SARS-CoV-2 infection and COVID-19 vaccination in pregnancy

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Abstract | SARS-CoV-2 infection poses increased risks of poor outcomes during pregnancy, including preterm birth and stillbirth. There is also developing concern over the effects of SARS-CoV-2 infection on the placenta, and these effects seem to vary between different viral variants. Despite these risks, many pregnant individuals have been reluctant to be vaccinated against the virus owing to safety concerns. We now have extensive data confirming the safety and effectiveness of COVID-19 vaccination during pregnancy, although it will also be necessary to determine the effectiveness of these vaccines specifically against newly emerging viral variants, including Omicron. In this Progress article, I cover recent developments in our understanding of the risks of SARS-CoV-2 infection in pregnancy, and how vaccination can reduce these.

Viruses that cause pneumonia, including severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), have long been known to be of particular concern during pregnancy[1]. So as the world entered the SARS-CoV-2 pandemic in early 2020, clinicians and scientists working in obstetrics knew that their patients were likely to be at increased risk. Initially, lockdowns and a tendency towards risk avoidance masked some of the increased risks associated with SARS-CoV-2 infection in pregnancy[2,3], but with the passing of time the risks have become clearer. Although pregnant people were excluded from the first trials of COVID-19 vaccines, the pressing need to protect this group meant that the vaccines were rolled out to them in advance of the completion of clinical trials, and we now have extensive real-world data confirming the safety and effectiveness of the vaccines during pregnancy. In this Progress article, I cover recent developments in our understanding of the risks of SARS-CoV-2 infection that are specific to pregnancy, and how vaccination can safely reduce these.

SARS-CoV-2 infection in pregnancy

Obstetric outcomes following SARS-CoV-2 infection. Pregnancy is associated with increased disease severity in those infected with SARS-CoV-2: a meta-analysis of 92 studies comparing outcomes for pregnant patients with COVID-19 with age and sex-matched non-pregnant patients with COVID-19 found that pregnancy increases the risk of needing intensive care (OR 2.13, 95% confidence interval (CI) 1.54–2.95), invasive ventilation (OR 2.59, CI 2.28–2.94) and extracorporeal membrane oxygenation (OR 2.02, CI 1.22–3.34), although the risk of all-cause mortality was not increased (OR 0.96, CI 0.79–1.18)[4]. A more recent meta-analysis of 111 studies, which compared outcomes for pregnant patients infected with SARS-CoV-2 with those who were not infected, found that infection significantly increased the odds of pre-mature delivery (OR 1.48, 95% CI 1.22–1.8), pre-eclampsia (OR 1.6, CI 1.2–2.1), stillbirth (OR 2.36, CI 1.24–4.46), neonatal mortality (OR 3.35, CI 1.07–10.5) and maternal mortality (OR 3.08, CI 1.5–6.3)[5].

Since the publication of these meta-analyses, further large studies have also found increased risks of maternal morbidity and mortality[6], preterm birth (PTB) and perinatal death associated with SARS-CoV-2 infection in pregnancy[7,8]. There is also evidence that both maternal[9] and neonatal[10] outcomes were worse during the Delta wave of the SARS-CoV-2 pandemic than in preceding periods.

The increased risk of PTB associated with SARS-CoV-2 infection seems to be driven largely by iatrogenic PTBs, with doctors opting to deliver the infant to try to save the critically ill patient[11]. The increased risk of stillbirth and pre-eclampsia are more likely to be associated with inflammatory changes affecting the placenta (FIG. 1).

SARS-CoV-2 and the placenta. The placenta expresses the cellular receptors for SARS-CoV-2, namely angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2)[12–15], and some patients with COVID-19 do become viraemic[16], meaning there is the potential for SARS-CoV-2 infection of the placenta. However, SARS-CoV-2 viraemia in pregnancy seems to be uncommon[12], and there is little placental co-expression of ACE2 and TMPRSS2, which is required for the canonical route of virus entry into the cell[12–14]. Moreover, placental expression of ACE2 declines over the course of pregnancy[15].

In addition to the general defences the placenta has against viral infection[17], these factors might be expected to protect the placenta from infection with SARS-CoV-2. Indeed, placental infection seems to be uncommon. However, SARS-CoV-2-associated coagulation and inflammation occur even in the absence of placental infection, most commonly manifesting as intervillous thrombosis and fibrin deposition[12,15,18–20]. The mucosal lining of the uterus is a maternal tissue into which the placenta implants and, in pregnancy, is called the decidua. Examination of the decidua in pregnancies affected by SARS-CoV-2 demonstrated local activation of maternal natural killer cells and T cells, including the expression of gene signatures associated with pre-eclampsia[15,21].

A more severe inflammatory syndrome occurs when the placenta does become infected; namely, SARS-CoV-2 placentitis. This is characterized by histiocytic inter-villositis, perivillous fibrin deposition and trophoblast necrosis, and is emerging as a risk factor for fetal distress or demise[22–26]. A series of 68 cases of SARS-CoV-2 placentitis associated with either stillbirth or neonatal death found that the causes of death were likely to be fetal hypoxic-ischaemic injury resulting from severe placental damage, rather than

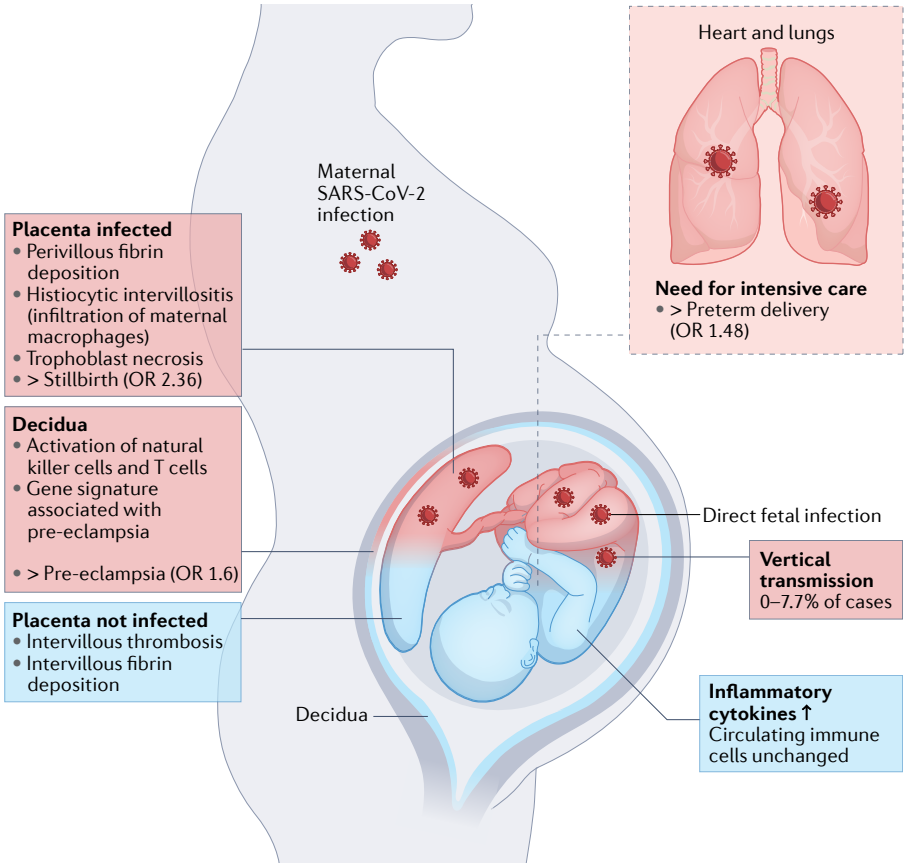

Fig. 1 | **Direct versus indirect effects of SARS-CoV-2 infection on the fetus and placenta.** Maternal SARS-CoV-2 infection can impact pregnancy in numerous ways. The need for intensive care associated with severe disease can necessitate delivering the infant, causing an increased rate of preterm delivery. Placental infection can be associated with SARS-CoV-2 placentitis, which is associated with an increased risk of stillbirth. Even in the absence of placental infection, inflammatory changes are observed in the decidua and placenta, and these may be linked to the increased risk of pre-eclampsia associated with SARS-CoV-2 infection in pregnancy. SARS-CoV-2 can also be vertically transmitted to infect the fetus, although this is uncommon. Blue indicates indirect outcomes on the fetus and placenta associated with maternal infection with SARS-CoV-2, whereas red indicates outcomes associated with direct fetal infection.

fetal infection with SARS-CoV-2. Indeed, placental infection with SARS-CoV-2 does not necessarily equate with fetal infection; in this case series, infection of the fetus was only confirmed in 2 of the 68 cases[26].

SARS-CoV-2 and the fetus. Numerous studies have reported SARS-CoV-2 infection in infants born to infected individuals. The largest of these have examined infection by nasopharyngeal swab, finding the rate at which infants test positive for SARS-CoV-2 as between 0.9 and 2.8%[27–30]. However, infants who test positive in this way have not necessarily been infected in utero, as they may have been infected by horizontal transmission shortly after birth.

Numerous smaller studies have examined umbilical cord blood to more accurately identify those neonates infected by vertical transmission. Although the fetus begins producing both IgG and IgM between 12 and 20 weeks of gestation, maternal IgG can cross the placenta so only the presence of IgM signals fetal exposure to antigen. In pregnancies affected by SARS-CoV-2 infection, detection of Spike-specific IgM in cord blood has been reported in between 0 and 7.7% of cases[21,27,31]. A systematic review of studies examining the presence of the viral genome in cord blood found it in 2.9% of cases[27], although since then a larger case series of 64 deliveries was unable to detect the viral genome in the umbilical cord blood of any infant[12].

Increased levels of inflammatory cytokines have been observed in the cord blood of neonates, even in the absence of placental infection[21,32]. It is unclear whether these cytokines were produced locally by the fetus or reflect maternal cytokines that have crossed the placenta[33]. However, the findings that immune cells in cord blood show higher cytokine production if the pregnancy was affected by SARS-CoV-2 infection and that IL-8 concentrations are generally higher in cord blood than that in maternal blood suggest that at least some of these cytokines may be produced by the neonate[32].

New variants, new outcomes? One important caveat to much of the preceding data is that they were collected in earlier waves of the pandemic, in which the predominant variants of SARS-CoV-2 were different from those we face now. Of particular concern is that reports of SARS-CoV-2 placentitis were rare in the first wave, caused by the original strain of SARS-CoV-2, but became increasingly common in the Alpha and Delta variant waves of the pandemic[24,25]. This demonstrates that we cannot necessarily assume that obstetric outcomes will be the same in the current wave, or in future ones, as they have been previously. At the time of writing, we do not have solid data on how the Omicron wave has affected pregnant people.

Vaccine safety in pregnancy

Benefits of vaccination in pregnancy. Vaccination in pregnancy to prevent maternal morbidity and mortality, or to confer passive immunity to the infant, has a long and successful history[34]. As early as 1879, it was noticed that infants born to individuals who received the smallpox vaccine during pregnancy were themselves protected, and similar observations were made for pertussis and tetanus vaccination in the middle of the twentieth century. Similar to SARS-CoV-2 infection, infection with influenza virus in pregnancy is associated with increased maternal morbidity and, as a result, influenza vaccination in pregnancy has been recommended in the United States since 1997, although it was not until 2005 that clinical trials formally demonstrated its benefits. In the United Kingdom, influenza and pertussis vaccination have been routinely offered in pregnancy since 2010 and 2012, respectively.

Safety of COVID-19 vaccination in pregnancy. The increased potential for severe consequences following SARS-CoV-2 infection in pregnancy makes COVID-19 vaccination of this population particularly attractive. However, pregnant patients naturally want to know whether vaccination is safe for them and their infants. Although we await clinical trial data in this population, pregnant people have been vaccinated

against COVID-19 since December 2020, and we now have safety data from more than 185,000 individuals vaccinated during pregnancy (TABLE 1).

Because the first countries to offer the COVID-19 vaccine in pregnancy, namely the United States and Israel, were using the mRNA vaccines BNT162b2 (Pfizer) and mRNA-1273 (Moderna), the first data available were on these vaccines. As a result, when other countries later made the vaccines available in pregnancy, many preferentially offered mRNA vaccines to this group. Because of this, mRNA-based COVID-19 vaccines have been most widely used in pregnancy and, therefore, the majority of safety data come from these vaccines.

A key finding with regards to safety is that IgM is not detected in umbilical cord blood following vaccination in pregnancy[31,35,36]. This indicates that the vaccine has not elicited an immune response in the fetus, suggesting that it has not crossed the placental barrier. In line with this, one study that looked for SARS-CoV-2 Spike mRNA or protein in placenta and cord blood following vaccination was unable to detect it[36]. COVID-19 vaccination in pregnancy is also not associated with pathological changes to the placenta[37]. These findings indicate that a direct effect of vaccination on fetal development is unlikely. However, local and systemic immune reactions to COVID-19 vaccination do occur in pregnant people, at roughly the same rate at which they occur in the general population[38–41]. Therefore, it is important to consider the possibility that the immune response to COVID-19 vaccination could affect the placenta or fetus and undertake epidemiological studies to determine whether it could be associated with any poor obstetric outcome. Such studies have taken one of three broad approaches: registry studies, case–control studies and cohort studies (TABLE 1).

Registry studies. Registry studies recruit participants at the time of vaccination, determine the outcomes of their pregnancies and compare the rates at which adverse events occur in the registry population relative to those seen either in the general pregnant population or during pregnancy historically. The first such study used the v-safe pregnancy registry of the US Centers for Disease Control and Prevention (CDC).

Table 1 | **Epidemiological studies on the safety of COVID-19 vaccination in pregnancy**

Study	Number of participants vaccinated in pregnancy	Country	Approach	Outcomes examined	Impact of COVID-19 vaccination	Ref.
v-safe pregnancy registry	5,096	United States	Registry	Stillbirth, preterm birth (PTB), small for gestational age (SGA), neonatal death, congenital abnormalities	None detected	38
				PTB, SGA, neonatal intensive care unit (NICU) admission, neonatal death, congenital abnormalities	None detected	42
				Miscarriage	None detected	43
BORN Ontario	64,234	Canada	Registry	PTB, stillbirth, SGA	None detected	44
Stock et al., 2022	18,399	Scotland	Registry	PTB, perinatal death	None detected	8
Bookstein-Peretz et al., 2021	390	Israel	Registry	Miscarriage, PTB, SGA, NICU admission	None detected	41
Norwegian National Health Registries	1,003	Norway	Case–control	Miscarriage	None detected	47
Vaccine Safety Datalink	31,080	USA	Case–control	Stillbirth	None detected	45
				Miscarriage	None detected	46
			Cohort	PTB, SGA	None detected	48
Wainstock et al., 2021	913	Israel	Cohort	PTB, pre-eclampsia, SGA	None detected	49
Blakeway et al., 2021	140	England	Cohort	PTB, stillbirth, SGA, NICU admission, congenital abnormalities	None detected	51
Maccabi Healthcare Services	24,288	Israel	Cohort	Miscarriage, PTB, stillbirth, pre-eclampsia, SGA, SARS-CoV-2 infection	Reduced risk of SARS-CoV-2 infection	52
			Cohort	PTB, SGA, congenital abnormalities, death and hospitalization of infants up to 6 months old	None detected	50
Theiler et al., 2021	140	United States	Cohort	PTB, stillbirth, pre-eclampsia, SGA, NICU admission, SARS-CoV-2 infection	Reduced risk of SARS-CoV-2 infection	53
UK Health Security Agency	58,165	United Kingdom	Cohort	PTB, stillbirth, SGA	None detected	54

Results from the 12 studies summarized show no increased risk of any poor obstetric outcome associated with COVID-19 vaccination. The total number of participants included in these studies is 185,309. This has been calculated as the sum of all participants, except for those in Blakeway et al.[51] and Stock et al.[8], who are also included in the UK Health Security Agency data and would otherwise be counted twice.

Among 713 people vaccinated in pregnancy who had given birth by 30 March 2021, the rates of adverse events were the same as have been reported historically[38], and a follow-up study looking at 1,613 vaccinated people who had given birth by September 2021 continued to find a normal rate of adverse events[42]. Focusing only on those vaccinated before 20 weeks, there was also no increased risk of miscarriage following vaccination[43].

The Better Outcomes Registry and Network (BORN) comprises 64,234 people vaccinated against COVID-19 during pregnancy in Ontario, Canada. Of the 31,343 individuals who had given birth by 31 October 2021, the rate of stillbirth, PTB or infants being born small for their gestational age was not increased, compared with either historical data or the background rate[44]. A study of 18,399 people vaccinated against COVID-19 during pregnancy in Scotland found no increased risk of PTB or neonatal mortality, compared with the general pregnant population[8]. An early registry study in Israel examined only 390 people vaccinated with BNT162b2 during pregnancy, but also found no increased risk of miscarriage, PTB or infants being born small for their gestational age[41].

Case–control studies. Case–control studies identify individuals who experience a predefined adverse event and determine whether those people are more likely to have experienced a particular exposure than those who did not experience the event. Two such studies have been done in the US Vaccine Safety Datalink system, which includes 31,080 people vaccinated during pregnancy. One of these studies found no indication that COVID-19 vaccination is linked to stillbirth[45]; the second found that people who experienced a miscarriage were no more likely to have been vaccinated in the preceding 28 days than those who did not miscarry[46]. A similar study carried out in Norway found that, among 18,447 pregnancies, those that ended in miscarriage were no more likely to have received a COVID-19 vaccine in either the preceding 3-week or 5-week period than those that continued[47].

Cohort studies. Cohort studies examine the outcomes for those who are vaccinated against COVID-19 in pregnancy, compared with the outcomes of a contemporary cohort of unvaccinated people. Because the participants in these studies have not been randomized to vaccination, there are systematic differences between those who chose to receive a COVID-19 vaccine and those who declined, although the majority of studies attempt to control for these variables, either with multivariate analysis[48–50] or by identifying pairs matched for potential confounders[51,52]. Among seven cohort studies there was no increased risk of miscarriage[52], pre-eclampsia[49,52,53] or any adverse outcome at the time of birth[48–54] associated with COVID-19 vaccination in pregnancy. One study that followed up infants after birth, to an average of 134 days, also found no increased risk of death or hospitalization in the first months of life in infants born following vaccination during pregnancy[50].

Although each of these approaches to addressing the question of COVID-19 vaccine safety in pregnancy has its own weakness, the findings from each approach lend weight to the others. Together with the sheer number of participants in these studies, this gives us confidence that COVID-19 vaccination is not associated with adverse pregnancy outcomes.

Vaccine efficacy

Effectiveness of COVID-19 vaccination in pregnancy. Although it is untrue to say that the immune system is weakened in pregnancy, it does differ from the non-pregnant state, with a shift away from cell-mediated immune responses. This is demonstrated by the long-standing observation that cell-mediated autoimmune diseases tend to go into remission during pregnancy, whereas antibody-mediated diseases can flare[55]. It is therefore not unreasonable to ask whether COVID-19 vaccination is as effective at preventing disease during pregnancy as it is in the broader population.

Early attempts to answer this question looked at vaccine immunogenicity in pregnant participants, compared with age and sex-matched non-pregnant controls. Two reports found that the titres of anti-Spike, anti-RBD (receptor binding domain of the Spike protein) and SARS-CoV-2 neutralizing antibodies were the same in the two groups[39,56]. Importantly, both of these studies found higher virus-specific antibody titres associated with COVID-19 vaccination compared with SARS-CoV-2 infection, underlining the benefits of vaccination even in those who have already been infected. A third study, using systems serology, also found that overall titres of antibodies did not differ between the groups but further revealed that after only one dose of vaccine, antibody effector functions were induced with delayed kinetics in the pregnant group compared with the non-pregnant group: following the second dose, there was no significant difference between the groups[57]. Comparing vaccine responses across trimesters using this approach, the same team also found a subtle reduction in antibody effector functions following vaccination in the second trimester, compared with vaccination in the first or third trimesters, which might reflect trimester-specific immune alterations that are known to be associated with a somewhat more quiescent state in the second trimester[58]. Comparing T cell responses, it was shown that Spike-induced production of IFNγ by total and central memory $CD4^+$ and $CD8^+$ T cells following vaccination did not differ between pregnant and non-pregnant groups[56].

More recently, two cohort studies from Israel have enabled an estimate of COVID-19 vaccine effectiveness during pregnancy, finding it to be roughly the same as in the general population[52,59]. UK surveillance data have not been used to model vaccine effectiveness, but nevertheless point to COVID-19 vaccination being effective in pregnancy, particularly against severe disease[60]. In Scotland, 68% of the pregnant population was unvaccinated by October 2021, but unvaccinated individuals accounted for 77.4% of all SARS-CoV-2 infections, 90.9% of COVID-19 hospitalizations and 98% of intensive care unit admissions among pregnant people; furthermore, all perinatal deaths following SARS-CoV-2 infection in pregnancy occurred in unvaccinated individuals[8]. These data sets were collected largely during the period when the Alpha variant was dominant, but with some contribution from the Delta wave. As the Omicron variant becomes prominent, it will be important to determine the effectiveness of vaccination specifically against this strain, how this varies following a booster dose and the extent to which protection wanes over time. It will also be necessary to determine the extent to which vaccination provides protection specifically against COVID-19-associated pregnancy complications.

Protection of infants by maternal COVID-19 vaccination. As expected, maternal IgG raised by vaccination during pregnancy crosses the placenta and is present in umbilical cord blood at birth[31,35,36,39,56,58,61–63], remaining detectable in the blood of more than half of infants at 6 months[61]. Transplacental transfer of IgG following vaccination against tetanus and pertussis

provides infants with protection against these diseases, and by analogy, COVID-19 vaccination in pregnancy may provide infants with some protection against COVID-19. Early estimates suggest that vaccination after 20 weeks of pregnancy is 80% effective (95% CI, 55–91%) and vaccination before 20 weeks is 32% effective (95% CI, 43–68%) at preventing hospitalization of infants younger than 6 months old with COVID-19 (REF.[64]).

This increased protection of infants following vaccination later in pregnancy is in line with findings that maximum cord blood antibody titres are achieved when vaccination occurs in the late second to early third trimester[62,63]. This is likely to reflect higher maternal IgG titres at the time of birth when vaccination has occurred more recently, as the efficiency of Spike-specific IgG transfer across the placenta is highest following vaccination in the first trimester[58]. However, it is important to be clear that the main benefit of COVID-19 vaccination in pregnancy is the reduction in risk of disease during pregnancy. Therefore, the timing of vaccination should seek to optimize protection during pregnancy, rather than that of the infant after birth.

Notably, the titres of anti-Spike antibodies seen in cord blood are lower following SARS-CoV-2 infection in pregnancy compared with COVID-19 vaccination in pregnancy[56,61]. This is likely to be a result of both lower maternal IgG titres being elicited by infection compared with vaccination[56,61] and also because the transport of SARS-CoV-2-specific antibodies is compromised following SARS-CoV-2 infection in the third trimester[12,65].

Conclusion

SARS-CoV-2 infection poses significant risks to pregnant people and their infants, but COVID-19 vaccination is safe in pregnancy. This underlies the recommendation that pregnant people receive the COVID-19 vaccine, which is now being made by public health bodies all over the world[66,67]. Despite these recommendations, in many countries uptake of the COVID-19 vaccine in pregnancy remains low, so it is essential that we continue to communicate this message to those who are making the decision about COVID-19 vaccination, for themselves and their infants. Although it is understandable that this group might feel cautious, the task has been made more difficult by the proliferation of misinformation about the safety of COVID-19 vaccination in pregnancy. Strong public health messaging is needed, but more importantly we must ensure that midwives and obstetricians are adequately equipped to counsel their patients on the benefits of COVID-19 vaccination.

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Competing interests
The author declared no competing interests.