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Opinion

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

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Association between COVID-19 and stillbirth

The coronavirus disease 2019 (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) reported that the risk of stillbirth was 2-fold higher in pregnant women with compared to those without COVID-19 (adjusted relative risk, 1.90; 95% CI, 1.69–2.15)[1]. Among 1 249 634 birth hospitalizations from March 2020 to September 2021, the rate of stillbirth was 13 per 1000 births in those with COVID-19 compared to 6 per 1000 births in those without. Moreover, the risk of stillbirth was higher during the period in which the Delta variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was predominant compared with during the pre-Delta period.

A national cohort 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 with compared to those without SARS-CoV-2 infection[2]. The Spanish Obstetric Emergency Group study, published in May 2021, reported a higher incidence of stillbirth in women who had SARS-CoV-2 infection during pregnancy compared with non-infected women (10/1347 (0.7%) *vs* 3/1607 (0.2%); $P = 0.023$)[3]. In the USA, an analysis of 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, which is an all-payer database encompassing approximately 20% of USA hospitalizations, demonstrated that the stillbirth rate was significantly higher in those with compared to those without COVID-19 (5 *vs* 3 per 1000 births; $P = 0.003$)[4].

Time-trend studies

A recent large study in India reported a doubling of the stillbirth rate in the second wave of the COVID-19 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 of studies on the effect of the COVID-19 pandemic on pregnancy outcomes found evidence of an increase in the rate of stillbirth during compared with before the pandemic[6]. A study analyzing data from the UK Obstetric Surveillance System (UKOSS), which included 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 stillbirth (4–5 per 1000 births)[7]. The stillbirth rate during the COVID-19 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 in 2019 did not find any evidence of an increase in the rate of stillbirth during the pandemic[9]. Of note, an analysis of data from the Global Pregnancy and Neonatal outcomes in COVID-19 (PAN-COVID) registry (1 January to 25 July 2020) and the American Academy of Pediatrics (AAP) Section on Neonatal–Perinatal Medicine (SONPM) National Perinatal COVID-19 registry (4 April to 8 August 2020) did not report an increase in the rate of stillbirth[10].

Several reports have highlighted the direct impact of COVID-19 in pregnancy. In The Netherlands, 58 of the 9620 known SARS-CoV-2-infected pregnancies, from 1 March 2020 to 7 December 2021, resulted in stillbirth, according to the most recent figures from The Netherlands Obstetric Surveillance System; however, the number of stillbirths in non-infected pregnancies for the same period was not reported[11]. Studies with a large sample size have demonstrated an increased rate of stillbirth in SARS-CoV-2-positive women compared with those who did not experience infection[1–4,12] (Table 1). However, the evidence is controversial, with several smaller studies reporting no significant increase in the rate of stillbirth in women with COVID-19. Possible reasons are a lack of statistical power to show a difference in the rate of 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 *vs* indirect effect of COVID-19 pandemic

It is important to consider whether any increase in the rate of 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 behavior of pregnant women or clinicians during the COVID-19 pandemic. The differences in the rate of stillbirth observed before and during the pandemic in time-trend studies are likely to be due to a combination of direct and indirect effects. Although cohort and case–control studies of pregnancies 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, UK, found that the incidence of stillbirth was significantly higher during the pandemic compared with in the prepandemic period[13]. However, the number of stillbirths was small. Notably, none of the women who had stillbirth had COVID-19[13], 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 considerable 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 callouts[2]. Many outpatient appointments were also converted from face-to-face visits to virtual (telephone or video call) appointments, and services were reduced across the board as staff were redeployed to help on COVID-19 wards[14]. Postnatal length of hospital stay was reduced, which may have been due to proactive 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[15]. Of note, a study from Melbourne, Australia, reported no difference in the stillbirth rate before *vs* during COVID-19 restriction measures in a setting with very low levels of infection[16].

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 and abdominal pain) was significantly reduced during the COVID-19 pandemic[17]. 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[18]. A retrospective analysis in India found that a substantially lower number of pregnant women were referred or hospitalized for tertiary care[19]. 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[19]. Women with a high-risk pregnancy are at greater risk of pregnancy-related mortality or morbidity than that caused by COVID-19. Given that these women 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 for the increased rate of stillbirth during the COVID-19 pandemic in women testing negative for SARS-CoV-2 at the time of admission with stillbirth, as compared with the prepandemic rate, 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[20]. Asymptomatic cases of COVID-19 are estimated to account for 25% of all COVID-19 cases[21]. Paradoxically, although pregnant women are more likely to experience severe SARS-CoV-2 infection, they are also more likely to be asymptomatic than their non-pregnant counterparts[11]. As a result,

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

		Women (n)		*Stillbirths* (n *per 1000 births*)		
Study	*Country*	*SARS-CoV-2 positive*	*SARS-CoV-2 negative**	*SARS-CoV-2 positive*	*SARS-CoV-2 negative**	*Statistic*
Allotey (2020)[12]	30 countries	1039	4755	26	9	OR, 2.84 (95% CI, 1.25–6.45)
Cruz Melguizo (2021)[3]	Spain	1347	1607	7.4	1.9	$P = 0.023$
Jering (2021)[4]	USA	6380	400 066	5	3	$P < 0.05$
Gurol-Urganci (2021)[2]	UK	3527	338 553	8.5	3.4	aOR, 2.21 (95% CI, 1.58–3.11)
DeSisto (2021)[1]	USA	21 653	1 227 981	12.6	6.4	aRR, 1.90 (95% CI, 1.69–2.15)

Only first author of each study is given. *Studies using historical controls were not included. aOR, adjusted odds ratio; aRR, adjusted relative risk; OR, odds ratio.

many women may have been unaware that they had SARS-CoV-2 infection during their pregnancy[21]. This is likely, given the high prevalence of COVID-19 worldwide and in the UK in March and April 2020[22].

The INTERCOVID Multinational Cohort Study, which was a large study that analyzed data from 18 countries and compared the rate of severe perinatal morbidity and mortality between 706 pregnant women with COVID-19 and 1424 pregnant controls, found a much higher rate in those with COVID-19 (17.0% *vs* 7.9%)[23]. Although indirect effects of the pandemic likely contributed to a rise in the rate of 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[24]; they are around twice as likely as their non-pregnant counterparts to require intensive care, assisted ventilation or extracorporeal membrane oxygenation or to die from COVID-19[25]. Evidence is emerging of an increased rate of adverse pregnancy outcomes other than stillbirth during the COVID-19 pandemic, either because of SARS-CoV-2 infection itself or because of the indirect effects of the pandemic.

A systematic review by Wei *et al.* of studies on the effect of COVID-19 on pregnancy outcome found that COVID-19 is associated with an increased risk of pre-eclampsia; there is evidence of a 'dose–response' relationship, with more severe COVID-19 associated with a greater increase in the risk of pre-eclampsia[26]. The mechanism underlying this is unclear; however, it has been hypothesized that SARS-CoV-2 may bind to angiotensin-converting enzyme 2 receptors, leading to dysfunction of the renin–angiotensin system and vasoconstriction[27–29]. Another study found evidence that COVID-19 can cause clinical manifestations similar to pre-eclampsia, but measurements of biomarkers indicated that these were distinguishable and distinct pathologies[30].

Wei *et al.* also reported an association of severe COVID-19 with gestational diabetes and preterm birth, as compared with mild COVID-19[26]. They 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[23,31–36], including the INTERCOVID Multinational Cohort Study, which found that women with COVID-19 were at increased risk of preterm birth (mainly medically indicated preterm birth)[23]. 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; therefore, the increase in the rate of preterm birth could in part be explained by an increase in the rate of stillbirth.

A systematic review of 40 studies found that maternal mental health was worse during the pandemic, as evidenced by higher mean Edinburgh postnatal depression score[6]. As a result of the pandemic, many women felt isolated and lacked their usual support networks. Maternal mental health disorder in pregnancy is a known risk factor for stillbirth[37].

It is important to understand the inequalities that the COVID-19 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[38]. Even before the pandemic, women from black, Asian and minority ethnic groups had worse pregnancy outcome than white women. A large study of more than 1 million pregnant women in England showed that this disparity did not widen during the pandemic[39].

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[40–63].

A study of 15 women with severe COVID-19 who delivered in the third trimester demonstrated that, compared with controls, placental histology in women with COVID-19 was significantly more likely to show one or more features of maternal vascular malperfusion, in particular, abnormal maternal vessels and intervillous thrombi[41]. There is an association between maternal vascular malperfusion and hypertensive disorders, including pre-eclampsia. However, despite this association, of the women whose placenta exhibited features of maternal vascular malperfusion, only one had a pregnancy-induced hypertensive disorder[41,64]. Maternal vascular malperfusion and fetal vascular malperfusion are commonly identified in the placenta in cases of stillbirth[48].

Placental histology in patients who had mild or asymptomatic COVID-19 before birth has also been studied. There was no evidence of increased inflammatory infiltrates in the placenta of women who no longer had active COVID-19 at birth, though there were signs of fetal and maternal vascular malperfusion[65].

A case–control study of 64 pregnant women found no evidence that COVID-19 during the third trimester influenced placental histology[66]. When compared with 64 control placentae, there was no difference in placental macro- or microscopic morphology. However, the placentae of women who had been treated with antiviral medication, low molecular weight heparin, hydroxychloroquine or antibiotics more frequently showed delayed villous maturation[66].

The effects of COVID-19 on placental histology are still being researched, and, so far, the available evidence is from very small samples. Further research is needed to

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

Study	*Placentae* (n)	*Fetal demise* (n)	*Findings*
Pulinx (2020)[40]	2 (twins)	2	SARS-CoV-2-positive placentae and amniotic fluid. HI in both placentae with intervillous fibrin deposition and ischemic necrosis of surrounding villi; nuclear debris and increase in erythroblasts in fetal circulation, as seen in fetal hypoxia. No chorioamnionitis.
Shanes (2020)[41]	16	1	MVM ($n=2$), clustered avascular villi ($n=4$), mural fibrin deposition in fetal vessels ($n=1$), delayed villous maturation ($n=4$), chorioangiosis ($n=4$), acute inflammatory pathology ($n=1$) and chronic inflammatory pathology ($n=2$).
Hosier (2020)[42]	1	1	Acute placental infection, HI, diffuse PVF and inflammatory infiltrate.
Shende (2021)[43]	1	1	Viral RNA detected in cytotrophoblast and syncytiotrophoblast cells. Generally avascular villi with PFD, fibrin decidual deposition with extensive leukocyte infiltration.
Baud (2020)[44]	1	1	Mixed inflammatory infiltrates (subchorial space neutrophils/monocytes), increased intervillous fibrin deposition and funisitis.
Stonoga (2021)[45]	1	1	Multifocal chronic HI.
Thomas (2021)[46]	197	4	Virus identified *in situ*, accompanied by intervillositis, in 2/197 placentae.
Dumont (2021)[47]	1	1	PFD with ischemic changes and necrosis of the villi, intervillous space with inflammatory cells and histiocytes.
Bunnell (2021)[48]	12	12	MVM ($n=5$), FVM ($n=5$). No massive PFD or HI.
Poisson (2021)[49]	1	1	Patchy acute chorionitis, diffuse infarction/villous necrosis of placental parenchyma which resulted in extensive vascular malperfusion.
Valdespino-Vázquez (2021)[50]	2 (twins)	2	Placental infarction, with diffuse PFD, active chronic HI and subchorial inflammation.
Garrido-Pontnou (2021)[51]	198	5	Nine SARS-CoV-2-infected placentae, diffuse trophoblastic damage common among fetal demises.
Bouachba (2021)[52]	5	3	Extreme preterm birth ($n=2$). Massive PFD, necrotic trophoblast/neutrophil or histiocyte infiltration and/or lymphocytes in places, numerous large intervillous thrombi. Severe chronic HI ($n=4$).
Schwartz (2021)[53]	11	5	Transplacental transmission of SARS-CoV-2 in six liveborn neonates. Liveborn: all six placentae had chronic HI and necrosis of syncytiotrophoblast. Stillborn/terminated: all five had SARS-CoV-2 infection of syncytiotrophoblast, chronic HI and syncytiotrophoblast necrosis.
Biringer (2021)[54]	1	1	No signs of amnionitis or funisitis. Intervillous inflammation/predominant HI, neutrophils and massive PFD, maternal floor infarctions, reduced and/or missing placental vascularity, absence of trophoblastic superficial layer.
Ozer (2021)[55]	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 (2021)[56]	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 (2021)[57]	61	5	Majority (59%) of placentae demonstrated PFD, 25% of placentae considered SGA, 77% showed features of MVM, 33% showed severe TPC.
Marinho (2021)[58]	1	1	MVM, FVM, necrotic villi, focal laminar necrosis, fibrinoid necrosis and thrombi in decidua, delayed villous maturation.
Libbrecht (2021)[59]	17	2	In three placentae: 70% syncytiotrophoblast necrosis, mild/moderate HI with mixed infiltrate (histiocytes, T-cells, neutrophils). No villitis. Strong, diffuse C4d deposition at syncytiotrophoblast surface.
Marton (2021)[60]	1	1	Necrosis of villous trophoblast, associated with chronic HI, massive PFD with up to 90% of intervillous spaces involved. Active viral replication in villous trophoblast cells.
Colson (2021)[61]	31	1	Infected placenta ($n=1$), signs of MVM ($n=6$), chronic HI (including SARS-CoV-2-positive placenta) ($n=3$), focal or diffuse chorioamnionitis ($n=8$).
Watkins (2021)[62]	7	1	All placentae positive for SARS-CoV-2 by RNA ISH; variable degrees of HI, PFD and trophoblast necrosis; FVM ($n=3$).
Zinserling (2021)[63]	1	1	SARS-CoV-2-positive infant, viral infection in several pancreata, brain, spleen and adrenals. Viral placentitis with chronic insufficiency and acute placental decompensation.

Only first author of each study is given. FVM, fetal vascular malperfusion; HI, histiocytic intervillositis; ISH, *in-situ* hybridization; MVM, maternal vascular malperfusion; PFD, perivillous fibrin deposition; PVF, perivascular fibrosis; SGA, small-for-gestational age; TPC, Tenney Parker changes.

understand fully the effect that SARS-CoV-2 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 16 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 COVID-19 vaccination at the same time as non-pregnant women of the same age[67]. This guidance is based on data from the USA, where more than 169 000 pregnant women have been vaccinated, and from 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[68,69]. 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[70,71] (355 299 women gave birth during this period). The stillbirth rate was found to be 3.35 per 1000 in vaccinated compared with 3.60 per 1000 in unvaccinated women, but the difference was not significant. Similarly, the rates of preterm birth and low birth weight were similar in those who received the vaccine compared with 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 SARS-CoV-2[67]. In August 2021, the CDC advised that pregnant women should receive a COVID-19 vaccine. Despite this, as of 29 September 2021, only 31% of pregnant women in the USA had been vaccinated against COVID-19[72]. The latest data from the UK on vaccine uptake among pregnant women showed a rate of 22% in August 2021[71].

During the vaccine rollout, pregnant women have not been prioritized over their non-pregnant peers of the same age. The mean age of women giving birth in the UK in 2019 was 30.7 years[73]. Assuming a similar average age in 2021, most pregnant women would not have been invited for their first vaccine dose until late May 2021, and those younger would not have received their first dose until much later (over 18s were not invited until 18 June 2021)[69,74]. Many pregnant women have been shielding throughout the pandemic[75], particularly as the evidence of increased risks to their own health and that of their baby accumulated. The increased risks to the woman, combined with the increased risks of adverse perinatal outcome, in particular stillbirth, caused by both the direct and indirect effects of COVID-19, suggest that pregnant women should be prioritized for receiving their

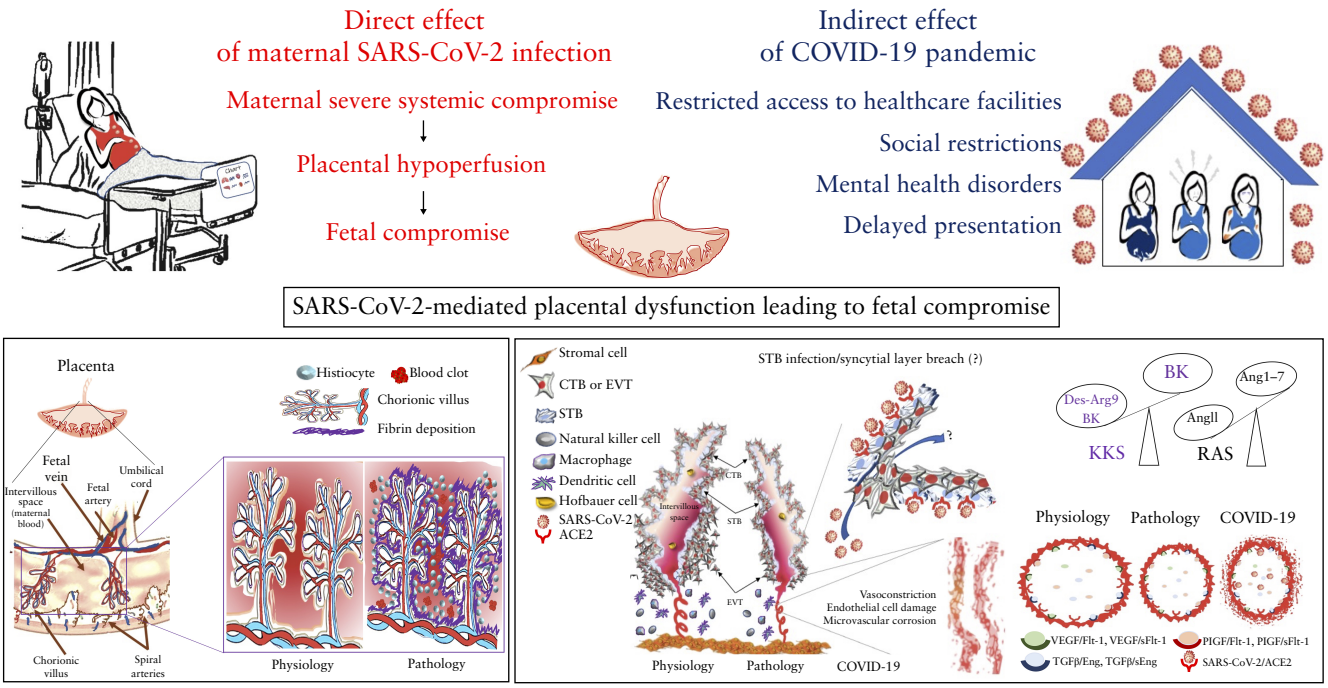

Figure 1 Direct and indirect effects of COVID-19 in pregnancy. Possible direct impacts of maternal SARS-CoV-2 infection include: (1) increased severe maternal morbidity, need for intensive care, assisted ventilation and extracorporeal membrane oxygenation, which may lead to maternal severe systemic compromise and fetal death; (2) systemic dysregulation of the renin–angiotensin system (RAS) and kallikrein–kinin system (KKS) pathways and levels of circulating angiogenic factors, vasoconstriction, endothelial cell damage and microvascular corrosion, which could potentially result in pre-eclampsia-like syndrome and stillbirth; and (3) breach of the syncytial layer due to infection of the syncytiotrophoblast, and chorionic intervillositis and fibrin deposition. Indirect consequences may be detrimental to maternal health, including reduced access to healthcare services due to changes in patient or clinician behavior, increased mental health strain, increased domestic violence due to lockdown and increased socioeconomic deprivation. ACE2, angiotensin-converting enzyme 2; Ang, angiotensin; BK, bradykinin; CTB, cytotrophoblast; EVT, extravillous trophoblast; PlGF, placental growth factor; (s)Eng, (soluble) endoglin; (s)Flt-1, (soluble) fms-like tyrosine kinase-1; STB, syncytiotrophoblast; TGFβ, transforming growth factor-β; VEGF, vascular endothelial growth factor.

first and second doses of vaccine, or booster dose in high-income countries in which most of the population has been vaccinated, over their non-pregnant peers of equivalent age.

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 vaccination hesitancy among pregnant women; a UK survey identified that only 53% of pregnant women reported an intention of getting the COVID-19 vaccine[76]. Further research is ongoing[77], but it is very important that pregnant women are reassured about the evidence supporting the safety of COVID-19 vaccination 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 between COVID-19 and stillbirth, offering induction of labor to women who test positive for SARS-CoV-2 infection may be beneficial, in particular in the third trimester, in which 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 between COVID-19 and 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[78,79], 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, and ensure that they are offered COVID-19 vaccination early.

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[80]. The secondary outcomes of the 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 prioritize vaccination[80].

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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