They also identified viral particles by electron microscopy [29] but such identification of virus by this method has been controversial [30]. Kirtsman et al. reported a case of probable congenital SARS-CoV-2 infection [31]. In this placenta there was extensive infiltration by inflammatory cells and extensive early infarction [31]. The inflammatory infiltrate consisted of a histiocytic intervillositis with lesser numbers of T and B lymphocytes and neutrophils [31]. The histiocytes were noted to cluster around villi [31]. Schoenmakers et al. identified a histiocytic intervillositis and syncytiotrophoblast injury in a placenta from the third trimester with a presentation of reduced fetal movements and where the delivered neonate developed multi-organ failure associated with negative neonatal SARS-CoV-2 testing [32]. Bertero et al. showed one of five placentas from COVID-19 affected mothers had a histiocytic intervillositis [33]. Sisman et al. reported a case with of possible vertical transmission with placental features of a chronic histiocytic intervillositis associated with villous karyorrhexis and necrosis [34]. SARS-CoV-2 was identified in syncytiotrophoblast by immunohistochemistry and its presence was also reported on electron microscopy [34]. Finally, Pulinx et al. reported the death of dichorionic diamniotic twins at 24 weeks gestation; placental examination showed extensive perivillous fibrin deposition, a chronic intervillositis and ischaemic necrosis of villi [35]. The virus was identified in syncytiotrophoblast by immunohistochemistry [35]. The authors proposed that their findings raised the possibility of vertical transmission and miscarriage due to the infection [35].

Although histiocytic intervillositis is not specific to COVID-19 infection, the virus was directly demonstrated within the syncytiotrophoblast in 8 of the 10 above reported chronic intervillositis cases by either in-situ hybridisation or immunohistochemistry [13,23,27–29]. It was similarly identified by immunohistochemistry in our case. This strongly supports the likelihood that the inflammation was directly related to the viral infection and represents a SARS-CoV-2 placentitis.

Diagnostically the main differential diagnosis for the gross placental appearance is massive perivillous fibrinoid deposition. The microscopic

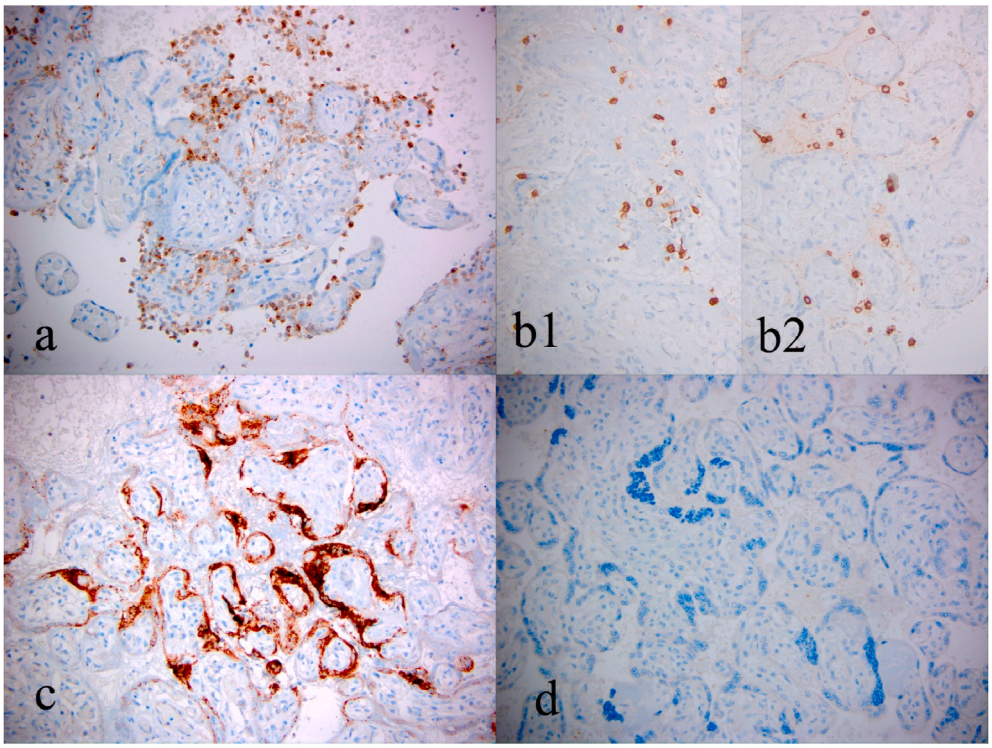

Fig. 3. Immunohistochemistry:a) A CD68 stain confirms that most cells involved in the intervillositis are histiocytes. b) Only occasional CD3 positive T-lymphocytes (b1) and CD20 positive B-lymphocytes (b2) are present. c) There is strong positive staining for SARS-CoV-2 in involved areas of the placenta. This staining is confined to villous trophoblast. d) Shows negative staining in a control placenta.

appearance of histiocytic intervillositis excludes this diagnosis however and, in our case, the apparent gross deposition of fibrinoid was actually caused by extensive clumping and adherence of villi caused by the inflammatory process. An MSB stain did not show significant fibrin-deposition (Fig. 1b) and matrix-type fibrinoid deposition, with embedded extravillous trophoblast, was not a feature. The main microscopic differential diagnosis is chronic histiocytic intervillositis, which is thought to represent an abnormal maternal immune response to paternal fetal antigens in the placenta. We agree with Kirtsman et al. in that the inflammatory process in SARS-CoV-2 placentitis seems to be subtly different with more "targeting" of the villous trophoblast by the histiocytic infiltrate while still sparing the villous stroma [31]. Both Kirtsman et al. and Pulinx et al. suggested that the trophoblast was showing infarction/ischaemic necrosis [31,35]; we would have a different interpretation and would suggest that the trophoblast necrosis was not ischaemic necrosis (infarction) and rather was necrosis either directly related to viral injury or the consequent inflammatory host response. There thus appears to be a form of placental disease that is specifically related to direct SARS-CoV-2 infection of placental villous trophoblast that represents a true SARS-CoV-2 placentitis. In the age of a COVID-19 pandemic, the placental appearance of a histiocytic intervillositis now has an additional important differential diagnosis that, for the pathologist, needs consideration and further diagnostic work-up. Interestingly, in 7 of the 11 examples of SARS-CoV-2 placentitis now reported, the authors suggested there was potential vertical transmission [13,27,28,31,34]. This may be related to ascertainment bias, but it is a fact worthy of further investigation as SARS-CoV-2 placentitis may turn out to be a potential marker for risk of vertical transmission. Evaluation of potential vertical transmission is limited in our case as the neonate was clinically well and was therefore not tested (in line with hospital protocols at the time). In the reports of 235 placentas included in this review, only 11 cases (4.7%) appear to show this pathology [13,27–29,31–35]. This would be in keeping with the apparent low rates of fetal complications and vertical transmission reported to date. As well as the potential for being a marker of vertical transmission, the amount of placental injury caused by the infection has the potential to be significant on its own. In our reported case, 25% of the parenchyma was diseased and likely unavailable for oxygen and nutrient transport. Such extensive disease may on its own contribute to a risk of fetal hypoxia-ischaemia in utero or around the time of birth. In our case there was reduced fetal movements and a non-reassuring CTG prior to delivery and the case of Schoenmakers et al. also presented with reduced fetal movements [32]. It is also possible that the miscarriage of twins reported by Pulinx et al. was directly related to the placental effects of the infection [35].

5. Conclusion

SARS-CoV-2 placentitis therefore appears to be an uncommon but distinctive complication of maternal COVID-19 infection and appears to have the potential to cause significant placental injury, potentially resulting in fetal compromise. Additional work is required to further investigate any previously reported associations but less specific placental pathologies, such as fetal vascular malperfusion and maternal vascular malperfusion. This will better the understanding of the significance of maternal infection with SARS-CoV-2 in pregnancy and the possible risks to the fetus.

6. Contribution to authorship

The authors declare that they have participated in this study as described below and have seen and approved the final manuscript. Dr Linehan acquired the data pertaining to the case report, reviewed the literature, drafted and edited the manuscript. Dr O 'Donoghue was responsible for the concept of the paper, reviewed the available literature and revised and edited the manuscript. Ms Dineen and Dr White performed the histological procedures in addition to the pathological analysis and interpretation and revised the manuscript. Prof Higgins

contributed to the acquisition of data and edited the manuscript. Dr Fitzgerald performed the histological procedures in addition to the pathological analysis and interpretation, analysed the available literature, drafted and edited the manuscript. All authors agree to be accountable for all aspects of the work.

Ethical approval

Ethical approval was not required for this case report. Patient permission was sought prior to drafting the manuscript and a consent form was signed by the patient.

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Declaration of competing interest

The authors declare that they have no conflicts of interest, professionally or financially, to hinder the publication of this work.

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