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ORIGINAL RESEARCH ARTICLE

SARS-CoV-2 placentitis and severe pregnancy outcome after maternal infection: A Danish case series

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Abstract

Introduction: SARS-CoV-2 infection during pregnancy may cause viral inflammation of the placenta, resulting in fetal demise even without fetal or newborn infection. The impact of timing of the infection and the mechanisms that cause fetal morbidity and mortality are not well understood.

Material and methods: To describe placental pathology from women with confirmed SARS-CoV-2 infection during pregnancy, a SARS-CoV-2 immunohistochemistry-positive

Abbreviation: FGR, fetal growth restriction

placenta and late miscarriage, stillbirth, neonatal death, or medically indicated birth due to fetal distress.

Results: The triad of trophoblastic necrosis, inflammatory intervillous infiltrates, and increased perivillous fibrinoid deposition was present in all 17 placentas; the pregnancies resulted in eight stillbirths, two late miscarriages (19 and 21 weeks' gestation), and seven liveborn children, two of which died shortly after delivery. The severity of maternal COVID-19 was not reflected by the extent of the placental lesions. In only one case, SARS-CoV-2 was detected in lung tissue samples from the fetus. The majority events (miscarriage, stillbirth, fetal distress resulting in indicated birth, or livebirth, but neonatal death) happened shortly after maternal SARS-CoV-2 infection was diagnosed. Seven of eight sequenced cases were infected with the Delta (B.1.617.2) virus strain.

Conclusion: We consolidate findings from previous case series describing extensive SARS-CoV-2 placentitis and placental insufficiency leading to fetal hypoxia. We found sparse evidence to support the notion that SARS-CoV-2 virus had infected the fetus or newborn.

KEYWORDS
COVID-19, placental insufficiency, placentitis, pregnancy, SARS-CoV-2

1 | INTRODUCTION

Infection with SARS-CoV-2 during pregnancy may influence pregnancy outcome by increasing the risk of preterm birth, mostly due to medically indicated birth, stillbirth, and neonatal death.[1,2]

Numerous studies have reported that vertical transmission of SARS-CoV-2 is rare,[3–7] and it has been proposed to classify the timing of mother-to-child transmission by positive SARS-CoV-2 findings by PCR from sterile and non-sterile fetal and placental samples, and SARS-CoV-2 placental immunohistochemistry.[8,9] However, maternal SARS-CoV-2 infection may influence the well-being of the fetus even though the fetus or the newborn is SARS-CoV-2 negative.[2] The fetus may suffer due to maternal clinical illness, viral pneumonia with hypoxia for example, and even without signs of fetal distress the infant may have to be delivered for maternal safety reasons. Also, the fetus may suffer from compromised gas, nutrient exchange and hormonal exposures due to placental inflammation and insufficiency caused by the virus but without the virus being found in the fetus or the newborn.[1,10]

During the time period where the SARS-CoV-2 B.1.617.2 (Delta) variant was dominant, several countries reported an increased rate of stillbirth in women with SARS-CoV-2 infection in late pregnancy.[11–13] Recent placental studies from pregnant women with SARS-CoV-2 have reported a characteristic triad of trophoblast necrosis, inflammatory intervillous infiltrates, and increased perivillous fibrinoid deposition along with a positive immunohistochemistry for SARS-CoV-2 antigens.[10,14]

The mechanisms behind an increase in perinatal morbidity and mortality in some pregnant women with SARS-CoV-2 infection remain unknown, since maternal transfer of the virus to the fetus is rare.[3–7] Thus, it becomes obvious to investigate placental tissue more thoroughly, particularly in women with less severe clinical disease and fetal demise or distress.

Key message

Severe SARS-CoV-2 placentitis was found in pregnancies ending in miscarriage, stillbirth, neonatal death and indicated delivery due to fetal distress from Danish women with COVID-19 infection during pregnancy.

The aim of this case series was to describe placental pathology from women with confirmed SARS-CoV-2 infection during pregnancy, a SARS-CoV-2 immunohistochemistry-positive placenta and late miscarriage, stillbirth, neonatal death, or medically indicated birth due to fetal distress.

2 | MATERIAL AND METHODS

We collected information from a nationwide case series. We defined a case as a pregnancy characterized by the following: (1) a positive SARS-CoV-2 PCR test (nasopharyngeal swab) during pregnancy; (2) a pregnancy outcome defined as late miscarriage between 12 and 22 weeks' gestation, stillbirth (from 22 gestational weeks), neonatal death, that is, death within 28 days after delivery, or indicated delivery due to fetal distress; (3) a placenta

available for histopathology; (4) a placenta-positive SARS-CoV-2 immunohistochemistry. Women who fulfilled the case definition, identified by fetal pathologists, and who delivered in Denmark during 2021 were invited to participate.

Baseline characteristics of the women enrolled in the study including maternal COVID-19 symptoms and treatment, pregnancy and neonatal outcomes, including information on fetal growth restriction (FGR) during pregnancy assessed by ultrasound (less than −22% of the expected weight for gestational age),[15] birthweight and gestational age at birth were retrieved from the Danish COVID19 in pregnancy database, which holds information from medical records, and the Danish Microbiological Database as described previously.[16,17] The severity of maternal symptoms were categorized by the following: (1) asymptomatic; (2) cough, no fever; (3) fever; (4) admission to Intensive Care Unit; (5) not available. Fetal pathologists collected information on placental pathology using structured forms designed for this case series.

SARS-CoV-2 PCR performed on amniotic fluid, the fetal side of placental tissue samples, and some also from the maternal side, were included when available. All stillbirths were autopsied, and SARS-CoV-2 PCR performed on tissue samples (lungs, heart, spleen, liver) and swabs (pharynx, rectum) were included when available. From liveborn, SARS-CoV-2 PCR performed on swabs (mouth, pharynx, axil) were included when available.

Placental histology was evaluated according to the Amsterdam Placental Consensus classification.[18] All placentas were investigated for the presence of SARS-CoV-2 by immunohistochemistry with the anti-SARS-CoV-2 Nucleocapsid Protein (Sino Biological) according to manufacturer instructions. Positive and negative controls were applied.

To evaluate placental infection, the standardized definition of SARS-CoV-2 placental infection described by Roberts et al.[19] as definite, probable, possible and unlikely infection was used. Mother-to-child transmission of SARS-CoV-2 was evaluated by the WHO definition[9] and by the classification system and case definition for SARS-CoV-2 infection in the fetus and neonate by Shah et al.[8]

Recommendations for vaccination (Pfizer-BioNTech COVID-19 vaccine [BNT162b2 mRNA]) in pregnancy were implemented in Denmark in July 2021.

2.1 | ETHICS STATEMENT

All the women that were included were covered by an overall approval for "the Danish nationwide prospective population-based study investigating the association between SARS-CoV-2 infection in pregnancy and clinical characteristics and maternal, delivery, and neonatal outcomes" by Aabakke et al.[16,20] The approval was granted by the Danish Patient Safety Authority on April 24, 2020 (reg. no. 31-1521-252) and the regional Data Protection Agency in Region Zealand on March 23, 2020 (reg. no. REG022-2020). All women included in this study also provided informed written consent.

3 | RESULTS

A total of 16 women fulfilled the case criteria; seven pregnancies resulted in eight stillbirths, two in late miscarriage, and seven in liveborn infants with indicated delivery due to fetal distress, two of whom died on the day of delivery.

3.1 | Timing of infection and delivery

Clinical information on women and newborn including gestational age at the positive SARS-CoV-2 test, vaccination status, maternal symptoms related to COVID-19, FGR, birthweight, gestational age at birth, and Apgar scores at 5 min is presented in Table 1.

Time from first positive SARS-CoV-2 test to delivery, placental pathology and microbiological findings are presented for stillbirths in Table 2., for liveborn in Table 3, and for late miscarriages in Table 4.

Time from first positive SARS-CoV-2 pharyngeal swab to delivery was between three and 71 days with a median of 11 days in all women and 12 days for women who experienced stillbirth. Two women were asymptomatic, three had cough but no fever. Nine had fever and one needed Intensive Care Unit care. The two late miscarriages occurred 3 days and 3 weeks after the woman tested positive for SARS-CoV-2 in 19 and 21 completed gestational weeks, respectively.

The gestational age at birth in women who experienced stillbirth was between 26 and 35 completed gestational weeks (median 31 weeks). Livebirths occurred between 26 and 34 completed gestational week (median 28 weeks) with two neonatal deaths immediately after birth at 28 and 32 completed gestational weeks. A total of 47% (8 of 17) fetuses were considered growth restricted.

One woman (no. XIII) received a dose of SARS-CoV-2 vaccine (Pfizer/BioNTech) at 23 completed gestational weeks, that is, 25 days before she tested positive; all other women were unvaccinated.

3.2 | Placental findings in relation to outcome

Placentitis caused by SARS-CoV-2 defined by the microscopic findings of the triad of trophoblastic necrosis, inflammatory intervillous infiltrates, and increased perivillous fibrinoid deposition was present in all cases, irrespective of the outcome of pregnancy.

Immunohistochemistry was strongly positive in a subset of the affected necrotic and viable syncytiotrophoblast cells (Figures 1 and 2).

Following the definition proposed by Roberts et al.[19] the percentage of placental infection associated with the presence of SARS-CoV-2 was between 60% and 90% for seven of eight stillbirths. One case (no. II) showed 90% infarction of the parenchyma due to decidual vessel thrombi, and an additional 5% of the parenchyma showed SARS-CoV-2 placentitis (Table 2). In the placentas of the two neonatal deaths (no. XIII and no. XV), 80% and 70% placentitis was found, respectively.

TABLE 1 Maternal and newborn characteristics from women with SARS-CoV-2 infection during pregnancy.

			Maternal characteristics						Newborn/fetal characteristics
Case No	Mothers age	Parity and plurality	Vaccination status at time of infection (Y/N, No. of doses)	Gestational age (GA) at first positive test (pharyngeal swab) and SARS-CoV-2 variant	COVID-19 symptoms	Symptom score 1 = asymptomatic 2 = cough, no fever 3 = fever 4 = admission to ICU 5 = not available	Treatment COVID-19 oxygen admission to intensive care unit (ICU) medication	Preparation delivery antenatal steroid MgSO4 (neuroprotection) antibiotics	Late miscarriage stillbirth liveborn neonatal death gestational age (GA) weight (deviation[a]) Apgar 5 min Umbilical artery pH/venous pH: Admission NICU
I	32	P1 Multiple pregnancy	N	24 weeks 3 days B.1.617.2	Fever flu-like symptoms	3			Stillbirth GA: 26 weeks 2 days weight: 640 (−36%)/600 (−40%)
II	35	P1 Singleton	N	25 weeks 6 days B.1.617.2	Fever cough sore throat headache limb and joint pain tiredness breathlessness flu-like symptoms	4	ICU Oxygen steroids Highdose LMWH		Stillbirth GA: 28 weeks 1 day weight: 1060 g (−12%)
III	32	P0 Singleton	N	28 weeks 1 day B.1.617.2	Cough limb and joint pain tiredness rhinorrhea	2			Stillbirth GA: 29 weeks 6 days weight: 1289 g (−20%)
IV	30	P1 Singleton	N	32 weeks 0 day B.1.617.2	Fever cough	3			Stillbirth GA: 33 weeks 0 day weight: 1911 g (−13%)
V	27	P0 Singleton	N	31 weeks 6 days B.1.617.2	Fever cough headache breathlessness rhinorrhea	3			Stillbirth GA: 33 weeks 1 day weight: 1855 (−16%)
VI	28	P1 Singleton	N	30 weeks 1 day	Unknown	5			Stillbirth GA: 34 weeks 5 days weight: 1848 g (−27%)
VII	28	P0 Singleton	N	34 weeks 3 days B.1.617.2	Fever Vomiting	3			Stillbirth GA: 35 weeks 5 days weight: 2235 g (−17%)
VIII	29	P0 Singleton	N	19 weeks 1 day	Asymptomatic	1			Late miscarriage GA: 19 weeks 4 days weight: 294 g (−11%)
IX	32	P1 Singleton	N	18 weeks 1 day	Fever	3			Late miscarriage GA: 21 weeks 1 day weight: 235 g (−39%)
X	28	P0 Singleton	N	24 weeks 3 days B.1.617.2	Fever Cough	3		Steroids (1 dose) MgSO4	Liveborn GA: 26 weeks 0 day weight: 650 g (−28%) Apgar 5 min:8 Umbilical artery pH: 7.02 admission NICU: 13 weeks
XI	36	P1 Singleton	N	27 weeks 0 day	Asymptomatic	1		Steroids (1 dose)	Liveborn GA: 27 weeks 3 days weight: 849 g (−26%) Apgar 5 min: NA Umbilical venous pH: NA Admission NICU: 8 weeks + 2 days

TABLE 1 (Continued)

			Maternal characteristics						Newborn/fetal characteristics
Case No	Mothers age	Parity and plurality	Vaccination status at time of infection (Y/N, No. of doses)	Gestational age (GA) at first positive test (pharyngeal swab) and SARS-CoV-2 variant	COVID-19 symptoms	Symptom score 1 = asymptomatic 2 = cough, no fever 3 = fever 4 = admission to ICU 5 = not available	Treatment COVID-19 oxygen admission to intensive care unit (ICU) medication	Preparation delivery antenatal steroid MgSO4 (neuroprotection) antibiotics	Late miscarriage stillbirth liveborn neonatal death gestational age (GA) weight (deviation[a]) Apgar 5 min Umbilical artery pH/venous pH: Admission NICU
XII	36	P0 Singleton	N	18 weeks 2 days	Cough sore throat	2		Steroids (2 doses) MgSO4	Liveborn GA: 28 weeks 3 days weight: 860 (−36%) Apgar 5 min: 9 Umbilical venous pH: 7.31 Admission NICU: 12 weeks + 0 day
XIII	35	P0 Singleton	Y, 1 dose Pfizer/BioNTech at GA 23 + 5	27 weeks 2 days	Fever cough sore throat headache flu-like symptoms	3		Steroids (1 dose) MgSO4	Neonatal death GA: 28 weeks 4 days weight: 1140 g (−16%) Apgar 5 min:2 Apgar 10 min: 2 umbilical venous pH: 6.76 Admission NICU: No
XIV	29	P1 Singleton	N	29 weeks 1 day	Fever cough sore throat	3			Liveborn GA: 30 weeks 0 day weight: 1235 g (−23%) Apgar 5 min: NA Umbilical venous pH: 7.33 Admission NICU: 5 weeks + 0 day
XV	30	P1 Singleton	N	31 weeks 2 days	Fever headache	3			Neonatal death GA: 32 weeks 4 days weight: 2000 (−4,8%) Apgar 5 min: NA Umbilical venous pH: 6.85 Admission NICU: No
XVI	28	P0 Singleton	N	32 weeks 2 days B.1.617.2	Sore throat	2			Liveborn GA: 34 weeks 6 days weight: 2095 (−19.2%) Apgar 5 min: 10 Umbilical artery pH/venous pH: NA admission NICU: 2 weeks + 0 day

Abbreviations: NICU, neonatal intensive care unit; NA, information not available; LMWH, low molecular weight heparin.

[a]Weight deviation according to Marsal.[15]

TABLE 2 Characteristics of SARS-CoV-2 placental immunohistochemistry positive placentas from stillbirth cases from women with SARS-CoV-2 infection during pregnancy.

Case no.	Time from first positive test to delivery (days)	Gestational age at delivery (weeks and days)	Placental pathology				SARS-CoV-2 PCR	
			Autopsy	Placentitis triade[a]	Other placental findings	Extent of SARS-CoV-2 placentitis (%)	Placenta/amniotic fluid	Fetal tissue/swab/umbilical cord
I	13	26 weeks 2 days	Yes	Yes	Hematoma, low weight	80	Amniotic fluid: negative	Umbilical cord: positive (B.1.617.2)
II	16	28 weeks 0 day	Yes	Yes	Thrombi in decidual vessels as cause of 90% infarction	5		Tissue spleen and lung: negative
III	11	29 weeks 6 days	Yes	Yes	Intervillous trombus	80	Amniotic fluid: negative	Tissue heart, lung: negative. Umbilical cord: positive (B.1.617.2)
IV	7	33 weeks 0 day	Yes	Yes	Hematoma	90		Tissue heart, lung, liver: negative. Swab pharynx: negative
V	9	33 weeks 1 day	Yes	Yes	No	70		Tissue heart, lung, spleen: negative Swab rectum: negative
VI	32	34 weeks 5 days	Yes	Yes	Hematoma, low weight	60–70	Placenta: negative	Tissue liver, lung, spleen, heart: negative
VII	9	35 weeks 5 days	Yes	Yes	No	80		Tissue lung: positive Tissue heart: negative Swab pharynx, rectum: positive

[a]Trophoblastic necrosis, intervillous infiltrate and perivillous fibrinoid infiltrate.

TABLE 3 Characteristics of SARS-CoV-2 placental immunohistochemistry positive placentas from liveborn cases from women with SARS-CoV-2 infection during pregnancy.

Case No	Time from first positive test to delivery (days)	Gestational age at delivery (weeks and days)	Neonatal death (Y/N)	Placental pathology				SARS-CoV-2 PCR	
				Autopsy	Placentitis triade[a]	Other placental findings	Extent of SARS-CoV-2 placentitis (%)	Placenta/amniotic fluid	Fetal tissue/swab umbilical cord
X	11	26 weeks 0 day	N	No	Yes	No	50		Swab pharynx: negative
XI	3	27 weeks 3 days	N	No	Yes	Low weight	80	Placenta fetal and maternal side: positive B.1.1.7	Swab pharynx 2 and 9 days postpartum: positive
XII	71	28 weeks 3 days	N	No	Yes	Hematoma	40		
XIII	9	28 weeks 3 days	Y	No	Yes	No	80	Placenta fetal side: PCR negative	
XIV	6	30 weeks 0 day	N		Yes	Subchoric hematoma	80	Placenta fetal side: positive	
XV	8	32 weeks 4 days	Y	Yes	Yes	No	70	Placenta fetal and maternal side: positive	Swabs: mouth, pharynx and axil: neg
XVI	18	34 weeks 5 days	N		Yes	No	95		

[a]Trophoblastic necrosis, intervillous infiltrate and perivillous fibrinoid infiltrate.

TABLE 4 Characteristics of SARS-CoV-2 placental immunohistochemistry positive placentas from cases with late miscarriage from women with SARS-CoV-2 infection during pregnancy.

Case no	Time from first positive test to delivery (days)	Placental pathology					SARS-CoV-2 PCR	
		GA at miscarriage	Autopsy	Placentitis triade[a]	Other placental findings	Extent of SARS-CoV-2 placentitis (%)	Placenta/amniotic fluid	Fetal tissue/ umbilical cord
VIII	3	19 weeks 41 days	No	Yes		30	Placenta fetal side: negative	Swab pharynx: negative
IX	21	21 weeks 1 day	Yes	Yes		80		

[a]Trophoblastic necrosis, intervillous infiltrate and perivillous fibrinoid infiltrate.

For the placentas of the remaining five livebirths, the level of SARS-CoV-2 placentitis varied between 40% and 95% (Table 3). For the two late miscarriages, the extent of SARS-CoV-2 placentitis was 30% and 80% (Table 4).

AI placentas fulfilled the criteria of being probable cases according to the standardized definition of placental infection by SARS-CoV-2 because immunohistochemistry positive placental tissue was an inclusion criterion.[19]

3.3 | SARS-CoV-2 PCR from fetal tissue and swabs

In six of eight stillbirths, SARS-CoV-2 PCR was performed on various fetal samples (Table 2). One case (no. VII) was positive (pharynx swab, rectal swab, and lung tissue). In cases no. I and no. III, umbilical cord blood was SARS-CoV-2 PCR Delta variant (B.1.617.2) positive but amniotic fluid negative (Table 2). For case no. XI, the Alpha variant (B.1.1.7) was found in swabs from the maternal and fetal side of the placenta. The remaining SARS-CoV-2 PCR results from liveborn and late miscarriages can be seen in Tables 3 and 4.

3.4 | Mother-to-child transmission of SARS-CoV-2

The Delta variant (B.1.617.2) was detected in (44%) of maternal nasopharyngeal samples.

Following the classification system proposed by Shah et al. for Maternal-Fetal-Neonatal SARS-CoV-2 infection[8] and WHO,[9] only case no. VII fulfilled the criteria for "confirmed congenital infection with stillbirth;" detection of the virus by PCR in fetal lung tissue. According to the WHO, the remaining seven stillbirths should be categorized as "unlikely SARS-CoV-2 transmission" because they were only placenta immunohistochemistry positive but fetal tissue PCR negative.

In cases no. I and no. III, SARS-CoV-2 was found in umbilical cord blood. However, because amniotic fluid and organ samples were SARS-CoV-2 PCR negative, these cases do not fulfill the criteria for "confirmed congenital infection in stillbirth" by Shah et al., and contamination from maternal blood is likely.

According to Shah et al., no liveborn infant could be considered a confirmed or probable case of congenital infection because none had a positive PCR test on umbilical cord blood, amniotic fluid, or nasopharyngeal swab. A SARS-CoV-2 positive nasopharyngeal swab from case no. XI was taken on day two after birth, thus fulfilling WHO's criteria for possible vertical transmission (placental tissue immunohistochemistry positive and PCR positive on a non-sterile sample taken 24–48 h after birth).

4 | DISCUSSION

We report 16 pregnancies with SARS-CoV-2 immunohistochemistry-positive, severely affected placentas resulting in two late miscarriages, eight stillbirths, and seven liveborn, including two neonatal

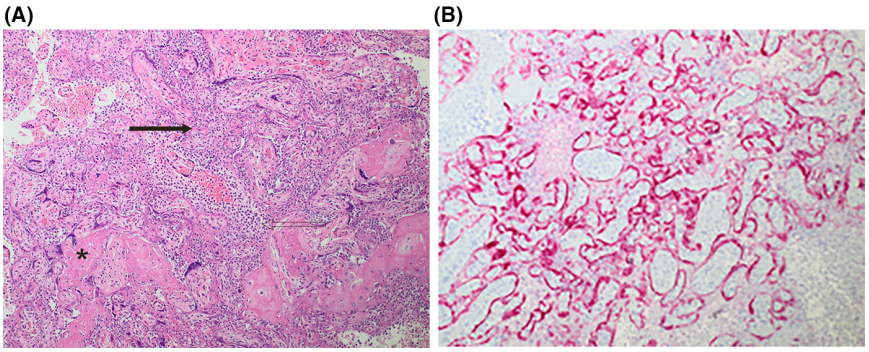

FIGURE 1 (A, B) Changes associated with Covid, placental pathology, liveborn. (A) Acute and chronic intervillositis (open arrow) with necrosis of the trophoblast layer (black arrow) accompanied by fibrin deposits (asterisk) (hematoxylin and eosin). (B) Severe acute respiratory syndrome coronavirus-2 (SARSCoV-2) nucleoprotein (NP) detected in the villous trophoblasts (red).

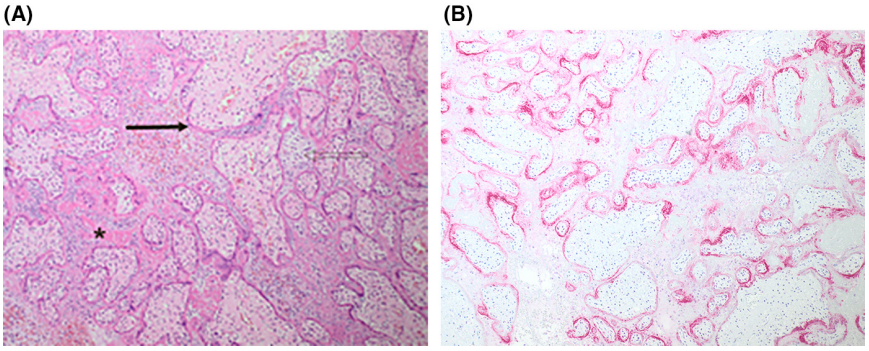

FIGURE 2 (A, B) Changes associated with Covid, placental pathology, stillbirth. (A) Acute and chronic intervillositis (open arrow) with necrosis of the trophoblast layer (black arrow) accompanied by abundant fibrin deposits (asterisk) (hematoxylin and eosin). (B) Severe acute respiratory syndrome coronavirus-2 (SARSCoV-2) nucleoprotein (NP) detected in the villous trophoblasts (red).

deaths and five with medically indicated births due to fetal distress. SARS-CoV-2 was only detected in fetal organ tissue samples from one case. The severity of maternal COVID-19 did not reflect the degree of placental lesions.

During the COVID-19 pandemic, a number of case studies have reported a characteristic triad of placental changes including trophoblast necrosis, inflammatory intervillous infiltrates, and increased perivillous fibrinoid deposition. This triad has been named SARS-CoV-2 placentitis. This has been found in pregnancies with a SARS-CoV-2 immunohistochemistry positive placenta presenting with signs of fetal distress or death after a SARS-CoV-2 infection during pregnancy.[10,14,21–23]

The major finding in this case series was the extent of placenta pathology. The placentas were meticulously evaluated according to the Amsterdam Placental Consensus classification and the standardized definition of placental SARS-CoV-2 infection[18,19] with a median involvement of 80% of placental tissue. This is striking, as placental SARS-CoV-2 infection is not found in all women with COVID-19 diagnosed in pregnancy. Edlow et al.[3] found no characteristic placental pathology in SARS-CoV-2 exposed placentas 44 from women with SARS- CoV-2 in pregnancy.

Since our case definition was a SARS-CoV-2 immunohistochemistry-positive placenta, all cases comply with possible in utero SARS-CoV-2 transmission according to the WHO. Nevertheless, SARS-CoV-2 PCR on organ tissue samples were negative in all but one case, which was the only confirmed positive case according to the acknowledged criteria.[8,9]

We also found a lack of an obvious association between the extent of placental damage and outcome severity. This may partly be due to the medically indicated births due to fetal distress.

A structured review of placental pathology and association with SARS-CoV-2 infection[24] included unselected samples and found that placental pathology did not seem to occur in the absence of perinatal complications. Our findings support the strong relation between placental pathology and fetal distress and stillbirth.

In a large, multicenter cohort study based information from health records, Piekos et al.[1] found an increased risk of medically indicated preterm birth due to fetal distress and stillbirth when COVID-19 diagnosed in early pregnancy. COVID-19 severity was unrelated to the severity of pregnancy outcome. In our cases, most adverse pregnancy outcomes happened shortly after maternal SARS-CoV-2 infection was diagnosed, with a median of 11 days from the first positive SARS-CoV-2 test to birth, and all but one woman experienced mild COVID-19 symptoms.

Our findings of the SARS-CoV-2 virus in only one fetus may be explained by the acute onset of rapidly developing placental insufficiency leading to severe fetal hypoxia prior to viral transmission to the fetus, as also suggested by Dubucs et al.[14] Furthermore, the

median time from maternal infection to birth was 11 days, and hypoxia may have developed so rapidly that growth restriction was not yet evident; we found that fewer than half the fetuses were growth restricted.

However, our findings were not entirely consistent as there was a short time from infection to delivery with FGR in case no. I (13 days from infection to delivery; FGR −36% and −40% (multiple pregnancy)), and a long time from infection to delivery with minor growth restriction in case no. VI (32 days from infection to delivery; FGR −27%).

The increasing evidence and clinical recognition of fetal death in women with SARS-CoV-2 infection in pregnancy has increased clinical awareness of the potentially rapidly developing fetal compromise. Some of the liveborn cases described in this study might therefore only be liveborn due to this awareness in clinicians who initiated careful and regular assessment of pregnant women with current or recent SARS-CoV-2 infection. Such regular assessments and timely interventions were implemented in Denmark late autumn 2021, that is, by the end of sampling the current cases. Three of five liveborn cases were born at the end of 2021.

According to our and other results, it seems that adverse pregnancy outcomes in SARS-CoV-2 during pregnancy are primarily caused by a pathological effect of the virus on the placenta rather than the transmission of virus to the fetus. Schwartz et al.[10] found similar results in a multinational study of 68 placentas from 64 stillbirths and four neonatal deaths in which the average placenta had 78% involvement with SARS-CoV-2 placentitis, and no evidence was found of fetal transmission of SARS-CoV-2 in the fetal deaths.

This is not a frequent event as 3385 COVID-19 cases were registered among 81.157 pregnant women in Denmark during the inclusion period (Section of Epidemiology, Department of Public Health, University of Copenhagen; Personal communication; February 8, 2023).

The fact that the Delta (B.1.617.2) virus strain variant was detected in seven of eight sequenced maternal nasopharyngeal samples as well as in the samples from one stillborn fetus (case no. III) suggests that this particular variant might be particularly pathogenic for placental tissue.

Our results consolidate the growing evidence that despite extensive SARS-CoV-2 placentitis that cause placental insufficiency and the associated severe fetal hypoxia, it is impossible to demonstrate that SARS-CoV-2 is the cause of morbidity or mortality in fetal or newborn infection.

None of the women in this study were fully vaccinated, which emphasizes the importance of encouraging vaccination in pregnancy.

5 | CONCLUSION

In this case study, we evaluated placental pathology in 16 women with SARS-CoV-2 infection, a SARS-CoV-2 immunohistochemistry positive placenta, and an adverse pregnancy outcome. SARS-CoV-2 placentitis by trophoblastic necrosis, intervillous infiltrate, and perivillous fibrinoid infiltrate was present in all placentas. Most adverse events happened shortly after the diagnosis of SARS-CoV-2 infection, and the severity of maternal COVID-19 infection did not seem to be reflected by the degree of placental lesions. Continuing investigations of placentas following COVID-19 infection during pregnancy, along with current and future vaccination strategies during pregnancy, will provide crucial insight into the influence of various virus variants on fetal and newborn morbidity and mortality.

AUTHOR CONTRIBUTIONS

SYN was project coordinator and wrote the draft version of the manuscript. LEH was in charge of communication with tending clinicians and collection of written consents. AJMA was in charge of collecting clinical information. TEO was in charge of the structured forms designed for this study. TEO, IBGJ, PWB, AP, collected information on placental pathology. TBH thoroughly reviewed and revised the manuscript. HBW, AS, GH, ETR, DT, JB, LLTA, AGHE and BFL collected clinical information and written consent from their respective patients and all authors reviewed and revised the manuscript.

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CONFLICT OF INTEREST STATEMENT

None.

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