Accepted: 2 March 2023

DOI: 10.1111/1471-0528.17476

BJOG An International Journal of Obstetrics and Gynaecology

RESEARCH ARTICLE

# Routine placental histopathology findings from women testing positive for SARS-CoV-2 during pregnancy: Retrospective cohort comparative study

**Charlotte S. Colley**[1,2] | **J. Ciaran Hutchinson**[3,4] | **Sara M. Whitten**[1,2] | **Dimitrios Siassakos**[1,2] | **Neil J. Sebire**[3,4] | **Sara L. Hillman**[1,2]

[1]University College London Hospitals (UCLH) NHS Foundation Trust, London, UK

[2]Institute for Women's Health, University College London (UCL), London, UK

[3]Great Ormond Street Hospital Institute of Child Health, University College London, London, UK

[4]National Institute for Health and Care Research, Great Ormond Street Hospital, Biomedical Research Centre, London, UK

**Correspondence**
Charlotte S. Colley, University College London Hospital, 235 Euston Road, London, NW1 2BU, UK.
Email: charlotte.colley@nhs.net

**Funding information**
University College London Global Challenge Engagement Office

## Abstract

**Objective:** To assess the impact of maternal Coronavirus disease 2019 (COVID-19) infection on placental histopathological findings in an unselected population and evaluate the potential effect on the fetus, including the possibility of vertical transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

**Design:** Retrospective cohort comparative study of placental histopathological findings in patients with COVID-19, compared with controls.

**Setting:** During the COVID-19 pandemic, placentas were studied from women at University College Hospital London who reported and/or tested positive for COVID-19.

**Population:** Of 10 508 deliveries, 369 (3.5%) women had COVID-19 during pregnancy, with placental histopathology available for 244 women.

**Methods:** Retrospective review of maternal and neonatal characteristics, where placental analysis had been performed. This was compared with available, previously published, histopathological findings from placentas of unselected women.

**Main outcome measures:** Frequency of placental histopathological findings and relevant clinical outcomes.

**Results:** Histological abnormalities were reported in 117 of 244 (47.95%) cases, with the most common diagnosis being ascending maternal genital tract infection. There was no statistically significant difference in the frequency of most abnormalities compared with controls. There were four cases of COVID-19 placentitis (1.52%, 95% CI 0.04%–3.00%) and one possible congenital infection, with placental findings of acute maternal genital tract infection. The rate of fetal vascular malperfusion (FVM), at 4.5%, was higher compared with controls ($p = 0.00044$).

**Conclusions:** In most cases, placentas from pregnant women infected with SARS-CoV-2 virus do not show a significantly increased frequency of pathology. Evidence for transplacental transmission of SARS-CoV-2 is lacking from this cohort. There is a need for further study into the association between FVM, infection and diabetes.

**KEYWORDS**
coronavirus, COVID-19, COVID-19 in pregnancy, COVID-19 pregnancy outcomes, placenta, placental pathology, placentitis, SARS-CoV-2, vertical transmission

## 1 | INTRODUCTION

On 30 January 2020 the Director-General of the World Health Organization announced an international public health emergency, as the novel coronavirus disease 2019 (COVID-19) outbreak was declared. Subsequently, the severe acute respiratory syndrome coronavirus 2 virus (SARS-CoV-2), which causes COVID-19 infection, has spread worldwide, accounting for over 756 million cases and over 6 million deaths.[1,2] Pregnant women with COVID-19 are at increased risk of maternal morbidity and mortality, compared with the non-pregnant population.[3]

Host infection with the SARS-CoV-2 virus acts through the angiotensin-converting enzyme 2 (ACE2) receptor, expressed by many but predominantly by alveolar epithelial cells. The spike glycoprotein on SARS-CoV-2 binds to subdomain 1 of ACE2, fusing the membranes and allowing the release of viral RNA into the host cell. Entry also requires S protein priming by the cellular transmembrane protease, serine 2 (TMPRSS2).[4–8] ACE2 expression has been found in the placental syncytiotrophoblast, cytotrophoblast, vascular smooth muscle and endothelium, suggesting that these can be infected by SARS-CoV-2.[9–11] Additionally, COVID-19 is associated with a hypercoagulable state through endothelial activation and dysfunction.[12,13]

COVID-19 during pregnancy has been reported as more severe, with increased rates of admission to intensive care, need for invasive ventilation and need for extracorporeal membrane oxygenation.[14,15] Therefore, pregnant women are considered to be at high risk, especially women with pre-existing medical conditions, advanced maternal age (>35 years), raised body mass index (>30 kg/m$^2$), non-white ethnic background and from deprived socio-economic areas.[14,16] An increased risk of preterm delivery and fetal growth restriction has been reported with maternal COVID-19 infection.[16–18] However, a meta-analysis including over 1100 cases shows significant heterogeneity between reported outcomes, although preterm birth remains significant.[19]

Robust evidence on the effect of COVID-19 on placental pathology is limited, with a possible reported increased frequency of maternal vascular malperfusion (MVM), intervillous thrombus and fetal vascular malperfusion (FVM).[18,20–22] COVID-19 placentitis is now recognised as a rare complication associated with adverse outcomes such as placental insufficiency and stillbirth, with characteristic positive trophoblast staining for SARS-CoV-2 and concomitant necrotising histiocytic intervillositis.[23–27] Other studies, however, have reported no relationship between most placental pathologies and COVID-19, compared with controls.[28,29]

Initial studies during the pandemic were often based on severe or highly preselected cases presented as case reports and small case series. The objective of this study was to evaluate, using published and routine standard approaches to clinical placental examination, whether histological abnormalities are present in the placentas of women with COVID-19, irrespective of their clinical presentation or outcome. We hypothesised that there is no effect of COVID-19 on the placenta.

## 2 | METHODS

This was a retrospective observational study involving a review of routine placental histological findings from women with COVID-19 in pregnancy, from March 2020 to February 2022, compared with historical published control data relating to placental pathological findings in unselected pregnancies delivering at or near term.[30] Therefore, the time period studied covered patients with COVID-19 in both the Alpha and Delta waves of the pandemic. Data were collected under the direction of the hospital trust-supported mandate from the Department of Health and Social Care, allowing the direct processing and presentation of patient information to expedite our understanding of the impact of COVID-19. No patient-identifiable features link any of the data presented.

All women at University College Hospital London who tested positive for COVID-19 antenatally (including those testing positive on admission in early labour, prior to induction or caesarean section) were included in this study. The cohort included patients who tested positive during inpatient hospital stays and during periods of antenatal care, as well as patients identified in the community and from self-reports of confirmed infection. Patients were included if they tested positive at home; however, this must have been reported to their midwife or obstetrician and documented in their electronic notes at the time of diagnosis. From March 2020, placentas were routinely submitted for clinical histopathological examination from patients with COVID-19 in pregnancy. Relevant maternal and neonatal clinical data were extracted from the hospital electronic records system (EPIC); data were reported as mean (standard deviation, SD) unless otherwise stated.

Placentas were submitted, following delivery, for routine histopathological examination to a single specialist centre as part of the pathway for routine clinical care. The histopathology request form was marked with the information 'COVID-19 in pregnancy' as the reason for referral. Placentas underwent routine macroscopic examination and histological sampling according to standard guidelines from the Royal College of Pathologists, including the standard histological sampling,[31] and were reported by perinatal pathology specialists. Placental pathological findings were classified according to the Amsterdam criteria, which includes FVM, MVM, delayed villous maturation, ascending intrauterine infection and villitis of unknown aetiology (VUE).[32]

Frequency of histological findings in our case group were compared with the frequency of histological findings in a previously published cohort of unselected third-trimester deliveries,[30] including 1153 women who delivered at 34–43 weeks of gestation, preceding the pandemic. The compare proportions test was used to compare frequencies between cohorts, with $p < 0.05$ considered significant. There was no patient involvement in the study because of the pandemic.

BJOG An International Journal of Obstetrics and Gynaecology



## 3 | RESULTS

Of 369 patients identified as having COVID-19 during pregnancy, the data set comprised placentas from 244 women that were available for histopathological evaluation. Unfortunately, placenta pathology was not available for 125 patients, as three patients miscarried, 19 patients were delivered at another unit and placentas were not sent for analysis in the remaining 103 patients. The maternal demographics and outcomes for this group are displayed in Table S1.

### 3.1 | Maternal characteristics

Mean maternal age was 33.5 years (SD 5.6 years) and the mean body mass index was 25.5 kg/m$^2$ at booking (SD 5.27 kg/m$^2$). Details of maternal demographics and neonatal outcomes are provided in Table 1, divided by trimester of pregnancy in which COVID-19 was diagnosed. There were eight cases with a hypertensive disorder of pregnancy, one case with pre-existing diabetes and 36 cases with gestational diabetes. COVID-19 was reported in 27 cases (11.1%) in the first trimester, 50 cases (20.5%) in the second trimester (12–24 weeks of gestation) and 167 cases (68.4%) in the third trimester up to delivery.

Of the 244-case cohort, five patients (2%) were admitted to the intensive care unit (ICU) during their pregnancy for the management of worsening COVID-19 infection, and these data are summarised in Table 2. One patient, at 32 weeks of gestation at the time of infection, required continuous positive airway pressure (CPAP) support, steroids and antibiotics in the ICU. She recovered, was discharged home and delivered a normally grown baby by elective caesarean section (for obstetric indications) at term. Risk factors for this patient having severe COVID-19 were a maternal age of >35 years and a body mass index of 35 kg/m$^2$. Placental pathology for this case was normal.

Placenta pathology showed non-specific ascending maternal genital tract infection in all four of the other cases and an additional diagnosis of FVM in one case, but none of these cases showed COVID-19 placentitis.

One patient was admitted with a superimposed chest infection after testing positive for COVID-19 in the third trimester. She was admitted to the ICU for CPAP and was treated with antibiotics, steroids and tocilizumab. This patient had gestational diabetes mellitus (GDM), which was controlled with metformin. She delivered a normally grown baby by emergency caesarean section at term for failure to progress and pyrexia in labour. Risk factors (for severe COVID-19) in this patient included a maternal age of >35 years and non-white ethnic background, contributing to

**TABLE 1** Maternal demographics and neonatal outcomes in our case group and controls.

| | Case group | | | Controls |
|---|---|---|---|---|
| | Trimester became COVID19 positive ($n=244$) | | | |
| | 1 | 2 | 3 | |
| | $n=27$ (11.1%) | $n=50$ (20.5%) | $n=167$ (68.4%) | $n=1153$ |
| Age (mean, SD) | 34.4 (5.8) | 34.4 (5.6) | 33.0 (5.6) | 30.9 (5.7) |
| BMI (mean, SD) | 26.4 (4.7) | 24.5 (4.4) | 25.6 (5.6) | – |
| Ethnic background (*n*, %) | | | | |
| Asian | 3 (11.5%) | 7 (15.2%) | 29 (18.1%) | – |
| Black | 1 (3.85%) | 4 (8.7%) | 16 (10.0%) | |
| White | 19 (73.1%) | 26 (56.5%) | 97 (60.6%) | |
| Other mixed background | 2 (7.7%) | 2 (4.4%) | 7 (4.4%) | |
| Other | 1 (3.85%) | 4 (8.7%) | 4 (2.5%) | |
| Not given | 0 (0.0%) | 3 (6.5%) | 7 (4.4%) | |
| Pregnancy induced hypertension/pre-eclampsia (*n*, %) | 1 (3.7%) | 1 (2.0%) | 6 (3.6%) | 57 (4.9%) |
| Gestational diabetes mellitus (*n*, %) | 2 (7.4%) | 7 (14.0%) | 27 (16.1%) | 46 (4%) |
| Maternal admission to intensive care unit (*n*, %) | 0 (0.0%) | 2 (4.0%) | 3 (1.8%) | |
| Admission to neonatal unit* (*n*, %) | 0 (0.0%) | 3 (6.0%) | 9 (5.4%) | 66 (5.7%) |
| Birthweight (grams) (mean, SD) | 3231 (443.6) | 3217 (600.9) | 3297 (547.1) | 3489 (495) |
| Delivery <37 weeks of gestation** (*n*, %) | 3 (11.0%) | 6 (12.0%) | 12 (7.2%) | |

Abbreviation: SD, standard deviation.

*Two sets of twins admitted to neonatal intensive care unit; **Three set of twins born preterm.

**TABLE 2** Risk factors, treatment given and outcome for patients admitted to the intensive care unit (ICU) with severe COVID-19 infection.

| Patient and risk factors for severe COVID-19 | Trimester tested positive for COVID-19 | ICU treatment | Delivery gestation | Birthweight (g) | Placental pathology |
|---|---|---|---|---|---|
| Patient 1<br>Age: 40 years<br>BMI: 35 kg/m$^2$<br>Ethnicity: white<br>Medical background: nil | 3 | Antibiotics, CPAP, steroids | $39^{+2}$ weeks | 3785 | Normal histology |
| Patient 2<br>Age: 45 years<br>BMI: 24 kg/m$^2$<br>Ethnicity: asian<br>Medical background: GDM on metformin | 3 | Antibiotics, CPAP, steroids, tocilizumab | $39^{+2}$ weeks | 3080 | 1. Ascending maternal genital tract infection<br>2. FVM |
| Patient 3<br>Age: 35 years<br>BMI: 20 kg/m$^2$<br>Ethnicity: asian<br>Medical background: nil | 3 | Antibiotics, CPAP, steroids, tocilizumab | $37^{+6}$ weeks | 2140* | Ascending maternal genital tract infection |
| Patient 4<br>Age: 35 years<br>BMI: 35.3 kg/m$^2$<br>Ethnicity: black<br>Medical background: GDM on insulin | 2 | ECMO | $38^{+4}$ weeks | 3100 | Ascending maternal genital tract infection |
| Patient 5<br>Age: 39 years<br>BMI: 27 kg/m$^2$<br>Ethnicity: white<br>Medical background: GDM on insulin | 2 | Intubated, considered for ECMO but responded to proning | $38^{+4}$ weeks | 3360 | Ascending maternal genital tract infection |

Abbreviations: CPAP, continuous positive airway pressure; ECMO, extracorporeal membrane oxygenation; FVM, fetal vascular malperfusion; ICU, intensive care unit.
*Birthweight on third centile.

her development of severe COVID-19. In addition to ascending maternal genital tract infection, this case showed FVM.

Similarly, another patient was admitted for CPAP and treated with steroids and tocilizumab after acquiring COVID-19 in the third trimester. She delivered an infant on the third centile by vaginal delivery at term. The only risk factor for this patient developing severe COVID-19 was having a non-white ethnic background.

The fourth patient was admitted to ICU for increasing oxygen requirements in the second trimester. Extracorporeal membrane oxygenation (ECMO) was required to treat respiratory deterioration. She recovered, was discharged in her third trimester and underwent an elective caesarean section for a normally grown baby, at term, for obstetric indications. This patient had GDM during the pregnancy that required insulin for blood glucose control. Risk factors for this patient included a maternal age of >35 years, a body mass index of 35 kg/m$^2$ and non-white ethnic background contributing to her development of severe COVID-19.

The final case of severe COVID-19 was admitted to the ICU in the second trimester for increasing oxygen requirements, but responded well to proning. This patient's only risk factor was a maternal age of >35 years. She developed insulin-dependent diabetes in the pregnancy and then had a vaginal delivery at term of a normally grown baby.

These cases had a variety of risk factors for severe COVID-19. In the five patients admitted to ICU, three had GDM, three were of non-white ethnic background, two had increased BMI, two were aged 35 years and three were over 35 years of age. There was one baby with severe fetal growth restriction, but the histopathology only showed ascending maternal genital tract infection.

## 3.2 | Neonatal characteristics

We reviewed the notes of 248 neonates from the 244 pregnancies; there were four sets of twins. There was one intrauterine death secondary to trisomy 18 and one termination of pregnancy for a chromosomal abnormality (the birthweight was not provided in these cases). The mean birthweight was 3273 g (SD 548 g). The smallest infant was born at $27^{+5}$ weeks of gestation, weighing 1079 g, and was delivered by emergency caesarean section for suspected chorioamnionitis and previous caesarean sections.

Within the cohort studied, one neonate tested positive for SARS-CoV-2 after being delivered in the second trimester for placental abruption. The infant was born with a normal weight for their gestation. Magnetic resonance imaging (MRI) of the brain suggested changes in keeping with prematurity and hypoxic-ischaemic encephalopathy (HIE) with an overt infectious component. All infection screening tests were negative except for three consecutive positive swabs for the SARS-CoV-2 virus on days 3, 5 and 9 of life. Placental pathology showed acute ascending maternal genital tract infection. The only maternal risk factor in pregnancy was pre-eclampsia and current

BJOG An International Journal of Obstetrics and Gynaecology



COVID-19 infection. Upon delivery, the neonate required immediate resuscitation, was intubated in theatre and then admitted directly to the neonatal intensive care unit. They were separated from their mother who tested positive for COVID-19, in accordance with hospital policy at the time, and therefore this may represent a case of vertical transmission.

## 3.3 | Placental histopathological findings

Some type of histological abnormality was identified in almost half (117 cases) of the placentas examined (48%), with 127 reports of no significant histological abnormality. This was greater than the 42% histological abnormality reported in the control cohort of 1153 placentas, with the majority of this increased rate being associated with ascending genital tract infection in the current group (Table 3). We have demonstrated the frequency of pathology by trimester in Table 4.

Ascending maternal genital tract infection was statistically more common in the COVID-19 group compared with published controls. Both FVM and MVM were also identified significantly more frequently but remained rare. There were no other statistically significant differences in placental pathology frequency between groups. There were four cases of COVID placentitis in this cohort.

All four cases of COVID placentitis were in women who developed COVID-19 in their third trimester and none were severe. There were three cases of COVID placentitis as a single diagnosis on histopathological examination: one was delivered by caesarean section for breech presentation at term and had a normally grown neonate, one had a term vaginal delivery of a normally grown neonate and the other was delivered by caesarean section at 34 weeks of gestation as a result of fetal monitoring concerns and the birthweight was on the tenth centile. In all three cases there were no concomitant maternal comorbidities.

The final case of COVID placentitis also had associated MVM. This patient had a term induction of labour for GDM leading to a vaginal delivery of a normally grown neonate.

## 3.4 | Concomitant maternal comorbidities

Placental histopathological findings were reviewed in cases with concomitant maternal comorbidities, including GDM, pre-existing diabetes, pre-eclampsia, pregnancy-induced hypertension (PIH) and essential hypertension. GDM occurred in 14.8% of our cohort, compared with the 4% found in our control group and the reported ≤5% rate found for all pregnant women.[30,33] In the group of patients with GDM, 65% had normal placental pathology, 15% had ascending maternal genital tract infection, 7.5% had MVM, 5% had VUE, 2.5% had choriangiosis, 2.5% had FVM and 2.5% had COVID placentitis.

**TABLE 3** Placental pathology in our cohort and in our controls.

| | Normal histology (*n*, %) | Ascending maternal genital tract infection (*n*, %) | MVM (*n*, %) | VUE (*n*, %) | FVM (*n*, %) | Chorangiosis (*n*, %) | MPVFD (*n*, %) | Chorangioma (*n*, %) | CHI (*n*, %) | Other lesion (not in control categories) (*n*, %) | COVID-placentitis (not in control categories) (*n*, %) | Total of all diagnoses (inc. others & COVID-19) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| This cohort ($n=244$) | 127 (52.0%) | 80 (32.8%) | 10 (4.1%) | 17 (7.0%) | 11 (4.5%) | 4 (1.6%) | 0 (0%) | 2 (0.8%) | 0 (0%) | 8 (3.3%) | 4 (1.6%) | 263 |
| Controls ($n=1153$) | 669 (58.0%) | 106 (9.2%) | 72 (6.2%) | 35 (3.0%) | 9 (0.8%) | 8 (0.7%) | 2 (0.2%) | 3 (0.3%) | 2 (0.2%) | N/A | N/A | 906 |
| *Z* score | −7.82 | 7.31 | −2.32 | 1.80 | 3.51 | 0.90 | −0.76 | 0.94 | −0.76 | | | |
| *p* | ≤0.00001 | ≤0.00001 | 0.02 | 0.073 | 0.00044 | 0.37 | 0.45 | 0.35 | 0.45 | | | |
| Prevalence (95% CI) | | | | | | | | | | | 1.52% (0.049%–3%) | |

Abbreviations: CHI, chronic histiocytic intervillositis; FVM, fetal vascular mal-perfusion; MPVFD, massive perivillous fibrin deposition; MVM, maternal vascular malperfusion; VUE, villitis of unknown aetiology.

**TABLE 4** Placental pathology by trimester of pregnancy the patient tested positive for COVID-19.

| Histological diagnosis | Trimester testing positive for COVID19 | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Ascending maternal genital tract infection | 8 | 18 | 54 |
| Chorangioma | 0 | 0 | 2 |
| Chorangiosis | 0 | 1 | 3 |
| COVID placentitis | 0 | 0 | 4 |
| FVM | 0 | 2 | 9 |
| MVM | 2 | 2 | 6 |
| Normal histology | 16 | 23 | 88 |
| Other lesion (not in control categories) | 2 | 1 | 5 |
| VUE | 0 | 7 | 10 |

Abbreviations: FVM, fetal vascular malperfusion; MVM, maternal vascular malperfusion; VUE, villitis of unknown aetiology.

# 4 | DISCUSSION

## 4.1 | Main findings

The findings of this study, which routinely examined placentas from women with COVID-19 in pregnancy, regardless of the severity of infection or pregnancy outcome, have demonstrated that most women with COVID-19 during pregnancy show no significantly increased rates of most placental histopathological findings, compared with historical controls, and the majority of cases result in normal live births. There was an increased rate of ascending genital tract infection compared with controls. However, this may be linked to initial selection bias, as placentas will have also been sent for histopathological examination for other indications (such as preterm delivery or chorioamnionitis), in addition to the mother having COVID-19 in pregnancy. Therefore, the increased rate of ascending genital tract infection is likely to be incidental.

In this study, most women with COVID-19 represented cases of infection identified from community testing, and hence these patients were likely to be symptomatic of COVID-19 to varying degrees. Patients were not selected based on other pregnancy complications. This contrasts with other studies that have largely assessed asymptomatic cases, such as those tested at delivery, or a small case series of highly preselected severely symptomatic hospital patients or those with adverse outcomes. This study also included placental pathology findings for patients with COVID-19 affecting all trimesters of pregnancy, giving us a broader interpretation of the effect of COVID-19 on the placenta.

## 4.2 | Interpretation (in light of other evidence)

In pregnancy, some diseases have a greater morbidity and mortality rate, such as influenza and varicella, with COVID-19 showing a similar pattern, given the changes seen in the immune system during pregnancy.[34] Furthermore, given that there is increased placental ACE2 expression with severe compared with asymptomatic or mild COVID-19,[35] this suggests that maternal disease severity may correlate with risk of vertical transmission. There were five cases of severe maternal COVID-19 infection in this series: one with normal placental pathology and four showing features of ascending maternal genital tract infection, of which one had additional FVM. None of these infants were infected with SARS-CoV-2. This is consistent with the opinion that the placenta acts as an immunological barrier to attempt to prevent the transmission of viruses to the fetus from the mother.[36] Additionally, recently published studies have suggested that transmembrane serine protease 2 (TMPRSS2), which is key for SARS-CoV-2 entry into the cell, is expressed by the placenta in varying levels during pregnancy. The placenta has been shown to not co-express TMPRSS2 with ACE2 at term or not express TMPRSS2 at term, which further supports the view that the placenta acts to prevent vertical transmission.[37,38] All evidence to date has indicated that there is a low chance of vertical transmission of SARS-CoV-2 from mother to fetus, and in support of this hypothesis, we had only one neonate test positive immediately after delivery.

Placental examination showing fetal thrombotic vasculopathy or FVM has been reported in association with other maternal viral infections, such as cytomegalovirus (CMV) infection.[39] FVM is also associated with maternal hypertensive disorders, diabetes and some coagulation abnormalities, and has been reported in association with fetal complications, including poor neurological outcome.[40] In this series there was an increased rate of FVM compared with controls, with only one of these patients having a hypertensive disorder of pregnancy. It is therefore possible that in a minority of cases maternal COVID-19 infection may predispose the pregnancy to FVM. The opposite might also be true: that women with FVM are more predisposed to testing positive for COVID-19. There has been recent evidence that women with FVM might have glucose dysmetabolism, similar to women with distal villous immaturity, yet never receive the diagnosis of GDM.[41] As GDM has been associated with a higher incidence of severe COVID-19,[42] including possibly in our cohort, the implications are potentially significant.[43] More study is needed into the association between FVM, undiagnosed GDM and the risk of severe infections.

## 4.3 | Clinical implications

Cases of possible vertical transmission of SARS-CoV-2 have been reported in association with chronic intervillositis.[44] In this larger case series of more unselected women with COVID-19, placentitis was rare. There were four cases of placentitis in the cohort of 244 women with COVID-19 during pregnancy, and one neonate tested positive for COVID-19. These data suggest that the prevalence of COVID-19 placentitis in a fairly unselected population is likely to be 1.52%

(4/263 pathologies; 95% CI 0.04%–3%). Of those with COVID placentitis, there was one premature neonate of birthweight on the tenth centile; however, there were no other significant maternal or neonatal outcomes. This is reassuring, compared with previously reported studies based on selected populations reporting poor perinatal outcomes.[25,27] Our findings suggest that in most women with COVID-19 in pregnancy there are no major differences in categories or frequency of placental pathology when cases are compared with a control, non-COVID-19 exposed population.

### 4.4 | Research implications

These results support observational data that the risk to the pregnant woman and neonate, although increased from baseline, remains low. The one case of neonatal SARS-CoV-2 infection where vertical transmission may have occurred emphasises the importance of a risk assessment of each individual case. Overall, this study has demonstrated that the routine pathological examination of placentas from women with COVID-19 does not add significant clinical value in the absence of other specific pregnancy complications that would indicate placental examination. It would be interesting to further our work by acquiring a cohort with severe COVID-19, as we had only five cases and therefore our interpretation of these results may be underpowered.

### 4.5 | Strengths and limitations

A limitation to this study was that it may not be an entirely unselected group of cases. Placentas undergoing histopathological examination were often sent for other reasons, such as clinical suspicion of infection or intrauterine growth restriction, in addition to the maternal history of COVID-19 in pregnancy. As healthcare professionals commonly sent placentas for these reasons, they were less likely to overlook sending it for examination for COVID-19 alone. By March 2021 it became routine practice, as part of our guidelines, to send placentas of all women affected by COVID-19 in pregnancy, therefore hopefully reducing selection bias. However, from our case group of 369 patients with COVID-19 in pregnancy, histopathological examination was not performed in 103 cases, of which 44% were from deliveries after our guideline was published. The COVID-19 pandemic was an evolving area, the patients often required high levels of care and we relied on clinical staff rather than research staff to send the placentas. Therefore, although we aimed for all placentas from women testing positive for COVID-19 to be examined, a minority were not.

Additionally, pathology examinations were not blinded to the background history of maternal COVID-19 infection. Similarly, as this was a retrospective observational study, we used controls from a published cohort (which included placental pathology from cases of ≥34 weeks of gestation, as opposed to those sent from any gestation) examined concurrently with the COVID-19 cohort. This was because contemporaneous placentas were only submitted for histopathological examination based on pregnancy complications, whereas the more appropriate control group were completely unselected pregnancies undergoing placental examination to represent baseline rates of histological findings.

## 5 | CONCLUSION

Overall, this review of 244 placentas from women with COVID-19 during pregnancy provides evidence of both the low risk of vertical transmission to the neonate and the lack of increased rates of most placental pathologies. There is need for further study into the associations among FVM, undiagnosed diabetes, and the risk and severity of infections.

### AUTHOR CONTRIBUTIONS

CSC and SLH designed the study. CSC, JCH, SMW and SLH were responsible for data collection. JCH and NJS performed the data analysis. CSC wrote the first draft of the article. CSC, JCH, SMW, DS, NJS and SLH (all authors) edited and reviewed the final version for publication.

### ACKNOWLEDGEMENTS

We are grateful for funding received from the University College London Global Engagement Office.

### CONFLICT OF INTEREST STATEMENT

None declared. Completed disclosure of interests form available to view online as supporting information.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

### ETHICS APPROVAL

Data were collected under the hospital trust-supported mandate from the Department of Health and Social Care. This was to allow direct processing and presentation of patient information to expedite our understanding of the impact of COVID-19. No patient-identifiable features link any of the data presented.

### ORCID

*Charlotte S. Colley* https://orcid.org/0000-0003-3052-0341

### REFERENCES

1. Organisation WH. Timeline: WHO's COVID-19 response. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/interactive-timeline
2. Organisation WH. WHO coronavirus (COVID-19) dashboard. Available from: https://covid19.who.int/
3. Villar J, Ariff S, Gunier RB, Thiruvengadam R, Rauch S, Kholin A, et al. Maternal and neonatal morbidity and mortality among pregnant

women with and without COVID-19 infection: The INTERCOVID Multinational Cohort Study. JAMA Pediatr. 2021;175(8):817–26.
4. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271–80.e8.
5. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003;426(6965):450–4.
6. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol. 2020;94(7):e00127-20.
7. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science. 2020;367(6485):1444–8.
8. Davidson AM, Wysocki J, Batlle D. Interaction of SARS-CoV-2 and other coronavirus with ACE (Angiotensin-Converting Enzyme)-2 as their main receptor: therapeutic implications. Hypertension. 2020;76(5):1339–49.
9. Bloise E, Zhang J, Nakpu J, Hamada H, Dunk CE, Li S, et al. Expression of severe acute respiratory syndrome coronavirus 2 cell entry genes, angiotensin-converting enzyme 2 and transmembrane protease serine 2, in the placenta across gestation and at the maternal-fetal interface in pregnancies complicated by preterm birth or preeclampsia. Am J Obstet Gynecol. 2021;224(3):298.e1–8.
10. Ashary N, Bhide A, Chakraborty P, Colaco S, Mishra A, Chhabria K, et al. Single-cell RNA-seq identifies cell subsets in human placenta that highly expresses factors driving pathogenesis of SARS-CoV-2. Front Cell Dev Biol. 2020;8:783.
11. Valdés G, Neves LA, Anton L, Corthorn J, Chacón C, Germain AM, et al. Distribution of angiotensin-(1–7) and ACE2 in human placentas of normal and pathological pregnancies. Placenta. 2006;27(2–3):200–7.
12. Abou-Ismail MY, Diamond A, Kapoor S, Arafah Y, Nayak L. The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. Thromb Res. 2020;194:101–15.
13. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020;395(10234):1417–8.
14. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ. 2020;370:m3320.
15. Zambrano LD, Ellington S, Strid P, Galang RR, Oduyebo T, Tong VT, et al. Update: characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status - United States, January 22–October 3, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(44):1641–7.
16. Knight M, Bunch K, Vousden N, Morris E, Simpson N, Gale C, et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. BMJ. 2020;369:m2107.
17. Pierce-Williams RAM, Burd J, Felder L, Khoury R, Bernstein PS, Avila K, et al. Clinical course of severe and critical coronavirus disease 2019 in hospitalised pregnancies: a United States cohort study. Am J Obstet Gynecol MFM. 2020;2(3):100134.
18. Shanes ED, Mithal LB, Otero S, Azad HA, Miller ES, Goldstein JA. Placental pathology in COVID-19. Am J Clin Pathol. 2020;154(1):23–32.
19. Di Toro F, Gjoka M, Di Lorenzo G, De Santo D, De Seta F, Maso G, et al. Impact of COVID-19 on maternal and neonatal outcomes: a systematic review and meta-analysis. Clin Microbiol Infect. 2021;27(1):36–46.
20. Baergen RN, Heller DS. Placental Pathology in Covid-19 Positive Mothers: Preliminary Findings. Pediatr Dev Pathol. 2020;23(3):177–80.
21. Mulvey JJ, Magro CM, Ma LX, Nuovo GJ, Baergen RN. Analysis of complement deposition and viral RNA in placentas of COVID-19 patients. Ann Diagn Pathol. 2020;46:151530.
22. Rebutini PZ, Zanchettin AC, Stonoga ETS, Prá DMM, de Oliveira ALP, Dezidério FDS, et al. Association between COVID-19 pregnant women symptoms severity and placental morphologic features. Front Immunol. 2021;12:685919.
23. Linehan L, O'Donoghue K, Dineen S, White J, Higgins JR, Fitzgerald B. SARS-CoV-2 placentitis: an uncommon complication of maternal COVID-19. Placenta. 2021;104:261–6.
24. Schwartz DA, Baldewijns M, Benachi A, Bugatti M, Collins RRJ, De Luca D, et al. Chronic histiocytic intervillositis with trophoblast necrosis is a risk factor associated with placental infection from coronavirus disease 2019 (COVID-19) and intrauterine maternal-fetal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission in live-born and stillborn infants. Arch Pathol Lab Med. 2021;145(5):517–28.
25. Schwartz DA, Avvad-Portari E, Babál P, Baldewijns M, Blomberg M, Bouachba A, et al. Placental tissue destruction and insufficiency from COVID-19 causes stillbirth and neonatal death from hypoxic–ischemic injury. Arch Pathol Lab Med. 2022;146(6):660–76.
26. Mao Q, Chu S, Shapiro S, Young L, Russo M, De Paepe ME. Placental SARS-CoV-2 distribution correlates with level of tissue oxygenation in COVID-19-associated necrotizing histiocytic intervillositis/perivillous fibrin deposition. Placenta. 2022;117:187–93.
27. Huynh A, Sehn JK, Goldfarb IT, Watkins J, Torous V, Heerema-McKenney A, et al. SARS-CoV-2 placentitis and intraparenchymal thrombohematomas among COVID-19 infections in pregnancy. JAMA Netw Open. 2022;5(3):e225345.
28. He M, Skaria P, Kreutz K, Chen L, Hagemann IS, Carter EB, et al. Histopathology of third trimester placenta from SARS-CoV-2-Positive women. Fetal Pediatr Pathol. 2022;41(3):403–12.
29. Smithgall MC, Liu-Jarin X, Hamele-Bena D, Cimic A, Mourad M, Debelenko L, et al. Third-trimester placentas of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-positive women: histomorphology, including viral immunohistochemistry and in-situ hybridization. Histopathology. 2020;77(6):994–9.
30. Pathak S, Lees CC, Hackett G, Jessop F, Sebire NJ. Frequency and clinical significance of placental histological lesions in an unselected population at or near term. Virchows Arch. 2011;459(6):565–72.
31. Evans C, Cox P. Tissue pathway for histopathological examination of the placenta2019. Available from: https://www.rcpath.org/uploads/assets/ec614dfa-007c-4a93-8173cb202a071a72/G108-Tissue-pathway-for-histopathological-examination-of-the-placenta.pdf
32. Khong TY, Mooney EE, Ariel I, Balmus NC, Boyd TK, Brundler MA, et al. Sampling and definitions of placental lesions: amsterdam placental workshop group consensus statement. Arch Pathol Lab Med. 2016;140(7):698–713.
33. Excellence NIfHaC. Diabetes in pregnancy: management from preconception to the postnatal period. www.nice.org.uk/guidance/ng32015
34. Jamieson DJ, Theiler RN, Rasmussen SA. Emerging infections and pregnancy. Emerg Infect Dis. 2006;12(11):1638–43.
35. Bourgonje AR, Abdulle AE, Timens W, Hillebrands JL, Navis GJ, Gordijn SJ, et al. Angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 and the pathophysiology of coronavirus disease 2019 (COVID-19). J Pathol. 2020;251(3):228–48.
36. Racicot K, Mor G. Risks associated with viral infections during pregnancy. J Clin Invest. 2017;127(5):1591–9.
37. Beesley MA, Davidson JR, Panariello F, Shibuya S, Scaglioni D, Jones BC, et al. COVID-19 and vertical transmission: assessing the expression of ACE2/TMPRSS2 in the human fetus and placenta to assess the risk of SARS-CoV-2 infection. BJOG. 2022;129(2):256–66.
38. Colson A, Depoix CL, Dessilly G, Baldin P, Danhaive O, Hubinont C, et al. Clinical and *in vitro* evidence against placenta infection at term by severe acute respiratory syndrome coronavirus 2. Am J Pathol. 2021;191(9):1610–23.
39. Iwasenko JM, Howard J, Arbuckle S, Graf N, Hall B, Craig ME, et al. Human cytomegalovirus infection is detected frequently in stillbirths and is associated with fetal thrombotic vasculopathy. J Infect Dis. 2011;203(11):1526–33.

40. Redline RW, Ravishankar S. Fetal vascular malperfusion, an update. APMIS. 2018;126(7):561–9.
41. Siassakos D, Bourne I, Sebire N, Kindinger L, Whitten SM, Battaglino C. Abnormal placental villous maturity and dysregulated glucose metabolism: implications for stillbirth prevention. J Perinat Med. 2022;50(6):763–8.
42. Kleinwechter HJ, Weber KS, Mingers N, Ramsauer B, Schaefer-Graf UM, Groten T, et al. Gestational diabetes mellitus and COVID-19: results from the CRONOS study. Am J Obstet Gynecol. 2022;227(4):631.e1–19.
43. Stacey T, Tennant P, McCowan L, Mitchell EA, Budd J, Li M, et al. Gestational diabetes and the risk of late stillbirth: a case–control study from England, UK. BJOG. 2019;126(8):973–82.
44. Patanè L, Morotti D, Giunta MR, Sigismondi C, Piccoli MG, Frigerio L, et al. Vertical transmission of coronavirus disease 2019: severe acute respiratory syndrome coronavirus 2 RNA on the fetal side of the placenta in pregnancies with coronavirus disease 2019-positive mothers and neonates at birth. Am J Obstet Gynecol MFM. 2020;2(3):100145.


## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Colley CS, Hutchinson JC, Whitten SM, Siassakos D, Sebire NJ, Hillman SL. Routine placental histopathology findings from women testing positive for SARS-CoV-2 during pregnancy: Retrospective cohort comparative study. BJOG. 2023;00:1–9. https://doi.org/10.1111/1471-0528.17476