SARS-COV2 placentitis and pregnancy outcome: A multicentre experience during the Alpha and early Delta waves of coronavirus pandemic in England

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Summary

Background Pregnant women with SARS-CoV-2 infection experience higher rates of stillbirth and preterm birth. A unique pattern of chronic histiocytic intervillositis (CHI) and/or massive perivillous fibrin deposition (MPFD) has emerged, coined as SARS-CoV-2 placentitis.

Methods The aim of this study was to describe a cohort of placentas diagnosed with SARS-CoV-2 placentitis during October 2020-March 2021. Cases with a histological diagnosis of SARS-CoV-2 placentitis and confirmatory immunohistochemistry were reported. Maternal demographic data, pregnancy outcomes and placental findings were collected.

Findings 59 mothers delivered 61 infants with SARS-CoV-2 placentitis. The gestational age ranged from 19 to 41 weeks with most cases (78.6%) being third trimester. 30 infants (49.1%) were stillborn or late miscarriages. Obese mothers had higher rates of pregnancy loss when compared with those with a BMI <30 [67% (10/15) versus 41% (14/34)]. 47/59 (79.7%) mothers had a positive SARS-CoV-2 PCR test either at the time of labour or in the months before, of which 12 (25.5%) were reported to be asymptomatic. Ten reported only CHI, two cases showed MPFD only and in 48 placentas both CHI and MPFD was described.

Interpretation SARS-CoV2 placentitis is a distinct entity associated with increased risk of pregnancy loss, particularly in the third trimester. Women can be completely asymptomatic and still experience severe placentitis. Unlike 'classical' MPFD, placentas with SARS-CoV-2 are generally normal in size with adequate fetoplacental weight ratios. Further work should establish the significance of the timing of maternal SARS-CoV-2 infection and placentitis, the significance of SARS-CoV2 variants, and rates of vertical transmission associated with this pattern of placental inflammation.

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Research in context

Evidence before this study

Published studies from UK Obstetric Surveillance System (UKOSS) showed that stillbirth incidence was three times higher among women affected by SARS-CoV-2. Placental compromise was considered likely to be one of the determining factors in the outcome of pregnancies affected by the virus through a pattern of injury called '*SARS-CoV-2 placentitis*'. A PubMed literature search was conducted using the terms: SARS-CoV2 placentitis, stillbirth and COVID-19, COVID-19 and pregnancy, SARS-CoV2 and pregnancy. Relevant articles published in English between March 2020 and 1st August 2021 were retrieved.

Added value of this study

Our study confirmed that SARS-CoV2 placentitis is a distinct pathological entity, usually characterised by the presence of massive perivillous fibrin deposition and chronic histiocytic intervillositis, and associates with increased risk of pregnancy loss, particularly in the third trimester. Pregnancy loss was higher among mothers with a high BMI.

Implications of all the available evidence

Our result may have relevance in the implementation of diagnostic and therapeutic options in these women. The findings add to the evidence base, but are preliminary and will need further confirmation.

Introduction

In July 2020, a study published by UK Obstetric Surveillance System (UKOSS) indicated that the incidence of stillbirth (11·5 per 1000 total births) among women affected by SARS-CoV-2 virus was almost three times the national rate (4·1 per 1000 total births).[1,2] Since then, the incidence of pregnancy complications such as spontaneous abortion, stillbirths and premature delivery have increased. This may be related to the higher transmission rate of new variants of SARS-CoV-2.[3,4]

In the second UKOSS study conducted from March to August 2020, the estimated incidence of hospitalisation with symptomatic SARS-CoV-2 was calculated to be 2·0 per 1000 pregnancies.[4] In this study women hospitalised with symptomatic SARS-CoV-2 were more likely to be overweight or obese and/or to be of Black, Asian or another minority ethnic group and/or and to have a relevant medical comorbidity, compared to pregnant women not infected with SARS-CoV-2. Although hospitalised pregnant women with symptomatic infection were more likely to be admitted to intensive care and require caesarean section delivery, the risk of poor outcomes was small.[4] There was no significant increase in the number of stillbirths or neonatal deaths between

March and August 2020 with 3% (*n* = 31) of hospitalised pregnant women with SARS-CoV-2 reporting pregnancy loss, compared to < 1% (*n* = 2) of those without SARS-CoV-2.[4]

Provisional data from UKOSS are concerning for an increased risk of severe illness in hospitalised pregnant women, though this is yet, to our knowledge, to be presented in a peer reviewed publication.

Placental compromise as a consequence of SARS-CoV2 maternal infection is likely to be one of the determining factors in the outcome of pregnancies affected by the virus. Various histopathological patterns have been described in the setting of SARS-CoV-2 infection including maternal vascular malperfusion, fetal vascular malperfusion, massive perivillous fibrin deposition, and inflammatory patterns including acute chorioamnionitis, chronic deciduitis, chronic villitis and chronic histiocytic intervillositis.[5] In the United Kingdom (UK), specialist paediatric and perinatal pathologists have noticed an increasing incidence of a rare placental pathology similar to chronic histiocytic intervillositis (CHI) associated with massive perivillous fibrin deposition (MPFD). This was first described in Ireland by Linehan et al., who demonstrated the presence of the virus within the syncytiotrophoblast compartment of the placenta and termed the pattern of injury 'SARS-CoV-2 placentitis'.[6] SARS-CoV-2 placentitis is suggested by other groups to be associated with increased risks of vertical transmission of the virus.[7,8]

Although both CHI and MPFD were known to affect the placentas of pregnant women *before* the SARS-CoV-2 pandemic, the incidence of both conditions is very low, reported as <1% of all pregnancies.[9] Non-SARS-CoV2 associated CHI and MPFD are both presumed to have an immunological basis, carry a very high recurrence risk, and are associated with intrauterine growth restriction in the fetus.[9] Whilst MPFD can be seen with some histiocytic infiltrates, in pre-pandemic placentas, the association of diffuse CHI and MPFD has seldom been reported.[10]

The study aim was to report on the collective experience of paediatric and perinatal pathologists across the UK with those placental histological features present in the context of SARS-CoV2 infection. Our objective was to characterise a cohort of placentas diagnosed with SARS-CoV-2 placentitis during the Alpha wave an describe the pregnancy outcome.

Methods

Study design and participants

Paediatric and Perinatal Pathologists from ten tertiary centres identified cases in which there was a histological diagnosis SARS-CoV-2 placentitis. This included cases of CHI or/and MPFD with SARS-CoV-2 infection proven with PCR (in 47/59 mothers and in 15/61

placentas). SARS-CoV-2 infection was confirmed in all placentas by positive immunohistochemical staining of the syncytiotrophoblast. With the exception of one case from March 2020, all other cases were from deliveries occurring between October 2020 and March 2021, during the peak of the Alpha wave. Maternal demographic data including ethnicity and Body Mass Index (BMI), were collected, along with maternal co-morbidities, and pregnancy outcomes including gestational age, birth weight and SARS-CoV-2 status of both the mother and baby. Placental findings including weight and histological diagnosis were also collected. The histological and demographic features were discussed during virtual meetings, and all authors had access to the database.

Transmission electron microscopy

In four cases, ultrathin sections of the placenta were examined by transmission electron microscopy.

In these four cases the tissue had been primarily fixed in 10% phosphate buffered formalin and processed to wax as per standard histological protocol. A portion was removed from the wax, chopped into mm cubes, dewaxed in xylene, rehydrated through graded alcohols to distilled water, followed by post-fixation in 2% aqueous osmium tetroxide; dehydrated through graded alcohols, acetone and into TAAB EMIX medium grade epoxy resin.

Following heat polymerisation (16 h at 65°Centigrades), resin blocks were sectioned using a Reichert ultracut E ultramicrotome at 0.6 μm, stained using 1% toluidine blue in 1% sodium tetraborate and examined light microscopically. The most appropriate block selected and thin-sectioned using a Diatome diamond knife at 85 nm. Thin-sections were stained in saturated uranyl acetate in 99% ethanol, and Reynold's lead citrate.

Sections were examined on a Philips 400 transmission electron microscope and photographed using images taken using AMT 16 megapixel mid mount digital camera XR16. Images taken in TIF format and converted to JPG with minimum compression.

In one case Covid-19 spike protein and RNA scope signal was detected and findings were published as a case report.[11]

Ethics

The Department of Clinical Governance considered that the study did not fall under the category of original research as no investigations were undertaken for research purposes and there was no control group established. The cases (demographics and histological findings) were anonymously discussed at online meetings. Clinical Governance concluded that this multicentric study did not require Ethical approval. Patients' consent was not required as no histological review was undertaken and the cases remained anonymised. The study was approved as a national audit project by Sheffield Children's NHS FT Clinical Governance, Registration SE1642.

Results

59 mothers delivered 61 infants in which each placenta had a pathological diagnosis of MPFD+/- CHI with positive immunohistochemical staining for SARS-CoV-2 spike protein in the syncytiotrophoblast. With the exception of one case from March 2020, all other cases were from deliveries between October 2020 and March 2021. The gestational age was available in 60 cases (except one un-booked pregnancy) and ranged from 19 to 41 completed weeks with a mean of 30 completed weeks. 48 cases were third trimester placentas (defined as 28 weeks and beyond), of which five had reached term (defined as 37 completed weeks and beyond), with the remaining known gestational ages second trimester placentas. Table 1 presents the pregnancy outcome and birthweight (this latter was not always available).

Maternal demographics (see Table 2)

Ethnicity. Maternal ethnicity was available in 52/59 cases, with 36 identifying as Caucasian ('white British' or 'white, European') and 16 of Black and minority ethnic groups (BAME; 10 Asian, 6 Black Caribbean or Black African).

BMI. BMI was available in 49 mothers, ranging from 18 to 55.2 kg/m². Of these, 14 (28.5%) had a BMI of 18.5 −25 kg/m², 20 (40.8%) had a BMI of between 25 and 30 kg/m² and 15 were obese; two (4.1%) had a BMI of 30−35 kg/m² and 13 (26.4%) were >35 kg/cm².

Co-morbidities. Thirty-eight had no reported previous medical history. 14 had some form of cardiovascular risk factor including hypertension ($n = 3$), and one each of deep vein thromboses, anti-cardiolipin antibodies, sickle cell trait, smoking in pregnancy, ex-smoker, gestational diabetes, Systemic Lupus Erythematous (SLE), and Haemolysis and Elevated Liver enzymes and Low Platelets (HELLP Syndrome). One mother had a 'heart murmur' and two others had congenital heart disease.

Three had known histories of depression, childhood malignancy, and Sjogren's syndrome.

Case Number	Month of delivery	Gestation (weeks +days)	Pregnancy Outcome	Birthweight	Personalised Growth Chart Calculation	WHO Growth Chart Centiles
1	Dec-20	32	stillbirth	1590	8th	—
2	Dec-20	41	stillbirth	2180	<1st	—
3	Dec-20	25	stillbirth	615	1st	—
4	Dec-20	29	livebirth	1225	—	50−75
5 (TWIN)	Jan-21	31	stillbirth	1630	11th	—
6 (TWIN)	Jan-21	31	stillbirth	1440	2nd	—
7	Jan-21	36	livebirth	2570	16th	—
8	Jan-21	34	livebirth	2130	22nd	—
9	Jan-21	33	stillbirth	1700	3rd	—
10	Jan-21	31	livebirth	1950	—	75−91
11	Jan-21	34	livebirth	not stated	—	Not known
12	Jan-21	34	livebirth	not stated	—	Not known
13	Feb-21	39	livebirth	3625	—	75−90th
14	Feb-21	36	livebirth	2300	—	9−25th
15	Mar-21	34	livebirth	1550	—	2−9th
16	Mar-21	35	livebirth	2530	—	50−75
17	Mar-21	31	livebirth	1460	—	25−50
18	Jan-21	20	Miscarriage	320	Not calculable	Not calculable-
19	April 2020	25	stillbirth	762	16	N/A
20	Jan-21	29	stillbirth	1174	2	N/A
21	Feb-21	19	Miscarriage	162	Not calculable	Not calculable
22	Dec 2020	26	stillbirth	760	4	—
23	Dec 2020	35	stillbirth	2000	3	—
24	Jan-21	27	Livebirth	718	1	—
25	Jan-21	30	stillbirth	1170	1	—
26	Jan-21	33	stillbirth	Not known	Not calculable	Not calculable
27	Feb-21	Unknown	stillbirth	1100	Not calculable	Not calculable
28	Nov-20	35+6	Livebirth	2195 g	4.3	—
29	Dec-20	30+5	Livebirth	1500 g	60	—
30	Jan-21	25+4	Stillbirth	775 g	32	—
31	Mar-20	32+4	Livebirth	1680	—	25−50
32	Nov-20	29+3	Stillbirth	1220	—	25−50
33	Mar-21	36+4	Livebirth	2280	—	9−25
34	Feb-21	34+4	Livebirth	2060	50	—
35	Dec-20	32+4	Stillbirth	2010	—	75−90
36	Jan-21	36+4	Stillbirth	2780	—	50−75
37	Feb-21	32	Livebirth	1364	—	9−25
38	Nov-20	26+4	Livebirth	700	—	9−25
39	Mar-21	32+6	Livebirth	1890	58.07	75−91
40	Mar-21	30+6	Livebirth	1320	—	25−50
41	Mar-21	34+4	Livebirth	2180	—	50−75
42	Mar-21	37+6	Livebirth	2550	—	9−25
43	Oct-20	34+2	Stillbirth	2020	11.7	—
44	Dec-20	31	Stillbirth	1395	—	25−50
45	Oct-20	37+3	Stillbirth	3150	—	50−75
46	Jun-20	37+3	Livebirth	2775	—	25−50
47 (TWIN)	Jan-21	28+5	Livebirth	1390	—	75−91
48 (TWIN)	Jan-21	28+5	Livebirth	1090	—	25−50
49	Jan-21	31+6	Livebirth	1930	—	75−91
50	Jan-21	33+2	Livebirth	1500	—	9
51	Jan-21	34+6	Livebirth	3050	—	91−98
52	Jan-21	33+2	Livebirth	1734	—	09−25

Table 1 (Continued)

Case Number	Month of delivery	Gestation (weeks +days)	Pregnancy Outcome	Birthweight	Personalised Growth Chart Calculation	WHO Growth Chart Centiles
53	Mar-21	41+4	Livebirth	2220	–	<0.4
54	Feb-21	28	Stillbirth	980	–	09 to 25
55	Jan-21	31	Stillbirth	1450	–	09 to 25
56	Jan-21	21+6	Miscarriage	428	Not calculable	Not calculable
57	Jan-21	22+1	Miscarriage	373	Not calculable	Not calculable
58	Jan-21	27	Stillbirth	855 g	–	9−25
59	Jan-21	23+1	Miscarriage	XX	Not calculable	Not calculable
60	Jan-21	32+6	Stillbirth	1738	–	50th
61	Feb-21	28+1	Stillbirth	910	9−25th	–

Table 1: **Pregnancy outcome.**

Antenatal complications. Six women had experienced reduced fetal movements in the current pregnancy (as clinical evidence of fetal compromise). Two reported antepartum haemorrhage and one presented with oligohydramnios.

Maternal SARS-CoV-2 status. 47/59 (79·7%) mothers had a positive SARS-CoV-2 Polymerase Chain Reaction (PCR) test either at the time of labour or in the months before. Two mothers (3.4%) had tested negative for SARS-CoV-2 at the time of delivery and were not known to have had SARS-CoV2 at any stage of their pregnancy. In 10 instances (16·9%), maternal SARS-CoV2 status was either not known to clinicians or unavailable.

Of the 47 mothers with a positive SARS-CoV-2 PCR test, 12 (25·5%) were reported to be asymptomatic. 22 (46·8%) reported symptoms at some stage including pyrexia ($n = 10$), breathlessness and cough ($n = 3$) and headaches ($n = 2$). Three had severe illness requiring intensive care admission. In the remaining 13 cases, symptoms were unknown (27·6%).

In 22 cases the timing of a SARS-CoV-2 positive test could be calculated in relation to the delivery date: five mothers tested positive on the day of delivery and four tested positive less than 7 days prior to delivery. Six mothers tested positive between 7 and 14 days prior to delivery, seven tested positive more than 2 weeks prior to delivery, including one who tested positive four months before delivery.

Placental features (see Table 3). There were 57 singleton placentas and 2 twin placentas; one dichorionic diamniotic (DCDA) and one monochorionic diamniotic (MCDA).

Placental weights. Placental trimmed weights (without membranes and cords) are routinely measured as part of placental pathology reporting, and the American Registry of Pathology (ARP) standards for placental weight percentiles and feto-placental weight ratios are used.[12] Three placental weight percentiles could not be calculated due to gestational age being omitted ($n = 1$) or gestational age below 22 weeks ($n = 2$), for which AFIP tables are not standardised. In this series, 47 out of the remaining 58 (81%) placentas had a normal placental weight for gestation (defined as 10−90th percentile). Eight of 58 (13·8%) were less than the 10th percentile, and three (5·2%) were reported greater than the 90th percentile.

Feto-placental weight ratio could be calculated in 51 placentas. Of these, 45 (88%) had normal fetoplacental weight ratios (defined as 10−90th percentiles), four (8%) were low (<10th percentile), and two (4%) were greater than the 90th percentile.

Histology. In two cases, the degree of macroscopic fibrin deposition was not described (3·3%) and in a further seven (11·5%), fibrin deposition was described as affecting less than 25% of the parenchyma. One (1·6%) reported 'multifocal' fibrin, but a percentage was not documented. Figure 1 depicts macroscopic appearances of a placenta with characteristic features of extensive fibrin deposition. MPFD was reported in 50 placentas (82%) and in 35 of these, fibrin deposition was reported as 'diffuse' or specified as involving more than 50% of the parenchyma. Histological examination revealed concurrent CHI in 48 of these cases (79% of all placentas in the series). Ten reported only CHI (16%). Figures 2-4 show the distinctive features displayed by the combined presence of MPVFD and CHI (Figure 2), syncytiotrophoblast necrosis (Figure 3) and the presence of dense perivillous fibrin without chronic histiocytic infiltrates as seen in one of the two cases which presented exclusively with MPVFD (Figure 4).

Other reported placental pathology included chronic deciduitis ($n = 4$; 6·6%), chronic chorioamnionitis ($n = 8$; 13%) fetal vascular malperfusion (2; 3·2%), eosinophilic/T-cell vasculitis ($n = 1$; 1·6%) intervillous haemorrhage ($n = 4$; 6·6%), acute chorioamnionitis ($n = 1$;

Case Number	Pregnancy Outcome	Maternal ethnicity	Maternal BMI	Maternal co-morbidities	Maternal COVID Status	Maternal Symptoms? Asymptomatic?	Date of Positive Test in relation to delivery
1	Stillbirth	White/Caucasian	18	—	positive	symptomatic	—
2	Stillbirth	Asian	19.6	Hypertension	positive	symptomatic	—
3	Stillbirth	Black African or Afro Caribbean	22.7	—	—	—	—
4	Livebirth	Asian	37	—	positive	—	—
5 + 6 (TWINs)	Stillbirth	Black African or Afro Caribbean	27.7	SLE, hyperthyroid	positive	asymptomatic	—
7	Livebirth	White/Caucasian	25.5	—	positive	symptomatic	—
8	Livebirth	Black African or Afro Caribbean	28.7	—	positive	symptomatic	—
9	Stillbirth	Asian	24.4	—	positive	asymptomatic	—
10	Livebirth	—	—	—	positive	Critical illness with intensive care	—
11	Livebirth	Black African or Afro Caribbean	26.9	Sickle cell trait	positive	symptomatic	10 days
12	Livebirth	—	—	—	—	—	—
13	Livebirth	—	—	—	positive	—	—
14	Livebirth	Asian	26.9	—	positive	asymptomatic	—
15	Livebirth	White/Caucasian	24	—	negative	—	—
16	Livebirth	White/Caucasian	21.5	—	positive	symptomatic	—
17	Livebirth	Black African or Afro Caribbean	24.5	—	negative	—	—
18	Miscarriage	White/Caucasian	36	Hypertension and Hepatitis C	positive	—	2 days
19	Stillbirth	White/Caucasian	27.9	—	positive	symptomatic	—
20	Stillbirth	White/Caucasian	22.9	Anticardiolipin antibodies, recurrent miscarriages	positive	Asymptomatic	—
21	Miscarriage	Black African or Afro Caribbean	27.4	Rheumatoid arthritis, intra-cranial hypertension, anxiety, depression, congenital heart disease	positive	Symptomatic	—
22	stillbirth	Asian	55.2	hypertension, asthma, hypo-thyreosis, multiple miscarriages	positive	Critical illness requiring inten-sive care	—
23	Stillbirth	Asian	27	Anaemia	positive	Symptomatic	9 days
24	Livebirth	White/Caucasian	26.6	—	Positive	Symptomatic	>1 month and on deliv-ery day
25	Stillbirth	White/Caucasian	30.1	Ex-smoker	Positive	Symptomatic	
26	Stillbirth	Asian	27		positive	Asymptomatic	0 day
27	Stillbirth	White/Caucasian	39	Smoker	positive	Asymptomatic	
28	Livebirth	White/Caucasian	21.79	—	Positive	Symptomatic	10 days
29	Livebirth	White/Caucasian	26.49	—	—	Critical illness requiring inten-sive care	0 days

Table 2 (Continued)

Case Number	Pregnancy Outcome	Maternal ethnicity	Maternal BMI	Maternal co-morbidities	Maternal COVID Status	Maternal Symptoms? Asymptomatic?	Date of Positive Test in relation to delivery
30	Stillbirth	White/Caucasian	22	—	Positive.	—	—
31	Livebirth	Asian	—	Congenital heart disease, Stroke	Positive	Symptomatic	0 days
32	Stillbirth	White/Caucasian	43.2	—	—	—	—
33	Livebirth	—	—	—	—	—	—
34	Livebirth	Asian	50	HELLP	Positive	—	>1 month
35	Stillbirth	White/Caucasian	35	—	Positive	Asymptomatic	—
36	Stillbirth	White/Caucasian	39.1	Gestational Diabetes	Positive	Symptomatic	—
37	Livebirth	White/Caucasian	42	Smoker	Positive	Asymptomatic	2 weeks
38	Livebirth	Asian	22.9	'Cardiac murmur'	Positive	Symptomatic	>2 months
39	Livebirth	White/Caucasian	18.4	—	—	—	—
40	Livebirth	White/Caucasian	25	—	Positive	—	—
41	Livebirth	—	—	Abruption	Positive	—	November 2020
42	Livebirth	White/Caucasian	27	—	—	—	—
43	Stillbirth	White/Caucasian	27.3	—	Positive	Asymptomatic	10 days-
44	Stillbirth	White/Caucasian	30	—	Positive	Asymptomatic	—
45	Stillbirth	White/Caucasian	39.4	—	Positive	Symptomatic	—
46	Livebirth	White/Caucasian	29.4	—	Positive	—	—
47+48 (TWIN)	Livebirth	White/Caucasian	27.22	—	Positive	—	
49	Livebirth	White/Caucasian	34.6	—	Positive	Symptomatic	0 days
50	Livebirth	White/Caucasian	22.7	Sjogren's syndrome	—	—	
51	Livebirth	White/Caucasian	41.91	—	Positive	—	0 days
52	Livebirth	White/Caucasian	26	—	Positive	Asymptomatic	3 weeks
53	Livebirth	White/Caucasian	29	Uterine fibroids	—	—	
54	Stillbirth	White/Caucasian	21.9	Depression and post-traumatic stress disorder	—	Symptomatic	
55	Stillbirth	White/Caucasian	42	—	Positive	Symptomatic	1 day
56	Miscarriage	—	—	—	Positive	—	2 weeks
57	Miscarriage	—	—	Childhood leukaemia and thyroid carcinoma	Positive	—	>2 weeks
58	Stillbirth	White/Caucasian	27	—	Positive	Symptomatic	
59	Miscarriage	White/Caucasian	—	—	Positive	Asymptomatic	>one week
60	Stillbirth	White/Caucasian	—	—	Positive	Symptomatic	One week
61	Stillbirth	White/Caucasian	27.2	Deep Vein Thrombosis	Positive	—	One week

Table 2: **Maternal demographics.**

Articles

Case Number	Gestation (weeks + days)	Placenta percentile	Fetoplacental weight centile	Fibrin Deposition	Intervillositis
1	32	10−25	50−75	Diffuse	Present
2	41	<3	10−25	Diffuse	Absent
3	25	25−50	25	Diffuse	Present
4	29	10−25	50−75	Diffuse	Present
5 (TWIN)	31	25−50 [a]	Not calculable	Diffuse	Absent
6 (TWIN)	31	25−50 [a]	Not calculable	Diffuse	Absent
7	36	25	50	Diffuse	Absent
8	34	50−75	10−25	Diffuse	Present
9	33	25−50	25−50	Diffuse	Present
10	31	75−90	10−25	Diffuse	Present
11	34	75	Not calculable	Diffuse	Present
12	34	25−50	Not calculable	Diffuse	Present
13	39	>95	<3rd	Diffuse	Present
14	36	10−25	50−75	>50%	Present
15	34	<10	10−25	Diffuse	Present
16	35	50−75	25−50	Diffuse	Present
17	31	50−75	5	25%	absent
18	20	75−90	Not calculable	Diffuse	Present
19	25	25	75	Diffuse (90%)	Present
20	29	50	25−50	Diffuse (100%)	Present
21	19	Not calculable	Not calculable	Diffuse (90%)	Present
22	26	90	25−50	Diffuse (95%)	Present
23	35	25	25−50	Diffuse (100%)	Present
24	27	25−50	50	Multifocal (50%)	Present
25	30	10	50	Diffuse (100%)	Present
26	33	50	Not calculable	Multifocal (50%)	Present
27	Unbooked	Not calculable	Not calculable	Diffuse (80%)	Present
28	35+6	5−10	75−90	>30%	Present
29	30+5	10−25	75−90	<10%	Present
30	25+4	50	50−75	~99%	Present
31	32+4	10−25	50−75	60−70%	Present
32	29+3	50−75	25	50%	Absent
33	36+4	90−95	10−25	30−40%	Present
34	34+4	25−50	25−50	50%	Present
35	32+4	50−75	25−50	90%	Present
36	36+4	25−50	50−75	90%	Present
37	32	25−50th	10−25	30%	Absent
38	26+4	10−25	50−75	50%	Absent
39	32+6	50−75	25−50	50%	Present
40	30+6	25−50	25−50	20%	Present
41	34+4	10−25	75−90	15%	Present
42	37+6	5−10	75−90	95%	Present
43	34+2	5−10	90−95	10%	Present
44	31	25−50	25−50	Absent	Present
45	37+3	25−50	75−90	75−80%	Present
46	37+3	<3	>97	10%	Present
47 (TWIN)	28+5	25−50	75−90	40%	Present
48 (TWIN)	28+5	25−50	75−90	40%	Present
49	31+6	50−75	50−75	Not documented	Present
50	33+2	10−25	25−50	45−50%	Present
51	34+6	90−95	50	Not documented	Present
52	33+2	50−75	3−5	40%	Present
53	41+4	3−5	10−25	>60%	Absent

Table 3 (Continued)

Case Number	Gestation (weeks + days)	Placenta percentile	Fetoplacental weight centile	Fibrin Deposition	Intervillositis
54	28	75−90	5−10	Diffuse	Absent
55	31	25−50	50−75	70%	Present
56	21+6	Not calculable	Not calculable	Diffuse (90%)	Present
57	22+1	<10	50−75	Diffuse (90%)	Present
58	27	25−50	50−75	Multifocal	Present
59	23+1	10−25	Not calculable	Diffuse (90%)	Present
60	32+6	50−75	10−25	Absent	Present
61	28+1	25−50	50−75	Diffuse (100%)	Absent

Table 3: **Placental pathology.**
  ᵃ Overall placental weight percentile calculated for MCDA twin.
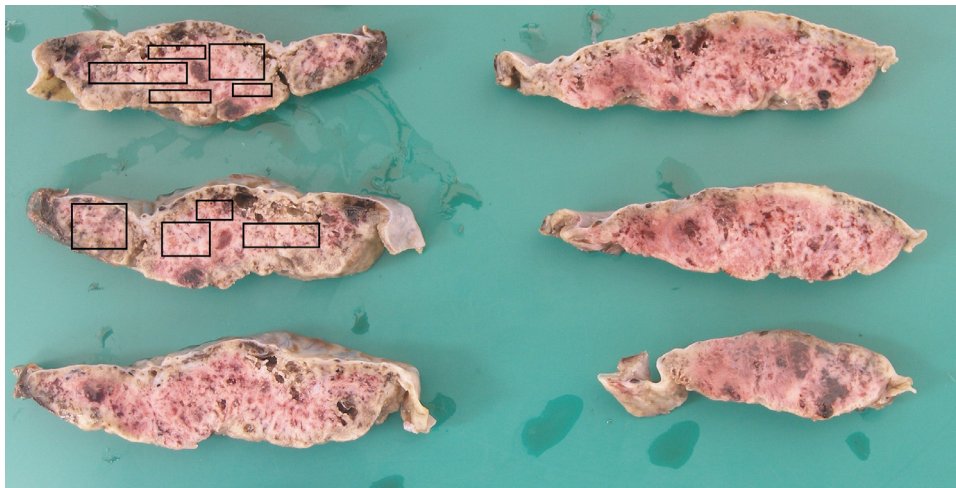
Figure 1. Macroscopic image of term placenta, serially sectioned, showing extensive fibrin deposition throughout the parcenchyma.
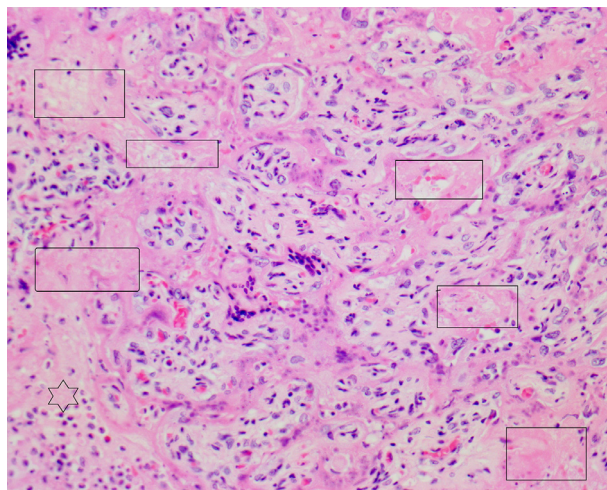
Figure 2. Haematoxylin and eosin stained section at x 200 magnification showing a placenta affected by an inflammatory cell infiltrates within the intervillous space with necrosis of the trophoblast and perivillous fibrin deposition.
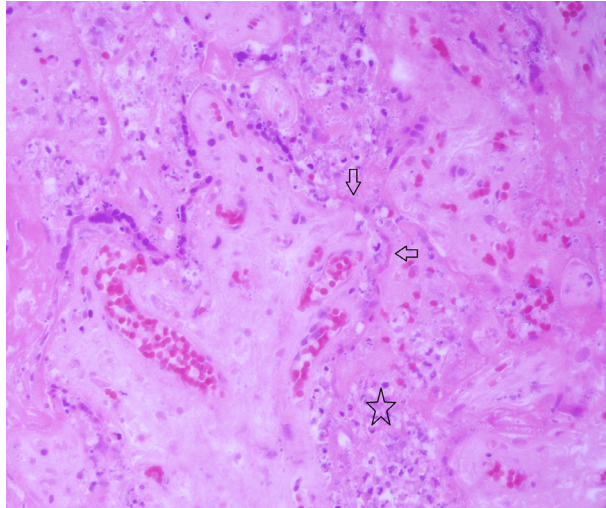
Figure 3. Haematoxylin and eosin stained section at x 400 magnification showing trophoblast necrosis characterised by 'smudging' of the nuclei and karyorrhectic debris within the intervillous space.

1.6%), chronic villitis ($n = 2$; 3·2%), maternal vascular malperfusion ($n = 1$; 1·6%), decidual vasculopathy ($n = 2$; 3·2%) and chorangiosis ($n = 1$; 1·6%).

All placentas demonstrated positive SARS-CoV-2 immunohistochemical expression in the syncytiotrophoblast, 14 (23%) also had SARS-CoV-2 positivity by PCR on placental tissue. This is shown in Figure 5.

One case that was also published separately as a case report also had in situ hybridisation, proving both the presence and the replication of virus in the syncitiotrophoblasts.[11]

Electron microscopy. Transmission electron microscopy was performed on 4 formalin-fixed paraffin processed placentas. A large number of particles measuring between 87 and 178 nm in diameter with spikes measuring 17 nm reminiscent of SARS-CoV2[13] were found within the extravillous polymerised fibrin (Figure 6) and within trophoblast cells (Figure 7) Both original magnification x20,000.

Pregnancy outcome. Of 61 infants delivered to 59 pregnancies, 30 were stillborn or miscarried (49.1%).

Six infants (four livebirths and two stillbirths) tested positive for SARS-CoV-2 by PCR following delivery (timing not specified). Five infants (two livebirths and three stillbirths) tested negative following delivery (timing not specified). For the remaining 50 infants the SARS-CoV-2 status was not known.
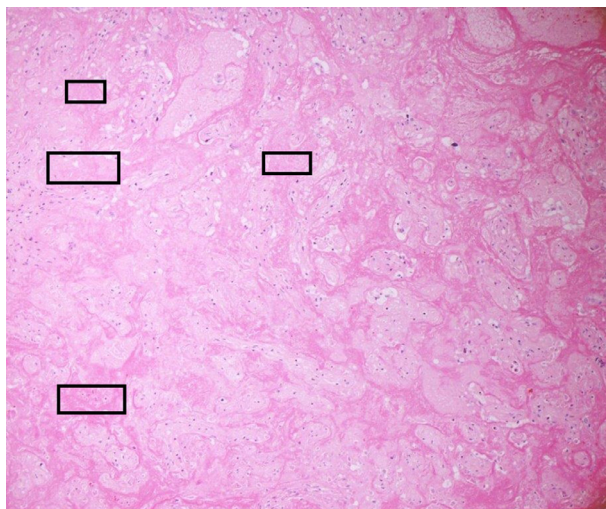
Figure 4. Immunohistochemical staining of placental parenchyma with SARS-CoV2 immunohistochemical stain (x200 magnification) with expression in the syncytiotrophoblast.
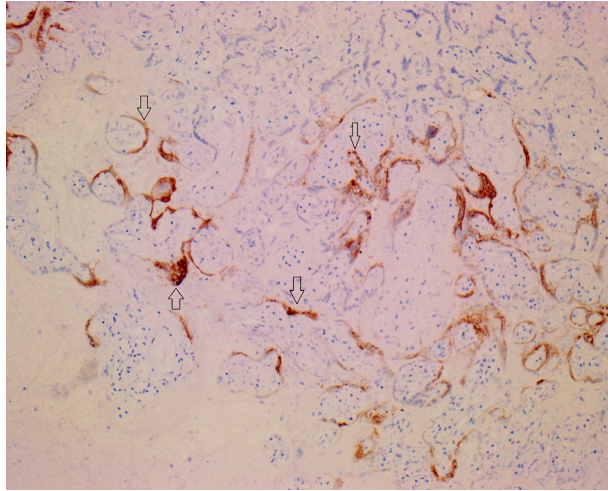
Figure 5. High magnification electron microscopy image of formalin fixed paraffin processed trophoblast cytoplasm showing possible Covid19 virion budding into endoplasmic reticulum (at 3 o'clock) and a couple of vacuoles containing 3 and 2 possible complete virus particles (at 7 o'clock and 11 o'clock). The spherical virus particles contain black dots, which are cross-sections through the viral nucleocapsid (as shown within rectangles).
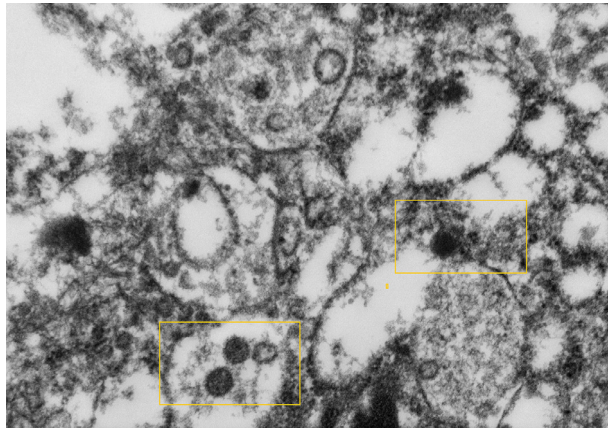

Figure 6. High magnification electron microscopy image of formalin fixed paraffin processed possible multiple Covid19 virions in apex of cytotrophoblast cell within vacuoles (as shown within rectangle).
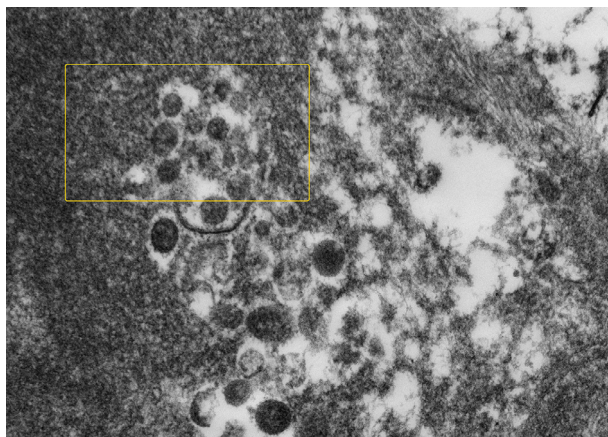
Figure 7. High magnification electron microscopy image of formalin fixed paraffin processed possible multiple Covid19 virions in perivillous fibrin lying free and within a vacuole (at 10 o'clock) (as shown within rectangle).

Of the 12 mothers who were known to be SARS-CoV-2 positive but who were reportedly asymptomatic (12 mothers, but 13 infants due to twin pregnancies) 75% ended in pregnancy loss ($n = 9$), compared to pregnancy loss rate of 50% in women who were symptomatic ($n = 11$).

Obese mothers (defined as BMI>30 kg/m²) had higher rates of pregnancy loss when compared with those with a BMI <30 [67% (10/15) versus 41% (14/34) respectively]

For BAME groups 8/16 (50%) pregnancies ended in pregnancy loss (one miscarriage, seven stillbirths). This was similar to the Caucasian mothers reporting 19/36 (52·7%) of pregnancy loss (one miscarriage and 18 stillbirths).

For 20 infants in which a personalised growth centile was provided; 11 were < 9th centile for the stated gestational age, and nine were reported to be within normal limits for the stated gestation (defined as 10−90th centile).

There were 31 cases in which a personalised growth centile was not available and growth was assessed using the UK WHO growth charts for close fetal and neonatal monitoring.[14] In cases in which the sex of the baby was not specified, both centiles for male and female were calculated and the lower percentile was selected. Using this method, three infants were less than the 9th percentile for the stated gestation, 25 were within normal limits (10−90th centile), and one baby was reported to be >90th centile for the stated age.

A birthweight was either not recorded or a centile could not be calculated in nine cases, including one early gestation, one monochorionic twin placenta and one of unknown gestation.

Discussion

To our knowledge, this is the largest audited case series of SARS-CoV-2 placentitis. 79% of placentas showed both MPFD with CHI, with 16% reporting just CHI and 3·3% only showing MPFD.

Assessing how the timing of SARS-CoV-2 infection correlates with the histological features is challenging, given the data was not available in just over one third of cases and is further complicated by lack of symptoms, nadirs in testing and delay in investigations in relation to acquisition of infection. However, it should be noted that 15/22 (68%) had a positive test within two weeks of delivery.

In this series many of the placentas complicated by SARS-COV2 placentitis were from mothers in whom no symptoms of SARS-CoV-2 infection were reported, however we did not know the symptomatology in 13 of 47 known SARS-CoV-2 positive mothers so conclusions cannot be reliably drawn. However, it is possible that only a fraction of placentas from mothers with SARS-CoV-2 infection are referred for pathological examination — and only in the case of poor placental outcomes.

Therefore, the true number of asymptomatic mothers with SARS-CoV-2 placentitis may be even higher than our data has shown.

In a recent UK cohort study, mothers with SARS-CoV-2 infection were reported to be nearly three times as likely to experience a preterm birth or stillbirth compared with mothers without SARS-CoV-2 infection.[1,2] The same paper highlighted the risks to women of BAME, high BMI and those with higher levels of social deprivation. Despite the known risks to women from BAME backgrounds with SARS-CoV-2 infection,[4] there were similar rates of pregnancy loss with SARS-CoV-2 placentitis in BAME women as Caucasians in our cohort (50% and 52·7% respectively).

The proportion of BAME women in our data was significantly higher than the national average at 32%.[15] This may be due to referral bias as some of the tertiary centres involved in this study provide services to areas in which there are much higher rates of BAME groups than the national average. Furthermore, the data in this study is from 10 participating referral centres out of >20 centres in the UK. It is therefore not possible to determine whether women from BAME groups are over-represented in our results.

There were higher rates of pregnancy loss in obese mothers compared with women with a BMI <30. It is well documented that obesity is a risk factor for severe SARS-CoV-2 infection and in isolation increases the risk of stillbirth,[16] and our results therefore would not be unexpected. It should however, be noted that as we do not have a control population of which to compare and given the variability in the demographics, like our comments relating to ethnicity, it is not possible to determine whether obese mothers are over represented our case series.

The placental weights were largely within normal limits for the gestational age (79%) and had normal feto-placental weight ratios (88%). This is in contrast to the pattern typically described in classical pre-pandemic MPFD in which placentas are described as small and firm.[9] Furthermore pre-pandemic MPFD is also often associated with intra-uterine growth restriction.[9] The histological picture in MPFD in SARS-CoV-2 placentitis differs from the pre-pandemic' MPFD mainly due to the presence of prominent CHI in the former, and the absence of extravillous trophoblast. Significant trophoblast necrosis was only described in a proportion of cases (28%). However, it is possible that this proportion is not truly reflective; many pathologists include this in the general histological description of SARS-CoV-2 placentitis (not reporting this feature separately) and in some instances the clinical significance may not have been appreciated on initial reporting as it can be a focal finding. The intervillous fibrin also appears less dense, without migration of extravillous trophoblast and can at times be associated with a mixed inflammatory cell infiltrate.

The pathophysiological mechanism behind the development of MPFD in the placentas of some mothers infected with SARS-CoV-2 remains to be elucidated. However, it may be possible that a synergistic effect of the immunological dysregulation induced by the virus and an underlying or acquired thrombophilia in the mother, or the fetus, triggers the CHI − trophoblast necrosis- MPFD pathway.

When calculable in 51 cases, the majority of babies in our cohort (34/51; 67%) were reported to have normal birth weight (defined as 10−90th centile on personalised or WHO generalised growth charts as available). There were however a greater proportion of small infants when using the personalised growth chart; 9/20 as opposed to 3/31 when using the WHO growth charts. This variation in infant weight likely reflects a degree of referral bias. Growth restriction (<10th percentile) is one of the referral criteria for placental examination according to the Royal College of Pathologists.[17] Placentas from infants who are small for gestation are more likely to be received, regardless of SARS-CoV2 status of the mother. Further, these cases are more likely to have a personalised growth centile calculated as part of referral practices. It is still not uniformly common practice for placentas to be referred for pathological examination purely on the basis of SARS-CoV2 infection, particularly if the mother is negative at the time of delivery, is asymptomatic or if the baby appears normally grown and healthy.

There was limited information on the number of babies testing positive for SARS-CoV-2. Details of 11 babies were available to the pathologists with six testing positive and five negatives, though the timing of the testing was not specified. At least one case of vertical transmission was confirmed in our series (paper under submission). No known cases of vertical transmission have been reported in the coronaviruses Severe Acute Respiratory Syndrome and Middle Eastern Respiratory Syndrome, though relatively few pregnancy cases were reported.[18]

A systematic review and meta-analysis of over 1000 neonates born to SARS-CoV-2 positive mothers, showed relatively low rates of vertical transmission, with 0·7−7% of neonates testing positive.[19] These results should be interpreted with caution given the risk of false positives from maternal contamination of the samples if nasopharyngeal swabs rather than umbilical cord blood are used. McDevitt et al. reported on universal screening at their hospital including neonates: eight tested positive for SARS-CoV-2, all born to asymptomatic mothers, seven of whom had tested negative on admission.[20] The neonatal tests were subsequently repeated, and each was reported to be negative. This was a curious finding, which raises the possibility of sample contamination and technical failure of the Real Time-PCR tests, though also could reflect previous maternal SARS-CoV-2 infection which has resolved, though placental infection

persists. Placental histology unfortunately was not available for correlation in any of these instances.

The proposed mechanism of placental infection relies on the presence of ACE2 receptors on syncytiotrophoblast,[21] with viral endocytosis supported by a host of transmembrane proteins including the transmembrane serine proteases (TMPRSS). Infection then triggers both a direct and indirect immunological response with the release of inflammatory cytokines.[22] Why the placentas of some women are affected in this way and others are not, is yet unestablished.

An investigation team from Yale compared the placental transcriptome in SARS-CoV-2 infected cases with matched controls, demonstrating that infected cases showed increased expression of genes associated with immune responses, suggesting a robust local response to respiratory infection even in the absence of localised placental infection.[23] The study reported changes in gene expression including upregulation of HSPA1A, which encodes the heat shock protein Hsp70, a proposed alarmin that has been implicated previously in placental vascular diseases and preeclampsia. The Yale team found a significant increase in the interactions between immune cells at the maternal-fetal interface in SARS-CoV-2 infected cases compared with non-infected controls. This is in keeping with the identification in our cases of SARS-CoV2 in the trophoblast -at the feto: maternal interface − both by histochemistry and electron microscopy.[18] Placental immune responses during maternal respiratory SARS-CoV-2 infection may contribute to the poor pregnancy outcomes and that active infection at the maternal-fetal interface is not required for immune activation at this distant site.[23]

We propose that CHI may be the initial response to SARS-CoV-2 infection, with fibrin deposition a secondary feature and/or associated with trophoblast necrosis. A study from Chen and Roberts in pre-pandemic placentas suggests that the pathologic increase in perivillous fibrin is a reaction to trophoblast damage/necrosis.[9] Prospective longitudinal studies are required to establish the pathophysiology further. This may be challenging given the number of women that can be completely asymptomatic for infection. However, all of the women whose placentas are included in this study are expected to be followed up closely during subsequent pregnancies and it will be interesting to see how many cases of MPFD or CHI recur outside of the pandemic.

Mothers with gestations affected by CHI often have elevated serum alpha-fetal protein and/or alkaline phosphatase due to placental damage.[9] These markers could potentially be used in the routine care and follow-up of SARS-CoV-2 infected pregnant women.

The limitations of our work include the inability to place our findings in the full context of SARS-CoV2 in pregnancy; namely comparison with outcomes of maternal SARS-CoV2 infection without the finding of

SARS-CoV2 placentitis, and the lingering question of what proportion of SARS-CoV2 positive mothers develop placentitis? These are difficult areas of interest to address as there is referral bias in placental examination, variation in each hospital policy including testing of asymptomatic patients, nadirs in positive SARS-Cov2 PCR tests and of course a host of epidemiological data and risks to consider. A well-designed prospective study, with a control population and a cohort of mothers with SARS-CoV2 infection without placentitis could provide some progress in this area, though all mothers symptomatic or not, would require SARS-CoV2 PCR and each placenta, regardless of pregnancy outcome would need to be assessed to generate accurate meaningful data. Another limitation of this national audit project was the lack of independent review and quantitative analysis of cases. Further, the histopathological pattern of SARS-CoV-2 placentitis in relation to SARS-CoV-2 variants may be another area of interest which is yet to be explored, given the rise in Delta variant at the time of writing. Utilisation of genomic sequencing and clinicopathological correlation is needed for further clarification.

To conclude, we have presented the largest case series of SARS-CoV-2 placentitis to date. In half of cases, the pregnancy ended in stillbirth or late miscarriage. Importantly, mothers who were reported as asymptomatic for SARS-CoV-2 showed the same placenta histological pattern and experienced a similar incidence of pregnancy loss to those reported as symptomatic. Obese mothers had higher rates of stillbirth compared to non-obese mothers with the same placental histology. Whilst most infants were of normal weight, the results of personalised growth centiles and generalised growth centiles varied greatly and may be affected by a degree of referral bias. Further work is required to establish the significance of the timing of maternal SARS-CoV-2 infection and its relation to SARS-CoV-2 placentitis, the significance of SARS-CoV2 variants in pregnancy, and rates of vertical transmission associated with this particular pattern of placental inflammation.

UKOSS findings have also shown that vaccine uptake in pregnant women is low compared to the general population, and that most hospitalised pregnant women are not fully vaccinated. The experiences of UK perinatal and paediatric pathologists have recently been acknowledged by Public Health England, and pregnant women are strongly advised to be vaccinated against SARS-CoV-2 infection.[24]

Data sharing statement

The authors will share Individual participant data that underlie the results reported in this article, after de-identification (text, tables and figures) as well as the audit project. Applicants willing to receive the data should apply between1 and 12 months after the manuscript has been published and should demonstrate that the proposed use of the data has been approved by an independent review committee ("learned intermediary") identified for this purpose. The data should be requested to the corresponding author Marta.Cohen@nhs.net

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