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COVID-19 and stillbirth: direct *vs* indirect effect of the pandemic

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An association between COVID-19 and stillbirth

The COVID-19 pandemic has had devastating effects on mortality and morbidity, including in pregnant women. Epidemiological studies have reported an association between COVID-19 and stillbirth. Despite the initial conflicting evidence, this association is now accepted.

Cohort and case-control studies

Recently, the USA Centers for Disease Control and Prevention (CDC) has reported[1] that the risk of stillbirth was two-fold higher in pregnant women with COVID-19 (adjusted relative risk [aRR] 1.90; 95% CI 1.69–2.15) compared to those without COVID-19. Among 1,249,634 birth hospitalizations during March 2020–September 2021, the rate of stillbirth in those with COVID-19 was 13 per 1000 births compared to 6 per 1000 births in those without. Moreover, the risk of stillbirth was higher during the period of SARS-CoV-2 Delta variant predominance than during the pre-Delta period.
A national study published in May 2021 with a sample size of over 340,000 pregnant women in England found that stillbirth occurred more frequently in those who had SARS-Cov-2 infection, compared to those without[2]. The Spanish Obstetric Emergency Group study has reported in May 2021 a higher incidence of stillbirth in women who had SARS-CoV-2 infection during pregnancy – 10 women in a cohort of 1347 infected women compared to 3 in the non-infected cohort of 1607 (p=0.023)[3]. In the USA researchers analyzed data on 406,446 women hospitalized for childbirth between April and November 2020 (6380 of whom tested positive for SARS-CoV-2) from the Premier Healthcare Database, an all-payer database encompassing approximately 20% of US hospitalizations[4]. The stillbirth rate was significantly higher in those with COVID-19 compared to those without (5 vs 3 per 1000 births, p=0.003)[4].

Time trend studies

A recent large study in India[5] reported doubling of the stillbirth rate in the second wave of the pandemic (34 per 1000 births between February 2021 and May 2021) compared with the first wave (15 per 1000 births between April 2020 and January 2021)[5]. In March 2021, a systematic review into pregnancy outcomes found evidence of an increase in stillbirth during the pandemic compared to before the pandemic[6]. The UK Obstetric Surveillance System (UKOSS) which studied pregnant women admitted to hospital with SARS-CoV-2 infection between March and April 2020 reported three stillbirths among 247 pregnant women which is around three times the national rate of stillbirths (4-5 per 1000 births)[7]. The stillbirth rate during the pandemic in India was significantly higher than that reported in 2019 (13.9 per 1000 births)[8]. However, a national study in England that compared the incidence of stillbirth during the COVID-19 pandemic from April to June 2020 with the same months of 2019 did not find any evidence of an increase in stillbirth during the pandemic[9].

Several studies reporting on the direct impact of COVID-19 in pregnancy, especially those with large sample size, have demonstrated an increase in stillbirths compared to pregnant women who did not experience the infection (Table 1). However, the evidence is controversial, with several smaller studies reporting no significant increase in stillbirths following COVID-19. One possible reason is the lack of statistical power to show a difference in stillbirth, failure to discriminate between the direct and indirect effects of the COVID-19 pandemic, differences in access to and availability of healthcare services, whether the study duration overlapped with a period of a lockdown, and the nature and severity of social restrictions or isolation during the lockdown.

Direct versus Indirect effect

It is important to consider whether any increase in stillbirth is due to the direct or indirect effects of the COVID-19 pandemic. Direct effects are those caused by maternal SARS-CoV-2 infection, while indirect effects are those resulting from changes in access to healthcare, or in the behaviour of pregnant women or clinicians, during the COVID-19 pandemic. The differences in stillbirths observed before and during the pandemic in the time trend studies are likely to be due to a combination of direct and indirect effects. Although the cohort and case-control studies of pregnancy during the pandemic examined primarily the direct effects of SARS-CoV-2 infection, indirect effects may also have contributed.

An early report from St George's Hospital in London found that the incidence of stillbirth was significantly higher in the pandemic compared with the pre-pandemic period[12]. However, the number of stillbirths was small. Notably, none of the women who had stillbirths had COVID-19[12], raising the possibility that the pathogenesis of their stillbirth was due to an indirect effect of the pandemic. Possible explanations include late presentation caused by hesitancy to attend hospital due to fear of exposure to SARS-CoV-2, or the altruistic desire not to further over-burden an already stretched health service (a subject that was receiving saturation coverage in the media at the time). The ambulance service was also under huge pressure, with documented long delays in attendance at both emergency and, in particular, non-emergency calls[2]. Many out-patient appointments were also converted from face to face to virtual (telephone or video calls), and services were reduced across the board as staff were redeployed to help on COVID-19 wards[13]. Postnatal length of hospital stay was reduced; this might have been due to pro-active early discharge by clinicians, or the desire of women to leave hospital earlier, either to reduce their chances of nosocomial infection, or to see loved ones who were not allowed to visit the hospital[14].

A follow-up study at St George's Hospital confirmed that attendance at the Maternity Triage (where women are seen with a range of concerns such as reduced fetal movements, vaginal bleeding, abdominal pain, etc) was significantly reduced during the pandemic[15]. This pattern was reflected nationally and internationally. In the UK, hospital attendance and admissions were dramatically reduced during the pandemic, and many pregnant women did not present for routine appointments[16]. A retrospective analysis in India found that substantially lower numbers of pregnant women were referred or hospitalized for tertiary care[17]. As in the UK, India had extensive public health campaigning, encouraging people to stay at home and avoid infection. Public transport was also reduced which made hospital attendance particularly challenging for women living in rural areas[17]. Women with high-risk pregnancies are at greater risk of pregnancy related mortality or morbidity than that caused by COVID-19. Given that they would normally receive more intensive antenatal care and surveillance than low-risk women, they would have been disproportionately disadvantaged by the reduction in services and attendance.

Another possible explanation in women testing negative for SARS-CoV-2 at the time of admission with stillbirth is that they may have had asymptomatic infection at an earlier stage in pregnancy, or symptomatic infection at a time when limited testing was available, as was the case in the UK early in the pandemic[18]. Asymptomatic cases of COVID-19 are estimated to account for 25% of cases[19]. In pregnancy, paradoxically, although pregnant women are more likely to suffer severe SARS-CoV-2 infection, they are also more likely to be asymptomatic than their non-pregnant counterparts[10]. As a result, many women may have been unaware that they had SARS-CoV-2 infection during their pregnancy[19]. This is likely, given the high prevalence of COVID-19 worldwide and in the UK in March and April 2020[20].

A large study that analyzed data from 18 countries and compared severe perinatal morbidity and mortality in 706 pregnant women with COVID-19 and 1424 pregnant controls found a much higher index of severe perinatal morbidity and mortality in those with COVID-19 (17% versus 7.9%)[21]. Although indirect effects of the pandemic likely contributed to a rise in stillbirth,

these data highlight the fact that a direct effect of COVID-19 in pregnancy on stillbirth is very likely.

COVID-19 and other adverse pregnancy outcomes

Pregnant women are at increased risk of developing severe complications of COVID-19: they are around twice as likely as their non-pregnant counterparts to require intensive care, assisted ventilation, extracorporeal membrane oxygenation (ECMO), or to die from COVID-19[22]. Evidence is emerging of other adverse pregnancy outcomes that have increased, either because of the SARS-CoV-2 infection or because of the negative impact of the pandemic.

A systematic review into COVID-19 and pregnancy outcomes found that COVID-19 is associated with an increased risk of preeclampsia; there is evidence of a 'dose-response' relationship, with more severe COVID-19 associated with a greater increase in the risk of preeclampsia[23]. The mechanism underlying this is unclear; however, scientists hypothesize that the SARS-CoV-2 virus may bind to angiotensin-converting enzyme 2 receptors, leading to renin-angiotensin system dysfunction and vasoconstriction[24]. Other researchers found evidence that COVID-19 can cause clinical manifestations similar to preeclampsia, but that on measuring biomarkers, they were distinguishable and distinct pathologies[25].

Wei *et al.* also reported an association between severe COVID-19, gestational diabetes and preterm birth when compared to mild COVID-19[23]. The researchers hypothesized that this could be due to the systemic inflammatory response caused by SARS-CoV-2 creating a suboptimal environment for placental growth and development. This observation has yet to be confirmed by other groups.

Several studies have demonstrated an association between SARS-CoV-2 and preterm birth[21,26-31], including the Intercovid national cohort study of 18 countries that found that women with COVID-19 were at increased risk of preterm birth (mainly medically indicated preterm birth)[21]. This association could potentially confound the association between the COVID-19 pandemic and stillbirth; iatrogenic preterm birth reduces the risk of stillbirth, potentially leading to an underestimation of the risk of stillbirth associated with SARS-CoV-2 infection. Conversely, when a baby is stillborn, the baby is delivered regardless of the gestational age; the increase in preterm births could in part be explained by an increase in stillbirths.

There is evidence that the pandemic has also adversely impacted other pregnancy outcomes. A systematic review of 40 studies found that maternal mental health was worse during the pandemic, as evidenced by higher mean Edinburgh postnatal depression scores[2]. The pandemic meant that many women felt very isolated and lacked their usual support networks. Maternal mental health disorder in pregnancy is a known risk factor for stillbirth[32].
It is important to understand the inequalities that the pandemic has highlighted, including in pregnant women. As in the non-pregnant population, pregnant women from Black, Asian, and minority ethnic groups are more likely to suffer the direct adverse effects of COVID-19[33]. Even before the pandemic, women from Black, Asian, and minority ethnic groups had worse pregnancy outcomes than White women; a large study of more than one million pregnant women in England showed that this disparity did not widen during the pandemic (*national data from England comparing pregnancy outcomes in 2019 and 2020/21; PloS Medicine 2021 accepted).*

Placental histology and possible mechanisms of stillbirth

Table 2 lists key studies reporting placental histopathological findings associated with stillbirth in pregnancies with maternal SARS-COV-2 infection.

A study of 15 women with severe acute COVID-19 leading to delivery in the third trimester demonstrated that, compared to controls, their placental histology was significantly more likely to show one or more features of maternal vascular malperfusion, in particular, abnormal maternal vessels and intervillous thrombi[35]. There is an association between maternal vascular malperfusion and hypertensive disorders including preeclampsia; however, despite this association, of the women whose placentas exhibited features of maternal vascular malperfusion, only one had a pregnancy induced hypertensive disorder[35,58]. Maternal vascular malperfusion and fetal vascular malperfusion are commonly identified in placentas where stillbirth has occurred[42].

Placental histology of patients who had mild or asymptomatic COVID-19 before birth has also been studied. There was no evidence of increased inflammatory infiltrates in the placentas of women who no longer had active COVID-19 at birth, though there were signs of fetal and maternal vascular malperfusion[59].

A case-control study of 64 pregnant women found no evidence that COVID-19 during the third trimester influenced placental histology. When compared to 64 control placentas, there was no difference in placental macro or microscopic morphology. However, the placentas of women who had been treated with antiviral medication, low molecular weight heparin, hydroxychloroquine or antibiotics, more frequently showed delayed villous maturation[60].

The effects of COVID-19 on placental histology are still being researched and so far, the evidence available is from very small sample sizes. Further research is needed to fully understand the effect that this infection can have on pregnancy and whether these changes contribute to a higher incidence of stillbirth (Figure 1).

Implications for COVID-19 vaccination in pregnancy

On the 16th April 2021, the UK Joint Committee on Vaccination and Immunisation (JCVI) released updated guidance, advising that all pregnant women in the UK should be offered a COVID-19 Vaccination at the same time as non-pregnant women of the same age[61]. This guidance is based on data from the United States where over 169,000 pregnant women have been vaccinated and, in the UK, where nearly 100,000 pregnant women have been vaccinated with no significant safety concerns raised and no indication of any harm to the fetus[62,63]. Recently, the UK government reported data from 24,759 pregnant women who had received at least one dose of COVID-19 vaccine prior to delivery in the 8-month period between January and August 2021[64,65] (355,299 women gave birth during this period). When compared to pregnant women who did receive the vaccine, the stillbirth rate for vaccinated women was 3.35 per 1000 (vs 3.60 per 1000). The stillbirth rate was not significantly different. Similarly, the rate of preterm birth and low birthweight were similar in those who received the vaccine compared to those who were unvaccinated. Prior to this, in the UK pregnant women were advised to consider having COVID-19 vaccination only if they had an underlying health condition or were working in areas involving a high risk of exposure to COVID-19[66]. In August 2021, the CDC advised that pregnant women should receive a COVID-19 vaccine. Despite this, as of 29th September 2021, only 31% of pregnant women in the US have been vaccinated against COVID-19[67]. The latest data in the UK on the vaccine uptake among pregnant women was 22% in August 2021[65].

During the vaccine rollout pregnant women have not been prioritized above their non-pregnant peers of the same age. The mean age for women giving birth in the UK in 2019 was 30.7 years[68]. Assuming a similar average age of giving birth in 2021, most pregnant women would not have been invited for their first vaccine until late May 2021, and those younger not received their first dose until much later – over 18s were not invited until the 18th June 2021[63,69] Many pregnant women have been shielding throughout the pandemic[70], particularly as the evidence of increased risks to their own health and that of their babies accumulated. The increased risks to the woman, combined with the increased risks of adverse perinatal outcomes, in

particular stillbirth, caused by both the direct and indirect effects of COVID-19, beg the question whether pregnant women should be prioritized over and above their non-pregnant peers of equivalent age. In high income countries where most of the population has been vaccinated, should pregnant women be prioritized above their age-equivalent peers for a booster dose?

As discussed above, the mental health of pregnant women has been particularly impacted by the pandemic, with fear of infection leading many to shield. Vaccinating pregnant women earlier would free them from shielding, thus reducing isolation and restoring their access to support networks. However, recent research has highlighted vaccine hesitancy among pregnant women; a UK survey reported that only 53% of pregnant women reported an intention of getting the COVID-19 vaccine[71]. More research is ongoing[72], but it is very important that pregnant women are reassured about the evidence supporting the safety of this vaccine in pregnancy and encouraged to be vaccinated as soon as possible.

Clinical implications

The evidence that COVID-19 increases the risk of stillbirth has clinical implications for the care of pregnant women. As discussed, pregnant women should be prioritized for vaccination. Given the possible association of COVID-19 and stillbirth, it may be that induction of labor should be offered to women who test positive for SARS-COV-2 infection, in particular in the third trimester where most of the available evidence of an association between COVID-19 and stillbirth exists.

Another possible clinical implication is treating women who have had SARS-CoV-2 infection in pregnancy as high-risk for the rest of the pregnancy. Given the reported association of COVID-19 with hypertensive disorders in pregnancy, closer monitoring of blood pressure and fetal growth should be offered to these women. None of these interventions is currently supported by robust evidence. Therefore, large prospective multicenter studies are urgently needed. Moreover, SARS-COV-2 infection is often asymptomatic, so consideration should be given to the introduction of weekly home SARS-CoV-2 testing for pregnant women, so that asymptomatic cases are identified early.

Research implications

Further research is needed into the risk factors associated with adverse outcomes due to COVID-19 in pregnant women, such as gestational age at, and severity of, infection. This would enable early identification of those at increased risk, facilitating the development of antenatal surveillance and targeted intervention, or ensure that they are offered COVID-19 vaccination early.

As mentioned above, it may be appropriate to offer induction of labor to women who test positive for SARS-CoV-2 during pregnancy. However, any such strategy would need clear, research backed guidelines, so that the best possible outcomes for both mother and baby are achieved.

We have recently developed an internally validated prediction model for critical COVID-19 and intensive care unit admission in pregnant women[73]. The secondary outcomes in this study included stillbirth. We developed two models and found that categorization as high risk using either model was associated with a higher incidence of maternal death. These models can be used to define criteria for high-risk women and thus target early interventions and priority vaccination[73].

Mechanistic studies, including larger studies investigating placental histology in women who have had SARS-COV-2 infection in pregnancy, are also needed. These will clarify the

pathogenesis of COVID-19 in pregnancy and the mechanisms by which adverse pregnancy outcomes occur.

There is mounting evidence of an association between COVID-19 and stillbirth. Further research is needed to understand the mechanisms underlying this association. Once these have been clarified, clinical practice should be adapted to ensure that the adverse effects of COVID-19 on pregnant women and their babies are mitigated.

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FIGURE LEGEND

Figure 1.

A. The direct impact of the maternal SARS-CoV-2 infection:

a. Severe maternal morbidity, need for intensive care, assisted ventilation and extracorporeal membrane oxygenation, which may lead to maternal severe systemic compromise and fetal death.
b. Evidence demonstrates that SARS-CoV-2 infection might cause systemic dysregulation of the RAS and KKS pathways and levels of circulating angiogenic factors, vasoconstriction, endothelial cell damage and microvascular corrosion. This could result in pre-eclampsia like syndrome and stillbirth.
c. Infection of the syncytiotrophoblast might lead to breach of the syncytial layer. Emerging placental evidence demonstrates chorionic intervillositis and fibrin deposition.

B. The indirect consequences may be detrimental to maternal health, including reduced access to healthcare services due to changes in patients' or clinicians' behaviour, increased mental health strain, increased domestic violence due to lockdown and increased socioeconomic deprivation.

Table 1. Large case control studies (including at least 1000 pregnancies with confirmed SARS-CoV-2 infection) reporting on the rate of stillbirth in pregnant women with SARS-CoV-2 infection compared to those without.

Study	**Country**	**Population**		**Stillbirths (per 1000 births)**		
		COVID-19 positive pregnant women	**COVID-19 negative pregnant women***	**COVID-19**	**Control**	**Statistics**
Allotey et al 2020 PregCOV-19 Systematic Review (updated 29/11/20)[10]	30 countries	1039	4755	26	9	OR (95% CI) 2.84 (1.25–6.45)
Cruz Melguizo *et al,* 2021 Spanish Obstetric Emergency Group[3]	Spain	1347	1607	7.4	1.9	P=0.023
Jering *et al,* 2021[4]	USA	6380	400066	5	3	P<0.05
Gurol-Urganci 2021[2]	UK	3527	338553	8.5	3.4	aOR (95%CI) 2.21 (1.58–3.11)
Netherlands Obstetric Surveillance System[11]	The Netherlands	9570		36		
De Sisto et al (CDC)[1]	USA	21653	1227 981	12.6	6.4	aRR (95% CI) 1.90 (1.69-2.15)

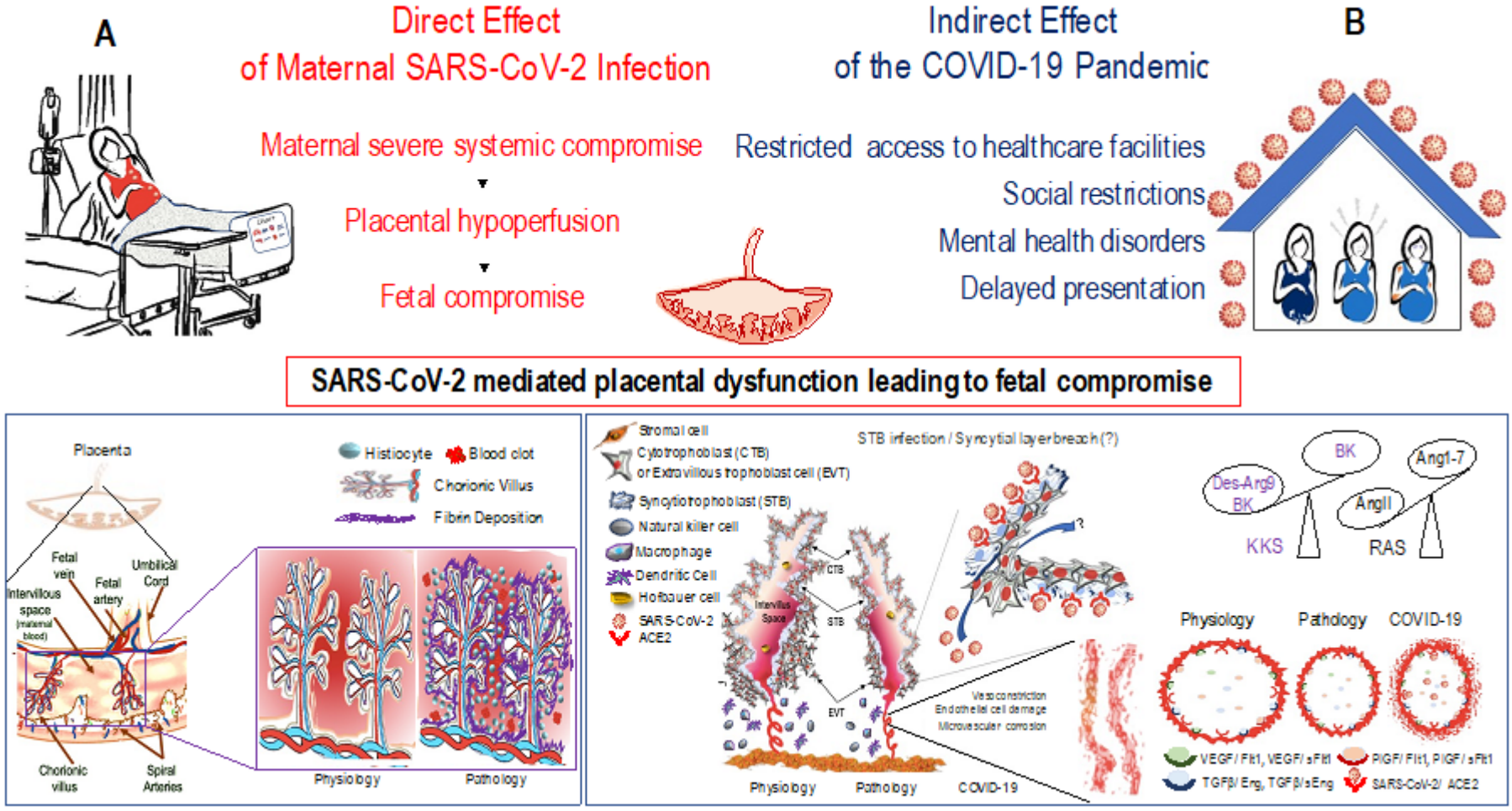
*Studies using historical controls were not included.
Adjusted odds ratio: aOR; adjusted relative risk: aRR

Table 2. Studies reporting placental histopathological findings associated with stillbirth in pregnancies with maternal SARS-COV- infection in pregnancy.

Studies	Number of placentas studied	Fetal demise	Findings
Pulinx *et al*, 2020[34]	2 (twins)	2	SARS-CoV-2 positive placenta and amniotic fluid. HI on both placentas with extensive intervillous FD and ischemic necrosis of surrounding villi; nuclear debris and an increase in erythroblasts in fetal circulation, as seen in fetal hypoxia. No chorioamnionitis.
Shanes *et al.* 2020[35]	16	1	2 had MVM, 4 showed clustered avascular villi,1 showed mural fibrin deposition in fetal vessels, 4 showed delayed villous maturation, 4 showed chorioangiosis, 1 showed acute inflammatory pathology and 2 showed chronic inflammatory pathology
Hosier *et al*. 2020[36]	1	1	Acute placental infection, HI, diffuse PVF and inflammatory infiltrate
Shende *et al*, 2020[37]	1	1	Viral RNA detecte in cytotrophoblast and syncytiotrophoblast cells. Generally avascular villi with PVF deposition, fibrin decidual deposition with extensive leukocyte infiltration.
Baud *et al*, 2020[38]	1	1	Mixed inflammatory infiltrates (subchorial space neutrophils / monocytes), increased intervillous fibrin deposition and funisitis
Stonoga *et al,* 2021[39]	1	1	Multifocal CHI
Thomas *et al.* 2021[40]	197	4	(3/4 stillborn tested SARS-CoV-2 positive). Virus identified in situ, accompanied by intervillositis, in 2 of 197 placentas
Dumont *et al,* 2021[41]	1	1	PFD with ischemic changes and necrosis of the villi, intervillous space with inflammatory cells and histiocytes
Bunnell *et al.* 2021[42]	12	12	5 showed MVM, 5 showed FVM, No MPFD or HI
Poisson *et al.* 2021[43]	1	1	Patchy acute chorionitis, diffuse infarction/villous necrosis of the placental parenchyma which resulted in extensive vascular malperfusion.
Valdespino-Vasquez *et al*, 2021[44]	2 placentas (twins)	2	Placental infarction, with diffuse perivillous fibrin, active CHI and subchorial inflammation.
Garrido-Pontnou *et al*, 2021[45]	198	5	9 SARS-CoV-2-infected placentas ($p = 0.0079$), diffuse trophoblastic damage common among 5 FD
Bouachba et al*,* 2021[46]	5	3	3 FD and 2 extreme preterm births. MPFD at places necrotic trophoblast/ neutrophil or histiocyte infiltration and/or lymphocytes, numerous large intervillous thrombi. Severe CHI in 4 cases.
Schwartz *et al*, 2021[47]	11	5	transplacental transmission of 6 live-born neonates; Liveborn: All 6 placentas had CHI and necrosis of

			the syncytiotrophoblast. stillborn/terminated: 5 had SARS-CoV-2 infection of syncytiotrophoblast, CHI and syncytiotrophoblast necrosis.
Biringer *et al*, 2021[48]	1	1	No signs of amnionitis or funisitis. Intervillous Inflammation /Predominant HI, neutrophils and MPFD, maternal floor infarctions, reduced and/or missing placental vascularity, absence of trophoblastic superficial layer.
Ozer *et al,* 2021[49]	1	1	Morphological features of unknown etiology villitis. Macrophages and CD4-positive T cells predominantly in villous tissue; high numbers of CD8-positive cells
Gioia *et al,* 2021[50]	1	1	Marked SARS-CoV-2 endotheliotropism, normal amniochorionic membranes, focal hemorrhagic area, fetal and maternal vessel thrombosis - luminal fibrin and platelet deposition, no sign of chorioamnionitis.
Meyer *et al*, 2021[51]	61	5	Majority of placentas demonstrated PVF deposition (59%). 25% of placentas considered SGA, 77% showed features of MVM, Severe TPC observed in 33% of placentas.
Marinho *et al,* 2021[52]	1	1	MVM, FVM, necrotic villi, focal laminar necrosis fibrinoid necrosis and thrombi in decidua, delayed villous maturation
Libbrecht et al, 2021[53]	17	2	In 3 placentas: 70% syncytiotrophoblast necrosis, mild /moderate HI with mixed infiltrate (histiocytes, T cells, neutrophils). No villitis. Strong, diffuse C4d deposition at syncytiotrophoblast surface
Marton *et al,* 2021[54]	1	1	Necrosis of villous trophoblast, associated with CHI, MPFD with up to 90% of intervillous spaces involved. Active viral replication in villous trophoblast cells.
Colson *et al*, 2021[55]	31	1	1 placenta infected, 6 showed signs of MVM, 3 CHI (including the SARS-CoV-2–positive placenta), 8 Focal or diffuse chorioamnionitis.
Watkins *et al*, 2021[56]	7	1	All placentas positive for SARS-CoV-2 by RNA ISH; variable degrees of histiocytic intervillositis, perivillous fibrin deposition, and trophoblast necrosis. 3 FMV
Zinserling et al 2021[57]	1	1	SARS-CoV-2 positive infant, viral infection in several pancreas, brain, spleen, and adrenals. Viral placentitis with chronic insufficiency and acute placental decompensation.

Fetal Demise: FD; *Histiocytic Intervillositis: HI;* Chronic *Histiocytic Intervillositis:CHI*; Maternal vascular malperfusion: MVM; fetal vascular malperfusion: FVM; *perivascular fibrosis*: PVF; Massive perivillous fibrin deposition: MPFD; in situ hybridization: IS



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