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RESEARCH ARTICLE

General Obstetrics

Clinical-pathological features in placentas of pregnancies with SARS-CoV-2 infection and adverse outcome: case series with and without congenital transmission

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Abstract

Objective: To correlate clinical outcomes to pathology in SARS-CoV-2 infected placentas in stillborn and live-born infants presenting with fetal distress.

Design: Retrospective, observational.

Setting: Nationwide.

Population: Five stillborn and nine live-born infants from 13 pregnant women infected with SARS-CoV-2 seeking care at seven different maternity units in Sweden.

Methods: Clinical outcomes and placental pathology were studied in 14 cases (one twin pregnancy) of maternal SARS-CoV-2 infection with impaired fetal outcome. Outcomes were correlated to placental pathology in order to investigate the impact of virus-related pathology on the villous capillary endothelium, trophoblast and other cells.

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Main outcome measures: Maternal and fetal clinical outcomes and placental pathology in stillborn and live-born infants.

Results: Reduced fetal movements were reported (77%) and time from onset of maternal COVID-19 symptoms to signs of fetal distress among live-born infants was 6 (3–12) days and to diagnosis of stillbirth 11 (2–25) days. Two of the live-born infants died during the postnatal period. Signs of fetal distress led to emergency caesarean section in all live-born infants with umbilical cord blood gases and low Apgar scores confirming intrauterine hypoxia. Five stillborn and one live-born neonate had confirmed congenital transmission. Massive perivillous fibrinoid deposition, intervillositis and trophoblast necrosis were associated with SARS-CoV-2 placental infection and congenital transmission.

Conclusions: SARS-CoV-2 can cause rapid placental dysfunction with subsequent acute fetal hypoxia leading to intrauterine fetal compromise. Associated placental pathology included massive perivillous fibrinoid deposition, intervillositis and trophoblast degeneration.

KEYWORDS
chronic histiocytic intervillositis, coronavirus, COVID-19, COVID-19 maternal-fetal transmission, fetal distress, maternal floor infarction, placental endothelial cells, placental pathology, SARS-CoV-2, SARS-CoV-2 placental infection, vertical SARS-CoV-2 transmission, villous macrophages

Tweetable abstract: SARS-CoV-2 can cause rapid placental dysfunction and intrauterine fetal compromise.

1 | INTRODUCTION

Following the emergence of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic, there was limited scientific knowledge on the impact of COVID-19 in pregnant women.[1-3] Recent studies have suggested that SARS-CoV-2 infection can lead to an increased risk of maternal death[4,5] and/or severe maternal morbidity.[2-8] Pregnant women with SARS-CoV-2 infection have been found to have higher rates of preterm delivery and caesarean section (CS) compared with non-infected pregnant women.[2,3,4,5,8,9,10] Evidence suggests that rates of stillbirth may have changed substantially during the pandemic,[11,12] with Khalil et al.[13] demonstrating a four-fold increase in the stillbirth rate in a cohort of mothers in Britain. These findings were reiterated in a multinational meta-analysis by Chmielewska et al.,[11] which even emphasised that some outcomes, such as stillbirth, had shown considerable disparity between high-resource and low-resource settings. In Sweden, recent studies have showed an increased risk for preterm delivery but not for stillbirth.[14,15]

Congenital transmission of SARS-CoV-2 has been convincingly reported in several case reports and series,[16-18] and thus placental pathology is of key interest.[19-21] SARS-CoV-2 antigens and nucleic acid have been identified most frequently in the placental villous syncytiotrophoblast,[22,23] but have also been identified to a lesser extent in the villous cytotrophoblast and in villous stromal macrophages (Hofbauer cells) and capillary endothelial cells.[24-27] For SARS-CoV-2, angiotensin-converting enzyme 2 (ACE2) is the undisputed receptor for cellular entry, and studies have shown strong and diffuse ACE2 staining in the cytotrophoblast and syncytiotrophoblast cells of placental villi, as well as in extravillous trophoblasts.[28,29] A handful of studies have reported that SARS-CoV-2 infection can lead to rapid placental dysfunction with fetal distress and imminent intrauterine demise of the fetus.[16,17,26] However, as congenital transmission is a rare event and not all infected pregnant women have poor obstetrical and neonatal outcomes, the possibility of fetal compromise due to COVID-19 in the mother is still debated.

Using a national Swedish case series of 13 women presenting with signs of fetal distress and COVID-19, we studied the clinical outcomes and placental pathology of 14 placentas (one twin pregnancy) infected by SARS-CoV-2 with and without congenital transmission. Our aim was to correlate clinical outcomes to placental pathology in stillborn and live-born infants presenting with fetal distress. To the best of our knowledge, this study represents the largest case series of placentas infected with SARS-CoV-2 among patients presenting with intrauterine fetal death after 22 weeks of gestation or having acute fetal distress.

2 | METHODS

The inclusion criteria for enrolment into this retrospective case series included women having pregnancies complicated by positive maternal testing for SARS-CoV-2; having an infant with an impaired perinatal outcome including stillbirth after 22 weeks of gestation or signs of severe fetal compromise leading to immediate delivery; and having

the placenta testing positive for SARS-CoV-2. Cases were collected throughout Sweden from 1 August 2020 to 16 December 2021. All the women had a positive test result for SARS-CoV-2 using reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) prior to delivery (with the exception of Case 5, see details in Results). The cases were enrolled from seven different Maternity and Delivery Units at tertiary or university hospitals in Sweden (Malmö, Lund, Helsingborg, Varberg, Stockholm, Uppsala and Linköping). Clinicians and pathologists involved were personally contacted by one of the authors (M.Z.) requesting confirmation of the clinical, laboratory and pathology findings. Informed written consent was obtained from all women involved in the study. Case numbers 1, 3, 4, 6, 8, 9, 12, 13 and 14 were included through the COVID-19 in Pregnancy and Early Childhood (COPE) study[30] using individual patient consent forms. Case numbers 2, 5, 7, 10 and 11 were included separately and individual consent forms were obtained for these patients as well. Additional consent was obtained from the women's partner where appropriate (in live-born cases). The study was performed in agreement with principles of the Declaration of Helsinki for Human Research. Patients were not involved in the development of the research reported in the study.

2.1 | Sampling

Blood samples, nasopharynx (NPH) and throat swabs from mothers, stillborn infants and neonates were collected according to clinical praxis. Neonatal nasopharyngeal swabs were taken within 24 hours of birth. If positive, testing was continued every 24 hours until the neonate was negative, whereafter the neonate was taken out of isolation. The incision into the placental disc parenchyma to obtain a placental tissue sample for RT-qPCR test in Cases 1–10 and 14 was performed after disinfection of the fetal and maternal surfaces as described by Baud et al.[31] The placental tissue was obtained by a triangulate section reaching the core of the placental disc and the remaining placenta was kept in formalin. For Cases 11–13, the standard practice of the pathology laboratory analysing the samples did not include disinfecting placental surfaces. A new blade, however, was used and no reports of any problem with contamination have been reported. Sample collection, processing and laboratory testing followed guidance from national guidelines and recommendations from the Swedish Public Health Authority.[32]

2.2 | Histopathology and immunohistochemistry

Placentas were subjected to gross pathological evaluation and any abnormalities were noted. Trimmed placental weights were recorded and compared with normal values adjusted for gestational age.[34] Following careful dissection of the placentas, representative tissues for microscopic examination were selected and submitted for routine histological processing. Haematoxylin and eosin staining was performed according to routine procedures. Immunohistochemistry was performed using standard methods with a polyclonal antibody to the SARS-CoV-2 nucleocapsid protein (40143-T62; Sino Biological) at a 1:2000 dilution. Appropriate positive and negative immunohistochemistry controls were performed. In Sweden, ACE2 detection and *in situ* RNA detection was only available in a few research environments. The available methods were therefore RT-qPCR and immunohistochemistry for SARS-CoV-2 nucleoprotein in Cases 1–10 and 14. For Cases 11–13, an RNA scope was available at that particular laboratory. Following staining, microscopic examination and diagnosis of the umbilical cord, extraplacental membranes and placental discs was conducted. Results of placental findings were reviewed by three specialists in placental pathology (D.A.S., D.G., N.P.).

2.3 | Clinical correlation

In each case, maternal and fetal/infant clinical data were obtained from hospital records. Body mass index (BMI) at the first antenatal care visit was recorded and the presence of significant placental pathology was assessed. Results from SARS-CoV-2 testing, including possible maternal-fetal transmission as defined by Shah et al.,[35] was also noted. Congenital infection with intrauterine fetal death/stillbirth or in live-born neonates was categorised into 'confirmed' and 'probable' cases.[35] Case 9[16] has been published previously, otherwise none of the other cases have been presented in the literature prior to submission of this paper.

3 | RESULTS

Five women (5/13, 38%) gave birth to stillborn infants (mean gestational age 33^{+0}, range 24^{+4} to 38^{+2} weeks). Eight mothers (8/13, 62%) gave birth to nine live-born infants (including one set of twins) (mean gestational age 32^{+3}, range 24^{+1} to 36^{+0} weeks). Two of the nine live-born infants died later during the postnatal period, a neonatal mortality rate of 22%. There were no full-term (37–42 weeks of gestation) infants delivered to women in this cohort. The maternal and fetal characteristics including placental pathology from the pregnant women presenting with stillbirth are reported in Table 1 and for live-born infants in Table 2. The villous syncytiotrophoblast from all placentas stained positively for SARS-CoV-2 nucleocapsid protein using immunohistochemistry, confirming that the placentas from all cases were infected with SARS-CoV-2 based on published immunohistochemical and molecular pathology criteria for determining placental infection.[36,37]

The majority of the women presented in their third trimester (11 of 13 women, 85%). Three of the five women (60%)

TABLE 1 Maternal, fetal and infant characteristics from five pregnant women with SARS-CoV-2 infection and stillbirth in which the placenta was confirmed to be infected with the coronavirus

	Case 1	Case 2	Case 3	Case 4	Case 5
Maternal and fetal characteristics					
Maternal age (years)	31	26	25	25	37
Gestational age (weeks) at					
Onset of maternal symptoms	34^{+4}	24^{+2}	32^{+5}	34^{+5}	31^{+0}
Positive maternal RT-qPCR	34^{+5}	23^{+3}	33^{+1}	34^{+6}	(Please see Results)
IUFD	35^{+1}	24^{+4}	34^{+1}	38^{+2}	33^{+0}
Parity	1	1	0	0	1
Body mass index (BMI) kg/m^2 at antenatal care visit	21	20	31	27	24
Maternal comorbidities	None	None	None	Hypothyroidism, Idiopathic thrombocytopenia purpura	None
Mother born in Sweden	Yes	Yes	No	No	No
Presenting symptoms at time of seeking healthcare services	Reduced fetal movements for 1 day Painful uterine contractions for 1 day	Fever 40 °C for 1 day Uterine contractions for 1 day	Reduced fetal movements for 1 day Uterine contractions, back pain, small bleeding for 1 day Difficulties in breathing, cough, fever on and off, nausea for 10 days	Reduced fetal movements for 1 day	Reduced fetal movements for 2 days Fever for 14 days Headache for 14 days Nausea/reduced apetite for 14 days
Fetal SARS-CoV-2 status using RT-qPCR[a]	Positive	Negative	Positive	Negative	Negative (Cycle Threshold just above threshold for positive test)
Birthweight (g)	2200	686	2190	2665	1920
Small-for-gestational age (SGA)[37]	No	No	No	No	No
Placental features and autopsy findings					
Vertical transmission (congenital infection with intrauterine fetal death/stillbirth)[34]	Confirmed	Confirmed	Confirmed	Confirmed	Confirmed (Note: fetal SARS-CoV-2 cycle threshold = 36.5, just above threshold for a positive test)
Placental weight (g)	N/A	236	376	401	305
Placental weight according to gestational week[33]	N/A	Normal	Normal	Underweight	Underweight
Trophoblast staining for SARS-CoV-2	++	++	++	++	++

(Continues)

TABLE 1 (Continued)

	Case 1	Case 2	Case 3	Case 4	Case 5
Fibrinoid deposits—type and percentage coverage of placental parenchyma	Massive perivillous fibrinoid deposition, 90%	Borderline perivillous fibrinoid deposition, 25%	Massive perivillous fibrinoid deposition, 80%	Massive perivillous fibrinoid deposition, 80%	Massive perivillous fibrinoid deposition, 85%
Intervillositis	• Acute intervillositis • Chronic histiocytic intervillositis	Acute intervillositis	Acute intervillositis	Chronic intervillositis	Chronic intervillositis
Trophoblast necrosis	++	++	++	−	−
Maternal vascular malperfusion	+	+	−	−	+
Karyorrhexis phenomena	+	+	−	−	−
Choriangiosis	+	−	−	−	−
Placental tissue SARS-CoV-2 RT-qPCR	+	+	+	+	+
Other important pathological features	Calcification	Umbilical cord: hypospiralised	Nucleated erythrocytes	Late development of chorionic villi, nucleated erythrocytes, sub-chorionitis	Necrosis of decidua basalis and capsularis
Fetus gender	Boy	Girl	Girl	Girl	Girl
Autopsy findings	Mild maceration. SARS-CoV-2 positive lung tissue. No congenital anomalies seen. Brain and liver size larger than reference values for gestational week 35. Blood trombosis in right atrium and umbilical cord vein. Petechial bleeding in epicardium	Appropriate for gestational age fetus with no visible congenital anomalies. Fetal lung tissue showing grooves of epithelial cell indicating suspected aspiration. No bacterial or virus infection could be shown. Normal genetic screening	Parents declined consent. No gross anomalies seen. Heart puncture RT-qPCR positive for SARS-CoV-2.	Parents declined consent. No gross anomalies seen.	Left hand was malformed with a shortening of two fingers and suspected absence of two metacarpal bones

[a]Reverse transcription quantitative polymerase chain reaction (RT-qPCR) using nasopharyngeal or heart puncture swab from fetus.

TABLE 2 Characteristics of pregnant women with SARS-CoV-2 infection presenting with signs of fetal distress and characteristics of their live-born infants including placental features

	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12,13 Diamniotic dichorionic twins	Case 14
Maternal characteristics								
Maternal age (years)	28	38	30	27	31	30	31	33
Gestational age (in weeks) at								
Onset of maternal symptoms	34^{+4}	21^{+3}	34^{+2}	34^{+1}	32^{+4}	23^{+0}	33^{+0}	28^{+4}
Positive maternal RT-qPCR	34^{+2} (contact tracing)	21^{+6}	34^{+5}	34^{+4}	32^{+5}	23^{+4}	33^{+4}	28^{+4}
Time of delivery	35^{+1}	31^{+6}	36^{+0}	34^{+4}	33^{+5}	24^{+1}	34^{+0}	29^{+3}
Parity	1	1	1	1	2	1	1	2
BMI (kg/m^2)	31	23	27	27	23	35	40	22
Maternal comorbidities	Depression, Gastric by-pass, gestational diabetes	None	None	None	None	Polycystic ovaries, Pregnant after ovulation stimulation	Depression, Asthma	Migraine
Mother born in Sweden	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Presenting symptoms	Reduced fetal movement for 1 day	Planned ultrasound scan due to bad obstetric history (Previous pregnancy: oligo-hydramnios, chorio-amnionitis with premature delivery)	Reduced fetal movements for 1 day	Reduced fetal movement for 1 day Dry cough-1 day Fever for 3 days Abdominal pain for 3 days	Reduced fetal movement for 3 days Maternal fever, 2–4 days ago	Reduced fetal movement for 2 days Fever for 8 days Blocked nose for 8 days	Reduced fetal movements-1 day	Cough for 6 days Sore throat for 6 days Uterine contractions for 1 day
Cardiotocograph (CTG) classification[38]	Pathological • Decreased baseline variability • Recurrent prolonged, late decelerations	Normal	Pathological • Repeated episodes of bradycardia	Pathological • Reduced baseline variability • Absence of accelerations • Recurrent prolonged, late decelerations	Pathological • Frequency 150/min • Absence of accelerations • Reduced baseline variability • Recurrent late decelerations	Pathological • Reduced baseline variability • Recurrent, late decelerations	Normal 12 hours prior to delivery Normal 12 hoursprior to delivery	Pathological • Reduced baseline variability • Recurrent variable decelerations and late decelerations
Mode of delivery	Emergency caesarean section	Semi-acute caesarean section	Emergency caesarean section	Emergency caesarean section	Emergency caesarean section	Emergency caesarean section	Emergency caesarean section	Emergency caesarean section
Indication for delivery	Pathological CTG pattern	Fetal blood flow velocimetry deterioration	Pathological CTG pattern	Pathological CTG pattern	Pathological CTG pattern	Pathological CTG pattern and BFC 2	Preeclampsia (high blood pressure and thrombocytopenia)	Pathological CTG pattern

TABLE 2 (Continued)

	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12,13 Diamniotic dichorionic twins		Case 14
Infant characteristics									
Apgar Score (1, 5, 10 minutes)	2, 4, 7	9, 10, 10	4, 8, 9	1, 4, 8	3, 5, 8	2, 5, 7	0, 0, 1	4, 7, 8	1, 5, 8
Umbilical cord blood gases (Units: lactate in mmol/litre, base excess [BE] in mEq/litre)	Arterial pH: 7.15 Arterial lactate: 11.5	NA	NA	Arterial pH: 7.20 Arterial lactate: 11.0 Vein pH: 7.22 Vein lactate: 10.1	Arterial pH: 7.21 Arterial BE: −7.6 Arterial lactate: 10 Vein pH: 7.26	Vein pH: 7.07 Vein BE: −15.5	Vein pH: 6.69 Vein BE: −22	Vein pH: 7.29 Vein BE: − 11	NA
Neonatal SARS-CoV-2 status (RT-qPCR using naso-pharyngeal swab within 24 hours of birth)	Negative	Negative	NA	Positive (Infant had no contact with parents prior to SARS-CoV-2 testing)	NA	Negative	Negative	Negative	Positive (Infant had no contact with parents prior to SARS-CoV-2 testing)
Birthweight (g)	2064	1200	2708	2310	1675	570	2182	1846	1370
Small-for-gestational age (SGA)[37]	Yes	Yes	No	No	Yes	Yes	No	Yes	No
Infant gender	Girl	Boy	Girl	Boy	Girl	Girl	Girl	Boy	Boy
Infant health at discharge	Thrombocytopenia before delivery, normalised 4 days postpartum	Healthy	Healthy	No spontaneous breathing directly after birth. Continuous positive airway pressure (CPAP) for 24 mins. No extra support was needed thereafter. Neonate discharged 14 days after birth.	Manual ventilation for 5 minutes directly after birth. There-after CPAP for 9 hrs. Due to prematurity + SGA, neonate was kept at the Neonatal ward for 8 days. Discharged after neonatal homecare for another 6 weeks.	Moved to the neonatal intensive care unit (NICU) due to a massive intra-cerebral bleed. Life support turned off day 2. Post-mortem showed intra-ventricular haem-orrhage (IVH) (grade 4) and fresh bleeding in the adrenal glands.	The neonate suffered from hypoxic ischaemic encephalopathy (HIE) grade III and intensive care was discontinued 6 days after birth. The neonate died 8 days after delivery.	Healthy	No spontaneous breathing after birth. Intubated with respirator day 1. Day 2: CPAP and developed IVH (grade 1). Recovering at the neonatal ward with high flow nasal cannula (HFNC) Day 18.
Placental features									
Vertical transmission (Congenital infection)[34]	Probable	Probable	Probable	Confirmed	Probable	Probable	Probable	Probable	Probable

TABLE 2 (Continued)

	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12,13 Diamniotic dichorionic twins		Case 14
Placental weight (grams)	325	256	594	342	294	156	400	283	300
Placental weight according to gestational week[33]	Underweight	Underweight	Overweight	Normal weight	Underweight	Underweight	Normal weight	Underweight	Normal weight
Trophoblast staining for SARS-CoV-2	+	+	+	+	+	+	+	+	+
Fibrinoid deposits, percentage distribution within placental parenchyma	Borderline massive perivillous fibrinoid deposition, 40%	–	Borderline massive perivillous fibrinoid deposition, 40%	Massive intervillous fibrinoid deposition, 75%	Massive intervillous fibrinoid deposition, 75%	Massive perivillous fibrinoid deposition, 90%	Massive perivillous fibrinoid deposition and infarcts, >90%	Borderline massive perivillous fibrinoid deposition with infarcts, 40%	Perivillous fibrinoid deposition with infarcts, 10%
Intervillositis	Acute intervillositis	–	Focal acute intervillositis	Acute intervillositis	Widespread focal acute-chronic inter-villousitis with 'Nuclear dust'	Widespread chronic histiocyte intervillositis	Widespread chronic histiocytic intervillositis	Widespread chronic histiocytic intervillositis	Chronic histiocytic intervillositis
Trophoblast necrosis	+	–	+	+	+	+	+	+	+
Maternal vascular malperfusion	+	–	+	–	–	–	+	–	–
Choriangiosis	–	–	–	+	+	–	+	+	–
Other placental findings	Agglutination of villi with inflammatory cells, increased villous maturation but no signs of maternal vasculopathy. Umbilical cord was hyperspiralised	Intraparenchymal infarctions covering 10% of the placenta tissue, plasma cell inflammation of the decidua capsularis and basalis. Immuno-chemistry for SARS-CoV-2 was positive focally	Acute villitis, maternal vasculopathy of hypertrophy type. The umbilical cord was hyper-spiralised with a marginal insertion.	Multiple regions of dense intervillous infiltrates of neutrophilic granulocytes and macrophages. SARS-CoV-2 nucleoprotein was strongly positive in the cytoplasm + nucleus of villous cytotropho-blasts and syncytio-trophoblasts in areas with intervillositis and fibrinoid depositions	Fibrinoid deposition focally transmural with accentuation on the maternal side of the placenta	Immunochemistry for SARS-CoV-2 was weakly positive in trophoblast cells but molecular analysis of (mRNA COVN and COVS) strongly positive in trophoblast cells and in placental parenchyma	Acute aterosis and thrombosis, villous necrosis and agglutination of villi with inflammatory cells. The umbilical cord was hyper-spiralised. Calcified areas were found within the parenchyma	Few maternal vessels with necrosis of blood vessel walls, agglutination of villi with inflammatory cells and calcified areas with the parenchyma	Strong, diffuse positivity for SARS-CoV-2 nucleoprotein in villous trophoblasts. Areas with intervillositis are dominated with MPO^+ granulocytes, $CD68^+$ macrophages/ histiocytes and to a lesser extent $CD3^+$ T-lymphocytes and minimally $CD20^+$ B-cells

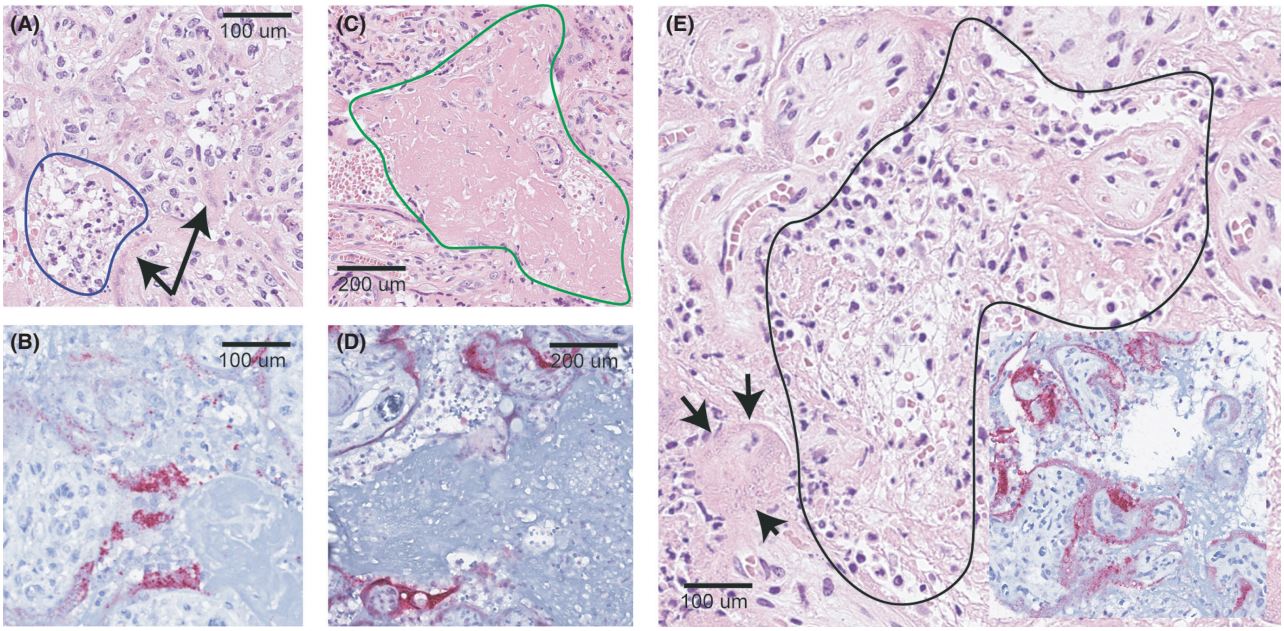

FIGURE 1 Histopathology of SARS-CoV-2 positive placentas. (A) Placental parenchyma stained with haematoxylin–eosin (HE) from Case 8 (live-born) showing acute intervillositis manifested by a mixed inflammatory infiltrated dominated by polymorphonuclear granulocytes in the intervillous space (blue demarcation) along with degeneration of villous trophoblasts (arrows). (B) Positive stain for SARS-CoV-2 nucleocapsid protein in villous trophoblasts in the same region as in (A) from Case 8. (C) HE-stain from Case 6 (live-born) demonstrating massive fibrinoid deposition in the intervillous space (green demarcation). (D) Positive stain for SARS-CoV-2 nucleocapsid protein in villous trophoblasts from the same region as in (C) in Case 6. (E) HE-stain of Case 3 (stillborn) showing acute intervillositis among reticulate deposition of fibrinoid (black demarcation) surrounded by degenerating villous trophoblasts (arrows). Inset shows positivity for SARS-CoV-2 nucleocapsid protein in the same region

presenting with intrauterine fetal demise (IUFD) were not born in Sweden, whereas six of the eight women (75%) with live-born infants were Swedish-born. Experiencing reduced fetal movements was the major reason for seeking healthcare in ten of the 13 cases (77%). High fever (>39°C) was reported in four of 13 cases (31%). All women had tested positive for SARS-CoV-2 using RT-qPCR, except for Case 5, where the mother had a negative nasopharyngeal swab. However, as her partner was COVID-19-positive, serum antibodies for SARS-CoV-2 confirmed COVID-19 in the mother.

Histopathological examination of the placentas revealed a spectrum of pathologically increased fibrinoid deposition that varied in severity up to massive perivillous fibrinoid deposition (MPFD) in 13 of the 14 placentas (93%), which varied in estimated mean percentage covering the placental parenchyma in stillborn cases (72%, range: 25%–90%) and live-born cases (58%, range: 10%–90%). The only case without fibrinoid deposition (Case 7) was a mother who had recovered from COVID-19 infection by the time of delivery, 10 weeks after confirmed infection. Another finding was the presence of intervillositis with acute inflammatory cells mixed with chronic inflammatory cells dominated by histiocyte-like cells ($CD68^+$), which was present in almost all placentas (13 of 14 placentas, 93%), Case 7 again being the exception (described in detail below). The degree of intervillous inflammation, which was of mixed inflammatory cell type (11 of 14 cases, 79%), varied between the different cases and also geographically within the parenchyma of each placental disc.

3.1 | Stillborn infants

Four of the five women (80%) presented in the third trimester and had experienced reduced fetal movements, and three of these women (60%) had even experienced painful uterine contractions (Table 1). The majority of the mothers had no significant comorbidities and only one had an abnormal BMI (Case 3: 31 kg/m^2). All five women had been concomitantly diagnosed with COVID-19 using an RT-qPCR except for Case 5, who had positive IgG antibodies for SARS-CoV-2. Two of the stillborn infants tested positive for SARS-CoV-2 (Case 1: positive lung tissue at autopsy; Case 3: positive swab obtained from heart puncture), while the RT-qPCR from the infant in Case 5 showed a cycle threshold value of 36.5, just above the threshold for a positive test. Of note, none of the stillborn infants was small-for-gestational age (SGA).[38] The onset of maternal signs and symptoms preceded IUFD diagnosis from 2 to 25 days, with a mean of 11 days, prior to diagnosis of fetal demise.

RT-qPCR for SARS-CoV-2 in placental tissue was positive in all cases (100%). Gross examination of the placentas from three of the five stillbirths (60%) showed that they were underweight in relation to the gestational week of the pregnancy (placental weight <10th percentile for gestational

age).[34] The syncytiotrophoblast of all five cases (100%) stained positive for SARS-CoV-2 nucleocapsid protein. Furthermore, all cases showed extensive fibrinoid deposition in the intervillous spaces (100%), from borderline to massive parenchyma involvement (Table 1; Figure 1). All five placentas demonstrated intervillositis (also termed chronic histiocytic intervillositis) composed of a mixture of acute and chronic inflammation, with some placentas showing a predominance of histiocytes (Cases 1, 4 and 5) and the others having predominantly neutrophils in the intervillous inflammatory infiltrate (Cases 2 and 3; Figure 1). Trophoblast necrosis was present in all five placentas (100%). Of note, cases varied with regard to the degree of intervillous inflammation. This was illustrated in the placentas from Cases 1, 4 and 5 where there was MPFD and the extent of chronic histiocytic intervillositis appeared to be more severe compared with Cases 6 and 8 (live-born infants, see below) (Figure 1), where borderline fibrinoid deposition was associated with less severe intervillositis.

Maternal vascular malperfusion including abnormalities such as placental hypoplasia,[34] placental infarction and retroplacental haemorrhage were found in Cases 1, 2 and 5 (60%). Villous stromal-vascular karyorrhexis, represented by erythrocyte extravasation and fragmentation, was noted in two cases (Cases 1 and 2). Similarly, nucleated fetal erythrocytes signalling fetal hypoxia were observed in the fetal chorionic vasculature of two cases (Cases 3 and 4).

3.2 | Live-born infants

Six of the nine (67%) women with live-born infants presented with reduced fetal movements as their major reason for seeking healthcare. Cardiotocography (CTG) tracings from Cases 6, 9, 11 and 14 (Figure S1) showed decreased variability in the fetal heart rate tracing. Late, prolonged decelerations portraying a pathological pattern[39] were seen in six of the nine live-born infants (67%) leading to emergency CS in which intrauterine hypoxia was confirmed by umbilical cord blood sampling (Table 2). Of note, all pregnancies were terminated before term with CS (100%). Low Apgar scores were also noted in eight of the nine live-born cases (89%). Routine SARS-CoV-2 testing in infants using RT-qPCR within 24 hours of birth showed a positive result in Cases 9 and 14. Intrauterine (congenital) transmission was confirmed in Case 9 using viral genomic testing of the mother and neonate.[16]

At birth, five of the live-born infants (56%) were SGA. The timing from onset of maternal COVID-19 symptoms to emergency CS due to signs of fetal distress varied from 3 to 12 days (mean: 6 days), with the exception of Case 7 (73 days, details below).

Similar to stillborn infants, five of the nine placentas were underweight (56%) and all showed borderline to massive fibrinoid deposition (mean 51%). Varying grades of intervillositis were seen. Focal intervillositis in which the inflammatory infiltrate was predominantly neutrophilic was seen in Cases 8 and 10, both female infants born by emergency CS in the third trimester of pregnancy due to pathological CTG changes. Intervillositis with a predominance of histiocytes was present in Cases 11, 12, 13 and 14 (Figure S2). Trophoblast necrosis was present in eight of nine placentas (89%).

Case 7 had both a unique clinical history as well as a distinct placental pathology. Ultrasonography evaluation at 24^{+6} weeks gestation showed severe oligohydramnios and intrauterine growth restriction (IUGR) with an estimated fetal weight of 496 g (–37%), pathological umbilical artery blood flow class (BFC) 3A[40] and signs of fetal brain sparing.[41] Maternal uterine artery blood flow was, however, unaffected. Three weeks previously, the mother had tested positive for SARS-CoV-2 with minor symptoms (fever). She was admitted to the prenatal unit for further testing and fetal observation. There were no CTG changes of concern, but two doses of 12 mg betamethasone were administered with a 24-hour interval to enhance fetal lung maturity. Serology for TORCH agents including cytomegalovirus, toxoplasmosis, rubella, herpes simplex and parvovirus were negative. Repeated blood flow velocimetry 2 days later showed slight improvement, with BFC 2, which was expected secondary to betamethasone administration, returning to BFC 3A after another 3 days. Chorionic villus sampling was performed as part of clinical routine to investigate possible genetic/chromosomal abnormalities as a cause of the very low estimated fetal weight and a normal Array-CGH (Comparative Genomic Hybridisation) was confirmed. The patient was discharged at 27^{+2} weeks with planned biweekly check-ups. Fetal growth had improved slightly at 28^{+6} weeks with an estimated fetal weight of 945 g (–33%). Umbilical artery blood flow had also improved to BFC 1 at 29^{+2} and remained stable until 31^{+2}, when it deteriorated to BFC 2. The patient was readmitted and received a 12-mg rescue dose of betamethasone at 31^{+2} weeks, and 6 g magnesium sulphate for fetal neuroprotection, whereafter an uncomplicated CS was performed. The placenta was small for gestational week 31 but lacked fibrinoid depositions. Instead, old infarcts were observed with plasma cell infiltration in both the decidua capsularis and basalis. Additionally, immunohistochemistry for SARS-CoV-2 was focally positive in the placenta.

Cases 12 and 13 relate to a woman spontaneously pregnant with diamniotic dichorionic twins. With a prior history of pre-eclampsia, she contacted the local maternity centre complaining of reduced fetal movements and cold-like symptoms, and a positive SARS-CoV-2 test. After an assessment of the mother's well-being and a normal CTG of the fetuses, she was sent home with a prescription for low molecular weight heparin (7500 IE per day) for 2 weeks as per the recommendation of the Swedish Society of Obstetrics and Gynaecology.[42] Four days after her positive SARS-CoV-2 test, the patient's blood pressure had risen to 145/100 and laboratory tests revealed that her platelet count had fallen from 46×10^9/litre to 26×10^9/litre, 7 hours later. It was decided to perform a CS with general anaesthesia following administration of a platelet concentrate. However, during

the surgery, the patient experienced an acute fall in her oxygen saturation to 80% (suspected bronchospasm secondary to asthma and COVID-19 infection). After the delivery of the infants, the woman was given betamethasone to induce bronchorelaxation. Twin 1 was a female born without signs of spontaneous life and having Apgar scores of 0, 0 and 1 at 1, 5 and 10 minutes, respectively. Cord blood gases, presumably from the umbilical vein, revealed a pH of 6.69 and base excess −22. Twin 2, a boy, had Apgar scores of 4, 7 and 8 at 1, 5 and 10 minutes, respectively. Twin 1 suffered from hypoxic ischaemic encephalopathy grade III and intensive care was discontinued 6 days after birth. Placental pathology from Twin 1 demonstrated MPFD with necrosis of chorionic villi that constituted more than 90% of the placental volume. Widespread chronic histiocytic intervillositis and signs of vascular malperfusion with acute atherosis and thrombosis in maternal decidual vessels was also observed. The placenta of Twin 2 was less affected, showing an estimated 40% of the placental volume covered by perivillous fibrinoid deposits (Table 2).

3.3 | Congenital transmission

Categories of SARS-CoV-2 transmission were defined according to Shah et al.,[35] with congenital infection with intrauterine fetal death 'confirmed' in Cases 1–5 where detection of the virus by RT-qPCR from *placental* tissue was seen in all cases and from *fetal* tissue seen in Cases 1 and 3 (Table 1). Similarly, congenital infection in live-born neonates was 'confirmed' in Cases 9 (viral genomic testing) and 'probable' infection in Cases 6–8 and 10–14 (Table 2). Associating the placental findings from the six confirmed cases of congenital transmission (Case 1–5 and 9) included a triad of MPFD, intervillositis and trophoblast necrosis. The intensity of fibrinoid deposition in the placental parenchyma varied from 25 to 90%. Maternal vascular malperfusion and karyorrhexis was seen in Cases 1, 2 and 5.

4 | DISCUSSION

4.1 | Main findings

This nationwide Swedish case series demonstrated the clinical outcomes and placental pathology in a unique series of women with SARS-CoV-2 infection in pregnancy presenting with fetal compromise. The majority of the women presented with a cardinal clinical symptom, namely, reduced fetal movements in the third trimester. In the case of a living fetus at the time of presentation, signs of fetal distress included pathological CTG patterns or umbilical blood flow changes that led to immediate termination of the pregnancies by CS. SARS-CoV-2 infection was the causative agent associated with fetal compromise in all cases leading to rapid placental dysfunction and intrauterine demise in five of the 14 cases reported, with two neonatal deaths. A triad of placental features were associated with the infection, namely, trophoblast degeneration, intervillositis and massive perivillous fibrinoid deposits.

4.2 | Strengths and limitations

To the best of our knowledge this is one of the largest case series on placental dysfunction in SARS-CoV-2 mothers with fetal compromise and congenital transmission. Another strength was that cases were collected from maternity centres throughout Sweden. This was of considerable importance, as the study was reporting on rare events such as congenital transmission. The findings from six confirmed cases of SARS-CoV-2 congenital transmission were reported, giving us the unique opportunity to stratify clinical outcomes and placental features in this special group of patients. Similarly, COVID-19 infection was confirmed in all cases using RT-qPCR, leaving little doubt about the cause of placental dysfunction.

Limitations of this study include its retrospective nature and the lack of a control group of mothers that had presented with COVID-19 without fetal impairment. Lack of biological samples including cord blood and amniotic fluid could also have aided in the classification of the 'probable' cases of congenital transmission. The authors also acknowledge that the vast majority of women presenting with SARS-CoV-2 infection during pregnancy have a normal perinatal outcome.[8,11] However, the aim of this study was to focus on the small subset of women who do suffer adverse perinatal outcomes and to highlight that SARS-CoV-2 can lead to or aggravate concurrent placental dysfunction with intrauterine hypoxia and stillbirth in rare cases.

4.3 | Interpretation

Reduced fetal movements have been associated with a higher rate placental lesions and adverse pregnancy outcome as compared with controls.[43] Additionally, accelerating fetal growth in the third trimester puts higher demands on optimal placental function. The fetus may therefore be more vulnerable to acute placental dysfunction in these weeks.[44] The pathological CTG changes seen included decreased variability, repeated episodes of late decelerations or bradycardia and the absence of accelerations, all of which have been associated with impaired uteroplacental function and intrauterine fetal hypoxia.[45] Similarly, low Apgar scores, abnormal umbilical cord arterial and venous pH and lactate confirmed hypoxia prior to birth.[46,47] SARS-CoV-2 infection was therefore the causative agent associated with fetal compromise in all cases, including the twin pregnancy (Cases 12 and 13) where the death of the Twin 1 may be associated to massive fibrin deposits extending over 90% of the placental parenchyma. Pregnant women with COVID-19 have been reported to develop a pre-eclampsia-like syndrome, which

may account for the high blood pressure and falling thrombocyte count noted in the mother with the twin pregnancy.[48]

The cases included in the study help elucidate the timing of fetal compromise after the first onset of maternal signs and symptoms of COVID-19 infection. We noted that, on average, IUFD was diagnosed 11 days and signs of fetal distress were identified 6 days after the onset of maternal COVID-19 symptoms. This would indicate that placental dysfunction can be triggered in a matter of a few days after COVID-19 infection, a recently reported finding.[49] Similarly, the placentas of both stillborn and live-born infants exhibited extensive fibrinoid deposits accompanied by villous necrosis characteristic of MPFD and intervillositis. Indeed, MPFD lesions have been strongly associated with intrauterine growth restriction (IUGR) and stillbirth,[50,51] as fibrin deposits obstruct the intervillous spaces so that maternal blood can no longer perfuse the chorionic villi, resulting in villous ischaemia and necrosis. Thus, the pathological features seen in placentas well explain the clinical outcomes of the stillborn and live-born infants included in the current study. Furthermore, these findings are indicative of a rapid, progressive and widespread destruction of functional placental tissue leading to acute fetal distress and the risk of IUFD within days of COVID-19 infection in the mother.

A wide spectrum of other pathological features was also seen that included intervillositis in 13 of 14 placentas, as well as findings resulting from maternal vascular malperfusion and trophoblast necrosis. Areas of more severe fibrinoid deposition were associated with a more severe inflammatory response with a mixed population of inflammatory cells being seen in the intervillous spaces. This feature was dissimilar to previous data where placentas with massive fibrinoid deposition appeared to have a less severe onslaught of intervillositis than in cases where the fibrinoid deposition was not as prominent.[23] In light of the spectrum of microscopic abnormalities present in SARS-CoV-2 infected placentas, it may be proposed that the changes illustrated may represent a form of villous repair in response to viral involvement of the trophoblast, which was present in all cases in this study.

When comparing placental features, there was no clear evidence that either Hofbauer cells or any other cell type was associated with a greater probability of maternal-fetal transmission. Similar to Schwartz et al.,[27] it seems probable that transplacental infection of the fetus with SARS-CoV-2 can occur in the absence of Hofbauer cell involvement. However, all cases having congenital transmission exhibited MPFD that was associated with intervillositis.

Some studies have indicated an increase in the stillbirth rate during the pandemic,[11-13] and newer virus strains have been associated with a significant increase of severe COVID-19 illness in mothers.[52] This study adds to growing data showing evidence of fetal compromise secondary to SARS-CoV-2 related placental dysfunction.[16,17,18,49] In addition to direct virus-related injury, indirect effects such as limitations in access to antenatal care during the pandemic or reluctance to go to the hospital when needed, for fear of contracting infection, might have caused the increase in stillbirths. Studies on the quality of maternal healthcare services during the pandemic, confirmed disparities in access to antenatal services across Europe[53] and the pandemic hanging as a 'shadow' over pregnant women[54]. However, population-based studies have only confirmed an increase in the number of medically indicated preterm births and shown no increase in spontaneous preterm births or stillbirths in Scandinavia.[14,15]

Congenital transmission is thankfully a rare event and the placental syncytiotrophoblast layer may therefore act as an effective barrier preventing the cascade of inflammatory events seen with congenital transmission of SARS-CoV-2.

5 | CONCLUSION

This study showed that SARS-CoV-2 infection in pregnant women can lead to placental dysfunction with consequent intrauterine hypoxia, fetal distress and, in some cases, stillbirth. The major symptom for seeking healthcare for women included into this study was reduced fetal movements in the third trimester. In women presenting with living fetuses, monitoring with CTG or umbilical cord blood flow showed abnormal findings indicating intrauterine hypoxia.

Of the placental features, trophoblast degeneration, intervillositis and massive perivillous fibrinoid deposits appear to be associated with placental SARS-CoV-2 infection, especially in cases with congenital transmission. Further studies are warranted to explore the mechanisms of virion transfer into and through the placenta and to understand why placental dysfunction occurs only in a small subset of pregnancies.

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CONFLICT OF INTERESTS

None declared. Completed disclosure of interest forms are available to view online as supporting information.

AUTHOR CONTRIBUTIONS

MZ and VS conceived the project, MZ performed the literature search, prepared the tables, figures, merged and interpreted all the data and wrote the manuscript draft. MZ, DG, AS, AKW, EW, LI, MN, MB, NP, SH and ÅS contributed with recruitment and description of cases from their departments. DAS contributed to the pathology discussion. DG and NP

performed the pathological examination and prepared the figures. All authors critically reviewed the manuscript for important intellectual content and approved it in its final version.

ETHICS APPROVAL

Women provided written informed consent to publication, available upon request. Additional consent was obtained from the women's partner were appropriate (in live-born cases). Cases 1, 3, 4, 6, 8, 9, 12, 13 and 14 are part of the COPE study and have given additional specific consent for publication of this case series. The COPE study has been granted national ethical approval by the Swedish Ethical Review Authority (dnr 2020-02189 and amendments 2020-02848, 2020-05016, 2020-06696, and 2021-00870). The case study was performed in agreement with principles of the Declaration of Helsinki.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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